INSTITUT NATIONAL D'ASSURANCE
MALADIE-INVALIDITE
SERVICE DES SOINS DE SANTE
Comité d' évaluation des pratiques
médicales en matière de médicaments

ADEQUATE USE OF HORMONAL CONTRACEPTION

Systematic literature review: full report

Consensus conference
May 16th 2013
Auditorium Lippens (Royal Library)
Brussels

This literature review was performed by vzw Farmaka asbl and was followed-up by a reading committee.

Researchers

Hera Decat MD, *vzw Farmaka asbl*
Griet Goesaert MD*, vzw Farmaka asbl*
Hilde Habraken Lic, *vzw Farmaka asbl*
Thérèse Leroy Lic, *vzw Farmaka asbl*
Gerben Vandermeiren MD, *vzw Farmaka asbl*
Dominique Boudry MD, *vzw Farmaka asbl*
Joachim Vandenhoven *MD, vzw Farmaka asbl*

Reading committee

Prof Dr Corinne Bouüaert (ULg)
Prof Dr Lieve Peremans (UA)
Dr Anne Verougstraete (ULB)
Prof Dr Steven Weyers (UGent)

Administrative and IT support

Stijn Dumon, *vzw Farmaka asbl*

Translation

Dynamics Translations
Wilkens c.s.
Miles NV

TABLE OF CONTENTS

ABBREVIATIONS

AE: adverse events
AMI: acute myocardial infaction
BMI: body mass index
CHC: combined hormonal contraception
CI : confidence interval
CMA: chlormadinone acetate
COC: combined oral contraceptive(s)
COCP: combined oral contraceptive pill
CPA: cyproterone acetate
Cu: copper
Cu-IUD: copper intra-uterine device
CVA: cerebrovascular accident
DB: double blind
DMPA: depot medroxyprogesterone acetate
DNG: dienogest
DRSP: drospirenone
DSG: desogestrel
E2: estradiol
E2V: estradiol valerate
EBM: evidence based medicine
EC: emergency contraception
EE: ethinyl estradiol
FSH: Follicle stimulating hormone
FU: follow-up
FU: follow-up
GP: general practitioner, general practice
GSD: gestodene
GTD: gestodene
HRT: hormone replacement therapy
IM: intramuscular
ITT: intention-to-treat analysis
IUCD: copper-containing intrauterine device
IUD: intra-uterine device
IUS: intra-uterine system
LNG: levonorgestrel
LNG-IUS: levonorgestrel intra-uterine system
MA: meta-analysis
MD : mean difference
MI: myocardial infarction
n: number of patients
N= number of studies

NA: not applicable
NET: norethindrone = norethisterone
NETA: norethindrone acetate
NGM: norgestimate
NOMAC= nomegestrol acetate
NR: not reported
NS: not statistically significant
NSAID: non-steroidal anti-inflammatory drug
NT: no statistical test
OC: (combined) oral contraception
OCP : oral contraceptive pill
OL: open label
OR : odds ratio
OTC: over the counter
p= p-value statistical test
PE: primary endpoint
PG: parallel group (RCT)
PID: pelvic inflammatory disease
Pla: placebo
PMS: premenstrual syndrome
PO: primary outcome
POInj: progestogen-only injectables
POP: progestogen-only pill
RCT: randomized controlled trial
RR: relative risk, rate ratio
SB: single blind
SC: subcutaneous
SR: systematic review
SS: statistically significant
STD: sexually transmitted disease
STI: sexually transmitted infection
TCu: T-shapped copper (IUD)
TNR: statistical test not reported
UKMEC: UK Medical Eligibility Criteria for Contraceptive Use
UPA: ulipristal
VAS: visual analogue scale
VTE: venous thrombo-embolism

1. Methodology

1.1. Introduction and scope

This systematic literature review was conducted in preparation of the consensus conference on 'Adequate use of hormonal contraception' which will take place on May 16th 2013.

1.1.1. Questions to the jury

The questions to the jury, as they were phrased by the organising committee of the RIZIV/INAMI are

1. **Types van hormonale contraceptie en respectievelijke werkzaamheid** ***Types de contraceptifs hormonaux et efficacité respective*** Vraag – *Question* 1 Wat is voor de verschillende hormonale contraceptiva : - hun theoretische contraceptieve werkzaamheid? - hun contraceptieve werkzaamheid in de praktijk (doeltreffendheid, effectiviteit)? - hun respectieve neveneffecten die klinisch relevant zijn voor een welbepaalde keuze (NB : buiten de specifieke domeinen die nadien worden besproken)? *Pour les différents moyens contraceptifs hormonaux, quelles sont :* *- leur efficacité contraceptive théorique ?* *- leur efficacité contraceptive dans la pratique ?* *- leurs effets indésirables respectifs, de pertinence clinique pour un choix préférentiel (NB : hors domaines spécifiques abordés par après) ?*
2. **Hormonale contraceptie in functie van bepaalde klachten, gynaecologische afwijkingen en/of gewenste positieve effecten - *La contraception hormonale en fonction de différentes plaintes, affections gynécologiques et/ou effets positifs souhaités*** Vraag – *Question* 2 Wat zijn de verwante indicaties (buiten contraceptie) van de verschillende hormonale contraceptiva en is er een onderling verschil (+ een voorkeurskeuze) voor: - de cycluscontrole - dysmenorroe - menorragie - acne - (functionele) ovariële cysten - premenstrueel syndroom - fibromyomatose

- endometriose
- mastodynie?

Quelles sont les indications connexes (hors contraception) des différents moyens contraceptifs hormonaux et existe-t-il une différence entre eux (+ un choix préférentiel) pour :
- le contrôle du cycle
- la dysménorhée
- les ménorragies
- l'acné
- les kystes ovariens (fonctionnels)
- le syndrome prémenstruel
- la fibromyomatose
- l'endométriose
- la mastodynie ?

3. **Praktische aspecten -** ***Aspects pratiques***
Vraag – *Question* 3

Correct gebruik van de verschillende hormonale contraceptiva
Bonne utilisation des différents moyens contraceptifs hormonaux
3.1. Op welk precies moment van de cyclus mag men beginnen met hormonale contraceptie (naargelang van het geneesmiddel, OC of IUD, quick start)?
3.1. A quel moment précis du cycle peut-on commencer une contraception hormonale (suivant le médicament, CO ou DIU, quick start) ?
3.2. Wat zijn de aanbevelingen wanneer men het hormonaal contraceptivum vergeet in te nemen?
3.2. Quelles sont les recommandations en cas d'oubli de la contraceptif hormonal ?
3.3. Tot welke leeftijd moet een hormonaal contraceptivum worden voorgeschreven?
3.3. Jusqu'à quel âge prescrire une contraceptif hormonal ?
3.4. Wat zijn de klinisch relevante medicamenteuze of andere interacties met de verschillende hormonale contraceptiva?
3.4. Quelles sont les interactions médicamenteuses ou autres, cliniquement pertinentes, avec les différents moyens contraceptifs hormonaux ?
3.5. Is het aangeraden om systematisch de bloeddruk, de bloedlipiden (cholesterolemie) en de glykemie te meten voordat hormonale contraceptie wordt voorgeschreven?
3.5. Est-il recommandé de systématiquement mesurer les chiffres de PA, les lipides sanguins (cholestérolémie) et la glycémie avant une prescription d'une contraception hormonale ?

4. **Veiligheid van hormonale contraceptie -** ***Sécurité de la contraception hormonale***
Vraag – *Question* 4

Veiligheid van hormonale contraceptie (kankers) - *Sécurité de la contraception hormonale (cancers)*
4.1. Wat is het risico op gynaecologische of andere kankers verbonden aan de verschillende hormonale contraceptiva?

4.1. Quel est le risque de cancers gynécologiques ou autres liés aux différents moyens contraceptifs hormonaux ?

Veiligheid van hormonale contraceptie (niet-cancereuze aandoeningen) - Sécurité de la contraception hormonale (affections non cancéreuses)

4.2. Wat is het risico op veneuze trombo-embolie verbonden aan de verschillende hormonale contraceptiva?

4.2. Quel est le risque thromboembolique veineux lié aux différents moyens contraceptifs hormonaux ?

4.3. Wat zijn de cardiovasculaire risico's (naast veneuze trombo-embolie) verbonden aan de verschillende hormonale contraceptiva?

4.3. Quels sont les risques cardiovasculaires (autres que la thromboembolie veineuse) liés aux différents contraceptifs hormonaux ?

4.4. Wat zijn de risico's op lever- en hepatobiliaire aandoeningen verbonden aan de hormonale contraceptiva (naast kanker)?

4.4. Quels sont les risques de troubles hépatiques et hépato-biliaires avec les contraceptifs hormonaux (hors cancer) ?

4.5. Wat is het effect van de verschillende hormonale contraceptiva op de (totale) mortaliteit?

4.5. Quel est l'effet des différents moyens contraceptifs hormonaux sur la mortalité (globale) ?

5. **Keuze van de hormonale contraceptie in de praktijk -**
Choix du moyen contraceptif hormonal dans la pratique

Vraag – *Question* 5

5.1. Welk hormonaal contraceptivum wordt eerst gekozen wanneer het niet om een specifieke situatie gaat?

5.1. Quel est le premier choix d'un moyen contraceptif hormonal hors situation particulière ?

5.2. Welke elementen bevorderen of verminderen de therapietrouw aan de verschillende hormonale contraceptiva?

5.2. Quels sont les éléments qui favorisent ou qui diminuent l'observance thérapeutique des différents moyens contraceptifs hormonaux ?

6. **Hormonale contraceptie aangepast aan bepaalde omstandigheden -**
Contraception hormonale adaptée à certaines situations

Vraag – *Question* 6

Welke hormonale contraceptiva moet men aanbevelen in geval van:
- chirurgische pre- en postoperatieve situatie
- tabaksverslaving
- coagulopathie en/of veneuze trombo-embolische voorgeschiedenis
- cardiovasculaire aandoening (AHT, myocardiale ischemie, CVA)
- migraine
- diabetes
- post partum
- post abortum.

Quelles sont les contraceptions hormonales à recommander en cas de :
- situation pré et post opératoire chirurgicale
- tabagisme
- coagulopathie et/ou antécédent thromboembolique veineux
- maladie cardiovasculaire (HTA, ischémie myocardique, AVC)

- migraine
- diabète
- post partum
- post abortum.

7. Noodcontraceptie - *Contraception d'urgence*
Vraag – *Question* 7

7.1. Wat zijn doeltreffende en veilige noodcontraceptiva?
7.1. Quelles sont les contraceptions d'urgence efficaces et sûres ?
7.2. Mogen noodcontraceptiva herhaaldelijk worden gebruikt?
7.2. Le recours à une contraception d'urgence répétée peut-elle être envisagée ?
7.3. Welke elementen bevorderen of belemmeren noodcontraceptie?
7.3. Quels sont les éléments favorisant ou faisant obstacle à une contraception urgente?

1.1.2. Research task of the literature group

The organising committee has specified the research task for the literature review as follows:

- To discuss selected guidelines regarding all questions to the jury. The UK Medical Eligibility Criteria 2009 report will be added as an annex.

- To search for systematic reviews, meta-analyses, RCTs (and large observational studies for rare safety endpoints) for the following populations, comparisons and endpoints:

<u>Populations</u>
The following populations are to be evaluated.

Hormonal contraception

- Women requiring contraception
- Women with or without a need for contraception, who have one of the following conditions
    - Irregular menstrual cycle (need for cycle control)
    - Dysmenorrhea
    - Menorrhagia
    - Acne
    - Functional ovarian cysts
    - Premenstrual syndrome
    - Perimenopause
    - Endometriosis, active or post-surgery
    - Uterine fibroids

Emergency contraception

- Women at risk of unintended pregnancy, requiring emergency contraception

Interventions/comparisons

Hormonal contraception

All studies that compare one hormonal contraceptive agent versus another hormonal contraceptive agent or versus the copper intrauterine device (IUD) will be selected.

For specific indications (see above list of medical conditions) comparisons versus placebo or no treatment will also be selected.

Emergency contraception

Hormonal methods currently commercialised, versus one another or versus copper IUD. Yuzpe method is excluded.

Only products with a registered indication in Belgium will be considered. These are listed here:

Combined hormonal contraception	
Combined oral contraception	Monophasic
	• ethinylestradiol 0,035mg + norethisterone 1mg • ethinylestradiol 0,05mg + levonorgestrel 0,125mg • ethinylestradiol 0,03mg + levonorgestrel 0,15mg • ethinylestradiol 0,02mg + levonorgestrel 0,1mg • ethinylestradiol 0,035mg + norgestimate 0,25mg • ethinylestradiol 0,03mg + desogestrel 0,15mg • ethinylestradiol 0,02mg + desogestrel 0,15mg • ethinylestradiol 0,03mg + gestodene 0,075mg • ethinylestradiol 0,02mg + gestodene 0,075mg • ethinylestradiol 0,015mg + gestodeen 0,06mg (24 active+4 pla) • ethinylestradiol 0,03mg + drospirenone 3mg • ethinylestradiol 0,02mg + drospirenon 3mg (24 active+4pla) or (21active(+/-7 pla) • ethinylestradiol 0,03mg + chloormadinon, acetate 2mg • estradiol 1,5mg + nomegestrol, acetate 2,5mg
	Biphasic
	• [I ethinylestradiol 0,04mg + desogestrel 0,025mg II ethinylestradiol 0,03mg + desogestrel 0,125mg]
	Triphasic
	• [I ethinylestradiol 0,03mg + levonorgestrel 0,05mg II ethinylestradiol 0,04mg + levonorgestrel 0,075mg III ethinylestradiol 0,03mg + levonorgestrel 0,125mg] • [I ethinylestradiol 0,03mg + gestodene 0,05mg II ethinylestradiol 0,04mg + gestodene 0,07mg III ethinylestradiol 0,03mg + gestodene 0,1mg] • [I ethinylestradiol 0,035mg + norethisterone 0,5mg II ethinylestradiol 0,035mg + norethisterone 0,75mg III ethinylestradiol 0,035mg + norethisterone 1mg]
	Quadriphasic

	• [I estradiol, valerate 3mg II estradiol, valerate 2mg + dienogest 2mg III estradiol, valerate 2mg + dienogest 3mg IV estradiol, valerate 1mg V placebo]
Combined transdermal patch	• ethinylestradiol 0,034mg + norelgestromin 0,203mg **/ 24u**
Combined vaginal ring	• ethinylestradiol 0,015mg + etonogestrel 0,12mg **/ 24u**

Progestogen-only contraception	
- Progestogen-only pill	• desogestrel 0.075mg • levonorgestrel 0.03mg
- Progestogen- only injectables	• medroxyprogesterone acetate 104mg/3m s.c. • medroxyprogesterone acetate 150mg/3m i.m.
- Progestogen-only implant	• etonogestrel 68mg s.c.
- Progestogen intra-uterine device	• levonorgestrel intra-uterine system (IUS) 52mg

Hormonal emergency contraception
• Levonorgestrel 2x0.75 mg or 1x1.5mg • Ulipristal 30mg

Endpoints

The following endpoints are to be reported:

- Pregnancy
- Adherence/compliance
- Bleeding irregularities: breakthrough bleeding, spotting, cycle control
- Weight
- Headache
- Mood changes
- Libido
- Local reactions specific to method
- Menorrhagia
- Dysmenorrhea
- Acne
- Functional ovarian cysts
- Premenstrual syndrome
- Perimenopausal symptoms
- Endometriosis pain or progression
- Cancer; gynaecological cancers: ovarian, cervical, endometrial, breast
- Cancer; other: liver, colorectal
- Cardiovascular disease (including hypertension, hyponatremia, hyperkaliemia for combined oral contraception containing drospirenone)
- Venous thrombo-embolism
- Mortality

Study criteria

- Efficacy
    - Design
        - RCT
        - Open label permitted. Too few studies about hormonal contraception are blinded. There are numerous studies about hormonal contraception that are open label, and these are selected in all systematic reviews and meta-analysis. We therefore chose to include open label studies in our literature review.
    - Duration of RCT: at least 6 months of intervention
    - Minimum number of participants: minimum 100 for both arms of study together. For studies with multiple treatment arms, we looked at the number of participants in comparisons relevant to our search.

- Safety
    - Information from the selected RCTs
    - Belgisch Centrum voor Farmacotherapeutische Informatie (BCFI), Federaal Agentschap voor Geneesmiddelen en Gezondheidsproducten (FAGG), European Medicines Agency (EMA), Meyler's Side Effects of Drugs (15th edition), Martindale: The complete drug reference (36th edition), Farmacotherapeutisch Kompas.
    - Additional information from large observational studies. In order of preference, we include systematic reviews and meta-analysis of prospective cohort studies, or single prospective studies. If no evidence is available, for selected endpoints, we include systematic reviews and meta-analysis of retrospective (also case-control) studies.

Guidelines

Only guidelines that report levels of evidence/recommendation are to be selected.
Only guidelines from 2008 onwards are to be selected.
Guidelines were selected and agreed upon through discussion with the organising committee, based on relevance for the Belgian situation.
Similarities and discrepancies between guidelines are to be reported.
The literature group will also report whether the guideline was developed together with other stakeholders (other healthcare professionals: pharmacists, nurses,… or patient representatives) and whether these guidelines are also targeting these groups.

1.2. Search strategy

1.2.1. Principles of systematic search

Relevant literature was searched in a stepwise approach.

- Firstly, sources that report and discuss data from systematic reviews, meta-analyses and original trials, like Clinical Evidence were consulted. Guidelines were consulted to look up additional relevant references.
- In a second step we have searched for large systematic reviews from reliable EMB-producers (NICE, AHRQ, the Cochrane library) that answer our research questions. One or more systematic reviews were selected as our basic source. From these sources, references of relevant publications were screened manually.
- In a third step, we conducted a systematic search for randomised controlled trials (RCTs), meta-analyses and smaller systematic reviews that were published after the search date of our selected systematic reviews.

The following electronic databases have been searched

- Medline (PubMed)
- Cochrane Library

A number of other sources were consulted additionally: relevant publications, indices of magazines available in the library of vzw Farmaka asbl: mainly independent magazines that are a member of the International Society of Drug Bulletins (ISDB) such as Geneesmiddelenbulletin (The Netherlands), Folia Pharmacotherapeutica (Belgium), La Revue Prescrire (France), Drug & Therapeutics Bulletin (UK), Therapeutics Letter (Canada), Geneesmiddelenbrief (Belgium), Arzneimittelbrief (Germany),…

Guidelines were searched through the link “evidence-based guidelines” on the website of vzw Farmaka asbl (www.farmaka.be) and on the website of CEBAM (www.cebam.be). These contain links to the national and most frequently consulted international guidelines, as well as links to ‘guideline search engines’, like National Guideline Clearinghouse.

1.2.2. Search strategy details

No single systematic review could answer all our research questions. We therefore combined information from FSRH guidelines, Cochrane systematic reviews and Clinical Evidence as a basis. We then searched Medline (Pubmed) for RCTs that were published after the search date of these publications.

FSRH Guidelines

The FSRH guidelines are based on a systematic search. The authors were contacted for more information on their search criteria. Information and evidence tables could be obtained for the guideline combined hormonal contraception. This guideline was used as a source document (FSRH 2012).

Cochrane systematic reviews

17 Cochrane systematic reviews met our search criteria and included RCTs that met our inclusion criteria and answered one of our research questions.
(Arowojolu 2012) (Cheng 2012) (Edelman 2005) (French 2004) (Gallo 2011a) (Gallo 2011b) (Grimes 2010) (Hofmeyr 2010) (Lawrie 2011) (Lopez 2011) (Lopez 2010a) (Lopez 2008) (Lopez 2012) (Polis 2007) (Van Vliet 2011a) (Van Vliet 2011b) (Wong 2009)

13 Cochrane systematic reviews met our search criteria but none of the included RCTs met our inclusion criteria or answered one of our research questions.
(Abou-Setta 2006) (Brown 2012) (Davis 2007)(Farquhar 2009) (Halpern 2010) (Hickey 2012) (Hughes 2007) (Lethaby 2005) (Lopez 2010b) (Power 2007) (Tang 2012) (Van Vliet 2006a) (Van Vliet 2006b)

Clinical evidence

4 systematic reviews met our search criteria and included studies that met our inclusion criteria.
(Pallavi 2011) (Duckitt 2012) (Kwan 2010) (Ferrero 2010)

3 systematic reviews met our search criteria but included studies did not meet our inclusion criteria.
(Lethaby 2011) (Burbos 2011) (Goyal 2011)

A search strategy was developed in Pubmed to find relevant RCTs that appeared after the search date of above publications (http://www.ncbi.nlm.nih.gov/pubmed/).
In some cases, when the selected systematic reviews were not sufficient (e.g. no search for all drugs), an additional search was conducted for RCTs that appeared before the search date of the selected systematic review.
The following search strategy was used:

(((("Contraceptive Agents, Female"[Mesh] OR (contracep* AND (combined OR patch OR ring OR pill)) AND (continu* OR menstrual suppression)) OR (("Contraceptive Agents, Female"[Mesh] OR contracep*) AND (patch OR ring))) AND (randomized controlled trial OR random*[TIAB] OR controlled clinical trial OR systematic[sb] OR medline[TIAB]) AND ("2009/08"[PDat] : "2013/01/07"[PDat]) OR (("Contraceptives, Oral"[Mesh] OR (contracep* AND (oral OR combin*)) OR (contracep* AND (((immediate OR timing) AND (start* OR begin* OR initiat*)) OR "quick start" OR starting day OR extended-cycle))) AND (randomized controlled trial OR random*[TIAB] OR controlled clinical trial OR systematic[sb] OR medline[TIAB]) AND ("2010/08"[PDat] : "2013/01/07"[PDat])) OR ((("Contraceptives, Oral"[Mesh] OR contracep*) AND (triphas* OR biphas* OR sequential OR multiphas* OR quadrophas* OR four phas*)) AND (randomized controlled trial OR random*[TIAB] OR controlled clinical trial OR systematic[sb] OR medline[TIAB]) AND ("2011/04"[PDat] : "2013/01/07"[PDat])) OR (("Contraceptives, Postcoital"[Mesh] OR "Contraception, Postcoital"[Mesh] OR (emergency AND contracep*) OR "morning after" OR ulipristal OR (levonorgestrel AND ((emergency OR postcoital))) AND (randomized controlled trial OR random*[TIAB] OR controlled clinical trial OR systematic[sb] OR medline[TIAB]) AND ("2011/06"[PDat] : "2013/01/07"[PDat])) OR (((progestin* OR progestogen* OR progesteron*) AND only AND contracep*) AND (randomized controlled trial OR random*[TIAB] OR controlled clinical trial OR systematic[sb] OR medline[TIAB]) AND ("2011/04"[PDat] : "2013/01/07"[PDat])) OR (("Intrauterine Devices, Medicated"[Mesh] OR LNG-IUS OR mirena[TIAB] OR "levonorgestrel-releasing intrauterine device") AND (randomized controlled trial OR random*[TIAB] OR controlled clinical trial OR systematic[sb] OR medline[TIAB]) AND ("2009/06"[PDat] : "2013/01/07"[PDat]))
OR ((("Contraceptive Agents, Female"[Mesh] OR contracep* OR etonogestrel) AND (implant* OR subderm*)) OR implanon[TIAB]) AND (randomized controlled trial OR random*[TIAB] OR controlled clinical trial OR systematic[sb] OR medline[TIAB]) AND ("2007/03"[PDat] : "2013/01/07"[PDat])) OR (("Medroxyprogesterone Acetate"[Mesh] OR DMPA OR (progestin OR progestogen)) AND (inject* OR intramusc*) AND contracep* AND (randomized controlled trial OR random*[TIAB] OR controlled clinical trial OR systematic[sb] OR medline[TIAB]) AND ("2004"[PDat] : "2013/01/07"[PDat])) OR (("Medroxyprogesterone Acetate"[Mesh] OR DMPA OR (progestin OR progestogen)) AND subcut* AND contracep* AND (randomized controlled trial OR random*[TIAB] OR controlled clinical trial OR systematic[sb] OR medline[TIAB]) AND ("1950"[PDat] : "2013/01/07"[PDat])))
OR
(Dysmenorrhea AND (((progestin* OR progestogen* OR progesteron*) AND only AND contracep*) OR ("Contraceptives, Oral"[Mesh] OR (contracep* AND (oral OR combin* OR pill))))
AND ("2009/12/01"[PDat] : "2013/01/07"[PDat]) AND (randomized controlled trial OR random*[TIAB] OR controlled clinical trial OR systematic[sb] OR medline[TIAB]))
OR
(("Leiomyoma"[Mesh] OR fibroid*[tiab]) AND ((("Contraceptive Agents, Female"[Mesh] OR contracep*) AND (patch OR ring)) OR ("Contraceptives, Oral"[Mesh] OR (contracep* AND (oral OR combin* OR pill))) OR ((progestin* OR progestogen* OR progesteron*) AND contracep*))
AND ("2009/05/01"[PDat] : "2013/01/07"[PDat]) AND (randomized controlled trial OR random*[TIAB] OR controlled clinical trial OR systematic[sb] OR medline[TIAB]))
OR
(("Premenstrual Syndrome"[Mesh] "Premenstrual Syndrome"[tiab] OR “premenstrual tension” [tiab]) AND ((("Contraceptive Agents, Female"[Mesh] OR contracep*) AND (patch OR ring))

OR ("Contraceptives, Oral"[Mesh] OR (contracep* AND (oral OR combin* OR pill)))
OR ((progestin* OR progestogen* OR progesteron*) AND contracep*))
AND ("2009/06/01"[PDat] : "2013/01/07"[PDat]) AND (randomized controlled trial OR random*[TIAB] OR controlled clinical trial OR systematic[sb] OR medline[TIAB]))
OR
(("Endometriosis"[Mesh] OR "Endometriosis"[tiab]) AND ("Contraceptives, Oral"[Mesh] OR (contracep* AND (oral OR combin* OR pill))) AND ("2009/11/01"[PDat] : "2013/01/07"[PDat]) AND (randomized controlled trial OR random*[TIAB] OR controlled clinical trial OR systematic[sb] OR medline[TIAB]))
OR
(((“ovarian cysts”[Title/Abstract] OR "Ovarian Cysts"[Mesh]) AND functional) AND ((("Contraceptive Agents, Female"[Mesh] OR contracep*) AND (patch OR ring)) OR ((progestin* OR progestogen* OR progesteron*) AND contracep*) OR ("Intrauterine Devices, Medicated"[Mesh] OR LNG-IUS OR mirena[TIAB] OR "levonorgestrel-releasing intrauterine device")OR(("Medroxyprogesterone Acetate"[Mesh] OR DMPA OR (progestin OR progestogen)) AND (inject* OR intramusc* OR subcut*) AND contracep*) OR ((("Contraceptive Agents, Female"[Mesh] OR contracep* OR etonogestrel) AND (implant* OR subderm*)) OR implanon[TIAB])) AND ("1950"[PDat] : "2013/01/07"[PDat]) AND (randomized controlled trial OR random*[TIAB] OR controlled clinical trial OR systematic[sb] OR medline[TIAB]))

1.3. Selection procedure

Inclusion criteria used to select relevant *meta-analyses and systematic reviews*:

- Research question in selected publication matched research question for this literature review
- Systematic search
- Systematic reporting of results
- Inclusion of randomised controlled trials
- Reporting of clinically relevant outcomes

Inclusion criteria for *randomised controlled trials (RCTs)* are mentioned in chapter 1.1. with relevant interventions, endpoints and study criteria.

Selection of relevant references was conducted by two researchers independently. Differences of opinion were resolved through discussion. A first selection of references was done based on title and abstract. When title and abstract were insufficient to reach a decision, the full article was read to decide on inclusion or exclusion.

Some publications were excluded for practical reasons:

- Publications unavailable in Belgian libraries
- Publications in languages other than Dutch, French, German and English

1.4. Assessing the quality of available evidence

To evaluate the quality of the available evidence, the GRADE system was used. In other systems that use 'levels of evidence', a meta-analysis is often regarded as the highest level of evidence. In the GRADE system, however, only the quality of the original studies is assessed. Whether the results of original studies were pooled in a meta-analysis is of no influence to the quality of the evidence. The GRADE system[3,4,5] assesses the following items:

Study design		+ 4	RCT
		+ 2	Observational
		+ 1	Expert opinion
Study quality		- 1	Serious limitation to study quality
		- 2	Very serious limitation to study quality
Consistency*		- 1	Important inconsistency
Directness**		- 1	Some uncertainty about directness
		- 2	Major uncertainty about directness
Imprecision***		- 1	Imprecise or sparse data
Publication bias		- 1	High probability of publication bias
For observational studies	Evidence of association	+ 1	Strong evidence of assciation (RR of >2 or <0.5)
		+ 2	Very strong evidence of association (RR of >5 or <0.2)
	Dose response gradient	+ 1	Evidence of a dose response gradient (+1)
	Confounders	+ 1	All plausible confounders would have reduced the effect
SUM		4	HIGH quality of evidence
		3	MODERATE quality of evidence
		2	LOW quality of evidence
		1	VERY LOW quality of evidence

*** Consistency** refers to the similarity of estimates of effect across studies. if there is important unexplained inconsistency in the results, our confidence in the estimate of effect for that outcome decreases. Differences in the direction of effect, the size of the differences in effect, and the significance of the differences guide the (inevitably somewhat arbitrary) decision about whether important inconsistency exists.

**** Directness:** there are two types of indirectness of evidence. The first occurs when considering, for example, use of one of two active drugs. Although randomised comparisons of the drugs may be unavailable, randomised trials may have compared one drug with placebo and the other with placebo. Such trials allow indirect comparisons of the magnitude of effect of both drugs. Such evidence is of lower quality than would be provided by head to head comparisons of the drugs. The second type of indirectness of evidence includes differences between the population, intervention, comparator to the intervention, and outcome of interest, and those included in the relevant studies.

*****Imprecision**: When studies include relatively few patients and few events and thus have wide confidence intervals, a guideline panel will judge the quality of the evidence to be lower.

More information on the GRADE Working Group website: http://www.gradeworkinggroup.org

In this literature review the criterium 'pubication bias' and the criteria specifically intended for observational studies (see table above) have not been assessed. This adapted version of GRADE therefore evaluates the following criteria:

Study design	+ 4	RCT
Study quality	- 1	Serious limitation to study quality
	- 2	Very serious limitation to study quality
Consistency	- 1	Important inconsistency
Directness	- 1	Some uncertainty about directness
	- 2	Major uncertainty about directness
Imprecision	- 1	Imprecise or sparse data
SUM	4	HIGH quality of evidence
	3	MODERATE quality of evidence
	2	LOW quality of evidence
	1	VERY LOW quality of evidence

In assessing the different criteria, we have applied the following rules.

.

Study design

In this literature review, all studies are RCTs (inclusion criterium). "Study design" is therefore not reported specifically in this report.

Study quality

To assess the methodological quality of RCTs, the Jadad score was used, in combination with the assessment of an "intention-to-treat"(ITT) analysis (all randomized patients in efficacy analysis). If a meta-analysis or a systematic review is used, quality of included studies was assessed. It is not the quality of the meta-analysis or systematic review that is considered in GRADE assessment, but only the quality of RCTs that were included in the meta-analysis/systematic review.

Jadad score:

1	Was the study described as randomized (this includes the use of words such as randomly, random and randomization)?	Yes	1
		No	0
1a	If the method of generating the randomization sequence was described, was it adequate (table of random numbers, computer-generated, coin tossing, etc.) or inadequate (alternating, date of birth, hospital number, etc.)?	Not described / NA	0
		Adequate	1
		Inadequate	-1
2	Was the study described as double-blind?	Yes	1
		No	0
2a	If the method of blinding was described, was it adequate (identical placebo, active placebo, etc.) or inadequate (comparison of tablet vs injection wit hno double dummy)?.	Not described / NA	0
		Adequate	1
		Inadequate	-1

3	Was there a description of withdrawals and drop-outs	Yes	1
		No	0

(Table reprinted from Duke University, Center for Clinical Health Policy Research. Drug Treatments for the Prevention of Migraine. AHCPR February 1999.)

Application in GRADE:
The following principle was applied as a minimal rule: 1 quality point was deducted if there was a problem with item 3 of the Jadad score ("was there a description of withdrawals and drop-outs"). Since "randomised" was an inclusion criterium, no point were deducted here, even if the method (item 1a and 1b of Jadad) was adequately described. Apart from Jadad, we also assessed whether an ITT analysis was performed. If this was not the case, a point was deducted. Points were only deducted for absence of ITT if follow-up was less than 80%. If follow-up percentage was not known, no extra point was deducted for ITT.
Other factors that can influence the assessment: moderate drop-out in studies with low event rates, problems with construction of study, selective outcome reporting…

Consistency

- Good "consistency" means that several studies have a comparable or consistent result. If only one study is available, consistency cannot be judged. This will be mentioned in the synthesis report as "NA" (not applicable).

- Consistency is judged by the literature group and the reading committee based on the total of available studies, whilst taking into account
    - Statistical significance
    - Direction of the effect if no statistical significance is reached. E.g. if a statistically significant effect was reached in 3 studies and not reached in 2 others, but with a non significant result in the same direction as the other studies, these results are considered consistent.
    - Clinical relevance: if 3 studies find a non-significant result, whilst a 4th study does find a statistically significant result, that has no clinical relevance, these results are considered consistent.
    - For meta-analyses: statistical heterogeneity

Directness

Directness addresses the extent in which we can generalise the data from a study to the real population (external validity). If the study population, the studied intervention and the control group or studied endpoint are not relevant, points can be deducted here. When indirect comparisons are made, a point is also deducted.

Imprecision

If we include systematic reviews or meta-analyses that include studies with <40 patients per study-arm (for a cross-over study: <40 patients in the complete study), a point is deducted for imprecision.

For meta-analyses and in comparisons with only one study: a point is deducted when power is inadequate (depends also on the sample size).

Application of GRADE when there are many studies for 1 endpoint:

Points are only deducted if the methodological problems have an important impact on the result. If 1 smaller study of poor quality confirms the results of 2 large good quality studies, no points are deducted.

1.5. Synopsis of study results

The complete report contains per research question

- Evidence tables (English) of systematic reviews or RCTs on which the answers to the study questions are based
- A short synopsis, consisting of a summary table and a text, with a quality assessment using an adjusted version of the GRADE system (English)

The synopsis report contains per research question

- A short synopsis, consisting of a summary table and a text, with a quality assessment using an adjusted version of the GRADE system.

The conclusions have been discussed and adjusted through discussions between the authors of the literature search and the reading committee of the literature group.

References

1. Clinical Evidence. A compendium of the best available evidence for effective health care. Website: http://clinicalevidence.bmj.com
2. Minerva is a journal for evidence-based medicine published in Belgium. Website: www.minerva-ebm.be
3. GRADE working group. http://www.gradeworkinggroup.org
4. GRADE working group. Grading quality of evidence and strength of recommendations. BMJ 2004;328:1490.
5. Guyatt G, Oxman A, Kunz R et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ 2008;336:924-6

2. Critical reflections of the reading committee and literature group

Study design

A lot of the studies are open label. Sometimes this is because blinding is difficult or impossible with certain contraceptive devices. But there are also many studies in which blinding was possible, that did not use blinding. We did not exclude these, simply because there would be too few studies left to report. An open label design decreases the reliability of the study results(1), mostly when endpoints are 'subjective'.

A good number of studies were not powered to detect differences in pregnancy rates between the studied contraceptives. Primary endpoints in these studies were usually bleeding patterns.

A lot of the studies report large (early) drop-out, limiting the reliability of the results at longer term.

Populations

Studies on emergency contraception excluded women who were taking hormonal contraception. This is unfortunate because we expect that a lot of women requesting emergency contraception are on some form of hormonal contraception. No information on interaction between emergency hormonal contraception and the daily hormonal contraception can be obtained from these studies.

Comparisons

Despite the seeming abundance of studies comparing different combined oral contraceptives, we lack evidence to draw firm conclusions on most of our research questions. This is due to poor study quality but also because of the large number of oral contraceptives with different compositions (estrogen or progestogen content) that are used today.

When two combined hormonal contraceptives are compared, it is usually unclear whether a difference is due to different estrogen content, different progestogen or the use of a different schedule.

There are very few studies comparing combined oral contraceptives with other forms of hormonal contraception. It would for example be very interesting to have more information on the comparison of long-acting forms of (hormonal) contraception versus hormonal contraception that is taken daily.

We could not include any study with the etonogestrel- implant, because all published studies compare this implant to another progestogen-only implant that is not commercialized in Belgium. No studies exist comparing this implant with other forms of contraception.

Endpoints

Pregnancy

Not all studies were powered to detect differences in pregnancy rates.

Most studies reporting pregnancy use the Pearl index. Methodologically the reporting of cumulative incidence using life tables would be more informative: Most mistakes in contraceptive use occur at the beginning of the treatment: pregnancy rate in the first year (or months) of use is expected to be higher than in the consecutive years.

In the literature, a difference is usually made between *treatment failure* (pregnancy occurring despite the correct use of the contraceptive) and *user failure* (pregnancy occurring because of incorrect use of the contraceptive). It is of course not always easy to distinguish between the two and the interpretation is susceptible to bias. Studies do not always report the perceived cause of the pregnancies that occurred. Studies sometimes exclude 'user failure' from the reported pregnancy rates. Because a lot of the studies in this literature review are reported in systematic reviews or meta-analyses, we do not always have information on the cause of the pregnancies that occurred in these studies.
Study conditions and patients included in studies differ from a real-life situation. We can assume that follow-up in studies is better and that the patients are more motivated to adhere to the contraceptive. It is important to realize that pregnancy rates in studies do not reflect pregnancy rates in real life.

Other endpoints
Most studies report bleeding outcomes. However, definitions for different types of bleeding are not always adequately reported and can differ from study to study.
Other 'frequent' adverse events, such as headache, mood changes, libido-changes, … are too sparsely reported to draw any real conclusions.

Observational studies – rare but serious adverse events
Rare but serious adverse events such as VTE cannot be detected by RCTs, since the population in an RCT is usually too small and the duration usually too short.
Observational studies can detect these events but have a major disadvantage: as a rule, causality cannot be proven and not all confounders can be corrected for. Level of evidence from observational studies is therefore usually lower than from RCTs.
Older observational studies have an additional problem: the composition and use of combined hormonal contraceptives has changed throughout the years: current combination pills have a lower estrogen content, women nowadays usually start the pill at a younger age and use it for a longer period of time. Caution is needed when drawing conclusions from these studies.

References:
(1) Chevalier P. Open-label versus dubbelblinde studies: is er een verschil in de resultaten? Minerva. 2012; 11(2); p25-25

3. Guidelines

3.1. Criteria for guideline selection

In order to be included, the guideline had to be of recent date (not older than 5 years) and had to report levels of evidence and/or grades of recommendation.
The following guidelines fulfilled these criteria:

3.2. Selected guidelines

Comprehensive guidelines

Domus Medica 2012	Peremans L, van Leeuwen E, Delvaux N, Keppens K, Yilkilkan H. Richtlijn voor goede medische praktijkvoering: Hormonale anticonceptie. Huisarts Nu 2012;41:S1-S32.

Method- specific guidelines

FSRH 2012 Combined	Faculty of Sexual and Reproductive Health Care (Royal College of Obstetricians and Gynaecologists). Combined hormonal contraception. Clinical effectiveness unit guidance. October 2011 (Updated august 2012). http://www.fsrh.org/pdfs/CEUGuidanceCombinedHormonalContraception.pdf
ACOG2011	The American College of Obstetricians and Gynecologists. Practice bulletin n° 121. Long-acting Reversible contraception: Implants and Intrauterine Devices. Obstet gynecol 2011; 118: 184-96
FSRH 2009 POP	Faculty of Sexual and Reproductive Health Care (Royal College of Obstetricians and Gynaecologists). Progestogen-only pills. Clinical Effectiveness Unit Guidance. November 2008 (Updated June 2009). http://www.fsrh.org/pdfs/CEUGuidanceProgestogenOnlyPill09.pdf.
FSRH 2009 POInj	Faculty of Sexual and Reproductive Health Care (Royal College of Obstetricians and Gynaecologists). Progestogen-only injectable contraception. Clinical effectiveness unit guidance. November 2008 (updated june 2009). http://www.fsrh.org/pdfs/CEUGuidanceProgestogenOnlyInjectables09.pdf
FSRH 2009 POI	Faculty of Sexual and Reproductive Health Care (Royal College of Obstetricians and Gynaecologists). Progestogen-only implants. Clinical effectiveness unit guidance. April 2008 (updated January 2009). http://www.fsrh.org/pdfs/CEUGuidanceProgestogenOnlyImplantsApril08.pdf

Missed hormonal contraceptives – specific guidelines

FSRH 2011	Faculty of Sexual and Reproductive Health Care (Royal College of Obstetricians and Gynaecologists). Missed pill recommendations. CEU statement. May 2011. http://www.fsrh.org/pdfs/CEUStatementMissedPills.pdf
SOGC 2008	Society of Obstetricians and Gynaecologists of Canada. SOGC Clinical practice guideline no. 219. Missed hormonal contraceptives: new recommendations. http://www.sogc.org/guidelines/documents/gui219ECO0811.pdf

Problem-specific guidelines

ACOG 2010 Noncontraceptive	The American College of Obstetricians and Gynecologists. Practice bulletin n° 110. Noncontraceptive uses of hormonal contraceptives. Obstet gynecol 2010; 115: 206-18
FSRH 2012 Drug interactions	Faculty of Sexual and Reproductive Health Care (Royal College of Obstetricians and Gynaecologists). Drug interactions with hormonal contraception. January 2011 (Updated January 2012). http://www.fsrh.org/pdfs/CEUGuidanceDrugInteractionsHormonal.pdf
FSRH 2010 Start	Faculty of Sexual and Reproductive Health Care (Royal College of Obstetricians and Gynaecologists). Quick starting Contraception. Clinical effectiveness unit guidance. September 2010. http://www.fsrh.org/pdfs/CEUGuidanceQuickStartingContraception.pdf
FSRH 2010 40+	Faculty of Sexual and Reproductive Health Care (Royal College of Obstetricians and Gynaecologists). Contraception for women aged over 40 years. Clinical Effectiveness Unit Guidance. July 2010. http://www.fsrh.org/pdfs/ContraceptionOver40July10.pdf
FSRH 2010 Young	Faculty of Sexual and Reproductive Health Care (Royal College of Obstetricians and Gynaecologists). Contraceptive choices for young people. March 2010. http://www.fsrh.org/pdfs/ceuGuidanceYoungPeople2010.pdf
RCOG 2010	Royal College of Obstetricians and Gynaecologists. Green-top Guideline no. 40. Venous thromboembolism and hormonal contraception. July 2010. http://www.rcog.org.uk/files/rcog-corp/GTG40VenousThromboEmbolism0910.pdf
SOGC 2010	Society of Obstetricians and Gynaecologists of Canada. SOGC Clinical practice guideline no. 252. Oral contraceptives and the risk of venous thromboembolism: an update. J. Obstet Gynaecol Can. 2010; 32:1192-204.

Emergency contraception – specific guidelines

ACOG 2010 Emergency	The American College of Obstetricians and Gynecologists. Practice bulletin n° 112. Emergency contraception. Obstet gynecol 2010; 115: 1100-09
FSRH 2012 Emergency	Faculty of Sexual and Reproductive Health Care (Royal College of Obstetricians and Gynaecologists). Emergency contraception. Clinical effectiveness unit guidance. August 2011 (updated January 2012) http://www.fsrh.org/pdfs/CEUguidanceEmergencyContraception11.pdf
SOGC2012	Society of Obstetricians and Gynaecologists of Canada. SOGC Clinical practice guideline no. 280. Emergency contraception. http://www.sogc.org/guidelines/documents/gui280CPG1209E_000.pdf

3.3. Summary of guidelines – comprehensive guidelines

Domus Medica 2012 Hormonal contraception	Grades of recommendation: 1. strong recommendation; the benefits clearly outweigh the disadvantages or risks 2. weak recommendation; there is a doubtful balance between benefits and risks
	Levels of evidence: A. good quality of evidence B. moderate quality of evidence C. low quality of evidence
	Included populations, interventions, outcomes: - (sexually active) women of reproductive age asking for hormonal contraception - combined oral contraceptives (COC), vaginal ring, patch, progestogen-only pills (POP), injection, implant, emergency contraception - pregnancy rate, adverse events
	Members of development group, target population: - general practitioners, gynecologists, pharmacologists - general practitioners (primary care)
	Recommendations: * Absolute contra indications for combined contraceptive pills are: - breastfeeding less than 6 weeks postpartum (Grade 1C) - age over 35 years and smoker (Grade 1B) - tromboembolism (arterial/venous) (Grade 1B/1C) - multiple cardiovascular risk factors - pulmonary hypertension - arterial hypertension: ≥95/160mmHg (Grade 2C) - use of anticoagulants for DVT (current or past) - major surgery with prolonged immobilization - coagulation disorders - migraine with aura (Grade 2B) - diabetes with nefropathy, retinopathy, neuropathy or other vascular complications - hepatitis or liver cirrhosis with elevated transaminases, some liver tumors (Grade 2C) - hormone sensitive tumors (breast cancer, estrogen sensitive carcinoma) - systemic lupus erythematosus (Grade 2C) * First choice contraception: - oral contraceptives are first choice, vaginal ring can be an alternative - women under 35 years: combined pill with ≤35µg ethinylestradiol plus second generation progestogen (30µg ethinylestradiol + levonorgestrel is most suitable) (Grade 1A) - women of 35 years or older: combined pill with ≤35µg ethinylestradiol plus second generation progestogen unless they smoke (Grade 1A) <15 cigarettes a day without cardiovascular risks: combined pills have risks (Grade 1B) ≥15 cigarettes a day with or without cardiovascular risks: don't take combined pills, opt for alternative contraception (Grade 1A)

	* When should we start or stop prescribing contraceptives? - There is no minimum age for contraception; combined contraceptive pills can be prescribed from menarche onwards, before menarche advise condoms (Grade 2C) - Contraception can be prescribed as long as women are sexually active, keep account of individual risk factors and wishes. Women older than 55 years are generally not fertile anymore. * Contraception after childbirth: - no contraception is needed during the first 21 days after child birth (Grade 1C) - breastfeeding women can use LAM (lactation amenorrhea method) during the first six months after child birth in case of full breastfeeding (breastfeeding at request of baby, day and night, no supplementary feeding) and no blood loss (Grade 1C) - use of combined contraceptive pills is not recommended for breastfeeding women in the first six weeks after child birth (Grade 2B); progesterone based contraceptives do not have a negative influence on milk production (Grade 1B) * Choice of contraception for women with specific medical conditions: - smoking and <35 y: use POP, IUD, implant or sterilization - BMI >30: use POP, IUD, implant or sterilization - liver enzyme inducing drugs (anti epileptics, St. John's wort, rifampicin): advise combined contraceptive pill with at least 50µg ethinylestradiol and additional barrier method (e.g. condom) until 4 weeks after stop medication - history of venous thrombosis: advise copper IUD - history of stroke or ischemic heart disease: advise POP, progesterone implant or IUD with levonorgestrel; progesterone injections are not recommended - acute or chronic liver disease: advise progesterone-only contraceptives (Grade 2C) - acne: use combined contraceptive pill Sparse evidence of efficacy of hormonal contraception on dysmenorrhea and menorrhagia (no recommendation). A few studies report no difference between progestogen only contraceptives and no studies exist comparing COCs and NSAIDs. Watchful waiting is better than treating ovarian cysts with COCs because functional cysts tend to disappear spontaneously. No information on PMS, fibromyomatosis, endometriosis, mastodynia in this guideline. * Minor adverse events: - spotting: main problem with progesterone-containing contraceptives check for STD or gynecological disorder add ethinylestradiol (mono or combined) but keep in mind that spotting is also possible with COCs, especially in case of smoking and poor adherence - weight changes: no evidence for COCs, weight gain is possible with progesterone injections, not implants - headache: no evidence for progesterone contraceptives - mood changes: no evidence for COCs or progesterone-containing

	contraceptives * Missed pills (>12h): recommendations only based on consensus - 1 missed pill: take missed pill , if >24h take 2 pills at once, no backup contraception needed - 2 missed pills: day 1-7: if coitus <5d ago: emergency contraception (condom use during 7d), if not take last missed pill and continue taking pills but sexual abstinence or condom use in the next 7d day 8-14: take last missed pill and continue taking pills but abstain from sexual intercourse or use condom in the next 7d day 15-21: take last missed pill and finish the pack, miss out the break and immediately start new pack OR stop one week (start counting from first missed pill) and start new pack * Emergency contraception: First choice is levonorgestrel 1.5mg, within 72h postcoitus. Consider copper IUD if unprotected coitus took place 6d before and 4d after probable ovulation, or within 120h postcoitus (IUD can be inserted up to 5d after probable ovulation) If woman does not wish an IUD, ullipristal can be an alternative, also within 120h postcoitus

3.4. Summary of guidelines – method-specific guidelines

FSRH 2012 Combined Hormonal Contraception	Grades of recommendation: A. Based on RCTs B. Based on other robust experimental or observational studies C. Based on limited evidence but the advice relies on expert opinion and has the endorsement of respected authorities Good Practice Point: where no evidence exists but where best practice is based on the clinical experience of the multidisciplinary group
	Levels of evidence: I.a. Evidence obtained from meta-analysis of randomized trials I.b. Evidence obtained from at least one RCT II.a. Evidence obtained from at least one well-designed controlled study, without randomisation II.b. Evidence obtained from at least one other type of well-designed quasi-experimental study III. Evidence obtained from well-designed non-experimental descriptive studies, correlation studies and case studies IV. Evidence obtained from expert committee reports or opinions and/or clinical experience of respected authorities
	Included populations, interventions, outcomes: - women seeking contraception - combined hormonal contraception (CHC) - efficacy, drug interactions, risks, non-contraceptive benefits, side effects
	Members of development group, target population: - gynecologists, obstetricians - health professionals
	Recommendations: * Efficacy: - Women can be informed that the efficacy of all CHCs is generally similar. (Grade B) * Initial assessments: - Health professionals should take a detailed history from women requesting CHC and should recheck the history at least annually. The history should include medical conditions such as migraine, drug use, family medical history, and lifestyle factors such as smoking. (Good Practice Point) - A blood pressure recording should be documented for all women prior to first prescription of CHC. (Grade C) - Body mass index (BMI) should be documented for all women prior to first prescription of CHC. (Good Practice Point) * Drug interactions: - Additional contraceptive precautions are not required when antibiotics that do not induce enzymes are used in conjunction with combined hormonal contraceptives (CHCs). (Grade C) - Women who do not wish to change from a combined method while on short-term treatment with an enzyme-inducing drug (and for 28 days after stopping treatment) may opt to continue using a combined oral contraceptive (COC)

	containing at least 30 µg ethinylestradiol (EE), the patch or ring along with additional contraception. An extended or tricycling regimen should be used and the hormone-free interval shortened to 4 days. Additional contraception should be continued for 28 days after stopping the enzyme-inducing drug. (Good Practice Point) - With the exception of the very potent enzyme inducers rifampicin and rifabutin, women who are taking an enzyme-inducing drug and who do not wish to change from COC or use additional precautions may increase the dose of COC to at least 50 µg EE (maximum 70 µg EE) and use an extended or tricycling regimen with a pill-free interval of 4 days. (Good Practice Point) - Women taking lamotrigine (except in combination with sodium valproate) should be advised that due to the risk of reduced seizure control whilst on CHC, and the potential for toxicity in the CHC-free week, the risks of using CHC may outweigh the benefits. (Grade C) - Women should be advised that ulipristal acetate (UPA) has the potential to reduce the efficacy of hormonal contraception. Additional precautions are advised for 14 days after taking UPA (9 days if using or starting the progestogen-only pill, 16 days for the estradiol valerate/dienogest pill) (outside product license) (Good Practice Point) * Risks, non-contraceptive health benefits and side effects: - Health professionals should be aware that compared to non-users, the risk of venous thromboembolism (VTE) with use of CHC is approximately doubled but that the absolute risk is still very low. (Grade B) - Health professionals prescribing CHCs should be guided by the individual's own personal preference, risk of VTE, any contraindications, possible non-contraceptive benefits and experience with other contraceptive formulations. (Grade B) - A personal history of VTE or a known thrombogenic mutation are conditions that represent an unacceptable health risk if CHC is used. (Grade C) - For women with a family history of VTE, a negative thrombophilia screen does not necessarily exclude all thrombogenic mutations. A thrombophilia screen is not recommended routinely before prescribing CHC. (Grade C) - Use of CHC in women aged ≥35 years who smoke is not recommended. (Grade B) - Health professionals should be aware that there may be a very small increase in the absolute risk of ischemic stroke associated with CHC use. (Grade B) - The risks of using CHC in women with properly taken blood pressure (BP) which is consistently elevated generally outweigh the advantages. Systolic BP ≥160 mmHg or diastolic BP ≥95 mmHg is a condition that represents an unacceptable health risk if CHC is used. (Grade C) - The risk of using CHC in women with a BMI ≥35kg/m2 usually outweighs the benefits. (Grade B) - Migraine with aura is a condition for which the use of CHC presents an unacceptable health risk. (Grade B) - Health professionals should be aware that any risk of breast cancer associated with CHC use is likely to be small, and will reduce with time after stopping. (Grade B) - Health professionals should be aware that CHC use may be associated with a small increase in the risk of cervical cancer which is related to duration of use. (Grade B) - Health professionals should check that women coming for CHC are up to date

	with cervical cytology screening in accordance with screening recommendations. (Good Practice Point) - Women can be advised that CHC use does not appear to have a negative effect on overall mortality. (Grade B) - Use of COC is associated with a reduced risk of ovarian and endometrial cancer that continues for several decades after stopping. (Grade B) Data also suggest a reduction in the incidence of ovarian cysts and benign ovarian tumours amongst women using COCs - Health professionals should be aware that CHC may help to improve acne. (Grade A) - Health professionals should be aware that COC use is associated with a reduction in the risk of colorectal cancer and this may also apply to other CHCs. (Grade B) - Health professionals should be aware that use of CHC may help to reduce menstrual pain and bleeding. (Grade C) Low-dose COC could possibly be used to treat pain associated with endometriosis. - Women can be advised that CHC may reduce menopausal symptoms. (Grade C) - Before starting CHC women should be advised about expected bleeding patterns both initially and in the longer term. (Good Practice Point) - Women can be advised that CHC may be associated with mood changes but there is no evidence that it causes depression. (Grade C) - Women can be advised that the current evidence does not support a causal association between CHC and weight gain. (Grade C) - Women taking CHC should be advised about reducing periods of immobility during flights over 3 hours. (Good Practice Point) - Women trekking to altitudes of >4500 m for periods of more than 1 week may be advised to consider switching to an alternative method. (Good Practice Point)

ACOG 2011 Long-acting reversible contraception	Grades of recommendation: A. Based on good and consistent scientific evidence B. Based on limited or inconsistent scientific evidence C. Based primarily on consensus and expert opinion
	Levels of evidence: I. Evidence obtained from at least one properly designed RCT II. 1. Evidence obtained from well-designed controlled trial without randomization 2. Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one center or research group 3. Evidence obtained from multiple time series with or without intervention III. Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees

	Included populations, interventions, outcomes: - (sexually active) women of reproductive age seeking (hormonal) contraception - implants and intrauterine devices - pregnancy rate, adverse events
	Members of development group, target population: - gynecologists, obstetricians - gynecologists, obstetricians
	Recommendations: * Level A: - routine antibiotic prophylaxis to prevent PID is not recommended before IUD insertion - insertion of a copper IUD is the most effective method of postcoital contraception when inserted up to 5 days after unprotected intercourse * Level B: - intrauterine devices may be offered to women with a history of ectopic pregnancy - insertion of the implant is safe at any time in non-breastfeeding women after childbirth - implants may be offered to women who are breastfeeding and more than 4 weeks after childbirth - insertion of an IUD or implant immediately after abortion or miscarriage is safe and effective * Level C: - theoretic concerns regarding milk production and infant growth and development exist with placement of an implant in breastfeeding women less than 4 weeks after childbirth - nulliparous women can be offered IUDs - for women at high risk for STDs (≤25y or multiple sex partners), it is reasonable to screen for STDs and place IUD when test results are available * Special conditions: - Heavy menstrual bleeding and spotting: long-term copper IUD users are more likely to discontinue the device because of menorrhagia and dysmenorrhea, whereas levonorgestrel intrauterine system users are more likely to discontinue the device because of amenorrhea and spotting. Patients should be adviced that menstrual bleeding and cramping may initially increase with use of the copper IUD (no level of recommendation). - Acne: is a commonly reported adverse effect of progesterone-only contraceptives. Overall, most women using the implant have either no change or an improvement in reports of acne and about one tenth of users experience a worsening of symptoms. - No information on functional ovarian cysts, fibromyomatosis, endometriosis, premenstrual syndrome or mastodynia in this guideline.

FSRH 2009 Progestogen-only pills	Grades of recommendation: A. Based on RCTs B. Based on other robust experimental or observational studies C. Based on limited evidence but the advice relies on expert opinion and has the endorsement of respected authorities Good Practice Point: where no evidence exists but where best practice is based on the clinical experience of the multidisciplinary group
	Levels of evidence: I.a. Evidence obtained from meta-analysis of randomized trials I.b. Evidence obtained from at least one RCT II.a. Evidence obtained from at least one well-designed controlled study, without randomisation II.b. Evidence obtained from at least one other type of well-designed quasi-experimental study III. Evidence obtained from well-designed non-experimental descriptive studies, correlation studies and case studies IV. Evidence obtained from expert committee reports or opinions and/or clinical experience of respected authorities
	Included populations, interventions, outcomes: - women seeking contraception - progestogen-only pills (POPs) - contraceptive efficacy, return of fertility, medical eligibility criteria, side effects, drug interactions, follow-up
	Members of development group, target population: - gynecologists, obstetricians - health professionals
	*UKMEC: Health professionals should be familiar with the UK Medical Eligibility Criteria for progestogen-only pills. (Good Practice Point) - UKMEC Category 3 “the risks may outweigh the advantages but use of a POP may be considered (decision about use required clinical judgement and/or referral to a specialist contraceptive provider”: The *initiation* of a POP in women with: ° A history of breast cancer (*no evidence of disease in the last 5 years*) ° Gestational trophoblastic neoplasia (*abnormal serum hCG*) ° Active viral hepatitis ° Severe decompensated cirrhosis ° Liver tumours (*benign and malignant*) ° Use of liver enzyme-inducing medication The *continuation* of a POP by women with: ° The occurrence of *new symptoms* or having a *new diagnosis* of ischaemic heart disease, stroke, or migraine with aura. - UKMEC Category 4 “poses an unacceptable health risk and a POP should not be used”: ° Current breast cancer Remark: uterine fibroids, benign ovarian tumours and cysts and endometriosis are specific conditions for which there is no restriction for the use of POPs (UKMEC 1).

	* Contraceptive efficacy: - Traditional progestogen-only pills work by altering cervical mucus to prevent sperm penetration and for some women ovulation is also inhibited. (Grade C) - The primary mode of action of the desogestrel-only pill is inhibition of ovulation. (Grade C) - If taken consistently and correctly POPs are more than 99% effective in preventing pregnancy. Failure rates for traditional POPs vary but are lower for women aged over 40 years compared to younger women. (Grade C) - Women should be advised to take one progestogen-only pill at or around the same time every day and without a pill-free interval. (Grade C) - There are no data to suggest that some progestogen-only pills are better at preventing pregnancy than others. (Grade B) - There is no evidence that the efficacy of progestogen-only pills (traditional or desogestrel-only) is reduced in women weighing >70kg and therefore the licensed use of one pill per day is recommended. (Grade B) * Missed pills: - Women may be advised that if a traditional progestogen-only pill is more than 3 hours late or a desogestrel-only pill is more than 12 hours late, they should: (i) take the late or missed pill now, (ii) continue pill taking as usual (this may mean taking two pills at the same time) and (iii) use condoms or abstain from sex for 48 hours after the pill is taken. (Grade C) - Some women may consider that the desogestrel-only pill, with the 12-hour window, will improve pill taking and they should be supported in this choice. (Good Practice Point) - If a woman vomits within 2 hours of pill taking, another pill should be taken as soon as possible. (Grade C) * Return of fertility: - There is no delay in return of fertility following discontinuation of a progestogen-only pill and therefore if pregnancy is not desired, then another effective method of contraception should be used. (Grade C) * Drug interactions: - Women using liver enzyme-inducing medications short term should be advised to use condoms in addition to progestogen-only pills and for at least 4 weeks after the liver enzyme-inducer is stopped. (Grade C) - Women using liver enzyme-inducing medications long term should be advised that the efficacy of progestogen-only pills is reduced and an alternative contraceptive method should be considered. (Grade C) - Women may be advised that the efficacy of progestogen-only pills is not reduced by use of non-liver enzyme-inducing antibiotics and additional contraceptive protection is not required. (Grade C) * Side effects: - Changes in bleeding patterns with progestogen-only pill use are common: 2 in 10 women have no bleeding, 4 in 10 women have regular bleeding and 4 in 10 women have irregular bleeding. (Grade C) - There is no evidence of a causal association between progestogen-only pill use and weight change. (Grade C) - Mood change can occur with progestogen-only pill use but there is no

	evidence of a causal association for depression. (Grade C) - There is no evidence of a causal association between the use of a progestogen-only pill and headache. (Good Practice Point) - Women of any age with a history of migraine (with or without aura) may safely use progestogen-only pills. (Grade C) - Women who develop new symptoms of migraine with aura while using progestogen-only pills should be advised to seek medical advice, as investigation may be appropriate. Continued use may be considered. (Grade C) - There is no causal association between progestogen-only pill use and cardiovascular disease (MI, VTE and stroke) or breast cancer. (Grade B) * Post partum / Following abortion: - Progestogen-only pills can be started up to and including day 5 of the normal menstrual cycle to provide immediate contraceptive protection. If started after this time condoms or abstinence are advised for 48 hours. (Grade C) - Progestogen-only pills can be started up to and including day 21 postpartum (*no additional contraceptive protection is required*). If started after this time condoms or abstinence are advised for 48 hours. (Grade C) - Progestogen-only pills can be started at the time of abortion or miscarriage (<24 weeks' gestation) or within 5 days. If started after this time condoms are required for the next 48 hours. (Grade C) * Follow-up: - In the absence of special problems, women may be given up to 12 months' supply of progestogen-only pills at their first and follow-up visits. Follow up should be tailored to the individual woman, who should be advised to return at any time if problems arise. (Grade C) - Women may be advised that a progestogen-only pill can be continued until the age of 55 years when natural loss of fertility can be assumed. Alternatively they can continue using a POP and have FSH concentrations checked on two occasions 1–2 months apart. If both FSH measurements are >30 IU/l this is suggestive of ovarian failure and they may continue with a progestogen-only pill or barrier contraception for one further year (or 2 years if aged <50 years). (Good Practice Point) - Women who have a change in bleeding pattern when using a progestogen-only pill need to be assessed and the risk of STIs, pregnancy or gynaecological pathology considered. (Good Practice Point) - There is no evidence that changing the type and dose of progestogen will improve bleeding but this may help some individuals. If, after exclusion of other causes, bleeding patterns are still unacceptable then an alternative contraceptive method may need to be considered. (Good Practice Point)

FSRH 2009 Progestogen-only injectable contraception	Grades of recommendation: A. Based on RCTs B. Based on other robust experimental or observational studies C. Based on limited evidence but the advice relies on expert opinion and has the endorsement of respected authorities Good Practice Point: where no evidence exists but where best practice is based on the clinical experience of the multidisciplinary group
	Levels of evidence: I.a. Evidence obtained from meta-analysis of randomized trials

	I.b. Evidence obtained from at least one RCT II.a. Evidence obtained from at least one well-designed controlled study, without randomisation II.b. Evidence obtained from at least one other type of well-designed quasi-experimental study III. Evidence obtained from well-designed non-experimental descriptive studies, correlation studies and case studies IV. Evidence obtained from expert committee reports or opinions and/or clinical experience of respected authorities
	Included populations, interventions, outcomes: - women seeking contraception - progestogen-only injectable contraception - contraceptive efficacy: failure rates, return of fertility, side effects, discontinuation, drug interactions, health concerns
	Members of development group, target population: - gynecologists, obstetricians - health professionals
	* Contraceptive efficacy: - The failure rate with the progestogen-only injectable given within license every 12 weeks is low: <4 in 1000 over 2 years. (Grade A) - There can be a delay of up to 1 year in the return of fertility after discontinuation of progestogen-only injectable contraception. (Grade C) - Women who do not wish to conceive should be advised to start another contraceptive method before or at the time of the next scheduled injection even if amenorrheic. (Good Practice Point) * Side effects: - Bleeding changes: Women should be informed about the altered bleeding patterns that usually occur with the use of a progestogen-only injectable contraceptive. (Good Practice Point) Spotting or light bleeding is common during progestogen-only injectable use, particularly in the first injection cycle. Up to 70% of DMPA users are amenorrheic at 1 year of use. (Grade B) - Weight change: Women should be advised that there is an association between DMPA use and weight gain. (Grade C) - Mood change, libido and headache: There is no evidence of a causal association between the use of progestogen-only injectable contraceptives and mood change, libido or headache. (Grade C) * Discontinuation: - Up to 50% of progestogen-only injectable contraceptive users will discontinue by 1 year, the most common reason for discontinuation is changes to bleeding pattern. (Grade B) - Women should be informed about the main reasons for discontinuation of progestogen-only injectable contraception and be given appropriate oral and written advice. (Grade A) - Women should be advised to return if they experience any signs of symptoms of infection at the site of injection. (Good Practice Point) * Health concerns:

	- Women should be informed that progestogen-only injectable contraceptive use is associated with a small loss of BMD, which is usually recovered after discontinuation. (Grade B) - Women should be advised that there is no available evidence on the effect of DMPA on long-term fracture risk. (Good Practice Point) - In women aged under 18 years DMPA can be used as first-line contraception after consideration of other methods. (Grade C) - Women using DMPA who wish to continue use should be reviewed every 2 years to assess individual situations and discuss the benefits and potential risks, and be supported in their choice of whether or not to continue. Use may continue to age 50 years. (Good Practice Point) Remark: uterine fibroids, benign ovarian tumours and cysts and endometriosis are specific conditions for which there is no restriction for the use of POPs (UKMEC 1). * Drug interactions: - Women should be informed that the efficacy of progestogen-only injectable contraception is not reduced with concurrent use of medication (including antibiotics and liver enzyme-inducing drugs) and the injection intervals do not need to be reduced. (Grade C) * Postpartum / following abortion or miscarriage: - Women can start a progestogen-only injectable contraceptive up to Day 21 postpartum to provide immediate contraceptive protection. If started after that time another method of contraception or abstinence is required for 7 days. (Grade C) - Progestogen-only injectable contraception can be safely used by women who are breastfeeding. (Grade B) - Progestogen-only injectable contraception may be given following surgical abortion (or second part of) medical abortion or miscarriage. If administered within 5 days after the abortion or miscarriage then additional contraceptive protection or abstinence is not required. (Grade C)

FSRH 2009 Progestogen-only implants	Grades of recommendation: A. Based on RCTs B. Based on other robust experimental or observational studies C. Based on limited evidence but the advice relies on expert opinion and has the endorsement of respected authorities Good Practice Point: where no evidence exists but where best practice is based on the clinical experience of the multidisciplinary group
	Levels of evidence: I.a. Evidence obtained from meta-analysis of randomized trials I.b. Evidence obtained from at least one RCT II.a. Evidence obtained from at least one well-designed controlled study, without randomisation II.b. Evidence obtained from at least one other type of well-designed quasi-experimental study III. Evidence obtained from well-designed non-experimental descriptive studies, correlation studies and case studies II. IV. Evidence obtained from expert committee reports or opinions

	and/or clinical experience of respected authorities
	Included populations, interventions, outcomes: - women seeking contraception - progestogen-only implants - contraceptive efficacy, adverse events
	Members of development group, target population: - gynecologists, obstetricians - health professionals
	Recommendations: * Contraceptive efficacy: - The pregnancy rate associated with the use of a progestogen-only implant is very low (<1 in 1000 over 3 y) (Grade B) - The overall risk of ectopic pregnancy is reduced when using progestogen-only implants when compared to using no contraception (Grade B) - Women with a BMI >30kg/m^2 can use a progestogen-only implant without restriction and without a reduction in contraceptive efficacy for the duration of the licensed use (Grade C) - There is no evidence of a delay in return of fertility following removal of a progestogen-only implant (Grade B) * Adverse events: - 20% of users will have no bleeding, while almost 50% will have infrequent, frequent or prolonged bleeding and the bleeding patterns are likely to remain irregular (Grade C) - There is no evidence of a causal association between use of a progestogen-only implant and weight change, mood change or loss of libido (Grade C) - Acne may improve, occur or worsen during the use of a progestogen-only implant (Grade C) - There is no evidence of a causal association between use of a progestogen-only implant and headache (Grade C) - Women of any age with a history of migraine (with or without aura) may use progestogen-only implants. If they develop new symptoms of migraine with aura while using progestogen-only implants, they should be advised to seek medical advice as investigation may be appropriate. (Grade C) - Clinicians should be aware that early discontinuation (up to 43% within 3 years) of progestogen-only implants is common (Grade C) - There is little or no increase in risk of venous thromboembolism associated with the use of a progestogen-only implant (Grade C) - Women using liver enzyme-inducing drugs short term (<3w) may choose to continue with a progestogen-only implant. Additional contraceptive protection such as condoms should be used and until 4 weeks after the drug has been stopped. Information should be given on the use of alternative contraception if liver enzyme-inducing drugs are to be used long term (Good Practice Point). * Non-contraceptive benefits: In common with other methods which suppress ovulation, progestogen-only implants may improve dysmenorrhea and the symptoms of endometriosis.

3.5. Summary of guidelines: Missed hormonal contraceptives

FSRH 2011 Missed pill recommendations	Grades of recommendation: None; this is a statement of the Clinical Effectiveness Unit of the Faculty of Sexual and Reproductive Healthcare
	Levels of evidence: none
	Included populations, interventions, outcomes: - women who have missed (more than 24 hours late) one or more contraception pills (or who started a pack late) and who had unprotected sexual intercourse - combined oral contraception (COC) - recommendations
	Members of development group, target population: - gynecologists, obstetricians - health professionals
	* Starting the pill: You can start the pill any time in your menstrual cycle if you are sure you are not pregnant. If you start the pill on the first day of your period you will be protected from pregnancy immediately. You can also start the pill up to, and including, the fifth day of your period and you will be protected from pregnancy immediately. If you start the pill at any other time in your menstrual cycle you will need to use additional contraception, such as condoms, for the first 7 days of pill taking. * If you forget to take a pill or start a pack late: Missing pills or starting the pack late may make your pill less effective. The chance of pregnancy after missing pills depends on when pills are missed and how many pills are missed. A pill is late when you have forgotten to take it at the usual time. A pill has been missed when it is more than 24 hours since the time you should have taken it. If you miss one pill anywhere in your pack or start the new pack 1 day late, you will still have contraceptive cover. However, missing two or more pills or starting the pack two or more days late (more than 48 hours late) may affect your contraceptive cover. As soon as you realise you have missed any pills, take the last pill you missed immediately. In particular, during the 7-day pill-free break your ovaries are not getting any effects from the pill. If you make this pill-free break longer by forgetting two or more pills, your ovaries might release an egg and there is a real risk of becoming pregnant. Follow the advice below. If you are not sure what to do, continue to take your pill and use additional contraception, such as condoms, and seek advice as soon as possible. If you have missed one pill, anywhere in the pack: - Take the last pill you missed now even if it means taking two pills in one day - Continue taking the rest of the pack as usual - No additional contraception needed - Take your 7-day break as normal. If you have missed two or more pills (i.e. more than 48 hours late), anywhere

	in the pack: - Take the last pill you missed now even if it means taking two pills in one day - Leave any earlier missed pills - Continue taking the rest of the pack as usual and use an extra method of contraception for the next 7 days - You may need emergency contraception (see below) - You may need to start the next pack of pills without a break (see below). * Emergency contraception: If you have had unprotected sex in the previous 7 days and you have missed two or more pills (i.e. more than 48 hours late) in the first week of a pack, you may need emergency contraception. Get advice from your contraception clinic, family doctor or a pharmacist about this. * Starting the next pack after missing two or more pills (more than 48 hours late): If seven or more pills are left in the pack after the last missed pill: - Finish the pack - Have the usual 7-day break. If less than seven pills are left in the pack after the missed pill: - Finish the pack and begin a new one the next day (this means missing out the break).

SOGC 2008 Missed hormonal contraceptives	Grades of recommendation: A. There is good evidence to recommend the clinical preventive action B. There is fair evidence to recommend the clinical preventive action C. The existing evidence is conflicting and does not allow to make a recommendation for or against use of the clinical preventive action; however, other factors may influence decision-making D. There is fair evidence to recommend against the clinical preventive action E. There is fair evidence to recommend against the clinical preventive action L. There is insufficient evidence (in quantity or quality) to make a recommendation; however, other factors may influence decision-making
	Levels of evidence: I: Evidence obtained from at least one properly randomized controlled trial II-1: Evidence from well-designed controlled trials without randomization II-2: Evidence from well-designed cohort (prospective or retrospective) or case-control studies, preferably from more than one center or research group II-3: Evidence obtained from comparisons between times or places with or without the intervention. Dramatic results in uncontrolled experiments (such as the results of treatment with penicillin in the 1940s) could also be included in this category III: Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees
	Included populations, interventions, outcomes: - women who failed to take hormonal contraception as directed - hormonal contraceptives - ovulation suppression, emergency and back-up contraception use, compliance

	Members of development group, target population: - gynecologists, obstetricians - health professionals
	- Instructions for what women should do when they miss hormonal contraception have been complex and women do not understand them correctly. (I) - The highest risk of ovulation occurs when the hormone-free interval is prolonged for more than seven days, either by delaying the start of combined hormonal contraceptives or by missing active hormone doses during the first or third weeks of combined oral contraceptives. (II) - Ovulation rarely occurs after seven consecutive days of combined oral contraceptive use. (II) Recommendations: - Health care providers should give clear, simple instructions, both written and oral, on missed hormonal contraceptive pills as part of contraceptive counseling. (III-A) - Health care providers should provide women with telephone/electronic resources for reference in the event of missed or delayed hormonal contraceptives. (III-A) - In order to avoid an increased risk of unintended pregnancy, the hormone-free interval should not exceed seven days in combined hormonal contraceptive users. (II-A) - Back-up contraception should be used after one missed dose in the first week of hormones until seven consecutive days of correct hormone use are established. In the case of missed combined hormonal contraceptives in the second or third week of hormones, the hormone-free interval should be eliminated for that cycle. (III-A) - Emergency contraception and back-up contraception may be required in some instances of missed hormonal contraceptives, in particular when the hormone-free interval has been extended for more than seven days. (III-A) - Back-up contraception should be used when three or more consecutive doses/days of combined hormonal contraceptives are missed in the second and third week until seven consecutive days of correct hormone use are established. For practical reasons, the scheduled hormone-free interval should be eliminated in these cases. (II-A) - Emergency contraception is rarely indicated for missed combined hormonal contraceptives in the second or third week of the cycle unless there are repeated omissions or failure to institute back-up contraception after the missed doses. In cases of repeated omissions of combined hormonal contraceptives, emergency contraception may be required, and back-up contraception should be used. Health care professionals should counsel women in these situations on alternative methods of contraception that do not demand such stringent compliance. (III-A)

3.6. Summary of guidelines: Problem-specific guidelines

ACOG 2010 Non-contraceptive uses of hormonal contraceptives	Grades of recommendation: A. Based on good and consistent scientific evidence B. Based on limited or inconsistent scientific evidence C. Based primarily on consensus and expert opinion
	Levels of evidence: I. Evidence obtained from at least one properly designed RCT II. 1. Evidence obtained from well-designed controlled trial without randomization 2. Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one center or research group 3. Evidence obtained from multiple time series with or without intervention III. Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees
	Included populations, interventions, outcomes: - women having menstrual irregularities or other specific conditions such as acne, migraine, leiomyomas, endometriosis - combined oral contraceptives (COC), vaginal ring, patch, progestogen-only pills (POP), injections and implants - effect on cycle control and specific conditions such as acne symptoms, bleeding, pain
	Members of development group, target population: - gynecologists, obstetricians - gynecologists, obstetricians
	Recommendations: * Level A: - Combined OCs should not be used to treat existing functional ovarian cysts. - Use of combined hormonal contraception has been shown to decrease the risk of endometrial and ovarian cancer. - Combined OCs have been shown to regulate and reduce menstrual bleeding, treat dysmenorrhea, reduce premenstrual dysphoric disorder symptoms, and ameliorate acne. - Continuous combined hormonal contraception, DMPA, and the levonorgestrel intrauterine system may be considered for long-term menstrual suppression. * Level B: - Based on the limited data available it appears overall that combined OCs do not increase the risk of development of uterine leiomyomas. - Hormonal contraception should be considered for the treatment of menorrhagia in women who may desire further pregnancies.

FSRH 2012 Drug interactions with hormonal contraception	Grades of recommendation: A. Based on RCTs B. Based on other robust experimental or observational studies C. Based on limited evidence but the advice relies on expert opinion and has the endorsement of respected authorities Good Practice Point: where no evidence exists but where best practice is based on the clinical experience of the multidisciplinary group
	Levels of evidence: I.a. Evidence obtained from meta-analysis of randomized trials I.b. Evidence obtained from at least one RCT II.a. Evidence obtained from at least one well-designed controlled study, without randomisation II.b. Evidence obtained from at least one other type of well-designed quasi-experimental study III. Evidence obtained from well-designed non-experimental descriptive studies, correlation studies and case studies II. IV. Evidence obtained from expert committee reports or opinions and/or clinical experience of respected authorities
	Included populations, interventions, outcomes: - women seeking contraception - combined hormonal contraception (COC), progestogen-only contraception, emergency contraception - drug interactions with hormonal contraception
	Members of development group, target population: - gynecologists, obstetricians - health professionals
	Recommendations: - All women starting enzyme-inducing drugs should be advised to use a reliable contraceptive method unaffected by enzyme inducers (e.g. progestogen-only injectable, copper-bearing intrauterine devices (Cu-IUDs) or the levonorgestrel-containing intrauterine system. (Grade C) - With the exception of the very potent enzyme inducers rifampicin and rifabutin, women who are on an enzyme-inducing drug and who do not wish to change from COC may increase the dose of COC to at least 50 µg EE (maximum 70 µg) and use an extended or tricycling regimen with a pill-free interval of 4 days. (Good Practice Point) - Women who request oral emergency contraception while using enzyme-inducing drugs or within 28 days of stopping them, should be advised to take a total of 3 mg levonorgestrel (two 1.5 mg tablets) as a single dose as soon as possible and within 120 hours of unprotected sexual intercourse (use of levonorgestrel >72 hours after unprotected sexual intercourse and double dose are outside the product license). (Grade C) - Ulipristal acetate is not advised in women using enzyme-inducing drugs or who have taken them within the last 28 days. (Grade C) - Women using drugs that affect gastric pH (e.g. antacids, H2 antagonists and proton pump inhibitors) and who require emergency contraception should be offered a Cu-IUD or levonorgestrel as the efficacy of ulipristal may be reduced. (Good Practice Point) - Women on lamotrigine monotherapy should be advised that due to the risk of reduced seizure control whilst on combined hormonal contraception (CHC), and

	the potential for toxicity in the CHC-free week, the risks of using CHC may outweigh the benefits. (Grade C)

FSRH 2010 Quick starting Contraception	Grades of recommendation: A. Based on RCTs B. Based on other robust experimental or observational studies C. Based on limited evidence but the advice relies on expert opinion and has the endorsement of respected authorities Good Practice Point: where no evidence exists but where best practice is based on the clinical experience of the multidisciplinary group
	Levels of evidence: I.a. Evidence obtained from meta-analysis of randomized trials I.b. Evidence obtained from at least one RCT II.a. Evidence obtained from at least one well-designed controlled study, without randomisation II.b. Evidence obtained from at least one other type of well-designed quasi-experimental study III. Evidence obtained from well-designed non-experimental descriptive studies, correlation studies and case studies IV. Evidence obtained from expert committee reports or opinions and/or clinical experience of respected authorities
	Included populations, interventions, outcomes: - women starting (emergency) contraception; quick starting means not waiting for the next menstrual cycle - combined oral contraception (COC), Qlaira (=sequential combined pill containing estradiol and dienogest), combined vaginal ring, transdermal patch, progestogen-only pills (POP), implants or injectables, levonorgestrel-releasing intrauterine system, copper-bearing intrauterine device - unintended pregnancy, benefits and disadvantages of quick starting
	Members of development group, target population: - gynecologists, obstetricians - health professionals
	* Benefits: Starting contraception immediately, rather than waiting for the next menses, may theoretically reduce the time a woman is at risk of pregnancy; prevent her forgetting information on correct use of the method; prevent waning enthusiasm for the method and use of a less reliable alternative method; avoid patient costs and barriers to returning for contraception (e.g. transport, time, childcare) and reduce health care costs by reducing the number of appointments. Women who have taken emergency contraception or who have irregular cycles may have an even longer wait for their next menses. It has been shown that there is a two- to three-fold higher risk of pregnancy in women who go on to have other episodes of sex in the same cycle that emergency contraception has been given compared to those who abstain. The quick start method might, therefore, be expected to reduce unintended pregnancy rates by improving initiation and continuation of contraceptives compared to conventional start methods. A Cochrane review has found limited evidence that immediate ('quick') start of hormonal contraception reduces unintended pregnancies or improves continuation rates.

	* Disadvantages: - Effects of fetal exposure to steroid hormones Inadvertent fetal exposure to contraceptive hormones is common, with a USA study estimating that approximately 70 000 fetuses are exposed to oral contraceptives annually. Most of the data on fetal outcomes relate to COC. The FSRH found no studies that specifically assessed exposure through quick starting contraception. Studies are often limited by their observational nature, potential confounding factors and small sample size. Reassuringly there have been no consistent findings of specific fetal abnormalities. - Bleeding patterns It has been suggested that quick starting contraception may be associated with more disruption to a woman's usual bleeding pattern than when initiating contraception at the beginning of the menstrual cycle. However, studies comparing quick start and conventional start of COC have demonstrated no significant difference in bleeding patterns. - Insertion of intrauterine contraceptives Contrary to previously held beliefs that the cervical canal is wider during menses and that this is the optimal time to insert an intrauterine method, there is no evidence that the cervix dilates during menses or that insertion of an intrauterine contraceptive is easier at this time. * Recommendations: - If a health professional is reasonably sure that a woman is not pregnant or at risk of pregnancy from recent unprotected sexual intercourse, contraception can be started immediately unless the woman prefers to wait until her next period. Such practice may be outside the product license/device instructions. (Good Practice Point) - If a health professional is reasonably sure that a woman is not pregnant but her preferred contraceptive method is not available, CHC, the POP or the progestogen-only injectable can be used as a bridging method. (Good Practice Point) - When starting intrauterine methods or co-cyprindiol (Dianette®, Clairette®) health professionals should take particular care to exclude pregnancy or risk of pregnancy from recent unprotected sexual intercourse. If pregnancy cannot be excluded, the Cu-IUD may only be started immediately if the criteria for use as emergency contraception are met; insertion of the levonorgestrel intrauterine system or initiation of co-cyprindiol should be delayed until pregnancy can be excluded. (Good Practice Point) - If pregnancy cannot be excluded (e.g. following administration of emergency contraception) but a woman is likely to continue to be at risk of pregnancy or has expressed a preference to start contraception without delay, immediate quick starting of CHC, the POP or progestogen-only implant may be considered. The woman should be informed of the potential risks and the need to have a pregnancy test at the appropriate time. (Good Practice Point) - Women requesting the progestogen-only injectable should ideally be offered a bridging method if pregnancy cannot be excluded, but immediate start is acceptable if other methods are not appropriate or acceptable. (Good Practice Point) - If contraception is quick started in a woman for whom pregnancy cannot be excluded, a pregnancy test should be advised no sooner than 3 weeks after the last episode of unprotected sexual intercourse. (Good Practice Point)

	- If pregnancy cannot be excluded and the woman's preferred method is not available or appropriate, CHC or POP may be used as bridging methods; the progestogen-only injectable should only be considered as a bridging method if other methods are not appropriate or acceptable. (Good Practice Point) - If starting hormonal contraception immediately after progesterone-only emergency contraception, condoms or avoidance of sex should be advised for 7 days (2 days for POP, 9 days for Qlaira). (Grade C) - If starting hormonal contraception immediately after ulipristal emergency contraception, we recommend condoms or avoidance of sex for 14 days (9 days if starting POP, 16 days for Qlaira) (outside product license). (Good Practice Point) - If pregnancy is diagnosed after starting contraception and the woman wishes to continue with pregnancy, the method should usually be stopped or removed. Intrauterine contraceptives should not be removed if pregnancy is diagnosed after 12 weeks' gestation.

FSRH 2010 Contraception for women aged over 40y	Grades of recommendation: A. Based on RCTs B. Based on other robust experimental or observational studies C. Based on limited evidence but the advice relies on expert opinion and has the endorsement of respected authorities Good Practice Point: where no evidence exists but where best practice is based on the clinical experience of the multidisciplinary group
	Levels of evidence: I.a. Evidence obtained from meta-analysis of randomized trials I.b. Evidence obtained from at least one RCT II.a. Evidence obtained from at least one well-designed controlled study, without randomisation II.b. Evidence obtained from at least one other type of well-designed quasi-experimental study III. Evidence obtained from well-designed non-experimental descriptive studies, correlation studies and case studies IV. Evidence obtained from expert committee reports or opinions and/or clinical experience of respected authorities
	Included populations, interventions, outcomes: - ≥40y-old women seeking contraception - combined hormonal contraception (CHC), long-acting reversible contraception, progestogen-only contraception, non-hormonal methods of contraception, emergency contraception - fertility/pregnancy, health benefits and risks
	Members of development group, target population: - gynecologists, obstetricians - health professionals
	* Sexual and reproductive health in 40+ year old women: - Fertility: women should be informed that although a natural decline in fertility occurs form their mid-30s, effective contraception is required to prevent unintended pregnancy. (Grade B) - Pregnancy: women should be informed that the risks of chromosomal abnormalities, miscarriage, pregnancy complications and of maternal morbidity and mortality increase for women aged over 40 years. (Grade B) - For most women, the 40s and 50s are a time when they move from normal

	ovulatory menstrual cycles to the cessation of ovulation and menstruation. During this time, intermittent ovulation and anovulation occur and women will experience shortening and/or lengthening of their menstrual cycle. Recommendations: No contraceptive method is contraindicated by age alone. (Grade C) The four most commonly reported contraceptive methods in 2008/2009 in the UK for women aged 40-49 years were sterilization (either own or partner), the pill, male condoms and intrauterine methods. * Long-acting reversible methods of contraception: - Women and their partners should be advised that very long-acting reversible contraception can be as effective as sterilization. (Grade C) - Return of fertility can be delayed for up to 1 year after discontinuation of pregestogen-only injectable contraception. (Grade C) * Combined hormonal contraception (CHC): - Dysmenorrhea and cycle control -> Use of CHC may help to reduce menstrual pain and bleeding (Grade C) There is a lack of data on which to draw firm conclusions about the role of progestogens in the treatment of pain associated with endometriosis. Both DMPA and levonorgestrel-IUS are acknowledged as possible treatments in the RCOG guideline on the investigation and management of endometriosis. - Menopausal symptoms -> women can be advised that in clinical practice CHC may reduce menopausal symptoms. (Grade C) - Ovarian and endometrial cancer -> CHC use provides a protective effect against ovarian and endometrial cancer that continues for 15 years or more after stopping CHC. (Grade B) Data also suggest a reduction in the incidence of ovarian cysts and benign ovarian tumours amongst women using COCs. - Benign breast disease -> there may be a reduction in the incidence of benign breast disease with CHC use. (Grade B) - Colorectal cancer -> there may be a reduction in the risk of colorectal cancer with CHC use. (Grade B) - Breast cancer -> there may be a small additional risk of breast cancer with CHC use, which reduces to no risk 10 years after stopping CHC. (Grade B) - Cardiovascular and cerebrovascular disease Women who are aged 35 years or over and smoke should be advised that the risks of using CHC usually outweigh the benefits. (Grade B) Clinicians should be aware that there may be a very small increased risk of ischemic stroke with CHC use. (Grade B) Women with cardiovascular disease, stroke or migraine with aura should be advised against the use of CHC. (Grade C) Hypertension may increase the risk of stroke and MI in those using CHC. (Grade B) Blood pressure should be checked before and at least 6 months after initiating a woman aged over 40 years on a CHC method and monitored at least annually thereafter. (Grade C) * Progestogen-only contraception (POC): - There is no conclusive evidence of a link between progestogen-only methods and breast cancer. (Grade B) - Progestogen-only methods may help to alleviate dysmenorrhea. (Grade C) - Women should be advised that altered bleeding patterns are common with

	use of POC. (Good Practice Point) - Women should be advised that the levonorgestrel-intrauterine system can be used for the treatment of heavy menstrual bleeding once pathology has been excluded. (Grade B) - Although data are limited, POC does not appear to increase the risk of stroke of or MI, and there is little or no increase in VTE risk. (Grade B) - Caution is required when prescribing depot medroxyprogesterone acetate to women with cardiovascular risk factors due to the effects of progestogens on lipids. (Grade C) * Non-hormonal contraception: - Women should be informed that spotting, heavier or prolonged bleeding and pain are common in the first 3-6 months of Cu-IUD use. (Grade C) - Men and women can be advised that when used consistently and correctly, male and female condoms are –respectively- up to 98% and 95% effective at preventing pregnancy. (Grade C) - Women can be advised that when used consistently and correctly with spermicide, diaphragm and caps are –respectively- estimated to be between 92% and 96% effective at preventing pregnancy. (Grade C) - When using lubricant with latex condoms a non-oil-based preparation is recommended. (Grade B) * Stopping contraception: - Women using non-hormonal methods of contraception can be advised to stop contraception after 1 year of amenorrhea if aged over 50 years, or 2 years if the woman is aged under 50 years. (Good Practice Point) - After counseling (about declining fertility, risks associated with insertion, and contraceptive efficacy), women who have a Cu-IUD containing ≥300mm^2 copper, inserted at or over the age of 40 years, can retain the device until the menopause or until contraception is no longer required. (Grade C) - Women using exogenous hormones should be advised that amenorrhea is not reliable indicator of ovarian failure. (Good Practice Point) - In women using contraceptive hormones, FSH levels may be used to help diagnose the menopause, but should be restricted to women over the age of 50 years and to those using progestogen-only methods. (Good Practice Point) - FSH is not a reliable indicator of ovarian failure in women using combined hormones, even if measured during the hormone-free interval. (Good Practice Point) - Women over the age of 50 years who are amenorrheic and wish to stop POC can have their FSH levels checked. If the level is ≥30IU/L contraception can be stopped after 1 year. (Good Practice Point) - Women who have their levonorgestrel-intrauterine system inserted for contraception at the age of 45 years or over can use the device for 7 years (off license) or if amenorrheic until the menopause, after which the device should be removed. (Good Practice Point) * Hormone replacement therapy and contraception: - Women using HRT should be advised not to rely on this as contraception. (Grade C) - Women can be advised that a POP can be used with HRT to provide effective contraception but the HRT must include progestogen in addition to estrogen. (Good Practice Point)

	- Women using estrogen replacement therapy may use the levonorgestrel-intrauterine device to provide endometrial protection. When used as the progestogen component of HRT, the levonorgestrel intrauterine device should be changed no later than 5 years after insertion (the license states 4 years), irrespective of age at insertion. (Grade A)

FSRH 2010 Contraceptive choices for young people	Grades of recommendation: A. Based on RCTs B. Based on other robust experimental or observational studies C. Based on limited evidence but the advice relies on expert opinion and has the endorsement of respected authorities Good Practice Point: where no evidence exists but where best practice is based on the clinical experience of the multidisciplinary group
	Levels of evidence: I.a. Evidence obtained from meta-analysis of randomized trials I.b. Evidence obtained from at least one RCT II.a. Evidence obtained from at least one well-designed controlled study, without randomisation II.b. Evidence obtained from at least one other type of well-designed quasi-experimental study III. Evidence obtained from well-designed non-experimental descriptive studies, correlation studies and case studies IV. Evidence obtained from expert committee reports or opinions and/or clinical experience of respected authorities
	Included populations, interventions, outcomes: - young people seeking contraception - combined hormonal contraception (CHC), long-acting reversible contraception, progestogen-only contraception, non-hormonal methods of contraception, emergency contraception - failure rates, non-adherence and discontinuation, health benefits, concerns and risks
	Members of development group, target population: - gynecologists, obstetricians - health professionals
	* Legal and ethical framework: - Practitioners may wish to inform a young person of the law in relation to sexual activity. (Good Practice Point) - A clinician should assess a young person's competence to consent to treatment by their ability to understand information provided, to weigh up the risks and benefits, and to express their own wishes. (Grade C) - Competence to consent to treatment should be assessed and documented at each visit where relevant (e.g. for under-16-year-olds). (Grade C) - Health professionals may wish to use checklists (e.g. Fraser Guidelines) to assess competence and risk when providing contraceptive advice or treatment to young people. (Good Practice Point) - Young people should always be made aware of the confidentiality policies for the service they are attending, including the circumstances in which confidentiality may need to be breached. (Grade C) - All sexual and reproductive health care services should have a named person identified as the local lead for child protection. (Grade C) - All staff involved in contraceptive services for young people should receive

	appropriate training to alert them to the possibility of exploitation or coercion. (Grade C) - Staff should know who they can contact for advice and how to act on child protection issues in accordance with local policy and procedures. (Grade C) * Contraceptive options for young people: - Young people should be informed about all methods of contraception, highlighting the benefits of long-acting reversible contraception (LARC). (Good Practice Point) - Young people may be advised to return for follow-up within 3 months of starting hormonal contraception. This allows side effects or other concerns to be addressed and helps ensure correct use of the method. (Good Practice Point) - Young people should be encouraged to return at any time if they develop problems with contraception. (Grade C) - Age alone should not limit contraceptive choices, including intrauterine methods. (Grade C) - Young people should be made aware of the different types of emergency contraception (EC) available, when they can be used and how they can be accessed. (Good Practice Point) - Even if presenting for EC within 72 hours of unprotected sexual intercourse (UPSI), women of all ages should be offered the copper-bearing intrauterine device or advised how they can access it. (Good Practice Point) * Young people's health concerns and risks: - Weight gain: Young people may be advised that there is no evidence of weight gain with combined hormonal contraception (CHC) use. (Grade B) Young people may be advised that weight gain can occur with depot medroxyprogesterone acetate (DPMA) use but there is little evidence of a causal association between other progestogen-only methods and weight gain. (Grade C) - Acne: Young people may be advised that combined oral contraception (COC) use can improve acne. (Grade B) Young women whose acne fails to improve with COC may wish to consider switching to a COC containing a less androgenic progestogen or one with a higher estrogen content. (Good Practice Point) Co-cyprindiol (Dianette®) is indicated to treat severe acne that has not responded to oral antibiotics. In those with less severe symptoms it should be withdrawn 3-4 months after the condition has resolved. For women with known hyperandrogenism, longer use with specialist review may be warranted. (Grade C) Young people should be advised that the progestogen-only implant may be associated with improvement, worsening or onset of acne. (Grade C) - Mood changes: Young people may be advised that hormonal contraception may be associated with mood changes but there is no evidence that hormonal contraceptives cause depression. (Grade C) - Fertility: Individuals should be advised that there is no delay in return of fertility following discontinuation of the progestogen-only pill or CHC. (Grade C)

	Individuals should be advised that there is no delay in return of fertility after discontinuation of intrauterine contraception or the progestogen-only implant. (Grade B) Individuals should be advised that there can be a delay of up to 1 year in the return of fertility after discontinuation of DMPA. (Grade C) - Bleeding patterns and dysmenorrhea: Individuals should be informed that altered bleeding patterns can occur with hormonal contraception use. (Grade C) Primary dysmenorrhea may improve with use of CHC. (Grade B) - Thrombosis: Young people may be informed that although the risk of venous thromboembolism is increased with CHC, the absolute risk is very small. (Grade B) - Cancer: Young people may be advised that COC use is not associated with an overall increased risk of cancer. (Grade B) Young people may be advised that COC use reduces the risk of ovarian cancer and that the protective benefit continues for 15 or more years after stopping. (Grade B) Young people may be advised that any increase in breast cancer with hormonal contraception use is likely to be small and to reduce after stopping. (Grade B) Young people may be advised that there may be a very small increase in the risk of cervical cancer with prolonged COC use. (Grade B) * Sexually transmitted infections and young people: - The correct and consistent use of condoms should be advised to reduce the risk of transmission of sexually transmitted infections (STIs). (Grade B) - When advising condom use, young people should be informed about correct use of condoms and lubricants, different sizes, types and shapes of condoms, and how to access further supplies, STI screening and emergency contraception. (Good Practice Point) - Young people should be advised to have STI tests 2 and 12 weeks after an incident of unprotected sexual intercourse. (Grade C)

RCOG 2010 Venous thromboembolism and hormonal contraception	Grades of recommendation: A. At least one meta-analysis, systematic reviews or randomised controlled trial rated as 1++ and directly applicable to the target population; or A systematic review of randomised controlled trials or a body of evidence consisting principally of studies rated as 1+, directly applicable to the target population and demonstrating overall consistency of results B. A body of evidence including studies rated as 2++ directly applicable to the target population and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 1++ or 1+ C. A body of evidence including studies rated as 2+ directly applicable to the target population and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 2++ D. Evidence level 3 or 4; or Extrapolated evidence from studies rated as 2+ Good practice point: Recommended best practice based on the clinical experience of the guideline development group
	Levels of evidence: 1++ High-quality meta-analyses, systematic reviews of randomised controlled trials or randomised controlled trials with a very low risk of bias 1+ Well-conducted meta-analyses, systematic reviews of randomised controlled trials or randomised controlled trials with a low risk of bias 1– Meta-analyses, systematic reviews of randomised controlled trials or randomised controlled trials with a high risk of bias 2++ High-quality systematic reviews of case–control or cohort studies or high quality case–control or cohort studies with a very low risk of confounding, bias or chance and a high probability that the relationship is causal 2+ Well-conducted case–control or cohort studies with a low risk of confounding, bias or chance and a moderate probability that the relationship is causal 2– Case–control or cohort studies with a high risk of confounding, bias or chance and a significant risk that the relationship is not causal 3 Non-analytical studies; e.g. case reports, case series 4 Expert opinion
	Included populations, interventions, outcomes: - women with a history of venous thromboembolism (deep vein thrombosis, pulmonary embolism and cerebral venous sinus thrombosis) seeking contraception - hormonal contraception: combined hormonal contraceptives such as pills, patch and vaginal ring, progestogen-only methods such as POP, injectable, implant and intrauterine system - risks of venous thromboembolism, risk factors of VTE, screening
	Members of development group, target population: - gynecologists, obstetricians - health professionals
	* Combined hormonal methods of contraception: - The relative risk of venous thromboembolism is increased with all combined hormonal contraceptives (pills, patch and vaginal ring). Nevertheless, the

	rarity of venous thromboembolism in women of reproductive age means that the absolute risk remains small. (B) - The relative risk of venous thromboembolism increases in the first few months after initiating combined hormonal contraception. This risk reduces with increasing duration of use but it remains above the background risk until the combined hormonal contraceptive is stopped. (B) * Progestogen-only methods of contraception: Progestogen-only pills, injectable, implants and the levonorgestrel-releasing intrauterine system do not appear to be associated with an increased risk of venous thromboembolism. (B) * Risk factors: - The United Kingdom Medical Eligibility Criteria for Contraceptive Use provides consensus-based recommendation for the use of contraception. A clinical history should be taken to identify any relevant medical conditions which may influence contraceptive choice. (Good practice point) - Women with current venous thromboembolism or previous venous thromboembolism should be advised against the use of combined hormonal contraception as this poses an unacceptable health risk. (C) - For women with current venous thromboembolism on anticoagulants or previous venous thromboembolism the use of progestogen-only contraception is safe. (C) - The use of combined hormonal contraception by women with a family history of VTE in a first-degree relative aged under the age of 45 years is not recommended. (C) - For women with a known thrombogenic mutation the use of combined hormonal contraception poses an unacceptable health risk. (C) -For women who are postpartum and not breastfeeding, combined hormonal contraception (pill, patch or vaginal ring) should not be initiated before day 21 postpartum. (Grade C) All hormonal contraception can be safely initiated immediately following a first- or second-trimester termination of pregnancy. (Grade C) - For women aged over 35 years who are current smokers or who have stopped smoking less than 1 year ago, the use of combined hormonal contraception is not recommended. (Grade C) - For women with a body mass index of 35 kg/m^2 or greater, the risks of combined hormonal contraception may outweigh the benefits. (Grade B) - Combined hormonal contraception should be discontinued and an alternative estrogen-free method used at least 4 weeks before major elective surgery where immobilisation is expected but does not need to be discontinued before minor surgery without immobilisation. (Grade B) - For women with medical conditions which may predispose to venous thromboembolism, the risks associated with use of combined hormonal contraceptives must be weighed against the benefits, including pregnancy prevention. (Good practice point)

	- Routine thrombophilia screening prior to hormonal contraceptive use is not recommended. (Grade C)

SOGC 2010 Oral contraceptives and the risk of venous thrombo-embolism	Grades of recommendation: A. There is good evidence to recommend the clinical preventive action B. There is fair evidence to recommend the clinical preventive action C. The existing evidence is conflicting and does not allow to make a recommendation for or against use of the clinical preventive action; however, other factors may influence decision-making D. There is fair evidence to recommend against the clinical preventive action E. There is fair evidence to recommend against the clinical preventive action L. There is insufficient evidence (in quantity or quality) to make a recommendation; however, other factors may influence decision-making
	Levels of evidence: I: Evidence obtained from at least one properly randomized controlled trial II-1: Evidence from well-designed controlled trials without randomization II-2: Evidence from well-designed cohort (prospective or retrospective) or case-control studies, preferably from more than one center or research group II-3: Evidence obtained from comparisons between times or places with or without the intervention. Dramatic results in uncontrolled experiments (such as the results of treatment with penicillin in the 1940s) could also be included in this category III: Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees
	Included populations, interventions, outcomes: - women seeking contraception - oral contraceptives - efficacy, risk of venous thromboembolism
	Members of development group, target population: - gynecologists, obstetricians - health professionals
	* Efficacy: - Modern oral contraceptives offer highly effective contraception and a range of non-contraceptive benefits. (I) * Risk of venous thromboembolism: - Venous thromboembolism, although rare, remains one of the serious adverse consequences of hormonal contraception. Best evidence indicates that venous thromboembolism rates in non-users of reproductive age approximate 4–5/10 000 women per year; rates in oral contraceptive users are in the range of 9–10/10 000 women per year. For comparison, venous thromboembolism rates in pregnancy approach 29/10 000 overall and may reach 300–400/10 000 in the immediate postpartum period. (II-1) - Research demonstrates that oral contraceptives with ≤35 µg of ethinyl estradiol carry a lower risk of venous thromboembolism than oral contraceptives with 50 µg. (II-2) Although preliminary data suggest a possible further reduction in venous thromboembolism with oral contraceptives with

	<35 µg ethinyl estradiol, robust data to support this conclusion are presently lacking. - Recent contradictory evidence and the ensuing media coverage of the venous thromboembolism risk attributed to the progestin component of certain newer oral contraceptive products have led to fear and confusion about the safety of oral contraceptives in general and drospirenone-containing oral contraceptives in particular. “Pill scares” of this nature have occurred in the past, with panic stopping of the pill, increased rates of unplanned pregnancy, and no subsequent decrease in venous thromboembolism rates. (II-3) - Two high quality research studies that addressed the venous thromboembolism risk associated with various oral contraceptives found comparable venous thromboembolism rates with drospirenone-containing oral contraceptives and other approved products. (II-1) - Two reports suggesting an increased risk of venous thromboembolism with drospirenone-containing oral contraceptives have significant methodological flaws that render their conclusions suspect. It seems likely that residual confounding could have distorted both the results and the conclusions of these reports. (II-3)

3.7. Summary of guidelines - Emergency contraception only

ACOG 2010 Emergency contraception	Grades of recommendation: A. Based on good and consistent scientific evidence B. Based on limited or inconsistent scientific evidence C. Based primarily on consensus and expert opinion
	Levels of evidence: I. Evidence obtained from at least one properly designed RCT II. 1. Evidence obtained from well-designed controlled trial without randomization 2. Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one center or research group 3. Evidence obtained from multiple time series with or without intervention III. Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees
	Included populations, interventions, outcomes: - women seeking emergency contraception after unprotected sexual intercourse - combined estrogen-progestin regimens, levonorgestrel-only regimen, ulipristal - pregnancy rate, adverse events
	Members of development group, target population: - gynecologists, obstetricians - gynecologists, obstetricians
	Recommendations: * Level A: - levonorgestrel-only regimen is more effective and is associated with less nausea and vomiting - the two 0.75mg doses of the levonorgestrel-only regimen are equally effective if taken 12-24h apart - the single-dose 1.5mg levonorgestrel-only regimen is as effective as the two-dose regimen taken 12h apart - to reduce the chance of nausea with the combined estrogen-progestin regimen, an antiemetic agent may be taken 1h before the first emergency contraception dose * Level B: - treatment with emergency contraception should be initiated as soon as possible after unprotected intercourse to maximize efficacy - emergency contraception should be made available to patients who request it up to 5 days after unprotected intercourse - no clinician examination or pregnancy testing is necessary before provision or prescription of emergency contraception * Level C: - emergency contraception should be offered or made available to women who have had unprotected or inadequately protected sexual intercourse and who

	do not desire pregnancy - emergency contraception may be made available to women with contraindications to the use of conventional oral contraceptive preparations - clinical evaluation is indicated for women who have used emergency contraception if menses are delayed by a week or more after the expected time or if lower abdominal pain or persistent irregular bleeding develops - information regarding effective long-term contraceptive methods should be made available whenever a woman requests emergency contraception - the copper IUD is appropriate for use as emergency contraception for women who desire long-acting contraception - emergency contraception may be used more than once, even within the same menstrual cycle - to maximize effectiveness, women should be educated about the availability of emergency contraception * Special conditions: - Irregular bleeding: after emergency contraception use, the menstrual period usually occurs within one week before or after the expected time. Some patients experience irregular bleeding or spotting in the week or month after treatment. Irregular bleeding associated with emergency contraception resolves without treatment. (No level of recommendation.) - Emergency contraception is not used to treat other specific conditions such as functional ovarian cysts, dysmenorrhea or menorrhagia, premenstrual syndrome, fibromyomatosis, endometriosis, mastodynia, acne,… This type of contraception is only used to prevent pregnancy after an unprotected or inadequately protected act of sexual intercourse.

FSRH 2012 Emergency contraception	Grades of recommendation: A. Based on RCTs B. Based on other robust experimental or observational studies C. Based on limited evidence but the advice relies on expert opinion and has the endorsement of respected authorities Good Practice Point: where no evidence exists but where best practice is based on the clinical experience of the multidisciplinary group
	Levels of evidence: I.a. Evidence obtained from meta-analysis of randomized trials I.b. Evidence obtained from at least one RCT II.a. Evidence obtained from at least one well-designed controlled study, without randomisation II.b. Evidence obtained from at least one other type of well-designed quasi-experimental study III. Evidence obtained from well-designed non-experimental descriptive studies, correlation studies and case studies IV. Evidence obtained from expert committee reports or opinions and/or clinical experience of respected authorities
	Included populations, interventions, outcomes: - women seeking emergency contraception after unprotected sexual intercourse - copper-bearing intrauterine device (Cu-IUD), levonorgestrel, ulipristal acetate - drug interactions, side effects, future contraception

	Members of development group, target population: - gynecologists, obstetricians - health professionals
	* Emergency contraception methods: - The copper-bearing intrauterine device (Cu-IUD) can be inserted up to 120 hours after the first episode of unprotected sexual intercourse or within 5 days of the earliest expected date of ovulation. (Grade C) - All eligible women presenting between 0 and 120 hours of unprotected sexual intercourse or within 5 days of expected ovulation should be offered a Cu-IUD because of the low documented failure rate. (Grade B) - The efficacy of ulipristal acetate has been demonstrated up to 120 hours and can be offered to all eligible women requesting emergency contraception during this time period. It is the only oral emergency contraception licensed for use between 72 and 120 hours. (Grade A) - Levonorgestrel can be used more than once in a cycle or for a recent indication even if there has been an earlier episode of UPSI outside the treatment window (>120 hours). (Grade C) - The efficacy of levonorgestrel has been demonstrated up to 96 hours; between 96 and 120 hours efficacy is unknown. Use of levonorgestrel beyond 72 hours is outside the product license. (Grade A) * Future/ongoing contraception: - Women should be advised that oral emergency contraception methods do not provide contraceptive cover for subsequent unprotected sexual intercourse and that they will need to use contraception or refrain from sex to avoid further risk of pregnancy. (Grade B) - If a woman is likely to continue to be at risk of pregnancy or has expressed a preference to start contraception immediately after emergency contraception, a health professional may 'quick start' combined hormonal contraception (excluding co-cyprindiol), the progestogen-only pill (POP) or implant, providing the woman has been appropriately informed and advised to have a pregnancy test in ≥3 weeks. (Good Practice Point) - Women requesting the progestogen-only injectable after emergency contraception should ideally be offered an alternative method until pregnancy can be excluded. The injectable should be started immediately only if other methods are not appropriate or acceptable and the woman has been appropriately informed and advised to have a pregnancy test in ≥3 weeks. (Good Practice Point) - Following administration of levonorgestrel, women continuing to use a hormonal method of contraception should be advised to use additional contraceptive precautions for 7 days (2 days for POP, 9 days for Qlaira®). (Grade C) - Following administration of ulipristal, women continuing to use a hormonal method of contraception should be advised to use additional contraceptive precautions for 14 days (9 days for POP, 16 days for Qlaira). * Drug interactions: - Women taking liver enzyme-inducing drugs (or who have stopped taking this medication within the last 28 days) should be advised that a Cu-IUD is the only method of emergency contraception not affected by these drugs. (Grade A) - Women taking liver enzyme-inducing drugs, including post-exposure HIV

	prophylaxis after sexual exposure (or who have stopped within the last 28 days), and who decline or are not eligible for a Cu-IUD, should be advised to take a dose of 3 mg levonorgestrel (two Levonelle® tablets) as soon as possible within 120 hours of UPSI (outside the product license). The efficacy of levonorgestrel after 96 hours is uncertain. (Grade C) - Women taking liver enzyme-inducing drugs should be advised not to use ulipristal during or within 28 days of stopping taking this medication. (Grade C) - Women should be advised not to use ulipristal if they are currently taking drugs that increase gastric pH (e.g. antacids, histamine H_2 antagonists and proton pump inhibitors). (Grade C) * Side effects: - Women should be advised to seek medical advice if they vomit within 2 hours of taking levonorgestrel or 3 hours of ulipristal administration. A repeat dose of the same method or a Cu-IUD may be offered if appropriate.(Good Practice Point) - Women should be advised about menstrual disturbances after oral EC use. If there is any doubt about whether menstruation has occurred, a pregnancy test should be performed ≥3 weeks after UPSI has occurred. (Good Practice Point)

SOGC 2012 Emergency contraception	Grades of recommendation: A. There is good evidence to recommend the clinical preventive action B. There is fair evidence to recommend the clinical preventive action C. The existing evidence is conflicting and does not allow to make a recommendation for or against use of the clinical preventive action; however, other factors may influence decision-making D. There is fair evidence to recommend against the clinical preventive action E. There is fair evidence to recommend against the clinical preventive action L. There is insufficient evidence (in quantity or quality) to make a recommendation; however, other factors may influence decision-making
	Levels of evidence: I: Evidence obtained from at least one properly randomized controlled trial II-1: Evidence from well-designed controlled trials without randomization II-2: Evidence from well-designed cohort (prospective or retrospective) or case-control studies, preferably from more than one center or research group II-3: Evidence obtained from comparisons between times or places with or without the intervention. Dramatic results in uncontrolled experiments (such as the results of treatment with penicillin in the 1940s) could also be included in this category III: Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees
	Included populations, interventions, outcomes: - women who seek emergency contraception after unprotected sexual intercourse - emergency contraceptive pills, post-coital insertion of copper IUD - efficacy, pregnancy rate, return of menstruation, side effects

	Members of development group, target population: - gynecologists, obstetricians - health professionals
	Summary statements: - Hormonal emergency contraception may be effective if used up to 5 days after unprotected intercourse. (II-2) - The earlier hormonal emergency contraception is used, the more effective it is. (II-2) - A copper IUD can be effective emergency contraception if used within 7 days after intercourse. (II-2) - Levonorgestrel emergency contraception regimens are more effective and cause fewer side effects than the Yuzpe regimen. (I) - Levonorgestrel emergency contraception single dose (1.5mg) and the 2-dose levonorgestrel regimen (0.75mg 12h apart) have similar efficacy with no difference in side effects. (I) - Of the hormonal emergency contraception regimens available in Canada (same availability in Belgium), levonorgestrel is the drug of choice. (I) - A pregnancy that results from failure of emergency contraception need not be terminated. (I) Recommendations: - Emergency contraception should be used as soon as possible after unprotected sexual intercourse. (A) - Emergency contraception should be offered to women if unprotected intercourse has occurred within the time it is known to be effective (5d for hormonal methods and up to 7d for a Cu-IUD). (B) - Women should be evaluated for pregnancy if menses have not begun within 21 days following emergency contraception treatment. (A) - During physician visits for periodic health examinations or reproductive health concerns, any woman in the reproductive age group who has not been sterilized may be counseled about emergency contraception in advance with detailed information about how and when to use it. (C)

3.8. Conclusions from guidelines

3.8.1. Conclusions – Practical considerations

First choice among combined hormonal contraceptives?

Only one guideline makes an actual recommendation as to a first choice of combined hormonal contraceptive (Domus Medica 2012). They advise a combined pill with ≤35µg ethinylestradiol plus second generation progestogen (30µg ethinylestradiol + levonorgestrel most suitable).

Quick starting contraception

Two guidelines give recommendations on quick starting contraception. One guideline on emergency contraception advises to have a pregnancy test in ≥3 weeks after the start of contraception immediately after emergency contraception (FSRH 2012 Emergency). Another specific guideline on quick starting contraception (FSRH 2010 Start) agrees upon this. It also states that health professionals can start contraception immediately instead of waiting until the next period if the health professional is reasonably sure that a woman is not pregnant or at risk of pregnancy from recent unprotected sexual intercourse. If the preferred method of contraception is not available, combined hormonal contraception, progesterone-only pill or injectable can be used as a bridging method. When starting intrauterine methods health professionals should take particular care to exclude pregnancy. If starting hormonal contraception immediately after progesterone-only emergency contraception, condoms or avoidance of sex should be advised for 7 days (2 days for POPs, 9 days for Qlaira). If starting contraception immediately after ulipristal, condoms or avoidance of sex are recommended for 14 days (9 days if starting POP, 16 days for Qlaira).

Missed pill recommendations

There is no consensus between several “Missed pill guidelines”.
The SOGC 2008 guideline recommends that back-up contraception should be used after one missed pill in the first week of hormones until 7 consecutive days of correct hormone use are established. In the case of missed combined hormonal contraceptives in the second or third week of hormones, the hormone-free interval should be eliminated for that cycle. When three or more consecutive doses of combined hormonal contraceptives are missed in the second or third week, back-up contraception should be used until 7 consecutive days of correct hormone use are established. For practical reasons, the scheduled hormone-free interval should be eliminated in these cases. The FSRH 2011 guideline on missed pills and the Domus Medica 2012 guideline on hormonal contraception give similar recommendations on missed pills. If you miss one pill, you will still have contraceptive cover. However, if you miss two or more pills, you should use an extra method of contraception for the next 7 days; you may need emergency contraception or need to start the next pack of pills without a break.
The FSRH 2011 missed pill recommendations consider a pill has been missed when it is more than 24 hours since the time you should have taken it. Domus Medica considers a pill missed if taken more than 12 hours late.
The FSRH 2009 guideline on progestogen-only pills (FSRH 2009 POP) consider a missed pill if a traditional POP is more than 3 hours late or a desogestrel-only pill is more than 12 hours late. Then condoms (or abstinence from sex) should be used for 48 hours after the pill is taken.
If a woman vomits within 2 hours of pill taking, another pill should be taken as soon as possible.

Age: when to start or stop hormonal contraception?

In the guidelines addressing this subject, it is agreed that age alone should not limit contraceptive choices. Domus Medica 2012 (Hormonal contraception) advises to use condoms before menarche, combined contraceptive pills can be prescribed from menarche onwards. Contraception can be prescribed as long as women are sexually active but individual risk factors and wishes should be taken into account. Women older than 55 years are generally not fertile anymore. FSRH 2010-Contraceptive choices for young people (FSRH 2010 Young) states that even intrauterine contraceptive methods can be used in young people. Young people should be encouraged to return to a health professional at any time if they develop problems with contraception e.g. side effects or other concerns.

The FSRH 2010 guidelines on Contraception for women over 40y old (FSRH 2010 40+), give several recommendations on different types of contraception. Women using non-hormonal methods can be advised to stop contraception after 1 year of amenorrhea if aged over 50 years, or 2 years if the woman is aged under 50 years. In women using contraceptive hormones, FSH levels may be used to help diagnose the menopause but should be restricted to women over the age of 50 years and to those using progestogen-only methods. Women who have a copper intrauterine device inserted at or over the age of 40 years, can retain the device until menopause or until contraception is no longer required. In the case of the levonorgestrel-intrauterine system, inserted at the age of 45 years or over, it can be used for 7 years (off license) or until menopause.

Drug interactions

Six guidelines mention drug interactions with hormonal contraception. Generally they correspond on recommendations although there are some inconsistencies in which dose of COCs should be used when taking enzyme-inducing drugs. Domus Medica 2012 recommends using a COC containing at least 30 µg ethinylestradiol along with additional contraception, while the specific Drug interactions guideline of FSRH (FSRH 2010 Drugs) advises to increase the dose of COC to at least 50 µg ethinylestradiol (maximum 70 µg) and use an extended or tricycling regimen with a pill-free interval of 4 days.

The efficacy of progestogen-only contraceptives is not reduced with concurrent use of medication (including antibiotics and liver enzyme-inducing drugs).

Women on lamotrigine therapy should be advised that due to the risk of reduced seizure control whilst on COCs, and the potential for toxicity in the hormone-free week, the risks of using combined hormonal contraception may outweigh the benefits.

Ulipristal is not advised in women using enzyme-inducing drugs or drugs that increase the gastric pH, or who have taken them within the last 28 days. (They should be advised to take 3 mg levonorgestrel or even better: use a copper-IUD as emergency contraception.) Ulipristal also has the potential to reduce the efficacy of hormonal contraception. Additional precautions are advised for 14 days after taking ulipristal (9 days if using POPs, 16 days for the estradiol valerate/dienogest pill).

3.8.2. Conclusions - Non-contraceptive benefits

- **Dysmenorrhea and menorrhagia:** six guidelines (Domus Medica 2012, ACOG 2011, ACOG 2010 Noncontraceptive, FSRH 2009 POI, FSRH 2010 Young and FSRH 2010 40+) are inconclusive about which contraception to use in case of painful or heavy menstrual bleeding. Combined hormonal or progestogen-only contraception may improve these conditions.
- **Functional ovarian cysts:** there is inconsistency in the recommendations on which contraception to use when women have ovarian cysts. Two guidelines (Domus Medica 2012, ACOG 2010 Noncontraceptive) claim that combined oral contraception should not be used to treat existing functional ovarian cysts; two other guidelines (FSRH 2012 combined, FSRH 2010 40+) suggest a reduction in the incidence of ovarian cysts in women using combined oral contraceptives. Yet two other guidelines (FSRH 2009 POP, FSRH 2009 POInj) regard ovarian cysts not as a restriction for the use of progestogen-only contraception.
- **Premenstrual syndrome:** only one guideline (ACOG 2010 Noncontraceptive) mentions this condition and reports that combined oral contraceptives have been shown to reduce premenstrual dysphoric disorder symptoms.
- **Fibromyomatosis:** three guidelines declare that combined oral contraceptives or progestogen-only contraception do not increase the risk of development of uterine fibroids and that there is no restriction in the use of hormonal contraception in case of such fibroids. (FSRH 2009 POP, FSRH 2009 POInj, ACOG 2010 Noncontraceptive)
- **Endometriosis:** five guidelines mention endometriosis but there is a lack of data on which to draw firm conclusions. Progestogen-only contraceptives or low-dose COCs can improve the pain associated with endometriosis. (FSRH 2009 POP, FSRH 2009 POInj, FSRH 2009 POI, FSRH 2010 40+, FSRH 2012 combined)
- **Mastodynia:** there is no information on breast pain in the guidelines.
- **Acne:** four guidelines recommend the use of combined oral contraception for acne. (Domus Medica 2012, ACOG 2010 Noncontraceptive, FSRH 2012 Combined, FSRH 2010 Young) Two guidelines mention acne as a common side effect of progestogen-only contraception. With this kind of contraception, acne may improve, occur or worsen. (ACOG 2011, FSRH 2009 POI)
- **Cycle control:** one guideline (FSRH 2012 Combined) says that COCs usually reduce menstrual bleeding. Four guidelines inform progestogen-only users that the bleeding pattern may alter: they can experience infrequent, frequent or prolonged bleeding. Spotting is common during progestogen-only injectable use but most women become amenorrheic within the first year of use.(FSRH 2009 POP, FSRH 2009 POInj, FSRH 2009 POI, FSRH 2010 40+)

3.8.3. Conclusions - Special situations

- **Post-partum:** three guidelines mention post-partum situation (Domus Medica 2012, FSRH 2009 POInj, RCOG 2010) and they all agree on the recommendation that in the first 21 days after child birth no contraception is needed. After that time, combined oral contraception or any other form of contraception should be initiated in non-breastfeeding women. In breastfeeding women, COCs are not recommended in the first six weeks after child birth. POPs however, have no negative influence on milk production and can be used safely.
- **Post-abortum:** three guidelines mention situation after miscarriage or abortion (FSRH 2009 POP, FSRH 2009 POInj, ACOG 2011) and they agree to start contraception immediately, or at least within 5 days post-abortum.
- **Diabetes:** only one guideline (Domus Medica 2012) mentions women with diabetes; diabetics with nefropathy, retinopathy, neuropathy or other vascular complications is an absolute contra indication for combined contraceptive pills.
- **Migraine:** five guidelines agree that migraine with aura is a condition for which the use of combined hormonal contraception presents an unacceptable health risk. (Domus Medica 2012, FSRH 2012 Combined, FSRH 2009 POP, FSRH 200p POI, FSRH 2010 40+) Progesterone-only contraception can be safely used by migraine patients with aura.
- **Smoking:** three guidelines recommend (strongly) against taking combined hormonal contraception in women aged ≥35 years who are smoking (or have stopped smoking less than one year ago). In smokers younger than 35 years POPs, IUD, implant or sterilisation can be used as contraception. (Domus Medica 2012, FSRH 2012 Combined, FSRH 2010 40+)
- **Surgery:** two guidelines (Domus Medica 2012, RCOG 2010) give recommendations for patients who need surgery. For major surgery combined hormonal contraception should be discontinued at least 4 weeks before surgery where immobilization is expected but not in the case of minor surgery.
- **Coagulopathy/VTE:** two guidelines (Domus Medica 2012, RCOG 2010) state that coagulation disorders and current or past arterial or venous thromboembolism are absolute contra indications for COCs. Progesterone-only contraception is safe to use in such conditions.
- **Cardiovascular diseases:**

Two guidelines (Domus Medica 2012, FSRH 2012 Combined) regard arterial hypertension ≥90/160mmHg as an absolute contraindication for COCs. Progestogen-only contraception does not appear to increase the risk of stroke or myocardial infarct (FSRH 2010 40+) yet Domus Medica does not recommend progesterone injections in women with a history of stroke or ischemic heart disease. All guidelines advise against the use of combined hormonal contraception in women with cardiovascular disease, stroke or migraine with aura.

3.8.4. Conclusions - Emergency contraception

Three guidelines (Domus Medica 2012, ACOG 2010 Emergency and SOGC 2012) recommend levonorgestrel 1.5 mg as first choice emergency contraception (within 3 days postcoitus). Alternatives are the copper-bearing intrauterine device and ulipristal acetate (within 5 days postcoitus).
The time frame differs in a few guidelines: SOGC 2012 Emergency contraception says that a copper-IUD can be effective emergency contraception if used within 7 days after unprotected sexual intercourse, whereas the other guidelines (Domus Medica 2012, ACOG 2010 Emergency, FSRH 2012 Emergency) state that it can be inserted up to 5 days postcoitus.
The FSRH 2012 guideline on Emergency contraception advises women continuing to use a hormonal method of contraception following administration of levonorgestrel, to use additional contraceptive precautions for 7 days (2 days for POP, 9 days for Qlaira). In the case of ulipristal , the additional contraceptives should be taken for 14 days (9 days for POP, 16 days for Qlaira).

4. Evidence tables and conclusions: Hormonal contraception: efficacy and safety

4.1. Combined hormonal contraception

4.1.1. Combined oral contraception: comparison of different progestogens: Evidence tables

4.1.1.1.Combined oral contraceptive with Gestodene vs combined oral contraceptive with Levonorgestrel (monophasic)

Ref	N/n	Comparison	Outcomes	
* Lawrie 2011 Design: SR +/- MA N= 30 n= 13923 Search date: March 2011	N=2 n=849	COC Gestodene vs COC Levonorgestrel (monophasic)	Pregnancy (N=2 : Loudon, 1990 ; Rabe, 1989)	0/405 (GSD) vs 0/412 (LNG) RR=0.00 (95% CI 0.0, 0.0) NS
			Discontinuation (N=2 : Loudon, 1990 ; Rabe, 1989)	40/405 (GSD) vs 61/412 (LNG) RR= 0.66 (95% CI 0.41, 1.05) NS p=0.078
			Reasons for discontinuation (N=1; Loudon, 1990)	side-effects (other than cycle disturbances) 16/229 (GSD) vs 18/227 (LNG) RR= 0.88 (95% CI 0.46, 1.68) NS p=0.70
				other medical reasons 4/229 (GSD) vs 5/227 (LNG) RR= 0.79 (95% CI 0.22, 2.92) NS p=0.73
				lost to follow-up 4/229 (GSD) vs 5/227 (LNG) RR= 0.79 (95% CI 0.22, 2.92) NS p=0.73
				method unrelated 4/229 (GSD) vs 7/227 (LNG) RR= 0.57 (95% CI 0.17, 1.91) NS p=0.57
			Cycle control (N=2 : Loudon, 1990 ; Rabe, 1989)	**intermenstrual bleeding (Loudon, 1990)** **70/229 (GSD) vs 98/227 (LNG)** **RR= 0.71 (95% CI 0.55, 0.91)** **SS in favour of gestodene p=0.0059**
				Spotting (Loudon, 1990) 47/229 (GSD) vs 42/227 (LNG) RR= 1.11 (95% CI 0.76, 1.61)

				NS p=0.59
				breakthrough bleeding (Loudon, 1990) 12/229 (GSD) vs 18/227 (LNG) RR= 0.66 (95% CI 0.33, 1.34) NS p=0.25
				absence of withdrawal bleed (Loudon, 1990 ; Rabe, 1989) 12/405 (GSD) vs 18/412 (LNG) RR= 0.78 (95% CI 0.38, 1.59) NS p=0.49
				abnormal cycles (Loudon, 1990) 90/229 (GSD) vs 102/227 (LNG) RR= 0.87 (95% CI 0.70, 1.09) NS p=0.22

* Characteristics of included studies: see under

Ref + design	n	Population	Duration	Comparison	Methodology
Loudon 1990 Randomized double blind trial	488	Women (UK) -aged 16-35 years -requesting oral contraception studied over 6 cycles, -standard contraindications being applied. Post-partum women excluded unless menstruation established for at least 2 cycles. 54% reported past OC use in each group. Exclusion criteria: women less than 16 years, DBP > 90 mm, amenorrhoea, medical contraindications to OC use.	6 cycles	Monophasic gestodene 75mcg / EE 30mcg vs monophasic levonorgestrel 150mcg /EE 30mcg 28-day cycles with 21 active pills and 7 days of no tablet taking	- Jadad score: 3/5 - FU: 80.5% completed the study and 1.97% lost to FU - ITT:no Other important methodological remarks: - Allocation concealment not described Sponsor: Not stated
Rabe 1989 Open randomized trial	361	Characteristics of participants, inclusion and exclusion criteria not mentioned. (across 5 European countries)	6 cycles	Monophasic gestodene 75mcg / EE 30mcg vs monophasic levonorgestrel 150mcg /EE 30mcg	- Jadad score: 2/5 - FU: 89.5% completed the study (and 10.5% lost to FU) - ITT: yes Other important methodological remarks: - Allocation concealment not described - Data for spotting and break through bleeding is presented according to cycles Sponsor: SCHERING AG

4.1.1.2. Combined oral contraceptive containing Desogestrel vs combined oral contraceptive containing Levonorgestrel (monophasic)

Ref	N/n	Comparison	Outcomes	
* Lawrie 2011 Design: SR +/- MA N= 30 n= 13923 Search date: March 2011	N=1 n=1027	COC Desogestrel vs COC Levonorgestrel (monophasic) (N=1 ; Winkler 2004)	Pregnancy	1/500 (DSG) vs 1/498 (LNG) RR=1.00 (95% CI 0.06, 15.88) NS p=1.0
			Discontinuation	96/500 (DSG) vs 114/498 (LNG) RR=0.84 (95% CI 0.66, 1.07) NS p=0.15
			Reasons for discontinuation	Pregnancy or desire for pregnancy 1/500 (DSG) vs 1/498 (LNG) RR=1.00 (95% CI 0.06, 15.88) NS p=1.0
				loss to follow-up 0/500 (DSG) vs 3/498 (LNG) RR=0.14 (95% CI 0.01, 2.75) NS p=0.20
				side effects (including cycle disturbance) **10/500 (DSG) vs 25/498 (LNG)** **RR=0.40 (95% CI 0.19, 0.82)** **SS in favour of DSG p=0.013**
				cycle disturbance 3/500 (DSG) vs 10/498 (LNG) RR=0.30 (95% CI 0.08, 1.08) NS p=0.065
			Side-effects	Breast tenderness 1/500 (DSG) vs 3/498 (LNG) RR=0.33 (95% CI 0.03, 3.18) NS p=0.34
				Headache 33/500 (DSG) vs 22/498 (LNG) RR=1.49 (95% CI 0.88, 2.53) NS p=0.13
				Migraine 1/500 (DSG) vs 2/498 (LNG) RR=0.50 (95% CI 0.05, 5.47)

				NS p=0.57 nausea/vomiting 0/500 (DSG) vs 1/498 (LNG) RR=0.33 (95% CI 0.01, 8.13) NS p=0.50

* Characteristics of included studies: see under

Ref + design	n	Population	Duration	Comparison	Methodology
Winkler 2004 Open randomised clinical trial	1027	healthy women (Germany and the Netherlands) -aged 18-45 -BMI between 18 and 29kg/m2. Excluded if: menses <24 days or >35 days; >35 and a smoker; use of concomitant or addictive drugs; mental disorder including depression; use of OC, IUD or implant within 1 month or depot injection within 6 months of enrolment. Overall, more pill switchers (59%) than pill starters (41%)	6 cycles. Washout period of one cycle	Monophasic DSG 150µg/EE20µg vs. monophasic LNG/EE 100µg/EE 20µg	- Jadad score:3/5 - FU: 76.7% completed the study - ITT: not clear Other important methodological remarks: -Allocation concealment not described - Published data and unpublished data/information obtained from authors. -Incomplete outcome cycle control data; more than 20% of cycle control data is missing ==> not included in Cochrane analysis - Possible selective reporting of reasons for discontinuation. 210/998 women discontinued the trial, only 35 of these women discontinued due to side effects, 54 were 'not willing to continue', eleven discontinued due to 'poor compliance' and 83 women discontinued for 'other' reasons. This lack of detail suggests selective or under-reporting of side-effects. Sponsor: NV ORGANON

4.1.1.3. Combined oral contraceptive containing Gestodene (Triphasic) vs combined oral contraceptive containing Norethindrone (= norethisterone) (triphasic)

Ref	N/n	Comparison	Outcomes	
* Lawrie 2011 Design: SR +/- MA N= 30 n= 13923 Search date: March 2011	N=1 n= 254	COC Gestodene vs COC Norethindrone (triphasic) (N=1 ; Weber-Diehl 1993)	Pregnancy	0/114 (GSD) vs 0/115 (NET) RR=0.00 (95% CI 0.0, 0.0) NS
			Discontinuation	16/114 (GSD) vs 27/115 (NET) RR=0.60 (95% CI 0.34, 1.05) NS p= 0.072
			Cycle control	**Spotting** **18/114 (GSD) vs 31/115 (NET)** **RR=0.59 (95% CI 0.35, 0.99)** **SS in favor of GSD p= 0.044**
				breakthrough bleeding 22/114 (GSD) vs 34/115 (NET) RR=0.65 (95% CI 0.41, 1.04 NS p= 0.075

* Characteristics of included studies: see under

Ref + design	n	Population	Duration	Comparison	Methodology
Weber-Diehl 1993 Open randomised clinical trial	254	Women (Germany) -aged 16 to 50 years. Inclusion, exclusion criteria not mentioned.	12 cycles	Triphasic Gestodene 50/70/100mcg+EE 30/40/30mcg vs triphasic Norethindrone 500/750/1000 mcg+ EE 35/35/35 mcg.	- Jadad score:2-3/5 - FU: 71.7% completed the study and 9.8% lost to FU - ITT: no Other important methodological remarks: -Allocation concealment not described - Figures for side-effects given as % in graphic form. Sponsor: Schering AG

4.1.1.4.. Combined oral contraceptive containing Gestodene vs combined oral contraceptive containing Desogestrel (monophasic)

Ref	N/n	Comparison	Outcomes	
* Lawrie 2011 Design: SR +/- MA N= 30 n= 13923 Search date: March 2011	N=7 n=5634	COC Gestodene vs COC Desogestrel (monophasic) (N=7)	Pregnancy (N=7)	10/2802 (GSD) vs 5/2822 (DSG) RR=1.85 (95% CI 0.64, 5.32) NS p=0.26
			Discontinuation (N=7)	534/2802 (GSD) vs 477/2822 (DSG) RR=1.11 (95% CI 1.00, 1.24) NS p=0.052
			Reasons for discontinuation	cycle disturbances (N=5) 17/1509 (GSD) vs 19/1536 (DSG) RR=0.93 (95% CI 0.48, 1.81) NS p=0.83
				Pregnancy (N=5) 7/1756 (GSD) vs 4/1778 (DSG) RR=1.77 (95% CI 0.51, 6.09) NS p=0.37
				side-effects (other than cycle disturbances) (N=5) **101/1756 (GSD) vs 60/1778 (DSG)** **RR=1.81 (95% CI 1.01, 3.23)** **SS p=0.045 in favor of DSG**
				other medical reasons (N=5) 37/1509 (GSD) vs 26/1536 (DSG) RR=1.28 (95% CI 0.48, 3.39) NS p=0.62
				lost to follow-up (N=4) 39/1383 (GSD) vs 45/1421 (DSG) RR=0.90 (95% CI 0.59, 1.37) NS p=0.61
				method unrelated (N=5) 58/1509 (GSD) vs 53/1536 (DSG) RR=1.01 (95% CI 0.76, 1.59) NS p=0.60
			Cycle control	spotting EE< 30mcg (N=1) 231/786 (GSD) vs 258/777 (DSG) RR=0.89 (95% CI 0.76, 1.03) NS p=0.10

				spotting EE = 30mcg (N=2) 28/565 (GSD) vs 43/570 (DSG) RR=0.70 (95% CI 0.37, 1.32) NS p=0.27
				breakthrough bleeding EE < 30 mcg(N=1) 46/786 (GSD) vs 56/777(DSG) RR=0.81 (95% CI 0.56, 1.18) NS p=0.28
				breakthrough bleeding EE = 30mcg (N=2) 15/565 (GSD) vs 20/570 (DSG) RR=0.76 (95% CI 0.39, 1.47) NS p=0.41
				absence of withdrawal bleed EE = 30mcg (N=1) 3/126 (GSD) vs 1/115 (DSG) RR=2.74 (95% CI 0.29, 25.95) NS p=0.38
				other menstrual problems (dysmenorrhoea) (N=2) 100/1325 (GSD) vs 97/1312(DSG) RR=1.08 (95% CI 0.64, 1.83) NS p=0.77
			Side-effects	breast tenderness (N=4) 149/1890(GSD) vs 167/1882(DSG) RR=0.77 (95% CI 0.50, 1.18) NS p=0.23
				Headache (N=3) 327/1714(GSD) vs 296/1706(DSG) RR=1.09 (95% CI 0.95, 1.25) NS p=0.24
				nausea/vomiting (N=4) 195/1890(GSD) vs 193/1882(DSG) RR=1.00 (95% CI 0.83, 1.21) NS p=0.98
				Nervousness (N=1) 28/786GSD) vs 36/777(DSG) RR=0.77(95% CI 0.47, 1.25) NS p=0.29

				others (vaginal discharge) (N=1) 6/176(GSD) vs 7/176(DSG) RR=0.86 (95% CI 0.29, 2.50) NS p=0.78
			Side-effects leading to discontinuation	breast tenderness (N=2) 8/665(GSD) vs 5/650(DSG) RR=1.19 (95% CI 0.01, 186.49) NS p=0.95
				Headache (N=3) 9/841(GSD) vs 11/826(DSG) RR=0.82 (95% CI 0.32, 2.10) NS p=0.69
				Migraine (N=1) 1/176(GSD) vs 0/176(DSG) RR=3.00 (95% CI 0.12, 73.14) NS p=0.67
				nausea/vomiting (N=3) 10/841(GSD) vs 7/826(DSG) RR=1.36 (95% CI 0.21, 9.03) NS p=0.75
				Nervousness (N=1) 2/176(GSD) vs 1/176(DSG) RR=2.00 (95% CI 0.18, 21.86) NS p=0.57
				Acne (N=2) 2/302(GSD) vs 0/291(DSG) RR=2.87 (95% CI 0.30, 27.40) NS p=0.36
				Weight gain (N=1) 1/176(GSD) vs 0/176(DSG) RR=3.00 (95% CI 0.12, 73.14) NS p=0.50

* Characteristics of included studies: see under

Ref + design	n	Population	Duration	Comparison	Methodology
Endrikat 1999	1563	Women (123 centres across 6 European countries) -18 to 35 years -willing for contraception for at least 12 months. Exclusion criteria: previous use of DSG/EE in this dose; known contraindication to OC use; use of injectables with in 6 months; genital pathology, bleeding not diagnosed, and migraine with menses and specific concomitant pathology	12 cycles	Monophasic gestodene 75 mcg+EE20 mcg versus monophasic desogestrel 150 mcg+EE20 mcg;	- Jadad score: 2/5 - FU: 71.3% completed the study and unclear lost to FU - ITT: yes Other important methodological remarks: -Technique of allocation concealment unclear -Random sequence generation unclear Sponsor: SCHERING AG
GSD Group 1999	1074	Healthy women (61 centres in Europe) -aged >18 years, -menstruating regularly -and not breast feeding Exclusion Criteria: smokers>36 years, history of thromboembolic disease, cardiovascular or cerebrovascular disease, abnormal pap smear,breast feeding and using concomitant medication which would interfere with study. There were comparable number of starters and switchers in each group. T here is no mention of a washout period. Work up at admission involved medical, obstetric and gynaecological history and examination,and pap smear testing	6 cycles	Monophasic gestodene 60 mcg/EE15 mcg given for 24 days versus monophasic desogestrel 150mcg/ EE20mcg given for 21 days. In this trial the oestrogen dose was 15 µg in GSD and 20 µg in the DSG group and so the data for cycle disturbances were not included in the meta-analysis.	- Jadad score: 2/5 - FU: 89.3% ended and 1.86% lost to FU - ITT:yes Other important methodological remarks: -Technique of allocation concealment unclear Sponsor: WYETH AYERST
Halbe 1998	595	women (Brazil) -at reproductive age -with regular menstrual cycles. Study setting is not mentioned.	6 cycles	Monophasic desogestrel 150 mcg+EE 30 mcg vs monophasic gestodene 75mcg+EE30 mcg	- Jadad score:2/5 - FU: 84,2% completed the study and 2.68% lost to FU - ITT: yes Other important methodological

		Exclusion criteria: Contraindication OC use, complete breast feeding and women on medication known to interact with OCs. Both starters (65%) and switchers(35%) were included No period of washout was given for the switchers			remarks: -Technique of allocation concealment unclear -The data on cycle control is expressed as subjects per cycle, rather than as overall subjects experiencing menstrual irregularities; therefore these data has not been included Sponsor: ORGANON NV
Koetsawang 1995	783	Healthy women (Thailand) -mean age of 26 years - regular menstrual cycles of at least 24 days. Exclusion criteria: known contraindications to OC use, use of medication and currently breast feeding. Work up included detailed medical history and physical exam.	6 cycles.	Monophasic desogestrel 150 mcg+EE 30 mcg versus monophasic gestodene 75 mcg+EE 30 mcg.	- Jadad score: 2/5 - FU: 86.8% completed the study and 5.5% lost to FU - ITT: not clear Other important methodological remarks: -Technique of allocation concealment unclear -Random sequence generation unclear Sponsor: ORGANON NV
L. America 1994	352	Women (Argentina, Brazil, Chile, Columbia, Venezuela) -age group 18-41 years seeking contraception, -sexually active, -non-nursing, 12 women in the gestodene group and 24 in the desogestrel group were switchers from other OCs. Exclusion criteria: women with thrombo-embolic disease, liver disease, oestrogen dependant neoplasia, disorders of lipid metabolism, other known contraindication to OCs	6 cycles	monophasic gestodene 75mcg / EE 30 mcg vs monophasic desogestrel 150mcg/ EE 30 mcg.	- Jadad score: 2/5 - FU: 91.8% completed the study and unclear % lost to FU - ITT: yes Other important methodological remarks: -Technique of allocation concealment unclear Sponsor: WYETH-AYERST

Serfaty 1998	1026	healthy women (52 centres in France) -aged 18-45, -sexually active -with regular cycles, -with normal lipid, and carbohydrate profiles -BMI within 18 to 29. Exclusion criteria: known contraindication to OC use, smokers >35 years, less than 2 months postpartum, use of injectable contraceptive within 6 months prior to study. Both starters and switchers were included.	6 cycles	monophasic desogestrel 150 mcg/ EE20mcg vs monophasic gestodene 75 mcg/ EE20mcg	- Jadad score: 2/5 - FU: 81.3% completed the study and unclear% lost to FU - ITT: no Other important methodological remarks: -Technique of allocation concealment unclear - Data on cycle control in graphical format from which it is not possible to deduce figures Sponsor: ORGANON NV
Zichella 1999	241	women (5 centres in Italy) -aged 18 to 40 - regular cycles -with no contraindication to OC use. All women were starters. Exclusion Criteria: history of thromboembolic disease, thrombophlebitis, jaundice in pregnancy, oestrogen dependant carcinomas, Diabetes Mellitus or impaired glucose tolerance, breast feeding and no history of OC use in preceding 3 months. A baseline history and medical examination was performed. All women were starters	6 cycles	Monophasic desogestrel 150 mcg/EE30mcg versus monophasic gestodene 75 mcg/EE30mcg	- Jadad score: 1-2/5 - FU: 84.2% completed the study and unclear% lost to FU - ITT: yes Other important methodological remarks: -Technique of allocation concealment unclear -Data on cycle control given in graphical form. Similarly the side effects are reported as percentages for cycles 1, 3 and 6 and have not been included in review. Sponsor: ORGANON NV

4.1.1.5. Combined oral contraceptive containing Gestodene vs combined oral contraceptive containing Norgestimate (monophasic)

Ref	N/n	Comparison	Outcomes	
* Lawrie 2011 Design: SR +/- MA N= 30 n= 13923 Search date: March 2011	N=1 n=189	COC Gestodene vs COC Norgestimate (monophasic) (N=1; Affinito 1993)	Pregnancy	0/91 (GSD) vs 0/83 (NGM) RR=0.00 (95% CI 0.0, 0.0) NS
			Discontinuation	6/91 (GSD) vs 9/83 (NGM) RR=0.61 (95% CI 0.23, 1.64) NS p=0.32
			Reasons for discontinuation.	cycle disturbances 0/91 (GSD) vs 0/83 (NGM) RR=0.00 (95% CI 0.0, 0.0) NS
				Pregnancy 0/91 (GSD) vs 0/83 (NGM) RR=0.00 (95% CI 0.0, 0.0) NS
				side-effects (other than cycle disturbances) 3/91 (GSD) vs 2/83 (NGM) RR=1.37 (95% CI 0.23, 7.99) NS p=0.73
				lost to follow-up 0/91 (GSD) vs 0/83 (NGM) RR=0.00 (95% CI 0.0, 0.0) NS
				other medical reasons 0/91 (GSD) vs 0/83 (NGM) RR=0.00 (95% CI 0.0, 0.0) NS
				method unrelated 3/91 (GSD) vs 6/83 (NGM) RR=0.46 (95% CI 0.12, 1.77) NS p=0.26
			Side-effects	breast tenderness 3/91 (GSD) vs 8/83 (NGM) RR=0.34 (95% CI 0.09, 1.25) NS p=0.10

				Headache 5/91 (GSD) vs 2/83 (NGM) RR=2.28 (95% CI 0.45, 11.44) NS p=0.32
				nausea/vomiting 4/91 (GSD) vs 2/83 (NGM) RR=1.82 (95% CI 0.34, 9.70) NS p=0.48
				other minor 5/91 (GSD) vs 8/83 (NGM) RR=0.46 (95% CI 0.19, 1.67) NS p=0.31

* Characteristics of included studies: see under

Ref + design	n	Population	Duration	Comparison	Methodology
Affinito 1993	189	Women (Italy) -in the age group 16 to 38 (if smokers then less than 35 years) using standard inclusion criteria, -history of at least 3 regular cycles, Exclusion criteria: excessive alcohol consumption, PAP smear > grade 3, SBP > 140 mmHg, DBP > 90, drug abuse, abnormal blood tests. Work-up at admission included gynaecological history, breast and cervical smear examination, medical and gynaecological examination	6 cycles	Monophasic gestodene 75 mcg+ EE 30 mcg versus monophasic norgestimate 250 mcg+ EE 35 mcg.	- Jadad score: 2/5 - FU: 91.4% completed the study and 7.93% lost to FU - ITT: not clear Other important methodological remarks: -Cycle control analysis is not included in the review as it uses the number of cycles in the denominator. Sponsor: WYETH-AYERST

4.1.1.6. Combined oral contraceptive containing Drospirenone vs combined oral contraceptive containing Levonorgestrel (monophasic)

Ref	N/n	Comparison	Outcomes	
* Lawrie 2011 Design: SR +/- MA N= 30 n= 13923 Search date: March 2011	N=3 n= 648	COC Drospirenone vs COC Levonorgestrel (monophasic),	Pregnancy (N=1 ; Suthipongse2004)	0/58 (DRSP) vs 0/57 (LNG) RR=0.00 (95% CI 0.0, 0.0) NS
			Discontinuation (N=2 ; Kelly 2010 ; Suthipongse2004)	91/342 (DRSP) vs 58/202 (LNG) RR=0.81 (95% CI 0.62, 1.06) NS p=0.12
			Reasons for discontinuation. (N=2 ; Kelly 2010 ; Suthipongse 2004)	Pregnancy or desire for pregnancy (N=1; Suthipongse2004) 0/58 (DRSP) vs 1/58 (LNG) RR=0.33 (95% CI 0.01, 8.02) NS p=0.50
				Loss to follow-up (N=2 ; Kelly 2010 ; Suthipongse 2004) 16/342 (DRSP) vs 15/202 (LNG) RR=0.59(95% CI 0.30, 1.16) NS p=0.12
				side effects (including cycle disturbance) (N=1 ; Kelly 2010) 14/282(DRSP) vs 13/142 (LNG) RR=0.54 (95% CI 0.26, 1.12) NS p=0.099
			Cycle control. (N=1 ; Kelly 2010)	intermenstrual bleeding 33/282(DRSP) vs 19/142 (LNG) RR=0.87 (95% CI 0.52, 1.48) NS p=0.62
			Side-effects (N=1 ; Kelly 2010)	breast tenderness 0/282(DRSP) vs 0/142 (LNG) RR=0.00 (95% CI 0.0, 0.0) NS
				Headache 35/282(DRSP) vs 15/142 (LNG) RR=1.17(95% CI 0.66, 2.08) NS p=0.58
				Migraine 8/282(DRSP) vs 5/142 (LNG) RR=0.81(95% CI 0.27,2.42) NS p=0.70

				nausea/vomiting 12/282(DRSP) vs 4/142 (LNG) RR=1.51(95% CI 0.50, 4.60) NS p=0.47
				Total 55/1128(DRSP) vs 24/568 (LNG) RR=1.15(95% CI 0.72, 1.82) NS p=0.56

* Characteristics of included studies: see under

Ref + design	n	Population	Duration	Comparison	Methodology
Kelly 2010	424	women -aged 16-40 (35yrs maximum for smokers) -having regular cycles and -requesting contraception; on no other hormonal treatment during the study (except for thyroxin and insulin). Excluded if there were contraindications to COC including a history of herpes, obesity or concurrent treatment with hepatic enzyme-inducing drugs. Two thirds of participants were COC switchers Baseline characteristics similar	7 cycles	Monophasic DRSP 3mg/EE 30µg versus monophasic LNG 150µg/EE 30µg	- Jadad score: 3-4/5 - FU: 66% ended the study and 6,4% lost to FU (high drop-out rate) - ITT: yes Other important methodological remarks: - Allocation concealed with the use of envelopes but not from the principle investigator - Report fails to include key cycle control data. Limited unpublished cycle control data obtained from authors Sponsor: BAYER-SCHERING AG
Suthipongse 2004	120	Women (Thailand) -aged 16-35 -requesting contraception. -no injectables or OCs within 6 months of	7 cycles	Monophasic DRSP 3mg/EE 30µg versus monophasic LNG 150µg/EE 30µg	- Jadad score: 2/5 - FU: 95.8% ended the study and 3.3%% lost to FU - ITT: no

		study; -minimum of three normal regular cycles following implant or IUD removal or abortion or delivery. Excluded if suspected pregnancy; breastfeeding or contraindication to COCs. All pill starters, no switchers. Started on the first day of menses.		Little data to contribute. Unpublished information requested fromauthors but not obtained	Other important methodological remarks: -Technique of allocation concealment unclear Sponsor: No sponsor declared. No conflict of interests declared.
Sangthawan 2005	104	Women (Bangkok, Thailand) -18-35 years -requesting COC for at least 6 months, -regular cycles lasting 21-35 days, -no injectables within 6 months and no OCs within 3 months of the study, 3 consecutive normal periods after the removal of contraceptive implant or IUD or post-abortion or delivery. Excluded if pregnancy or suspected pregnancy, breastfeeding,smokers, and if contraindications according to WHO categories 2, 3, 4	6 cycles	Monophasic DRSP 3mg/EE 30µg versus monophasic LNG/EE 30µg OnlyPremenstrual symptoms. Little usable data. Additional unpublished information sought but not obtained	- Jadad score: 2/5 - FU: unclear, 2.9% Lost to FU - ITT: unclear Other important methodological remarks: -Technique of allocation concealment unclear Sponsor: No sponsor declared.

4.1.1.7. Combined oral contraceptive containing Drospirenone vs combined oral contraceptive containing Desogestrel (monophasic)

Ref	N/n	Comparison	Outcomes	
* Lawrie 2011 Design: SR +/- MA N= 30 n= 13923 Search date: March 2011	N=6 n=4742	COC Drospirenone vs COC Desogestrel (monophasic),	Pregnancy (N=6)	18/3013 (DRSP) vs 10/1402 (DSG) RR=0.95 (95% CI 0.39, 2.33) NS p=0.91
			Discontinuation (N=6)	632/3174 (DRSP) vs 294/1531 (DSG) RR=1.06 (95% CI 0.93, 1.20) NS p=0.40
			Reasons for discontinuation.	cycle disturbances (N=3 ; Anttila 2009, Foidart 2000, Gruber 2006) 16/891 (DRSP) vs 15/886 (DSG) RR=1.05 (95% CI 0.52, 2.14) NS p=0.89
				Pregnancy or desire for pregnancy (N=4; Anttila 2009, Gruber 2006, Guang-Sheng 2010, Huber 2000) 48/2702 (DRSP) vs 15/1055 (DSG) RR=0.94 (95% CI 0.51, 1.70) NS p=0.83
				Loss to follow-up (N=4; Anttila 2009, Gruber 2006, Guang-Sheng 2010, Huber 2000) 54/2703 (DRSP) vs 20/1057 (DSG) RR=1.14 (95% CI 0.66, 1.98) NS p=0.63
				method unrelated (N=2; Huber 2000; Kriplani 2010) 154/1710 (DRSP) vs 38/448 (DSG) RR=1.02 (95% CI 0.73, 1.44) NS p=0.90
				side effects (including cycle disturbance) (N=5; Anttila 2009, Gruber 2006, Guang-Sheng 2010, Huber 2000; Kriplani 2010) 222/2732(DRSP) vs 65/1086 (DSG) RR=1.24(95% CI 0.87, 1.76) NS p=0.23
				Reason not specified (N=3; Anttila 2009, Gruber 2006, Guang-Sheng 2010) **15/1022(DRSP) vs 24/638 (DSG)** **RR=0.51 (95% CI 0.26, 0.99)**

				SS in favor of DRSP p=0.048
			Cycle control.	intermenstrual bleeding(N=2; Gruber 2006, Huber 2000) 523/1900 (DRSP) vs 142/639 (DSG) RR=0.97 (95% CI 0.83, 1.14) NS p=0.71
			Side-effects	breast tenderness (N=5; Anttila 2009, Foidart 2000, Guang-Sheng 2010, Huber 2000; Kriplani 2010) **174/2953 (DRSP) vs 63/1305 (DSG)** **RR=1.39 (95% CI 1.04, 1.86)** **SS in favor of DSG p=0.028**
				Headache (N=5; Anttila 2009, Foidart 2000, Guang-Sheng 2010, Huber 2000; Kriplani 2010) 229/2400(DRSP) vs 108/1334 (DSG) RR=1.48 (95% CI 0.68, 3.22) NS p=0.32
				Migraine (N=3; Foidart 2000, Gruber 2006, Huber 2000;) 45/2342(DRSP) vs 19/1084 (DSG) RR=0.95 (95% CI 0.55, 1.64) NS p=0.86
				nausea/vomiting (N=6) 122/3173(DRSP) vs 40/1528(DSG) RR=1.46 (95% CI 0.96, 2.21) NS p=0.074
				other minor (abdominal pain) (N=4; Foidart 2000, Guang-Sheng 2010, Huber 2000, Kriplani 2010) 60/2724(DRSP) vs 31/1087(DSG) RR=0.91 (95% CI 0.58, 1.44) NS p=0.68
				Depression (N=2; Foidart 2000, Gruber 2006) 7/662(DRSP) vs 7/666(DSG) RR=0.96 (95% CI 0.25, 3.73) NS p=0.95
				Alopecia (N=1; Gruber 2006) 3/220(DRSP) vs 1/221(DSG) RR=3.01 (95% CI 0.32, 28.75) NS p=0.34

				Dizziness (N=1 Guang-Sheng 2010) 7/573(DRSP) vs 2/195(DSG) RR=1.19 (95% CI 0.25, 5.69) NS p=0.83

* Characteristics of included studies: see under

Ref + design	n	Population	Duration	Comparison	Methodology
Anttila 2009	453	Healthy women (from centres in Austria, Finland, Lithuania and Estonia) -aged 18-35 years (30 years for smokers) Excluded criteria were: contraindication to COC use, pregnancy, BMI>30, lactation or abortion within 3 months, hypersensitivity to study drug, suspicious cervical smear within 6months, use of DSG,DRSP or IUS/IUD within 1 cycle of treatment, use of depot contraception within last 6 cycles before start of treatment. Approximately 55% were switchers.	7 cycles	Monophasic DRSP 3mg/EE 20µg (24 active tablets and 4 placebos) versus monophasic DSG 150µg/EE 20µg (21 active /7 placebos)	- Jadad score: 2-3/5 - FU: 86.5% completed the study and 1.1% lost to FU - ITT: yes Other important methodological remarks: -Technique of allocation concealment unclear -Denominators of data reported not clear. (attrition bias) -Discontinuation data not reported. Cycle control data presented in such a way that comparisons cannot be made and so were not used for this review Sponsor: BAYER-SCHERING AG
Foidart 2000	900	Healthy women (Europe : Belgium, Germany, NL). -between 18 to 35 years, , -menstruating and seeking OC use. Exclusion Criteria: obesity, liver, vascular and	26 months	Monophasic drospirenone 3 mg+EE30 mcg (Yasmin) versus monophasic desogestrel 150 mcg +EE30 mcg for 21 days	- Jadad score: 2/5 - FU: 69.2% completed the study - ITT: no Other important methodological remarks:

		metabolic disease, genital infection, use of diuretics or drugs known to affect hepatic enzymes. Both starters and switchers were included. Regular follow-up during study and for 3 months after completion			-Technique of allocation concealment unclear - Cycle control is given in terms of cycles rather than subjects and has therefore not been included. Sponsor: SCHERING
Gruber 2006	445	Healthy women (Italy, Belgium, the Czech Republic and the United Kingdom) -aged 15-35 years (excluding smokers over 30 years) Excluded if there were contraindications to COC use, use if depot contraceptives within 6 months of study, use of DSG or DRSP OC within one cycle of study; childbirth, abortion or lactation within three cycles of study or a suspicious cervical smear result	7 cycles	Monophasic DRSP 3mg/EE 20µg versus monophasic DSG150µg/EE 20µg. Treatment started on first day of menses or withdrawal bleed. Both had 21 active tablets and 7 Placebos Weight decreased in the DRSP group (-0.22kg (SD 2.25) vs +0.45kg (2.94) in the DSG group.	- Jadad score: 2-3/5 - FU: 86.7% completed the study and 2.9% lost to FU - ITT: yes Other important methodological remarks: -No allocation concealment -> 20% of cycle control data missing and so is not included in this review. -Data on side-effects not published but obtained after contacting the authors Sponsor: SCHERING
Guang-Sheng 2010	786	Healthy women (China) -aged 20 to 35 years. -three normal cycles before study; -willingness to use no other forms of hormonal treatment; -normal smear; -normal breast and gynaecological examination; -at least 3 normal cycles since abortion or delivery; -no systemic diseases.	13 cycles	Monophasic DRSP 3mg/EE 30µg vs.monophasicDSG150µg/EE 30µg over 13 cycles. Both treatments had 21 active days and 7 placebos. Started on first day of menses Satisfaction reported: 478/573 (83.4%) DRSP participants satisfied vs.	- Jadad score: 2-3/5 - FU: 86.5% completed the study and 4.7% lost to FU - ITT: no Other important methodological remarks: -Technique of allocation concealment unclear - Cycle control data reported as mean (SD) for pre-specified 90 day reference periods.

		Included first time users or past COC user with wash-out of 3 months		130/195 (66.7%) DSG participants.	Sponsor: BAYER
Huber 2000	2098	Women(Europe) -aged 18 to 35 years Exclusion criteria: pregnancy, lactation, liver disease, metabolic or vascular diseases, tumours, genital infections, drug/alcohol abuse, on medication such as diuretics or those causing interaction with OCs. Both starters and switchers were included with switchers being given one cycle of wash out	13 cycles	Monophasic drospirenone 3 mg/EE30 mcg (n=1680) versus monophasic desogestrel 150 mcg/EE30 mcg (n=418) Pills were given in 28 day packs. There is no information on day of pill start	- Jadad score: 2-3/5 - FU: 77.6% completed the study and 0.9% lost to FU - ITT: yes Other important methodological remarks: -Technique of allocation concealment unclear Sponsor: SCHERING AG
Kriplani 2010	60	Women (India) - with Polycystic Ovarian Syndrome (PCOS) defined by the presence of any two of the following: oligomenorrhoea and/or anovulation, clinical or biochemical signs of hyperandrogenism, PCO morphology on ultrasound (12 or more follicles in each ovary or increased ovarian volume>10ml), -*and requesting contraception*. Excluded if they had hypothyroidism, hyperprolactinaemia, hormonal treatment within 6 months, smoking, alcohol, recent surgery for PCOS, contraindications to COC or adrenal insufficiency on ACE inhibitors or ATII blockers.	6 cycles	Monophasic DRSP 3mg/EE 30µg versus monophasic DSG150µg/EE 30µg Baseline difference in weight was 68.3kg [±12.4 SD] in the DRSP group vs. 60.44kg [±7.56 SD] (p=0.04) in the DSG group. At 6months, the DRSP group had mean weight loss of -1.25 kg vs mean weight gain in the DSG group of +1.11kg no SDs given). More acne experienced in the DSG group.	- Jadad score: 2-3/5 - FU: 96.7% completed the study - ITT: yes Other important methodological remarks: -Technique of allocation concealment adequate -Unpublished data provided by primary author No funding/conflict of interest

4.1.1.8. Combined oral contraception: comparison of different progestogens: Authors' conclusions

Women using COCs containing second-generation progestogens may be less likely to discontinue than those using COCs containing first-generation progestogens. Based on one small double-blind trial, third-generation progestogens may be preferable to secondgeneration preparations with regard to bleeding patterns but further evidence is needed. Without blinding as to treatment group, comparisons between the various "generations" of progestogens used in COCs cannot be made. Until this widespread methodological flaw is overcome in better trials conducted according to CONSORT guidelines and internationally accepted definitions, no further conclusions can be drawn.

4.1.1.bis. Combined oral contraception: comparison of different progestogens: Summary and conclusions

Monophasic gestodene 75mcg / EE 30mcg vs monophasic levonorgestrel 150mcg /EE 30mcg (N=2;Loudon 1990, Rabe 1989)
Monophasic desogestrel 150µg/EE20µg vs. monophasic levonorgestrel /EE 100µg/EE 20µg (N=1;Winkler 2004)
Triphasic Gestodene 50/70/100mcg+EE 30/40/30mcg vs triphasic Norethindrone 500/750/1000 mcg+ EE 35/35/35 mcg. (N=1; Weber-Diehl 1993)
Monophasic gestodene 75 mcg+EE20 mcg versus monophasic desogestrel 150 mcg+EE20 mcg (N=7;Endrikat 1999, GSD Group 1999, Halbe 1998, Koetsawang 1995, L. America 1994, Serfaty 1998, Zichella 1999)
Monophasic gestodene 75 mcg+ EE 30 mcg versus monophasic norgestimate 250 mcg+ EE 35 mcg. (N=1; Affinito 1993)
Monophasic Drospirenone 3mg/EE 30µg versus monophasic levonorgestrel 150µg/EE 30µg (N=3 ; Kelly 2010 ; Suthipongse 2004 Sangthawan 2005)
Monophasic Drospirenone 3mg/EE 20µg (24 active tablets and 4 placebos) versus monophasic desogestrel 150µg/EE 20µg (21 active /7 placebos) (N=6; Anttila 2009, Foidart 2000, Gruber 2006, Guang-Sheng 2010, Huber 2000, Kriplani 2010)
(All studies from Lawrie 2011)

N/n	Duration	Comparison	Results				
N= 21 n= 13296	6 -26 cycles **Population** Healthy women Age: 15-50	**Monophasic gestodene 75mcg / EE 30mcg vs monophasic levonorgestrel 150mcg /EE 30mcg** (N=2;Loudon 1990, Rabe 1989) 6 cycles	Pregnancy (N=2)	RR=0.00 (95% CI 0.0, 0.0) NS			
			Discontinuation (N=2)	RR= 0.66 (95% CI 0.41, 1.05) NS p=0.078			
			Absence of withdrawal bleed (N=2)	RR= 0.78 (95% CI 0.38, 1.59) NS p=0.49			
				Quality -1 (low Jadad)	Consistency OK	Directness OK	Imprecision OK
				Grade assessment: *moderate quality of evidence*			
			Intermenstrual bleeding (Loudon, 1990)	**70/229 (GSD) vs 98/227 (LNG)** **RR= 0.71 (95% CI 0.55, 0.91)** **SS in favour of gestodene p=0.0059**			
			Spotting (Loudon, 1990)	47/229 (GSD) vs 42/227 (LNG) RR= 1.11 (95% CI 0.76, 1.61) NS p=0.59			
			Breakthrough bleeding (Loudon, 1990)	12/229 (GSD) vs 18/227 (LNG) RR= 0.66 (95% CI 0.33, 1.34) NS p=0.25			
				Quality OK	Consistency NA (N=1)	Directness OK	Imprecision OK
				Grade assessment: *high quality of evidence*			
		Monophasic desogestrel 150µg/EE20µg vs. monophasic levonorgestrel /EE 100µg/EE 20µg (N=1;Winkler 2004) 6 cycles	Pregnancy	1/500 (DSG) vs 1/498 (LNG) RR=1.00 (95% CI 0.06, 15.88) NS p=1.0			
			Total Discontinuation	96/500 (DSG) vs 114/498 (LNG) RR=0.84 (95% CI 0.66, 1.07) NS p=0.15			
			Discontinuation due to side effects (including cycle disturbance)	**10/500 (DSG) vs 25/498 (LNG)** **RR=0.40 (95% CI 0.19, 0.82)** **SS in favour of DSG p=0.013**			
				Quality -1 (FU<80%, open label)	Consistency NA	Directness OK	Imprecision OK
				Grade assessment: *moderate quality of evidence*			

		Triphasic Gestodene 50/70/100mcg +EE 30/40/30mcg vs triphasic Norethindrone 500/750/1000 mcg+ EE 35/35/35 mcg. (N=1; Weber-Diehl 1993) 12 cycles	Pregnancy	0/114 (GSD) vs 0/115 (NE) RR=0.00 (95% CI 0.0, 0.0) NS
			Discontinuation	16/114 (GSD) vs 27/115 (NE) RR=0.60 (95% CI 0.34, 1.05) NS p= 0.072
			Spotting	**18/114 (GSD) vs 31/115 (NE)** **RR=0.59 (95% CI 0.35, 0.99)** **SS; less spotting with GSD p= 0.044**
			Breakthrough bleeding	22/114 (GSD) vs 34/115 (NE) RR=0.65 (95% CI 0.41, 1.04 NS p= 0.075
				Quality: -1 (no ITT, FU<80%,open) / Consistency: NA / Directness: -1 (population not described) / Imprecision: OK
				Grade assessment: *low quality of evidence*
		Monophasic gestodene 75 mcg+EE20 mcg versus monophasic desogestrel 150 mcg+EE20 mcg (N=7;Endrikat 1999, GSD Group 1999, Halbe 1998, Koetsawang 1995, L. America 1994, Serfaty 1998, Zichella 1999) 6 -12 cycles	Pregnancy (N=7)	RR=1.85 (95% CI 0.64, 5.32) NS p=0.26
			Discontinuation (N=7)	RR=1.11 (95% CI 1.00, 1.24) NS p=0.052
				Quality: -1 (low Jadad) / Consistency: OK / Directness: OK / Imprecision: OK
				Grade assessment: *moderate quality of evidence*
			Discontinuation due to side effects (other than cycle disturbance) (N=5; Endrikat 1999, Halbe 1998, Koetsawang 1995, L. America 1994, Zichella 1999)	**RR=1.81 (95% CI 1.01, 3.23)** **SS; less discontinuation with DSG p=0.045**
				Quality: -1 (low Jadad) / Consistency: OK / Directness: OK / Imprecision: OK
				Grade assessment: *moderate quality of evidence*
			Discontinuation due to cycle disturbance) (N=5; GSD Group 1999, Halbe 1998, Koetsawang 1995, L. America 1994, Zichella 1999)	RR=0.93 (95% CI 0.48, 1.81) NS p=0.83
				Quality: -1 (low Jadad) / Consistency: OK / Directness: OK / Imprecision: OK
				Grade assessment: *moderate quality of evidence*
		Monophasic gestodene 75 mcg+ EE 30 mcg versus monophasic norgestimate 250 mcg+ EE 35	Pregnancy	0/91 (GSD) vs 0/83 (NGM) RR=0.00 (95% CI 0.0, 0.0) NS
			Discontinuation	6/91 (GSD) vs 9/83 (NGM) RR=0.61 (95% CI 0.23, 1.64) NS p=0.32
			Discontinuation due to cycle disturbances	0/91 (GSD) vs 0/83 (NGM) RR=0.00 (95% CI 0.0, 0.0) NS

		mcg. (N=1; Affinito 1993) 6 cycles	Discontinuation due to side effects (other than cycle disturbances)	3/91 (GSD) vs 2/83 (NGM) RR=1.37 (95% CI 0.23, 7.99) NS p=0.73
				Quality: -1(low Jadad, ITT?) / Consistency: NA / Directness: OK / Imprecision: OK
				Grade assessment: *moderate quality of evidence*
		Monophasic Drospirenone 3mg/EE 30µg versus monophasic levonorgestrel 150µg/EE 30µg (N=3 ; Kelly 2010 ; Suthipongse 2004 Sangthawan 2005) 6-7 cycles	Pregnancy (N=1 ; Suthipongse2004)	0/58 (DRSP) vs 0/57 (LNG) RR=0.00 (95% CI 0.0, 0.0) NS
				Quality: -1(low Jadad, ITT?) / Consistency: NA (N=1) / Directness: OK / Imprecision: OK
				Grade assessment: *moderate quality of evidence*
			Discontinuation (N=2 ; Kelly 2010 ; Suthipongse 2004)	RR=0.81 (95% CI 0.62, 1.06) NS p=0.12
				Quality: -1 / Consistency: OK / Directness: OK / Imprecision: OK
				Grade assessment: *moderate quality of evidence*
			Discontinuation due to side effects (including cycle disturbance) (N=1 ; Kelly 2010)	14/282(DRSP) vs 13/142 (LNG) RR=0.54 (95% CI 0.26, 1.12) NS p=0.099
			Intermenstrual bleeding (N=1 ; Kelly 2010)	33/282(DRSP) vs 19/142 (LNG) RR=0.87 (95% CI 0.52, 1.48) NS p=0.62
				Quality: -1 (FU<80%) / Consistency: NA (N=1) / Directness: OK / Imprecision: OK
				Grade assessment: *moderate quality of evidence*
		Monophasic Drospirenone 3mg/EE 20µg (24 active tablets and 4 placebos) versus monophasic desogestrel 150µg/EE 20µg (21 active /7 placebos) (N=6; Anttila 2009, Foidart 2000, Gruber 2006, Guang-Sheng 2010, Huber 2000, Kriplani 2010) 6cycles -26 months	Pregnancy (N=6)	RR=0.95 (95% CI 0.39, 2.33) NS p=0.91
			Discontinuation (N=6)	RR=1.06 (95% CI 0.93, 1.20) NS p=0.40
			nausea/vomiting (N=6)	122/3173(DRSP) vs 40/1528(DSG) RR=1.46 (95% CI 0.96, 2.21) NS p=0.074
				Quality: -1 (low jadad) / Consistency: OK / Directness: OK / Imprecision: OK
				Grade assessment: *moderate quality of evidence*
			Discontinuation due to side effects (including cycle disturbance) (N=5; Anttila 2009, Gruber 2006, Guang-Sheng 2010, Huber 2000; Kriplani 2010)	RR=1.24(95% CI 0.87, 1.76) NS p=0.23
				Quality: -1 (low jadad) / Consistency: OK / Directness: OK / Imprecision: -1
				Grade assessment: *moderate quality of evidence*
			Discontinuation	RR=1.05 (95% CI 0.52, 2.14)

			due to cycle disturbances (N=3 ; Anttila 2009, Foidart 2000, Gruber 2006)	NS p=0.89			
				Quality -1 (low jadad)	Consistency OK	Directness OK	Imprecision OK
				Grade assessment: *moderate quality of evidence*			
			intermenstrual bleeding (N=2; Gruber 2006, Huber 2000)	RR=0.97 (95% CI 0.83, 1.14) NS p=0.71			
				Quality -1 (low jadad)	Consistency OK	Directness OK	Imprecision OK
				Grade assessment: *moderate quality of evidence*			
			breast tenderness (N=5; Anttila 2009, Foidart 2000, Guang-Sheng 2010, Huber 2000; Kriplani 2010)	**RR=1.39 (95% CI 1.04, 1.86)** **SS ; less breast tenderness with DSG p=0.028**			
				Quality -1 (low jadad)	Consistency OK	Directness OK	Imprecision OK
				Grade assessment: *moderate quality of evidence*			

A Cochrane review (Lawrie, 2011) including 30 studies with 13923 women has compared oestroprogestin contraceptive pills containing different types of progestins in terms of efficacy and adverse events.
We have selected only the studies (N=21; n=13296) involving contraceptive pills available in Belgium. Seven comparisons were therefore considered.
Overall, the quality of the studies was low and most of the studies were sponsored by the pharmaceutical industry (17/21).

We report the most significant data for each comparison below:

Monophasic gestodene 75mcg/EE 30mcg vs. monophasic levonorgestrel 150mcg/EE 30mcg
There is no statistically significant difference in terms of efficacy and discontinuation between the monophasic pills containing gestodene and levonorgestrel. With regard to cycle control, less intermenstrual bleeding was observed with pills containing gestodene.
GRADE: moderate to high quality of evidence

Monophasic desogestrel 150µg/EE20µg vs. monophasic levonorgestrel /EE 100µg/EE 20µg
There is no statistically significant difference in terms of efficacy between the monophasic pills containing desogestrel and levonorgestrel. In terms of discontinuation, a statistically significant difference was observed, with less discontinuation related to adverse events (including cycle irregularities) with pills containing desogestrel, but no difference with regard to the discontinuation figures (all causes combined).
GRADE: moderate quality of evidence

Triphasic Gestodene 50/70/100 mcg + EE 30/40/30mcg vs. triphasic Norethindrone 500/750/1000 mcg+ EE 35/35/35 mcg.
There is no statistically significant difference in terms of efficacy and discontinuation between the triphasic pills containing gestodene and norethisterone. With regard to cycle control, however, less spotting was observed with pills containing gestodene.
GRADE: low quality of evidence

Monophasic gestodene 75 mcg + EE20 mcg versus monophasic desogestrel 150 mcg + EE20 mcg
There is no statistically significant difference in terms of efficacy between the monophasic pills containing gestodene and desogestrel. In terms of discontinuation, a statistically significant difference was observed, with less discontinuation related to adverse events (other than cycle irregularities) with pills containing desogestrel, but no difference with regard to the discontinuation figures (all causes combined).
GRADE: moderate quality of evidence

Monophasic gestodene 75 mcg+ EE 30 mcg versus monophasic norgestimate 250mcg+ EE 35 mcg.
There is no statistically significant difference in terms of efficacy, discontinuation and adverse events between the monophasic pills containing gestodene and norgestimate.
GRADE: moderate quality of evidence

Monophasic Drospirenone 3mg/EE 30µg versus monophasic levonorgestrel 150µg/EE 30µg
There is no statistically significant difference in terms of efficacy, discontinuation and adverse events between the monophasic pills containing drospirenone and levonorgestrel.
GRADE: moderate quality of evidence

Monophasic Drospirenone 3mg/EE 20µg (24 active tablets and 4 placebos) versus monophasic desogestrel 150µg/EE 20µg (21 active/7 placebos)
Compared to monophasic pills containing desogestrel, there is no statistically significant difference in terms of efficacy and discontinuation with the monophasic pills containing drospirenone. However, in terms of adverse events, complaints of breast tenderness and nausea are more common in the drospirenone group.
GRADE: moderate quality of evidence

In conclusion, few differences were observed among the various progestins.
All these results remain to be confirmed in double-blind studies of better quality

4.1.2. Combined oral contraception containing ethinylestradiol 20µg versus >20µg: Evidence tables

4.1.2.1. Combined oral contraceptives containing desogestrel 150µg : EE 20 µg versus EE 30 µg

Ref	N/n	Comparison	Outcomes	
* Gallo 2011a Design: SR+/- MA N= 21 n= 13882 Search date: Nov 2010	N=2 n=1058	EE 20 µg and desogestrel 150 µg versus EE 30 µg and desogestrel 150 µg	Pregnancy per woman (N=1; Akerlund, 1993)	2/485 (EE20DSG) vs 3/497 (EE30DSG) OR=0.69 (95% CI 0.12, 3.97) NS p = 0.67
			Discontinuation – overall (N=1; Akerlund, 1993)	174/500 (EE20DSG) vs 154/500 (EE30DSG) OR=1.20 (95% CI 0.92, 1.56) NS p = 0.18
			Discontinuation - mood changes (N=1; Akerlund, 1993)	15/500 (EE20DSG) vs 10/500 (EE30DSG) OR=1.51 (95% CI 0.68, 3.33) NS p = 0.31
			Discontinuation - irregular bleeding (N=1; Akerlund, 1993)	**27/500 (EE20DSG) vs 10/500 (EE30DSG)** **OR=2.59 (95% CI 1.35, 5.00)** **SS in favor of EE30DSG p = 0.0044**
			Discontinuation – nausea (N=1 ; Basdevant, 1993)	1/33 (EE20DSG) vs 1/25 (EE30DSG) OR=0.75 (95% CI 0.04, 12.64) NS p = 0.84
			Amenorrhea - cycle 6 (N=1; Akerlund, 1993)	15/354 (EE20DSG) vs 11/367(EE30DSG) OR=1.43 (95% CI 0.65, 3.12) NS p = 0.37
			Irregular bleeding - cycle 3 (N=1; Akerlund, 1993)	**94/383(EE20DSG) vs 68/395 (EE30DSG)** **OR=1.56 (95% CI 1.10, 2.20)** **SS in favor of EE30DSG p = 0.012**
			Duration of irregular bleeding in days - cycle 3 (N=1; Akerlund, 1993)	**4.4 ±3.1(EE20DSG) vs 3.7±2.5 (EE30DSG)** **Mean difference= 0.70 (95% CI 0.30, 1.10)** **SS in favor of EE30DSG p = 0.00054**
			Duration of irregular bleeding in days - cycle 6 (N=1; Akerlund, 1993)	3.8 ±2.3(EE20DSG) vs 3.9±2.6 (EE30DSG) Mean difference= -0.10 (95% CI -0.46, 0.26) NS p = 0.58
			Dizziness (N=1; Akerlund, 1993)	**6/485 (EE20DSG) vs 0/497 (EE30DSG)** **OR=7.65 (95% CI 1.54, 38.08)** **SS in favor of EE30DSG p = 0.013**
			Dysmenorrhea	17/485 (EE20DSG) vs 12/497 (EE30DSG)

			(N=1; Akerlund, 1993)	OR=1.46 (95% CI 0.70, 3.06) NS p = 0.31
			Headache (N=1; Akerlund, 1993)	28/485 (EE20DSG) vs 17/497 (EE30DSG) OR=1.71 (95% CI 0.94, 3.11) NS p = 0.078
			Increased weight (N=1; Akerlund, 1993)	**15/485 (EE20DSG) vs 6/497 (EE30DSG)** **OR=2.46 (95% CI 1.04, 5.84)** **SS in favor of EE30DSG p = 0.041**
			Irregular bleeding (N=1; Akerlund, 1993)	**48/485 (EE20DSG) vs 30/497 (EE30DSG)** **OR=1.69 (95% CI 1.07, 2.69)** **SS in favor of EE30DSG p = 0.025**
			Mood change (N=1; Akerlund, 1993)	**28/485 (EE20DSG) vs 15/497 (EE30DSG)** **OR=1.93 (95% CI 1.05, 3.56)** **SS in favor of EE30DSG p = 0.035**
			Nausea, diarrhea, vomiting (N=1; Akerlund, 1993)	22/485 (EE20DSG) vs 16/497 (EE30DSG) OR=1.42 (95% CI 0.74, 2.72) NS p = 0.29
			Prolonged withdrawal bleeding (N=1; Akerlund, 1993)	**25/485 (EE20DSG) vs 13/497 (EE30DSG)** **OR=1.98 (95% CI 1.03, 3.78)** **SS in favor of EE30DSG p = 0.039**

* Characteristics of included studies: see under

Ref + design	n	Population	Duration	Comparison	Methodology
Akerlund 1993	1000	Women -aged 18 to 35 (Norway sites) or 18 to 40 (Sweden and Denmark sites) years. Excluded heavy smoking among women 35 years of age; risk factors for or history of certain diseases; lactation; and certain antibiotics	12 cycles	EE 20 µg and desogestrel 150 µg (N=500) versus EE 30 µg and desogestrel 150 µg (N=500) 'Withdrawal' bleeding defined as bleeding that began within the pill-free period and did not exceed eight days. 'Irregular' bleeding defined as any other bleeding	- Jadad score: 4/5 - FU: 67% completed the study - ITT: no (per protocol analysis) Other important methodological remarks: -Technique of allocation concealment not reported. Sponsor: Pharmaceutical company
Basdevant 1993	58	Healthy women -with regular menses -non-obese Excluded lactation; recent birth or abortion; recent steroid treatment; venous or arterial disease; diabetes; hyperlipidemia; eating disorders; smokers; hypertension; gynecological tumors; cancer; and certain drugs	6 cycles	EE 20 µg and desogestrel 150 µg (N=33) versus EE 30 µg and desogestrel 150 µg (N=25)	- Jadad score: 2-3/5 - FU: 76% completed study - ITT: no Other important methodological remarks: -Technique of allocation concealment not reported. Sponsor: NR

4.1.2.2. Combined oral contraceptives : EE 20 µg and desogestrel 150 µg versus EE 30 µg and gestodene 75 µg

Ref	N/n	Comparison	Outcomes	
* Gallo 2011a Design: SR +/- MA N= 21 n= 13882 Search date: Nov 2010	N=3 n= 3925	EE 20 µg and desogestrel 150 µg versus EE 30 µg and gestodene 75 µg	Pregnancy per woman (N=2 ; Bruni 2000, Teichmann 1995)	3/1014 (EE20DSG) vs 3/1013 (EE30GSD) OR=1.00 (95% CI 0.20, 4.96) NS p = 1.0
			Discontinuation – overall (N=3 ; Bruni 2000, Kirkman 1994, Teichmann 1995)	235/1515 (EE20DSG) vs 229/1518 (EE30GSD) OR=1.03 (95% CI 0.85, 1.26) NS p = 0.76
			Discontinuation - abdominal pain (N=1 ; Teichmann 1995)	6/209 (EE20DSG) vs 4/207 (EE30GSD) OR=1.49 (95% CI 0.43, 5.22) NS p = 0.53
			Discontinuation - adverse event (N=3 ; Bruni 2000, Kirkman 1994, Teichmann 1995)	126/1515 (EE20DSG) vs 100/1518 (EE30GSD) OR=1.28 (95% CI 0.98, 1.68) NS p = 0.070
			Discontinuation - breast tension (N=1 ; Teichmann 1995)	1/209(EE20DSG) vs 2/207(EE30GSD) OR=0.51 (95% CI 0.05, 4.90) NS p = 0.56
			Discontinuation – colpitis (N=1 ; Teichmann 1995)	1/209(EE20DSG) vs 1/207(EE30GSD) OR=0.99 (95% CI 0.06, 15.89) NS p = 0.99
			Discontinuation - depressive mood (N=1 ; Teichmann 1995)	1/209(EE20DSG) vs 2/207(EE30GSD) OR=0.51 (95% CI 0.05, 4.90) NS p = 0.56
			Discontinuation – dizziness (N=1 ; Teichmann 1995)	**4/209(EE20DSG) vs 0/207(EE30GSD) OR=7.43 (95% CI 1.04, 53.09) SS in favor of EE30GSD p = 0.046**
			Discontinuation – headache (N=1 ; Teichmann 1995)	5/209(EE20DSG) vs 4/207(EE30GSD) OR=1.24 (95% CI 0.33, 4.65) NS p = 0.75
			Discontinuation – hypertension (N=1 ; Teichmann 1995)	1/209(EE20DSG) vs 0/207(EE30GSD) OR=7.32 (95% CI 0.15, 368.86) NS p = 0.32
			Discontinuation - hypomenorrhea. (N=1; Kirkman 1994)	2/501(EE20DSG) vs 0/505(EE30GSD) OR=7.46 (95% CI 0.47, 119.49) NS p = 0.16
			Discontinuation - intermenstrual bleeding	3/209(EE20DSG) vs 4/207(EE30GSD)

			(N=1 ; Teichmann 1995)	OR=0.74 (95% CI 0.17, 3.30) NS p = 0.69
			Discontinuation – menorrhagia (N=1; Kirkman 1994)	2/501(EE20DSG) vs 2/505(EE30GSD) OR=1.01 (95% CI 0.14, 7.18) NS p = 0.99
			Discontinuation - menstrual disorder (N=1; Kirkman 1994)	1/501(EE20DSG) vs 2/505(EE30GSD) OR=0.52 (95% CI 0.05, 4.98) NS p = 0.57
			Discontinuation - metrorrhagia. (N=3 ; Bruni 2000, Kirkman 1994)	**22/1306(EE20DSG) vs 9/1311(EE30GSD)** **OR=2.35 (95% CI 1.16, 4.77)** **SS in favor of EE30GSD p = 0.018**
			Discontinuation – nausea (N=1 ; Teichmann 1995)	4/209(EE20DSG) vs 4/207(EE30GSD) OR=0.99 (95% CI 0.24, 4.01) NS p = 0.99
			Discontinuation - nervousness. (N=1 ; Teichmann 1995)	3/209(EE20DSG) vs 0/207(EE30GSD) OR=7.39 (95% CI 0.76, 71.43) NS p = 0.084
			Discontinuation - pruritus. (N=1 ; Teichmann 1995)	1/209(EE20DSG) vs 0/207(EE30GSD) OR=7.32 (95% CI 0.15, 368.86) NS p = 0.32
			Discontinuation – vomiting (N=1 ; Teichmann 1995)	5/209(EE20DSG) vs 1/207(EE30GSD) OR=3.82 (95% CI 0.76, 19.10) NS p = 0.10
			Irregular bleeding - cycle 3 (N=1; Kirkman 1994)	**104/456(EE20DSG) vs 46/454(EE30GSD)** **OR=2.51 (95% CI 1.77, 3.56)** **SS in favor of EE30GSD p <0.00001**
			Irregular bleeding - cycle 6 (N=1; Kirkman 1994)	**69/411(EE20DSG) vs 43/412(EE30GSD)** **OR=1.72 (95% CI 1.15, 2.55)** **SS in favor of EE30GSD p=0.0079**
			Amenorrhea - cycle 3 (N=1; Kirkman 1994)	10/456(EE20DSG) vs 4/454(EE30GSD) OR=2.38 (95% CI 0.83, 6.82) NS p =0.11
			Amenorrhea - cycle 6 (N=1; Kirkman 1994)	2/411(EE20DSG) vs 6/412(EE30GSD) OR=0.37 (95% CI 0.09, 1.47) NS p =0.16
			Abdominal pain	32/805 (EE20DSG) vs 27/806(EE30GSD)

			(N=1 ; Bruni 2000)	OR=1.19 (95% CI 0.71, 2.01) NS p =0.50
			Acne (N=1 ; Bruni 2000)	15/805 (EE20DSG) vs 16/806(EE30GSD) OR=0.94 (95% CI 0.46, 1.91) NS p =0.86
			Breast pain (N=1 ; Bruni 2000)	42/805 (EE20DSG) vs 49/806(EE30GSD) OR=0.85 (95% CI 0.56, 1.30) NS p =0.45
			Decreased libido (N=1 ; Bruni 2000)	7/805 (EE20DSG) vs 11/806(EE30GSD) OR=0.64 (95% CI 0.25, 1.62) NS p =0.34
			Depression (N=1 ; Bruni 2000)	16/805 (EE20DSG) vs 21/806(EE30GSD) OR=0.76 (95% CI 0.40, 1.46) NS p =0.41
			Dizziness (N=1 ; Bruni 2000)	6/805 (EE20DSG) vs 10/806(EE30GSD) OR=0.60 (95% CI 0.23, 1.62) NS p =0.32
			Dysmenorrhea (N=1 ; Bruni 2000)	17/805 (EE20DSG) vs 18/806(EE30GSD) OR=0.94 (95% CI 0.48, 1.85) NS p =0.87
			Emotional lability (N=1 ; Bruni 2000)	16/805 (EE20DSG) vs 22/806(EE30GSD) OR=0.72 (95% CI 0.38, 1.38) NS p =0.33
			Flatulence (N=1 ; Bruni 2000)	7/805 (EE20DSG) vs 12/806(EE30GSD) OR=0.59 (95% CI 0.24, 1.45) NS p =0.25
			Headache (N=1 ; Bruni 2000)	118/805 (EE20DSG) vs 111/806(EE30GSD) OR=1.08 (95% CI 0.81, 1.42) NS p =0.61
			Menstrual disorder (N=1 ; Bruni 2000)	10/805 (EE20DSG) vs 10/806(EE30GSD) OR=1.00 (95% CI 0.41, 2.42) NS p =1.0
			Metrorrhagia (N=1 ; Bruni 2000)	**46/805 (EE20DSG) vs 28/806(EE30GSD)** **OR=1.67 (95% CI 1.05, 2.66)** **SS in favor of EE30GSD p =0.032**
			Migraine	10/805 (EE20DSG) vs 4/806(EE30GSD)

			(N=1 ; Bruni 2000)	OR=2.38 (95% CI 0.83, 6.80) NS p =0.11
			Nausea (N=1 ; Bruni 2000)	31/805 (EE20DSG) vs 27/806(EE30GSD) OR=1.16 (95% CI 0.68, 1.95) NS p =0.59
			Pain (N=1 ; Bruni 2000)	15/805 (EE20DSG) vs 11/806(EE30GSD) OR=1.37 (95% CI 0.63, 2.97) NS p =0.43
			Vaginal moniliasis (N=1 ; Bruni 2000)	13/805 (EE20DSG) vs 9/806(EE30GSD) OR=1.45 (95% CI 0.62, 3.36) NS p =0.39
			Vomiting (N=1 ; Bruni 2000)	16/805 (EE20DSG) vs 13/806(EE30GSD) OR=0.48 (95% CI 0.19, 1.17) NS p =0.11
			Weight gain (N=1 ; Bruni 2000)	13/805 (EE20DSG) vs 19/806(EE30GSD) OR=0.68 (95% CI 0.34, 1.38) NS p =0.29
			Weight gain in kg (N=1; Kirkman 1994)	**0.4±2 (EE20DSG) vs 0.6±0.2 (EE30GSD)** **Mean difference= -0.20 (95% CI -0.40, 0.00)** **SS in favor of EE20DSG p = 0.045**

* Characteristics of included studies: see under

Ref + design	n	Population	Duration	Comparison	Methodology
Bruni 2000	2419	Women -'over the legal age of consent' and -less than 42 years of age -with regular menses. Excluded estrogen or progestogen hypersensitivity; pregnancy; lactation; and certain disorders	13 cycles	EE 20 µg and desogestrel 150 µg (N=805) versus EE 30 µg and gestodene 75 µg (N=806) versus EE 30-40-30 µg and gestodene 50-70-100 µg (N=808) Bleeding terms not defined.	- Jadad score:2 /5 - FU: 71% completed study - ITT: unclear Other important methodological remarks: -Technique of allocation concealment not reported. Sponsor: Pharmaceutical company
Kirkman 1994	1006	Healthy women (Denmark, Italy, New Zealand and the UK.) -over 30 years of age with regular menses. Excluded smokers over 34 years of age, select drug use, and lactation	6 cycles.	EE 20 µg and desogestrel 150 µg (N=501) versus EE 30 µg and gestodene 75 µg (N=505) 'Withdrawal' bleeding episode was defined as a sequence of one or more days of bleeding or spotting that began during the pill-free period and was bounded by two consecutive days without bleeding. Results, though, were reported for 'irregular' bleeding', which was never defined	- Jadad score: 3/5 - FU: 87% completed study. - ITT: unclear Other important methodological remarks: -Technique of allocation concealment not reported. Sponsor: Pharmaceutical company
Teichmann 1995	500	Healthy women (Poland) -normal-weight, -sexually active -aged 19 to 40 years -seeking oral contraception -with regular menses. Excluded recent hormonal medication and certain other drugs; smokers; and contraindications to oral contraception	2 pretreatment and 12 treatment cycles	EE 20 µg and desogestrel 150 µg versus EE 30 µg and gestodene 75 µg. Bleeding terms not defined.	- Jadad score:3/5 - FU: 63% completed study - ITT: unclear Other important methodological remarks: -Technique of allocation concealment not reported. Sponsor: ?

4.1.2.3. Combined oral contraceptives: EE20 µg and desogestrel 150 µg versus EE 30-40-30 µg and gestodene 50-70-100 µg

Ref	N/n	Comparison	Outcomes	
* Gallo 2011a Design: meta-analysis N= 21 n= 13882 Search date: Nov 2010	N=1 n=2419	EE 20 µg and desogestrel 150 µg versus EE 30-40-30 µg and gestodene 50-70-100 µg (N=1 ; Bruni)	Pregnancy per woman	2/805 (EE20DSG) vs 2/808(EE30-40-30/GSD50-70-100) OR=1.00(95% CI 0.14, 7.14) NS p =1.0
			Discontinuation - overall	132/805 (EE20DSG) vs 125/808(EE30-40-30/GSD50-70-100) OR=1.07(95% CI 0.82, 1.40) NS p =0.61
			Discontinuation - adverse reaction	62/805 (EE20DSG) vs 47/808(EE30-40-30/GSD50-70-100) OR=1.35(95% CI 0.91, 1.99) NS p =0.13
			Discontinuation – metrorrhagia	10/805 (EE20DSG) vs 3/808(EE30-40-30/GSD50-70-100) OR=2.97(95% CI 1.00, 8.85) NS p =0.051
			Abdominal pain	32/805 (EE20DSG) vs 27/808(EE30-40-30/GSD50-70-100) OR=1.20(95% CI 0.71, 2.01) NS p =0.50
			Acne	15/805 (EE20DSG) vs 20/808(EE30-40-30/GSD50-70-100) OR=0.75(95% CI 0.38, 1.46) NS p =0.40
			Breast pain	42/805 (EE20DSG) vs 59/808(EE30-40-30/GSD50-70-100) OR=0.70(95% CI 0.47, 1.05) NS p =0.084
			Decreased libido	7/805 (EE20DSG) vs 7/808(EE30-40-30/GSD50-70-100) OR=1.00(95% CI 0.35, 2.87) NS p =0.99
			Depression	16/805 (EE20DSG) vs 15/808(EE30-40-30/GSD50-70-100) OR=1.07(95% CI 0.53, 2.18) NS p =0.85
			Dizziness	6/805 (EE20DSG) vs 16/808(EE30-40-30/GSD50-70-100) OR=0.40(95% CI 0.17, 0.93) NS p =0.033
			Dysmenorrhea	17/805 (EE20DSG) vs 14/808(EE30-40-30/GSD50-70-100) OR=1.22 (95% CI 0.60, 2.49) NS p =0.58

			Emotional lability.	16/805 (EE20DSG) vs 18/808(EE30-40-30/GSD50-70-100) OR=0.89 (95% CI 0.45, 1.76) NS p =0.74
			Flatulence	7/805 (EE20DSG) vs 6/808(EE30-40-30/GSD50-70-100) OR=1.17(95% CI 0.39, 3.49) NS p =0.78
			Headache	118/805 (EE20DSG) vs 115/808(EE30-40-30/GSD50-70-100) OR=1.04(95% CI 0.78, 1.37) NS p =0.81
			Menstrual disorder	10/805 (EE20DSG) vs 7/808(EE30-40-30/GSD50-70-100) OR=1.43(95% CI 0.55, 3.73) NS p =0.46
			Metrorrhagia	**46/805 (EE20DSG) vs 20/808(EE30-40-30/GSD50-70-100)** **OR=2.28(95% CI 1.39, 3.73)** **SS in favor of EE30-40-30/GSD50-70-100 p =0.0010**
			Migraine	10/805 (EE20DSG) vs 12/808(EE30-40-30/GSD50-70-100) OR=0.83(95% CI 0.36, 1.94) NS p =0.67
			Nausea	31/805 (EE20DSG) vs 42/808(EE30-40-30/GSD50-70-100) OR=0.73(95% CI 0.46, 1.17) NS p =0.19
			Pain	15/805 (EE20DSG) vs 7/808(EE30-40-30/GSD50-70-100) OR=2.10(95% CI 0.90, 4.86) NS p =0.084
			Vaginal moniliasis	13/0805 (EE20DSG) vs 6/808(EE30-40-30/GSD50-70-100) OR=2.11(95% CI 0.86, 5.22) NS p =0.10
			Vomiting	6/805 (EE20DSG) vs 7/808(EE30-40-30/GSD50-70-100) OR=0.86(95% CI 0.29, 2.56) NS p =0.79
			Weight gain	13/805 (EE20DSG) vs 21/808(EE30-40-30/GSD50-70-100) OR=0.62(95% CI 0.31, 1.22) NS p =0.17

* Characteristics of included studies: see under

Ref + design	n	Population	Duration	Comparison	Methodology
Bruni 2000	2419	Women -'over the legal age of consent' and -less than 42 years of age -with regular menses. Excluded estrogen or progestogen hypersensitivity; pregnancy; lactation; and certain disorders	13 cycles	EE 20 µg and desogestrel 150 µg (N=805) versus EE 30 µg and gestodene 75 µg (N=806) versus EE 30-40-30 µg and gestodene 50-70-100 µg (N=808) Bleeding terms not defined.	- Jadad score:2 /5 - FU: 71% completed study - ITT: unclear Other important methodological remarks: -Technique of allocation concealment not reported. Sponsor: Pharmaceutical company

4.1.2.4. Combined oral contraceptives : EE 20 µg and gestodene 75 µg versus EE 30 µg and gestodene 75 µg

Ref	N/n	Comparison	Outcomes	
* Gallo 2011a Design: SR +/- MA N= 21 n= 13882 Search date: Nov 2010	N=4 n= 903	EE 20 µg and gestodene 75 µg versus EE 30 µg and gestodene 75 µg	Pregnancy per woman (N=2; Endrikat 1997, Taneepanichskul 2002)	1/504 (EE20GSD) vs 2/295(EE30GSD) OR=0.23(95% CI 0.02, 2.55) NS p =0.23
			Discontinuation - overall (N=2; Endrikat 1997, Taneepanichskul 2002)	110/504 (EE20GSD) vs 59/295(EE30GSD) OR=1.14(95% CI 0.80, 1.63) /NS p =0.46
			Discontinuation - adverse event (N=3; Brill 1996, Endrikat 1997, Winkler 1996)	48/480 (EE20GSD) vs 19/273(EE30GSD) OR=1.46(95% CI 0.86, 2.46) NS p =0.16
			D iscontinuation – intermenstrual Bleeding (N=1; Brill 1996)	0/32 (EE20GSD) vs 0/32(EE30GSD) OR=0.0(95% CI 0.0, 0.0) NS
			Discontinuation - metrorrhagia (N=1; Winkler 1996)	0/20(EE20GSD) vs 1/20(EE30GSD) OR=0.14(95% CI 0.0, 6.82) NS p=0.32
			Breakthrough bleeding - cycle 3 (N=1; Taneepanichskul 2002)	1/59(EE20GSD) vs 0/55(EE30GSD) OR=6.90(95% CI 0.14, 348.82) NS p=0.33
			Breakthrough bleeding - cycle 6 (N=1; Taneepanichskul 2002)	0/59(EE20GSD) vs 1/55(EE30GSD) OR=0.13(95% CI 0.00, 6.36) NS p=0.30
			Spotting - cycle 3 (N=1; Taneepanichskul 2002)	2/59(EE20GSD) vs 3/55(EE30GSD) OR=0.61(95% CI 0.10, 3.66) NS p=0.59
			Spotting - cycle 6 (N=1; Taneepanichskul 2002)	1/59(EE20GSD) vs 1/55(EE30GSD) OR=0.93(95% CI 0.06, 15.10) NS p=0.96
			Acne (N=2; Brill 1996, Endrikat 1997)	18/459(EE20GSD) vs 8/248(EE30GSD) OR=1.35(95% CI 0.60, 3.08) NS p=0.47
			Breast tension or tenderness (N=3; Brill 1996, Endrikat 1997, Taneepanichskul 2002)	40/518(EE20GSD) vs 20/303(EE30GSD) OR=1.18(95% CI 0.68, 2.05) NS p=0.56

			Change in libido (N=1; Endrikat 1997)	14/428(EE20GSD) vs 4/221(EE30GSD) OR=1.72(95% CI 0.64, 4.61) NS p=0.28
			Chloasma (N=1; Taneepanichskul 2002)	2/59(EE20GSD) vs 2/55(EE30GSD) OR=0.93(95% CI 0.13, 6.79) NS p=0.94
			Depressive moods (N=2; Brill 1996, Endrikat 1997)	14/459(EE20GSD) vs 4/248(EE30GSD) OR=2.12(95% CI 0.80, 5.66) NS p=0.13
			Diarrhea (N=1; Taneepanichskul 2002)	1/59(EE20GSD) vs 3/55(EE30GSD) OR=0.33(95% CI 0.05, 2.43) NS p=0.28
			Dizziness (N=2; Endrikat 1997, Taneepanichskul 2002)	13/487(EE20GSD) vs 5/276(EE30GSD) OR=1.52(95% CI 0.57, 4.02) NS p=0.40
			Edema (N=1; Endrikat 1997)	3/428(EE20GSD) vs 3/221(EE30GSD) OR=0.41(95% CI 0.09, 2.66) NS p=0.41
			Headache (N=2; Brill 1996, Endrikat 1997)	54/459(EE20GSD) vs 33/248(EE30GSD) OR=0.98(95% CI 0.60, 1.59) NS p=0.93
			Nausea (N=2; Brill 1996, Endrikat 1997)	29/459(EE20GSD) vs 15/248(EE30GSD) OR=1.27(95% CI 0.66 2.45) NS p=0.48
			Nausea and vomiting (N=1; Taneepanichskul 2002)	2/59(EE20GSD) vs 1/55(EE30GSD) OR=1.84(95% CI 0.19, 18.04) NS p=0.60
			Nervousness (N=1; Endrikat 1997)	15/428(EE20GSD) vs 5/221(EE30GSD) OR=1.51(95% CI 0.59, 3.87) NS p=0.39
			Varicose conditions (N=1; Endrikat 1997)	5/428(EE20GSD) vs 3/221(EE30GSD) OR=0.86(95% CI 0.20, 3.72) NS p=0.84
			Vomiting (N=2; Brill 1996, Endrikat 1997)	6/459(EE20GSD) vs 6/248(EE30GSD) OR=0.68(95% CI 0.20 2.25) NS p=0.53

			Weight gain >2 kg (N=1; Endrikat 1997)	48/296(EE20GSD) vs 24/156(EE30GSD) OR=1.06(95% CI 0.63 1.81) NS p=0.82
			Weight gain in kg (N=1; Taneepanichskul 2002)	50.6 ±6.5(EE20GSD) vs 52.1±8.2 (EE30GSD) Mean difference= -1.5(95% CI -4.23, 1.23) NS p = 0.28

* Characteristics of included studies: see under

Ref + design	n	Population	Duration	Comparison	Methodology
Brill 1996	64	Women (unreported location) -aged 18 to 35 years -with regular menses. Excluded smokers over 30 years of age; pregnancy; certain diseases; certain drugs; intrauterine device use; overweight or dieting; and heavy alcohol use	13 cycles.	EE 20 µg and gestodene 75 µg (N=32) versus EE 30 µg and gestodene 75 µg (N=32)	- Jadad score: 1/5 - FU: NR - ITT: no Other important methodological remarks: -Technique of allocation concealment not reported. -Did not report bleeding outcomes. Sponsor: Pharmaceutical company
Endrikat 1997	649	Healthy women -aged 18 to 39 years - sexually active -who wanted contraception for at least 12 months. Excluded recent depot-contraceptives; certain diseases; and contraindications for oral contraceptive use	12 treatment cycles	EE 20 µg and gestodene 75 µg (N=428) versus EE 30 µg and gestodene 75 µg (N=221) 'Intermenstrual' bleeding was defined as either spotting or breakthrough bleeding. The definition for 'intermenstrual' bleeding did not specify cycle days	- Jadad score: 3/5 - FU: 75% (488/649) completed study. - ITT: no Other important methodological remarks: -Technique of allocation concealment not reported. Sponsor: Pharmaceutical company
Taneepanichskul 2002	150	Women (one site in Thailand) -aged 18 to 35 years,	12 treatment	EE 20 µg and gestodene 75 µg (N=76) versus EE 30 µg and	- Jadad score: 2/5 - FU: 76% (114/150) completed

		-willing to use contraception for over 12 complete cycles with at least a three month washout period. Excluded contraindications to OCuse; liver, vascular or metabolic diseases; tumor; pregnancy; unclassified and genital bleeding	cycles Three-month wash-out period for OC users.	gestodene 75 µg (N=74) 'Regular' cycle was defined as periodic withdrawal bleeding every 28±7days. 'Breakthrough bleeding' was defined as intermenstrual bleeding that did not require sanitary protection	study. - ITT: yes Other important methodological remarks: -Technique of allocation concealment not reported. Sponsor: Pharmaceutical company
Winkler 1996	40	Healthy women (unreported location) -aged 18 to 30 -with regular menses. Excluded contraindications to oral contraceptive use; smoking; and certain drugs	6 treatment cycles,	EE 20 µg and gestodene 75 µg (N=20) versus EE 30 µg and gestodene 75 µg (N=20) Did not report bleeding outcomes.	- Jadad score: 1/5 - FU: NR - ITT: no Other important methodological remarks: -Technique of allocation concealment not reported. Sponsor: Pharmaceutical company

4.1.2.5. Combined oral contraception containing ethinylestradiol 20µg versus >20µg: Authors' conclusions

While COCs containing 20 µg EE may be theoretically safer, this review did not focus on the rare events required to assess this hypothesis. Data from existing randomized controlled trials are inadequate to detect possible differences in contraceptive effectiveness. Low-dose estrogen COCs resulted in higher rates of bleeding pattern disruptions. However, most trials compared COCs containing different progestin types, and changes in bleeding patterns could be related to progestin type as well as estrogen dose. Higher followup rates are essential for meaningful interpretation of results.

4.1.2.bis. Combined oral contraception containing ethinylestradiol 20µg versus >20µg: Summary and conclusions

<table>
<tr><td colspan="5">Ethinyl estradiol 20µg and desogestrel 150µg versus ethinyl estradiol 30µg and desogestrel 150µg. (Basdevant 1993, Akerlund 1993 from Gallo 2011a)</td></tr>
<tr><th>N/n</th><th>Duration</th><th>Population</th><th>Results</th><th></th></tr>
<tr><td rowspan="15">N=2,
n=
1058</td><td rowspan="15">6-12 cycles</td><td rowspan="15">-women 18-40y
-exclusion of CV disease and risk factors

-Basdevant: Healthy women with regular menses, non-obese.</td><td rowspan="3">Pregnancy
N=1
(Akerlund 1993)</td><td>2/485 vs 3/497
OR: 0.69 (0.12-3.97)
NS</td></tr>
<tr><td><u>Quality</u>
-1 no ITT and low FU
<u>Consistency</u>
NA
<u>Directness</u>
OK
<u>Imprecision</u>
OK</td></tr>
<tr><td>Grade assessment: moderate quality of evidence</td></tr>
<tr><td rowspan="3">Discontinuation overall
N=1
(Akerlund 1993)</td><td>174/500 vs 154/500:
OR: 1.20 (0.92-1.56)
NS</td></tr>
<tr><td><u>Quality</u>
-1
<u>Consistency</u>
NA
<u>Directness</u>
OK
<u>Imprecision</u>
OK</td></tr>
<tr><td>Grade assessment: moderate quality of evidence</td></tr>
<tr><td rowspan="3">Discontinuation due to irregular bleeding
N=1
(Akerlund 1993)</td><td>27/500 vs 10/500
OR=2.59 (95% CI 1.35, 5.00)
SS in favor of EE30DSG p = 0.0044</td></tr>
<tr><td><u>Quality</u>
-1
<u>Consistency</u>
NA
<u>Directness</u>
OK
<u>Imprecision</u>
OK</td></tr>
<tr><td>Grade assessment: moderate quality of evidence</td></tr>
<tr><td rowspan="3">Dysmenorrhea
N=1
(Akerlund 1993)</td><td>17/485 vs 12/497
OR=1.46 (95% CI 0.70, 3.06)
NS</td></tr>
<tr><td><u>Quality</u>
-1
<u>Consistency</u>
NA
<u>Directness</u>
OK
<u>Imprecision</u>
OK</td></tr>
<tr><td>Grade assessment: moderate quality of evidence</td></tr>
<tr><td rowspan="3">Increased weight
N=1
(Akerlund 1993)</td><td>15/485 (EE20DSG) vs 6/497 (EE30DSG)
OR=2.46 (95% CI 1.04, 5.84)
SS in favor of EE30DSG p = 0.041</td></tr>
<tr><td><u>Quality</u>
-1
<u>Consistency</u>
NA
<u>Directness</u>
OK
<u>Imprecision</u>
OK</td></tr>
<tr><td>Grade assessment: moderate quality of evidence</td></tr>
</table>

- From A Cochrane review we selected two studies for comparison of ethinyl estradiol 20µg with desogestrel 150µg versus ethinyl estradiol 30µg and desogestrel 150µg. The study of Akerlund is the most important of these. The authors report that the studies have insufficient power to demonstrate a difference in the number of pregnancies.

No difference in the number of unwanted pregnancies can be demonstrated.

GRADE: moderate quality of evidence

Overall, there is no difference in the number of women who discontinue the contraception. More women (OR 2.59) in the group with 20µg EE stop due to irregular bleeding.

GRADE: moderate quality of evidence

No difference could be demonstrated at the dysmenorrhoea endpoint.

GRADE: moderate quality of evidence

In this study, there was more weight gain in women who took the pill with 20µg.

GRADE: moderate quality of evidence

Ethinyl estradiol 20µg and desogestrel 150µg versus ethinyl estradiol 30µg and gestodene 75µg. (Bruni 2000, Kirkman 1994, Teichmann 1995; from Gallo 2011a).

N/n	Duration	Population	Results				
N=3, n= 3925	6-13 cycles	-healthy women 18-42y -1 study: >30y -regular menses -exclusion of CV disease and risk factors	Pregnancy N=2 (Bruni 2000, Teichmann 1995)	3/1014 vs 3/1013 OR=1.00 (95% CI 0.20, 4.96) NS p = 1.0			
				Quality -1 for no blinding	Consistency OK	Directness OK	Imprecision OK
				Grade assessment: *moderate quality of evidence*			
			Discontinuation overall N=3	235/1515 vs 229/1518 OR=1.03 (95% CI 0.85, 1.26) NS p = 0.76			
				Quality -1 for no blinding	Consistency OK	Directness OK	Imprecision OK
				Grade assessment: *moderate quality of evidence*			
			Irregular bleeding N=1 (Kirkman 1994)	At cycle 3: 104/456 vs 46/454 **OR=2.51 (95% CI 1.77, 3.56)** **SS in favor of EE30GSD p <0.00001** At cycle 6: 69/411 vs 43/412 **OR=1.72 (95% CI 1.15, 2.55)** **SS in favor of EE30GSD p=0.0079**			
				Quality -1 for no blinding	Consistency NA	Directness OK	Imprecision OK
				Grade assessment: *moderate quality of evidence*			
			Metrorrhagia N=1 (Bruni 2000)	46/805 vs 28/806 **OR=1.67 (95% CI 1.05, 2.66)** **SS in favor of EE30GSD p =0.032**			
				Quality -1 for no blinding	Consistency NA	Directness OK	Imprecision OK
				Grade assessment: *moderate quality of evidence*			
			Dysmenorrhea N=1 (Bruni 2000)	17/805 vs 18/806 OR=0.94 (95% CI 0.48, 1.85) NS p =0.87			
				Quality -1 for no blinding	Consistency NA	Directness OK	Imprecision OK
				Grade assessment: *moderate quality of evidence*			
			Weight gain in kg N=1 (Kirkman 1994)	0.4±2 vs 0.6±0.2 **Mean difference= -0.20 (95% CI -0.40, 0.00)** **SS in favor of EE20DSG p = 0.045**			
				Quality -1 for no blinding	Consistency NA	Directness OK	Imprecision OK
				Grade assessment: *moderate quality of evidence*			

- From a Cochrane review we selected three studies for comparison of ethinyl estradiol 20µg with desogestrel 150µg versus ethinyl estradiol 30µg and gestodene 75µg. The studies are underpowered to demonstrate a difference in the number of pregnancies. In addition, it is difficult to compare bleeding due to lack of uniformity in recording.

No difference can be demonstrated in the number of unwanted pregnancies.
GRADE: moderate quality of evidence

Overall, there is no difference in the number of women who discontinue the contraception.
GRADE: moderate quality of evidence

In the group with 20µg EE and desogestrel 150µg there are more women with irregular bleeding and with metrorrhagia.
GRADE: moderate quality of evidence

In this study there was less weight gain in women who took the pill with 20µg. This difference amounted to barely 200 grams after 6 cycles.
GRADE: moderate quality of evidence

Ethinyl estradiol 20 µg and desogestrel 150 µg versus ethinyl estradiol 30-40-30 µg and gestodene 50-70-100 µg. (Bruni 2000 from Gallo 2011a).

N/n	Duration	Population	Results				
N=1, n= 2419	13 cycles	-healthy women <42y -regular menses -exclusion of CV disease and risk factors	Pregnancy	2/805 vs 2/808 OR=1.00(95% CI 0.14, 7.14) NS p =1.0			
				Quality -2 for no blinding, no ITT and low FU	Consistency NA	Directness OK	Imprecision OK
				Grade assessment: *Low quality of evidence*			
			Discontinuation overall	132/805 vs 125/808 OR=1.07(95% CI 0.82, 1.40) NS p =0.61			
				Quality -2	Consistency NA	Directness OK	Imprecision OK
				Grade assessment: *Low quality of evidence*			
			Metrorrhagia	46/805 vs 20/808 **OR=2.28(95% CI 1.39, 3.73)** **SS in favor of EE30-40-30/GSD50-70-100 p =0.0010**			
				Quality -2	Consistency NA	Directness OK	Imprecision OK
				Grade assessment: *Low quality of evidence*			
			Dysmenorrhea	17/805 vs 14/808 OR=1.22 (95% CI 0.60, 2.49) NS p =0.58			
				Quality -2	Consistency NA	Directness OK	Imprecision OK
				Grade assessment: Low *quality of evidence*			
			Menstrual disorder	10/805 vs 7/808 OR=1.43(95% CI 0.55, 3.73) NS p =0.46			
				Quality -2	Consistency NA	Directness OK	Imprecision OK
				Grade assessment: *Moderate quality of evidence*			

- A study selected from a Cochrane review investigated the comparison of ethinyl estradiol 20µg with desogestrel 150µg versus ethinyl estradiol 30-40-30µg and gestodene 50-70-100µg.

No difference can be demonstrated in the number of unwanted pregnancies.

GRADE: low quality of evidence

Overall, there is no difference in the number of women who discontinue the contraception.

GRADE: low quality of evidence

There are more women with metrorrhagia in the group with 20µg EE and desogestrel 150µg.

GRADE: Low quality of evidence

Ethinyl estradiol 20 µg and gestodene 75 µg versus ethinyl estradiol 30µg and gestodene 75µg. (Brill 1996 (a), Winkler 1996 (b), Endrikat 1997 (c), Taneepanichskul (d) 2002 from Gallo 2011a).

N/n	Duration	Population	Results				
N=4, n= 903	6-13 cycles	-healthy women 18-39y -regular menses -exclusion of CV disease and risk factors	Pregnancy N=2 (Endrikat 1997, Taneepanichskul 2002)	1/504 vs 2/295 OR=0.23(95% CI 0.02, 2.55) NS p =0.23			
				Quality -2 incomplete reporting, no ITT and low FU	Consistency OK	Directness OK	Imprecision OK
				Grade assessment: *low quality of evidence*			
			Discontinuation overall N=2 (Endrikat 1997, Taneepanichskul 2002)	110/504 vs 59/295 OR=1.14(95% CI 0.80, 1.63) NS p =0.46			
				Quality -2	Consistency OK	Directness OK	Imprecision OK
				Grade assessment: *low quality of evidence*			
			Discontinuation due to metrorrhagia N=1 (Winkler 1996)	0/20 vs 1/20 OR=0.14(95% CI 0.0, 6.82) NS p=0.32			
				Quality -2 incomplete reporting, no ITT and low FU	Consistency NA	Directness OK	Imprecision -1
				Grade assessment: very *low quality of evidence*			
			Breakthrough bleeding N=1 (Taneepanichskul 2002)	At cycle 3: 1/59vs 0/55 OR=6.90(95% CI 0.14, 348.82) NS p=0.33 At cycle 6: 0/59 vs 1/55 OR=0.13(95% CI 0.00, 6.36) NS p=0.30			
				Quality -2	Consistency NA	Directness OK	Imprecision -1
				Grade assessment: very *low quality of evidence*			
			Weight gain in kg N=1 (Taneepanichskul 2002)	50.6 ±6.5 vs 52.1±8.2 Mean difference= -1.5(95% CI -4.23, 1.23) NS p = 0.28			
				Quality -2	Consistency NA	Directness OK	Imprecision OK
				Grade assessment: *low quality of evidence*			

- From a Cochrane review we selected four studies for the comparison of ethinyl estradiol 20µg with gestodene 75µg versus ethinyl estradiol 30µg and gestodene 75µg. There is insufficient power to demonstrate a difference in the number of pregnancies. In addition, it is difficult to compare bleeding due to the lack of uniformity in recording.

No difference can be demonstrated in the number of unwanted pregnancies.
GRADE: low quality of evidence

Overall, there is no difference in the number of women who discontinue the contraception.
GRADE: low quality of evidence

Neither can a difference in weight or a difference in breakthrough bleeding be demonstrated.
GRADE: low quality of evidence

4.1.3. Combined oral contraception: triphasic vs monophasic. Evidence tables.

4.1.3.1. Triphasic combined oral contraceptive containing levonorgestrel versus monophasic combined oral contraceptives

Ref	N/n	Comparison	Outcomes	
* Van Vliet 2011a Design: Systematic review and meta-analysis Search date: Aug 2011 N= 23 n= 20818	N= 8	**Triphasic LNG 50-75-125 μg and EE 30-40-30 μg versus monophasic LNG 150 μg and EE 30 μg**	Pregnancy per woman within 6 cycles (N=2; Chen,1987 ; Zador,1979)	2/350 (Tri) vs 3/328(Mono) OR=0.64 (95% CI 0.10, 3.91) NS p = 0.63
			Pregnancy per woman within 12 cycles (N=5: Carlborg, 1983; Dunson, 1993; Engebretsen, 1987 ; Ramos, 1989 ; Saxena, 1992)	3/2094(Tri) vs 2/2051 (Mono) OR= 1.35 (95% CI 0.25, 7.22) NS p = 0.72
			Proportion of cycles with spotting within 6 cycles (N=2; Carlborg, 1983; Zador, 1979)	**254/3682(Tri) vs 415/3608 (Mono) OR= 0.57 (95% CI 0.48, 0.67) SS in favor of triphasic p <0.00001**
			Proportion of cycles with breakthrough bleeding within 6 cycles (N=2; Carlborg, 1983; Zador, 1979)	**125/3682(Tri) vs 190/3608 (Mono) OR= 0.63 (95% CI 0.50, 0.80) SS in favor of triphasic p <0.00011**
			Proportion of cycles with spotting within 12 cycles (N=1; Carlborg, 1983)	**192/3197(Tri) vs 318/3275 (Mono) OR= 0.59 (95% CI 0.49, 0.72) SS in favor of triphasic p <0.00001**
			Proportion of cycles with breakthrough bleeding within 12 cycles (N=1; Carlborg, 1983)	**86/3197(Tri) vs 147/3275 (Mono) OR= 0.59 (95% CI 0.45, 0.77) SS in favor of triphasic p =0.00012**
			Proportion of women with intermenstrual bleeding within 12 cycles (N=1; Dunson ,1993)	38/495(Tri) vs 44/484(Mono) OR= 0.83 (95% CI 0.53, 1.31) NS p = 0.43
			Proportion of women with spotting at cycle 6 (N=1; Ramos, 1989)	1/523(Tri) vs 4/509(Mono) OR= 0.24 (95% CI 0.03, 2.17) NS p = 0.20
			Proportion of women with breakthrough bleeding at cycle 6 (N=1; Ramos, 1989)	5/523(Tri) vs 2/509(Mono) OR= 2.45 (95% CI 0.47, 12.67) NS p = 0.29
			Proportion of women with spotting at	1/440(Tri) vs 1/456(Mono)

			cycle 12 (N=1; Ramos, 1989)	OR= 1.04 (95% CI 0.06, 16.62) NS p = 0.98
			Proportion of women with breakthrough bleeding at cycle 12 (N=1; Ramos, 1989)	1/440(Tri) vs 2/456(Mono) OR= 0.52(95% CI 0.05, 5.72) NS p = 0.59
			Proportion of cycles with amenorrhea within 6 cycles (N=1;Zador ,1979)	13/1440(Tri) vs 21/1337(Mono) OR= 0.57(95% CI 0.28, 1.14) NS p = 0.11
			Proportion of cycles with amenorrhea within 12 cycles (N=1; Carlborg, 1983)	**20/3197(Tri) vs 74/3275 (Mono)** **OR= 0.27 (95% CI 0.17, 0.45)** **SS in favor of triphasic p <0.00001**
			Proportion of women with amenorrhea within 12 cycles (N=1; Dunson, 1993)	3/495(Tri) vs 2/484(Mono) OR= 1.47(95% CI 0.24, 8.83) NS p = 0.67
			Total discontinuation within 6 cycles (N=4 : Carlborg, 1983; Chen, 1987 ; Kashanian, 2010 ; Zador, 1979)	120/922(Tri) vs 114/907(Mono) OR= 1.04(95% CI 0.78, 1.37) NS p = 0.80
			Total discontinuation within 12 cycles (N=4; Dunson, 1993; Engebretsen, 1987 ; Ramos, 1989 ; Saxena, 1992)	884/1677(Tri) vs 818/1633(Mono) OR= 1.13(95% CI 0.97, 1.31) NS p = 0.13
			Discontinuation due to medical reasons within 12 cycles (N=3; Dunson, 1993; Ramos, 1989; Saxena, 1992)	131/1527 (Tri) vs 119/1483(Mono) OR= 1.12(95% CI 0.71, 1.76) NS p = 0.64
			Discontinuation due to cycle disturbances within 12 cycles (N=3; Dunson, 1993; Engebretsen, 1987; Saxena, 1992)	19/1076 (Tri) vs 16/1033(Mono) OR= 1.11(95% CI 0.56, 2.21) NS p = 0.77
			Discontinuation due to intermenstrual bleeding within 12 cycles (N=1: Ramos, 1989)	7/601 (Tri) vs 5/600(Mono) OR= 1.40(95% CI 0.44, 4.44) NS p = 0.57

	N=3	**Triphasic LNG 50-75-125 µg and EE 30-40-30 µg versus monophasic DSG 150 µg and EE 30 µg**	Pregnancy per woman within 6 cycles (N=1; Lachnit-Fixson, 1984)	1/278 (Tri) vs 0/277(Mono) OR= 3.00(95% CI 0.12, 73.96) NS p = 0.50
			Pregnancy per woman within 12 cycles (N=2; Dieben ,1984 ;Ismail, 1991)	6/571 (Tri) vs 0/575(Mono) OR= 7.22(95% CI 0.88, 59.00) NS p = 0.065
			Proportion of cycles with spotting within 6 cycles (N=1; Dieben ,1984)	251/2617 (Tri) vs 218/2618(Mono) OR= 1.17(95% CI 0.97, 1.41) NS p = 0.11
			Proportion of cycles with spotting within 6 cycles (N=1; Lachnit-Fixson, 1984)	**98/1536 (Tri) vs 252/1524(Mono)** **OR= 0.34(95% CI 0.27, 0.44)** **SS in favor of triphasic p < 0.00001**
			Proportion of cycles with breakthrough bleeding within 6 cycles (N=1; Dieben ,1984)	251/2617 (Tri) vs 218/2618(Mono) OR= 1.17(95% CI 0.97, 1.41) NS p = 0.11
			Proportion of cycles with breakthrough bleeding within 6 cycles (N=1; Lachnit-Fixson, 1984)	**18/1536 (Tri) vs 43/1524(Mono)** **OR= 0.41(95% CI 0.23, 0.71)** **SS in favor of triphasic p < 0.0016**
			Proportion of cycles with spotting and breakthrough bleeding within 6 cycles (N=2; Dieben ,1984 ; Lachnit-Fixson, 1984)	**20/4153 (Tri) vs 40/4142(Mono)** **OR= 0.50(95% CI 0.29, 0.86)** **SS in favor of triphasic p < 0.013**
			Proportion of cycles with spotting within 12 cycles (N=1; Dieben ,1984)	257/2709 (Tri) vs 224/2769(Mono) OR= 1.19(95% CI 0.99, 1.44) NS p = 0.11
			Proportion of cycles with breakthrough bleeding within 12 cycles (N=1; Dieben ,1984)	178/2709 (Tri) vs 168/2769(Mono) OR= 1.09(95% CI 0.88, 1.35) NS p = 0.44
			Proportion of cycles with spotting and breakthrough bleeding within 12 cycles (N=1; Dieben ,1984)	15/2709 (Tri) vs 24/2769(Mono) OR= 0.64 (95% CI 0.33, 1.22) NS p = 0.17
			Proportion of women with staining/spotting within 12 cycles (N=1; Ismail, 1991)	6/98 (Tri) vs 4/99(Mono) OR= 1.55 (95% CI 0.42, 5.67) NS p = 0.51
			Proportion of women with moderate flow intermenstrual bleeding within 12 cycles	5/98 (Tri) vs 2/99 (Mono) OR= 2.61 (95% CI 0.49, 13.77)

			(N=1; Ismail, 1991)	NS p = 0.26
			Proportion of women with spotting at cycle 6 (N=1; Dieben ,1984)	21/399 (Tri) vs 16/398 (Mono) OR= 1.33 (95% CI 0.68, 2.58) NS p = 0.41
			Proportion of women with breakthrough bleeding at cycle 6 (N=1; Dieben ,1984)	24/399 (Tri) vs 16/398 (Mono) OR= 1.53 (95% CI 0.80, 2.92) NS p = 0.20
			Proportion of women with spotting and breakthrough bleeding at cycle 6 (N=1; Dieben ,1984)	1/399 (Tri) vs 2/398 (Mono) OR= 0.50 (95% CI 0.04, 5.51) NS p = 0.57
			Proportion of cycles with amenorrhea within 6 cycles (N=1; Dieben ,1984)	206/2617 (Tri) vs 194/2618(Mono) OR= 1.07(95% CI 0.87, 1.31) NS p = 0.53
			Proportion of cycles with amenorrhea within 6 cycles (N=1; Lachnit-Fixson, 1984)	**3/1536 (Tri) vs 14/1524(Mono)** **OR= 0.21(95% CI 0.06, 0.74)** **SS in favor of triphasic p < 0.015**
			Proportion of cycles with amenorrhea within 12 cycles (N=1; Dieben ,1984)	210/2709 (Tri) vs 205/2769(Mono) OR= 1.05(95% CI 0.86, 1.28) NS p = 0.63
			Proportion of women with amenorrhea within 12 cycles (N=1; Ismail, 1991)	3/98 (Tri) vs 2/99(Mono) OR= 1.53 (95% CI 0.25, 9.37) NS p = 0.64
			Proportion of women with amenorrhea at cycle 6 (N=1; Dieben ,1984)	28/399 (Tri) vs 21/398 (Mono) OR= 1.35 (95% CI 0.76, 2.43) NS p = 0.31
			Total discontinuation within 6 cycles (N=2; Dieben ,1984 ; Lachnit-Fixson, 1984)	110/751 (Tri) vs 110/752 (Mono) OR= 1.00 (95% CI 0.75, 1.33) NS p = 0.99
			Discontinuation due to medical reasons within 6 cycles (N=2; Dieben ,1984 ; Lachnit-Fixson, 1984)	69/751 (Tri) vs 86/752 (Mono) OR= 0.71 (95% CI 0.36, 1.43) NS p = 0.34
			Discontinuation due to cycle disturbances within 6 cycles (N=1; Dieben ,1984)	23/473 (Tri) vs 22/475 (Mono) OR= 1.05 (95% CI 0.58, 1.92 NS p = 0.87
			Total discontinuation within 12 cycles (N=1; Ismail, 1991)	41/98 (Tri) vs 33/99(Mono) OR= 1.44 (95% CI 0.81, 2.57)

				NS p = 0.22
			Discontinuation due to medical reasons within 12 cycles (N=1; Ismail, 1991)	7/98 (Tri) vs 5/99(Mono) OR= 1.45 (95% CI 0.44, 4.72) NS p = 0.54
			Discontinuation due to cycle disturbances within 12 cycles (N=1; Ismail, 1991)	3/98 (Tri) vs 0/99(Mono) OR= 7.29 (95% CI 0.37, 143.08) NS p = 0.19

	N=1	**Triphasic LNG 50-75-125 µg and EE 30-40-30 µg versus monophasic NET 1000 µg and EE 35 µg**	Proportion of women with intermenstrual bleeding within 12 cycles (N=1; Reiter, 1990)	15/132 (Tri) vs 23/128(Mono) OR= 0.59 (95% CI 0.29, 1.18) NS p = 0.13
			Proportion of women with amenorrhea within 12 cycles (N=1; Reiter, 1990)	**0/132 (Tri) vs 16/128(Mono)** **OR= 0.03 (95% CI 0.00, 0.43)** **SS in favor of triphasic p = 0.011**

* Characteristics of included studies: see under

Ref + design	n	Population	Duration	Comparison	Methodology
Chen 1987 Double-blind, randomized controlled trial. (in China)	279	women -aged 23-34 years -ability to record menstrual cycle on a diary -have normal physical examination and PAP smear. Exclusion criteria were diabetes mellitus, heart, liver, kidney or nervous system disease, cancer, hypertension, use of hormones 2 months prior to the study, use of injectable contraceptives 6 months prior to the study	6 cycles.	**Triphasic LNG 50-75-125 μg and EE 30-40-30 μg (n= 96)** **versus** **monophasic LNG 150 μg and EE 30 μg (n=93)** **versus** versus monophasic NET 600 μg and EE 35 μg	- Jadad score:4/5 - FU: 82% - ITT:No Other important methodological remarks: - Allocation concealment not described -The report does not provide an a priori hypothesis or a sample size or power calculation. "Sponsor": the World Health Organization
Zador 1979 Randomized controlled trial without blinding. (sites in Sweden, Great Britain and Germany)	489	women -had to meet the requirements for the prescription of oral contraceptives in accordance with established medical practice. Limited information about baseline demographics. The paper does not report if switchers were included in the study	6 cycles.	**Triphasic LNG 50-75-125 μg and EE 30-40-30 μg (**6/5/10 regimen) **versus monophasic LNG 150 μg and EE 30 μg (**21 days)	- Jadad score: 1-2/5 - FU: 85.3% - ITT:unclear, yes by cochrane Other important methodological remarks: -Method of allocation concealment not described -The report does not provide an a priori hypothesis or a sample size or power calculation. - Breakthrough bleeding was defined as intermenstrual bleeding that required the use of sanitary protection and spotting as all other cases including slight brownish discharge Sponsor: Schering

Carlborg 1983 Randomized controlled trial (12 sites in Sweden)	862	women -had to fulfill the current recommendations for oral contraceptive use. Limited information on baseline characteristics. Switchers were included in the study Data on side effects were recorded if reported spontaneously	6 and 12 cycles	Three arms: **Triphasic LNG 50-75-125 μg and EE 30-40-30 μg** (n=210 for 6 cycles of whom n=89 continued for an additional 6 cycles) versus **Triphasic LNG 50-75-125 μg and EE 30-40-30 μg** , (n=207 for 6 cycles of whom n=93 continued for an additional 6 cycles) versus **monophasic LNG 150 μg and EE 30 μg** (n= 418 for 6 cycles of whom n=189 continued for an additional 6 cycles)	- Jadad score:4 /5 - FU: 82.1% (6 first cycles) - ITT:No Other important methodological remarks: -Report does not mention the use of allocation concealment. Communication with the author indicated allocation concealment by numbered pharmacy packages -The report does not provide an a priori hypothesis or a sample size or power calculation. - Breakthrough bleeding was defined as intermenstrual bleeding which required the use of sanitary protection and spotting as all other cases. Sponsor: Schering
Dunson, 1993 Randomized controlled trial without blinding. (5 sites in Sudan, Sri Lanka, Chile, Ecuador and Dominican Republic)	1088	healthy women -aged 18 to 35 years - sexually active -at least one normal menstrual period since the last pregnancy or the last use of a steroidal contraceptive. Exclusion criteria were contraindications to oral contraceptive use, termination of pregnancy less than 42 days prior to admission if not breastfeeding or termination of pregnancy less than 4 months prior to admission if breastfeeding. Switchers were included in the	12 cycles	**Triphasic LNG 50-75-125 μg and EE 30-40-30 μg versus monophasic LNG 150 μg and EE 30 μg**	- Jadad score:2/5 - FU: 23%(39% lost to FU, 38% early discontinuation) - ITT: yes Other important methodological remarks: -Allocation concealment not described in report. Communication with the authors indicated allocation concealment by use of sequentially-numbered, opaque, sealed envelopes. -The report does not provide an a priori hypothesis or a sample size calculation. - Outcome measures cycle control and side effects differ between the various sites - The report does not describe the definitions of breakthrough bleeding and spotting.

		study.			Sponsor: Family Health International
Engebretsen 1987 Randomized controlled trial without blinding. (5 sites in Norway)	300	women -aged 15 to 35 years -who did not use oral contraceptives in the month prior to the study at. The participants group had a high rate of abortus provocatus. Exclusion criteria were a history of thrombosis or thrombophlebitis, liver-disease, cancer, history of herpes gestationis, pregnancy, hypertension and oral contraceptive use in the month prior to the study	12cycles.	**Triphasic LNG 50-75-125 μg and EE 30-40-30 μg (**6/5/10 days regimen) **versus** **monophasic LNG 150 μg and EE 30 μg (**21 days)	- Jadad score: 1-2/5 - FU: 70,3% - ITT:no, yes by cochrane Other important methodological remarks: -No information on allocation concealment - Limited information on outcome measures - The report does not provide an a priori hypothesis or a sample size or power calculation. - The report does not describe the definitions of spotting and breakthrough bleeding. - unclear whether the pregnancies were caused by method failures solely or by both method and user failures Sponsor: no information on support
Ramos 1989 Randomized controlled trial with blinding of investigators and participants. (18 sites in the Philippines)	1800	The report does not describe the inclusion and exclusion criteria for the study. Switchers were included in the study. 27% to 32% of the participating women lactated at the time of admission	12 cycles	**Triphasic LNG 50-75-125 μg and EE 30-40-30 μg (**6/5/10 days regimen) (n=601) **versus** **monophasic LNG 150 μg and EE 30 μg (**21 days) (n=600) Breakthrough bleeding was defined as intermenstrual bleeding that required the use of sanitary protection, and spotting as intermenstrual bleeding which required	- Jadad score:4 /5 - FU: 73,7% - ITT: no Other important methodological remarks: -The report does not provide an a priori hypothesis or a sample size or power calculation. Sponsor: United Nations Population Fund and by (Wyeth-Ayerst) (Pascual Laboratories)

				no use of pads	
Saxena 1992 Open randomized controlled trial. (11 sites in India)	721	women -in reproductive age exposed to the risk of pregnancy Exclusion criteria were contraindications for oral contraceptive use. The paper does not report if switchers were included	12 cycles	**Triphasic LNG 50-75-125 μg and EE 30-40-30 μg (**6/5/10 days regimen and 7 days of placebo tablets) **versus monophasic LNG 150** **μg and EE 30 μg (**21 days and 7 days of placebo tablets) Bleeding pattern was analyzed according to the recommendations by Rodriguez 1976	- Jadad score: 3 /5 - FU: 36,5% (large early discontinuation) - ITT: no, yes by Cochrane Other important methodological remarks: -The report does not provide an a priori hypothesis or a sample size or power calculation. - unclear whether the pregnancies were caused by method failures solely or by both method and user failures Sponsor: Indian Council of Medical Research
Dieben 1984 Open Randomized controlled trial (sites in 6 European countries)	948	Healthy, women -fertile -with a regular cycle -and normally exposed to the risk of pregnancy. Exclusion criteria were history of thromboembolic disease, thrombophlebitis, disturbance of liver function, jaundice or a history of jaundice in pregnancy, mammary carcinoma,estrogen-dependent tumor, undiagnosed genital bleeding, sickle-cell anemia, porphyria cutanea tarda, cardiovascular disease, treatment with rifampicin, tetracyclines, phenylhydantoin and phenobarbitone, no spontaneous menstruation	6 and 12 cycles	**Triphasic LNG 50-75-125 μg and EE 30-40-30 μg** N=473 for 6 cycles of whom N=38 continued for an additional 6 cycles) **versus** **monophasic DSG 150 μg and EE 30 μg (**21 days) N=475 for 6 cycles of whom N=54 continued for an additional 6 cycles)	- Jadad score: 1/5 - FU: 84,9% - ITT: No; yes by Cochrane Other important methodological remarks: -Report describes outcome measures unclearly. - The report does not provide an a priori hypothesis or a sample size or power calculation. - no concealment of the allocation sequence - Withdrawal bleeding was defined as bleeding which begins in the tablet-free period; spotting as scanty bleeding outside the tablet-free period that does not require any hygienic measures or at most one sanitary pad per day; and breakthrough

		postpartum or postabortal, breastfeeding			bleeding as bleeding that is not spotting and which cannot be considered as withdrawal bleeding. Sponsor: Organon (manufacturer of the studied monophasic DSG/EE pill)
Ismail 1991 Open Randomized controlled trial (Malaysia)	200	Healthy women -aged 18 to 35 years -sexually active, -willing to rely exclusively upon the pills as the only method of contraception -and had at least one menstrual period since the last pregnancy. Exclusion criteria were contraindications to oral contraceptives, termination of pregnancy less than 42 days prior to admission and breastfeeding. Switchers were included in the study	12 cycles	**Triphasic LNG 50-75-125 μg and EE 30-40-30 μg (**6/5/10 days regimen) **versus monophasic DSG 150 μg and EE 30 μg (**21 days) The report does not describe the definitions of breakthrough bleeding and spotting	- Jadad score: 2-3/5 - FU: 50% (mainly early discontinuation) - ITT:No Other important methodological remarks: -The method of collecting the data on cycle control and side effects is unclear -The report does not provide an a priori hypothesis or a sample size or power calculation. Sponsor: Family Health International
Lachnit-Fixson 1984 Randomized controlled trial. (sites in Austria, Germany, the Netherlands and the United Kingdom)	555	The report does not provide inclusion/exclusion criteria for the study. Little information about baseline demographics. The paper does not report if switchers were included in the study	6 cycles.	**Triphasic LNG 50-75-125 μg and EE 30-40-30 μg (**6/5/10 days regimen) **versus monophasic DSG 150μg and EE 30 μg (**21 days)	- Jadad score: 1/5 - FU: 84.5%? - ITT:unclear. yes by Cochrane Other important methodological remarks: -No information on allocation concealment - The report does not provide an a priori hypothesis. Report states a sample size, yet the sample size calculation is unclear. - Data on side effects were recorded if reported spontaneously. - The report does not describe the

					definitions of breakthrough bleeding and spotting Sponsor: Schering (manufacturer of the studied triphasic levonorgestrel/ethinylestradiol pill)
Reiter 1990 Open randomized controlled trial (sites in the U.S.A.) Three arms study	477	Women -aged 18 years or older. Exclusion criteria were contraindications to oral contraceptive use. Little information about baseline demographics. All participants were first-time oral contraceptive users	12 cycles.	Triphasic NET 500-750-1000 µg and EE 35 µg (n= 117) versus **Triphasic LNG 50-75-125 µg and EE 30-40-30 µg** (n=132) versus NET 1000 µg and EE 35 µg (n=128) .	- Jadad score:2 /5 - FU: 79% (early discontinuation) - ITT:no; yes by Cochrane Other important methodological remarks: - No allocation concealment - The report does not provide an a priori hypothesis or a sample size or power calculation. - The report contains no references to other studies. - Limited information on outcome measures - no reporting of data regarding pregnancy - Breakthrough bleeding was defined as any spotting or bleeding between menstrual periods, and amenorrhea as the absence of spotting or bleeding during the expected time of the menstrual period Sponsor: Planned Parenthood Federation of America

Remarks
Follow up defined as postrandomisation exclusions, early discontinuation or lost to follow up

4.1.3.2. Triphasic combined oral contraceptive containing norethisterone versus monophasic combined oral contraceptives

Ref	N/n	Comparison	Outcomes	
* Van Vliet 2011a Design: meta-analysis N= 23 n= 20818 Search date: Aug 2011	N=1 n=477	Triphasic NET 500-750-1000 µg and EE 35 µg versus monophasic NET 1000 µg and EE 35 µg	Proportion of women with intermenstrual bleeding within 12 cycles (N=1; Reiter, 1990)	22/117 (Tri) vs 23/128(Mono) OR= 1.06 (95% CI 0.55, 2.02) NS p = 0.87
			Proportion of women with amenorrhea within 12 cycles (N=1; Reiter, 1990)	**4/117 (Tri) vs 16/128(Mono)** **OR= 0.25 (95% CI 0.08, 0.76)** **SS in favor of triphasic p = 0.015**

* Characteristics of included studies: see under

Ref + design	n	Population	Duration	Comparison	Methodology
Reiter 1990 Open randomized controlled trial (sites in the U.S.A.)	477	Women -aged 18 years or older. Exclusion criteria were contraindications to oral contraceptive use. Little information about baseline demographics. All participants were first-time oral contraceptive users	12 cycles.	Triphasic NET 500-750-1000 µg and EE 35 µg (n= 117) vs **Triphasic LNG 50-75-125 µg and EE 30-40-30 µg** (n=132) versus NET 1000 µg and EE 35 µg (n=128) Breakthrough bleeding was defined as any spotting or bleeding between menstrual periods, and amenorrhea as the absence of spotting or bleeding during the expected time of the menstrual period.	- Jadad score:2 /5 - FU: 79% (early discontinuation) - ITT:no, yes by Cochrane Other important methodological remarks: - No allocation concealment - The report does not provide an a priori hypothesis or a sample size or power calculation. - The report contains no references to other studies. - Limited information on outcome measures - no reporting of data regarding pregnancy Sponsor: Planned Parenthood Federation ofAmerica

4.1.3.3. Triphasic combined oral contraceptive containing gestodene versus monophasic combined oral contraceptives

Ref	N/n	Comparison	Outcomes	
* Van Vliet 2011a Design: meta-analysis N= 23 n= 20818 Search date: Aug 2011	N=2	**Triphasic GTD 50-70-100 µg and EE 30-40-30 µg versus monophasic DSG 150 µg and EE 30 µg**	Pregnancy per woman within 6 cycles (N=1: Andrade, 1993)	1/250 (Tri) vs 0/230(Mono) OR= 2.77 (95% CI 0.11, 68.38) NS p = 0.53
			Pregnancy per woman within 12 cycles (N=1 :Agoestina, 1987)	1/84 (Tri) vs 1/84(Mono) OR= 1.00 (95% CI 0.06, 16.26) NS p = 1.0
			Proportion of cycles with spotting within 6 cycles (N=1; Andrade, 1993)	108/1328 (Tri) vs 100/1187(Mono) OR= 0.96 (95% CI 0.72, 1.28) NS p = 0.79
			Proportion of cycles with breakthrough bleeding within 6 cycles (N=1: Andrade, 1993)	25/1328 (Tri) vs 27/1187(Mono) OR= 0.82 (95% CI 0.48, 1.43) NS p = 0.49
			Proportion of cycles with spotting and breakthrough bleeding within 6 cycles (N=1:Andrade, 1993)	**40/1328 (Tri) vs 71/1187(Mono)** **OR= 0.49 (95% CI 0.33, 0.73)** **SS in favor of triphasic p = 0.00038**
			Proportion of women with spotting at cycle 6 (N=2 :Agoestina, 1987; Andrade, 1993)	17/266(Tri) vs 15/244Mono) OR= 1.03 (95% CI 0.50, 2.12) NS p = 0.94
			Proportion of women with breakthrough bleeding at cycle 6 (N=1 :Agoestina, 1987)	8/79Tri) vs 8/79(Mono) OR= 1.00 (95% CI 0.36, 2.81) NS p = 1.0
			Proportion of women with breakthrough bleeding (with or without spotting) at cycle 6 (N=1:Andrade, 1993)	6/187 (Tri) vs 9/165(Mono) OR= 0.57 (95% CI 0.20, 1.65) NS p = 0.30
			Proportion of women with spotting at cycle 12 (N=1 :Agoestina, 1987)	6/73 (Tri) vs 4/71(Mono) OR= 1.50 (95% CI 0.40, 5.56) NS p = 0.54
			Proportion of women with breakthrough bleeding at cycle 12 (N=1 :Agoestina, 1987)	5/73 (Tri) vs 5/71(Mono) OR= 0.97 (95% CI 0.27, 3.51) NS p = 0.96
			Proportion of cycles with amenorrhea within 6 cycles	4/1261 (Tri) vs 6/1142(Mono) OR= 0.60 (95% CI 0.17, 2.14)

			(N=1:Andrade, 1993)	NS p = 0.43
			Proportion of cycles with amenorrhea within 12 cycles (N=1:Andrade, 1993)	5/1328 (Tri) vs 7/1187(Mono) OR= 0.82 (95% CI 0.48, 1.43) NS p = 0.49
			Proportion of women with amenorrhea at cycle 6 (N=2 :Agoestina, 1987; Andrade, 1993)	1/266(Tri) vs 2/244Mono) OR= 0.49 (95% CI 0.04, 5.56) NS p = 0.57
			Proportion of women with amenorrhea at cycle 12 (N=2 :Agoestina, 1987; Andrade, 1993)	1/73 (Tri) vs 3/71(Mono) OR= 0.31 (95% CI 0.03, 3.10) NS p = 0.32
			Total discontinuation within 6 cycles (N=2 :Agoestina, 1987; Andrade, 1993)	54/334(Tri) vs 55/314Mono) OR= 0.89 (95% CI 0.59, 1.35) NS p = 0.58
			Discontinuation due to medical reasons within 6 cycles (N=1:Andrade, 1993)	26/250(Tri) vs 27/230(Mono) OR= 0.87 (95% CI 0.49, 1.54) NS p = 0.64
			Discontinuation due to cycle disturbances within 6 cycles (N=1:Andrade, 1993)	5/250(Tri) vs 6/230(Mono) OR= 0.76 (95% CI 0.23, 2.53) NS p = 0.66
			Total discontinuation within 12 cycles (N=1 :Agoestina, 1987)	11/84(Tri) vs 13/84(Mono) OR= 0.82 (95% CI 0.35, 1.96) NS p = 0.66
			Discontinuation due to medical reasons within 12 cycles (N=1 :Agoestina, 1987)	2/84(Tri) vs 1/84(Mono) OR= 2.02 (95% CI 0.18, 22.76) NS p = 0.57
	N=1	**Triphasic GTD 50-70-100 µg and EE 30-40-30 µg versus monophasic DSG 150 µg and EE 20 µg**	Pregnancy per woman within 13 cycles (N=1 :Bruni, 2000)	2/808(Tri) vs 2/805(Mono) OR= 1.00 (95% CI 0.14, 7.09) NS p = 1.0
			Total discontinuation within 13 cycles. (N=1 :Bruni, 2000)	234/808(Tri) vs 219/805(Mono) OR= 1.09 (95% CI 0.88, 1.36) NS p = 0.43
			Discontinuation due to medical reasons within 13 cycles. (N=1 :Bruni, 2000)	65/808(Tri) vs 75/805(Mono) OR= 0.85 (95% CI 0.60, 1.21) NS p = 0.36

		Triphasic GTD 50-70-100 µg and EE 30-40-30 µg versus monophasic GTD 75 µg and EE 30 µg	Pregnancy per woman within 13 cycles (N=1 :Bruni, 2000)	2/808(Tri) vs 3/806(Mono) OR= 0.66 (95% CI 0.11, 3.99) NS p = 0.65
			Total discontinuation within 13 cycles. (N=1 :Bruni, 2000)	234/808(Tri) vs 245/806(Mono) OR= 0.93 (95% CI 0.75, 1.16) NS p = 0.53
			Discontinuation due to medical reasons within 13 cycles. (N=1 :Bruni, 2000)	65/808(Tri) vs 59/806(Mono) OR= 1.11 (95% CI 0.77, 1.60) NS p = 0.58

* Characteristics of included studies: see under

Ref + design	n	Population	Duration	Comparison	Methodology
Agoestina 1987 Randomized controlled trial. (3 sites in Indonesia)	170	Healthy women. Exclusion criteria were contraindications to oral contraceptives, use of hormonal contraceptives within the previous 3 cycles before enrollment and current pregnancy. The mean age of the 2 groups of participants differs.	12 cycles	Triphasic GTD 50-70-100 g and EE 30-40-30 g (6/5/10 days regimen) versus monophasic DSG 150 g and EE 30 g (21 days)	- Jadad score:2 /5 - FU: 85.7% - ITT:no; yes by Cochrane Other important methodological remarks: - The report does not provide an a priori hypothesis or a sample size or power calculation. - The report does not describe the definitions of breakthrough bleeding and spotting Sponsor: Schering (manufacturer of the studied triphasic gestodene/ethinylestradiol pill)

Andrade 1993 Open randomized controlled trial (14 study sites in Europe and New Zealand)	480	Healthy women -Age <40 years of age who were -at risk of becoming pregnant and had -regular 21 to 35 day menstrual cycles The report does not provide exclusion criteria for the study. Switchers were included in the study	6 and 12 cycles.	Triphasic GTD 50-70-100 g and EE 30-40-30 g (6/5/10 days regimen) (n=250 for 6 cycles of whom n=13 continued for an additional 6 cycles) versus monophasic DSG 150 g and EE 30 g (n=230 for 6 cycles of whom n=8 continued for an additional 6 cycles) (21 days)	- Jadad score: 2/5 - FU: 83% (mainly early discontinuation) - ITT: no; yes by Cochrane Other important methodological remarks: - No information on allocation concealment - The report does not describe an a priori hypothesis or sample size or power calculation. - The report does not describe the definitions of breakthrough bleeding and spotting. Sponsor: The paper does not report information on support
Bruni 2000 Open randomized controlled trial (18 countries worldwide) Three arms study	2419	Women -age 18 to 41 years -regular menstrual cycles. Exclusion criteria were hypersensitivity to estrogens or progestogens, current pregnancy, breastfeeding, disorders that might interfere with the study protocol. Little information about baseline demographics. The paper does not report if switchers were included in the study	13 cycles.	Triphasic GTD 50-70-100 µg GTD and EE 30-40-30 µg, (n=808) versus monophasic GTD 75 µg and 30 µg EE (for 21 days, n=806) versus monophasic 150 µg DSG and 20 µg EE (for 21 days, n=805)	- Jadad score: 2/5 - FU: 58,2% (mainly early discontinuation) - ITT:no, yes by Cochrane Other important methodological remarks: -No information on allocation concealment -The report does not describe an a priori hypothesis or sample size or power calculation. - The report does not describe the definitions of breakthrough bleeding and spotting. Sponsor: Wyeth-Ayerst

4.1.3.4. Triphasic combined oral contraceptives versus monophasic combined oral contraceptives: Authors' conclusions

The available evidence is insufficient to determine whether triphasic OCs differ from monophasic OCs in effectiveness, bleeding patterns or discontinuation rates. Therefore, we recommend monophasic pills as a first choice for women starting OC use. Large, high quality RCTs that compare triphasic and monophasic OCs with identical progestogens are needed to determine whether triphasic pills differ from monophasic OCs. Future studies should follow the recommendations of Belsey orMishell on recording menstrual bleeding patterns and the CONSORT reporting guidelines.

4.1.3.bis. Combined oral contraception: triphasic vs monophasic. Summary and conclusions.

Triphasic levonorgestrel 50-75-125µg/ethinylestradiol 30-40-30µg
vs Monophasic levonorgestrel 150µg/ethinylestradiol 30µg (Chen 1987, Zador 1979, Carlborg 1983, Dunson 1993, Engebretsen 1987, Ramos 1989, Saxena 1992, Kashanian 2010 from Van Vliet 2011)
vs Monophasic desogestrel 150µg/ethinylestradiol 30µg (Lachnit-Fixson 1984, Dieben 1984, Ismail 1991 from Van Vliet 2011)
vs Monophasic norethindrone° 1000µg/ethinylestradiol 35µg (Reiter 1990 from Van Vliet 2011a)

N/n	Duration	Comparison	Results				
N= 12 n= 7719	6-12 cycles **Population** Healthy women Age: 18-35y	Triphasic LNG 50-75-125µg /EE 30-40-30µg vs Monophasic LNG 150µg /EE 30µg	Pregnancy per woman within 12 cycles (N=5: Carlborg, 1983; Dunson, 1993; Engebretsen, 1987; Ramos, 1989; Saxena, 1992)	OR= 1.35 (95% CI 0.25, 7.22) NS p = 0.72			
				Quality -1 (low Jadad)	Consistency OK	Directness OK	Imprecision OK
				Grade assessment: *moderate quality of evidence*			
			Proportion of cycles with spotting within 12 cycles (N=1; Carlborg, 1983)	192/3197(Tri) vs 318/3275 (Mono) OR= 0.59 (95% CI 0.49, 0.72) **SS in favour of triphasic** p <0.00001			
			Proportion of women with spotting at cycle 12 (N=1; Ramos, 1989)	1/440(Tri) vs 1/456(Mono) OR= 1.04 (95% CI 0.06, 16.62) NS p = 0.98			
				Quality OK	Consistency -1	Directness OK	Imprecision OK
				Grade assessment: *moderate quality of evidence*			
			Proportion of cycles with breakthrough bleeding within 12 cycles (N=1; Carlborg, 1983)	86/3197(Tri) vs 147/3275 (Mono) OR= 0.59 (95% CI 0.45, 0.77) **SS in favour of triphasic** p =0.00012			
			Proportion of women with intermenstrual bleeding within 12 cycles (N=1; Dunson ,1993)	38/495(Tri) vs 44/484(Mono) OR= 0.83 (95% CI 0.53, 1.31) NS p = 0.43			
				Quality OK	Consistency -1	Directness OK	Imprecision OK
				Grade assessment: *moderate quality of evidence*			
			Proportion of cycles with amenorrhea within 12 cycles (N=1; Carlborg, 1983)	20/3197(Tri) vs 74/3275 (Mono) OR= 0.27 (95% CI 0.17, 0.45) **SS; less amenorrhea with triphasic p <0.00001**			
			Proportion of women with amenorrhea within 12 cycles (N=1; Dunson, 1993)	3/495(Tri) vs 2/484(Mono) OR= 1.47(95% CI 0.24, 8.83) NS p = 0.67			
				Quality OK	Consistency -1	Directness OK	Imprecision OK
				Grade assessment: *moderate quality of evidence*			
			Total discontinuation within 12 cycles	OR= 1.13(95% CI 0.97, 1.31) NS p = 0.13			

			(N=4; Dunson, 1993; Engebretsen, 1987 ; Ramos, 1989 ; Saxena, 1992)	Quality -1 (low Jadad)	Consistency OK	Directness OK	Imprecision OK
				Grade assessment: *moderate quality of evidence*			
		Triphasic LNG 50-75-125 µg and EE 30-40-30 µg vs Monophasic DSG 150 µg and EE 30 µg	Pregnancy per woman within 12 cycles (N=2; Dieben, 1984 ;Ismail, 1991)	OR= 7.22(95% CI 0.88, 59.00) NS p = 0.065			
				Quality -1 (low Jadad)	Consistency NA	Directness OK	Imprecision -1(wide CI)
				Grade assessment: *low quality of evidence*			
			Proportion of cycles with spotting within 6 or 12 cycles (N=2; Dieben ,1984; Lachnif-Fixson 1984)	*(Dieben 1984):within 12 cycles* OR= 1.19(95% CI 0.99, 1.44) NS p = 0.11 *(Lachnit-Fixson 1984): within 6 cycles* OR= 0.34(95% CI 0.27, 0.44) **SS in favor of triphasic p < 0.00001**			
				Quality -1 (low Jadad)	Consistency -1	Directness OK	Imprecision OK
				Grade assessment: *low quality of evidence*			
			Proportion of cycles with breakthrough bleeding within 12 cycles (N=1; Dieben ,1984)	*(Dieben 1984):within 12 cycles* OR= 1.09(95% CI 0.88, 1.35) NS p = 0.44 *(Lachnit-Fixson 1984): within 6 cycles* **OR= 0.41(95% CI 0.23, 0.71)** **SS in favor of triphasic p < 0.0016**			
				Quality -1	Consistency -1	Directness OK	Imprecision OK
				Grade assessment: *low quality of evidence*			
			Proportion of cycles with amenorrhea within 12 cycles (N=1; Dieben ,1984)	OR= 1.05(95% CI 0.86, 1.28) NS p = 0.63			
				Quality -2 (very low Jadad)	Consistency NA	Directness OK	Imprecision OK
				Grade assessment: *low quality of evidence*			
			Total discontinuation within 12 cycles (N=1; Ismail, 1991)	OR= 1.44 (95% CI 0.81, 2.57) NS p = 0.22			
				Quality -1 (low Jadad)	Consistency NA	Directness OK	Imprecision OK
				Grade assessment: *moderate quality of evidence*			
		Triphasic LNG 50-75-125 µg / EE 30-40-30 µg vs Monophasic NET 1000 µg / EE 35 µg	Proportion of women with intermenstrual bleeding within 12 cycles (N=1; Reiter, 1990)	OR= 0.59 (95% CI 0.29, 1.18) NS p = 0.13			
				Quality -1 (low Jadad, no ITT)	Consistency NA	Directness OK	Imprecision OK
				Grade assessment: *moderate quality of evidence*			
			Proportion of women with amenorrhea within 12 cycles (N=1; Reiter, 1990)	OR= 0.03 (95% CI 0.00, 0.43) **SS ; less amenorrhea with triphasic** p = 0.011			
				Quality -1 (low Jadad, no ITT)	Consistency NA	Directness OK	Imprecision OK
				Grade assessment: *moderate quality of evidence*			

Triphasic norethindrone° 500-750-1000µg/ethinylestradiol 35µg vs Monophasic norethindrone° 1000µg/ ethinylestradiol 35µg (Reiter 1990 from Van Vliet 2011a)							
N/n	**Duration**	**Comparison**	**Results**				
N=1, n=477	12 cycles	Triphasic NET 500-750-1000 µg / EE 35 µg versus Monophasic NET 1000 µg / EE 35 µg	Proportion of women with intermenstrual bleeding within 12 cycles (N=1; Reiter, 1990)	OR= 1.06 (95% CI 0.55, 2.02) NS p = 0.87			
				Quality -1 (low Jadad, no ITT)	Consistency NA	Directness OK	Imprecision OK
				Grade assessment: *moderate quality of evidence*			
			Proportion of women with amenorrhea within 12 cycles (N=1; Reiter, 1990)	OR= 0.25 (95% CI 0.08, 0.76) **SS; less amenorrhea with triphasic** p = 0.015			
				Quality -1 (low Jadad, no ITT)	Consistency NA	Directness OK	Imprecision OK
				Grade assessment: *moderate quality of evidence*			

Triphasic gestodene 50-70-100µg/ethinylestradiol 30-40-30µg
vs Monophasic desogestrel 150µg/ ethinylestradiol 30µg (Andrade 1993, Agoestina 1987 from Van Vliet 2011a)
vs Monophasic desogestrel 150µg/ ethinylestradiol 20µg (Bruni 2000 from Van Vliet 2011a)
vs Monophasic gestodene 75µg/ ethinylestradiol 30µg (Bruni 2000 from Van Vliet 2011a)

N/n	Duration	Comparison	Results				
N= 3 n= 3069	6-13 cycles **Population** Healthy women Age: 18-41y	Triphasic GTD 50-70-100 µg and EE 30-40-30 µg versus Monophasic DSG 150 µg and EE 30 µg	Pregnancy per woman within 12 cycles (N=1 :Agoestina, 1987)	OR= 1.00 (95% CI 0.06, 16.26) NS p = 1.0			
				Quality -1 (low Jadad)	Consistency OK	Directness OK	Imprecision -1 (small study)
				Grade assessment: *low quality of evidence*			
			Proportion of cycles with spotting and breakthrough bleeding within 6 cycles (N=1:Andrade, 1993)	OR= 0.49 (95% CI 0.33, 0.73) **SS in favour of triphasic** p = 0.00038			
				Quality -1 (low Jadad)	Consistency OK	Directness OK	Imprecision OK
				Grade assessment: *moderate quality of evidence*			
			Proportion of women with spotting at cycle 12 (N=1 :Agoestina, 1987)	OR= 1.50 (95% CI 0.40, 5.56) NS p = 0.54			
				Quality -1 (low Jadad)	Consistency OK	Directness OK	Imprecision OK
				Grade assessment: *moderate quality of evidence*			
			Proportion of women with breakthrough bleeding at cycle 12 (N=1 :Agoestina, 1987)	OR= 0.97 (95% CI 0.27, 3.51) NS p = 0.96			
				Quality -1 (low Jadad)	Consistency OK	Directness OK	Imprecision -1 (small study)
				Grade assessment: *low quality of evidence*			
			Proportion of cycles with amenorrhea within 12 cycles (N=1:Andrade, 1993)	OR= 0.82 (95% CI 0.48, 1.43) NS p = 0.49			
				Quality -1 (low Jadad)	Consistency OK	Directness OK	Imprecision OK
				Grade assessment: *moderate quality of evidence*			
			Total discontinuation within 12 cycles (N=1 :Agoestina, 1987)	OR= 0.82 (95% CI 0.35, 1.96) NS p = 0.66			
				Quality -1 (low Jadad)	Consistency OK	Directness OK	Imprecision -1 (small study)
				Grade assessment: *low quality of evidence*			
		Triphasic GTD 50-70-100 µg and EE 30-40-30 µg versus Monophasic DSG 150 µg and EE 20 µg	Pregnancy per woman within 13 cycles (N=1; Bruni, 2000)	OR= 1.00 (95% CI 0.14, 7.09) NS p = 1.0			
				Quality -1 (low Jadad)	Consistency NA	Directness OK	Imprecision OK
				Grade assessment: *moderate quality of evidence*			
			Total discontinuation within 13 cycles (N=1; Bruni, 2000)	OR= 1.09 (95% CI 0.88, 1.36) NS p = 0.43			
				Quality -1 (low Jadad)	Consistency NA	Directness OK	Imprecision OK
				Grade assessment: *moderate quality of evidence*			

		Triphasic GTD 50-70-100 µg and EE 30-40-30 µg versus Monophasic GTD 75 µg and EE 30 µg	Pregnancy per woman within 13 cycles (N=1; Bruni, 2000)	OR= 0.66 (95% CI 0.11, 3.99) NS p = 0.65			
				Quality	Consistency	Directness	Imprecision
				-1 (low Jadad)	NA	OK	OK
				Grade assessment: *moderate quality of evidence*			
			Total discontinuation within 13 cycles (N=1; Bruni, 2000)	OR= 0.93 (95% CI 0.75, 1.16) NS p = 0.53			
				Quality	Consistency	Directness	Imprecision
				-1 (low Jadad)	NA	OK	OK
				Grade assessment: *moderate quality of evidence*			

° norethindrone = norethisterone

- A Cochrane Review (Van Vliet 2011a) of 23 studies with more than twenty thousand women compared various triphasic contraceptive pills to monophasic contraceptive pills. We selected only the studies with pills available on the Belgian market and grouped them per type of triphasic pill. There were many endpoints and the results of the various studies were not always consistent, partly due to the heterogeneity of the studies. Definitions of bleeding pattern (spotting, breakthrough bleeding) were often missing or varied from study to study.
In addition, many of these usually old studies did not apply the intention-to-treat principle, whilst the follow-up was sometimes low. We have reported the most important data below.

** Triphasic Levonorgestrel + ethinyl estradiol versus monophasic combination pills*

- There was no significant difference in the efficacy of the contraceptives versus the monophasic preparations.

GRADE: low to moderate quality of evidence

- In some studies bleeding patterns were found to be in favour of the triphasic pills, i.e. less spotting, fewer breakthrough bleeds, less amenorrhoea. In other studies no significant difference could be demonstrated for these endpoints.
GRADE: low to moderate quality of evidence

- The total number of women that stopped their treatment during the study period was not significantly different between the various types of combination pills.

GRADE: moderate quality of evidence

** Triphasic Norethisterone + ethinyl estradiol versus monophasic combination pills*

- There was no significant difference in the number of women with inter-menstrual bleeding between norethisterone in monophasic or triphasic form.

GRADE: moderate quality of evidence

- Significantly more women who took the monophasic combination pill for a year had amenorrhoea.

GRADE: moderate quality of evidence

** Triphasic Gestodene + ethinyl estradiol versus monophasic combination pills*

- There was no significant difference in the efficacy of the contraceptives.

GRADE: low to moderate quality of evidence

- Most of the studies with the triphasic gestodene combination pill reported no significant difference for bleeding (spotting, breakthrough bleeding, amenorrhoea) in comparison to the monophasic combination pill. For one combined endpoint “number of cycles with spotting and breakthrough bleeding over 6 cycles”, one

study of moderate quality reported a benefit of the triphasic combination pill (with gestodene) over the monophasic combination pill (with desogestrel).

GRADE: moderate quality of evidence

- There was also no significant difference between triphasic and monophasic combination pills in the various studies as far as discontinuation was concerned.

GRADE: low to moderate quality of evidence

Conclusion:
The current data are not sufficient to evaluate whether there is a real difference between triphasic and monophasic combination pills, both for efficacy and for bleeding patterns.

4.1.4. Combined oral contraception: quadriphasic vs monophasic. Evidence tables

Ref	N/n	Comparison	Outcomes	Results
Van Vliet 2011b* Design: SR + MA Search date: May 2011	N= 1 n= 846	Quadriphasic dienogest/estradiol valerate vs monophasic levonorgestrel/ ethinylestradiol (LNG 100 µg and 20 µg EE)	Pregnancy	No of women reporting pregnancy (n=798): 0/399 vs 1/399 RR=0.33 (0.01 – 8.16), NS
			Withdrawal bleeding (PE)	Proportion of women with withdrawal bleeding: At cycle 1 (n=784): 309/392 vs 351/392 **RR=0.88 (0.83 – 0.94), SS** At cycle 2 (n=780): 304/391 vs 362/389 **RR=0.84 (0.79 – 0.89), SS** At cycle 3 (n=773): 320/388 vs 361/385 **RR=0.88 (0.83 – 0.93), SS** At cycle 4 (n=762): 317/381 vs 353/381 **RR=0.90 (0.85 – 0.95), SS** At cycle 5 (n=748): 297/373 vs 346/375 **RR=0.86 (0.81 – 0.92), SS** At cycle 6 (n=746): 307/372 vs 346/374 **RR=0.89 (0.84 – 0.94), SS** At cycle 7 (n=743): 298/372 vs 342/371 **RR=0.87 (0.82 – 0.92), SS**
			Bleeding duration	Median 4.0 days vs 5.0 days (p<0.05)
			Spotting/bleeding (PE)	Proportion of women with intracyclic bleeding: At cycle 1 (n=784): 73/392 vs 67/392 RR=1.09 (0.81 – 1.47), NS At cycle 2 (n=780): 64/391 vs 46/389 RR=1.38 (0.97 – 1.97), NS At cycle 3 (n=773): 50/388 vs 54/385 RR=0.92 (0.64 – 1.31), NS At cycle 4 (n=762): 61/381 vs 42/381 **RR=1.45 (1.01 – 2.10), SS** At cycle 5 (n=748): 40/373 vs 38/375 RR=1.06 (0.70 – 1.61), NS At cycle 6 (n=746): 39/372 vs 37/374 RR=1.06 (0.69 – 1.62), NS

				At cycle 7 (n=743): 48/372 vs 38/371 RR=1.26 (0.84 – 1.88), NS No of intracyclic bleeding episodes: At cycle 1 (n=784): Mean diff=0.0 (-0.07 – 0.07), NS At cycle 2 (n=780): **Mean diff=0.10 (0.04 – 0.16), SS** At cycle 3 (n=773): Mean diff=0.0 (-0.06 – 0.06), NS At cycle 4 (n=762): **Mean diff=0.10 (0.04 – 0.16), SS** At cycle 5 (n=748): Mean diff=0.0 (-0.06 – 0.06), NS At cycle 6 (n=746): Mean diff=0.0 (-0.05 – 0.05), NS At cycle 7 (n=743): Mean diff= 0.0 (-0.05 – 0.05), NS Mean (SD) no of bleeding/spotting days in ref. period 1 (Days 1-90) (n=798): 17.3 (10.4) vs 21.5 (8.6) **Mean Diff= -4.20 (-5.52, -2.88), SS** Mean (SD) no of bleeding/spotting days in ref. period 2(Days 91-180) (n=798): 13.4 (9.3) vs 15.9 (7.1) **Mean diff= -2.50 (-3.65 – -1.35), SS** Mean (SD) no of bleeding/spotting episodes in ref. period 1(Days 1-90) (n=798): 3.7 (1.4) vs 4.1 (0.9) **Mean diff= -0.40 (-0.56, -0.24), SS** Mean (SD) no of bleeding/spotting episodes in ref. period 2(Days 91-180) (n=798): 3 (1.3) vs 3.1 (0.9)

				Mean diff= -0.10 (-0.26 – 0.06), NS
			Discontinuation	No of women discontinuing due to adverse effects (n=798): 13/399 vs 13/399 RR=1.0 (0.47 – 2.13), NS
			Adverse events	No of women reporting adverse events (n=798): 108/399 vs 102/399 RR=1.06 (0.84 – 1.34), NS
			Breast pain	No of women reporting breast pain (n=798): 13/399 vs 4/399 **RR=3.25 (1.07 – 9.88), SS**
			Headache	No of women reporting headache (n=798): 7/399 vs 7/399 RR=1.0 (0.35 – 2.82), NS
			Acne	No of women reporting acne (n=798): 5/399 vs 9/399 RR=0.56 (0.19 – 1.64), NS
			Alopecia	No of women reporting alopecia (n=798): 3/399 vs 4/399 RR=0.75 (0.17 – 3.33), NS
			Migraine	No of women reporting migraine (n=798): 2/399 vs 5/399 RR=0.4 (0.08 – 2.05), NS
			Increase in body weight	No of women reporting increase in body weight (n=798): 2/399 vs 4/399 RR=0.5 (0.09 – 2.71), NS

* Characteristics of included studies: see below

Ref + design	N	Population	Duration	Comparison	Methodology
Ahrendt 2009 Double-blind RCT	846 randomised	women at 34 sites in Europe age 18-50 years Exclusion criteria were pregnancy; lactation; fewer than 3 menstrual cycles following childbirth, abortion or lactation; current use of an IUD; BMI more than 30 kg/m2; use of long-acting progestins within 6 months prior to the study entry; hypersensitivity to study drug ingredients; known or suspected malignant or pre-malignant disease; more than 10 cigarettes per day when aged 18 to 30 years or smoking when aged older than 30 years; use of other sex steroids Starters and switchers were included in the study	7 cycles	Quadriphasic dienogest/estradiol valerate (E2V 3 mg on days 1 and 2, DNG 2 mg and E2V 2 mg on days 3 to 7, DNG 3 mg and E2V 2 mg on days 8 to 24, E2V 1 mg on days 25 and 26 and placebo on days 27 and 28) vs. monophasic levonorgestrel/ ethinylestradiol (LNG 100 µg and 20 µg EE on days 1 to 21 and placebo on days 22 to 28)	- Jadad score: 4/5 - FU: 94% - ITT: Communication with the authors indicated an analysis according to intention-to-treat without further specification Methodological remarks -' The study was descriptive in nature and was not designed to show equivalence or non-inferiority' The report does not provide an a priori hypothesis. The report states a sample size which was chosen to obtain an acceptable estimate of the number of women required to permit acceptably precise comparisons between groups for the number of bleeding/spotting days per reference period. Post-hoc analysis for differences in bleeding patterns and cycle control outcomes.

Authors' conclusions

The available evidence is insufficient to determine whether quadriphasic differ from monophasic oral contraceptives in contraceptive effectiveness, bleeding pattern, minor side effects and acceptability. Studies that compare quadriphasic and monophasic oral contraceptives with an identical progestogen and estrogen type are needed to determine whether the quadriphasic approach differs from the monophasic approach. Studies that compare quadriphasic pills with monophasic pills containing 30 µg ethinylestradiol are indicated to determine whether quadriphasic oral contraceptives have an advantage over the current, first choice oral contraceptive. Until then,we recommend monophasic pills containing 30 µg estrogen as the first choice for women starting oral contraceptive use.

4.1.4.bis. Combined oral contraception: quadriphasic vs monophasic. Summary and conclusions

Quadriphasic dienogest/estradiol valerate vs Monophasic levonorgestrel 100µg/ethinylestradiol 20µg* (Ahrendt 2009 from Van Vliet 2011b)							
N/n	**Duration**	**Population**	**Results**				
N= 1 n= 846	7 cycles	Healthy women Age: 18-50y	Pregnancy	0/399 vs 1/399 RR=0.33 (0.01 – 8.16), NS			
				Quality -1 (no a priory hypothesis)	Consistency NA	Directness OK	Imprecision -1 (underpowered)
				Grade assessment: *low quality of evidence*			
			Spotting/ bleeding days (mean n°) (PE)	(Days 1-90) **17.3 (10.4) vs 21.5 (8.6)** **Mean Diff= -4.20 (-5.52, -2.88), SS less with quadriphasic** (Days 91-180) **13.4 (9.3) vs 15.9 (7.1)** **Mean diff= -2.50 (-3.65, -1.35), SS less with quadriphasic**			
				Quality -1 (no a priory hypothesis)	Consistency NA	Directness OK	Imprecision OK
				Grade assessment: *moderate quality of evidence*			
			Withdrawal bleeding (proportion of women with withdrawal bleeding)	**SS at all 7 cycles** **Less women with withdrawal bleeding with quadriphasic** RR=0.79-0.90			
				Quality -2(no power calculation, post hoc)	Consistency NA	Directness OK	Imprecision OK
				Grade assessment: *low quality of evidence*			
			Spotting/ bleeding (proportion of women with spotting/bleeding)	**NS** at all cycles, **except for cycle 4**: RR=1.45 SS in favor of quadriphasic COCs			
				Quality -2	Consistency NA	Directness OK	Imprecision OK
				Grade assessment: *low quality of evidence*			
			Discontinuation due to AEs	RR=1.0 (0.47 – 2.13), NS			
				Quality -1	Consistency NA	Directness OK	Imprecision -1
				Grade assessment: *low quality of evidence*			
			Breast pain	RR=3.25 (1.07 – 9.88) **SS in favor of monophasic COC**			
				Quality -1	Consistency NA	Directness OK	Imprecision -1
				Grade assessment: *low quality of evidence*			
			Acne	RR=0.56 (0.19 – 1.64), NS			
				Quality -1	Consistency NA	Directness OK	Imprecision -1
				Grade assessment: *low quality of evidence*			
			Migraine	RR=0.4 (0.08 – 2.05), NS			
				Quality -1	Consistency NA	Directness OK	Imprecision -1
				Grade assessment: *low quality of evidence*			
			Increase in body weight	RR=0.5 (0.09 – 2.71), NS			
				Quality -1	Consistency NA	Directness OK	Imprecision -1
				Grade assessment: *low quality of evidence*			

** Quadriphasic dienogest/estradiol valerate*
(E2V 3 mg on days 1 and 2, DNG 2 mg and E2V 2 mg on days 3 to 7, DNG 3 mg and E2V 2 mg on days 8 to 24, E2V 1 mg on days 25 and 26 and placebo on days 27 and 28)
versus
Monophasic levonorgestrel/ethinylestradiol (LNG 100 µg and 20 µg EE on days 1 to 21 and placebo on days 22 to 28)

- There are few studies that compare quadriphasic combination pills to monophasic COCs. Ideally, identical progestagen and oestrogen combinations should be compared in order to evaluate whether quadriphasic pills have an advantage over the monophasic variants.
This Cochrane Review found 1 study that compares dienogest/oestradiol valerate (quadriphasic) to levonorgestrel 100 µg/ ethanyl estradiol 20 µg (monophasic). This was a double-blind RCT over seven cycles in 846 healthy women of childbearing age.

- There was no significant difference in the efficacy of the contraceptives. However, the study did not have sufficient power to demonstrate a difference.

GRADE: low quality of evidence

- Users of the quadriphasic pill appear to report fewer bleeding and spotting days than women on the monophasic pill with 100 µg LNG and 20 µg EE. The number of women experiencing withdrawal bleeding was significantly lower in the quadriphasic group compared to the monophasic group. However, the study set-up was not good enough to draw strong conclusions from this.

GRADE: low quality of evidence

- A comparable number of women stopped their treatment due to adverse events; the difference was not significant.
- Significantly more women using the quadriphasic pill reported painful breasts compared to women using the monophasic pills. There was no significant difference between both groups for other adverse events such as weight gain, acne and migraine.

GRADE: low quality of evidence

4.1.5. Combined hormonal contraception: contraceptive patch vs pill. Evidence tables.

4.1.5.1. Contraceptive patch vs triphasic combined oral contraceptive containing levonorgestrel

Ref	N/n	Comparison	Outcomes	Results
Lopez 2010* Design: meta-analysis Search date: December 2009	N= 2 n= 1099	Skin patch releasing norelgestromin 150 µg + EE 20 µg vs COC levonorgestrel 50/75/125 µg + EE 30/40/30 µg	Pregnancy per cycle	[Âudet 2001] 5/5240 vs 7/4167 OR=0.57 (0.18 - 1.77), NS Kaplan-Meier cumulative pregnancy rates: 6-cycle rate: 0.6 (0 – 1.2) vs 1.2 (0.2 – 2.1) 13-cycle rate: 1.3 v(0 – 2.7) vs 1.8 (0.2 – 3.4)
			Discontinuation: overall	[Audet 2001, Kluft 2008] **OR=1.59 (1.26 – 2.00), SS**
			Discontinuation: adverse events	[Audet 2001, Kluft 2008] **OR=2.28 (1.61 – 3.25), SS**
			Compliance per cycle**	[Audet 2001] **OR=2.05 (1.83 – 2.29), SS**
			Breakthrough bleeding or spotting	[Audet 2001] Cycle 6: OR=1.36 (0.93 – 1.98), NS Cycle 13: OR=0.76 (0.49 – 1.18), NS
			Headache	[Âudet 2001] OR= 0.99 (0.77 – 1.27), NS
			Breast discomfort	[Âudet 2001] **OR=3.09 (2.26 – 4.22), SS**
			Dysmenorrhea	[Âudet 2001] **OR= 1.43 (1.03 – 1.99), SS**
			Abdominal pain	[Âudet 2001] OR=0.96 (0.66 – 1.41), NS

* Characteristics of included studies: see below

**Remarks
Compliance: (regimen adherence) - Proportion of women or cycles with self-reported correct use of assigned device

Ref + design	n	Population	Duration	Comparison	Methodology
Audet 2001 PG RCT	1030 for 6 cycles 465 for 13 cycles	Sexually active, healthy women from the United States and Canada age 18-45y regular menses	13 cycles	Patch (releasing norelgestromin 150 µg + EE 20 µg daily; n=591 for 6 cycles and n=265 for 13 cycles) versus oral contraceptive (levonorgestrel 50-75-125 µg + EE 30-40-30 µg; n=439 for 6 cycles and n=200 for 13 cycles)	- Jadad score: 3/5 - FU: 69% ; patch 33% dropout vs. COC 24% dropout - ITT: yes The first third of women enrolled were to receive 13 treatment cycles and the remaining women were to receive 6 cycles
Kluft 2008 PG RCT	104	Healthy non-smoking women from the Netherlands Age 18-45y	6 cycles	1) Transdermal patch (containing norelgestromin 6 mg/ EE 0.75 mg) (n=36) 2) Monophasic COC (desogestrel 150 µg/ EE 20 µg) (n=35) 3) Triphasic COC (levonorgestrel 50/75/125 µg/ EE 30/40/30 µg) (n=33)	- Jadad score: 3/5 - FU: 99% - ITT: yes

4.1.5.2. Contraceptive patch vs monophasic combined oral contraceptive containing desogestrel

Ref	N/n	Comparison	Outcomes	Results
Lopez 2010* Design: meta-analysis Search date: December 2009	N= 2 n=1588	Skin patch releasing norelgestromin 150 µg + EE 20 µg vs COC desogestrel 150 µg + EE 20 µg	Pregnancy per woman	[Urdl 2005] OR=1.49 (0.30 – 7.53) Kaplan- Meier cummulative pregnancy rates : 6-cycle rate 0.5 (0 – 1) vs 0.3 (0 – 0.8) 13-cycle rate 0.5 (0 – 1) vs 0.3 (0 – 0.8)
			Discontinuation: overall	[Urdl 2005, Kluft 2008] **OR= 1.56 (1.18 – 2.06), SS**
			Discontinuation: adverse events	[Urdl 2005, Kluft 2008] **OR= 2.11 (1.44 – 3.11), S**
			Compliance per cycle	[Urdl 2005] **OR= 2.76 (2.35-3.24), SS**
			Breakthrough bleeding and spotting	[Urdl 2005] Cycle 3: OR= 0.92 (0.69 – 1.24), NS Cycle 13: OR= 0.65 (0.46 – 0.92), NS
			Breast discomfort or pain	[Urdl 2005] **OR= 2.98 (2.29 – 3.90), SS**
			Headache	[Urdl 2005] OR= 0.82 (0.64 – 1.05), NS
			Abdominal pain	[Urdl 2005] OR= 0.98 (0.71 – 1.36), NS
			Vaginitis	[Urdl 2005] OR= 0.95 (0.62 – 1.46), NS
			Dysmenorrhea	[Urdl 2005] OR= 1.15 (0.72 – 1.83), NS
			vomiting	[Urdl 2005] **OR=1.88 (1.12 – 3.16), SS**

* Characteristics of included studies: see below

**Remarks

Compliance: (regimen adherence) - Proportion of women or cycles with self-reported correct use of assigned device

Ref + design	n	Population	Duration	Comparison	Methodology
Urdl 2005 PG RCT	1517	Healthy women in 65 centers in Europe and South Africa Age 18 to 45 years Normal menses	6 cycles (two thirds of women) 13 cycles (one third of women)	1) 20 cm2 patch releasing norelgestromin 150 µg + EE 20 µg daily versus 2) COC containing desogestrel 150 µg + EE 20 µg.	- Jadad score: 3/5 - FU: 81%; patch 21% dropout and COC 16% dropout. - ITT: modified intention to treat
Kluft 2008 PG RCT	104	Healthy non-smoking women from the Netherlands Age 18-45y	6 cycles	1) Transdermal patch (containing norelgestromin 6 mg/ EE 0.75 mg) (n=36) 2) Monophasic COC (desogestrel 150 µg/ EE 20 µg) (n=35) 3) Triphasic COC (levonorgestrel 50/75/125 µg/ EE 30/40/30 µg) (n=33)	- Jadad score: 3/5 - FU: 99% - ITT: yes

4.1.5.3.Combined hormonal contraceptives: contraceptive patch vs pill Authors' conclusions

(Conclusions patch and vaginal ring combined)

Effectiveness was similar for the methods compared. The patch could lead to more discontinuation while the vaginal ring showed little difference. The patch group had better compliance than the COC group but more side effects. Ring users generally had fewer adverse events than COC users but more vaginal irritation and discharge. High losses to follow up can affect the validity of the results.

4.1.5.bis. Combined hormonal contraception: contraceptive patch vs pill. Summary and conclusions

<table>
<tr><td colspan="6">Skin patch norelgestromin 150µg + EE 20µg vs COC levonorgestrel 50-75-125µg + EE 30-40-30µg (Audet 2001, Kluft 2008 from Lopez 2010)</td></tr>
<tr><th>N/n</th><th>Duration</th><th>Population</th><th colspan="3">Results</th></tr>
<tr><td rowspan="20">N=2,
n=
1099</td><td rowspan="20">6-13 cycles</td><td rowspan="20">- Healthy women
- Age: 18-45y</td><td rowspan="3">Pregnancy per cycle
N=1
(Audet 2001)</td><td colspan="3">5/5240 vs 7/4167
OR=0.57 (0.18 - 1.77), NS
Kaplan-Meier cumulative pregnancy rates:
6-cycle rate: 0.6 (0 – 1.2) vs 1.2 (0.2 – 2.1)
13-cycle rate: 1.3 v(0 – 2.7) vs 1.8 (0.2 – 3.4)</td></tr>
<tr><td><u>Quality</u>
-1 (drop out)</td><td><u>Consistency</u>
NA</td><td><u>Directness</u>
OK</td><td><u>Imprecision</u>
OK</td></tr>
<tr><td colspan="4">Grade assessment: moderate quality of evidence</td></tr>
<tr><td rowspan="3">Discontinuation overall
N=2</td><td colspan="3">OR=1.59 (1.26 – 2.00), SS in favour of COC</td></tr>
<tr><td><u>Quality</u>
-1 (drop out)</td><td><u>Consistency</u>
NA</td><td><u>Directness</u>
OK</td><td><u>Imprecision</u>
OK</td></tr>
<tr><td colspan="4">Grade assessment: moderate quality of evidence</td></tr>
<tr><td rowspan="3">Discontinuation adverse events
N=2</td><td colspan="3">OR=2.28 (1.61 – 3.25), SS in favour of COC</td></tr>
<tr><td><u>Quality</u>
-1 (drop out)</td><td><u>Consistency</u>
NA</td><td><u>Directness</u>
OK</td><td><u>Imprecision</u>
OK</td></tr>
<tr><td colspan="4">Grade assessment: moderate quality of evidence</td></tr>
<tr><td rowspan="3">Compliance per cycle
N=1
(Audet 2001)</td><td colspan="3">OR=2.05 (1.83 – 2.29), SS in favour of patch</td></tr>
<tr><td><u>Quality</u>
-1 (drop out)</td><td><u>Consistency</u>
NA</td><td><u>Directness</u>
OK</td><td><u>Imprecision</u>
OK</td></tr>
<tr><td colspan="4">Grade assessment: moderate quality of evidence</td></tr>
<tr><td>Breakthrough bleeding or spotting
N=1
(Audet 2001)</td><td colspan="3">Cycle 6: OR=1.36 (0.93 – 1.98), NS
Cycle 13: OR=0.76 (0.49 – 1.18), NS</td></tr>
<tr><td>Breast discomfort
N=1
(Audet 2001)</td><td colspan="3">OR=3.09 (2.26 – 4.22), SS in favour of COC</td></tr>
<tr><td>Dysmenorrhea
N=1
(Audet 2001)</td><td colspan="3">OR= 1.43 (1.03 – 1.99), SS in favour of COC</td></tr>
<tr><td rowspan="2"></td><td><u>Quality</u>
-1 (drop out)</td><td><u>Consistency</u>
NA</td><td><u>Directness</u>
OK</td><td><u>Imprecision</u>
OK</td></tr>
<tr><td colspan="4">Grade assessment: moderate quality of evidence</td></tr>
</table>

Compliance (regimen adherence) - Proportion of women or cycles with self-reported correct use of assigned device

Skin patch norelgestromin 150µg + EE 20µg vs COC desogestrel 150µg + EE 20µg (Urdl 2005, Kluft 2008 from Lopez 2010)							
N/n	**Duration**	**Population**	**Results**				
N=2, n= 1588	6-13 cycles	- Healthy women - Age: 18-45y	Pregnancy per woman N=1 (Urdl 2005)	OR=1.49 (0.30 – 7.53) Kaplan- Meier cumulative pregnancy rates : 6-cycle rate 0.5 (0 – 1) vs 0.3 (0 – 0.8) 13-cycle rate 0.5 (0 – 1) vs 0.3 (0 – 0.8)			
				Quality OK	Consistency NA	Directness OK	Imprecision OK
				Grade assessment: *high quality of evidence*			
			Discontinuation overall N=2	**OR= 1.56 (1.18 – 2.06), SS in favour of COC**			
				Quality OK	Consistency NA	Directness OK	Imprecision OK
				Grade assessment: *high quality of evidence*			
			Discontinuation adverse events N=2	**OR= 2.11 (1.44 – 3.11), SS in favour of COC**			
				Quality OK	Consistency NA	Directness OK	Imprecision OK
				Grade assessment: *high quality of evidence*			
			Compliance per cycle N=1 (Urdl 2005)	**OR=2.05 (1.83 – 2.29), SS in favour of patch**			
				Quality OK	Consistency NA	Directness OK	Imprecision OK
				Grade assessment: *high quality of evidence*			
			Breakthrough bleeding or spotting N=1 (Urdl 2005)	Cycle 3: OR= 0.92 (0.69 – 1.24), NS Cycle 13: OR= 0.65 (0.46 – 0.92), NS			
			Breast discomfort N=1 (Urdl 2005)	**OR= 2.98 (2.29 – 3.90), SS in favour of COC**			
			Dysmenorrhea N=1 (Urdl 2005)	OR= 1.15 (0.72 – 1.83), NS			
			Vomiting N=1 (Urdl 2005)	**OR=1.88 (1.12 – 3.16), SS in favour of COC**			
				Quality OK	Consistency NA	Directness OK	Imprecision OK
				Grade assessment: *high quality of evidence*			

Compliance (regimen adherence) - Proportion of women or cycles with self-reported correct use of assigned device

- 3 RCTs from the Cochrane systematic review of Lopez 2010 compared hormonal contraception in the form of a skin patch with the combination pill (including one study with 3 arms).
Two studies compared the patch with the triphasic pill with levonorgestrel. There was a high dropout rate in one of the larger studies (Audet 2001): one third of the patch users versus one quarter of the pill users.
Two studies compared the patch to the monophasic pill with desogestrel 150µg + EE 20µg.

- The contraceptive efficacy was equivalent in both groups.

GRADE: moderate to high quality of evidence

- In all the studies the participants in the patch group stopped more, for all reasons as well as due to adverse events. The (self-reported) therapy compliance per cycle was however better in the patch group than in the oral contraception group.

GRADE: moderate to high quality of evidence

- Users of the patches reported significantly more breast tenderness and dysmenorrhoea in comparison to users of the triphasic levonorgestrel-containing pill. There was no significant difference in breakthrough bleeding and spotting between the patch and the aforementioned pill.
In the comparison of the contraceptive patch and the monophasic desogestrel-containing pill, there was no significant difference in breakthrough bleeding, spotting or dysmenorrhoea, but there was a significant difference for the adverse events mastodynia and emesis.

GRADE: moderate to high quality of evidence

4.1.6. Combined hormonal contraception: contraceptive vaginal ring vs pill. Evidence tables.

4.1.6.1. Vaginal ring versus combined oral contraceptive containing levonorgestrel 150µg and ethinylestradiol 30µg

Ref	N/n	Comparison	Outcomes	Results
Lopez 2010a* Design: meta-analysis Search date: December 2009	N= 2 n= 1115	Vaginal ring releasing etonogestrel 120 µg + EE 15 µg vs. Levonorgestrel 150 µg + EE 30 µg	Pregnancy per woman	[Duijkers 2004a, Oddsson 2005] OR=1.01 (0.29 – 3.51), NS
			Pregnancy per cycle	[Oddsson 2005] OR= 1.03 (0.30 – 3.55), NS
			Discontinuation: overall (6 or 13 cycles)	[Duijkers 2004a, Oddsson 2005] OR= 1.06 (0.81 - 1.38), NS
			Discontinuation: adverse events	[Duijkers 2004a, Oddsson 2005] OR= 1.33 (0.89 – 2.00), NS
			Compliance per cycle	[Oddsson 2005] OR= 1.07 (0.96 – 1.20), NS
			Breakthrough bleeding	[Oddsson 2005] Cycle 6: **OR= 0.22 (0.05 - 0.88), SS** Cycle 13: OR=0.15 (0.01 – 2.45), NS
			Breakthrough spotting	[Oddsson 2005] Cycle 6: OR= 0.67 (0.36 – 1.24), NS Cycle 13: OR=1.01 (0.38 – 2.67), NS
			Breast tenderness	[Oddsson 2005] OR=0.43 (0.09 – 2.01), NS
			Breast pain	[Oddsson 2005] OR=2.25 (0.99 – 5.14), NS
			Abdominal pain	[Duijkers 2004a, Oddsson 2005] OR= 1.70 (0.63 – 4.57), NS
			Headache	[Duijkers 2004a, Oddsson 2005] OR=1.30 (0.80 – 2.10), NS
			dysmenorrhea	[Oddsson 2005] OR= 1.86 (0.77 – 4.52), NS
			Vaginitis	[Duijkers 2004a, Oddsson 2005]

				OR= 2.84 (1.34 – 6.01), SS
			Genital pruritus	[Oddsson 2005] **OR= 4.58 (1.14 – 18.41), SS**
			Leukorrhea	[Duijkers 2004a, Oddsson 2005] **OR= 6.42 (2.71 – 15.22), SS**
			Weight increase	[Duijkers 2004a, Oddsson 2005] OR=0.93 (0.41 – 2.13), NS
			Nervousness	[Duijkers 2004a] OR= 8.24 (0.50 – 134.35), NS
			depression	[Duijkers 2004a] OR= 0.14 (0.01 – 2.32), NS
			Libido decrease	[Oddsson 2005] OR= 0.81 (0.32 – 2.05), NS
			Leg pain	[Oddsson 2005] OR= 2.27 (0.65 – 7.88), NS
			Urinary tract infection	[Oddsson 2005] OR=7.51 (0.78 – 72.32), NS
			Acne	[Oddsson 2005] **OR= 0.23 (0.08 – 0.63), SS**

* Characteristics of included studies: see below

Ref + design	N	Population	Duration	Comparison	Methodology
Duijkers 2004a PG RCT	85	women of 3 centers in the Netherlands, England an Scotland 18 to 40 y	6 treatment cycles	Vaginal ring releasing etonogestrel 120 µg + EE 15 µg daily (n=44) versus COC containing levonorgestrel 150 µg + EE 30 µg (n=41)	- Jadad score: 3/5 - FU: 81%; ring 30% dropout and COC 7% dropout. - ITT: modified intention to treat
Oddsson 2005 PG RCT	1030	Healthy women from 11 countries in Europe and South America 18 y or older	13 treatment cycles	Vaginal ring releasing etonogestrel 120 µg + EE 15 µg daily (n=512) versus COCcontaining levonorgestrel 150 µg + EE 30 µg (n=518)	- Jadad score: 3/5 - FU: 68%; ring 33% dropout and COC 31% dropout - ITT: modified intention to treat

4.1.6.2. Vaginal ring versus combined oral contraceptive containing levonorgestrel 100µg and ethinylestradiol 20µg

Ref	N/n	Comparison	Outcomes	Results
Lopez 2010a* Design: meta-analysis Search date: December 2009	N= 3 n= 427	Vaginal ring releasing etonogestrel 120 µg + EE 15 µg vs. COC levonorgestrel 100 µg + EE 20 µg	Pregnancy per woman	[Sabatini 2006, Veres 2004] OR=0.14 (0.00 – 7.00), NS
			Discontinuation overall	[Sabatini 2006, Veres 2004, Elkind-Hirsch 2007] OR=0.66 (0.39 – 1.11), NS
			Discontinuation: adverse events	[Sabatini 2006, Veres 2004] OR=0.48 (0.20 – 1.11), NS
			Noncompliance per woman	[Veres 2004] **OR=3.99 (1.87 – 8.52), SS**
			Early or late withdrawal bleeding	[Sabatini 2006] Cycle 6: **OR=0.23 (0.07 – 0.70), SS** Cycle 12: **OR=0.21 (0.05 – 0.86), SS**
			Irregular bleeding	[Sabatini 2006] Cycle 6: **OR=0.36 (0.15 – 0.87), SS** [Sabatini 2006] Cycle 12: **OR=0.34 (0.12-0.94), SS**
			Breakthrough bleeding	[Elkind-Hirsch 2007] Cycle 5: 0.07 (0.00 – 1.42), NS
			Planned to use method	[Veres 2004] **OR=2.49 (1.23 – 5.05), SS**
			Headache	[Sabatini 2006] Cycle 6: OR=0.80 (0.32 -2.02), NS Cycle 12: OR=0.65 (0.23 – 1.86), NS
			Breast tenderness	[Sabatini 2006, Elkind-Hirsch 2007] Cycles 5 & 6: OR=0.63 (0.22 – 1.79), NS [Sabatini 2006]

				Cycle 12: OR=0.66 (0.18 – 2.34), NS
			Irritability	[Sabatini 2006] Cycle 6: **OR=0.26 (0.08 – 0.88), SS** Cycle 12: OR=0.28 (0.08 – 1.01), NS
			Depression	[Sabatini 2006] Cycle 6: OR=0.31 (0.08 – 1.19), NS Cycle 12: OR=0.23 (0.05 – 1.03), NS
			Mood swings	[Elkind-Hirsch 2007] Cycle 5: OR=0.77 (0.05 – 12.92), NS
			Vaginal dryness	[Sabatini 2006] Cycle 6: **OR= 0.12 (0.03 – 0.47), SS** Cycle 12: **OR=0.13 (0.03 – 0.65), SS**
			Vaginal yeast infection/discomfort	[Elkind-Hirsch 2007] Cycle 5: OR=6.02 (0.30 – 122.32), NS
			Hot flashes	[Elkind-Hirsch 2007] Cycle 5: OR=0.25 (0.01 – 6.38), NS

* Characteristics of included studies: see below

Ref + design	N	Population	Duration	Comparison	Methodology
Sabatini 2006 PG RCT	282 (188 for this comparison)	women with regular menstrual cycles, sexually active	12 treatment cycles	Vaginal ring releasing etonogestrel 120 µg + EE 15 µg daily versus COC containing levonorgestrel (LNG) 100 µg + EE 20 µg versus COC containing gestodene (GSD) 60 µg + EE 15 µg	- Jadad score: 3/5 - FU: 78%; Loss after treatment: ring 12%, LNG 22%, GSD 32%. - ITT: no
Veres 2004 CO RCT	80	Women, recruited by flyer and newspaper by a metropolitan university-affiliated clinic in the USA 18-45y	3 cycles for each treatment	Vaginal ring releasing etonogestrel 120 µg + EE 15 µg daily versus COC containing levonorgestrel 100 µg + EE 20 µg;	- Jadad score: 3/5 - FU: 80%; total loss: ring 18%, COC 23% - ITT: no
Elkind-Hirsch 2007 PG RCT	65	Healthy women from Louisiana (USA) 18-40y	5 cycles	1) Vaginal ring (releasing etonogestrel 120 µg plus EE 15 µg daily) (n=34) 2) OC containing levonorgestrel 100 µg plus 20 µg (n=31)	- Jadad score: 2/5 - FU: no losses reportedExclusions: 35% ring and 35% COC; includes women who never used study product and who discontinued early. - ITT: yes

4.1.6.3. Vaginal ring versus combined oral contraceptive containing gestodene 60µg and ethinylestradiol 15µg

Ref	N/n	Comparison	Outcomes	Results
Lopez 2010a* Design: meta-analysis Search date: December 2009	N= 1 n= 282 (n=186 for this comparison)	Vaginal ring releasing etonogestrel 120 µg + EE 15 µg vs. COC gestodene 60 µg + EE 15 µg	Pregnancy per woman	OR=0.0 (0.0-0.0), NS
			Discontinuation: overall	**OR=0.32 (0.16 – 0.66), SS**
			Discontinuation: adverse events	**OR=0.32 (0.15 – 0.70), SS**
			Early or late withdrawal bleeding	Cycle 6: **OR=0.18 (0.07 – 0.46), SS** Cycle 12: **OR=0.19 (0.05 – 0.73), SS**
			Irregular bleeding	Cycle 6: **OR=0.26 (0.11 – 0.57), SS** Cycle 12: **OR=0.33 (0.12 – 0.91), SS**
			Headache	Cycle 6: OR=0.87 (0.34 – 2.24), NS Cycle 12: OR=0.63 (0.22 – 1.82), NS
			Breast tenderness	Cycle 6: OR=0.69 (0.21 – 2.20), NS Cycle 12: OR=0.64 (0.18 – 2.29), NS
			irritability	Cycle 6: **OR=0.28 (0.08 – 0.99), SS** Cycle 12: OR=0.31 (0.08 – 1.16), NS
			Depression	Cycle 6: OR=0.35 (0.08 – 1.42), NS Cycle 12: OR=0.21 (0.5 – 0.84), SS
			Vaginal dryness	Cycle 6: **OR=0.11 (0.04 – 0.32), SS** Cycle 12: **OR=0.12 (0.03 – 0.50), SS**

* Characteristics of included studies: see below

Ref + design	N	Population	Duration	Comparison	Methodology (sponsor NR in Cochrane)
Sabatini 2006 PG RCT	282	women with regular menstrual cycles, sexually active	12 treatment cycles	Vaginal ring releasing etonogestrel 120 µg + EE 15 µg daily versus COC containing levonorgestrel (LNG) 100 µg + EE 20 µg versus COC containing gestodene (GSD) 60 µg + EE 15 µg	- Jadad score: 3/5 - FU: 78%; Loss after treatment: ring 12%, LNG 22%, GSD 32%. - ITT: no

4.1.6.4. Vaginal ring versus combined oral contraceptive containing drospirenone 3mg and ethinylestradiol 30µg

Ref	N/n	Comparison	Outcomes	Results
Lopez 2010a* Design: meta-analysis Search date: December 2009	N= 1 n= 1017	Vaginal ring releasing etonogestrel 120 µg + EE 15 µg Vs. COC drospirenone 3 mg + EE 30 µg (comparison 9)	Pregnancy per woman	OR= 0.30 (0.05 – 1.76), NS
			Discontinuation: overall	OR=1.19 (0.90 – 1.58), NS
			Discontinuation: adverse events	OR=1.26 (0.85 – 1.88), NS
			Headache	OR=0.88 (0.55 – 1.43), NS
			Vaginitis	**OR=2.19 (1.09 – 4.38), SS**
			Leukorrhea	**OR=2.82 (1.19 – 6.70), SS**
			Breast pain	OR=0.67 (0.35 – 1.26), NS
			Breakthrough bleeding or spotting days	Cycle 6: **Mean diff = 2.00 (1.57 – 2.43), SS** Cycle 13: Mean diff = -0.10 (-0.34 – 0.14), NS
			Withdrawal bleeding days	Cycle 6: **Mean diff= -0.30 (-0.50 - -0.10), SS** Cycle 13: Mean diff= -0.20 (-0.40 – 0.00), NS

* Characteristics of included studies: see below

Ref + design	n	Population	Duration	Comparison	Methodology (sponsor NR in Cochrane)
Ahrendt 2006 PG RCT	1017	Women in 10 European countries At least 18y	13 treatment cycles	Vaginal ring releasing etonogestrel 120 µg + EE 15 µg daily versus COC containing drospirenone 3 mg + EE 30 µg;	- Jadad score: 3/5 - FU: 70%; total loss: ring 31% and COC 28% - ITT: no Remark: doubts about validity of the results because of high loss to follow-up (30%) and no intention to treat analysis.

Ref	n/Population	Duration	Comparison	Outcomes				Methodological
Mohamed 2011 Design: OL PG RCT	n= 600 mean age: <u>Inclusion</u> 17–42 y; regular menstrual cycles; at risk of becoming pregnant; sought contraception. <u>Exclusion</u> CI for contraceptive steroid use; use of an injectable hormonal contraceptive 6 m prior to study initiation; use of a hormone medicated intrauterine device or any other hormonal contraceptive within 2 months prior to the study begin; abortion or breastfeeding within 2 months before starting trial medication; abnormal cervical smear diagnosed during screening; prolapse of the uterine cervix, cystocele; rectocele before or during screening	12 cycles	NuvaRing vs. COC (30 µg EE and 3mg Drospirenone)	Efficacy				- Jadad score ○ RANDO: 1/2 ○ BLINDING: 0/2 ○ ATTRITION: 1/1 - FU: 80.7 % - ITT: no - Multicenter: 1 center in Cairo, Egypt - Sponsor: not reported
				Breakthrough bleeding	NuvaRing: 11.3% COC: 14.7% **P<0.05 in favour of NuvaRing** **<->** Table 3 "the differences between NuvaRing and COC were **not statistically significant**"			
				No withdrawal bleeding	NuvaRing: 2.1% COC: 2.9%		NT	
				Pregnancy	NuvaRing: 0% COC: 0.7%		NT	
				Mean systolic blood pressure		B	6m	12m
					NuvaRing:	114.6	113.9	114.4
					COC:	117.3	125.6	126.2
						NS	NS	NS
				Mean diastolic blood pressure		B	6m	12m
					NuvaRing:	72.4	73.2	71.8
					COC:	71.5	81.5	79.7
						NS	NS	NS
				Safety				
				No (%) with adverse effect	NuvaRing	COC		
				Nausea	7 (2.9)	11 (4.5)		NS
				Vomiting	1 (0.4)	3 (1.2)		NS
				Leucorrhea	**10 (4.2)**	**2 (0.8)**		**SS**
				Vaginitis	**11 (4.6)**	**3 (1.2)**		**SS**
				Headache	19 (7.9)	17 (6.9)		NS
				Mastalgia	8 (3.3)	6 (2.4)		NS
				Weight increase	**4 (1.7)**	**11 (4.5)**		**SS**
				Acne	**1 (0.4)**	**12 (4.9)**		**SS**
				Decreased libido	**8 (3.3)**	**2 (0.8)**		**SS**
				Emotional lability	**1 (0.4)**	**11 (4.5)**		**SS**
				Dysmenorrhea	7 (2.9)	3 (1.2)		NS
				Experiencing adverse effects	79 (33.1)	70 (28.6)		NS

4.1.6.5. Vaginal ring versus combined oral contraception. Cochrane authors' conclusions (Lopez 2010a)

(conclusions for patch and vaginal ring combined)

Effectiveness was similar for the methods compared. The patch could lead to more discontinuation while the vaginal ring showed little difference. The patch group had better compliance than the COC group but more side effects. Ring users generally had fewer adverse events than COC users but more vaginal irritation and discharge. High losses to follow up can affect the validity of the results

4.1.6.bis. Combined hormonal contraception: contraceptive vaginal ring vs pill. Summary and conclusions

<table>
<tr><td colspan="6">Vaginal ring etonogestrel 120µg + EE 15µg vs COC levonorgestrel 150µg + EE 30µg
(Duijkers 2004a, Oddson 2005 from Lopez 2010a)</td></tr>
<tr><td>N/n</td><td>Duration</td><td>Population</td><td colspan="3">Results</td></tr>
<tr><td rowspan="20">N= 2

n=
1115</td><td rowspan="20">6-13 cycles</td><td rowspan="20">- Healthy women
- Age: 18-45y</td><td rowspan="3">Pregnancy per cycle
N=2</td><td colspan="3">OR=1.03 (0.30 – 3.55), NS</td></tr>
<tr><td><u>Quality</u>
-1 (large drop-out)</td><td><u>Consistency</u>
OK</td><td><u>Directness</u>
OK</td><td><u>Imprecision</u>
OK</td></tr>
<tr><td colspan="4">Grade assessment: moderate quality of evidence</td></tr>
<tr><td rowspan="3">Discontinuation overall (6 or 13 cycles)
N=2</td><td colspan="4">OR= 1.06 (0.81 - 1.38), NS</td></tr>
<tr><td><u>Quality</u>
-1</td><td><u>Consistency</u>
OK</td><td><u>Directness</u>
OK</td><td><u>Imprecision</u>
OK</td></tr>
<tr><td colspan="4">Grade assessment: moderate quality of evidence</td></tr>
<tr><td rowspan="3">Discontinuation adverse events
N=2</td><td colspan="4">OR= 1.33 (0.89 – 2.00), NS</td></tr>
<tr><td><u>Quality</u>
-1</td><td><u>Consistency</u>
OK</td><td><u>Directness</u>
OK</td><td><u>Imprecision</u>
OK</td></tr>
<tr><td colspan="4">Grade assessment: moderate quality of evidence</td></tr>
<tr><td rowspan="3">Compliance per cycle

N=1
(Oddsson 2005)</td><td colspan="4">OR= 1.07 (0.96 – 1.20), NS</td></tr>
<tr><td><u>Quality</u>
-1</td><td><u>Consistency</u>
OK</td><td><u>Directness</u>
OK</td><td><u>Imprecision</u>
OK</td></tr>
<tr><td colspan="4">Grade assessment: moderate quality of evidence</td></tr>
<tr><td rowspan="3">Breakthrough bleeding

N=1
(Oddsson 2005)</td><td colspan="4">Cycle 6: OR= 0.22 (0.05 - 0.88), SS
Cycle 13: OR=0.15 (0.01 – 2.45), NS</td></tr>
<tr><td><u>Quality</u>
-1</td><td><u>Consistency</u>
OK</td><td><u>Directness</u>
OK</td><td><u>Imprecision</u>
OK</td></tr>
<tr><td colspan="4">Grade assessment: moderate quality of evidence</td></tr>
<tr><td>Breast pain
N=1
(Oddsson 2005)</td><td colspan="4">OR=2.25 (0.99 – 5.14), NS</td></tr>
<tr><td>Dysmenorrhea
N=1
(Oddsson 2005)</td><td colspan="4">OR= 1.86 (0.77 – 4.52), NS</td></tr>
<tr><td>Vaginitis
N=2</td><td colspan="4">OR= 2.84 (1.34 – 6.01), SS</td></tr>
<tr><td>Genital pruritus
N=1
(Oddsson 2005)</td><td colspan="4">OR= 4.58 (1.14 – 18.41), SS</td></tr>
<tr><td>Leukorrhea
N=2</td><td colspan="4">(Duijkers 2004a, Oddsson 2005)
OR= 6.42 (2.71 – 15.22), SS</td></tr>
<tr><td>Weight increase
N=2</td><td colspan="4">(Duijkers 2004a, Oddsson 2005)
OR=0.93 (0.41 – 2.13), NS</td></tr>
<tr><td>Acne
N=1
(Oddsson 2005)</td><td colspan="4">OR= 0.23 (0.08 – 0.63), SS</td></tr>
<tr><td rowspan="2"></td><td><u>Quality</u>
-1</td><td><u>Consistency</u>
OK</td><td><u>Directness</u>
OK</td><td><u>Imprecision</u>
OK</td></tr>
<tr><td colspan="4">Grade assessment: moderate quality of evidence</td></tr>
</table>

<table>
<tr><td colspan="5">Vaginal ring etonogestrel 120µg + EE 15µg vs COC levonorgestrel 100µg + EE 20µg
(Sabatini 2006, Veres 2004, Elkind-Hirsch 2007 from Lopez 2010a)</td></tr>
<tr><td>N/n</td><td>Duration</td><td>Population</td><td colspan="2">Results</td></tr>
<tr><td rowspan="27">N= 3
n= 427</td><td rowspan="27">6-12 cycles</td><td rowspan="27">- Healthy women
- Age: 18-45y</td><td rowspan="3">Pregnancy per woman

N=2
(Sabatini 2006, Veres 2004)</td><td colspan="4">OR=0.14 (0.00 – 7.00), NS</td></tr>
<tr><td><u>Quality</u>
-1 (low Jadad)</td><td><u>Consistency</u>
OK</td><td><u>Directness</u>
OK</td><td><u>Imprecision</u>
OK</td></tr>
<tr><td colspan="4">Grade assessment: moderate quality of evidence</td></tr>
<tr><td rowspan="3">Discontinuation overall

N=3</td><td colspan="4">OR=0.66 (0.39 – 1.11), NS</td></tr>
<tr><td><u>Quality</u>
-1</td><td><u>Consistency</u>
OK</td><td><u>Directness</u>
OK</td><td><u>Imprecision</u>
<u>OK</u></td></tr>
<tr><td colspan="4">Grade assessment: moderate quality of evidence</td></tr>
<tr><td rowspan="3">Discontinuation adverse events

N=2
(Sabatini 2006, Veres 2004)</td><td colspan="4">OR=0.48 (0.20 – 1.11), NS</td></tr>
<tr><td><u>Quality</u>
-1</td><td><u>Consistency</u>
OK</td><td><u>Directness</u>
OK</td><td><u>Imprecision</u>
OK</td></tr>
<tr><td colspan="4">Grade assessment: moderate quality of evidence</td></tr>
<tr><td rowspan="3">Noncompliance per woman

N=1
(Veres 2004)</td><td colspan="4">OR=3.99 (1.87 – 8.52), SS</td></tr>
<tr><td><u>Quality</u>
-1</td><td><u>Consistency</u>
OK</td><td><u>Directness</u>
OK</td><td><u>Imprecision</u>
-1 (small study)</td></tr>
<tr><td colspan="4">Grade assessment: low quality of evidence</td></tr>
<tr><td rowspan="3">Early or late withdrawal bleeding

N=1
(Sabatini 2006)</td><td colspan="4">Cycle 6: OR=0.23 (0.07 – 0.70), SS
Cycle 12: OR=0.21 (0.05 – 0.86), SS</td></tr>
<tr><td><u>Quality</u>
-1</td><td><u>Consistency</u>
OK</td><td><u>Directness</u>
OK</td><td><u>Imprecision</u>
OK</td></tr>
<tr><td colspan="4">Grade assessment: moderate quality of evidence</td></tr>
<tr><td rowspan="3">Irregular bleeding

N=1
(Sabatini 2006)</td><td colspan="4">Cycle 6: OR=0.36 (0.15 – 0.87), SS
Cycle 12: OR=0.34 (0.12-0.94), SS</td></tr>
<tr><td><u>Quality</u>
-1</td><td><u>Consistency</u>
OK</td><td><u>Directness</u>
OK</td><td><u>Imprecision</u>
OK</td></tr>
<tr><td colspan="4">Grade assessment: moderate quality of evidence</td></tr>
<tr><td rowspan="3">Breakthrough bleeding

N=1
(Elkind-Hirsch 2007)</td><td colspan="4">Cycle 5: 0.07 (0.00 – 1.42), NS</td></tr>
<tr><td><u>Quality</u>
-1 (low Jadad)</td><td><u>Consistency</u>
OK</td><td><u>Directness</u>
OK</td><td><u>Imprecision</u>
-1 (small study)</td></tr>
<tr><td colspan="4">Grade assessment: low quality of evidence</td></tr>
<tr><td rowspan="3">Vaginal dryness

N=1
(Sabatini 2006)</td><td colspan="4">Cycle 6: OR= 0.12 (0.03 – 0.47), SS
Cycle 12: OR=0.13 (0.03 – 0.65), SS</td></tr>
<tr><td><u>Quality</u>
-1</td><td><u>Consistency</u>
OK</td><td><u>Directness</u>
OK</td><td><u>Imprecision</u>
OK</td></tr>
<tr><td colspan="4">Grade assessment: moderate quality of evidence</td></tr>
<tr><td rowspan="3">Vaginal yeast infection / discomfort

N=1
(Elkind-Hirsch 2007)</td><td colspan="4">Cycle 5: OR=6.02 (0.30 – 122.32), SS</td></tr>
<tr><td><u>Quality</u>
-1</td><td><u>Consistency</u>
OK</td><td><u>Directness</u>
OK</td><td><u>Imprecision</u>
-1</td></tr>
<tr><td colspan="4">Grade assessment: low quality of evidence</td></tr>
</table>

Vaginal ring etonogestrel 120µg + EE 15µg vs COC gestodene 60µg + EE 15µg (Sabatini 2006 from Lopez 2010a)							
N/n	**Duration**	**Population**	**Results**				
N= 1 n=186	12 cycles	women with regular menstrual cycles, sexually active	Pregnancy per woman	OR=0.0 (0.0-0.0), NS			
				Quality -1 (low Jadad)	Consistency OK	Directness OK	Imprecision -1 (small study)
				Grade assessment: *low quality of evidence*			
			Discontinuation overall	**OR=0.32 (0.16 – 0.66), SS**			
				Quality -1	Consistency OK	Directness OK	Imprecision -1
				Grade assessment: *low quality of evidence*			
			Discontinuation adverse events	**OR=0.32 (0.15 – 0.70), SS**			
				Quality -1	Consistency OK	Directness OK	Imprecision -1
				Grade assessment: *low quality of evidence*			
			Early or late withdrawal bleeding	Cycle 6: **OR=0.18 (0.07 – 0.46), SS** Cycle 12: **OR=0.19 (0.05 – 0.73), SS**			
				Quality -1	Consistency OK	Directness OK	Imprecision -1
				Grade assessment: *low quality of evidence*			
			Irregular bleeding	Cycle 6: **OR=0.26 (0.11 – 0.57), SS** Cycle 12: **OR=0.33 (0.12 – 0.91), SS**			
				Quality -1	Consistency OK	Directness OK	Imprecision -1
				Grade assessment: *low quality of evidence*			
			Vaginal dryness	Cycle 6:**OR=0.11 (0.04 – 0.32), SS** Cycle 12:**OR=0.12 (0.03 – 0.50), SS**			
				Quality -1	Consistency OK	Directness OK	Imprecision -1
				Grade assessment: *low quality of evidence*			

Vaginal ring etonogestrel 120µg + EE 15µg vs COC drospirenone 3mg + EE 30µg (Ahrendt 2006 from Lopez 2010a) and Mohamed 2011							
N/n	**Duration**	**Population**	**Results**				
N= 2 n= 1617	13 cycles	Healthy sexually active women At least 17y	Pregnancy per woman (Ahrendt 2006, Mohamed 2011)	Ahrendt 2006: OR= 0.30 (0.05 – 1.76), NS Mohamed 2011: ring 0% vs COC 0.7%, NT			
				Quality -1 (low FU, no ITT)	Consistency OK	Directness OK	Imprecision OK
				Grade assessment: *moderate quality of evidence*			
			Discontinuation: overall (Ahrendt 2006)	OR=1.19 (0.90 – 1.58), NS			
				Quality -1 (low FU, no ITT)	Consistency OK	Directness OK	Imprecision OK
				Grade assessment: *moderate quality of evidence*			
			Discontinuation: adverse events (Ahrendt 2006)	OR=1.26 (0.85 – 1.88), NS			
				Quality -1 (low FU, no ITT)	Consistency OK	Directness OK	Imprecision OK
				Grade assessment: *moderate quality of evidence*			
			Breakthrough bleeding or spotting days (Ahrendt 2006, Mohamed 2011)	Ahrendt 2006: Cycle 6: **Mean diff = 2.00 (1.57 – 2.43), SS** Cycle 13: Mean diff = -0.10 (-0.34 – 0.14), NS Mohamed 2011: Cycle 12: Ring 11.3% vs COC 14.7%, **SS in favour of ring**			
				Quality -1 (low FU, no ITT)	Consistency -1	Directness OK	Imprecision OK
				Grade assessment: *low quality of evidence*			
			Withdrawal bleeding days (Ahrendt 2006)	Cycle 6: **Mean diff= -0.30 (-0.50 - -0.10), SS** Cycle 13: Mean diff= -0.20 (-0.40 – 0.00), NS			
				Quality -1 (low FU, no ITT)	Consistency OK	Directness OK	Imprecision OK
				Grade assessment: *moderate quality of evidence*			
			Vaginitis (Ahrendt 2006, Mohamed 2011)	Ahrendt 2006: **OR=2.19 (1.09 – 4.38), SS** Mohamed 2011: **ring 4.6% vs COC 1.2%, SS**			
			Leukorrhea (Ahrendt 2006, Mohamed 2011)	Ahrendt 2006: **OR=2.82 (1.19 – 6.70), SS** Mohamed 2011: **ring 4.2% vs COC 0.8%, SS**			
			Breast pain (Ahrendt 2006, Mohamed 2011)	Ahrendt 2006: OR=0.67 (0.35 – 1.26), NS Mohamed 2011: ring 3.3% vs COC 2.4%, NS			
			Weight gain (Mohamed 2011)	**Ring 1.7% vs COC 4.5%, SS**			
			Acne (Mohamed 2011)	**Ring 0.4% vs COC 4.9%, SS**			
				Quality -1 (low FU, no ITT)	Consistency OK	Directness OK	Imprecision OK
				Grade assessment: *moderate quality of evidence*			

- Six RCTs from the meta-analysis of Lopez 2010 and one RCT (Mohamed 2011) compared hormonal contraception in the form of a vaginal ring with various combination pills (levonorgestrel 100-150µg – EE 20-30µg, gestodene 60µg – EE 15µg, drospirenone 3µg – EE 30µg). Some studies include fewer than 100 participants in total. There was also often a high dropout rate, approximately one third in each treatment group.

- The difference in the number of pregnancies between the two groups was not significant.

GRADE: low to moderate quality of evidence

- An equivalent number of participants discontinued their treatment in both groups in the studies. Ring users were less therapy-compliant than pill users in one (small) study, but there was no significant difference between the groups in other studies. The general conclusion in the Cochrane review is that there are contradictory data.

GRADE: low to moderate quality of evidence

- Users of the vaginal ring had significantly more vaginitis and leucorrhoea compared to users of the combination pill, although they had less difficulty with vaginal dryness.
Ring users reported in two studies less acne and in one study less weight gain than pill users.
Cycle control is often significantly better in treatment with the vaginal ring than with the combination pill.

GRADE: low to moderate quality of evidence

4.1.7. Combined oral contraception containing nomegestrol acetate v drospirenone. Evidence tables.

Ref	n/Population	Duration	Comparison	Outcomes		Methodological
115_westhoff_2012 Design: RCT (OL) (PG)	n= 2281 mean age: 27.7y (85% 18-35y) <u>Inclusion</u> - 18-50y women at risk for pregnancy (no condoms) and in need of contraception - BMI 17-35 <u>Exclusion</u> - WHO Medical Eligibility Criteria	13 cycles (=1 woman-year)	Nomegestrol acetate + 17β–estradiol (24-4d regimen) Vs Drospirenone + ethinyl estradiol (21-7d regimen)	Efficacy		- Jadad score o RANDO: 2/2 o BLINDING: 0/2 o ATTRITION: 1/1 - FU: 97% received treatment, 61% completed treatment (12% lost to follow-up) - ITT: 'yes', all women who completed at least 1 cycle - Other important methodological remarks: Approximately 41% and 38% of recipients in the respective groups discontinued treatment before the end of the trial - Sponsor: Merck & Co Inc.
				Pearl Index 18-35y (PE)	Nomac 1.27 (95% CI: 0.66-2.22) Drsp 1.89 (95% CI: 0.69-4.11) Difference between groups NS	
				Pregnancy rate (1-y cumulative) Life table analysis	Nomac 1.22 (95% CI: 0.69-2.16) Drsp 1.82 (95% CI: 0.81-4.05)	
				Scheduled bleeding (mean number of days)	Nomac 5.9 -> 4.1 Drsp 9.8 -> 11.6 **SS difference between groups (p<0.001)**	
				Spotting (mean number of days)	Nomac 8.9 -> 5.4 Drsp 7.9 -> 7.7 **SS difference between groups (p<0.05)**	
				Safety		
				Acne	Nomac 16.4% vs Drsp 8.7%	
				Weight gain	Nomac 9.5% vs Drsp 5.2%	
				Irregular withdrawal bleeding	Nomac 9.1% vs Drsp 0.5%	
				Metrorrhagia	Nomac 5.8% vs Drsp 2.7%	
				Serious adverse events	Nomac 1.8% vs Drsp 0.9%	

- The mean number of bleeding days was substantially lower for all reference periods in the nomegestrol acetate and 17β-estradiol group compared with drospirenone and ethinyl estradiol (p<0.001).
- The mean number of spotting days was significantly lower with nomegestrol acetate and 17β-estradiol for reference period 3 and 4 (end of study). Treatment groups were similar with regard to spotting in the first two reference periods (start of study).
- There was no significant difference in contraceptive efficacy between treatment groups.
- In the investigational group (nomegestrol acetate and 17β-estradiol) the most frequently reported adverse events were acne (16.4%), weight gain (9.5%) and irregular bleeding (9.1%).

Author's conclusion:
Nomegestrol acetate and 17β-estradiol were well tolerated and provided excellent contraceptive efficacy and acceptable cycle control.

Ref	n/Population	Duration	Comparison	Outcomes		Methodological
245_mansour_2011 Design: RCT (OL) (PG)	n= 2152 mean age: 28y (83% 18-35y) <u>Inclusion</u> - 18-50y women at risk for pregnancy and in need of contraception - BMI 17-35 <u>Exclusion</u> - Contraindications for contraceptive steroids - Abnormal cervical smear - Abnormal laboratory tests - Injectable hormonal contraceptive in past 4-6m - Use of enzyme-inducing or inhibiting drugs	13 cycles (=1 woman-year)	Nomegestrol acetate + 17β–estradiol (24-4d regimen) Vs Drospirenone + ethinyl estradiol (21-7d regimen)	**Efficacy**		- Jadad score o RANDO: 2/2 o BLINDING: 0/2 o ATTRITION: 1/1 - FU: 99% received treatment (n=2126), 74% completed treatment (n=1552), 28% discontinued prematurely, 3% lost to follow-up - ITT: 'yes', all women who took at least one dose of trial medication - Multicenter: in Europe, Asia and Australia - Sponsor: MSD
				Pearl Index 18-35y (PE)	Nomac 0.38 (95% CI: 0.10-0.97) Drsp 0.81 (95% CI: 0.17-2.35) Difference between groups NS	
				Pregnancy rate 18-35y (1-y cumulative) Life table analysis	Nomac 0.40 (95% CI: 0.15-1.06) Drsp 0.77 (95% CI: 0.25-2.39) Difference between groups NS	
				Vaginal bleeding/spotting (mean number of days)	Nomac 14.9 -> 10.6* Drsp 18.5 -> 19.2 TNR	
				Acne (SE)	Improvement: Nomac 15.9% vs Drsp 20.1% NT	
					Worsening: Nomac 9.9% vs Drsp 4.01% NT	
				Safety		
				Acne (newly developed)	Nomac 11.1% vs Drsp 5.1% NT	
				Weight gain (mean)	Nomac 63.4kg -> 64.4kg Drsp 63.7kg -> 64.0kg **SS difference between groups (p=0.001)**	
				Irregular withdrawal bleeding	Nomac 11.7% vs Drsp 0.4% NT	
				Headache	Nomac 6.6% vs Drsp 6.2% NT	
				Serious adverse events (number of patients)	Nomac 1 (0.06%) vs Drsp 2 (0.4%) NT	

* The data showed a lower mean number of bleeding/spotting days in the nomegestrol acetate and 17β-estradiol group compared with drospirenone and ethinyl estradiol group across the reference periods. For nomegestrol acetate and 17β-estradiol the number of bleeding-spotting days declined, while for drospirenone and ethinyl estradiol the numbers remained the same over time. The difference between the two treatments increased with time to about 8.6 days per reference period, and was largely caused by an excess of bleeding days with drospirenone and ethinyl estradiol as compared to nomegestrol acetate and 17β-estradiol.

- Scheduled withdrawal bleedings were shorter and lighter among users of nomegestrol acetate and 17β-estradiol and were sometimes absent altogether. Intracyclic bleeding/spotting was infrequent in both groups, and decreased over time.
- Type and frequence of adverse events were similar to those typically reported for combined oral contraceptives.

4.1.7.bis. Combined oral contraception containing nomegestrol acetate v drospirenone. Summary and conclusions

Nomegestrol acetate + 17β–estradiol vs Drospirenone + ethinyl estradiol (a. Westhoff 2012, b. Mansour 2011)							
N/n	**Duration**	**Population**	**Results**				
N=2, n= 4433	1 woman-year (13 cycles)	- Age: 18-50y (>80% 18-35y) women at risk for pregnancy, in need of contraception - BMI 17-35	Pregnancy (PE) in 18-35y old	Reported in 2/2 studies a. Pearl Index 18-35y (PE): Nomac 1.27 vs Drsp 1.89 Difference between groups NS b. Pearl Index 18-35y (PE): Nomac 0.38 vs Drsp 0.81 Difference between groups NS			
				Quality OK	Consistency OK	Directness OK	Imprecision OK
				Grade assessment: *high quality of evidence*			
			Scheduled bleeding (mean number of days)	Reported in 1/2 studies a. Nomac 5.9 -> 4.1 vs Drsp 9.8 -> 11.6 **SS difference between groups (p<0.001)**			
				Quality -1 (OL, early drop-out high)	Consistency NA	Directness OK	Imprecision OK
				Grade assessment: *moderate quality of evidence*			
			Spotting (mean number of days)	Reported in 1/2 studies a. Nomac 8.9 -> 5.4 vs Drsp 7.9 -> 7.7 **SS difference between groups (p<0.05)**			
				Quality -1 (OL, early drop-out high)	Consistency NA	Directness OK	Imprecision OK
				Grade assessment: *moderate quality of evidence*			
			Vaginal bleeding/spotting (mean number of days)	Reported in 1/2 studies b. Nomac 14.9 -> 10.6 vs Drsp 18.5 -> 19.2 TNR "Scheduled withdrawal bleedings were shorter and lighter among users of nomegestrol acetate and 17β-estradiol and were sometimes absent altogether. Intracyclic bleeding/spotting was infrequent in both groups, and decreased over time."			
				Grade assessment: *NA*			
			Acne	Reported in 2/2 studies a. Nomac 16.4% vs Drsp 8.7% b. Nomac 11.1% vs Drsp 5.1% NT			
				Grade assessment: *NA*			
			Weight gain	Reported in 2/2 studies a. Nomac 9.5% vs Drsp 5.2% NT b. Nomac 63.4kg -> 64.4kg vs Drsp 63.7kg -> 64.0kg **SS difference between groups (p=0.001)**			
				Quality -1 (OL, NT)	Consistency OK	Directness OK	Imprecision OK
				Grade assessment: *moderate quality of evidence*			

- Two randomised studies compared nomegestrol acetate + 17β–estradiol with drospirenone + ethinyl estradiol in more than four thousand fertile women.
There was no significant difference in Pearl index between the two combination pills; the contraceptive efficacy was equivalent.

GRADE: high quality of evidence

- According to one study, the difference in days with bleeding or spotting between the nomegestrol pill and the drospirenone pill is significant; in the other study, statistical significance was not reported.

GRADE: *moderate quality of evidence*

- The most common adverse events with both combination pills were acne and weight gain. The 'acne' endpoint was not examined statistically.

GRADE: *NA*

- Weight gain was significantly greater in the group that used nomegestrol.

GRADE: *moderate quality of evidence*

4.1.8. Combined hormonal contraception: continuous vs cyclic use. Evidence tables

4.1.8.1. Systematic review

Ref	N/n	Comparison	Outcomes	
* Edelman 2010 Design: meta-analysis N= 8 n=2745 Search date: sept 2009	N=1	30 ug ethinyl estradiol and 150 ug levonorgestrel, 28-day versus 91-day cycles for one year	Pregnancy	4/456 (continuous) vs 3/226 (cyclic) OR= 0.64 (95%CI 0.13, 3.12) NS p=0.58
			Mean total bleeding days (bleeding + spotting) for entire study period (364 days)	48.2±44(continuous) vs 50.8±27 (cyclic) Mean difference=-2.60 (95%CI-8.03, 2.83) NS p=0.35
			Mean bleeding days only for entire study period (364 days)	**22.7±22.8(continuous) vs 37 ±19.6 (cyclic)** **Mean difference=-14.30 (95%CI-17.65, -10.95)** **SS in favor of continuous regimen p=0.00001**
			Symptoms: Headache	**96/456 (continuous) vs 63/226 (cyclic)** **OR= 0.69 (95%CI 0.48, 1.00)** **SS* in favor of continuousregimen p=0.048** *reported as SS by Cochrane authors
			Overall adherence based on self reported diary	21/456 (continuous) vs 15/226 (cyclic) OR= 0.68 (95%CI 0.34,1.34) NS p=0.27
			Discontinuation for bleeding reasons	**35/456 (continuous) vs 4/226 (cyclic)** **OR= 2.99 (95%CI 1.50,5.93)** **SS in favor of cyclic regimen p=0.0018**
			Overall Discontinuation	**185/456 (continuous) vs 65/226 (cyclic)** **OR= 1.66 (95%CI 1.19, 2.31)** **SS in favor of cyclic regimen p=0.0026**
	N=1	30 ug ethinyl estradiol and 150 ug desogestrel, 28-day versus 70-day cycles for one year	Pregnancy	0/198 (continuous) vs 0/96 (cyclic)
			Discontinuation for bleeding reasons	**26/198(continuous) vs 2/96 (cyclic)** **OR= 3.59 (95%CI 1.57,8.22)** **SS in favor of cyclic regimen p=0.0025**
			Overall discontinuation	83/198 (continuous) vs 32/96 (cyclic) OR= 1.43 (95%CI 0.87,2.36) NS p=0.16
	N=1	15 µg ethinyl estradiol and 120	Pregnancy, 28-day versus 91-day	1/105 (91-day cycle) vs 0/108 (cyclic)

		µg etonogestrel, 28-day versus 49-day versus 364-day cycle. (Contraceptive ring)		OR= 3.11 (95%CI 0.13, 77.33) NS p=0.49
			Total bleeding days, 28-day versus 49-day	8/49(49-day cycle) vs 5/28 (cyclic) OR= 0.9 (95%CI 0.26, 3.07) NS p=0.86
			Total Bleeding Days, 28-day versus 91-day	19/91 (91-day cycle) vs 5/28 (cyclic) OR= 1.21 (95%CI 0.41, 3.61) NS p=0.73
			Total bleeding days, 28-day versus 364-day	89/364(364-day cycle) vs 5/28 (cyclic) OR= 1.49(95%CI 0.55, 4.03) NS p=0.43
			Adherence to a 7-day hormone free interval, 28-day versus 49-day	2/107 (49-day cycle) vs 3/108 (cyclic) OR= 0.67 (95%CI 0.11, 4.07) NS p=0.66
			Adherence to a 7-day hormone free interval, 28-day versus 91-day	3/105 (91-day cycle) vs 3/108 (cyclic) OR= 1.03 (95%CI 0.20, 5.22) NS p=0.97
			Discontinuation for bleeding reasons, 28-days versus 49-days	**5/107 (49-day cycle) vs 0/108 (cyclic)** **OR= 7.75 (95%CI 1.32, 45.48)** **SS in favor of cyclic p=0.023**
			Discontinuation for bleeding reasons, 28-day versus 91-day	**13/105 (91-day cycle) vs 0/108 (cyclic)** **OR= 8.59 (95%CI 2.80, 26.30)** **SS in favor of cyclic p=0.00017**
			Discontinuation for bleeding reasons, 28-day versus 364-day	**20/109 (364-day cycle) vs 0/108 (cyclic)** **OR= 8.87 (95%CI 3.54, 22.21)** **SS in favor of cyclic p=0.00001**
			Overall discontinuation, 28-day versus 49-day	30/107 (49-day cycle) vs 25/108 (cyclic) OR= 1.29 (95%CI 0.7, 2.38) NS p=0.41
			Overall discontinuation, 28-day versus 91-day	**40/105 (91-day cycle) vs 25/108 (cyclic)** **OR= 2.02 (95%CI 1.13, 3.61)** **SS in favor of cyclic p=0.018**
			Overall discontinuation, 28-day versus 364-day	**45/109 (364-day cycle) vs 25/108 (cyclic)** **OR= 2.28 (95%CI 1.29, 4.03)** **SS in favor of cyclic p=0.0044**

* Characteristics of included studies: see under

Ref + design	n	Population	Duration	Comparison	Methodology
Anderson 2003 Randomized clinical trial. Open label. Multicentered trial (47 U.S. sites)	682	Age: 18-40 years old. At risk for pregnancy. No COC contraindications	1y	30 ug ethinyl estradiol and 150 ug levonorgestrel, 28-day versus 91-day cycles for one year	- Jadad score: 2/5 - FU: 63.3% - ITT: yes, but this study excluded patients from Pearl index calculations who were noncompliant with their assigned pill-dosing regimen - Sponsor: Barr
Cachrimanidou 1993 Randomized clinical trial	294	Age: 18-39 years old. At risk for pregnancy. No COC contraindications	1y	30 ug ethinyl estradiol and 150 ug desogestrel, 28-day versus 70-day cycles for one year	- Jadad score:1/5 - FU: 60.9% - ITT: unclear Other important methodological remarks: - method of randomization not reported - inclusion and exclusion criteria unclear - allocation concealment unclear - Sponsor: Organon
Miller 2005 Randomized controlled trial. Multicentered (10 European and 10 US sites)	429	Age: premenopausal and 18 years old or older Regular menstrual cycles Not breastfeeding or postpartum, or postabortion within last month No COC contraindications No use of drugs that interfere with contraceptive steroids No abnormal pap	1y	15 µg ethinyl estradiol and 120 µg etonogestrel, 28-day versus 49-day versus 364-day cycle. (Contraceptive ring)	- Jadad score: 3/5 - FU: 67.4% - ITT: yes Other important methodological remarks: - Adequate allocation concealment - Computer-generated randomization - Centralized automated assignment system Sponsor: Organon

Remarks

Once allocation to treatment groups had occured, actual treatment was unblinded for both participants and investigators in all of the studies.

Several authors evaluated bleeding using definitions adapted from the World Health Organization (WHO) (Suvisaari 1996). The WHO bleeding definitions state that spotting is bloody vaginal discharge that does not require protection and bleeding requires protection. Cachrimandou (Cachrimanidou 1993) and Miller (Miller 2005) defined 'spotting' as requiring no or at most one sanitary napkin per day and 'bleeding' as requiring at least two sanitary pads per day.

Only one trial (Cachrimanidou 1993) consistently had higher numbers of bleeding and spotting days for continuous cycles, but the authors did not include any of the withdrawal bleeding/spotting days in these calculations, which would have then demonstrated less bleeding/spotting days for the continuous cycle group.==> data not shown in MA

Authors' conclusions

Evidence from existing randomized control trials comparing CHCs given continuously (greater than 28 days of active combined hormones) to traditional monthly cyclic dosing (21 days of active hormone and 7 days of placebo) is of good quality. However, the variations in type of hormones and time length for continuous dosing make a formal meta-analysis impossible. Future studies should choose a previously described type of CHC and dosing regimen. More attention needs to be directed towards participant satisfaction and menstruation-associated symptoms.

4.1.8.2. RCT. Flexible extended vs fixed extended vs conventional regimen (Drospirenone 3mg + ethinyl estradiol 20µg)

Ref	n/Population	Duration	Comparison	Outcomes			Methodological
Klipping 2012a *Klipping 2012b* Design: RCT (OL) (PG)	n= 1166 *(n= 783 in extension phase°)* mean age: 24.8y <u>Inclusion</u> - Women 18-35y - Requesting contraceptive protection - Good general health - Normal cervical smear in prior 6m <u>Exclusion</u> - >30y-old smokers - Using other contraceptive methods - Sterilization - Pregnant or lactating - BMI <18 or >30 - Any vascular disease or coagulation disorder - Known hypersensitivity to study drugs	1y *+1y extension*	Drospirenone 3mg + ethinyl estradiol 20µg Flexible extended Vs Fixed extended Vs Conventional regimen*	Efficacy			- Jadad score o RANDO: 2/2 o BLINDING: 0/2 o ATTRITION: 1/1 - FU: 81% completed treatment *(91% of subjects entering safety extension completed extra year)* - ITT: full analysis set was defined as all women who received at least one dose of study medication and for whom at least one clinical observation was available - Multicenter: 37 centers in 3 countries (Canada, Germany, The Netherlands) - Sponsor: Bayer
				Bleeding/spotting days (mean number of days during 1 year) (PE)	Flex: 41.0d (95%CI: 38.8-43.3) Fix: 60.9d (95%CI: 53.9-67.9) Con: 65.8 (95%CI: 62.2-69.4) Between group difference Flex-Con **SS in favour of flexible extended regimen (p<0.0001)** Between group difference Fix-Con NT		
				Pearl index (PE) with flexible extended regimen during 2 years	Flex: 0.64 (95%CI: 0.28-1.26) NR for Fix and Con		
				Cumulative pregnancy rate up to 2 years (PE)	Flex: 1.28% (95%CI: 0.62-2.66) NR for Fix and Con		
				Withdrawal bleeding (mean length of episodes) (SE)	Flex: 7.5-14.2d Fix: 2.0-10.5d Con: 4.4-5.2d		
				Intracyclic bleeding/spotting (max. length of episodes) (SE)	Flex: 4.1d Fix: 16.5d Con: 5.8d		
				Safety			
				At least one AE	Flex: 64.6% Fix: 71.8% Con: 69.4% NT	*Flex: 53.9%* *Fix: 51.3%* *Con: 67.1%* *NT*	
				Treatment withdrawn due to AE	Flex: 4.0% Fix: 4.8% Con: 2.5% NT	*Flex: 1.0%* *Fix: 0%* *Con: 2.4%* *NT*	
				Headache	Flex: 12.8% Fix: 17.7% Con: 17.1%	*Flex: 5.5%* *Fix: 6.7%* *Con: 12.9%*	

					NT	*NT*	
				Dysmenorrhea	Flex: 4.5% Fix: 4.3% Con: 6.5% NT		
				Vomiting	Flex: 4.4% Fix: 5.3% Con: 3.2% NT		
				Breast pain	Flex: 3.1% Fix: 3.3% Con: 3.2% NT		
				Body weight	Remained stable in all three regimens	*Mean weight gain (+1kg) in all regimens*	
				Mortality	*No deaths reported in this study*		
				Serious AE	*Flex: 3.0%* *Fix: 3.3%* *Con: 1.4%* *NT*		
				Endometrial thickness	*Flex: 3.69mm* *Fix: 4.10mm* *Con: 3.37mm* *NT*		
				Endometrial characteristics	*No abnormal findings were identified, including no hyperplasia, carcinomas, sarcomas, carcinomatous or other types of metaplasia or cervical carcinomas*		
				Ovarian morphology	*No abnormal findings*		

4.1.8.bis. Combined hormonal contraception: continuous vs cyclic use. Summary and conclusions

<table>
<tr><td colspan="5">Combined hormonal contraception* cyclical use (28d) vs extended cycle (70d vs 91d vs 120d vs 364d)
(From Edelman 2005: a. Anderson 2003, b. Cachrimanidou 1993, c. Miller 2005), (d. Klipping 2012a and 2010b)</td></tr>
<tr><th>N/n</th><th>Duration</th><th>Population</th><th>Results</th><th></th></tr>
<tr><td rowspan="12">N= 4
n=2571</td><td rowspan="12">1 year</td><td rowspan="12">Age: 18-40y
Healthy females
At risk for pregnancy
No COC contra-indications</td><td rowspan="3">Pregnancy
N=4
(a. Anderson 2003, b. Cachrimanidou 1993, c. Miller 2005, d. Klipping 2012)</td><td>(a) 4/456 (continuous 91d) vs 3/226 (cyclic 28d) -> NS
(b) 0/198 (continuous 70d) vs 0/96 (cyclic 28d) -> NT
(c) 1/105 (91-day cycle 364d) vs 0/108 (cyclic 28d) -> NS
(d) Pearl-index : 0.64 (flexible regimen 24-120d), NR for other regimens -> NT</td></tr>
<tr><td><u>Quality</u>
-2 (low Jadad, low FU)
<u>Consistency</u>
OK
<u>Directness</u>
OK
<u>Imprecision</u>
OK</td></tr>
<tr><td>Grade assessment: low quality of evidence</td></tr>
<tr><td rowspan="3">Total bleeding days (bleeding + spotting) during 1y
N=3
(a. Anderson 2003, b. Cachrimanidou 1993, d. Klipping 2012)</td><td>(a) 48d (continuous 91d) vs 51d (cyclic 28d) -> NS
(c) 82d (continuous 91d) vs 65d (cyclic 28d) -> NS
89d (continuous 364d) vs 65d (cyclic 28d) -> NS
(d) 41d (flexible 24-120d) vs 66d (cyclic 28d) -> SS (p<0.0001)
61d (fixed 120d) vs 66d (cyclic 28d) -> NT</td></tr>
<tr><td><u>Quality</u>
-1 (low Jadad)
<u>Consistency</u>
OK
<u>Directness</u>
OK
<u>Imprecision</u>
OK</td></tr>
<tr><td>Grade assessment: moderate quality of evidence</td></tr>
<tr><td rowspan="3">Intracyclic bleeding/spotting (max. length of episodes)
N=1
(Klipping 2012)</td><td>4.1d (flexible 24-120d continuous) vs 16.5d (fixed 120d continuous) vs 5.8d (cyclic 28d)</td></tr>
<tr><td><u>Quality</u>
-1 (low Jadad)
<u>Consistency</u>
OK
<u>Directness</u>
OK
<u>Imprecision</u>
OK</td></tr>
<tr><td>Grade assessment: moderate quality of evidence</td></tr>
<tr><td rowspan="3">Discontinuation due to bleeding
N=3
(a. Anderson 2003, b. Cachrimanidou 1993, c. Miller 2005)</td><td>(a) 35/456 (continuous 91d) vs 4/226 (cyclic 28d)
OR= 2.99 (95%CI 1.50,5.93)
SS in favor of cyclic regimen p=0.0018
(b) 26/198(continuous 70d) vs 2/96 (cyclic 28d)
OR= 3.59 (95%CI 1.57,8.22)
SS in favor of cyclic regimen p=0.0025
(c) 13/105 (continuous 91d) vs 0/108 (cyclic 28d)
OR= 8.59 (95%CI 2.80, 26.30)
SS in favor of cyclic p=0.00017
20/109 (continuous 364d) vs 0/108 (cyclic 28d)
OR= 8.87 (95%CI 3.54, 22.21)
SS in favor of cyclic p=0.00001</td></tr>
<tr><td><u>Quality</u>
-1 (low Jadad)
<u>Consistency</u>
OK
<u>Directness</u>
OK
<u>Imprecision</u>
-1 (low FU)</td></tr>
<tr><td>Grade assessment: moderate quality of evidence</td></tr>
</table>

*Combined hormonal contraception:

(a) 30 µg ethinyl estradiol and 150 µg levonorgestrel, 28-day versus 91-day cycles

(b) 30 µg ethinyl estradiol and 150 µg desogestrel, 28-day versus 70-day cycles

(c) 15 µg ethinyl estradiol and 120 µg etonogestrel, 28-day versus 91-day versus 364-day cycle (contraceptive ring)

(d) 3 mg drospirenone + 20 µg ethinyl estradiol 28-day (24d active +4d hormone-free) versus fixed extended 120-day versus flexible extended 24-120-day where women could choose the length of continuous intake, they were advised to have a 4-day tablet-free interval if bleeding and/or spotting occurred for three consecutive days

- We selected from a Cochrane review three studies in which continuous intake of the combination pill (and in one study also the vaginal ring with oestroprogestagens) for three or more cycles was compared with standard intake (21d hormone intake + 7d hormone-free interval, or in the case of drospirenone, 24d + 4d). A more recent RCT also studied the drospirenone-containing combination pill in a flexible regimen of 24 to 120 days of hormone intake to reduce intracyclic bleeding.

- These studies had insufficient power to demonstrate differences in contraceptive reliability. In some studies no pregnancies occurred in one or more arms. Meta-analysis was not conducted due to the different hormone compositions of the contraceptives compared and the different duration of continuous intake. In the individual studies there appeared to be no difference in contraceptive reliability for the two strategies.

GRADE: low quality of evidence

- There proved to be no significant difference in the total number of days of bleeding between the various fixed regimens. One study with drospirenone did report significantly fewer days of bleeding in the flexible regimen in which women could choose how many days in a row they took the pill, between 24 and 120 days, in comparison to the standard 28d cycle regimen. In almost all the studies, a significant difference in discontinuation of the treatment due to bleeding was reported in favour of cyclic pill intake compared to continuous intake.

GRADE: moderate quality of evidence

4.1.9. Combined hormonal contraception: effect on weight. Evidence tables.

4.1.9.1. Levonorgestrel 100 µg and EE 20 µg versus placebo: effect on weight

Ref	N/n	Comparison	Outcomes	Result
Gallo 2011b Design: MA Search date: 31 May 2011	N= 1 n= 721	Levonorgestrel 100 µg and EE 20 µg versus placebo	Mean weight change in kg (cycle 6)	Mean diff= 0.30 (-0.23 – 0.83), NS

* Characteristics of included studies: see below

Ref + design	N	Population	Duration	Comparison	Methodology
Coney 2001 DB PG RCT	721	32 sites in USA, Canada and Australia. Healthy women age ≥ 14 with regular menses and moderate facial acne. Excluded: recent abnormal cervical cytology; pregnancy; willing to use non-hormonal contraception if at risk of pregnancy; contraindications to oral contraceptive use; recent oral or injectable hormones; recent use of certain drugs	6 cycles	Levonorgestrel 100 µg and EE 20 µg (n=359) versus placebo (n=362)	- Jadad score: 4/5 - FU: 60,3% - ITT: no -Methodological remarks: high dropout rate and no ITT

4.1.9.2. Skin patch versus placebo: effect on weight

Ref	N/n	Comparison	Outcomes	Result
Gallo 2011b Design: MA Search date: 31 May 2011	N= 1 n= 136	Skin patch norelgestromin 150 µg and EE 20 µg versus placebo	Gained >5% baseline weight (cycle 9)	OR=0.95 (0.30 – 2.98), NS
			Lost >5% baseline weight (cycle 9)	OR=0.27 (0.04 – 1.82), NS

* Characteristics of included studies: see below

Ref + design	n	Population	Duration	Comparison	Methodology
Sibai 2001 DB PG RCT	136	Study location not described Inclusion and exclusion criteria not described	9 cycles	Contraceptive skin patch releasing norelgestromin 150 µg and EE 20 µg daily (n=92) versus placebo (n=44).	- Jadad score: 2/5 - FU: NR - ITT: ? - Methodological remarks: initial number assigned to each study group not reported; loss to FU not reported, unclear if the number of participants with weight outcomes was the number of women randomized

4.1.9.3. Desogestrel 150 µg and EE 20 µg versus gestodene 75 µg and EE 20 µg: effect on weight

Ref	N/n	Comparison	Outcomes	Result
Gallo 2011b Design: MA Search date: 31 May 2011	N= 2 n= 2.589	Desogestrel 150 µg and EE 20 µg versus gestodene 75 µg and EE 20 µg	Gained >2 kg	[Serfaty 1998] Cycle 6: OR=0.84 (0.58 – 1.22), NS [Endrikat 1999] Cycle 12: OR=1.13 (0.85 – 1.49), NS
			Lost >2 kg	[Serfaty 1998] Cycle 6: **OR=1.65 (1.13 – 2.41), SS in favor of gestodene** [Endrikat 1999] Cycle 12: OR=0.95 (0.68 – 1.33), NS

* Characteristics of included studies: see below

Ref + design	n	Population	Duration	Comparison	Methodology
Serfaty 1998 OL PG RCT	1.026	52 sites in Paris, France Healthy, normal-weight women age 18 to 45 years (18 to 35 years for smokers) with regular menses and normal plasma lipid and carbohydrate levels. Excluded:contraindications to oral contraception; recent injectable, implant, or intrauterine contraceptive use; recent birth or abortion; use of certain drugs	6 cycles	Desogestrel 150 µg and EE 20 µg (n=515) versus gestodene 75 µg and EE 20 µg (n=511)	- Jadad score: 3/5 - FU: 81.3% - ITT: no
Endrikat 1999 OL PG RCT	1.563	123 sites in France, Austria, the UK, The Netherlands, Switzerland and Italy. Healthy women age 18 to 35 years with regular menses. Excluded: current use of oral contraceptive containing 150 µg desogestrel and 20 µg EE; contraindications to oral contraceptive use; recent depot-contraceptives use; unclassified genital bleeding; excessive smoking	12 cycles	Gestodene 75 µg and EE 20 µg (n=786) versus desogestrel 150 µg and EE 20 µg (n=777)	- Jadad score: 2/5 - FU: 65.7% - ITT: no (87 women were excluded from analysis for prototol violations) -Methodological remarks: high dropout rate (34.3%);

4.1.9.4. Desogestrel 150 µg and EE 30 µg versus levonorgestrel 50-75-125 µg and EE 30-40-30 µg: effect on weight

Ref	N/n	Comparison	Outcomes	Result
Gallo 2011b Design: MA Search date: 31 May 2011	N= 1 n= 555	Desogestrel 150 µg and EE 30 µg versus levonorgestrel 50-75-125 µg and EE 30-40-30 µg	Gained >2 kg (cycle 6)	**OR=3.29 (1.84 – 5.88), SS in favor of levonorgestrel**

* Characteristics of included studies: see below

Ref + design	n	Population	Duration	Comparison	Methodology
Lachnit-Fixxson 1984 PG RCT (blinding NR)	555	Multicenter trial in Austria, Germany, The Netherlands and the UK. Inclusion and exclusion criteria not described.	6 cycles	Desogestrel 150 µg and EE 30 µg (n=277) versus triphasic: levonorgestrel 50-75-125 µg and EE 30-40-30 µg (n=278)	- Jadad score: 2/5 - FU: 84.5% - ITT: no

4.1.9.5. Prolongued Desogestrel 150 µg and EE 30 µg versus standard desogestrel 150µg and EE 30µg: effect on weight

Ref	N/n	Comparison	Outcomes	Result
Gallo 2011b Design: MA Search date: 31 May 2011	N= 1 n= 294	Prolonged desogestrel and EE regimen versus standard desogestrel and EE regimen	Mean weight change in kg (cycle 12)	Mean diff=0.57 (-0.42 – 1.56) , NS

* Characteristics of included studies: see below

Ref + design	n	Population	Duration	Comparison	Methodology (sponsor NR in Cochrane)
Cachrimanidou 1993 PG RCT (blinding NR)	294	Three sites in Sweden Healthy women age 18 to 39 years at risk of pregnancy. Excluded “generally accepted” contraindications of OC use.	12 cycles	Prolonged regimen (desogestrel 150 µg and EE 30 µg; nine pill weeks and one pill-free week;n=198) versus standard regimen (desogestrel 150 µg and EE 30 µg; three pill weeks and one pill-free week; n=96)	- Jadad score: 1/5 - FU: loss to FU not reported; 115 women discontinued early - ITT: no

4.1.9.6. Drospirenone 3 mg and EE 20 µg versus desogestrel 150 µg and EE 20 µg: effect on weight

Ref	N/n	Comparison	Outcomes	Result
Gallo 2011b Design: MA Search date: 31 May 2011	N=1 n= 445	Drospirenone 3 mg and EE 20 µg versus desogestrel 150 µg and EE 20 µg	Mean weight change in kg (cycle 7)	**Mean diff= -0.67 (-1.16 - -0.18), SS in favor of drospirenone**

* Characteristics of included studies: see below

Ref + design	n	Population	Duration	Comparison	Methodology (sponsor NR in Cochrane)
Gruber 2006 OL PG RCT	445	25 centers in 4 countries (Italy, UK, Czech Republic, and Belgium). Healthy women aged 18 to 35 years, except for smokers over 30 years. Exclusion: contraindications for COC use; use of DMPA in past 6 months or OC with desogestrel or drospirenone in last cycle; childbirth, abortion, or lactation in last 3 cycles; suspect cervical smear	7 cycles	Drospirenone 3 mg and EE 20 µg (n=222) versus desogestrel 150 µg and EE 20 µg (n= 223)	- Jadad score: 3/5 - FU: 97% - ITT: no

4.1.9.7. Gestodene 75 µg and EE 20 µg versus gestodene 75 µg and EE 30 µg effect on weight

Ref	N/n	Comparison	Outcomes	Result
Gallo 2011b Design: MA Search date: 31 May 2011	N= 1 n= 649	Gestodene 75 µg and EE 20 µg versus gestodene 75 µg and EE 30 µg	Gained >2 kg (cycle 12)	[Endrikat 1997] OR=1.06 (0.63 – 1.81), NS
			Lost >2 kg (cycle 12)	[Endrikat 1997] OR=1.13 (0.63 - 2.03), NS

* Characteristics of included studies: see below

Ref + design	n	Population	Duration	Comparison	Methodology (sponsor NR in Cochrane)
Endrikat 1997 DB PG RCT	649	10 sites in Germany. Healthy, sexually active women age 18 to 39 years. Excluded recent depot-contraceptive use; pregnancy; liver, vascular, and metabolic diseases; tumors; unclassified genital bleeding	12 cycles	Gestodene 75 µg and EE 20 µg (n=428) versus gestodene 75 µg and EE 30 µg (n=221)	- Jadad score: 2/5 - FU: loss to follow-up not reported, 24.8% discontinued early or excluded by the sponsor - ITT: no

4.1.9.8. Gestodene 75 µg and EE 30 µg versus desogestrel 150 µg and EE 20 µg: effect on weight

Ref	N/n	Comparison	Outcomes	Result
Gallo 2011b Design: MA Search date: 31 May 2011	N= 2 n= 1.056	Gestodene 75 µg and EE 30 µg versus desogestrel 150 µg and EE 20 µg	Mean body mass percentage change (cycle 6)	[Coenen 1996] Mean diff=0.70 (-1.32 – 2.72), NS
			Mean weight change in kg (cycle 6)	[Kirkman 1994] mean diff= 0.20 (0.00 – 0.40), NS

* Characteristics of included studies: see below

Ref + design	N	Population	Duration	Comparison	Methodology
Coenen 1996 OL PG RCT	100 (50 for this comparison)	Unspecified location. Healthy women age 18 to 38 years with regular menses. Excluded: obesity; pregnancy; recent pregnancy; lactation; contraindications to oral contraceptives; certain medications; heavy smoking	One pre-treatment cycle and 6 treatment cycles.	Norgestimate 250 µg and EE 35 µg (n=25) versus gestodene 75 µg and EE 30 µg (n= 25) versus desogestrel 150 µg and EE 30 µg (n=25) versus desogestrel 150 µg and EE 20 µg (n=25)	- Jadad score: 2/5 - FU: loss to FU not reported; 3 women in gestodene group and 4 in the desogestrel 20 µg discontinued early (14%) - ITT: no
Kirkman 1994 OL PG RCT	1.006	66 sites in Denmark, Italy, New Zealand and the United Kingdom Healthy women over age 30 years. Excluded: irregular menses; smoking among those over age 34 years; lactation; high blood pressure; certain drug use	6 cycles	Gestodene 75 µg and EE 30 µg (n=505) versus desogestrel 150 µg and EE 20 µg (n= 501)	- Jadad score: 3/5 - FU: 89% - ITT: no

4.1.9.9. Gestodene 75 µg and EE 30 µg versus desogestrel 150 µg and EE 20 µg: effect on weight

Ref	N/n	Comparison	Outcomes	Result
Gallo 2011b Design: MA Search date: 31 May 2011	N= 4 n= 1.838	Gestodene 75 µg and EE 30 µg versus desogestrel 150 µg and EE 30 µg	Gained >2 kg (cycle 6)	[Brill 1991, Halbe 1998, Koetsawang 1995] OR=1.18 (0.87 – 1.60), NS
			Mean body mass percentage change (cycle 6)	[Coenen 1996] Mean diff= 0.8 (-1.18 – 2.78), NS

* Characteristics of included studies: see below

Ref + design	N	Population	Duration	Comparison	Methodology
Brill 1991 PG RCT (no information on blinding)	605 (410 for this comp.)	Multicenter trial in Germany Healthy, sexually-active women age 16 to 45 years with regular menses. Excluded: contraindications to oral contraceptive use; recent oral contraceptive use; certain drug use; abnormal Pap smear	6 cycles	Gestodene 75 µg and EE 30 µg (n=209) versus desogestrel 150 µg and EE 30 µg (n=201) versus norgestimate 250 µg and EE 35 µg (n=195)	- Jadad score: 2/5 - FU: 87.4% - ITT: no
Halbe 1998 OL PG RCT	595	8 sites in Brazil Healthy, reproductive-age women with regular menses and at risk for pregnancy. Excluded: contraindications to oral contraceptive use, lactation, certain drugs, malnutrition	6 cycles	Desogestrel 150 µg and EE 30 µg (n=316) versus gestodene 75 µg and EE 30 µg (n=279)	- Jadad score: 2/5 - FU: 84.2% - ITT: no
Koetsawang 1995 OL PG RCT	783	6 cites in Thailand Healthy women of fertile age with regular menses. Excluded: contraindications to oral contraceptive use; lactation; certain drugs	6 cycles	Desogestrel 150 µg and EE 30 µg (n=394) versus gestodene 75 µg and EE 30 µg (n=389)	- Jadad score: 3/5 - FU: 86.8% - ITT: no
Coenen 1996	100 (50 for	Unspecified location	6 cycles	Norgestimate 250 µg and EE 35 µg	- Jadad score: 1/5

OL PG RCT	this comp.)	Healthy women age 18 to 38 years with regular menses. Excluded obesity; pregnancy; recent pregnancy; lactation; contraindications to oral contraceptives; certain medications; heavy smoking		(N=25) versus gestodene 75 µg and EE 30 µg (n= 25) versus desogestrel 150 µg and EE 30 µg (n=25) versus desogestrel 150 µg and EE 20 µg (n=25)	- FU: ? (4 women in the norgestimate, 3 women in the gestodene, 1 woman in the desogestrel/EE 30 µg, and 4 women in the desogestrel/EE 20 µg group discontinued early; loss to follow up not reported. - ITT: no

4.1.9.10. Gestodene 75 µg and EE 30 µg versus norgestimate 250 µg and EE 35 µg: effect on weight

Ref	N/n	Comparison	Outcomes	Result
Gallo 2011b Design: MA Search date: 31 May 2011	N= 1 n= 404	Gestodene 75 µg and EE 30 µg versus norgestimate 250 µg and EE 35 µg	Gained >2 kg (cycle 6)	OR=1.54 (0.92 – 2.60), NS

* Characteristics of included studies: see below

Ref + design	n	Population	Duration	Comparison	Methodology
Brill 1991 PG RCT (no information on blinding)	605 (410 for this comp.)	Multicenter trial in Germany Healthy, sexually-active women age 16 to 45 years with regular menses. Excluded: contraindications to oral contraceptive use; recent oral contraceptive use; certain drug use; abnormal Pap smear	6 cycles	Gestodene 75 µg and EE 30 µg (n=209) versus desogestrel 150 µg and EE 30 µg (n=201) versus norgestimate 250 µg and EE 35 µg (n=195)	- Jadad score: 2/5 - FU: 87.4% - ITT: no

4.1.9.11. Levonorgestrel 100 µg and EE 20 µg versus levonorgestrel 150 µg and EE 30 µg: effect on weight

Ref	N/n	Comparison	Outcomes	Result
Gallo 2011b Design: MA Search date: 31 May 2011	N= 1 n= 505	Levonorgestrel 100 µg and EE 20 µg versus levonorgestrel 150 µg and EE 30 µg	Gained >2 kg (cycle 6)	OR=1.26 (0.74 – 2.15), NS
			Lost >2 kg (cycle 6)	OR=1.31 (0.70 – 2.44), NS

* Characteristics of included studies: see below

Ref + design	n	Population	Duration	Comparison	Methodology
Endrikat 2001 OL PG RCT	760 (505 for this comp)	30 sites in Germany Healthy, normal weight women age 18 to 35 years. Excluded: high blood pressure; heavy smoking; established contraindications to oral contraceptive use; recent depot-contraceptive use; unexplained vaginal bleeding; migraine headaches during menstruation	13 cycles	Levonorgestrel 100 µg and EE 20 µg (n=380) versus norethisterone 500 µg and EE 20 µg (n=255) versus levonorgestrel 150 µg and EE 30 µg (n=125; study standard). 767 women were randomized; however, the sum of the number of women assigned to each group totaled 760 women. The remaining seven women were not described	- Jadad score: 3/5 - FU: 79% - ITT: no

4.1.9.12. Levonorgestrel 150 µg and EE 30 µg versus gestodene 75 µg and EE 30 µg: effect on weight

Ref	N/n	Comparison	Outcomes	Result
Gallo 2011b Design: MA Search date: 31 May 2011	N= 1 n= 456	Levonorgestrel 150 µg and EE 30 µg versus gestodene 75 µg and EE 30 µg	Mean weight change in kg (cycle 6)	Mean diff=0.70 (0.14 – 1.26), NS

* Characteristics of included studies: see below

Ref + design	n	Population	Duration	Comparison	Methodology
Loudon 1990 DB PG RCT	456	31 sites in the UK Women age 16 to 35 years. Excluded: high blood pressure; amenorrhea; post-partum women without resumption of menses; thrombotic disorders; history of sickle-cell anemia, lipid metabolism disorders, or herpes; liver diseases; abnormal vaginal bleeding of unknown origin; certain neoplasias; pregnancy; lactation	6 months	Gestodene 75 µg and EE 30 µg (n=229) versus levonorgestrel 150 µg and EE 30 µg (n=227)	- Jadad score: 3/5 - FU: 80.9% - ITT: no

4.1.9.13. Levonorgestrel 50-75-125 µg and EE 30-40-30 µg versus levonorgestrel 150 µg and EE 30 µg: effect on weight

Ref	N/n	Comparison	Outcomes	Result
Gallo 2011b Design: MA Search date: 31 May 2011	N= 1 n= 342	Levonorgestrel 50-75-125 µg and EE 30-40-30 µg versus levonorgestrel 150 µg and EE 30 µg	Mean weight change in kg (cycle 6)	Mean diff= -0.02 (-0.06 – 0.03), NS

* Characteristics of included studies: see below

Ref + design	n	Population	Duration	Comparison	Methodology
Kashanian 2010 PG RCT (blinding NR)	342	Public health centers in Iran Women seeking contraception at public health centers. Inclusion criteria: married, age 17 to 40 years, regular menstruation, no signs or symptoms similar to adverse effects of pills before using them, no prior OCP use. Exclusion criteria: contraindication to pills, systemic disorders or drug use, breastfeeding, delivered < 3 weeks previously; use of injectable contraceptive in past 6 months or implant in past 3 months; abnormal Pap smear, abnormal blood cholesterol and triglycerides, and being illiterate, omitting one or more pills during the cycles, stopping taking pills, using other contraceptives along with OCPs, acute severe diarrhea and vomiting, and pregnancy	6 cycles	Levonorgestrel 150 µg and EE 30 µg (n=171) versus levonorgestrel 50-75-125 µg and EE 30-40-30 µg (n=171)	- Jadad score: 3/5 - FU: 91.9% - ITT: no

4.1.9.14. Norgestimate 250 µg and EE 35 µg versus desogestrel 150 µg and EE 30 µg: effect on weight

Ref	N/n	Comparison	Outcomes	Result
Gallo 2011b Design: MA Search date: 31 May 2011	N= 1 n= 396	Norgestimate 250 µg and EE 35 µg versus desogestrel 150 µg and EE 30 µg	Gained >2 kg (cycle 6)	OR= 1.15 (0.65 – 2.06), NS

* Characteristics of included studies: see below

Ref + design	n	Population	Duration	Comparison	Methodology
Brill 1991 PG RCT (blinding NR)	605 (396 for this comp.)	Multicenter trial in Germany Healthy, sexually-active women age 16 to 45 years with regular menses. Excluded: contraindications to oral contraceptive use; recent oral contraceptive use; certain drug use; abnormal Pap smear	6 cycles	Gestodene 75 µg and EE 30 µg (n=209) versus desogestrel 150 µg and EE 30 µg (n=201) versus norgestimate 250 µg and EE 35 µg (n=195)	- Jadad score: 2/5 - FU: 87.4% - ITT: no

4.1.9.15. Vaginal ring versus levonorgestrel 150 µg and EE 30 µg: effect on weight

Ref	N/n	Comparison	Outcomes	Result
Gallo 2011b Design: MA Search date: 31 May 2011	N= 1 n= 1.030	Vaginal ring etonogestrel 120 µg and EE 15 µg versus levonorgestrel 150 µg and EE 30 µg	Gain >=7% body weight (cycle 13)	OR=0.84 (0.55 – 1.28), NS
			Lost >=7% body weight (cycle 13)	OR=1.39 (0.83 – 2.32), NS

* Characteristics of included studies: see below

Ref + design	n	Population	Duration	Comparison	Methodology
Oddsson 2005 OL PG RCT	1.030	Healthy women from 11 countries in Europe and South America 18 y or older Excluded if OC contraindicated, DMPA use in previous 6 months, postpartum or postabortion within 2months of start, breastfeeding within 2months, abnormal cervical smear, or drugs that could interfere with contraceptive metabolism	13 cycles	Vaginal ring releasing etonogestrel 120 µg + EE 15 µg daily (n=512) versus COCcontaining levonorgestrel 150 µg + EE 30 µg (n=518)	- Jadad score: 3/5 - FU: 71% - ITT: modified intention to treat

4.1.9.16. Vaginal ring versus versus drospirenone 3 mg and EE 30 µg: effect on weight

Ref	N/n	Comparison	Outcomes	Result
Gallo 2011b Design: MA Search date: 31 May 2011	N= 1 n= 1.017	Vaginal ring etonogestrel 120 µg and EE 15 µg versus drospirenone 3 mg and EE 30 µg	Mean weight change in kg (cycle 13 or last assessment)	**Mean diff=0.40 (0.03 – 0.77), SS** in favor of COC

* Characteristics of included studies: see below

Ref + design	n	Population	Duration	Comparison	Methodology (sponsor NR in Cochrane)
Milsom 2006 OL PG RCT	1.017	women, at least 18 years old, seeking contraception. Exclusion criteria: contraindication for hormonal contraception, abortion or breastfeeding in past 2months, injectable hormonal contraceptive use in past 6months, abnormal cervical smear during screening, use in past 2 months of drugs that interfere with metabolism of hormonal contraceptives	13 cycles	Vaginal ring releasing etonogestrel 120 µg + EE 15 µg daily versus COC containing drospirenone 3 mg + EE 30 µg	- Jadad score: 3/5 - FU: 68% - ITT: modified ITT

Combined hormonal contraception: effect on weight. Authors' conclusions

Available evidence was insufficient to determine the effect of combination contraceptives on weight, but no large effect was evident.

Trials to evaluate the link between combination contraceptives and weight change require a placebo or non-hormonal group to control for other factors, including changes in weight over time.

4.1.9.bis. Combined hormonal contraception: effect on weight. Summary and conclusions

Combined oral contraceptives vs. placebo

<table>
<tr><td colspan="8">Levonorgestrel 100 µg + Ethinyl estradiol 20 µg vs. placebo (Coney 2001)
(from Gallo 2011b)</td></tr>
<tr><th>N/n</th><th>Duration</th><th>Population</th><th>Results</th><td colspan="4"></td></tr>
<tr><td rowspan="3">N=1,
n= 721</td><td rowspan="3">6 cycles</td><td rowspan="3">- Healthy women
- Age: ≥14y
- regular menses and moderate facial acne</td><td rowspan="3">Mean weight change in kg at cycle 6</td><td colspan="4">Mean diff= 0.30 (95% CI -0.23, 0.83),
NS</td></tr>
<tr><td><u>Quality</u>
- 1 (low FU, no ITT)</td><td><u>Consistency</u>
NA</td><td><u>Directness</u>
OK</td><td><u>Imprecision</u>
OK</td></tr>
<tr><td colspan="4">Grade assessment: moderate quality of evidence</td></tr>
</table>

In a 2011 Cochrane review we identified one placebo-controlled study with a combination pill that reports weight outcomes. The pill studied contains levonorgestrel 100 µg + ethinyl estradiol 20 µg. There is no significant difference between the combination pill and placebo in the average weight change after 6 cycles.
GRADE: moderate quality of evidence

Contraceptive patch vs. placebo

<table>
<tr><td colspan="8">Skin patch norelgestromin 150 µg + Ethinyl Estradiol 20 µg (Sibai 2001)
(from Gallo 2011b)</td></tr>
<tr><th>N/n</th><th>Duration</th><th>Population</th><th>Results</th><td colspan="4"></td></tr>
<tr><td rowspan="5">N=1,
n= 136</td><td rowspan="5">9 cycles</td><td rowspan="5">- not described</td><td rowspan="3">Gained >5% baseline weight at cycle 9</td><td colspan="4">OR=0.95 (95% CI 0.30, 2.98), NS</td></tr>
<tr><td><u>Quality</u>
-2 (low JADAD, number randomised, FU, ITT, not reported)</td><td><u>Consistency</u>
NA</td><td><u>Directness</u>
-1 (study population not reported)</td><td><u>Imprecision</u>
OK</td></tr>
<tr><td colspan="4">Grade assessment: very low quality of evidence</td></tr>
<tr><td rowspan="3">Lost >5% baseline weight at cycle 9</td><td colspan="4">OR=0.27 (95% CI 0.04, 1.82), NS</td></tr>
<tr><td><u>Quality</u>
-2</td><td><u>Consistency</u>
NA</td><td><u>Directness</u>
-1</td><td><u>Imprecision</u>
OK</td></tr>
<tr><td colspan="4">Grade assessment: very low quality of evidence</td></tr>
</table>

In a 2011 Cochrane review we identified one placebo-controlled study with a contraceptive patch that reports weight outcomes. The patch studied contains norelgestromin 150 µg + ethinyl estradiol 20 µg. There is no significant difference between this patch and placebo in the number of women with weight change of more than 5% after 9 cycles.
GRADE: very low quality of evidence

Combined oral contraceptives vs combined oral contraceptives

Desogestrel 150 µg + Ethinyl Estradiol 20 µg vs. gestodene 75 µg + Ethinyl Estradiol 20 µg (Serfaty 1998, Endrikat 1999)
Desogestrel 150 µg and Ethinyl Estradiol 30 µg vs. levonorgestrel 50-75-125 µg + Ethinyl Estradiol 30-40-30 µg (Lachnit-Fixxson 1984)
Prolonged regimen desogestrel 150 µg + Ethinyl Estradiol 30 µg vs. standard regimen desogestrel 150 µg + Ethinyl Estradiol 30 µg (Cachrimanidou 1993)
Drospirenone 3 mg + Ethinyl Estradiol 20 µg vs. desogestrel 150 µg + Ethinyl Estradiol 20 µg (Gruber 2006)
Gestodene 75 µg + Ethinyl Estradiol 20 µg vs. gestodene 75 µg + Ethinyl Estradiol 30 µg (Endrikat 1997)
Gestodene 75 µg and Ethinyl Estradiol 30 µg vs. desogestrel 150 µg + Ethinyl Estradiol 20 µg (Coenen 1996, Kirkman 1994)
Gestodene 75 µg + Ethinyl Estradiol 30 µg vs. desogestrel 150 µg + Ethinyl Estradiol 30 µg (Brill 1991, Halbe 1998, Koetsawang 1995, Coenen 1996)
Gestodene 75 µg + Ethinyl Estradiol 30 µg vs. norgestimate 250 µg + Ethinyl Estradiol 35 µg (Brill 1991)
Levonorgestrel 100 µg + Ethinyl Estradiol 20 µg vs. levonorgestrel 150 µg + Ethinyl Estradiol 30 µg (Endrikat 2001)
Levonorgestrel 150 µg +Ethinyl Estradiol 30 µg vs. gestodene 75 µg + Ethinyl Estradiol 30 µg (Loudon 1990)
Levonorgestrel 50-75-125 µg + Ethinyl Estradiol 30-40-30 µg vs. levonorgestrel 150 µg + Ethinyl Estradiol 30 µg (Kashanian 2010)
Norgestimate 250 µg + Ethinyl Estradiol 35 µg vs. desogestrel 150 µg + Ethinyl Estradiol 30 µg (Brill 1991)

(all from Gallo 2011b)

N/n	Duration	Population	Results				
N=14, n= 9.179	12 cycles	- Healthy women - Age: 16 - 45 y - regular menses - 4 studies include only patients with normal weight	Gained ≥ 2 kg	At cycle 6: DSG150+EE20 vs. GSD75+EE20: *(Serfati)* OR=0.84 (95% CI 0.58, 1.22), NS GSD75+EE30 vs. DSG150+EE30: *(Brill, Halbe, Koetsawang)* OR=1.18 (95% CI 0.87, 1.60), NS GSD75+EE30 vs. NGM250+EE35: *(Brill)* OR=1.54 (95% CI 0.92, 2.60), NS LNG100+EE20 vs. LNG150+EE30: *(Endrikat 2001)* OR=1.26 (95% CI 0.74, 2.15), NS NGM250+EE35 vs DSG150+EE30: (Brill) OR=1.15 (95% CI 0.65, 2.06), NS At cycle 12: DSG150+EE20 vs. GSD75+EE20: *(Endrikat 1999)* OR=1.13 (95% CI 0.85, 1.49), NS GSD75+EE20 vs GSD75+EE30: *(Endrikat 1999)* OR= 1.06 (95% CI 0.63, 1.81), NS			
				Quality -1	Consistency OK	Directness OK	Imprecision OK
				Grade assessment: *moderate quality of evidence*			
				At cycle 6: *(Lachnit)* DSG150+EE30 vs. LNG50-75-125+EE30-40-30: **OR=3.29 (95% CI 1.84, 5.88), SS in favor of levonorgestrel**			
				Quality -1	Consistency NA	Directness OK	Imprecision OK
				Grade assessment: *moderate quality of evidence*			
			Lost ≥ 2 kg	DSG150+EE20 vs. GSD75+EE20 At cycle 6 *(Serfati)*: **OR=1.65 (95% CI 1.13, 2.41), SS**			
				Quality OK	Consistency OK	Directness OK	Imprecision OK
				Grade assessment: *high quality of evidence*			

				DSG150+EE20 vs. GSD75+EE20 At cycle 12 (Endrikat 1999): OR=0.95 (95% CI 0.68, 1.33), NS			
				Quality -2 (low JADAD, low FU, no ITT)	Consistency OK	Directness OK	Imprecision OK
				Grade assessment: *low quality of evidence*			
				GSD75+EE20 vs. GSD75+EE30 At cycle 12 (Endrikat 1997): OR=1.13 (95% CI 0.63, 2.03), NS			
				Quality -2	Consistency OK	Directness OK	Imprecision OK
				Grade assessment: *low quality of evidence*			
				LNG100+EE20 vs. LNG150+EE30 At cycle 13 *(Endrikat 2001)* OR=1.31 (95% CI 0.70, 2.44), NS			
				Quality OK	Consistency OK	Directness OK	Imprecision OK
				Grade assessment: *high quality of evidence*			
			Mean weight change	Prolonged regimen DSG150 + EE30 vs. standard regimen DSG150 + EE30 At cycle 12 *(Cachrimanidou 1993):* Mean difference in weight change= 0.57 kg (95% CI -0.42, 1.56), NS			
				Quality -2 (low JADAD, low FU, no ITT)	Consistency NA	Directness OK	Imprecision OK
				Grade assessment: *low quality of evidence*			
				DRSP 3 mg + EE20 vs. DSG150 + EE20 At cycle 7 *(Gruber 2006):* **Mean difference in weight change= -0.67 kg (95% CI -1.16, -0.18), SS in favor of drospirenone**			
				Quality OK	Consistency NA	Directness OK	Imprecision OK
				Grade assessment: *high quality of evidence*			
				GSD75 + EE30 vs. DSG150 + EE20 At cycle 6 *(Coenen 1996, Kirkman 1994):* mean difference in body mass % change= 0.70 (95% CI -1.32, 2.72), NS *(Kirkman 1994):* mean difference in weight change= 0.20kg (95% CI 0.00, 0.40), NS GSD75 + EE30 vs. DSG150 + EE30 At cycle 6 *(Coenen 1996)*: Mean difference in body mass % change= 0.8 (-1.18, 2.78), NS			
				Quality -1 (1 study serious limitations, 1 study OK)	Consistency OK	Directness OK	Imprecision OK
				Grade assessment: *moderate quality of evidence*			
				LNG150 + EE30 vs. GSD75 + EE30 *At cycle 6 (Loudon 1990):* Mean difference in weight change= 0.70 kg (95% CI 0.14, 1.26), NS			
				Quality	Consistency	Directness	Imprecision

				OK	NA	OK	OK
				Grade assessment: *high quality of evidence*			
				LNG50-75-125 + EE30-40-30 vs. LNG150 + EE30 *At cycle 6 (Kashanian 2010):* Mean difference in weight change= -0.02 kg (95% CI -0.06, 0.03), NS			
				Quality OK	Consistency NA	Directness OK	Imprecision OK
				Grade assessment: *high quality of evidence*			

In a 2011 Cochrane Review we identified 14 studies that compared combination pills for weight outcome.
- Six studies compare combination pills for the number of women with a weight gain of at least 2 kg:

De combination desogestrel 150 µg + ethinyl estradiol 30 µg gives a weight gain of at least 2 kg after 6 cycles in significantly more women than the combination levonorgestrel 50-75-125 µg + ethinyl estradiol 30-40-30 µg. For other combination pills studied, there is no significant difference after 6 cycles or after 12 cycles.
GRADE: moderate quality of evidence

- Four studies compare combination pills for the number of women with a weight loss of at least 2 kg:

After six cycles there are significantly more women with a weight loss of at least 2 kg for the combination desogestrel 150 µg + ethinyl estradiol 20 µg than for the combination gestodene 75 µg + ethinyl estradiol 20 µg.
GRADE: high quality of evidence

After twelve cycles there is no significant difference between the combination desogestrel 150 µg + ethinyl estradiol 20 µg and the combination gestodene 75 µg + ethinyl estradiol 20 µg with regard to the number of women with a weight loss of at least 2 kg.
GRADE: low quality of evidence

After twelve cycles there is no significant difference between the combination gestodene 75 µg + ethinyl estradiol 20 µg and the combination gestodene 75 µg + ethinyl estradiol 30 µg with regard to the number of women with a weight loss of at least 2 kg.
GRADE: low quality of evidence

After thirteen cycles there is no significant difference between levonorgestrel 100 µg + ethinyl estradiol 20 µg and the combination levonorgestrel 150 µg + ethinyl estradiol 30 µg with regard to the number of women with a weight loss of at least 2 kg.
GRADE: high quality of evidence

- Six studies compare combination pills for the average variation in body weight:

After twelve cycles there is no significant difference in weight variation between a prolonged regimen with desogestrel 150 µg + ethinyl estradiol 30 µg and a standard regimen with desogestrel 96 µg + ethinyl estradiol 30 µg.
GRADE: low quality of evidence

After seven cycles there is a significant difference in weight variation between the combination drospirenone 3 mg + ethinyl estradiol 20 µg and the combination desogestrel 150 µg + ethinyl estradiol 20 µg, in favour of the combination with drospirenone (weight decreased on average vs. increased on average with desogestrel).
GRADE: high quality of evidence

After six cycles there is no significant difference in weight variation between the combination gestodene 75 µg + ethinyl estradiol (20 of 30 µg) and the combination desogestrel 150 µg + ethinyl estradiol (20 or 30 µg).

GRADE: moderate quality of evidence

After six cycles there is no significant difference in weight variation between the combination levonorgestrel 150 µg + ethinyl estradiol 30 µg and the combination gestodene 75 µg + ethinyl estradiol 30 µg.
GRADE: high quality of evidence

After six cycles there is no significant difference in weight variation between the combination levonorgestrel 50-75-125 µg + ethinyl estradiol 30-40-30 µg and the combination levonorgestrel 150 µg + ethinyl estradiol 30 µg.
GRADE: high quality of evidence

It is difficult to compare the various oral contraceptive pills with each other due to their different compositions. In addition, the amount of data is limited to one study for most comparisons. The authors of the Cochrane review conclude that there is insufficient evidence to determine the effect of the various combination pills on weight. There is a need for comparative studies that also include a group receiving placebo or a non-hormonal form of contraception.

Vaginal ring vs. combined oral contraceptives

Vaginal ring etonogestrel 120µg + Ethinyl Estradiol 15µg vs. levonorgestrel 150µg + Ethinyl Estradiol 30µg (Oddsson 2005)
Vaginal ring etonogestrel 120µg + Ethinyl Estradiol 15µg vs. drospirenone 3mg + Ethinyl Estradiol 30µg (Milsom 2006)

(from Gallo 2011b)

N/n	Duration	Population	Results				
N=2, n= 2.047	13 cycles	- Healthy women - Age: ≥ 18y	Gain ≥ 7% of body weight at cycle 13	Reported in 1/2 studies (Oddsson 2005) OR=0.84 (95% CI 0.55, 1.28) NS			
				Quality -1 (low FU and modified ITT)	Consistency NA	Directness OK	Imprecision OK
				Grade assessment: *moderate quality of evidence*			
			Lost ≥ 7% of body weight at cycle 13	Reported in 1/2 studies (Oddsson 2005) OR=1.39 (95% CI 0.83, 2.32) NS			
				Quality -1	Consistency NA	Directness OK	Imprecision OK
				Grade assessment: *moderate quality of evidence*			
			Mean weight change in kg at cycle 13 or last assessment	Reported in 1/2 studies (Milsom 2006) Mean diff=0.40 (95% CI 0.03, 0.77) **SS in favor of COC**			
				Quality -1	Consistency NA	Directness OK	Imprecision OK
				Grade assessment: *moderate quality of evidence*			

In a 2011 Cochrane review we identified two studies that compare a vaginal ring (etonogestrel + ethinyl estradiol) with a combination pill for the weight outcome.

- There is greater weight gain with the vaginal ring than with oral drospirenone + ethinyl estradiol after 13 cycles, but the absolute difference in weight change is small.
GRADE: moderate quality of evidence

- There is no significant difference between the vaginal ring and oral levonorgestrel + ethinyl estradiol with regard to the number of women with a change in body weight of at least 7% after 13 cycles.
GRADE: moderate quality of evidence

4.1.10. Combined oral contraception containing drospirenone: effect on blood pressure. Evidence tables

Ref	N/n	Comparison	Duration	Outcomes	
Koltun 2008	458	DRSP 3mg + EE 20µg Vs placebo	6 treatment cycles	Blood pressure	*"Mean systolic and diastolic blood pressure and heart rate were comparable at baseline between the two treatment groups. For these three parameters, there were minimal changes in the means over time during the treatment phase in both treatment groups. In addition, there were no statistically significant differences in the change from baseline to end point in mean blood pressure between the two treatment groups"*

Ref	N/n	Comparison	Duration	Outcomes			
Westhof 2012 Mansour 2011	N=2, n= 4433	NOMAC + 17β–estradiol (24-4d) vs DRSP 3mg + EE 30µg (21-7d)	13 cycles	Blood pressure	*"Laboratory and blood pressure measurements showed no remarkable changes in values from baseline in either treatment group"*		
Foidart 2000	900	DRSP 3 mg+EE30µg vs DSG150 µg +EE30µg	26 cycles		*"blood pressure was essentially unchanged"*		
Suthipongse 2004	120	DRSP 3mg + EE 30µg vs LNG 150µg + EE 30 µg	7 cycles			3 mg DRSP/30 µg EE (n = 58)	150 µg LNG/30 µg EE (n = 57)
					Systolic (mmHg)	103.5 ± 5.1	107.8 ± 6
					Diastolic (mmHg)	62.9 ± 4.3	66.7 ± 5.6
					Results reported as SS. No p value reported. Comparison unclear		
Mohamed 2011	600	Vaginal ring releasing etonogestrel 120 µg + EE 15 µg vs DRSP 3mg + EE 30 µg	12 cycles		"*Differences in blood pressure, blood sugar levels, lipid profile, liver enzyme activity, and anticoagulant activity were not statistically significant"* Mean BP reported, see chapter …		
Ahrendt 2006	1017		13 cycles		*"There were also no clinically relevant or statistically significant differences between treatment groups in changes from baseline for diastolic and systolic blood pressure"*		

Characteristics of included studies: see elsewhere

4.1.10.bis. Combined oral contraception containing drospirenone: effect on blood pressure.Summary and conclusions

One placebo-controlled trial and 6 comparative trials reported on blood pressure when using combined oral contraceptives containing drospirenone. Overall, reporting of blood pressure was poor and actual figures were not mentioned in most trials.

The placebocontrolled trial found no significant difference in change from baseline to study end between a combined oral contraceptive containing 3mg drospirenone /20µg ethinylestradiol and placebo (Koltun 2008).

A combined oral contraceptive containing 3mg drospirenone/30µg ethinylestradiol was compared to
-an oral contraceptive containing nomgestrol acetate2.5mg/17beta estradiol 1.5mg (Westhof 2012, Mansour 2011)
-desogestrel 150µg/ethinylestradiol 30µg (Foidart 2000)
- the vaginal ring (Mohamed 2011, Ahrendt 2006)
No significant difference was found in change from baseline for blood pressure, but statistics were not always reported.

A combined oral contraceptive containing 3mg drospirenone/30µg ethinylestradiol was compared to levonorgestrel 150µg/ethinylestradiol 30µg in one small open label trial. A significant difference was observed for both systolic and diastolic blood pressure at the end of the trial, but p value was not reported and it was unclear how the comparison was made (Suthipongse 2004)

Overall, combined oral contraceptives containing drospirenone do not seem to have an effect on blood pressure, when compared to placebo or to other oral contraceptives.

GRADE: low quality of evidence

4.2. Progestogen only pill

4.2.1. Desogestrel-75µg versus levonorgestrel-30µg. Evidence tables

Ref	n/Population	Duration	Comparison	Outcomes		Methodological
Collaborative 1998 (from Grimes 2010) Design: RCT -DB	n= 1320 healthy sexually active women (979 using a desogestrel pop and 327 using a levonorgestrel pop) mean age: 18 to 45 years <u>Inclusion</u> -breastfeeding, switchers (use of oral contraceptives within past 2months), or starters (not a switcher or breastfeeding) -Mean cycle length between 24 and 35 days and intraindividual variation +/- 3 days -Body weight between 80% and 130% of ideal. <u>Exclusion</u> -contraindications to steroids, -prior ectopic pregnancy, -pelvic inflammatory disease -symptomatic functional ovarian cysts	13 treatment periods of 28 days	desogestrel 75 µg/day versus levonorgestrel 30 µg/day	Efficacy		- Jadad score ○ RANDO:2 /2 ○ BLINDING: 2/2 ○ ATTRITION: 1/1 - FU: 98.94 % - ITT: no Other important methodological remarks This trial lacked the power to differentiate between pregnancy rates. (comment of MA Authors) - Multicenter: 44 centers .. countries - Sponsor: NV Organon
				Pregnancy	DSG : 3/979 LNG : 4/327 0.31% vs 1.22% RR : 0.27 [CI : 0.06, 1.19] NS	
				Safety		
				Discontinuation because of adverse events	1.22 [0.81, 1.84] NS	
				Discontinuation because of irregular bleeding	1.32 [0.99, 1.78] NS p=0.062	
				Discontinuation for all reasons	1.21 [0.99, 1.47] NS p=0.057	

4.2.1.bis. Desogestrel-75µg versus levonorgestrel-30µg. Summary and conclusions

<table>
<tr><td colspan="6">Desogestrel 75µg/d vs Levonorgestrel 30µg/d (Collaborative 1998)</td></tr>
<tr><td>N/n</td><td>Duration</td><td>Population</td><td colspan="3">Results</td></tr>
<tr><td rowspan="12">N= 1,
n=
1320</td><td rowspan="12">13 cycles</td><td rowspan="12">- Healthy sexually active women
- Age: 18-45y</td><td rowspan="4">Pregnancy</td><td colspan="3">RR=0.27 (95%CI: 0.06-1.19), NS</td></tr>
<tr><td><u>Quality</u>
OK</td><td><u>Consistency</u>
NA</td><td><u>Directness</u>
OK</td><td><u>Imprecision</u>
-1
(underpowered)</td></tr>
<tr><td colspan="4">Grade assessment: moderate quality of evidence</td></tr>
<tr><td rowspan="4">Discontinuation: AEs</td><td colspan="4">RR=1.22 (95%CI: 0.81-1.84), NS</td></tr>
<tr><td><u>Quality</u>
OK</td><td><u>Consistency</u>
NA</td><td><u>Directness</u>
OK</td><td><u>Imprecision</u>
OK</td></tr>
<tr><td colspan="4">Grade assessment: high quality of evidence</td></tr>
<tr><td rowspan="4">Discontinuation: irregular bleeding</td><td colspan="4">RR=1.32 (95%CI: 0.99-1.78)
p=0.062, NS</td></tr>
<tr><td><u>Quality</u>
OK</td><td><u>Consistency</u>
NA</td><td><u>Directness</u>
OK</td><td><u>Imprecision</u>
OK</td></tr>
<tr><td colspan="4">Grade assessment: high quality of evidence</td></tr>
<tr><td rowspan="4">Discontinuation: total</td><td colspan="4">RR=1.21 (95%CI: 0.99, 1.47)
p=0.057, NS</td></tr>
<tr><td><u>Quality</u>
OK</td><td><u>Consistency</u>
NA</td><td><u>Directness</u>
OK</td><td><u>Imprecision</u>
OK</td></tr>
<tr><td colspan="4">Grade assessment: high quality of evidence</td></tr>
</table>

- A double blind RCT in more than thousand healthy sexually active women compared two kinds of POPs (progestogen-only pills): desogestrel 75 µg versus levonorgestrel 30 µg.

No significant difference in contraceptive efficacy was reported between both pills, however the study was underpowered.

GRADE: moderate quality of evidence

There was also no significant difference in the number of women who discontinued their treatment.

GRADE: high quality of evidence

4.2.2. Progestogen-only pill versus combined oral contraceptive. Evidence tables

Ref	n/Population	Duration	Comparison	Outcomes		Methodological
Sheth 1982 (from Grimes 2010) Design: RCT (DB) (PG)	n= 265 (n= 518 for all 4 arms) mean age:25.5 2 centers: India and Yugoslavia <u>Inclusion</u> healthy, no CI for OC use (such as hypertension, heart disease, diabetes), 18-35; >28d postpartum, menstruating, lactating>165d, no OC use <28d, no long acting injectable contraceptives <90d, regular menstrual cycle 21d-35d <u>Exclusion</u> - Not stated	2y	levonorgestrel 150µg + ethinylestradiol 30µg (n= 137) vs Levonorgestrel 30µg (n= 128) 4- arm study: mestranol 50µg + norethisterone 1mg (n= 123) norethisterone 350µg (n= 130)	Efficacy		- Jadad score ○ RANDO:1/2 ○ BLINDING: 1/2 ○ ATTRITION: 1/1 - FU: high drop-out, low losses to follow –up (2%) - ITT: unclear; Investigators excluded participants from analysis for noncompliance - Other important methodological remarks - Only half of intended sample size achieved - No power calculation provided, no primary endpoint defined - Poor statistics - Sponsor: WHO
				discontinuation for accidental pregnancy (cumulative life- table discontinuation rates)	at 360 days EE30/LNG150: 2.7% LNG30: 9.5% no specific p-value reported (p= 0.077 for all 4 comparisons; NS) at 676 days EE30/LNG150: 4.5% LNG30: 9.5% p=0.089 for this comparison NS	
				- for bleeding disturbances (cumulative life- table discontinuation rates)	at 360 days EE30/LNG150: 9.7% LNG30: 26.0 no specific p-value reported (p= 0.052 for all 4 comparisons); NS	
				- for all gastro-intestinal reasons(cumulative life- table discontinuation rates)	at 360 days EE30/LNG150: 11.1% LNG30: 5.7% no specific p-value reported (p=0.011 for all 4 comparisons; (MES/NET: 2.5%; NET35: 2.5%))	
				- for all central nervous system reasons(cumulative life- table discontinuation rates)	at 360 days EE30/LNG150: 2.7% LNG30: 9.5% no specific p-value reported (p<0.001 for all 4 comparisons; (MES/NET: 13.9%; NET35 5.9%))	
				- for all causes(cumulative life-table discontinuation rates)	at 360 days EE30/LNG150: 52.6% LNG30: 60.9%	

					no specific p-value reported (p=0.805 for all 4 comparisons) at 676 days EE30/LNG150: 70.5% LNG30: 74.2% no specific p-value reported (p=0.768 for all 4 comparisons)	
				Safety		
				frequent bleeding (% of women) (cycle <24days)	at cycle 10-12 EE30/LNG150: 14.3% LNG30: 42% no specific p-value reported (p<0.001) for all 4 comparisons; MES/NET: 22.0%; NET35 34.6%))	
				irregular bleeding (shortest cycle <24 d, longest cycle >35d)	at cycle 10-12 EE30/LNG150: 1.6% LNG30: 6.0% no specific p-value reported (p<0.05) for all 4 comparisons; MES/NET: 6.0%; NET35 5.8%))	

4.2.2.bis. Progestogen-only pill versus combined oral contraceptive. Summary and conclusions

<table>
<tr><td colspan="5">Levonorgestrel 150µg + ethinylestradiol 30µg versus levonorgestrel 30µg (Sheth 1982)</td></tr>
<tr><td>N/n</td><td>Duration</td><td>Population</td><td>Results</td><td></td></tr>
<tr><td rowspan="6">N=1
n= 265</td><td rowspan="6">2 years</td><td rowspan="6">- Healthy women
- mean age 25.5y</td><td>- discontinuation for accidental pregnancy
(cumulative life- table discontinuation rates)</td><td>at 360 days
EE30/LNG150: 2.7%
LNG30: 9.5%
no specific p-value reported

at 676 days
EE30/LNG150: 4.5%
LNG30: 9.5%
p=0.089 for this comparison; NS</td></tr>
<tr><td colspan="2"><u>Quality</u>
-1 high drop out, no ITT
<u>Consistency</u>
NA</td><td><u>Directness</u>
OK</td><td><u>Imprecision</u>
-1 unclear (no CI)</td></tr>
<tr><td colspan="4">Grade assessment: low quality of evidence</td></tr>
<tr><td>- discontinuation for bleeding disturbances
(cumulative life- table discontinuation rates)</td><td colspan="3">at 360 days
EE30/LNG150: 9.7%
LNG30: 26.0
no specific p-value reported
(p= 0.052 for all 4 comparisons); NS</td></tr>
<tr><td><u>Quality</u>
-2</td><td><u>Consistency</u></td><td><u>Directness</u></td><td><u>Imprecision</u>
-1</td></tr>
<tr><td colspan="4">Grade assessment: very low quality of evidence</td></tr>
<tr><td>- discontinuation for all causes
(cumulative life- table discontinuation rates)</td><td colspan="3">at 360 days
EE30/LNG150: 52.6%
LNG30: 60.9%
no specific p-value reported
(p=0.805 for all 4 comparisons)

at 676 days
EE30/LNG150: 70.5%
LNG30: 74.2%
no specific p-value reported
(p=0.768 for all 4 comparisons)</td></tr>
<tr><td><u>Quality</u>
-2</td><td><u>Consistency</u></td><td><u>Directness</u></td><td><u>Imprecision</u>
-1</td></tr>
<tr><td colspan="4">Grade assessment: very low quality of evidence</td></tr>
</table>

- This RCT randomised women into four groups. 1 group received a combined oral contraceptive containing 30µg ethinylestradiol + 150µg levonorgestrel, 1 group received the progestogen-only pill containing levonorgestrel 30µg. The two other groups received either a combined oral contraceptive or a progestogen-only pill that are not available in Belgium. We only consider the comparison of contraceptives available on the Belgian market.

At 1 year and at 2 years, the cumulative pregnancy rate was lower with the combination of levonorgestrel 150µg + ethinylestradiol 30µg than with levonorgestrel 30µg only. However, the difference did not reach statistical significance. A possible lack of power and a high drop-out rate limits our conclusions.

GRADE: low quality of evidence

Discontinuation for bleeding disturbances at 1 year was lower with the combination of levonorgestrel 150µg + ethinylestradiol 30µg than with levonorgestrel 30µg only, however, no specific p-value was reported. P-value for the difference between all 4 comparisons was 0.052.

GRADE: very low quality of evidence

Overall discontinuation was very high in all groups.

4.3. Progestogen-only injectable contraception

4.3.1. Copper intra-uterine device versus depot medroxyprogesterone acetate (or combined hormonal contraception). Evidence tables.

Ref	N/n	Comparison	Outcomes	
* Hofmeyr 2010 Design: SR + MA Search date: Feb 2010	N= 2 n= 967	IUCD versus DMPA/OC	Pregnancy	**16/482 (IUCD) vs 31/1455 (DMPA)** **OR=0.45 (95% CI 0.24, 0.84)** **SS in favor of IUCD p = 0.012**
			Discontinuation of allocated method Feldblum, 2005	**6/168 (IUCD) vs 36/170 (DMPA)** **OR=0.14 (95% CI 0.06, 0.34)** **SS in favor of IUCD p = 0.000014**
			Stringer, 2007	**146/286 (IUCD) vs 38/313 (DMPA and/or OC)** **OR=7.55 (95% CI 5.00, 11.38)** **SS in favor of mixed hormonal contraception p <0.00001**
			Pelvic inflammatory disease (Hagar's criteria)	3/481(IUCD) vs 0/456 (DMPA) OR=3.90 (95% CI 0.44, 34.91) NS p = 0.22

* Characteristics of included studies: see unde

Ref + design	n	Population	Duration	Comparison	Methodology (sponsor NR in Cochrane)
Feldblum 2005 (Pilot trial in family planning clinics in Brazil, Guatamala, Egypt and Vietnam)	368	Women - sexually active, -requiring contraception and -willing to use either IUD or DMPA for a period of at least a year. Excluded if medical contraindications to IUD or DMPA; pregnancy; suspected of having a current STI;currently using an IUD; DMPA injection within the past 6 months.	12 months	IUD (TCu 380A) inserted vs 3-monthly injections of 150mg DMPA.	- Jadad score:2-3 /5 - FU: 32% - ITT:? Other important methodological remarks: -Sequentially numbered, sealed, opaque envelopes were used for allocation concealment - pilot trial Sponsor: Family Health International
Stringer 2007 (2 primary clinics in Lusaka, Zambia)	599	HIV-infected postnatal women -≥16 years old. -desired contraception for at least two years, -reported two or less sexual partners in the previous year. Excluded if advanced HIV disease (WHO stage III or IV), a history of a bleeding disorder, a history of PID within previous 5 years or < 16 years old.	24 months	IUD (TCu 380A) vs hormonal contraception (either DMPA (150mg) or the OCP offered) If OCP, levonorgestrel 0.03mg/d only for six months, then switched to the COCP with levonorgestrel 0.15mg and estradiol 0.03mg/d).	- Jadad score: 2-3/5 - FU: 27.5% - ITT:? Other important methodological remarks: -Sequentially numbered, sealed, opaque envelopes were used for allocation concealment

Authors' conclusions

In the populations studied, the IUD was more effective than hormonal contraception with respect to pregnancy prevention.

4.3.1.bis. Copper intra-uterine device versus depot medroxyprogesterone acetate (or combined hormonal contraception). Summary and conclusions

<table>
<tr><td colspan="6">Cu-intrauterine device vs depot medroxyprogesterone acetate
(Feldblum 2005 and Stringer 2007 from Hofmeyr 2010)</td></tr>
<tr><td>N/n</td><td>Duration</td><td>Population</td><td>Results</td><td colspan="2"></td></tr>
<tr><td rowspan="9">N=2,
n= 967</td><td rowspan="9">12-24m</td><td rowspan="9">a. Healthy sexually active women

b. HIV+ postnatal women</td><td rowspan="3">Pregnancy
N=2</td><td colspan="2">OR=0.45 (95% CI 0.24, 0.84)
p = 0.012, SS in favour of Cu-intrauterine device</td></tr>
<tr><td><u>Quality</u>
-1 (low FU)</td><td><u>Consistency</u>
OK</td><td><u>Directness</u>
-1 (mixed control in 1 trial)</td><td><u>Imprecision</u>
OK</td></tr>
<tr><td colspan="4">Grade assessment: low quality of evidence</td></tr>
<tr><td rowspan="3">Discontinuation
N=2</td><td colspan="4">(Feldblum 2005):
OR=0.14 (95% CI 0.06, 0.34)
p = 0.000014, SS in favour of Cu-intrauterine device
(Stringer 2007):
OR=7.55 (95% CI 5.00, 11.38)
p <0.00001, SS in favour of mixed hormonal contraception</td></tr>
<tr><td><u>Quality</u>
-1</td><td><u>Consistency</u>
-1</td><td><u>Directness</u>
-1</td><td><u>Imprecision</u>
OK</td></tr>
<tr><td colspan="4">Grade assessment: very low quality of evidence</td></tr>
<tr><td rowspan="3">PID (pelvic inflammatory disease)
N=2</td><td colspan="4">OR=3.90 (95% CI 0.44, 34.91)
NS, p = 0.22</td></tr>
<tr><td><u>Quality</u>
-1</td><td><u>Consistency</u>
OK</td><td><u>Directness</u>
-1</td><td><u>Imprecision</u>
OK</td></tr>
<tr><td colspan="4">Grade assessment: low quality of evidence</td></tr>
</table>

There are few studies of good quality that compare the contraceptive efficacy of the depot injection to that of the copper IUD.
The populations of the two studies included in a Cochrane review were heterogeneous: the study by Feldblum examined healthy women, the study by Stringer was performed on HIV positive participants. In this latter study, the control group of the copper IUD was also mixed; the majority received DMPA, whilst some were given the combination pill. Finally, it should be noted that the follow-up for both studies was unusually low, namely 32 % and 27 % respectively.

- The number of pregnancies was significantly lower in the group of women with a copper IUD compared to those using the depot injection as a contraceptive method.

GRADE: low quality of evidence

- The number of women that stopped their treatment was different for both studies. For Feldblum there was a significant difference between both groups in favour of the copper IUD; for Springer the exact opposite applied: in that study significantly fewer women dropped out in the group receiving the depot injection (or the combination pill).

GRADE: very *low quality of evidence*

- No significant difference was observed in the occurrence of “pelvic inflammatory disease” between both treatment groups.

GRADE: low quality of evidence

4.3.2. Depot medroxyprogesterone acetate: Intramuscular versus subcutaneous injection. Evidence tables

Ref	n/Population	Duration	Comparison	Outcomes		Methodological
Kaunitz 2009 Design: SB PG RCT (investigator blinded)	n= 535 mean age: 26 y <u>Inclusion</u> Women aged between 18 and 35 years who were sexually active and who desired long-term contraception; regular menstruation (average cycle length of 25–35 days); negative urine pregnancy test; willingness to rely upon DMPA-SC or DMPA-IM for contraception for at least 2 years (eight doses in total). <u>Exclusion</u> having used oral contraceptives, contraceptive implants, or hormone-medicated intrauterine devices in the previous 2 months or having had DMPA-IM administered in the 10 months before enrollment; lumbar spine or femur BMD T-score of less than −1.0 or a history of pathologic or	2y	depot medroxyprogesterone acetate subcutaneous injection (104 mg/ 0.65 mL; DMPA-SC) (n=267) Vs depot medroxyprogesterone acetate intramuscular injection (150mg/mL once every 3 months; DMPA-IM) (n=268)	Efficacy		- Jadad score o RANDO: 2/2 o BLINDING: 1/2 o ATTRITION: 1/1 - FU: 42% - ITT: modified ITT (all participants who received at least one dose of study medication and made at least one visit after receiving the first dose) - Other important methodological remarks: very high dropout rate (DMPA-SC: n=150; DMPA-IM: n=159) - Multicenter: 36 sites in the United States, 9 sites in Canada, and 3 sites in Brazil - Sponsor: Pfizer
				2y treatment failure cumulative pregnancy rate (life table method) (PE)	a) Based on 4344 woman-cycles of exposure in the DMPA-SC group and 4281 woman-cycles of exposure in the DMPA-IM group: DMPA-SC: 0% DMPA-IM: 0.8% (0.00 – 2.37) NT b) Based on 3565 woman-cycles of exposure to DMPA-SC and 3442 woman-cycles of exposure to DMPA-IM, excluding the months when barrier contraception was used or no intercourse occurred: DMPA-SC: 0% DMPA-IM: 0.75% NT - One of the 265 women in the ITT efficacy cohort in the DMPA-IM group became pregnant within the study period and discontinued DMPA at the 21-month visit. - None of the 263 women in the DMPA-SC ITT efficacy cohort became pregnant during the study period.	
				2y Pearl index (defined as the number of pregnancies per 100 woman-years of exposure)	a) Based on 4344 woman-cycles of exposure in the DMPA-SC group and 4281 woman-cycles of exposure in the DMPA-IM group: DMPA-SC: 0	

	compression fracture; abnormal cervical cytology; undiagnosed abnormal genital bleeding; known or suspected pregnancy; history of breast cancer, thrombotic event, hepatic or renal disease, alcoholism or other drug abuse; uncontrolled hypertension, active hepatic or renal disease, type 1 diabetes, or poorly controlled type 2 diabetes; taking anticancer agent aminoglutethimide.				DMPA-IM: 0.28 (0.00 – 0.83) NT b) Based on 3565 woman-cycles of exposure to DMPA-SC and 3442 woman-cycles of exposure to DMPA-IM, excluding the months when barrier contraception was used or no intercourse occurred: DMPA-SC: 0 DMPA-IM: 0.35 NT	
				Mean weight increase at 2 y	DMPA-SC: 3.4kg DMPA-IM: 3.5kg NT	
				Safety		
				No (%) of treatment-emergent AE occurring in >=5% of women in either study group: Weight increase Headache Nasopharyngitis Nausea Injection site reaction Acne Depression or mood changes Urinary tract infection Sinusitis Decreased libido Abdominal pain Intermenstrual Abnormal cervical smear bleeding Total	DMPA-SC / DMPA-IM 33 (12.5) / 39 (14.7) 35 (13.3) / 33 (12.4) 25 (9.5) / 34 (12.8) 15 (5.7) / 24 (9.0) 21 (8.0) / 1 (0.4) 20 (7.6) / 20 (7.5) 20 (7.6) / 19 (7.1) 20 (7.6) / 6 (2.3) 19 (7.2) / 14 (5.3) 8 (3.0) / 16 (6.0) 6 (2.3) / 16 (6.0) 15 (5.7) / 15 (5.6) 9 (3.4) / 14 (5.3) 143 (54.4%) / 149 (56%) NT
				Dropout due to weight increase		
				Serious adverse events (not	DMPA-SC: 3.8%	

				described)	DMPA-IM: 2.3% NS (TNR)	
				Amenorrheic	At year 1: DMPA-SC: 64.1% DMPA-IM: 61.1% NT At year 2: DMPA-SC: 71.0% DMPA-IM: 80.0% NT	

4.3.2.bis. Depot medroxyprogesterone acetate: Subcutaneous versus intramuscular injection. Summary and conclusions

DMPA subcutaneous vs DMPA intramuscular (Kaunitz 2009)				
N/n	**Duration**	**Population**	**Results**	
N=1, n= 535	2y	- Healthy sexually active women - Age: 18-35y (mean: 26y) - requesting long-term hormonal contraception	Pregnancy (2y cumulative rate, life table method) (PE)	DMPA-SC 0% vs DMPA-IM 0.8% (0.00-2.37) NT
				Grade assessment: *NA (not applicable)*
			2y Pearl index	DMPA-SC 0 vs DMPA-IM 0.35 (0.00-0.83) NT
				Grade assessment: *NA*
			Weight increase (mean, at 2y)	DMPA-SC: 3.4kg DMPA-IM: 3.5kg NT
				Grade assessment: *NA*

In a single-blind RCT of 535 women between the ages of 18 and 35 years, the participants were randomised between subcutaneous or intramuscular administration of depot medroxyprogesterone acetate. This study had a high drop-out in both groups, resulting in a follow-up of only 42 % after 2 years.
One woman became pregnant in the intramuscular group, none in the subcutaneous group. The difference was not subjected to statistical testing.

GRADE: NA (not applicable)

In both DMPA groups the average body mass increased by approximately 3.5 kg, though this difference was also not subjected to statistical testing.

GRADE: NA

4.4. Levonorgestrel intra-uterine system

4.4.1. Levonorgestrel intra-uterine system versus copper –intra-uterine device (Cu >250mm2). Evidence tables

Ref	N/n	Comparison	Outcomes	Result
French 2010 * Design: meta-analysis Search date: July 2009	N=2 n= 3155 for this comparison	LNG-IUS vs Cu-IUD>250mm2	Pregnancy	At 1 year: [Sivin 1994, Baveja 1989] Life table diff= -0.16 (-0.65 – 0.34), NS [Sivin 1994] Rate ratio=1.01 (0.71 - 5.82), NS 2/7680 vs 2/7740 Single decrement life table prob (SE)=0,3 (0,2) vs 0,3 (0,2) [Baveja 1989] Single decrement life table prob (SE)=0.0 (0.4) vs 0.8 (0.4) At 2 years: [Sivin 1994] Rate ratio=0.30 (0.07 - 1.24), NS 2/19644 women months vs 7/20436 women months [Baveja 1989] Single decrement life table prob (SE)=0.0 (0.5) vs 1.0 (0.5) Life table diff=-1 (-2.39 – 0.39), NS At 3 years: [Baveja 1989] Rate ratio=0.11 (0.01 - 2.12), NS 0/10589 women months vs 4/10869 women months Single decrement life table prob (SE)=0.0 (0.5) vs 1.0 (0.5) Life table diff=-1 (-2.39 – 0.39), NS At 5 years: [Sivin 1994]

				Rate ratio=0.66 (0.25 - 1.75), NS 6/34944 women months vs 10/38268 women months Single decrement life table prob (SE)= 1.1 (0.5) vs 1.4 (0.4) Life table diff=-0.3 (-1.56 – 0.96), NS
			Planned pregnancy after discontinuation	At 1 year: [Sivin 1994] 39/49 vs 28/37 OR=1.25 (0.45 - 3.48), NS
			Expulsion	At 1 year: [Sivin 1994, Baveja 1989] Life table diff=0.84 (-1.19 – 2.88), NS [Sivin 1994] Rate ratio=1.11 (0.72 - 1.71), NS 43/7680 women months vs 39/7740 women months Single decrement life table prob (SE)= 6.4 (1.0) vs 5.8 (1.9) [Baveja 1989] Single decrement life table prob (SE)= 6.5 (1.2) vs 5.3 (1.1) At 2 years: [Baveja 1989] Single decrement life table prob (SE)=9.2 (1.4) vs 7.1 (1.3) Life table diff=2.1 (-1.64 – 5.84), NS At 3 years: [Baveja 1989] Single decrement life table prob (SE)=10.6 (1.6) vs 7.6 (1.4) Life table diff=3 (-1.17 – 7.17), NS At 5 years: [Sivin 1994] **Rate ratio=1.53 (1.13-2.07), SS** 99/34944 women months vs 71/38268 women months Single decrement life table prob (SE)= 11.8 (1.2) vs 7.4 (0.9) **Life table diff=4.4 (1.46 – 7.34), SS**

			Ectopic pregnancy	At 1 year: [Sivin 1994] 0/7680 women months vs 0/7740 women months At 2 years: [Sivin 1994] 0/19644 women months vs 0/20436 women months At 5 years: [Sivin 1994] Rate ratio=0.22 (0.01 - 4.56) 0/34944 women months vs 2/38268 women months
			Embedded	At 5 years: [Sivin 1994] Rate ratio=7.0 (0.36 – 135.52), NS 3/34944 women months vs 0/38268 women months
			Continuation	At 1 year: [Sivin 1994, Baveja 1989] Rate ratio=0.97 (0.90 - 1.06), NS [[Baveja 1989] 339/4809 women months vs 350/4599 women months [Sivin 1994] 743/11892 women months vs 791/12084 women months life table prob (SE)=73.5 (1.4) vs 79.8 (1.3) Life table diff=-6.3 (-10.00 – 2.56), NS At 2 years: [Sivin 1994, Baveja 1989] Rate ratio=0.94 (0.86 - 1.04), NS 298/34944 women months vs 335/38268 women months life table prob (SE)=33 (1.5) vs 40.6 (1.6) [Baveja 1989] 257/8321 women months vs 276/8333 women months

				[Sivin 1994] **life table diff=-8.1 (-12.40 - -3.80), SS** At 3 years: [Baveja 1989] Rate ratio=0.89 (0.71 - 1.11), NS 150/10589 women months vs 170/10869 women months At 5 years: [Sivin 1994] Rate ratio= 0.91 (0.78 - 1.06), NS 298/34944 women months vs 335/38268 women months life table prob (SE)= 33 (1.5) vs 40.6 (1.6) **life table diff=-7.6 (-11.90 - -3.30), SS**
			Amenorrhoea (events per total potential number of women at follow-up)	At 3 months [Sivin 1994] 41/215 vs 20/226 **OR=2.35 (1.37 - 4.04), SS** At 3 years: [Sivin 1994] 75/120 vs 12/139 **OR=11.08 (6.61 - 18.57), SS** Total : [Sivin 1994] 116/335 vs 32/365 **OR=5.29 (3.64 - 7.68), SS**
			Prolonged bleeding (events per total potential number of women at follow-up)	At 3 months: [Sivin 1994] 42/215 vs 19/226 OR=0.88 (0.55 – 1.39), NS At 3 years: [Sivin 1994] 0/120 vs 4/139 OR=0.15 (0.02 - 1.10), NS

				Total: [Sivin 1994] 42/335 vs 53/365 OR=0.80 (0.51 – 1.26), NS
			Discontinuation: all menstrual	At 1 year: [Sivin 1994, Baveja 1989] **Life table diff=6.91 (2.87 – 10.94), SS** [Sivin 1994] **Rate ratio=1.48 (1.02 – 2.14), SS** At 2 years: [Baveja 1989] **Life table diff=11.1 (6.26 – 15.94), SS** At 3 years: [Baveja 1989] **Life table diff=14.5 (8.78 – 20.22), SS** At 5 years: [Sivin 1994] **Rate ratio= 1.48 (1.23 – 1.79), SS**
			Discontinuation: menstrual – bleeding & pain	At 5 years: [Sivin 1994] **Rate ratio=0.71 (0.56 – 0.89), SS** **Life table diff=-7.9 (-10.89 - -4.91), SS**
			Discontinuation: menstrual: pain only	At 1 year: [Sivin 1994] Rate ratio=0.80 (0.41 – 1.56), NS Life table diff=-0.9 (-2.86 – 1.06), NS
			Discontinuation: menstrual: absence of menstrual bleeding	At 1 year: [Sivin 1994] **Rate ratio=65.51 (4.01 – 1069.85), SS** [Sivin 1994, Baveja 1989] **Life table diff=5.04 (3.19 – 6.90), SS**

				At 2 years: [Baveja 1989] **Life table diff=9.5 (6.27 – 12.73), SS** At 3 years: [Baveja 1989] **Life table diff=13.3 (9.30 – 17.30), SS** At 5 years: [Sivin 1994] **Rate ratio=48.92 (16.93 – 141.36), SS** **Life table diff=19.3 (16.14 – 22.46), SS**
			Pelvic Inflammatory Disease (PID)	At 1 year: [Sivin 1994] Rate ratio=1.23 (0.50 - 3.03), NS 10/7680 women months vs 8/7740 women months Single decrement life table prob (SE)= 1.6 (0.5) vs 1.3 (0.4) Life table diff=0.3 (-0.96 – 1.56), NS
			Discontinuation: adverse event	At 3 years: [Baveja 1989] Rate ratio=1.03 (0.18 – 5.92), NS

* Characteristics of included studies: see below

Ref + design	n	Population	Duration	Comparison	Methodology
Baveja 1989 RCT	2118 randomised	women from family planning clinics, India Age 18-40y Proven fertility Regular menses	3y	LNG-20 IUS [n=475] vs CuT 380Ag IUD [n=434] vs CuT220C IUD [n=496] vs CuT200B IUD [n=500]	- Jadad score: 3/5 - neither the study nor the analysis was blind - FU: 90% - ITT: no - characteristics of women lost to follow up or withdrawn not provided - distinguished between user or method failure if pregnancy occurred
Sivin 1994 RCT	2226 randomised	Women from family planning clinics in Singapore, Brazil, Egypt and USA Age 18-38y Parous	7y	LNG-20 IUS [n=1125] vs. CuT 380Ag IUD [n=1121]	- Jadad score: 3/5 - women blinded to method - FU: - ITT:? - characteristics of women lost to follow up or withdrawn not provided - distinguished between user or method failure if pregnancy occurred

Authors' conclusions (all comparisons)

Evidence suggests there is no difference in pregnancy rates among LNG-20 IUS and IUD >250mm2. The LNG-20 IUS more effectively prevented intrauterine and extrauterine pregnancies than IUDs <=250mm2.

. Continuation rates for LNG- 20 IUS and non-hormonal IUDs were similar. Lack of menstrual bleeding was the main reason for discontinuation of LNG-20 IUS.

4.4.1.bis. Levonorgestrel intra-uterine system versus copper –intra-uterine device (Cu >250mm2). Summary and conclusions

<table>
<tr><td colspan="6">LNG-IUS vs Cu-IUD>250mm2 (Sivin 1994 and Baveja 1989 from French 2010).</td></tr>
<tr><td>N/n</td><td>Duration</td><td>Population</td><td colspan="3">Results</td></tr>
<tr><td rowspan="12">N=2,
n=
3155</td><td rowspan="12">3-7y</td><td rowspan="12">-women from family planning clinics
-18-40y</td><td rowspan="4">Pregnancy
N=2</td><td colspan="3">At 1y (N=2): life table diff: -0.16 (-0.65 – 0.34) NS
rate ratio: 1.01 (0.71 – 5.82) NS
At 3y (Baveja): rate ratio: 0.11 (0.01 – 2.12) NS
At 5y (Sivin): rate ratio: 0.66 (0.25 – 1.75) N s</td></tr>
<tr><td><u>Quality</u>
-1 for incomplete reporting FU</td><td><u>Consistency</u>
OK</td><td><u>Directness</u>
OK</td><td><u>Imprecision</u>
OK</td></tr>
<tr><td colspan="4">Grade assessment: moderate quality of evidence</td></tr>
<tr><td rowspan="3">Amenorrhoea

N=1 (Sivin 1994)</td><td colspan="3">At 3 months:
OR 2.35 (1.37 – 4.04)
SS in favour of LNG IUS
At 3 years:
OR 11.08 (6.61 – 18.57)
SS in favour of LNG IUS</td></tr>
<tr><td><u>Quality</u>
-1 for incomplete reporting</td><td><u>Consistency</u>
NA</td><td><u>Directness</u>
OK</td><td><u>Imprecision</u>
OK</td></tr>
<tr><td colspan="4">Grade assessment: moderate quality of evidence</td></tr>
<tr><td rowspan="3">Discontinuation due to AE

N=1 (Sivin 1994)</td><td colspan="3">At 5 years:
rate ratio 0.71 (0.56 – 0.89)
SS in favour of LNG IUS</td></tr>
<tr><td><u>Quality</u>
-1</td><td><u>Consistency</u>
NA</td><td><u>Directness</u>
OK</td><td><u>Imprecision</u>
OK</td></tr>
<tr><td colspan="4">Grade assessment: moderate quality of evidence</td></tr>
<tr><td rowspan="3">PID

N=1 (Sivin 1994)</td><td colspan="3">At 1 year:
rate ratio: 1.23 (0.50-3.03)
NS</td></tr>
<tr><td><u>Quality</u>
-1</td><td><u>Consistency</u>
NA</td><td><u>Directness</u>
OK</td><td><u>Imprecision</u>
OK</td></tr>
<tr><td colspan="4">Grade assessment: moderate quality of evidence</td></tr>
</table>

- These two studies included in a Cochrane review compared a hormone IUD (LNG –IUS) with a copper IUD (>250 mm2). The studies contain an adequate number of patients, but are of moderate quality. Both studies distinguish between failure of the treatment or failure of the user in the event of pregnancy.

No difference between the two IUDs in the number of pregnancies is demonstrated.

GRADE: moderate quality of evidence

Women with a hormonal IUD have a greater chance of amenorrhoea. Moreover, the risk ratio increases with time: 2.35 after 3 months, 11.08 after 3 years.

GRADE: moderate quality of evidence

One study was able to demonstrate after 5 years that significantly fewer women discontinue the contraception in the group that received a hormonal IUD.

GRADE: moderate quality of evidence

No significant difference appeared between the treatment groups in the occurrence of pelvic inflammatory disease.

GRADE: Moderate quality of evidence

4.4.2. Levonorgestrel intra-uterine system versus copper –intra-uterine device (Cu ≤250mm2). Evidence tables

Ref	N/n	Comparison	Outcomes	Result
French 2010 * Design: meta-analysis July 2009 Search date:	N= 3 n= 5013 for this comparison	LNG-IUS vs Cu-IUD<250mm2	Pregnancy	At 1 year: [Andersson 1994, Luukkainen 1986] **Rate ratio=0.12 (0.03 – 0.49), SS** Evidence of heterogenity [Baveja 1989] Single decrement life table probabilities (SE) = 0.0 vs. CuT 220C 0.0 and vs. CuT 200B 0.9 (0.4) Life table diff=-0.90 (-2.01 – 0.21), NS [Andersson 1994] 1/18664 women months vs. 8/9326 women months [Luukkainen 1986] 1/1654 women months vs. 4/1708 women months At 2 years: [Andersson 1994, Baveja 1989 **Rate ratio=0.07 (0.02 – 0.19), SS** [Baveja 1989] Single decrement life table probabilities (SE) = 0.0 vs. CuT 220C 0.0 and vs. CuT 200B 0.9 (0.4) Life table diff=-0.90 (-2.01 – 0.21), NS At 3 years: [Baveja 1989] 0/10589 women months vs. 7/24225 women months (vs. CuT 220C 1/12076 women months and vs. CuT 220B 6/12149 women months) Single decrement life table probabilities (SE) = 0.0 vs. CuT 220C 0.3 (0.3) and vs. CuT 200B 1.6 (0.6)

				Life table diff=-0.56 (-1.30 – 0.18), NS [Andersson 1994] 3/46200 women months vs. 24/23568 women months At 5 years: [Andersson 1994] 5/67380 women months vs. 35/33312 women months [Luukkainen 1986] 1/5495 women months vs. 7/5176 women months [Andersson 1994, Luukkainen 1986] **Rate ratio=0.08 (0.04 – 0.18), SS**
			Continuation	At 1 year: [Andersson 1994, Baveja 1989] Rate ratio 1.03 (0.96 – 1.11), NS Evidence of heterogenity [Andersson 1994] 1362/18664 women months vs. 680/9326 women months [Baveja 1989] 339/4809 women months vs. 791/9814 women months At 2 years: [Baveja 1989] 257/8321 women months vs. 617/18819 women months Rate ratio=0.93 (0.80 – 1.07), NS At 3 years: [Andersson 1994, Baveja 1989] Rate ratio=0.98 (0.80 – 1.07), NS [Andersson 1994] 902/46200 women months vs. 435/23568 women months

				[Baveja 1989] 150/10589 women months vs. 344/24255 women months At 5 years: [Andersson 1994, Luukkainen 1986] Rate ratio=1.04 (0.92 – 1.18), NS Evidence of heterogenity [Andersson 1994] 67/5495 women months vs. 53/5176 women months [Luukkainen 1986] 736/67380 women months vs. 315/33312 women months
			Expulsion	At 1 year: [Andersson 1994] 62/18664 women months vs. 32/9326 women months Rate ratio=0.71 (0.02 – 1.13), NS [Baveja 1989] Single decrement life table probabilities (SE) = 6.5 (1.2) vs. CuT 220C 4.8 (1.0) and vs. CuT 200B 4.9 (1.0) Life table diff=1.65 (-0.51 – 3.81), NS At 2 years: [Luukkainen 1986] 1/3083 women months vs. 9/2989 women months **Rate ratio=0.11 (0.02 – 0.6), SS** [Baveja 1989] Single decrement life table probabilities (SE) = 9.2 (1.4) vs. CuT 220C 7.1 (1.2) and vs. CuT 200B 7.7 (1.3) Life table diff=1.81 (-0.80 – 4.41), NS At 3 years: [Baveja 1989]

				Life table diff=2.2 (-0.75 – 5.14), NS At 5 years [Luukkainen 1986] 2/5495 women months vs. 7/5176 women months Rate ratio=0.27 (0.06 – 1.13), NS
			Ectopic pregnancy	At 1 year: [Andersson 1994, Luukkainen 1986] Rate ratio=0.72 (0.07 – 6.91), NS [Andersson 1994] 0/18664 women months vs. 1/9326 women months [Luukainen 1986] 1/1654 women months vs. 0/1708 women months At 3 years: [Andersson 1994] 1/46200 women months vs. 5/23568 women months **Rate ratio=0.1 (0.02 – 0.62), SS** At 5 years: 1/67380 women months vs. 7/33312 women months **Rate ratio=0.07 (0.01 – 0.41), SS**
			Pelvic Inflammatory Disease	At 1 year: [Luukkainen 1986] 0/1654 women months vs. 0/1708 women months At 2 years: [Luukkainen 1986] Rate ratio=0.4 (0.01 – 1.13), NS
			Discontinuation: all menstrual	At 1 year: [Baveja 1989] Single decrement life table probabilities (SE) = 13.8 (1.7) vs. CuT 220C 6.0 (1.1) and vs.

				CuT 200B 5.7 (1.1) **Life table diff=7.95 (5.14 – 10.76), SS** [Andersson 1994] 153/18664 women months vs. 65/9326 women months Rate ratio=1.18 (0.88 – 1.57), NS At 2 years: [Baveja 1989] Single decrement life table probabilities (SE) = 21.9 (2.1) vs. CuT 220C 9.9 (1.4) and vs. CuT 200B 8.8 (1.4) **Life table diff=12.55 (9.05 – 16.05), SS** At 3 years: [Baveja 1989] Single decrement life table probabilities (SE) = 27.9 (2.3) vs. CuT 220C 15.4 (1.9) and vs. CuT 200B 14.6 (1.9) **Lifte table diff=12.9 (8.77 – 17.03), SS** At 5 years: [Luukkainen 1986] 26/5495 women months vs. 21/5176 women months Rate ratio=1.17 (0.66 – 2.06), NS
			Discontinuation: menstrual – bleeding & pain	At 5 years: [Luukkainen 1986] 11/5495 women months vs. 21/5176 women months Rate ratio=0.49 (0.24 – 1.01), NS
			Discontinuation: absence of menstrual bleeding	At 1 year: [Baveja 1989] **Life table diff=5.07 (3.36 – 6.77), SS** At 2 years: [Baveja 1989] **Life table diff=9.80 (10.80 – 16.41), SS**

				At 3 years: [Baveja 1989] **Life table diff=13.60 (10.80 – 16.41), SS** At 5 years: [Luukkainen 1986] 15/5495 women months vs. 0/5176 women months **Rate ratio=29.2 (1.75 – 488.04), SS**
			Discontinuation: adverse event	At 1 year: [Andersson 1994] 42/18664 women months vs. 21/9326 women months Rate ratio=1.0 (0.59 – 1.68), NS At 3 years: [Baveja 1989] Total: 2/10589 women months vs. 4/24225 women months (vs. CuT220C 0/12076 women months and vs. CuT200B 4/12149 women months) rate ratio=1.14 (0.24 – 5.38), NS At 5 years: [Luukkainen 1986] 5/5495 women months vs. 6/5176 women months Rate ratio=0.78 (0.25 – 2.44), NS
			Planned pregnancy after discontinuation of method	At 1 year: [Andersson 1994] OR=1.24 (0.67 – 2.29), NS At 2 years: [Andersson 1994] OR= 1.29 (0.67 – 2.46), NS
			headaches	At 5 years: [Andersson 1994] OR=1.62 (0.53 – 4.92), NS

			Breast tenderness	At 5 years: [Andersson 1994] OR=1.45 (0.35 – 6.07), NS
			Acne	At 5 years: [Andersson 1994] OR=3.01 (0.95 – 9.51), NS
			Nausea	At 5 years: [Andersson 1994] OR=4.18 (0.20 – 86.13), NS
			Ovarian cysts	At 1 year: [Andersson 1994] 12/18664 women months vs. 4/9326 women months

* Characteristics of included studies: see below

Ref + design	n	Population	Duration	Comparison	Methodology
Andersson 1994 RCT	2758 randomised	Women from family planning clinics in Denmark, Finland, Hungary, Norway and Sweden Age 18-38 years Parous Not breast feeding	5y	LNG-20 IUS [n=1821] vs. Nova-T IUD [n=937]	- Jadad score: 2/5 - open label - FU: 91% - ITT: no
Luukkainen 1986 RCT	484 randomised	Women from family planning clinics in Finland and Brazil Age 18-40 years Proven fertility Not breast feeding	2 y	LNG-20 and LNG-30 IUSs [n=164 and 163, respectively] vs. Nova-T IUD [n=157]	- Jadad score: 2/5 - FU: 91% - ITT: not clear
Baveja 1989 RCT	2118 randomised	Indian women Age 18-40y Proven fertility Regular menses	3y	LNG-20 IUS [n=475] vs CuT 380Ag IUD [n=434] vs CuT220C IUD [n=496] vs CuT200B IUD [n=500]	- Jadad score: 3/5 - neither the study nor the analysis was blind - FU: 90% - ITT: no - characteristics of women lost to follow up or withdrawn not provided - distinguished between user or method failure if pregnancy occurred

Authors' conclusions (all comparisons)

Evidence suggests there is no difference in pregnancy rates among LNG-20 IUS and IUD >250mm2. The LNG-20 IUS more effectively prevented intrauterine and extrauterine pregnancies than IUDs <=250mm2.

Continuation rates for LNG- 20 IUS and non-hormonal IUDs were similar. Lack of menstrual bleeding was the main reason for discontinuation of LNG-20 IUS.

4.4.2.bis. Levonorgestrel intra-uterine system versus copper –intra-uterine device (Cu ≤250mm2). Summary and conclusions

<table>
<tr><td colspan="6">LNG-IUS vs Cu-IU<250mm2 (Andersson 1994, Luukkainen 1986 and Baveja 1989 from French 2010).</td></tr>
<tr><td>N/n</td><td>Duration</td><td>Population</td><td colspan="3">Results</td></tr>
<tr><td rowspan="10">N=3,
n=
5013</td><td rowspan="10">2-5y</td><td rowspan="10">-women from family planning clinics
-18-40y</td><td rowspan="4">Pregnancy
N=3</td><td colspan="3">At 1y:
life table diff (Baveja 1989):
-0.90 (-2.01 – 0.21) NS
rate ratio (Luukkainen 1986, Baveja 1989):
0.12 (0.03 – 0.49)
SS in favour of LNG IUS
At 3y (Baveja 1989):
life table diff: -0.56 (-1.30 -0.18)
NS
At 5y (Andersson 1994, Baveja 1989):
rate ratio: 0.08 (0.04 – 0.18)
SS in favour of LNG-IUS</td></tr>
<tr><td><u>Quality</u>
-1 for incomplete reporting</td><td><u>Consistency</u>
OK</td><td><u>Directness</u>
OK</td><td><u>Imprecision</u>
OK</td></tr>
<tr><td colspan="4">Grade assessment: moderate quality of evidence</td></tr>
<tr><td rowspan="4">Discontinuation due to AE
N=3</td><td colspan="4">At 1 year (Andersson 1994):
rate ratio: 1 (0.59 – 1.68) NS
At 3 years (Baveja 1989):
rate ratio: 1.14 (0.24 – 5.38) NS
At 5 years (Luukkainen 1986)
rate ratio: 0.78 (0.25-2.44) NS</td></tr>
<tr><td><u>Quality</u>
-1 for incomplete reporting</td><td><u>Consistency</u>
OK</td><td><u>Directness</u>
OK</td><td><u>Imprecision</u>
OK</td></tr>
<tr><td colspan="4">Grade assessment: moderate quality of evidence</td></tr>
<tr><td rowspan="3">PID
N=1 (Luukkainen 1986)</td><td colspan="4">At 2 years (1/3): rate ratio: 0.4 (0.01-1.13) NS</td></tr>
<tr><td><u>Quality</u>
-1 for incomplete reporting</td><td><u>Consistency</u>
NA</td><td><u>Directness</u>
OK</td><td><u>Imprecision</u>
OK</td></tr>
<tr><td colspan="4">Grade assessment: moderate quality of evidence</td></tr>
</table>

- These three studies included in a Cochrane review compared a hormone intra-uterine system (LNG –IUS) with a copper IUD(<250 mm2). In two studies (Andersson 1994 and Luukkainen 1986) the Nova-T IUD was used; in another study (Baveja 1989) three different copper IUDs were used: CuT 380Ag, CuT 220C or CuT 200B. The studies contain more than 5000 patients in total, but are of low quality.

In two of the three studies, women who received a hormonal IUS had less chance of becoming pregnant than women with a copper IUD <250 mm2.

GRADE: moderate quality of evidence

No significant difference appeared in the number of women who discontinue the contraception due to adverse events.

GRADE: moderate quality of evidence

No significant difference appeared between the treatment groups in the occurrence of pelvic inflammatory disease.

GRADE: moderate quality of evidence

4.4.3. Levonorgestrel intra-uterine system versus combined oral contraceptives. Evidence tables

Ref	N/n	Comparison	Outcomes	Result
French 2004 * Design: SR + meta-analysis Search date:	N= 1 n= 193	LNG-IUS vs combined oral contraceptives	Discontinuation: hormonal	At 1 year: [Suhonen 2004] 4/1128 women months vs. 9/1188 women months Rate ratio=1.00 (0.32 – 3.07), NS
			Discontinuation: planning pregnancy	At 1 year: [Suhonen 2004] Rate ratio=0.21 (0.01 – 4.39), NS
			Discontinuation: patient choice	At 1 year: [Suhonen 2004] Rate ratio=1.40 (0.48 – 4.02), NS
			headaches	At 1 year: [Suhonen 2004] 56/94 vs 59/99 OR=1.00 (0.56 – 1.77), NS
			Breast tenderness	At 1 year: [Suhonen 2004] 34/94 vs 18/99 **OR=2.48 (1.32 – 4.68], SS**
			acne	At 1 year: [Suhonen 2004] 55/94 vs 44/99 OR= 1.75 (1.00 – 3.08), NS
			Absence of menstrual bleeding	At 1 year: [Suhonen 2004] 20/94 vs 1/99 **OR=8.00 (3.24 – 19.75), SS**
			Prolonged bleeding	At 1 year: [Suhonen 2004] 48/94 vs 58/99 OR=0.74 (0.42 – 1.30), NS

* Characteristics of included studies: see below

Ref + design	n	Population	Duration	Comparison	Methodology
[Suhonen 2004]	200 randomised	Helsinki Finland, Family-planning clinics 18-25 years nulliparous	1 year	LNG-IUS vs. oral contraceptives	- Jadad score: 3/5 - FU: 97% - ITT: no

Remarks:

In the Cochrane review, the table with characteristics of included studies states 'randomisation technique: no mention'. However in the original publication there is the following remark 'Nulliparous women aged 18–25 and seeking contraception were randomized into two equal-sized groups in blocks of eight subjects.' This leads to an extra point in the Jadad score.

4.4.3.bis. Levonorgestrel intra-uterine system versus combined oral contraceptives. Summary and conclusions

<table>
<tr><td colspan="6">LNG-IUS vs combined oral contraceptives (Suhonen 2004 from French 2010).</td></tr>
<tr><td>N/n</td><td>Duration</td><td>Population</td><td colspan="3">Results</td></tr>
<tr><td rowspan="11">N=1,
n= 193</td><td rowspan="11">1y</td><td rowspan="11">-women from family planning clinics
-18-25u
-nulliparous</td><td>Pregnancy
N=1</td><td colspan="3">No pregnancies were observed.
NT</td></tr>
<tr><td colspan="3">Grade assessment: NA</td></tr>
<tr><td rowspan="3">Discontinuation (patient choice)</td><td colspan="3">At 1 year:
rate ratio: 1.40 (0.48-4.02)
NS</td></tr>
<tr><td><u>Quality</u>
-1 for incomplete reporting</td><td><u>Consistency</u>
NA</td><td><u>Directness</u>
OK</td><td><u>Imprecision</u>
OK</td></tr>
<tr><td colspan="3">Grade assessment: moderate quality of evidence</td></tr>
<tr><td rowspan="3">Absence of menstrual bleeding</td><td colspan="3">At 1 year:
OR: 8 (3.24-19.75)
SS in favour of LNG-IUS</td></tr>
<tr><td><u>Quality</u>
-1 for incomplete reporting</td><td><u>Consistency</u>
NA</td><td><u>Directness</u>
OK</td><td><u>Imprecision</u>
OK</td></tr>
<tr><td colspan="3">Grade assessment: moderate quality of evidence</td></tr>
<tr><td rowspan="3">Breast tenderness</td><td colspan="3">At 1 year:
OR: 2.48 (1.32-4.68)
SS more in LNG-IUS-group</td></tr>
<tr><td><u>Quality</u>
-1 for incomplete reporting</td><td><u>Consistency</u>
NA</td><td><u>Directness</u>
OK</td><td><u>Imprecision</u>
OK</td></tr>
<tr><td colspan="3">Grade assessment: moderate quality of evidence</td></tr>
</table>

- This study included in a Cochrane review compared the levonorgestrel intra-uterine system (LNG –IUS) with combined oral contraceptives.

No pregnancy was reported in either group. No statistical evaluation was conducted.

GRADE: not applicable

No significant difference appeared in the number of patients who discontinued the contraception.

GRADE: moderate quality of evidence

Women with the hormone IUD had a greater chance of amenorrhoea and a greater chance of breast sensitivity.

GRADE: moderate quality of evidence

4.5. Progestogen-only implant

No studies met our inclusion criteria

4.6. Immediate start of hormonal contraception versus start at next menstrual period

4.6.1. Immediate versus conventional start of combined oral contraceptives. Evidence tables

Ref	N/n	Comparison	Outcomes	
* Lopez 2008 Design: SR +/- MA N= 5 n= 2427 Search date: Sept 2010	N=1 n=1720	Immediate versus conventional start of OCs	Pregnancy per woman	66/802 (immediate) vs 72/788 (conventional) OR= 0.89 (95%CI 0.63, 1.26) NS p=0.52
			Pregnancy per young woman (<18 years old)	17/272 (immediate) vs 28/267 (conventional) OR= 0.58 (95%CI 0.31, 1.06) NS p=0.076
			Serious adverse events	15/837 (immediate) vs 11/846 (conventional) OR= 1.38 (95%CI 0.64, 3.00) NS p=0.41
			Bleeding	The study groups had similar bleeding profiles

* Characteristics of included studies: see under

Ref + design	n	Population	Duration	Comparison	Methodology
Westhoff 2007 Open label RCT (USA)	1720	young women -requesting OCs -< 25 years old, - not pregnant, -sexually active, -no OC in past 7 days or DMPA in 6 months, -no desire for pregnancy in next 6 months, -no lactational amenorrhea. Exclusion criteria (IRB required): postpartum or postabortion if less than 18 years old	6 months	Immediate start (n=856) versus conventional initiation (n=864) of OC. Immediate: first pill was taken under direct observation. Conventional: instructed to take first pill during next period. Clinician preference determined OC brand and number of pill packs or prescriptions provided.	- Jadad score:3 /5 - FU: 84% - ITT: No Other important methodological remarks: -Unclear allocation concealment (numbered opaque envelopes.) -Insufficient data were reported for calculating method discontinuation. -Power was 63% to detect pregnancy decrease from 11% to 7% -Medical records were used to identify pregnancy in 96 women who missed both follow ups

4.6.1.bis. Immediate versus conventional start of combined oral contraceptives. Summary and conclusions

<table>
<tr><td colspan="6">Immediate start COCs vs Conventional start COCs (Westhoff 2007 from Lopez 2008)</td></tr>
<tr><td>N/n</td><td>Duration</td><td>Population</td><td colspan="3">Results</td></tr>
<tr><td rowspan="9">N=1,
n=
1720</td><td rowspan="9">6m</td><td rowspan="9">- Healthy women requesting COCs
- Age <25y
- not pregnant
- sexually active</td><td rowspan="3">Pregnancy per woman</td><td colspan="3">OR= 0.89 (95%CI 0.63, 1.26)
NS p=0.52</td></tr>
<tr><td><u>Quality</u>
-2 (OL, no ITT, inadequate power)</td><td><u>Consistency</u>
NA</td><td><u>Directness</u>
OK</td><td><u>Imprecision</u>
OK</td></tr>
<tr><td colspan="4">Grade assessment: low quality of evidence</td></tr>
<tr><td rowspan="3">Pregnancy per young woman (<18 years old)</td><td colspan="3">OR= 0.58 (95%CI 0.31, 1.06)
NS p=0.076</td></tr>
<tr><td><u>Quality</u>
-2 (low Jadad)</td><td><u>Consistency</u>
NA</td><td><u>Directness</u>
OK</td><td><u>Imprecision</u>
OK</td></tr>
<tr><td colspan="4">Grade assessment: low quality of evidence</td></tr>
<tr><td rowspan="3">Serious AEs</td><td colspan="3">OR= 1.38 (95%CI 0.64, 3.00)
NS p=0.41</td></tr>
<tr><td><u>Quality</u>
-1 (low Jadad)</td><td><u>Consistency</u>
NA</td><td><u>Directness</u>
OK</td><td><u>Imprecision</u>
-1</td></tr>
<tr><td colspan="4">Grade assessment: low quality of evidence</td></tr>
</table>

- From a Cochrane review, we selected a large RCT with young women, which compared the immediate start of combination pills to the conventional method where a woman starts taking the pill on the first day of the next menstruation.
There was no significant difference in the occurrence of pregnancies in both groups, nor in the sub-group of girls under the age of 18 years.

GRADE: low quality of evidence

The number of severe adverse events did not differ significantly between both treatment methods.

GRADE: low quality of evidence

4.6.2. Immediate versus conventional start of depot medroxyprogesterone acetate IM. Evidence tables

Ref	N/n	Comparison	Outcomes	
* Lopez 2008 Design: SR +/- MA N= 5 n= 2427 Search date: Sept 2010	N=1 n=333	Immediate DMPA versus contraceptive bridge to DMPA	Pregnancy per woman	**3/101 (immediate DMPA) vs 25/232 (Immediate bridge)** **OR= 0.36 (95%CI 0.16, 0.84)** **SS in favor of immediate DMPA p=0.018**
			Discontinued method before 6 months	71/101 (immediate DMPA) vs 182/232 (Immediate bridge) OR= 0.64 (95%CI 0.37, 1.11) NS p=0.11
			Very satisfied with method at 6 months	**57/69 (immediate DMPA) vs 109/158 (Immediate bridge)** **OR= 1.99 (95%CI 1.05, 3.77)** **SS in favor of immediate DMPA p=0.034**
			Adverse events	0/101 (immediate DMPA) vs 0/232 (Immediate bridge)

* Characteristics of included studies: see under

Ref + design	n	Population	Duration	Comparison	Methodology (sponsor NR in Cochrane)
Rickert 2007 Open label RCT (USA)	333	women -age 14 to 26 years who sought care at a family planning clinic and were interested in using DMPA. Exclusion criteria: currently menstruating, pregnant, or breastfeeding; contraindication to hormonal contraception; using DMPA (within past 14 weeks); consistently used birth control pills, patch, ring, or other prescription contraception method in past 30 days; history of serious mental illness	6months	Immediate DMPA (depot medroxyprogesterone acetate) versus 'bridge' method (choice of pills, patch, or ring with a 21-day supply prior to first DMPA injection)	- Jadad score: 3/5 - FU: 68% - ITT: yes (except satisfaction) Other important methodological remarks: -Unclear allocation concealment (sequential sealed envelopes) -Sample size calculation based on ability to detect difference in continuation rates of 17% (not pregnancy) - High losses to follow up threaten validity

4.6.3. Immediate versus conventional start of contraception: Cochrane authors' conclusions (Lopez 2008)

We found limited evidence that immediate start of hormonal contraception reduces unintended pregnancies or increases method continuation. However, the pregnancy rate was lower with immediate start of DMPA versus another method. More studies are needed of immediate versus conventional start of the same hormonal contraceptive.

4.6.2.bis. Immediate versus conventional start of depot medroxyprogesterone acetate IM. Summary and conclusions

Immediate start DMPA vs Bridge method before start DMPA (Rickert 2007 from Lopez 2008)							
N/n	**Duration**	**Population**	**Results**				
N=1, n= 333	6m	- Healthy women interested in using DMPA - Age 14-26y - not pregnant or breastfeeding - sexually active	Pregnancy per woman	3/101 (immediate DMPA) vs 25/232 (bridge) OR= 0.36 (95%CI 0.16, 0.84), p=0.018 **SS in favour of immediate DMPA**			
				Quality -2 (low FU, inadequate power)	Consistency NA	Directness OK	Imprecision OK
				Grade assessment: *low quality of evidence*			
			Discontinuation	OR= 0.64 (95%CI 0.37, 1.11) NS p=0.11			
				Quality -1	Consistency NA	Directness OK	Imprecision OK
				Grade assessment: *moderate quality of evidence*			
			High satisfaction with method	OR= 1.99 (95%CI 1.05, 3.77), p=0.034 **SS in favour of immediate DMPA**			
				Quality -1	Consistency NA	Directness OK	Imprecision OK
				Grade assessment: *moderate quality of evidence*			
			AEs	0 vs 0			

- A Cochrane review included an RCT that compared young women who started depot medroxyprogesterone acetate (DMPA) immediately with the bridging method where a woman is given another form of contraception before the first DMPA injection on the first day of the next menstruation.
There were significantly fewer pregnancies in the group of women who started with DMPA treatment immediately compared to the group that had to wait for their first injection (OR = 0.36).

GRADE: low quality of evidence

- The number of women that stopped their treatment did not differ significantly between the treatment methods.

GRADE: moderate quality of evidence

- Significantly more women were very satisfied with their treatment method in the group that started with DMPA injections immediately compared to the group that first received another method whilst waiting for their first DMPA injection (OR nearly 2.0).

GRADE: moderate quality of evidence

- No adverse events were reported in any of the treatment groups.

5. Evidence tables and conclusions. Hormonal contraception: specific indications

5.1. Dysmenorrhoea

5.1.1. Dysmenorrhoea. Combined oral contraceptives versus placebo

No studies met our inclusion criteria

5.1.2. Dysmenorrhoea. Combined oral contraceptives versus combined oral contraceptives. Evidence tables

Ref	N/n	Comparison	Outcomes	Result
Wong 2009 Design: SR +/- MA N=10 Search date: November2008	N= 2 n= 626	Ethinyl estradiol 0.02mg, 0.075mg gestodene Vs. Ethinyl estradiol 0.02mg, 0.15mg desogestrel	Pain improvement	219/324 vs. 196/302 OR=1.11 (0.79 - 1.57), NS
			Withdrawals from treatment	45/324 vs. 37/302 OR=1.15 (0.72 – 1.83) , NS

* Characteristics of included studies: see below

Ref + design	n	Population	Duration	Comparison	Methodology
Endrikat 1999 OL PG RCT	1563 randomised which included women with no dysmenorrhoea	Location: France, Austria, United Kingdom, the Netherlands, Switzerland and Italy Mean age: 25y Inclusion: aged 18 to 35 years old, desire for contraception for at least 12 months Exclusion: contraindications to OC use, various pathologies, unclassified genital bleeding, history of migraine accompanying menstrual bleeding, pregnancy.	12 cycles	Ethinyl estradiol 0.02mg, 0.075mg gestodene vs Ethinyl estradiol 0.02mg, 0.15mg desogestrel	- Jadad score: 2/5 - FU: total group 71.3% (228 withdrawals from gestodene group and 221 from desogestrel group), no number reported for women with dysmenorrhoea only - ITT: no, 87 women were excluded from the analysis because of protocol violations
Serfaty 1998 OL PG RCT	1016 randomized; 213 women with dysmenorrhoea	Location: France Mean age: 26y Inclusion: regular menstrual cycles (24-35 days cycles), aged 18-45 years old, BMI of 18-29 kg/m2 Exclusion: smokers, contraindications to OC use, drugs use, women who had just given birth or had an abortion.	6 cycles	Ethinyl estradiol 0.02mg, 0.075mg gestodene vs Ethinyl estradiol 0.02mg, 0.15mg desogestrel	- Jadad score: 2/5 - FU: 82,1% (85 dropouts from desogestrel and 97 from gestodene group) - ITT: no (173/213 women with dysmenorrhoea analysed)

Ref	N/n	Comparison	Outcomes	Result
Wong 2009 Design: SR+/- MA N=10 Search date: November 2008	N= 1 n= 349	Ethinyl estradiol 0.02mg and 0.15mg desogestrel vs Ethinyl estradiol 0.02mg and 0.01mg levonorgestrel	Pain improvement	149/178 vs. 158/171 **OR=0.44 (0.23 – 0.84), SS in favour of desogestrel OCP**
			Withdrawals from treatment	13/178 vs. 3/171 **OR=4.41 (1.23 – 15.77), SS in favour of desogestrel OCP**

* Characteristics of included studies: see below

Ref + design	n	Population	Duration	Comparison	Methodology (sponsor NR in Cochrane)
Winkler 2004 OL PG RCT	1027 randomised; 349 with dysmenorrhoea	Location: Germany and the Netherlands Mean age: 28y Inclusion: Women aged 18 to 45 years old, BMI of 18 to 29 kg/m2 Exclusion: smoking, concomitant medication or addictive drugs, psychiatric disorders, using injectable hormonal contraceptives within 6 months of enrolment	6m	Ethinyl estradiol 0.02mg and 0.15mg desogestrel vs Ethinyl estradiol 0.02mg and 0.01mg levonorgestrel	- Jadad score: 3/5 - FU: 76.7% for total group, no dropouts reported for women with dysmenorrhea only - ITT: yes Methodological remarks 349 of the initial group randomised had dysmenorrhoea and no dropouts reported

Authors' conclusions

There is no evidence of a difference between different OCP preparations.

5.1.2.bis. Dysmenorrhoea. Combined oral contraceptives versus combined oral contraceptives. Summary and conclusions

<table>
<tr><td colspan="6">Gestodene 75µg + Ethinyl estradiol 20 µg vs Desogestrel 150µg + Ethinyl estradiol 20µg (Endrikat 1999 and Serfaty 1998 from Wong 2009)</td></tr>
<tr><th>N/n</th><th>Duration</th><th>Population</th><th colspan="3">Results</th></tr>
<tr><td rowspan="6">N=2,
n= 626</td><td rowspan="6">6-12 cycles</td><td rowspan="6">- Women with regular cycles and dysmenorrhea
- Age: 18-45y (mean: 25.5y)</td><td rowspan="3">Pain improvement</td><td colspan="3">219/324 vs 196/302
OR=1.11 (CI: 0.79-1.57), NS</td></tr>
<tr><td><u>Quality</u>
-1 (low Jadad, OL, no ITT)</td><td><u>Consistency</u>
OK</td><td><u>Directness</u>
OK</td><td><u>Imprecision</u>
-1 (small study, lot of loss to FU)</td></tr>
<tr><td colspan="4">Grade assessment: low quality of evidence</td></tr>
<tr><td rowspan="3">Discontinuation</td><td colspan="3">45/324 vs 37/302
OR=1.15 (CI: 0.72-1.83), NS</td></tr>
<tr><td><u>Quality</u>
-1 (low Jadad)</td><td><u>Consistency</u>
OK</td><td><u>Directness</u>
OK</td><td><u>Imprecision</u>
-1 (small study, lot of loss to FU)</td></tr>
<tr><td colspan="4">Grade assessment: low quality of evidence</td></tr>
</table>

- In two open label RCTs performed in the late 1990s, the effect of a combination pill with gestodene was compared to a combination pill with desogestrel in women with dysmenorrhoea. The quality of these studies is low primarily due to the high drop-out and the lack of an intention-to-treat analysis. These studies also included women without dysmenorrhoea and did not always state how many women were included.
No significant difference could be demonstrated in pain relief between these two combination pills.

GRADE: low quality of evidence

- Adverse effects were not reported, but the difference in stopping the treatment was not significantly different between both groups.

GRADE: low quality of evidence

<table>
<tr><td colspan="6">Ethinyl estradiol 0.02mg and 0.15mg desogestrel vs Ethinyl estradiol 0.02mg and 0.01mg levonorgestrel (Winkler 2004 from Wong 2009)</td></tr>
<tr><th>N/n</th><th>Duration</th><th>Population</th><th colspan="3">Results</th></tr>
<tr><td rowspan="6">N=1,
n= 349 out of 1027</td><td rowspan="6">6m</td><td rowspan="6">-Women requiring contraception, subgroup of women with dysmenorrhea
- Age: 18-45y (mean: 28y)</td><td rowspan="3">Pain improvement</td><td colspan="3">149/178 vs 158/171
OR=0.44 (CI: 0.23-0.84), SS in favour of desogestrel</td></tr>
<tr><td><u>Quality</u>
-2(low Jadad, subgroup)</td><td><u>Consistency</u>
OK</td><td><u>Directness</u>
OK</td><td><u>Imprecision</u>
OK</td></tr>
<tr><td colspan="4">Grade assessment: low quality of evidence</td></tr>
<tr><td rowspan="3">Discontinuation</td><td colspan="3">13/178 vs 3/171
OR=4.41 (CI: 1.23-15.77), SS in favour of desogestrel</td></tr>
<tr><td><u>Quality</u>
-2 (low Jadad, subgroup)</td><td><u>Consistency</u>
OK</td><td><u>Directness</u>
OK</td><td><u>Imprecision</u>
OK</td></tr>
<tr><td colspan="4">Grade assessment: low quality of evidence</td></tr>
</table>

In 1 open label RCT, a combination pill with desogestrel was compared to a combination pill with levonorgestrel. A sub-group of 349 women had dysmenorrhoea. There was a high drop-out in the study, but the drop-out in the sub-group was not reported. This limits the reliability of the results.
In the sub-group of women with dysmenorrhoea we saw that the combination pill with desogestrel provided significantly greater improvements in pain than the combination pill with levonorgestrel. There was a lower drop-out rate for the combination pill with desogestrel.

GRADE: *low quality of evidence*

5.2. Heavy menstrual bleeding

5.2.1. Heavy menstrual bleeding. Combined oral contraceptives versus placebo. Evidence tables

Ref	n/Population	Duration	Comparison	Outcomes		Methodological
Fraser 2011 Design: DB PG RCT	n= 231 mean age: 39y <u>Inclusion</u> healthy women, aged 18y or over, with idiopathic heavy, prolonged or frequent menstrual bleeding (confirmed during a 90-day run-in phase), normal result after endometrial biopsy or simple endometrial hyperplasia in the 6 months prior to study entry <u>Exclusion</u> abnormal transvaginal ultrasound or abnormal values forlaboratory examination; history of endometrial ablation, undergone dilatation and curettage in the	11 m (Run-in 90 days, treatment 196 days, FU 30 days)	Sequential (quadriphasic) estradiol valerate/dienogest (E2V/DNG)(n=149) vs. placebo (n=82) The use of medications intended to relieve women of their HMB (e.g. sex steroids, NSAIDs, tranexamic acid) was not allowed throughout the whole study.	Efficacy		- Jadad score o RANDO: 2/2 o BLINDING: 2/2 o ATTRITION: 1/1 - FU: 79% - ITT: yes Multicenter: 34 centres in Australia and Europe (Czech Republic, Finland, Germany, Hungary, the Netherlands, Poland, Sweden, the UK and Ukraine) Sponsor: Bayer HealthCare Pharmaceuticals
				Patients with complete response* (PE, ITT population)	E2V/DNG: 29.5% Placebo: 1.2% CI of difference NR **SS, p<0.0001**	
				Reduction in mean blood loss in the group of subjects defined as heavy bleeders (>90% of ITT population)	Reduction of 20% 50% 80% E2V/DNG: 94% 84% 50% Placebo: 40% 12% 0% NT	
				Reduction in volume of mean blood loss	ITT population: graphical presentation only, NT Complete responder analysis (n=168): E2V/DNG: -458.4ml Placebo: -93.2 ml Mean adj diff= 373 ml (490 ml – 255 ml) CI of difference NR p<0.0001	
				Reduction in the number of bleeding days	Only in women with available data (n=170): E2V/DNG: -3.7d Placebo: -2.1d CI of difference NR p=0.0186	
				Reduction in the number of spotting days	Only in women with available data (n=170): E2V/DNG: +2.1 Placebo: -0.2 NT	
				Safety		
				Subject reported AE, n (%)	E2V/DNG (n=145) Placebo (n=81) Acne 5 (3.4) 3 (3.7)	

	2 months preceding the study; organic pathology (chronic endometritis, adenomyosis, endometriosis, endometrial polyps, leiomyomas or uterine malignancy); unwilling to discontinue the use of tranexamic acid or NSAIDs during menses; BMI >32; women of 35y or older who smoked; contraindications for the use of combined OCs				Back pain 3 (2.1) 4 (4.9) Breast pain 8 (5.5) 0 (0.0) Breast tenderness 6 (4.1) 3 (3.7) Headache 21 (14.5) 12 (14.8) 'Menorrhagia' 1 (0.7) 4 (4.9) Vomiting 3 (2.1) 4 (4.9) NT	
				Dropout rate due to AE	E2V/DNG: 9.7% Placebo: 6.2% NT	
				Serious adverse events	E2V/DNG: chronic cholecystitis, n = 1; breast cancer in situ, n = 1 Placebo: vertigo and panic attack, n= 1; spontaneous abortion and suspicion of abnormal pregnancy, n= 1. The case of breast cancer in situ, a 4-cm lesion, was diagnosed 5 months after initiating treatment in a women aged 45 years. This event was considered to be possibly related to treatment.	

*Complete response to treatment was defined as a composite of the following components: no bleeding episodes lasting more than 7 days; no more than four bleeding episodes overall; no bleeding episodes with a blood loss volume of 80 ml or more; no more than one bleeding episode increase from baseline; no more than 24 days of bleeding overall; and no increase from baseline in the total number of bleeding days.
In addition, patients recruited because of the presence of prolonged bleeding were required to demonstrate a decrease of at least 2 days in the maximum duration of a bleeding episode.
Similarly, in patients recruited because of the presence of heavy bleeding, the blood loss volume per bleeding episode had to be <80 ml and had to represent a decrease of at least 50% relative to the average blood loss volume per episode during the study recruitment phase (where the qualifying bleeding episodes were those with an MBL volume of at least 80 ml).

Ref	n/Population	Duration	Comparison	Outcomes		Methodological
Jensen 2011 Design: DB PG RCT	n= 190 mean age: 37y <u>Inclusion</u> ≥ 18 years; heavy menstrual bleeding, prolonged menstrual bleeding, frequent menstrual bleeding, or any combination; willing to use a barrier method of contraception and to use (and collect) all sanitary protection items (pads and tampons); normal endometrial biopsy or, at most, mild simple endometrial hyperplasia during the 6 months before study entry. Women older than 40 years had to have follicle-stimulating hormone level of less than 40 milli-international units/mL. <u>Exclusion</u> abnormal transvaginal ultrasonogram or clinically significant abnormal values at laboratory examination; endometrial ablation or dilatation and curettage	7 cycles	estradiol valerate/dienogest (E2V/DNG)(n=120) vs. placebo (n=70) The use of medications intended to relieve women of their HMB (e.g. sex steroids, NSAIDs, tranexamic acid) was not allowed throughout the whole study.	Efficacy		- Jadad score o RANDO: 2/2 o BLINDING: 2/2 o ATTRITION: 1/1 - FU: 71% - ITT: yes Multicenter: 47 centers in the United States and Canada Sponsor: Bayer HealthCare Pharmaceuticals
				Proportion of patients with a complete response during last 90 days of treatment (PE, ITT)*	E2V/DNG: 29.2% Placebo: 2.9% **CI NR; P<0.001**	
				Reduction in mean blood loss in the group of subjects defined as heavy bleeders (76% of ITT population)	Reduction of 20% 50% 80% E2V/DNG: 91% 80% 45% Placebo: 51% 17% 5% NT	
				Reduction in volume of mean blood loss	Only women with data available: (n=125) E2V/DNG: -353ml Placebo: -130ml **Mean adj diff= -252ml (-339ml to -165ml), SS, p<0.001**	
				Reduction in the number of bleeding days	Only women with data available(n=128) E2V/DNG: -2.8d Placebo: -2.2d **p=0.024**	
				Reduction in the number of spotting days	Only women with data available(n=128) E2V/DNG: +1.7d Placebo: -0.2d NT	
				Safety		
				Subject reported AE, n (%)	E2V/DNG (n=119) Plac (n=66) Acne 6 (.05%) 0 (0%) Anemia 2 (1.7%) 4 (6.1%) Breast pain 5 (4.2%) 0 (0%) Breast tenderness 4 (3.4%) 1 (1.5%) Headache 5 (4.2%) 9 (13.6%) Metrorrhagia 6 (5.0%) 0(0%) Migraine 3 (2.5%) 0(0%) Weight increase 7 (5.9%) 0 (0%) Vaginal infection 3 (2.5%) 0 (0%) NT	
				Dropout rate due to AE	E2V/DNG: 9.2% Placebo: 6.1%	

	in the 2 months before the study; organic pathology; use of agents intended for the treatment of symptoms of abnormal uterine bleeding; BMI> 32; smoking more than 10 cigarettes per day (in women>35 years); contraindications for the use of combined OCPs.				NT	
				Treatment-emergent adverse events	E2V/DNG: 67.2% Placebo: 54.5% NT	
				Serious adverse events	E2V/DNG: 1 myocardial infarction Placebo: 1 hospitalization for a suicide attempt. The myocardial infarction (acute small non–ST-elevation infarct) occurred 2 days after the last dose of study medication in a 46-year-old woman who had a history of hyperlipidemia and a family history of cardiovascular disease	

*Complete response was defined as no bleeding episodes that lasted more than 7 days, no more than four bleeding episodes overall, no bleeding episodes that involved a blood loss volume of 80 mL or more, no more than one bleeding episode increase from baseline, no more than 24 days of bleeding overall, and no increase from baseline in an individual participant's total number of bleeding days.

5.2.1.bis. Heavy menstrual bleeding. Combined oral contraceptives versus no treatment. Summary and conclusions

<table>
<tr><td colspan="6">Estradiol valerate/dienogest vs placebo (Fraser 2011, Jensen 2011)</td></tr>
<tr><th>N/n</th><th>Duration</th><th>Population</th><th>Results</th><th colspan="3"></th></tr>
<tr><td rowspan="11">N=2,
n= 421
(a: 231
b: 190)</td><td rowspan="11">7 cycles</td><td rowspan="11">- Women with idiopathic heavy menstrual bleeding, prolonged menstrual bleeding or any combination
- Age: ≥18y (mean: 38y)</td><td rowspan="3">Proportion of women with complete response to treatment (%)
N=2</td><td colspan="3">(Fraser 2011):
E2V/DNG 29.5% vs Placebo 1.2% SS, p<0.0001
(Jensen 2011):
E2V/DNG 29.2% vs Placebo 2.9% CI NR p<0.001</td></tr>
<tr><td><u>Quality</u>
-1 (composite EP)</td><td><u>Consistency</u>
OK</td><td><u>Directness</u>
OK</td><td><u>Imprecision</u>
OK</td></tr>
<tr><td colspan="4">Grade assessment: moderate quality of evidence</td></tr>
<tr><td rowspan="3">Reduction in volume of mean blood loss
N=2</td><td colspan="3">(Fraser 2011):
ITT: graphical presentation only, NT
complete responder analysis (n=168):
E2V/DNG -458.4ml vs Placebo -93.2 ml
Mean adj diff= 373 ml (490 ml – 255 ml) CI NR, p<0.0001
(Jensen 2011):
only women with data available (n=125):
E2V/DNG -353ml vs Placebo -130ml
Mean adj diff= -252ml (-339ml to -165ml), SS, p<0.001</td></tr>
<tr><td><u>Quality</u>
-1 (unclear reporting)</td><td><u>Consistency</u>
OK</td><td><u>Directness</u>
OK</td><td><u>Imprecision</u>
OK</td></tr>
<tr><td colspan="4">Grade assessment: moderate quality of evidence</td></tr>
<tr><td rowspan="3">Reduction in number of bleeding days
N=2</td><td colspan="3">(Fraser 2011):
only women with available data (n=170):
E2V/DNG -3.7d vs Placebo -2.1d, CI NR, p=0.0186
(Jensen 2011):
only women with data available(n=128):
E2V/DNG -2.8d vs Placebo -2.2d, p=0.024</td></tr>
<tr><td><u>Quality</u>
-1</td><td><u>Consistency</u>
OK</td><td><u>Directness</u>
OK</td><td><u>Imprecision</u>
OK)</td></tr>
<tr><td colspan="4">Grade assessment: moderate quality of evidence</td></tr>
<tr><td rowspan="3">Reduction in number of spotting days
N=2</td><td colspan="3">(Fraser 2011):
only in women with available data (n=170):
E2V/DNG +2.1 vs Placebo -0.2, NT
(Jensen 2011):
only women with data available(n=128):
E2V/DNG +1.7d vs Placebo -0.2d, NT</td></tr>
<tr><td colspan="4">Grade assessment: NA</td></tr>
<tr><td>Metrorrhagia, self-reported
N=1
(Jensen 2011)</td><td colspan="3">COC 5.0% vs pla 0%, NT</td></tr>
<tr><td>Discontinuation due to AE
N=2</td><td colspan="3">(Fraser 2011): COC 9.7% vs pla 6.2%, NT
(Jensen 2011): COC 9.2% vs pla 6.1%, NT</td></tr>
</table>

*Complete response to treatment was defined as a composite of the following components: no bleeding episodes lasting more than 7 days; no more than four bleeding episodes overall; no bleeding episodes with a blood loss volume of 80 ml or more; no more than one bleeding episode increase from baseline; no more than 24 days of bleeding overall; and no increase from baseline in the total number of bleeding days.

- Two double-blind placebo-controlled studies of each approximately 200 women with metrorrhagia examined the effects of the sequential combination pill (oestradiol valerate and dienogest) versus placebo over seven menstrual cycles.
The proportion of participants who experienced a complete response to the treatment was significantly greater in the pill group than in the placebo group. The definition of a complete response was fairly complex.

GRADE: moderate quality of evidence

There was a significantly greater reduction in average blood loss and in the number of bleeding days with the sequential combination pill compared to the placebo.

GRADE: moderate quality of evidence

- The safety endpoints were not subjected to statistical testing.

GRADE: NA

This is the only study that examined the effect of combined hormonal contraception versus placebo for heavy menstrual bleeding.

5.2.2. Heavy menstrual bleeding. Levonorgestrel intra-uterine system vesus combined oral contraceptives. Evidence tables

Ref	n/Population	Duration	Comparison	Outcomes		Methodological
Shabaan 2011 Design: OL PG RCT	n= 112 mean age: 39y <u>Inclusion</u> self-described heavy menstrual bleeding, 20–50 years old, regular cycle <u>Exclusion</u> pregnancy,history of ectopic pregnancy, puerperal sepsis, pelvic inflammatory disease, evidence of defective coagulation, ultrasound abnormalities including fibroid, history or evidence of malignancy or hyperplasia in the endometrial biopsy, incidental adnexal abnormality on ultrasound, contraindications to COC, previous endometrial ablation or resection, uninvestigated postcoital bleeding, untreated abnormal cervical cytology	12m	Levonorgestrel-releasing intrauterine system (LNG-IUS) vs. 30 mcg ethinyl estradiol + 150 mcg levonorgestrel (COC)	Efficacy		- Jadad score ○ RANDO: 2/2 ○ BLINDING: 0/2 ○ ATTRITION: 0/1 - FU: 85% - ITT: yes Single center in Egypt Sponsor: The LNG-IUS was provided by Bayer Schering Pharma AG, Bayer Healthcare (Germany); funding for laboratory work by the Assiut University, Egypt. Treatment failure was defined as the initiation of an alternative medical treatment or the need for surgery
				% of women with treatment failure	LNG-IUS: 11% COC: 32% **HR=0.30 (0.14 – 0.73), SS, p=0.007**	
				Reduction in menstrual blood loss by alkaline hematin at 12m	LNG-IUS: 87.4% COC: 35.0% **p= 0.013**	
				Reduction in pictorial blood assessment chart (PBLAC) score at 6m	LNG-IUS: 89.5% COC: 41.6% **p<0.001**	
				Reduction in PBLAC score at 12m	LNG-IUS: 86.6% COC: 2.5% **p<0.001**	
				Total bleeding days per year	LNG-IUS: 34.5d COC: 65.1d **p<0.001**	
				Total spotting days per year	LNG-IUS: 20.7d COC: 18.0d p=0.273	
				Safety		
				NR		

5.2.2.bis. Heavy menstrual bleeding. Levonorgestrel intra-uterine system vesus combined oral contraceptives. Summary and conclusions

<table>
<tr><td colspan="6">Levonorgestrel-releasing intrauterine system vs ethinyl estradiol 30µg + levonorgestrel 150µg (Shabaan 2011)</td></tr>
<tr><td>N/n</td><td>Duration</td><td>Population</td><td colspan="3">Results</td></tr>
<tr><td rowspan="15">N=1,
n= 112</td><td rowspan="15">12m</td><td rowspan="15">- Women with heavy menstrual bleeding (self-reported)
- Age: 20-50y</td><td rowspan="3">Women with treatment failure (%)</td><td colspan="3">LNG-IUS: 11%
COC: 32%
HR=0.30 (0.14 – 0.73), SS, p=0.007</td></tr>
<tr><td><u>Quality</u>
-1 (low Jadad)</td><td><u>Consistency</u>
NA</td><td><u>Directness</u>
OK</td><td><u>Imprecision</u>
-1 (small study)</td></tr>
<tr><td colspan="4">Grade assessment: low quality of evidence</td></tr>
<tr><td rowspan="3">Reduction in menstrual blood loss by alkaline hematin at 12m</td><td colspan="3">LNG-IUS: 87.4%
COC: 35.0%
p= 0.013</td></tr>
<tr><td><u>Quality</u>
-1</td><td><u>Consistency</u>
NA</td><td><u>Directness</u>
OK</td><td><u>Imprecision</u>
-1</td></tr>
<tr><td colspan="4">Grade assessment: low quality of evidence</td></tr>
<tr><td rowspan="3">Reduction in pictorial blood assessment chart (PBLAC) score</td><td colspan="3">At 6m: LNG-IUS 89.5% vs COC 41.6%
p<0.001
At 12m: LNG-IUS 89.5% vs COC 41.6%
p<0.001</td></tr>
<tr><td><u>Quality</u>
-2 (low Jadad, subjective endpoint + OL)</td><td><u>Consistency</u>
NA</td><td><u>Directness</u>
OK</td><td><u>Imprecision</u>
-1</td></tr>
<tr><td colspan="4">Grade assessment: very low quality of evidence</td></tr>
<tr><td rowspan="3">Total bleeding days per year</td><td colspan="3">LNG-IUS: 34.5d
COC: 65.1d
p<0.001, SS</td></tr>
<tr><td><u>Quality</u>
-1</td><td><u>Consistency</u>
NA</td><td><u>Directness</u>
OK</td><td><u>Imprecision</u>
-1</td></tr>
<tr><td colspan="4">Grade assessment: low quality of evidence</td></tr>
<tr><td rowspan="3">Total spotting days per year</td><td colspan="3">LNG-IUS: 20.7d
COC: 18.0d
p=0.273, NS</td></tr>
<tr><td><u>Quality</u>
-1</td><td><u>Consistency</u>
NA</td><td><u>Directness</u>
OK</td><td><u>Imprecision</u>
-1</td></tr>
<tr><td colspan="4">Grade assessment: low quality of evidence</td></tr>
</table>

Treatment failure was defined as the initiation of an alternative medical treatment or the need for surgery

- In a relatively small study, women with self-reported heavy menstrual bleeding were randomised into two groups – they received either a hormone IUD or a combination pill containing levonorgestrel – and were followed for one year. Treatment failure (defined as switching to another medical treatment or surgery) was seen statistically less often with the levonorgestrel IUD (HR = 0.30; 95 % CI 0.14 – 0.73).

GRADE: low quality of evidence

- Women with heavy menstrual bleeding experienced a greater reduction in the PBLAC score (evaluation method for menstrual blood loss) with a hormonal IUD than women taking the pill. A significant difference between both groups, in favour of the hormonal IUD, was also found with use of the standard method to measure blood loss (alkaline haematin test). (p = 0.013).

GRADE: very low to low quality of evidence

- The total number of bleeding days per year was significantly greater in the pill group than in the hormonal IUD group, but this was not the case for the total number of days with spotting.

GRADE: low quality of evidence

- No endpoints were reported in relation to adverse events and safety.

5.3. Acne

5.3.1. Acne. Combined hormonal contraception versus placebo. Evidence tables

Ref	N/n	Comparison		
Arowojolu, 2012* Design: meta-analysis Search date: Jan 2012 N= 31 n= 12579	N=2 n=721	LNG 100 µg / EE 20 µg versus placebo	Mean change in total lesion count	**Mean difference=-9.98 (95% CI -16.51, -3.45)** **SS in favor of treatment(LNG) p= 0.0027**
			Clinician assessment of women with clear or almost clear lesions at cycle 6 (4 point scale)	**145/280 (LNG) vs 119/291 (PLA)** **OR=1.56 (95% CI 1.13, 2.18)** **SS in favor of treatment (LNG) p = 0.0078**
			Participant self-assessment of acne lesion improvement	**228/281(LNG) vs 193/291 (PLA)** **OR= 2.13 (95% CI 1.47, 3.09)** **SS in favor of treatment (LNG)p = 0.000064**
			Discontinuation due to non-acne adverse event (N=1; Thiboutot)	9/174 (LNG) vs 6/176 (PLA) OR=1.54 (95% CI 0.55, 4.31) NS p = 0.42
			Discontinuation due to lack of acne improvement (N=1; Thiboutot)	7/174 (LNG) vs 8/176 (PLA) OR=0.88 (95% CI 0.31, 2.47) NS p = 0.81
	N=3 n=1068	DRSP 3 mg / EE 20 µg versus placebo (data for combined analysis were very limited)	Mean percent change in total lesion counts at cycle 6 (N=1;Bayer)	**66.79 ±31.45(DRSP) vs 37.71±118.73 (PLA)** **Mean difference= 29.08 (95% CI 3.13, 55.03)** **SS in favor of treatment p = 0.028**
			Clear or almost clear (investigator assessment) at cycle 6. (N=2; Bayer-Maloney)	**82/291(DRSP) vs 32/284 (PLA)** **OR = 3.02 (95% CI 1.99 to 4.59)** **SS in favor of treatment (DRSP) p < 0.00001**
			Participants classified (participant assessment) as 'improved' at cycle 6 (N=1;Bayer)	**75/79(DRSP) vs 62/73 (PLA)** **OR = 3.06 (95% CI 1.06 to 8.85)** **SS in favor of treatment (DRSP) p =0.039**
			Discontinuation due to adverse event (N=3)	37/625 (DRSP) vs 24/626 (PLA) OR = 1.57 (95% CI 0.94 to 2.62) NS p=0.087
			Discontinuation due to reason other than adverse event (N=1;Bayer)	8/89 (DRSP)vs 11/90 (PLA) OR = 0.71(95% CI 0.28 to 1.84) NS p=0.48

	N=1 n=387	CMA 2 mg / EE 30 µg versus placebo	Responders (>= 50% decrease in facial papules and pustules) at cycle 6	**161/251 (CMA) vs 55/126 (PLA)** **OR = 2.31 (95% CI 1.50, 3.55)** **SS in favor of treatment (CMA) p = 0.00015**
			Discontinuation due to adverse event	**14/251 CMA) vs 1/126 (PLA)** **OR = 3.49 (95% CI 1.17, 10.40)** **SS in favor of placebo p = 0.025**

* Characteristics of included studies: see under

Ref + design	n	Population	Duration	Comparison	Methodology
Leyden 2002 RCT Double blind	371	healthy women -age ≥ 14 years -regular menstrual cycles -moderate facial acne - normal or low grade abnormal Papanicolaou smear within the past 6 months, negative pregnancy test and agreement to use a non-hormonal contraceptive if at risk of pregnancy; Exclusion: women with contraindications to OCs, smoking in women over 35 years old or use of sex hormones within 6months of enrollment	6 treatment cycles	LNG 100 µg / EE 20 µg versus placebo	- Jadad score: 5/5 - FU: 66.31% (246/371) - ITT: yes, by Cochrane Other important methodological remarks: No information on allocation concealment (selection bias)
Thiboutot 2001 RCT Double-blind	350	healthy women -age ≥ 14 years -regular menstrual cycles -moderate facial acne -Washout period of 6 months for injectable hormones, 3 months for oral or implantable hormones and 2 to 6 weeks for systemic or topical acne treatment. Exclusion: women with contraindications to OCs,	6 treatment cycles.	LNG 100 µg / EE 20 µg versus placebo	- Jadad score: 5/5 - FU: 64,57%(226/350) - ITT: no Other important methodological remarks: Allocation was concealed in sealed envelopes labeled according to the randomization code. Did not specify whether envelopes were opaque

Bayer 2011 RCT Double-blind Multicenter In China	179	Healthy women, -age 14 to 45 years - >1 year post-menarche -moderate acne vulgaris Exclusion: women with contraindications to COCs, smoking in women over 30 years old pregnancy, lactation (< 3 menstrual cycles since delivery, abortion, or lactation); obesity (Body Mass Index > 30 kg/m2);hypersensitivity to ingredient of studydrug; any disease or condition that may worsen under hormonal treatment	6 treatment cycles.	DRSP 3 mg plus EE 20 µg versus a placebo	- Jadad score: 5/5 - FU: 91,06% (163/179) - ITT:no: all patients who received at least one dose of study drug were analysed Sponsor: Bayer Schering Pharma Other important methodological remarks: No information on allocation concealment (selection bias)
Koltun 2008 RCT Double-blind Multicenter	458	women, -age 14 to 45 years, -at least 1menstruation within last 3 months; -minimum of 20 inflammatory (papules or pustules) and 20 non-inflammatory (comedones) facial lesions. - negative pregnancy test and normal Pap smear and agreed not to use topical or systemic acne treatment. Exclusion: Women with contraindications for COC use; use of additional steroid hormones, heparin,warfarin, hydantoins, barbiturates, phenytoin, primidone, carbamazepine, rifampicin,griseofulvin, topiramate, felbamate, ritonavir and products containing St John's wort,spironolactone, and continuous use of antibiotics; having acne and atopy, comedonal acne or acne conglobata, sandpaper acne or acne with multiple large nodes; cysts, fistular comedones,or abscessing fistular ducts; taking medication with "acne-inducing effect."	6 treatment cycles.	DRSP 3 mg plus EE 20 µg versus a placebo	- Jadad score:5/5 - FU: 94% - ITT: no Other important methodological remarks: -No information on allocation concealment (selection bias) -Results were presented in figures without actual numbers to use in analysis, except for discontinuation

Maloney 2008 RCT Double-blind Multicenter	431	women, age 14 to 45 years (age 14 to 30 years if smoked >10 cigarettes/day, 14 to 35 years if smoked<10 cigarettes/day, and 14 to 45 years for nonsmokers) - at least 1 menstruation within last 3 months; -with minimum of 20 inflammatory (papules or pustules)and 20 non-inflammatory (comedones) facial lesions classified as grade 3, 4, or 5. -normal Pap smear in last 6 months -agreed not to use topical or systemic acne treatment. Exclusion criteria: contraindications for COC use; use of additional steroid hormones, heparin,warfarin, hydantoins, barbiturates, phenytoin, primidone, carbamazepine, rifampicin,griseofulvin, topiramate, felbamate, ritonavir and products containing St John's wort,spironolactone, and continuous use of antibiotics; having acne and atopy, comedonal acneor acne conglobata, sandpaper acne or acne with multiple large nodes; cysts, fistular comedones,or abscessing fistular ducts	6 treatment cycles.	DRSP 3 mg plus EE 20 µg versus a placebo	- Jadad score: 5/5 - FU: 95% - ITT:yes Other important methodological remarks: -No information on allocation concealment (selection bias) - This study had insufficient for analysis in this review due to presenting outcome data in figures without absolute numbers or simply describing selected results in the text
Plewig 2009 RCT Double-blind Multicenter (Europe)	387	women, -age 18 to 40 years old (smokers up to age 30) -moderate papulopustular acne of face. - instructed to use condoms -not allowed to take hormonal contraception or topical or systemic moderate acne therapy during the trial Exclusion criteria: systemic moderate acne therapy (e.g., with 'antiandrogens' or retinoids) in past 6 months; hormonal combinations containing 'antiandrogens,' norgestimate or desogestrel in past 3 months; oral antibiotic or topical moderate acne treatment in past 4 weeks	6 treatment cycles	CMA 2 mg plus EE 30 µg versus placebo	- Jadad score: 3/5 - FU: 81,91% (317/387) - ITT:: no. all patients who received at least one dose of study drug were analysed (n= 377) Study was sponsored by Grünenthal GmbH Other important methodological remarks: -No information on allocation concealment (selection bias)

5.3.1.bis. Acne. Combined hormonal contraception versus placebo. Summary and conclusions

Levonorgestrel 100µg + Ethinyl estradiol 20µg (Leyden 2002, Thiboutot 2001)
Drospirenone 3mg/d + Ethinyl estradiol 20µg (Bayer 2011, Koltun 2008, Maloney 2008)
Chlormadinone 2mg/d + Ethinyl estradiol 30µg vs placebo (Plewig 2009)
(all from Arowojolu 2012)

N/n	Duration	Population	Results				
N= 6 n= 2176	6 cycles	- healthy women - age: 14-45y - regular menstrual cycles - moderate acne vulgaris - normal Pap smear	Total lesion count (mean change, %)	Reported in 5/6 studies Mean difference=-9.98 (95% CI -16.51, -3.45) **SS in favor of treatment (LNG) p= 0.0027** (N=2) Mean difference= 29.08 (95% CI 3.13, 55.03) **SS in favor of treatment (DRSP) p= 0.028** (N=3)			
				Quality OK	Consistency OK	Directness OK	Imprecision OK
				Grade assessment: *high quality of evidence*			
			Responders (≥50% improvement acne lesions)	Reported in 1/6 studies 161/251 (CMA) vs 55/126 (PLA) OR = 2.31 (95% CI 1.50, 3.55) **SS in favor of treatment (CMA) p = 0.00015**			
				Quality -1 (low Jadad)	Consistency NA	Directness OK	Imprecision OK
				Grade assessment: NA			
			Discontinuation due to AE	Reported in 6/6 studies OR= 0.88 NS difference (LNG vs PLA) OR= 0.71 NS difference (DRSP vs PLA) OR=3.49 **SS in favor of placebo (CMA vs PLA)**			
				Quality OK	Consistency -1	Directness OK	Imprecision OK
				Grade assessment: *moderate quality of evidence*			

- We identified six placebo-controlled studies with combination pills that report acne outcomes from a 2012 Cochrane Review. Due to the differing compositions of the pills studied, no meta-analysis was conducted. The studied pills that are available on the Belgian market, were levonorgestrel 100µg + ethinyl estradiol 20 µg, drospirenone 3mg + ethinyl estradiol 20 µg and chlormadinone + ethinyl estradiol 30 µg.
All the combination pills appeared to cause an improvement in acne lesions and were at this endpoint significantly better than placebo.

GRADE: high quality of evidence

Users of the chlormadinone-containing pills discontinued their treatment significantly more due to adverse events in comparison with placebo. This was not the case for pills with levonorgestrel or drospirenone.

GRADE: moderate quality of evidence

5.3.2. Acne. Combined hormonal contraception versus combined hormonal contraception. Evidence tables.

Ref	N/n	Comparison	Outcomes	
* Arowojolu, 2012 Design: meta-analysis Search date:Jan 2012 N= 31 n= 12579	N=1 n=128	DRSP 3mg - EE30 vs CPA 2mg EE 35	Mean percentage change in total acne count at cycle 9	-37.5 ±56.2(DRSP) vs -35.0±69.9(CPA) Mean difference= -2.50 (95% CI -26.96, 21.96) NS p = 0.84
	N=1 n=424	DRSP 3mg - EE30 vs LNG 150 EE30	Discontinuation due to acne deterioration no other endpoints extractable	**4/282 (DRSP) vs 11/142 (LNG)** **OR=0.16 (95% CI 0.05, 0.47)** **SS in favor of DRSP p = 0.00088**
	N=2 n=355	DSG 25-125 µg / EE 40-30 vs CPA 2 mg / EE 35	Women with pustules or nodules at cycle 4 N=1 Dieben	33/59 (DSG) vs 31/62 (CPA) OR=1.27 (95% CI 0.62, 2.58) NS p = 0.52
			Women with moderate acne at cycle 6 N=1 Vartiainen	32/68 (DSG) vs 29/68 (CPA) OR=1.19 (95% CI 0.61, 2.34) NS p = 0.61
			Women with severe acne at cycle 6 N=1 Vartiainen	4/68 (DSG) vs 2/68 (CPA) OR=2.00 (95% CI 0.39, 10.21) NS p = 0.41
			Mean change in comedone count at cycle 4 N=1 Dieben	-10.2 ±21.5(DSG) vs -13.9±29.1(CPA) Mean difference= 3.7 (95% CI -5.39, 12.79) NS p = 0.42
			Mean comedone count at cycle 6 N=1 Vartiainen	**5.7 ±10.8(DSG) vs 2.8±5.2(CPA)** **Mean difference= 2.9 (95% CI 0.05, 5.75)** **SS in favor of CPA p = 0.046**
			Mean change in papule count at cycle 4 N=1 Dieben	-7.1 ±10.9(DSG) vs -6.5±8.9(CPA) Mean difference= -0.60 (95% CI -4.16, 2.96) NS p = 0.74
			Mean papule count at cycle 6 N=1 Vartiainen	6 ±7.9(DSG) vs 4.2±4.8(CPA) Mean difference= 1.8 (95% CI -0.40, 4.00) NS p = 0.11
			Mean change in pustule count at cycle 4 N=1 Dieben	-2.9±6.2(DSG) vs -5.2±7.5(CPA) Mean difference= 2.30 (95% CI -0.15, 4.75) NS p = 0.065
			Mean pustule count at cycle 6 N=1 Vartiainen	1.2 ±4.5(DSG) vs 0.4±1.8(CPA) Mean difference= 0.8 (95% CI -0.35, 1.95)

				NS p = 0.17
			Discontinuation due to non-acne adverse event N=1 Vartiainen	6/84 (DSG) vs 4/88 (CPA) OR=1.60 (95% CI 0.45, 5.73) NS p = 0.47
			Discontinuation due to worsening of acne N=1 Vartiainen	1/84 (DSG) vs 1/88 (CPA) OR=1.05 (95% CI 0.06, 16.90) NS p = 0.97
	N=2 n=1378	DSG 150 µg / EE 30 µg versus GSD 75 µg / EE 30 µg	Women without acne at cycle 6 (N=2; Halbe, Koetsawang)	549/619 (DSG) vs 486/561 (GSD) OR=1.17 (95% CI 0.82, 1.66) NS p = 0.38
			Women with mild acne at cycle 6 (N=2; Halbe, Koetsawang)	57/619 (DSG) vs 68/561(GSD) OR=0.76 (95% CI 0.52, 1.10) NS p = 0.14
			Women with moderate or severe acne at cycle 6 (N=2; Halbe, Koetsawang)	13/619 (DSG) vs 7/561(GSD) OR=1.78 (95% CI 0.73, 4.32) NS p = 0.20
			Discontinuation due to side effects (N=2; Halbe, Koetsawang)	**40/710 (DSG) vs 57/668 (GSD)** **OR=0.61 (95% CI 0.40, 0.93)** **SS in favor of DSG p = 0.022**
	N=1 n=199	LNG 150 µg / EE 30 µg versus CMA 2 mg / EE 30 µg	Women with >= 50% reduction in pustules and papules at cycle 12	45/98 (LNG) vs 60/101 (CMA) OR=0.58 (95% CI 0.33, 1.02) NS p = 0.057
			Women with selfassessed acne improvement at cycle 12	**61/70 (LNG) vs 78/79 (CMA)** **OR=0.16 (95% CI 0.04, 0.57)** **SS p = 0.0049**
	N=1 n=150	LNG 150 µg / EE 30 µg versus CPA 2 mg / EE 35 µg,	Mean change in total acne lesions at cycle 6	-14.1±32.4(LNG) vs -16.6±13.5(CPA) Mean difference= 2.50 (95% CI -8.81, 13.81) NS p = 0.66
			Women with dermatologist global ”good” acne assessment at cycle 6	**11/36 (LNG) vs 28/45 (CPA)** **OR=0.29 (95% CI 0.12, 0.68)** **SS p = 0.0049**
			Women with ”good” acne self-assessment at cycle 6	**11/36 (LNG) vs 30/44 (CPA)** **OR=0.23 (95% CI 0.09, 0.54)** **SS p = 0.00087**
			Discontinuation due to side effects	6/37 (LNG) vs 6/48 (CPA) OR=1.35 (95% CI 0.40, 4.60)

				NS p = 0.63
	N=1 n=1027	DSG 150 µg / EE 20 µg versus LNG 100 µg / EE 20 µg	Improvement in comedones at week 25.	**71/266 (DSG) vs 49/258(LNG)** **OR=1.55 (95% CI 1.03 to 2.32)** **SS in favor of DSG p = 0.036**
			Improvement in papules at week 25	63/266 (DSG) vs 61/258(LNG) OR =1.00 (95% CI 0.67, 1.50) NS p=0.99
			Improvement in pustules at week 25	46/266 (DSG) vs 32/258 (LNG) OR =1.47 (95% CI 0.91, 2.38) NS p = 0.12
			Scores for Psychological General Well-Being Index at week 25	3.2 ±11.5 (DSG) vs 2.1±10.9 (LNG) Mean difference= 1.10 (95% CI -0.83, 3.03) NS p = 0.26
			Adverse events related to treatment	31/500 (DSG) vs 32/498 (LNG) OR= 0.96 (95% CI 0.58, 1.60) NS p = 0.88
	N=1 n=2152	NOMAC 2.5 mg / E2 1.5 mg versus DRSP 3 mg / EE 30 µg	Clinician assessment of worsening of acne after cycle 13 (all participants)	**154/1561(NOMAC) vs 21/522 (DRSP)** **OR= 2.14 (95% CI 1.49-3.05)** **SS in favour of DRSP (more worsening with NOMAC)**
			Clinician assessment of improved acne after cycle 13 (all participants)	**248/1561 (NOMAC) vs 105/522 (DRSP)** **OR= 0.74 (95% CI 0.57-0.96)** **SS in favour of DRSP**
			Clinician assessment of worsening acne after cycle 13 (participants with acne at baseline)	**37/512 (NOMAC) vs 3/171 (DRSP)** **OR= 2.69 (95% CI 1.29-5.63)** **SS in favour of DRSP (more worsening with NOMAC)**
			Clinician assessment of improved acne after cycle 13 (participants with acne at baseline)	**248/512 (NOMAC) vs 105/171 (DRSP)** **OR= 0.60 (95% CI 0.42-0.84)** **SS in favour of DRSP**
			Discontinuation due to acne	**53/1591 (NOMAC) vs 1/535 (DRSP)** **OR= 3.56 (95% CI 1.91-6.63)** **SS in favour of DRSP**

* Characteristics of included studies: see under

Ref + design	n	Population	Duration	Comparison	Methodology (sponsor NR in Cochrane)
Van Vloten 2002 RCT Multicenter trial in The Netherlands and Germany.	128	healthy women, -age16 to 35 years -mild-to-moderate facial acne (at least 8 papulopustular lesions) and minor seborrhea or hair growth on upper lip, chin and chest. Excluded certain medical conditions, lack of least one normal menstrual cycle following recent birth, abortion or lactation, obesity, use of injectable depot contraceptives in prior 6 months, severe acne (multiple large nodes, cysts, fistular comedos or abscessing fistular ducts), anti-androgenic hormone treatment in prior 3 months or isotretinoin treatment in prior 12 months	9 treatment cycles	DRSP 3mg - EE30 vs CPA 2mg EE 35	- Jadad score: 3/5 - FU: 76.6% - ITT:no Other important methodological remarks: -No information on allocation concealment (selection bias)
Kelly 2010 RCT Double-blind	424	Healthy women, -age 16 to 40 years (up to age 35 if smoker), - established menstrual cycle and requesting contraception -healthy gynecological status by exam and cervical smear -willing to not use other hormonal treatment (except thyroxine and insulin). Exclusion criteria: contraindication to combined OC, history of herpes, obesity, concurrent treatment with preparation that induces hepatic enzymes	7 treatment cycles	DRSP 3 mg plus EE 30 µg (21 + 7 regimen) vs LNG 150 µg plus EE 30 µg	- Jadad score: : 3/5 -FU: 66% discontinuation and losses -ITT: unclear Study was funded by Bayer Schering Pharma. Other important methodological remarks: -No information on allocation concealment (selection bias) -This study had insufficient for analysis in this review due to presenting outcome data in figures without absolute numbers or simply describing selected results in the text. - population: women requiring

					contraception, (not necessarily having acne)
Dieben 1994 RCT Multicenter open trial in 4 European countries.	183	women -age18 to 35 years -with at least 5 facial acne lesions. Excluded women with contraindications to COC use	4 treatment cycles	biphasic DSG 25-125 µg / EE 40-30 vs CPA 2 mg / EE 35	- Jadad score: 2/5 - FU: 74.3% (136/183) - ITT: No Other important methodological remarks: -Randomization list was generated by sponsors. -High risk of selection bias: no allocation concealment was done (open randomization list)
Vartiainen RCT Multicenter, open trial in Belgium, Finland and the Netherlands.	172	women -aged 16 to 35 years and weighing 45 to 85 kg - with acne. Excluded women with very severe acne needing oral antimicrobial or retinoid acid, use ofeither trial medications prior to the study, concomitant use of barbiturates, anticonvulsants, griseofulvin, phenylbutazone, rifampicin, penicillin, tetracycline or anti-acne medication	6 treatment cycles	biphasic DSG 25-125 µg / EE 40-30 vs CPA 2 mg / EE 35	- Jadad score: 2/5 - FU: 79.1% (136/172) - ITT:No Other important methodological remarks: Methods of allocation concealment not described.
Halbe 1998 Open trial Multicenter Brazil	595	healthy women -fertile age -with regular ovulatory cycles. Excluded women with contraindications to oral contraceptives, breast feeding or regular use of drugs that impair the efficacy of oral contraceptives	6 treatment cycles	DSG 150 µg / EE 30 µg versus GSD 75 µg / EE 30 µg	- Jadad score: 2/5 -FU:84, 20% (501/595) -ITT:No ? Other important methodological remarks: -No information on allocation concealment (selection bias)
Koetsawang 1995 Multicenter, open trial in Thailand.	783	healthy women -fertile age (No specific age range was reported)	6 treatment cycles	DSG 150 µg / EE 30 µg versus GSD 75 µg / EE 30 µg	- Jadad score : 3/5 -FU: 86,72% (679/783) -ITT: No?

		-with regular cycles. Excluded women with contraindications to oral contraceptives, complete breast feeding or regular use of drugs that impair oral contraceptives			efficacy sur 679 Safety sur 783 Other important methodological remarks: -No information on allocation concealment (selection bias)
Worret 2001 Single-blinded (investigator) Multicenter trial in Germany	199	women -aged18 to 40 years (smokers up to 30 years) - mild to moderate acne on the face	12 treatment cycles	LNG 150 µg / EE 30 µg versus CMA 2 mg / EE 30 µg	- Jadad score:2/5 - FU:75.4% - ITT: yes by Cochrane Other important methodological remarks: -No information on allocation concealment (selection bias) - blinding unclear
Carlborg 1986 RCT Multicenter trial in Sweden. Three arms study (+ comparison with CPA 2mg/EE50)	160	healthy women -over 15 years of age -with at least 8 lesions on the face. Excluded women with contraindications to COCs	6 treatment cycles.	LNG 150 µg / EE 30 µg versus CPA 2 mg / EE 35 µg,	- Jadad score: 5/5 - FU: 78.1% (125/160) - ITT:no Other important methodological remarks: -Randomization by manufacturer. -No information on allocation concealment.
Winkler 2004 Open-label, randomized controlled trial	1027	Women with good physical and mental condition -age 18 to 45 years, -sexually active, -with body mass index from 18 to 29 kg/m2. Exclusion criteria: menstrual cycle < 24 days or > 35 days, being older than 35 years and smoking, taking concomitant medications or addictive drugs, or having a mental or psychiatric disorder or depression that might interfere with the trial, using OCs, IUD.	6 treatment cycles	DSG 150 µg / EE 20 µg versus LNG 100 µg / EE 20 µg	- Jadad score:2/5 -FU: 47,5%* -ITT: No Other important methodological remarks: -Report had limited data for analysis *"Losses were 22%inDSGGroup and 25%for LNG group according to the report. However, change data for the main outcomes indicated losses of 47% and 48%, respectively"

		Also excluded were those who had contraceptive implant within past month or injectable contraceptive within past 6 months			--No information on allocation concealment. - population of women requiring contraception, not necessarily having acne
Mansour 2011 RCT, open label	2152	Inclusion - 18-50y women at risk for pregnancy and in need of contraception - BMI 17-35 Exclusion - Contraindications for contraceptive steroids - Abnormal cervical smear - Abnormal laboratory tests - Injectable hormonal contraceptive in past 4-6m Use of enzyme-inducing or inhibiting drugs	13 cycles	NOMAC 2.5mg / E2 1.5mg vs DRSP 3 mg / EE 30 µg	- Jadad score: 3/5 - FU: 99% received treatment (n=2126), 74% completed treatment (n=1552) - ITT: no Other important methodological remarks: - population: women requiring contraception, not necessarily having acne

Follow up defined as excluded, discontinued early or lost to follow up

Combined oral contraceptives for Acne. Author's Conclusions

COCs containing CMA or CPA seem to improve acne better than LNG; however, this finding is based on limited evidence. A DRSP-COC may be more effective than NGM or NOMAC/E2 but the trials used different methods to assess acne severity assessments. Comparisons between other COCs were either conflicting or showed no significant difference in their ability to reduce acne.How COCs compare to alternative acne treatments is unknown since only one trial addressed this issue.

5.3.2.bis. Acne. Combined hormonal contraception versus combined hormonal contraception. Summary and conclusions

Drospirenone 3mg/d + Ethinyl estradiol 30µg vs Cyproterone 2mg + Ethinyl estradiol 35µg (Van Vloten 2002)
Drospirenone 3mg/d + Ethinyl estradiol 30µg vs Levonorgestrel 150µg + Ethinyl estradiol 30µg (Kelly 2010)
Desogestrel 25-125µg + Ethinyl estradiol 20-30µg vs Cyproterone 2mg (CPA) + Ethinyl estradiol 35µg (Dieben 1994, Vartiainen 2001)
Desogestrel 150µg + Ethinyl estradiol 30µg vs Gestodene 75µg + Ethinyl estradiol 30µg (Halbe 1998, Koetsawang 1995, Mango 1996)
Levonorgestrel 150µg + Ethinyl estradiol 30µg vs Chlormadinone 2mg/d + Ethinyl estradiol 30µg (Worret 2001)
Levonorgestrel 150µg + Ethinyl estradiol 30µg vs Cyproterone 2mg + Ethinyl estradiol 35µg (Carlborg 1986)
Desogestrel 150µg + Ethinyl estradiol 30µg vs Levonorgestrel 100µg + Ethinyl estradiol 20µg (Winkler 2004)
Nomegestrol acetate 2.5mg + E2 1.5 mg vs Drospirenone 3mg/d + Ethinyl estradiol 30µg (Mansour 2011)
(all from Arowojolu 2012)

N/n	Duration	Results					
N= 10 n= 5823	6-13 cycles **Population** - healthy women - age: 14-45y - regular menstrual cycles - mostly women with (moderate) acne vulgaris - normal Pap smear	DRSP 3mg + EE 30 vs CPA 2mg + EE 35 N=1 (Van Vloten 2002)	Mean percentage change in total acne count at cycle 9	Mean difference= -2.50 (95% CI -26.96, 21.96) NS p = 0.84			
				Quality -1 (low Jadad)	Consistency OK	Directness OK	Imprecision -1 (small trial)
				Grade assessment: *low quality of evidence*			
		DRSP 3mg + EE30 vs LNG 150µg + EE 30 N=1 (Kelly 2010)	Discontinuation due to acne deterioration	4/282 (DRSP) vs 11/142 (LNG) **OR=0.16 (95% CI 0.05, 0.47)** **SS in favor of DRSP p = 0.00088**			
				Quality -1 (low FU, ITT?)	Consistency OK	Directness -1	Imprecision OK
				Grade assessment: *low quality of evidence*			
		DSG 25-125 µg / EE 40-30 vs CPA 2 mg / EE 35 N=2 a. Dieben 1994 b. Vartiainen 2001	Women with moderate acne at cycle 6	N=1 (b) OR=1.19 (95% CI 0.61, 2.34) NS p = 0.61			
			Women with severe acne at cycle 6	N=1 (b) OR=2.00 (95% CI 0.39, 10.21) NS p = 0.41			
			Discontinuation (non-acne adverse event)	N=1 (b) OR=1.60 (95% CI 0.45, 5.73) NS p = 0.47			
			Discontinuation (worsening of acne)	N=1 (b) OR=1.05 (95% CI 0.06, 16.90) NS p = 0.97			
				Quality -1 (low Jadad, no ITT)	Consistency OK	Directness OK	Imprecision -1(wide CI)
				Grade assessment: *moderate quality of evidence*			
		DSG 150µg + EE 30 vs GSD 75µg + EE 30 µg N=3 a. Halbe 1998 b. Koetsawang 1995 c. Mango 1996 (too small)	Women without acne at cycle 6	(N=2: a, b) OR=1.17 (95% CI 0.82, 1.66) NS p = 0.38			
			Women with moderate or severe acne at cycle 6	(N=2: a,b) OR=1.78 (95% CI 0.73, 4.32) NS p = 0.20			
			Discontinuation (side effects)	(N=2: a, b) **OR=0.61 (95% CI 0.40, 0.93)** **SS in favor of DSG p = 0.022**			
				Quality -1 (no ITT)	Consistency OK	Directness OK	Imprecision OK

				Grade assessment: *moderate quality of evidence*			
		LNG 150 µg / EE 30 vs CMA 2 mg / EE 30 µg N=1 (Worret 2001)	≥50% reduction pustules and papules cycle 12	OR=0.58 (95% CI 0.33, 1.02) NS p = 0.057			
			self assessed acne improve-ment at cycle 12	**OR=0.16 (95% CI 0.04, 0.57) SS in favor of CMA p = 0.0049**			
				Quality -1 (low Jadad, (single)blinding unclear)	Consistency OK	Directness OK	Imprecision OK
				Grade assessment: *moderate quality of evidence*			
		LNG 150 µg / EE 30 µg vs CPA 2 mg / EE 35 µg N=1 (Carlborg 1986)	Mean change in total acne lesions (cycle 6)	Mean difference= 2.50 (95% CI -8.81, 13.81) NS p = 0.66			
			Women with dermatologist ”good” acne assessment (cycle 6)	**OR=0.29 (95% CI 0.12, 0.68) SS in favor of CPA p = 0.0049**			
			Women with ”good” acne self-assessment (cycle 6)	**OR=0.23 (95% CI 0.09, 0.54) SS in favor of CPA p = 0.00087**			
			Discontinuation due to side effects	OR=1.35 (95% CI 0.40, 4.60) NS p = 0.63			
				Quality -1 (low FU, no ITT)	Consistency OK	Directness OK	Imprecision -1 (small trial)
				Grade assessment: *low quality of evidence*			
		DSG 150 µg / EE 20 µg vs LNG 100 µg / EE 20 µg N=1 (Winkler 2004)	Improvement comedones week 25	**OR=1.55 (95% CI 1.03 to 2.32) SS in favor of DSG p = 0.036**			
			Improvement in papules / pustules week 25	OR =1.00 (95% CI 0.67, 1.50) NS p=0.99 / OR =1.47 (95% CI 0.91, 2.38) NS p = 0.12			
			Adverse events related to treatment	OR= 0.96 (95% CI 0.58, 1.60) NS p = 0.88			
				Quality -1 (low FU, no ITT)	Consistency OK	Directness OK	Imprecision OK
				Grade assessment: *moderate quality of evidence*			
		NOMAC 2.5 mg / E2 1.5 mg versus DRSP 3 mg / EE 30 µg N=1 (Mansour 2011)	Clinician assessment of worsening acne after cycle 13 (participants with acne at baseline)	**37/512 (NOMAC) vs 3/171 (DRSP) OR= 2.69 (95% CI 1.29-5.63) SS in favour of DRSP (more worsening with NOMAC)**			
			Clinician assessment of improved acne after cycle 13 (participants with	**248/512 (NOMAC) vs 105/171 (DRSP) OR= 0.60 (95% CI 0.42-0.84) SS in favour of DRSP**			

			acne at baseline)				
			Discontinuation due to acne	**53/1591 (NOMAC) vs 1/535 (DRSP)** **OR= 3.56 (95% CI 1.91-6.63)** **SS in favour of DRSP**			
				Quality -1 (OL, early dropout high)	Consistency OK	Directness OK	Imprecision OK
				Grade assessment: *moderate quality of evidence*			

- We selected 11 studies from a 2012 Cochrane Review that compared various combination pills with regard to acne outcomes, although no standard method exists to assess acne severity. Because of the different compositions of the pills studied, no meta-analysis was conducted. The studies contraceptive pills that are commercialised in Belgium are drospirenone 3 mg + ethinyl estradiol 30 µg, chlormadinone 2 mg + ethinyl estradiol 30µg, levonorgestrel 100 or 150 µg + ethinyl estradiol 20 or 30 µg, desogestrel 25-125 µg + ethinyl estradiol 30-40 µg, cyproterone 2 mg + ethinyl estradiol 35 µg and gestodene 75 µg + ethinyl estradiol 30 µg, nomegestrol acetate 2.5mg + 17β-estradiol 1.5mg.

We discuss the results per comparison.

- DRSP 3 mg + EE 30 µg versus CPA 2 mg + EE 35 µg: no significant difference in acne lesions
GRADE: low quality of evidence

- DRSP 3mg + EE 30 µg versus LNG 150 µg + EE 30 µg: significant difference in discontinuation of the pill due to acne deterioration, in favour of drospirenone. The population involved women with or without acne.
GRADE: low quality of evidence

- DSG 25-125 µg + EE 30-40 µg versus CPA 2 mg + EE 35 µg: no significant difference in acne development.
GRADE: low quality of evidence

- DSG 150 µg + EE 30 µg versus GSD 75 µg + EE 30 µg: no significant difference in acne lesions, but a significant difference in discontinuation of treatment due to adverse events, in favour of desogestrel.
GRADE: moderate quality of evidence

- LNG 150 µg + EE 30 µg versus CMA 2 mg + EE 30 µg: no significant difference in the number of papules and pustules, but a significant difference in self-reporting of improvement in acne in favour of chlormadinone.
GRADE: moderate quality of evidence

- LNG 150 µg + EE 30 µg versus CPA 2 mg + EE 35 µg: no significant difference in acne lesions or discontinuation of treatment due to adverse events, but a significant difference in the assessment of both the dermatologists and the patients themselves in favour of cyproterone.
GRADE: low quality of evidence

- DSG 150 µg + EE 20 µg versus LNG 100 µg + EE 20 µg: no significant difference in the number of papules and pustules, but a significant difference in the number of comedones in favour of desogestrel; no difference in undesirable effects.
GRADE: moderate quality of evidence

- NOMAC 2.5 mg/E2 1.5 mg versus DRSP 3 mg/EE 30 µg: significantly more acne deterioration with NOMAC and more acne improvement with DRSP, as assessed by a clinician after 13 cycles. There was also significantly more discontinuation of NOMAC due to acne in comparison with DRSP.
GRADE: moderate quality of evidence

It is difficult to compare the various oral contraceptive pills with each other due to their different compositions. Moreover, the amount of data is limited for each comparison and the quality of evidence is rather low. The authors of the Cochrane systematic review conclude that in the available studies, few major and consistent differences are found between the various COCs.

COCs with chlormadinone or cyproterone acetate appear to improve acne more than pills containing levonorgestrel, although not for all endpoints: only on the basis of patient self-reporting and assessment of the clinician. The level of evidence is low.
The combination pill with drospirenone appears to be more efficacious than nomegestrol acetate and 17β-estradiol at all endpoints.

5.4. Functional ovarian cysts

5.4.1. Functional ovarian cysts. Combined hormonal contraceptives versus expectant management. Evidence tables

Ref	N/n	Comparison	Outcomes	Result
Grimes 2011 cysts Design: SR + MA Search date: June 2011	N= 1 n= 141	Desogestrel 150 µg + ethinyl estradiol 20 µg Vs. Expectant management	Resolution of cyst by six months	51/67 vs. 62/74 OR=0.62 (0.27 – 1.42), NS

* Characteristics of included studies: see below

Ref + design	n	Population	Duration	Comparison	Methodology (sponsor NR in Cochrane)
Bayar 2005 RCT, blinding not reported	141	premenopausal women in Turkey, < 50 years old, with low serum CA-125 antigen and ovarian cyst detected by transvaginal ultrasonography in the first 5 days of the menstrual cycle. No exclusion criteria were reported	24 m	Desogestrel 150 µg + ethinyl estradiol 20 µg Vs. Expectant management	- Jadad score:2/5 - FU: 100% - ITT: yes

This systematic review also included 4 small studies (n=257) that compared other COC (Desogestrel 150µg +EE 30µg, Triphasic LNG = EE 30-40µg, Levonorgestrel 100 + EE 20µg, Levonorgestrel 150µg + EE 30µg) with expectant management for functional ovarian cysts. Study duration was 2-3 months. Resolution of cysts by the end of the trial was not significantly different to placebo in all trials.

Authors' conclusions
Although widely used for treating functional ovarian cysts, combined oral contraceptives appear to be of no benefit. Watchful waiting for two or three cycles is appropriate. Should cysts persist, surgical management is often indicated.

5.4.1.bis. Functional ovarian cysts. Combined hormonal contraceptives versus expectant management. Summary and conclusions

<table>
<tr><td colspan="6">Desogestrel 150µg + Ethinyl estradiol 20µg vs expectant management (Bayar 2005 from Grimes 2011)</td></tr>
<tr><td>N/n</td><td>Duration</td><td>Population</td><td colspan="3">Results</td></tr>
<tr><td rowspan="3">N=1,
n= 141</td><td rowspan="3">24m</td><td rowspan="3">- Pre-menopausal Turkish women
- Age <50y
- low serum CA-125 antigen
- Ovarian cyst detected by transvaginal US in first 5d of cycle</td><td rowspan="3">Resolution of cyst by 6m</td><td colspan="3">51/67 vs. 62/74
OR=0.62 (0.27 – 1.42), NS</td></tr>
<tr><td><u>Quality</u>
-1 (low Jadad)</td><td><u>Consistency</u>
NA</td><td><u>Directness</u>
-1 (specific population)</td><td><u>Imprecision</u>
OK</td></tr>
<tr><td colspan="4">Grade assessment: low quality of evidence</td></tr>
</table>

-A Cochrane systematic review compared a treatment with the combination pill to “watchful waiting” in women with a functional ovarian cyst discovered using ultrasound.
From this review, we selected 1 randomised study of 141 Turkish pre-menopausal women with a functional ovarian cyst (Bayar 2005), where six months of treatment with desogestrel 150 µg + EE 20 µg was compared to watchful waiting. There appeared to be no significant difference between both methods of treatment.

This Cochrane review included another 4 studies that compared a combination pill to an expectative approach in women with a functional cyst. These studies were small and brief (2 – 3 months). None of the comparisons revealed a significant difference compared to a placebo.

GRADE: low quality of evidence

5.5. Premenstrual syndrome

5.5.1. Premenstrual syndrome. Combined hormonal contraception versus combined hormonal contraception. Evidence tables

Ref	N/n	Comparison	Outcomes	Result
Lopez 2012 Design: MA of RCT's Search date: 20 Dec 2011:	N= 1 n= 900	Drospirenone 3 mg plus EE 30 µg (DRSP/EE30) versus desogestrel 150 µg plus EE 30 µg (DSG150/EE30)	Premenstrual symptoms reported during 26 cycles.	OR=0.87 (0.63 – 1.22), NS
			Adverse events: Nausea Headache Breast pain Abdominal pain Acne Depression migraine AE related to treatment Total adverse events	 OR=1.33 (0.69 – 2.58), NS OR=0.78 (0.52 – 1.17), NS OR=1.34 (0.87 – 2.05), NS OR=0.75 (0.35 – 1.59), NS OR=0.51 (0.18 – 1.42), NS OR=1.51 (0.43 – 5.24), NS OR=1.01 (0.40 – 2.56), NS OR=1.02 (0.78 – 1.33), NS OR=0.81 (0.60 – 1.11), NS
			Spotting, cycles 2 to 26	Per woman (n=887): OR=0.92 (0.67 – 1.26), NS Per cycle (n=16.951): OR=0.98 (0.87 – 1.11), NS
			Breakthrough bleeding, cycles 2 to 26.	Per woman (n=887): OR=1.01 (0.43 – 2.35), NS Per cycle (n=16.951): OR=1.14 (0.69 – 1.91), NS

* Characteristics of included studies: see below

Ref + design	n	Population	Duration	Comparison	Methodology
Foidart 2000 OL PG RCT	900	healthy women attending outpatient clinics for contraception counseling. Inclusion criteria: 18 to 35 years (30 y for smokers), willingness to not use other hormones or contraceptive methods (other than condoms to prevent sexually transmitted diseases) and to have regular medical checks and self-checks. Both new users and switchers from other OCs were allowed, as long as the women had not used OCs with drospirenone or desogestrel. Exclusion criteria: liver, vascular, or metabolic disease; obesity; genital infection; use of preparations known to affect hepatic enzyme activity, diuretics, or preparations for treating PMS	26 treatment cycles	Drospirenone 3 mg plus ethinyl estradiol (EE) 30 µg (N=450) versus desogestrel 150 µg plus EE 30 µg (N=450). Regimen included 21 days of active pills followed by 7 tablet free days. No wash-out period was used for participants switching from other OCs	- Jadad score: 2/5 - FU: 71% - ITT: modified ITT (included only women who received at least one dose of study drug)

Authors' conclusions

Drospirenone 3 mg plus ethinyl estradiol 20 µg may help treat premenstrual symptoms in women with severe symptoms, that is, premenstrual dysphoric disorder. The placebo also had a large effect. We do not know whether the combined oral contraceptive works after three cycles, helps women with less severe symptoms, or is better than other oral contraceptives. Larger and longer trials of higher quality are needed to address these issues. Trials should follow CONSORT guidelines.

5.5.1.bis. Premenstrual syndrome. Combined hormonal contraception versus combined hormonal contraception. Summary and conclusions

<table>
<tr><td colspan="6">Drospirenone 3mg/Ethinylestradiol 30µg vs Desogestrel 150µg/Ethinylestradiol 30µg (Foidart 2000 from Lopez 2012)</td></tr>
<tr><td>N/n</td><td>Duration</td><td>Population</td><td colspan="3">Results</td></tr>
<tr><td rowspan="5">N=1
N=900</td><td rowspan="5">26 cycles</td><td rowspan="5">Healthy women
Age: 18-35y</td><td rowspan="2">Premenstrual symptoms</td><td colspan="3">OR=0.87 (0.63-1.22), NS</td></tr>
<tr><td><u>Quality</u>
-1 (low Jadad)</td><td><u>Consistency</u>
NA</td><td><u>Directness</u>
-1 (healthy women)</td><td><u>Imprecision</u>
OK</td></tr>
<tr><td colspan="4">Grade assessment: low quality of evidence</td></tr>
<tr><td rowspan="3">Adverse events</td><td colspan="4">Nausea: OR=1.33 (0.69-2.58), NS
Headache: OR=0.78 (0.52-1.17), NS
Breast pain: OR=1.34 (0.87-2.05), NS
Breakthrough bleeding: OR=1.14 (0.69-1.91), NS
Total AEs related to drug: OR=1.02 (0.78-1.33), NS</td></tr>
<tr><td><u>Quality</u>
-1 (low Jadad)</td><td><u>Consistency</u>
NA</td><td><u>Directness</u>
OK</td><td><u>Imprecision</u>
OK</td></tr>
<tr><td colspan="4">Grade assessment: moderate quality of evidence</td></tr>
</table>

- A Cochrane systematic review by Lopez examined the effect of oral hormonal contraception with drospirenone on pre-menstrual syndrome.

We selected 1 study from this review that compared drospirenone 3 mg / ethinyl estradiol 30 µg with desogestrel 150 µg / ethinyl estradiol 30 µg in healthy women.

- In healthy women, there was no significant difference in pre-menstrual symptoms between the drospirenone combination pill and the desogestrel combination pill. There was also no significant difference in adverse events.

GRADE: *low to moderate quality of evidence*

This Cochrane review also reported on three short (3 cycles) placebo-controlled studies of women diagnosed with PMDD (pre-menstrual dysphoric disorder). (Yonkers 2005, Pearlstein 2005, Freeman 2001)

- The results were not clear. Drospirenone 3 mg with 20 µg ethanyl estradiol demonstrated a significant difference in the number of patients that responded well to the treatment (fewer PMDD symptoms) (Yonkers 2005, Pearlstein 2005 from Lopez 2012). A smaller study found no difference with Drospirenone 3 mg and 30 µg ethanyl estradiol versus placebo (Freeman 2001 from Lopez 2012).

The studies used different endpoints with regards to pre-menstrual symptoms, which made it difficult to compare the studies.

More studies, with a longer duration, are necessary in order to evaluate the efficacy of the combination pill on pre-menstrual syndrome.

5.6. Endometriosis

5.6.1. Endometriosis. Postoperative continuous combined oral contraceptives versus placebo. Evidence tables

Ref	n/Population	Duration	Comparison	Outcomes				Methodological
Sesti 2007 Design: DB PG RCT	n= 234 mean age: 29y – 31y <u>Inclusion</u> women who underwent conservative pelvic surgery for symptomatic endometriosis stage III–IV reproductive age, (=< 40 years); symptoms related to endometriosis; laparoscopic or laparotomic diagnosis of severe endometriosis stage III–IV; pregnancy wish; nulliparity. <u>Exclusion</u> gastrointestinal and urologic diseases that might cause painful pelvic symptoms; a diagnosis of concomitant neoplastic diseases or current or chronic pelvic inflammatory disease; previous surgical treatment for	6 months treatment +follow-up at 12 months	Postoperative treatment of Placebo (n=115) Vs GnRH-a (tryptorelin or leuprorelin every 28 days, n=42) Vs Continuous estroprogestin (n=40) Vs Dietary therapy (vitamins, mineral salts, lactic ferments, fish oil, n=37)	Efficacy				- Jadad score ○ RANDO: 2/2 ○ BLINDING: 1/2 ○ ATTRITION:1 /1 - FU: 95% - ITT: no - Methodological remarks: no primary outcome selected - 1 center in Rome, Italy - Sponsor: not reported
				dysmenorrhoea (VAS 0-10)		Baseline	12m	
					Placebo:	7.9	6.4	
					GnRH-a:	7.7	5.9	
					Estroprogestin:	8.2	5.5	
					Dietary therapy:	8.1	6.4	
					estroprogestin better than placebo (p<0.001)			
				Nonmenstrual pelvic pain (VAS 0-10)		Baseline	12m	
					Placebo:	8.0	6.2	
					GnRH-a:	8.4	5.0	
					Estroprogestin:	8.5	5.0	
					Dietary therapy:	8.5	4.7	
					estroprogestin better than placebo (p<0.001)			
				Deep dyspareunia (VAS 0-10)		Baseline	12m	
					Placebo:	6.8	4.8	
					GnRH-a:	6.9	4.3	
					Estroprogestin:	6.8	4.5	
					Dietary therapy:	7.2	5.0	
					estroprogestin better than placebo (p<0.001)			
				Quality of life (SF36)	Graphical presentation of results “increase of scores for all domains of SF-36 was observed in all women at 12 months’ follow-up, independently by the treatment randomly assigned” NT			

	endometriosis; contraindications to estrogens and progestins.			Safety		
					“The women who received continuous low-dose oral contraceptive reported spotting, bloating, weight gain, and headache, but these side effects were generally well tolerated.” No details reported	

5.6.1.bis. Endometriosis. Postoperative continuous combined oral contraceptives versus placebo. Summary and conclusions

<table>
<tr><td colspan="6">Postoperative continuous combined oral contraceptive (COC) vs placebo (Sesti 2007)</td></tr>
<tr><td>N/n</td><td>Duration</td><td>Population</td><td colspan="3">Results</td></tr>
<tr><td rowspan="13">N=1,
n= 145 in two treatment arms</td><td rowspan="13">12m (=6m treatment + 6m follow-up)</td><td rowspan="13">- Nulliparous women who underwent conservative pelvic surgery for symptomatic endometriosis stage III-IV

- Age: ≤40y (mean 30y)</td><td rowspan="4">Dysmenorrhea (VAS 0-10)</td><td colspan="3">Baseline: COC 8.2 vs pla 7.9
At 12m: COC 5.5 vs pla 6.4
P<0.001, SS in favour of COC</td></tr>
<tr><td><u>Quality</u>
OK</td><td><u>Consistency</u>
NA</td><td><u>Directness</u>
OK</td><td><u>Imprecision</u>
-1 (small study)</td></tr>
<tr><td colspan="4">Grade assessment: moderate quality of evidence</td></tr>
<tr><td rowspan="4">Non-menstrual pelvic pain (VAS 0-10)</td><td colspan="3">Baseline: COC 8.5 vs pla 8.0
At 12m: COC 5.0 vs pla 8.5
P<0.001, SS in favour of COC</td></tr>
<tr><td><u>Quality</u>
OK</td><td><u>Consistency</u>
NA</td><td><u>Directness</u>
OK</td><td><u>Imprecision</u>
-1</td></tr>
<tr><td colspan="4">Grade assessment: moderate quality of evidence</td></tr>
<tr><td rowspan="4">Deep dyspareunia (VAS 0-10)</td><td colspan="3">Baseline: COC 6.8 vs pla 6.8
At 12m: COC 4.5 vs pla 4.8
P<0.001, SS in favour of COC</td></tr>
<tr><td><u>Quality</u>
OK</td><td><u>Consistency</u>
NA</td><td><u>Directness</u>
OK</td><td><u>Imprecision</u>
-1</td></tr>
<tr><td colspan="4">Grade assessment: moderate quality of evidence</td></tr>
<tr><td rowspan="2">Quality of life</td><td colspan="3">Graphical representation of results
“Increase of scores for all domains of SF-36 questionnaire in all women at 12 months’ follow-up.”
NT</td></tr>
<tr><td colspan="4">Grade assessment: NA (not applicable)</td></tr>
<tr><td>Safety</td><td colspan="3">No details reported:
Spotting, bloating, weight gain, headache,…
“Side effects were well tolerated.”</td></tr>
</table>

- An RCT of 145 women who underwent surgery due to severe endometriosis compared the continuous administration for six months of the combination pill with placebo and then followed these women for a further six months.
The continuous administration of an combined oral contraceptive scored significantly better than the placebo for the endpoints dysmenorrhoea, non-menstrual pelvic pain and deep dyspareunia.

GRADE: moderate quality of evidence

- A graphical representation shows that all women had an improved quality of life after one year, measured using the SF-36 questionnaire, although this was not subjected to statistical testing.

GRADE: NA (not applicable)

- The adverse events were not reported in detail.

5.6.2. Endometrioma. Postoperative cyclical combined oral contraceptives versus continuous combined oral contraceptives versus placebo or no treatment. Evidence tables

Ref	n/Population	Duration	Comparison	Outcomes		Methodological
Sesti 2009 Design: SB PG RCT	n= 259 mean age:29y - 31y <u>Inclusion</u> women who underwent laparoscopic unilateral/ bilateral cystectomy for endometrioma reproductive age (<=40y); moderate to severe endometriosis-related pain symptoms; laparoscopic diagnosis of endometrioma; first laparoscopic surgery for endometriosis, complete excision of all evident ovarian and peritoneal disease; ultrasonographic and clinical follow-up after surgery. <u>Exclusion</u> Patients who received 6 months estrogen-suppressing drugs before first surgery; contra-indicationsto estrogens and progestins; previous surgical treatment for endometriosis; surgical findings of concomitant deeply infiltranting endometriosis	18 months after surgery	Postoperative treatment of placebo (n=65) Vs. GnRH-a (trytorelin or leuprorelin, n=65) Vs. continuous low-dose monophasic oral contraceptive (n=64) Vs. dietary therapy (vitamins, minerals salts, lactic ferments, fish oil)(n=65) The nature of placebo was sodium phosphate, administered as intramuscular injections or as oral tablets	Efficacy		- Jadad score ○ RANDO: 2/2 ○ BLINDING: 1/2 ○ ATTRITION: 1/1 - FU: 93% - ITT: no - 1 center in Rome, Italy - Sponsor: not reported
				Recurrence of endometrioma (PO)	Placebo: 16.6% GnRH-a: 10.3% Estroprogestin: 15.0% Dietary therapy: 17.8% Placebo vs GnRH-a: p=0.316, NS Placebo vs estroprogestin: p=0.803, NS Placebo vs dietary therapy: p=0.544, NS	
				Reoperation	Placebo: 30.0% GnRH-a: 33.3% Estroprogestin: 44.4% Dietary therapy: 36.7% NT	
				Safety		
				No of women that withdrew due to side effects	Total: n=11 GnRH-a: n=7 (hot flushes, vaginal dryness, reduced libido Oral contraceptives: n=4 (breakthrough bleeding, headache, breast tension, nausea, weight gain. NT	

Ref	n/Population	Duration	Comparison	Outcomes		Methodological
Seracchioli 2010a Design: OL PG RCT	n= 239 mean age: 29-30y <u>Inclusion</u> women who underwent laparoscopic excision for symptomatic ovarian endometrioma Nulliparous 20 -40 y, not attempting to conceive either at the time of study entry or for at least 2 years after surgery <u>Exclusion</u> Patients having contraindications to OC therapy, unwillingness to tolerate the absence of menstruation, or lack of the desire to postpone pregnancy for at least 2 years after surgery	24 months	Postoperative treatment: No use (n=79) vs Cyclic use (21/28 days) of low dose monophasic combined OC (ethynil E2, 0.020 mg, and gestodene, 0.075 mg daily)(n=81) vs continuous use of low dose monophasic combined OC (ethynil E2, 0.020 mg, and gestodene, 0.075 mg daily) (n=79)	Efficacy		- Jadad score ○ RANDO: 2/2 ○ BLINDING: 0/2 ○ ATTRITION: 0/1 - FU: 91% - ITT: no - Methodological remarks: no primary outcome selected; no information on clinical symptoms - 1 center in Bologna, Italy - Sponsor: not reported
				Endometrioma recurrence rate	No use: 29% Cyclic use: 15% Continuous use: 8% p=0.003	
				Recurrence-free survival	Graphical presentation Kaplan-Meyer survival analysis demonstrated a significant difference in recurrence-free survival between nonusers versus cyclic and continuous users, respectively (cyclic users: p=0.012; continuous users: p=0.006) for the whole follow-up. However, no significant differences were detected between cyclic and continuous users (p=0.21) for the whole follow-up	
				Safety		
				Study withdrawal	Ten nonusers (12.6 %) did not complete the study because four of them achieved a spontaneous pregnancy before 24 months of the control period and six started to receive OCP therapy because of dysmenorrhea. Six patients (7.4 %) among the cyclic users did not complete the treatment period: two of them for causes unrelated to endometriosis recurrence and four for side effects attributable to OC therapy. Six women (7.6%) among the continuous users did not complete the treatment period: two of them for causes unrelated to endometriosis recurrence and four for side effects attributable to OC therapy. NT	

Ref	n/Population	Duration	Comparison	Outcomes		Methodological
Seracchioli 2010b Design: OL PG RCT	n= 311 mean age: 28.7 – 30.2y <u>Inclusion</u> women who underwent laparoscopic excision for symptomatic ovarian endometrioma Nulliparous 20 – 40y, not attempting to conceive either at the time of study entry or for at least 2 years after surgery; ultrasonographic diagnosis of ovarian endometrioma and reported symptoms related to endometriosis, <u>Exclusion</u> Patients having contraindications to OC therapy, or lack of desire to postpone pregnancy for at least 2 years after surgery;	24 months	Postoperative treatment: No use Vs. Continuous low-dose monophasic combined OC (ethinyl E2, 0.020 mg and gestodene, 0.075 mg daily) Vs. cyclic (21 days followed by a 7 day pill free period) low-dose monophasic combined OC (ethinyl E2, 0.020 mg and gestodene, 0.075 mg daily)			- Jadad score o RANDO: 2/2 o BLINDING: 0/2 o ATTRITION: 1/1 - FU: 88% - ITT: no - Methodological remarks: no primary outcome selected - Multicenter:1 center in Italy - Sponsor: not reported
				Dysmenorrhea (10 point VAS)	Graphical presentation of results The VAS scores for dysmenorrhea reported by continuous users were significantly lower than the scores reported by cyclic and nonusers for the entire study period (p<0.0005). At 12, 18, and 24 months postoperatively, cyclic users reported significantly lower VAS scores for dysmenorrhea than nonusers (p=0.017, p=0.001, p<0.0005, respectively)< Nonusers show a significant worsening in pain intensity from 6–24 months.	
				Dysmenorrhea recurrence rate	Graphical presentation of results Lower in continuous users for the entire study periode (p<0.0005); lower in cyclic users versus nonusers at 18 (p=0.01) and 24 months (p=0.009) The Kaplan-Meier survival analysis demonstrated a significant difference among the three groups about the first occurrence of moderate-to-severe dysmenorrhea: the cumulative pain-free survival was significantly higher in continuous users versus cyclic users (P<.0005) and in cyclic users versus nonusers with an evident difference after 18 months postoperatively (P=0.01)	
				Dyspareunia (10 point VAS)	Graphical presentation of results The VAS scores for dyspareunia reported at 6, 12, and 24 months postoperatively did not significantly differ among continuous, cyclic, and nonusers, whereas at 18 months after the surgical intervention, continuous users showed a lower VAS score than nonusers (p=0.04)	
				Dyspareunia recurrence rate	Graphical presentation of results No significant difference among the study groups	

	gastrointestinal or urologic diseases or the diagnosis of current pelvic inflammatory disease, which might cause painful pelvic symptoms not related to endometriosis				TheKaplan-Meier survival analysis demonstrated no significant differences in terms of cumulative pain-free survival for dyspareunia among the three groups.	
				Chronic pelvic pain (10 point VAS)	Graphical presentation of results The VAS scores for chronic pelvic pain did not significantly differ among the three groups for the entire study period.	
				Chronic pelvic pain recurrence rate	Graphical presentation of results No significant difference among the study groups TheKaplan-Meier survival analysis demonstrated no significant differences in terms of cumulative pain-free survival for chronic pelvic pain among the three groups.	
				Safety		
				Study withdrawal	Seventeen patients of the nonusers (16.3 %) did not complete the study because 7 achieved a spontaneous pregnancy before 24 months of the control period and 10 started OC pill therapy because of dysmenorrhea. Eleven patients (10.6 %) among the cyclic users did not complete the treatment period: three for causes unrelated to endometriosis recurrence and eight for side effects attributable to OC therapy. Nine women (8.6%) among the continuous users did not complete the treatment period: three for causes unrelated to endometriosis recurrence and six for side effects attributable to OC therapy.	

* It is unclear whether the populations of Seracchioli 2010a and 2010b are different or if there is an overlap

5.6.2.bis. Endometrioma. Postoperative cyclical combined oral contraceptives versus continuous combined oral contraceptives versus placebo or no treatment. Summary and conclusions

<table>
<tr><td colspan="5">Postoperative Cyclic COC vs Continuous COC vs placebo/no therapy (Sesti 2009, Seracchioli 2010a and 2010b*)</td></tr>
<tr><td>N/n</td><td>Duration</td><td>Population</td><td colspan="2">Results</td></tr>
<tr><td rowspan="18">Recurrence
N=2,
n= 368

Pain
N=1
n= 311</td><td rowspan="18">Sesti 2009 treatment 6m, FU 18m

Seracchioli 2010a/b 24m</td><td rowspan="18">- Women of reproductive age who had surgery for endometrioma
- Age: ≤40y (mean 30y)</td><td rowspan="4">Recurrence of endometrioma (PE)
N=2
(Sesti 2009, Seracchioli 2010a)</td><td colspan="4">(Sesti 2009):
6m continuous COC 15.0% vs pla 16.6%, p=0.803, NS
(Seracchioli 2010a):
24 m cyclic COC 15% vs continuous COC 8% vs no COC 29%, p=0.003 (SS difference for continuous and cyclic vs pla)</td></tr>
<tr><td><u>Quality</u>
-2 (low Jadad, poor statistical analysis)</td><td><u>Consistency</u>
OK</td><td><u>Directness</u>
OK</td><td><u>Imprecision</u>
OK</td></tr>
<tr><td colspan="4">Grade assessment: low quality of evidence</td></tr>
<tr><td rowspan="3">Recurrence-free survival
N=1
(Seracchioli 2010a)</td><td colspan="4">Graphical presentation: significant difference between non-users versus cyclic (p=0.012) and continuous users (p=0.006)</td></tr>
<tr><td><u>Quality</u>
-2</td><td><u>Consistency</u>
NA</td><td><u>Directness</u>
OK</td><td><u>Imprecision</u>
OK</td></tr>
<tr><td colspan="4">Grade assessment: low quality of evidence</td></tr>
<tr><td rowspan="3">Dysmenorrhea (VAS 0-10)
N=1
(Seracchioli 2010b)</td><td colspan="4">Graphical presentation: scores significantly lower in continuous users than cyclic and non-users (p<0.0005)</td></tr>
<tr><td><u>Quality</u>
-2</td><td><u>Consistency</u>
NA</td><td><u>Directness</u>
OK</td><td><u>Imprecision</u>
OK</td></tr>
<tr><td colspan="4">Grade assessment: low quality of evidence</td></tr>
<tr><td rowspan="3">Dyspareunia (VAS 0-10)
N=1
(Seracchioli 2010b)</td><td colspan="4">Graphical presentation:
NS at 6, 12 and 24m
at 18m after surgery, continuous users showed lower VAS score than non-users (p=0.01)</td></tr>
<tr><td><u>Quality</u>
-2</td><td><u>Consistency</u>
NA</td><td><u>Directness</u>
OK</td><td><u>Imprecision</u>
OK</td></tr>
<tr><td colspan="4">Grade assessment: low quality of evidence</td></tr>
<tr><td rowspan="3">Chronic pelvic pain (VAS 0-10)
N=1
(Seracchioli 2010b)</td><td colspan="4">Graphical presentation: NS (test not reported)</td></tr>
<tr><td><u>Quality</u>
-2</td><td><u>Consistency</u>
NA</td><td><u>Directness</u>
OK</td><td><u>Imprecision</u>
OK</td></tr>
<tr><td colspan="4">Grade assessment: low quality of evidence</td></tr>
<tr><td rowspan="2">Study withdrawal due to AEs
N=3</td><td colspan="4">(Sesti 2009):
0.02% continuous COC vs 0% placebo
(Seracchioli 2010a/b):
cyclic COC 5.9% vs cont. COC 5.1% vs no therapy 0%
NT</td></tr>
<tr><td colspan="4">Grade assessment: NA</td></tr>
</table>

* It is unclear whether the populations of Seracchioli 2010a and 2010b are different or if there is an overlap

- Several RCTs followed women after surgery for endometrioma.
In one study (Sesti 2009), the women received either continuous administration of the combination pill or a placebo for 6 months, with a follow-up of 18 months.
There were three arms in the other study (/studies) (Seracchioli 2010a/b): cyclical or continuous administration of the combination pill or no treatment for 24 months.

The number of recurrences of endometrioma did not differ significantly with 6 months continuous administration of COC compared to placebo.
The number of recurrences after 24 months of treatment was significantly lower with cyclical or continuous administration of COC compared to no treatment.

GRADE: low quality of evidence

- In the study by Seracchioli, the continuous pill users reported a significantly lower pain score for dysmenorrhoea than those that used the pill cyclically or received no treatment. In this same study, there were no significant differences during the study period between the treatment groups for chronic pelvic pain and dyspareunia (except for this last endpoint at the time point 18 months post-surgery: lower VAS score with continuous pill use).

GRADE: low quality of evidence

- All studies reported the drop-out rate due to adverse events, but this was not subjected to statistical testing.

GRADE: NA

5.7. Perimenopause

No studies could be identified

5.8. Uterine fibroids

No studies met our inclusion criteria

6. Evidence tables and conclusions
Emergency contraception.

6.1. Emergency contraception. Levonorgestrel versus ulipristal. Evidence tables

Ref	N/n	Comparison	Outcomes	
Cheng 2012* Design: meta-analysis Search date: July 2011 N= 100 n= 55666	N=2 n=3893 for this comparison	UPA vs LNG UPA 30mg (micronized) or 50mg (unmicronised) LNG 2x 0.75 mg split dose regimen or LNG 1.5 single dose (administered within 72 h: Creinin 2006 or within 120 h: Glasier 2010)	Observed number of pregnancies (treatment within 0-72 h)	22/1619 (UPA) vs 35/1626 (LNG) RR=0.63 [95% CI 0.37, 1.07] NS p=0.089
			Observed number of pregnancies (treatment within 24 h)	5/585 (UPA) vs 14/600 (LNG) RR= 0.40 (95% CI 0.15-1.05) NS p= 0.064
			Observed number of pregnancies (treatment 24 -48h)	13/596 (UPA) vs 10/617 (LNG) RR= 1.33 (95% CI 0.59-3.00) NS p= 0.49
			Observed number of pregnancies (treatment within 48-72h)	4/437 (UPA) vs 11/409(LNG) RR= 0.34 (95% CI 0.11-1.06) NS, p= 0.064
			The following comparisons contain all the five-day data from Glasier 2010 combined with the three-day data from Creinin 2006)	
			Observed number of pregnancy (all women)	**22/1716 (UPA) vs 38/1732 (LNG)** **RR=0.59 [95% CI 0.35, 0.99]** **SS in favor of UPA p=0.044**
			Observed number of pregnancy (by risk status)**	High-risk women: 5/89 (UPA) vs 6/82 (LNG) RR=0.79 [95% CI 0.25, 2.46] NS p=0.68
				Low-risk women : 17/1625 (UPA) vs 32/1649 (LNG) **RR=0.54 [95% CI 0.30, 0.97]** **SS in favour of UPA p=0.039**
			Menses early	**Early** **199/1788 (UPA) vs 462/1805(LNG)** **RR=0.43 [95% CI 0.37, 0.50]** **SS (return before the expected date less frequent with UPA) p<0.00001**
			Menses delayed	**Delay** **371/1788 (UPA) vs 227/1805(LNG)** **RR=1.65 [95% CI 1.42, 1.92]** **SS (return after the expected date more frequent with UPA) p<0.00001**

			Nausea	170/1879 (UPA) vs 150/1891(LNG) RR=1.14 [0.93, 1.41] NS p=0.20
			Vomiting (Creinin 2006 only)	2/775 (UPA) vs 2/774(LNG) RR=1.00 [95% CI 0.14, 7.07] NS p= 1.0
			Breast tenderness (Creinin 2006 only)	16/775 (UPA) vs 15/774(LNG) RR=1.07 [95% CI 0.53, 2.14] NS p=0.86
			Headache	242/1879 (UPA) vs 240/1891(LNG) RR=1.02 [95% CI 0.87, 1.20] NS p=0.82
			Dizziness	77/1879 (UPA) vs 73/1891(LNG) RR=1.06 [95% CI 0.78, 1.45] NS p=0.70
			Fatigue	98/1879 (UPA) vs 81/1891(LNG) RR=1.22 [95% CI 0.91, 1.62] NS p=0.18
			Lower abdominal pain (Creinin 2006 only)	12/775 (UPA) vs 11/774(LNG) RR=1.15 [95% CI 0.69, 1.90] NS p=0.60
			Diarrhoea (Creinin 2006 only)	31/775 (UPA) vs 27/774(LNG) RR=1.09 [0.48, 2.45] NS p=0.84
			Spotting/bleeding after treatment (Creinin 2006 only)	5/775 (UPA) vs 7/774(LNG) RR=0.71 [0.23, 2.24] NS p=0.56
			Dysmenorrhoea (Glasier 2010 only)	142/1104 (UPA) vs 160/1117(LNG) RR=0.90 [95% CI 0.73, 1.11] NS p=0.32
			Abdominal pain (Glasier 2010 only)	56/1104 (UPA) vs 75/1117(LNG) RR=0.76 [95% CI 0.54, 1.06] NS p=0.10

* Characteristics of included studies: see under

**Risk status:
◦ high-risk - women who had further acts of intercourse during the same cycle in which EC was used,
◦ low-risk - women without further acts of coitus during that cycle.

Authors' remarks:

Since the Creinin 2006 trial did not recruit participants who had unprotected intercourse after 72 hours, the rationale of combining all five-day data from the Glasier 2010 trial in the analysis is debatable. It is noted that the Glasier 2010 trial was single blind (participants blinded, investigator not blinded), slightly more participants were excluded in the UPA group than in the control group in the analysis and the manufacturer was involved in trial.

Ref + design	n	Population	Duration	Comparison	Methodology
Creinin 2006 RCT (double –blind)	1672	-≥18 years of age -requesting EC within 72 h after unprotected intercourse -not using any hormonal contraception -recent history of regular menstrual cycles (24-42 days); ≥1 normal menstrual cycle (2 menses) was required after delivery, abortion or discontinuation of hormonal contraceptive	follow-up 5-7 d after expected onset of menses, then repeat visits, duration unclear	UPA 50mg (unmicronised) single-dose orally plus a placebo 12 h later vs LNG 0.75 mg split-dose regimen within 72 hours.	- Jadad score:5/5 - FU: 93% "Loss of follow-up: UPA 40/832; LNG 54/840 Post-randomisation exclusions: UPA 17/832; LNG 12/840 » - ITT:no Non inferiority study Sponsor: federal funds (NICH, NIH,…)
Glasier 2010 RCT (single –blind)	2221	-≥16 years of age requesting EC within 5 days after unprotected intercourse -regular menstrual cycles - not using any hormonal contraception	follow-up 5-7 d after expected onset of menses (or up to 60 days)	UPA 30mg single-dose (micronized) orally plus a placebo 12 h later vs LNG 1.5 single dose	- Jadad score:4/5 (single blind) - FU: 85.5%(lost to follow up 4%, post randomization exclusions 10%) - ITT: no Non inferiority study Excluded for analysis: - >35y - unknown pregnancy status after study - Lost to follow up -those aged over 35 years (n=145), -women with unknown follow-up pregnancy status (n=46), - those who reenrolled in the study (n=36). - Seven pregnancies judged to have occurred before emergency contraception was taken (n=4) or at least 10 days after treatment (n=3) were also excluded. Sponsor: HRA Pharma

Authors' conclusions

UPA seemed slightly more effective than LNG In order to demonstrate the relative effectiveness of UPA against LNG more data are needed. The effectiveness of LNG, UPA and mifepristone in relation to time since unprotected intercourse is not confirmed and more studies are needed.

6.1.bis. Emergency contraception. Levonorgestrel versus ulipristal. Summary and conclusions

<table>
<tr><th colspan="6">Ulipristal 50 mg unmicronised or 30mg micronized vs levonorgestrel 2x0.75mg or 1x1.5 mg within 72 or 120 hours (Creinin 2006 and Glasier 2010) from Arowojolu 2012</th></tr>
<tr><th>N/n</th><th>Population</th><th>Results</th><th colspan="3"></th></tr>
<tr><td rowspan="11">N=2
n=3893</td><td rowspan="11">-≥16 years of age requesting EC within 3 or 5 days after unprotected intercourse
-regular menstrual cycles
- not using any hormonal contraception</td><td rowspan="3">Observed number of pregnancies (treatment within 0-72 h)</td><td colspan="3">22/1619 (UPA) vs 35/1626 (LNG)
RR=0.63 [95% CI 0.37, 1.07]
NS p=0.089</td></tr>
<tr><td><u>Quality</u>
-1 (unclear exclusions, different treatment regimens)</td><td><u>Consistency</u>
OK</td><td><u>Directness</u>
OK</td><td><u>Imprecision</u>
OK</td></tr>
<tr><td colspan="4">Grade assessment: moderate quality of evidence</td></tr>
<tr><td>Menses early</td><td colspan="4">199/1788 (UPA) vs 462/1805(LNG)
RR=0.43 [95% CI 0.37, 0.50]
SS (less frequent with UPA) p<0.00001</td></tr>
<tr><td>Menses delayed</td><td colspan="4">371/1788 (UPA) vs 227/1805(LNG)
RR=1.65 [95% CI 1.42, 1.92]
SS (more frequent with UPA) p<0.00001</td></tr>
<tr><td>Spotting/bleeding after treatment (Creinin 2006 only)</td><td colspan="4">5/775 (UPA) vs 7/774(LNG)
RR=0.71 [0.23, 2.24] NS p=0.56</td></tr>
<tr><td>Abdominal pain (Glasier 2010 only)</td><td colspan="4">56/1104 (UPA) vs 75/1117(LNG)
RR=0.76 [95% CI 0.54, 1.06] NS p=0.10</td></tr>
<tr><td>Nausea</td><td colspan="4">170/1879 (UPA) vs 150/1891(LNG)
RR=1.14 [0.93, 1.41] NS p=0.20</td></tr>
<tr><td rowspan="3">Vomiting (Creinin 2006 only)</td><td colspan="4">2/775 (UPA) vs 2/774(LNG)
RR=1.00 [95% CI 0.14, 7.07] NS p= 1.0</td></tr>
<tr><td><u>Quality</u>
-1</td><td><u>Consistency</u>
OK</td><td><u>Directness</u>
OK</td><td><u>Imprecision</u>
OK</td></tr>
<tr><td colspan="4">Grade assessment: moderate quality of evidence</td></tr>
</table>

- A Cochrane systematic review found 2 RCTs that compared ulipristal with levonorgestrel as an emergency contraceptive. Despite the different treatment regimens and different time intervals after unprotected sexual contact, a meta-analysis was conducted. One study compared UPA 50 mg (unmicronised) with LNG 2x0.75 mg (12-hr interval) administered within 72 hr after unprotected contact. The other study compared UPA 30mg (micronized) with LNG 1x 1.5mg within 120 hr after unprotected sexual contact. Both studies were non-inferiority studies that demonstrated no significant difference between UPA and LNG for the period <72 hr.

Meta-analysis shows no statistically significant difference between UPA and LNG when they are administered within 72 hours after unprotected sexual contact.

GRADE: moderate quality of evidence

With LNG, the menses are observed to occur earlier than expected significantly more often than with UPA. With UPA, the menses are observed to occur later than expected significantly more often.
No significant difference has been established with regard to spotting or blood loss, abdominal pain, nausea or vomiting.

GRADE: moderate quality of evidence

The author of one of the studies (Glasier 2010) also conducted a meta-analysis of both these studies. This author does report a statistically significant difference between UPA and LNG when administered within 72

hours (OR= 0.58 (95% CI 0.33-0.99); p =0.046). It is not clear whether the difference of a few patients in the calculation or a different method of calculation is the explanation for this.

6.2. Emergency contraception. Advance provision versus standard care. Evidence tables

Ref	N/n	Comparison	Outcomes	Result
Polis 2007 Design: MA Search date: November 2009	N= 11 n= 7.695	advance provision vs. standard provision of emergency contraception	Pregnancy rate (at 12 month follow-up)	*[Hu 2005, Jackson 2003, Lo 2004, Raymond 2006, Schreiber 2009]* OR=0.98 (0.76 – 1.25), NS (n=4.728)
			Pregnancy rate (at 7 month follow-up)	*[Schwartz 2008]* OR=0.48 (0.18 – 1.29), NS (n=265)
			Pregnancy rate (at 6 month follow-up)	*[Belzer 2005, Ekstrand 2008, Gold 2004, Hu 2005, Jackson 2003, Lo 2004, Raine 2005, Raymond 2006]* OR= 0.92 (0.70 – 1.20), NS (n=6.329)
			Pregnancy rate (at 3 month follow-up)	*[Hazari 2000]* OR=0.49 (0.09 – 2.74), NS (n=198)
			Pregnancy for levonorgestrel regimens only	*[Belzer 2005, Ekstrand 2008, Lo 2004, Raine 2005, Raymond 2006, Schreiber 2009, Schwartz 2008]* OR=0.82 (0.64 – 1.05), NS (n=4.271)
			Ever use of emergency contraceptives during trial	*[Ekstrand 2008, Gold 2004, Hazari 2000, Hu 2005, Jackson 2003, Lo 2004, Raine 2005, Raymond 2006, Schreiber 2009, Schwartz 2008]* **OR=2.47 (1.80 – 3.40), SS** (n=6.971)
			Multiple uses of emergency contraceptives during trial	*[Hu 2005, Raine 2005, Raymond 2006]* **OR= 4.13 (1.77 – 9.63), SS** (n=4.574)
			Mean time interval between unprotected intercourse and use of emergency contraception	*[Ekstrand 2008, Lo 2004]* **Mean diff= -12.98 (-16.66 - -9.31), SS** (n=1.315)

* Characteristics of included studies: see below

Authors' conclusions

Advance provision of emergency contraception did not reduce pregnancy rates when compared to conventional provision. Results from primary analyses suggest that advance provision does not negatively impact sexual and reproductive health behaviors and outcomes. Women should have easy access to emergency contraception, because it can decrease the chance of pregnancy. However, the interventions tested thus far have not reduced overall pregnancy rates in the populations studied.

Ref + design	n	Population	Duration	Comparison	Methodology (sponsor NR in Cochrane)
Belzer 2005 OL RCT	160	adolescent mothers, 13-20 yrs, mostly Hispanic, receiving case - management services in a large metropolitan area. Excluded if attempting to get pregnant or using implant or an IUD	12 m	1 course levonorgestrel-only regimen (two tabs 0.75 mg levonorgestrel), to be taken in two doses 12 h apart. Replacement pack provided if package used or lost. vs. EC info only	- Jadad score: 3/5 - FU: 69% - ITT: no - Methodological remarks: large loss to follow up at 6m (31%) and no ITT; controls significantly more likely to report condom use and sexual activity at baseline; differences not controlled for in analysis; not powered to detect differences in pregnancy rates
Ekstrand 2008 OL RCT	420	teens requesting EC in a local youth clinic in medium-sized university town in Sweden Age 15-19y	6 m	requested dose plus extra dose (1.5 mg levonorgestrel taken as a single dose), plus 10 condoms and a leaflet on EC and condom use vs. requested dose of EC	- Jadad score: 3/5 - FU: 78% - ITT: no - Methological remarks: large loss to follow up (22%); not powered to detect differences in pregnancy rates
Gold 2004 OL RCT	301	sexually-active adolescents in Southwestern Pennsylvania, primarily minority and low-income Age 15-20y Excluded if using IUD, implant, injectable, if living in foster care or group home, or if had other characteristics which could threaten follow-up	6 m	From study start until April 2000: one course Yuzpe regimen 200 mcg ethinyl estradiol plus 2mg norgestrel, plus an extra dose in case of vomiting, in addition to diphenhydramine. After April 2000: levonorgestrel-only regimen (two tabs of levonorgestrel 0.75 mg). Participants could obtain two additional courses over six mo period by request, regardless of whether unprotected intercourse had occurred. Participants also received counseling and EC info. vs. EC on request at the clinic and EC info	- Jadad score: 3/5 - FU: 74% - ITT: no - Methodological remarks: large loss to follow-up (26% at 6m - for reasons other than pregnancy), and loss to follow-up differential by treatment group (33% in advance provision group, 19% in control group); not powered to detect differences in pregnancy

Hazari 2000 OL RCT	200	condom-using women in Mumbai, India, generally low SES and mostly between the ages of 25-34 yrs. Excluded if pregnant at baseline as determined by history of last enstrual period and recent unprotected intercourse, vaginal exam, or if required, urine pregnancy test and ultrasonography	3 m	one course Yuzpe regimen (50 µg ethinyl estradiol and 0.25mg levonorgestrel) to be taken in two doses 12 h apart. Replacement pills were provided on request at the clinic. vs. EC on request at the clinic. Both groups were provided with condoms	- Jadad score: 3/5 - FU: 99% - ITT: no not powered to detect differences in pregnancy rates
Hu 2005 OL RCT	2.000	post-partum women in Shanghai hospital. Excluded if planning on using an IUD or hormonal contraception	12 m	three courses of mifepristone (10mg) vs. only information on EC (levonorgestrel available in China OTC). All participants received ten condoms	- Jadad score:3 /5 - FU: 83% - ITT: no - Methodological remarks: originally powered to detect a difference in pregnancy rates, but pregnancy rates much lower than expected, reducing statistical power; inappropriately excluded those who chose IUD and sterilization; high potential for crossover due to OTC levonorgestrel
Jackson 2003 OL RCT	370	post-partum, low income, racially diverse English- or Spanish-speaking women at public inner-city hospital in San Francisco. Excluded if major contraindications to estrogen use, post-partum tubal ligation or partner with vasectomy, employees of Labor and Delivery at the hospital, enrolled in another study, or difficult to reach for follow-up (lack of a phone, psychiatric disorder, untreated substance abuse, plans for relocation)	12 m	one course of Yuzpe regimen (eight tabs 0.15 mg levonorgestrel plus 30µg ethinyl estradiol), educational session, verbal and written instructions. Additional pills available on request. vs. routine counseling	- Jadad score: 3/5 - FU: 69% - ITT: no - Methodological remarks: blinded personnel conducted follow up and analysis; large loss to follow up (31%); not powered to detect differences in pregnancy rates

Lo 2004 OL RCT	1.030	women, attending two Hong Kong clinics using “less effective contraceptive methods” (condoms, spermicide, fertility awareness based methods, withdrawal, or nothing) Age 18-45 y.	12 m	three courses (two tabs 0.75 mg levonorgestrel), to be taken in two doses 12h apart, and up to three more courses if needed. vs. EC on request at clinic	- Jadad score: 3/5 - FU: 96% - ITT: no not powered to detect differences in pregnancy rates
Raine 2005 OL RCT	1.228	English or Spanish speaking women, sexually active in past 6m, largely uninsured and low-income, at moderately high risk for negative reproductive health outcomes, living in the San Francisco Bay area, attending four California family planning clinics, available for six mo follow-up. Age 15-24 y Excluded if pregnant or desiring pregnancy, using hormonal contraception or IUD, or if had unprotected intercourse during the past three days or were requesting EC at enrollment	6 m	three courses (two tabs 0.75 mg levonorgestrel), to be taken in two doses 12 h apart, within 72 hours of intercourse. vs. EC on demand at a clinic.	- Jadad score: 3/5 - FU: 93% - ITT: no
Raymond 2006 OL RCT	1.490	sexually active women, who did not desire pregnancy and were attending clinics inNevada and North Carolina. Age 14-24 y Excluded if using or planning on using sterilization, IUD, hormonal contraception, or if pregnant or breastfeeding in past 6 w	12 m	two courses (two tabs of 0.75 mg levonorgestrel) to be taken together in one dose. More courses provided, attempt to ensure two packages on hand at all times vs. EC on request at a clinic	- Jadad score: 3/5 - FU: 94% - ITT: yes

Schreiber 2009 OL RCT	50	English-speaking women recruited from a hospital post-partum unit who had delivered a live infant and were planning to parent, who desired to delay pregnancy for at least one year, and who were in good general health. Age 14-19y. Excluded if had allergy to levonorgestrel, current substance abuse, or plans to relocate outside of Philadelphia.	12 m	one package of emergency contraceptive pills (Plan B) with routine instructions about EC as well as the chosen primary contraceptive method, a prescription for chosen primary method when applicable, or the first dose of injectable contraception (if injectable contraception was the chosen method). The intervention group had access to additional packages of Plan B upon request. vs. discharged with instructions about chosen primary contraceptive method and a prescription or first dose for that method	- Jadad score: 3/5 - FU: 76% - ITT: yes - Methodological remarks: large loss to follow up (24%) ; not powered to detect differences in pregnancy rates
Schwartz 2008 OL RCT	446	English-speaking adult women from waiting areas of two urgent care clinics in San Francisco who had a phone and no plans to relocate. Age 18-45 y Excluded if pregnant, had a hysterectomy or tubal ligation, had an IUD, had a partner with vasectomy, or a lesbian	7 m	a single package of two 0.75 mg levonorgestrel pills and computerized counseling on EC. vs. computerized counseling about pre-conception folate and a sample of folate	- Jadad score: 3/5 - FU: 59% - ITT: no - Methodological remarks: large loss to follow up (41%); not powered to detect differences in pregnancy rates

6.2.bis. Emergency contraception: Advance provision versus standard care. Summary and conclusions

<table>
<tr><td colspan="7">Advance vs standard provision emergency contraception (Belzer 2005, Ekstrand 2008, Gold 2004, Hazari 2000, Hu 2005, Jackson 2003, Lo 2004, Raine 2005, Raymond 2006, Schwartz 2008, Schreiber 2009) from Polis 2007</td></tr>
<tr><td>N/n</td><td>Duration</td><td>Population</td><td>Results</td><td colspan="3"></td></tr>
<tr><td rowspan="15">N=11, n= 7695</td><td rowspan="15">3-12 cycles</td><td rowspan="15">- Healthy women
- Age: 14-45y (mostly teens)
- Exclusion: tubal ligation, using IUD, implant or injectable contraception, trying to get or being pregnant</td><td>Pregnancy rate (at 6 month follow-up)

N=8
(Belzer 2005, Ekstrand 2008, Gold 2004, Hu 2005, Jackson 2003, Lo 2004, Raine 2005, Raymond 2006)</td><td colspan="3">OR= 0.92 (0.70 to 1.20), NS</td></tr>
<tr><td><u>Quality</u>
-1 (no ITT)</td><td><u>Consistency</u>
OK</td><td><u>Directness</u>
OK</td><td><u>Imprecision</u>
OK</td></tr>
<tr><td colspan="4">Grade assessment: moderate quality of evidence</td></tr>
<tr><td>Pregnancy rate (at 12 month follow-up)

N=5
(Hu 2005, Jackson 2003, Lo 2004, Raymond 2006, Schreiber 2009)</td><td colspan="3">OR=0.98 (0.76 to 1.25), NS</td></tr>
<tr><td><u>Quality</u>
-1 (low FU)</td><td><u>Consistency</u>
OK</td><td><u>Directness</u>
OK</td><td><u>Imprecision</u>
OK</td></tr>
<tr><td colspan="4">Grade assessment: moderate quality of evidence</td></tr>
<tr><td>Use of emergency contraception (once or more during trial)

N=10
(Ekstrand 2008, Gold 2004, Hazari 2000, Hu 2005, Jackson 2003, Lo 2004, Raine 2005, Raymond 2006, Schreiber 2009, Schwartz 2008)</td><td colspan="3">OR=2.47 (1.80 to 3.40)
SS favours advance provision</td></tr>
<tr><td><u>Quality</u>
-1 (low Jadad)</td><td><u>Consistency</u>
OK</td><td><u>Directness</u>
OK</td><td><u>Imprecision</u>
OK</td></tr>
<tr><td colspan="4">Grade assessment: moderate quality of evidence</td></tr>
<tr><td>Multiple uses of emergency contraception during trial

N=3
(Hu 2005, Raine 2005, Raymond 2006)</td><td colspan="3">OR= 4.13 (1.77 to 9.63)
SS favours advance provision</td></tr>
<tr><td><u>Quality</u>
-1 (low Jadad)</td><td><u>Consistency</u>
OK</td><td><u>Directness</u>
OK</td><td><u>Imprecision</u>
OK</td></tr>
<tr><td colspan="4">Grade assessment: moderate quality of evidence</td></tr>
<tr><td>Mean time interval between unprotected intercourse and use of emergency contraception
N=2
(Ekstrand 2008, Lo 2004)</td><td colspan="3">Mean diff= -12.98 (-16.66 to -9.31), SS favours advance provision</td></tr>
<tr><td><u>Quality</u>
-1 (low Jadad)</td><td><u>Consistency</u>
OK</td><td><u>Directness</u>
OK</td><td><u>Imprecision</u>
OK</td></tr>
<tr><td colspan="4">Grade assessment: moderate quality of evidence</td></tr>
</table>

- A meta-analysis of eleven RCTs of women of childbearing age (mainly teenagers) compared making emergency contraception available in advance in case unprotected sexual contacts occurred to the dispensing of emergency contraception after unprotected intercourse as per normal procedure.
Dispensing emergency contraception in advance did not significantly reduce the number of pregnancies, despite the fact that the emergency contraception could be used more often and more quickly.

GRADE: low to moderate quality of evidence

7. Evidence from observational studies Hormonal contraception: Serious but rare adverse events

7.1. Cancer overall

OC use is associated with a decreased risk of ovarian cancer, endometrial cancer, and colorectal cancer (see below). The risk of cervical cancer is increased (see below) and the risk of breast cancer may be slightly increased (see below). The net effect on the incidence of all cancers seems positive.

A very large long-running British cohort study with more than 45,000 participants and more than one million women-years observed (Hannaford 2007) gives us further information. Between 1968 and 1996 these women were closely monitored by their GP, a large proportion of women was then further, less intensively, followed up in the databases of the National Health Services until 2004. The authors report both the data of the "GP-cohort" (less long term follow up, but more detailed information) as that of the entire cohort (longer follow up, but less detailed information). In the entire cohort, the overall cancer incidence was significantly lower among women who had taken the pill, compared with women who never took the pill (RR: 0.88, 95% BI: 0.83 to 0.94) in the GP-cohort, the difference was not significant. On average, the women in this study took the pill for 44 months. The risk of cancer was increased with prolonged use (RR for use for 8 years or more (vs. no use): 1.22, 95% BI: 1.07 to 1.39). 75% of the pills used in the study contained 50 µg oestrogen, 3% were progesterone-only pills. Because during her life a woman often takes different pills with different oestrogen dose, subgroup analysis according to pill composition was impossible.

Overall Cancer: Use of hormonal contraception versus no use
Hannaford 2007

Design	N/n	Population	Risk factor	Outcome	Results*
cohort	n = 45950 Full cohort: 1084066 person years GP cohort 555666 person years	- women (18-60 y, mean age at recruitment 29), - married or in a stable relationship - follow-up 36y	- ever use hormonal contraception versus never use	Overall cancer incidence	Full cohort: **RR: 0.86** **95%CI: 0.77-0.96** GP cohort RR 0.97 95%CI: 0.88-1.06
			≥ 8 y hormonal contraception vs never use		**GP cohort** **RR 1.22** **95%CI: 1.07-1.39**

*adjusted for age, parity, smoking, and social class

Recently, mortality data from this study (with extended follow up to 2007) was also published. This confirms the above data: in the entire cohort, mortality due to cancer was lower in the group who ever used hormonal contraception, compared with women who had never taken the pill (RR: 0.85, 95% BI: 0.78 to 0.93), again the difference was not significant in the GP cohort (Hannaford 2010).

All cancer mortality: Use of hormonal contraception versus no use Hannaford 2010					
Design	**N/n**	**Population**	**Risk factor**	**Outcome**	**Results***
cohort	n = 46112 Full cohort: 1 197 181 person years GP cohort 579 752 person years	- women (18-60 y, mean age at recruitment 29), - married or in a stable relationship - follow-up 39y	- ever use hormonal contraception versus never use	All cancer mortality	**Full cohort:** **RR: 0.85** **95%CI: 0.78-0.93** GP cohort RR 0.88 95%CI: 0.75-1.04
			≥ 8 y hormonal contraception vs never use		GP cohort RR 0.96 95%CI: 0.77 to 1.20
*adjusted for age, parity, smoking, and social class					

Since cancer incidence and pill use differ from country to country, these results must be interpreted with caution. The current pill use is also different: with a shift to lower doses of hormones on the one hand, but on the other hand to an earlier start and therefore longer lasting pill use. The effects on cancer incidence are not known.

Grade

Overall cancer risk and cancer mortality decreased with use of hormonal contraception						
Quality -	Consistency -	Directness -1	Imprecision -	Large effect? -	Dose response? -	Confounding? -
Grade assessment: *very low quality of evidence*						

7.2. Increased risk of breast cancer

7.2.1. General

Individual studies give no clear results with regard to the risk of breast cancer by use of oral contraceptives. Early studies (higher doses of oestrogen, first-generation progestogens) did not seem to show any effect, while in more recent studies however, seem indeed to show a slight increase in the breast cancer risk (with lower concentrations of oestrogens, 2nd and 3rd generation progestogens, but an earlier and prolonged use).

A 15 year old meta-analysis of observational studies found a limited increased risk of breast cancer among current users of the combined pill. This increased risk persisted until 10 years after cessation of use. The risk appeared to increase with increasing duration of intake (weak trend: p = 0.05). There was no association between the age of starting and breast cancer risk, although the risk was highest among those who started taking the pill before age 20 (RR 1.22; no statistics reported). (WHO 1996)

Breast cancer: Use of hormonal contraception versus no use
WHO 1996

Design	N/n	Population	Risk factor	Results	
MA	N = 54 n = 153,536	Observational studies with women with breast cancer and information on contraceptive use (mostly published in the 80ies)	Current use hormonal contraception versus never use	Breast cancer risk	**RR: 1.24** **p < 0.00001**
			Use of hormonal contraception stopped < 5 y versus never use	Breast cancer risk	**RR: 1.16** **p = 0.00001**
			Use of hormonal contraception stopped < 10 y versus never use	Breast cancer risk	**RR: 1.07** **p = 0.009**
			Use of hormonal contraception stopped > 10 y versus never use	Breast cancer risk	NS

A large meta-analysis of observational studies established an increased risk of breast cancer in women younger than 50 years who had previously taken the pill compared with those who never used the pill. The researchers found that the risk increases when the pill was used before the first full-term pregnancy, especially when using more than 4 years for this first pregnancy. The data in this meta-analysis was not sufficient or insufficient to further differentiate between duration of use, time since last use or hormone composition of the pill (Kahlenborn 2006). All studies were carried out between 1980 and 2000, a period where the pill can be compared with the current use (lower doses of oestrogen, but earlier start, prolonged use).

Breast cancer: Use of hormonal contraception versus no use Kahlenborn 2006					
Design	**N/n**	**Population**	**Risk factor**	**Results**	
MA	N = 37 n = 43,041	observational studies on premenopausal* breast cancer with information on contraceptive use *premenopausal= < 50 years	Current use hormonal contraception versus never use	Premenopausal breast cancer risk	**RR: 1.19 (95%CI:1.09-1.29)**
			Nullipara	Premenopausal breast cancer risk	NS
			Nullipara with > 4 y of use	Premenopausal breast cancer risk	NS
			Para	Premenopausal breast cancer risk	**RR: 1.29 (95%CI:1.20-1.40)**
			In case of use before first pregnancy	Premenopausal breast cancer risk	**RR: 1.44 (95%CI:1.28-1.62)**
			In case of use after first pregnancy	Premenopausal breast cancer risk	**RR: 1.15 (95%CI:1.06-1.26)**
			In case of > 4 y of use before first pregnancy	Premenopausal breast cancer risk	**RR: 1.52 (95%CI:1.26-1.82)**

The large cohort study of Hannaford showed no significant differences between pill users and non-users with regard to breast cancer risk. It also established no connection with duration of use or time since last use (Hannaford 2007 and 2010).

Breast cancer: Use of hormonal contraception versus no use Hannaford 2007					
Design	**N/n**	**Population**	**Risk factor**	**Results***	
cohort	n = 45.950 Full cohort: 1.084.066 person years GP cohort 555.666 person years	- women (18-60 y, mean age at recruitment 29), - married or in a stable relationship - follow-up 36y	Ever use hormonal contraception versus never use	Breast cancer incidence	Full cohort: RR: 0,98 95%CI: 0,87-1,10 GP cohort: RR 1,02 95%CI: 0,88-1,20
*adjusted for age, parity, smoking, and social class					

Breast cancer: Use of hormonal contraception versus no use Hannaford 2007					
Design	**N/n**	**Population**	**Risk factor**	**Results***	
cohort	n = 45.950 Full cohort: 1.084.066 person years GP cohort 555.666 person years	- women (18-60 y, mean age at recruitment 29), - married or in a stable relationship - follow-up 36y	Ever use hormonal contraception versus never use	Breast cancer incidence	Full cohort: RR: 0,98 95%CI: 0,87-1,10 GP cohort: RR 1,02 95%CI: 0,88-1,20
*adjusted for age, parity, smoking, and social class					

A recent meta-analysis of 12 studies (Nelson 2012) evaluated the risk of breast cancer in women aged 40-49 years and found no association between previous pill use and breast cancer. When data from a screening program for breast cancer was analysed, an association was found between current oral contraceptive use and breast cancer, compared with past use or never use (Nelson 2012).

Breast cancer in women 40-49y: Use of hormonal contraception versus no use Nelson 2012					
Design	**N/n**	**Population**	**Risk factor**	**Results**	
MA	N = 12	studies published in the past 16 y with women with breast cancer and information on contraceptive use	Ever use hormonal contraception versus never use	Breast cancer risk	RR: 1.08 (95%CI:0.96-1.23)
			Use of oral contraceptives <5y	Breast cancer risk	RR: 1.10 (95%CI:0.93-1.29)
			Use of oral contraceptives 5-9y	Breast cancer risk	RR: 1.15 (95%CI:0.94-1.40)
			Use of oral contraceptives ≥10y	Breast cancer risk	RR: 1.07 (95%CI:0.95-1.19)
BCSC 1997	n = 380,585 Mammography data 1994-2010	Women 40-49y who where eligible for screening mammography	Current use of oral contraceptives versus former or never use	Breast cancer risk	**RR: 1.30** **(95%CI:1.13-1.49)**

Conclusion

The FSRH guideline states that there may be a slightly increased risk of breast cancer due to pill use, but this disappears 10 years after cessation of use. They rely, however, on a meta-analysis from the 90s and do not mention the meta-analysis of Hannaford (2007), that seemed to show no increased risk of breast cancer (FSRH 2010 40+). A slightly increased risk of early breast cancer with the pill can however not be excluded on the basis of all the above data.

Grade

Breast cancer risk increased with (current) use of hormonal contraception						
Quality -	Consistency -	Directness -1	Imprecision -	Large effect? -	Dose response? -	Confounding? -
Grade assessment: *very low quality of evidence*						

7.2.2. Women with a positive family history of breast cancer

For women with a positive family history of breast cancer, there is no contraindication for these agents. Several observational studies have shown that there is no difference in cancer incidence among women with a positive history of breast cancer who used the pill and those who did not (UKMEC 2009). This is confirmed by a recent systematic review (based on 10 observational studies and a large meta-analysis) (Gaffield 2009).

This is different for women who are known carriers of mutations in BRCA1 and / or BRCA2. Several observational studies seem to indicate an increased breast cancer risk when these women use oral contraceptives; these studies are not equivocal and sometimes contradict each other (in terms of mutation, duration of exposure, age of onset of hormonal contraception) (Narod 2002 and Haile 2006).

Breast cancer: Use of hormonal contraception versus no use Narod 2002					
Design	**N/n**	**Population**	**Risk factor**	**Results**	
Case-control	n = 2,622	- cases: patients with BRCA1 or BRCA2 mutation and breast cancer - controls: patients with BRCA1 or BRCA2 mutation without breast cancer	Use of oral contraceptives	Breast cancer risk	**BRCA1: OR: 1.20** **95%CI: 1.02-1.40** BRCA2: OR: 0.94 (95%CI:0.72-1.24)
			Use of oral contraceptives <5y	Breast cancer risk	BRCA1: NS BRCA2: subgroup too small for further analysis
			Use of oral contraceptives ≥ 5y	Breast cancer risk	**BRCA1: OR 1.33** **95%CI: 1.11-1.60** BRCA2: subgroup too small for further analysis
			Use of oral contraceptives before the age of 30y	Breast cancer risk	**BRCA1: OR 1.29** **95%CI: 1.09-1.52** BRCA2: subgroup too small for further analysis

Breast cancer: Use of hormonal contraception versus no use Haile 2006					
Design	**N/n**	**Population**	**Risk factor**	**Results**	
Case-control	N = 804	-cases: patients with BRCA1 or BRCA2 mutation and breast cancer -controls: patients with BRCA1 or BRCA2 mutation without breast cancer	Use of oral contraceptives for ≥1y	Breast cancer risk	BRCA1: NS BRCA2: NS
			Use of oral contraceptives for >5y	Breast cancer risk	BRCA1: NS **BRCA2: OR: 2.06** **95%CI: 1.08-3.94**
			≥4 y of contraceptive use before first pregnancy	Breast cancer risk	BRCA1: NS **BRCA2: OR: 3.46** **95%CI: 2.10-5.70**
			≥4 y of contraceptive use before age of 30	Breast cancer risk	BRCA1: NS **BRCA2: OR: 2.20** **95%CI: 1.26-3.85**

A recent meta-analysis of observational studies found no increased risk of breast cancer in patients with these mutations and oral contraceptive use, even with prolonged use or use before the age of 20 years. However, the authors found an increased risk with older preparations with a higher dose of oestrogen than those currently available. Moreover, they also found a beneficial effect of oral contraceptive use on the incidence of ovarian cancer in women with these mutations (Iodice 2010).

Breast cancer: Use of hormonal contraception versus no use Iodice 2010					
Design	**N/n**	**Population**	**Risk factor**	**Results**	
MA	N = 5 n = 5,809	Case-control and cohort trials	use of hormonal contraception versus never use	Breast cancer risk	BRCA1: NS BRCA2: NS

Given the current uncertainty, in the eyes of many, oestroprogestative associations remain relatively contraindicated in carriers of BRCA1 and BRCA2 mutations (UKMEC 2009).

Grade

Breast cancer risk increased with BRCA-mutation and use of combined oral contraception						
Quality -	Consistency -	Directness -1	Imprecision -	Large effect? -	Dose response? -	Confounding? -
Grade assessment: *very low quality of evidence*						

7.2.3. Progestogen only

A meta-analysis of observational studies shows a similar trend with POPs as with combination pills: slightly increased risk of breast cancer up to 10 years after use, thereafter no longer. The increase in breast cancer risk was not statistically significant, many studies were underpowered because only a small portion of the women studied took the mini pill (CKS POM, WHO 1996). Some sources report these findings as a possibly slightly increased breast cancer risk (CKS POM), while others simply state that there is no increased breast cancer risk with POPs (FSRH 2009 POP; FSRH 2010 40 +).

Breast cancer: Use of progestin-only pill versus no use WHO 1996					
Design	**N/n**	**Population**	**Risk factor**	**Results**	
MA	0.8% of study population (N = 54 n = 153,536)	Observational studies with women with breast cancer and information on contraceptive use (mostly published in the 80ies)	Use of progestin-only pill in the past 5y versus never use hormonal contraception	Breast cancer risk	RR: 1.17 p = 0.06
			Use of progestin-only pill > 10y versus never use hormonal contraception	Breast cancer risk	RR: 0.99 NS

The large meta-analysis of observational studies of the WHO (see above) shows no increase in breast cancer risk among users of the contraceptive injection (which, however, only included a small proportion of the study population (WHO 1996).

Breast cancer: Use of progestin-only injection versus no use WHO 1996					
Design	**N/n**	**Population**	**Risk factor**	**Results**	
MA	1.5% of study population (N = 54 n = 153,536)	Observational studies with women with breast cancer and information on contraceptive use (mostly published in the 80ies)	Use of progestin-only injection in the past 5y versus never use hormonal contraception	Breast cancer risk	RR: 1.17 NS
			Use of progestin-only pill > 10y versus never use hormonal contraception	Breast cancer risk	RR: 0.94 NS

Grade

Breast cancer risk not increased with progestogen-only pill						
Quality - 1	Consistency -	Directness -	Imprecision -	Large effect? -	Dose response? -	Confounding? -
Grade assessment: *very low quality of evidence*						

Breast cancer risk not increased with progestogen-only injectable						
Quality - 1	Consistency -	Directness -	Imprecision -	Large effect? -	Dose response? -	Confounding? -
Grade assessment: *very low quality of evidence*						

7.3. Increased risk of cervical cancer

In a large meta-analysis of observational studies it was observed that the risk of cervical cancer increased with the duration of the use of oral contraceptives (p <0.0001), but it decreased as a function of time since the last ingestion (p <0.0001). . OC use for less than 5 years is not associated with an increased risk of invasive cervical cancer (RR: 0.97: 95% BI :0,90-1, 04); with use of 5 years and longer an increase in this risk is seen (RR: 1.90, 95% BI :1,69-2, 13). Ten years after use, the risk of invasive cervical cancer was no longer increased (ICESCC 2007). Figures for carcinoma in situ were similar, just as the figures in HPV-positive women. There was insufficient data available for analysis in function of the composition of the hormone pills.

Cervical Cancer Use of hormonal contraception versus no use ICESCC 2007					
Design	**N/n**	**Population**	**Risk factor**	**Outcome**	**Results**
MA	n = 52,082	Observational studies with an outcome of cervical cancer (invasive or in situ) with information on use of hormonal contraceptives	hormonal contraception (current and previous) for > 5y versus never use	Cervical cancer risk	**RR: 1.90 (95%CI:1.69-2.13)**

In the large cohort study of Hannaford (see above) in users of oral contraceptives both incidence and mortality from invasive cervical cancer were increased, but the differences with non-users were not significant. Again, an increase in risk was seen with duration of use (significantly increased from 8 years and more) and a decrease in function of the duration since last use (from 15 years after use) (Hannaford 2007 and 2010).

Cervical cancer: Use of hormonal contraception versus no use Hannaford 2007					
Design	**N/n**	**Population**	**Risk factor**	**Outcome**	**Results***
Cohort	- n = 45.950 -complete cohort: 1.084.066 person years -primary care cohort: 555.666 person years	- Women 18-60y, mean 29y - married or with stable relation ship - follow-up 36y	ever use hormonal contraception versus never use	Invasive cervical cancer incidence	- complete cohort: RR: 1,33 95%CI: 0,92-1,94 - primary care cohort: RR 1,49 95%CI: 0,97-2,28
			hormonal contraception > 8y vs never use		**- primary care cohort :** **RR=2,73** **(95% BI 1,61-4,61)**
*adjusted for age, parity, smoking, and social class					

Cervical cancer: Use of hormonal contraception versus no use Hannaford 2007					
Design	**N/n**	**Population**	**Risk factor**	**Outcome**	**Results***
Cohort	- n = 45.950 -complete cohort: 1.084.066 person years -primary care cohort: 555.666 person years	- Women 18-60y, mean 29y - married or with stable relation ship - follow-up 36y	ever use hormonal contraception versus never use	Invasive cervical cancer incidence	- complete cohort: RR: 1,33 95%CI: 0,92-1,94 - primary care cohort: RR 1,49 95%CI: 0,97-2,28
			hormonal contraception > 8y vs never use		**- primary care cohort :** **RR=2,73** **(95% BI 1,61-4,61)**
*adjusted for age, parity, smoking, and social class					

Grade

Cervical cancer risk and mortality risk increased with long term use of combined hormonal contraception						
Quality -	Consistency -	Directness - 1	Imprecision -	Large effect? -	Dose response? +1	Confounding? -
Grade assessment: *low quality of evidence*						

7.4. Reduced risk of endometrial cancer

The risk of cancer of the uterine body (the vast majority of these cancers are endometrial cancer) decreases with use of hormonal contraception. The latest information about this comes from the publications by Hannaford. It shows both in the entire cohort, as in the GP cohort a significant decrease in the incidence of these cancers. The mortality of cervical cancer has decreased significantly (but not significantly in the GP cohort) (Hannaford 2007 and 2010).

Uterine body cancer: Use of hormonal contraception versus no use Hannaford 2007					
Design	**N/n**	**Population**	**Risk factor**	**Outcome**	**Results***
Cohort	- n = 45.950 -complete cohort: 1.084.066 person years -primary care cohort: 555.666 person years	- Women 18-60y, mean 29y - married or with stable relation ship - follow-yp 36y	ever use hormonal contraception versus never use	Uterine body cancer incidence	**- complete cohort:** **RR: 0,58** **95%CI: 0,42-0,79** **- primary care cohort:** **RR 0,47** **95%CI: 0,27-0,81**
*adjusted for age, parity, smoking, and social class					

Uterine body cancer: Use of hormonal contraception versus no use Hannaford 2007					
Design	**N/n**	**Population**	**Risk factor**	**Outcome**	**Results***
Cohort	- n = 45.950 -complete cohort: 1.084.066 person years -primary care cohort: 555.666 person years	- Women 18-60y, mean 29y - married or with stable relation ship - follow-yp 36y	ever use hormonal contraception versus never use	Uterine body cancer incidence	**- complete cohort:** **RR: 0,58** **95%CI: 0,42-0,79** **- primary care cohort:** **RR 0,47** **95%CI: 0,27-0,81**
*adjusted for age, parity, smoking, and social class					

These results are consistent with the results of a systematic review of case-control and cohort studies, in which a protective effect of oestroprogestative associations which were found in the incidence of endometrial cancer (Mueck 2010).

Due to lack of data no statement can be made about preparations containing only progestin.

Grade

Uterine body cancer and mortality risk decreased with use of combined hormonal contraception						
Quality	Consistency	Directness	Imprecision	Large effect?	Dose response?	Confounding?
-	-	- 1	-	+1	-	-
Grade assessment: *low quality of evidence*						

7.5. Reduced risk of ovarian cancer

A meta-analysis of 45 observational studies found a reduced risk of ovarian cancer among users of the pill versus non-users (RR 0.73, 95% CI: 0.70 to 0.76) (CGESOC 2008). The drop in risk appeared to increase with the duration of OC use (p for trend <0.00001) and persisted for more than 15 years after cessation of use.

Ovarian cancer: Use of hormonal contraception versus no use CGESOC 2008					
Design	**N/n**	**Population**	**Risk factor**	**Outcome**	**Results**
MA	N = 45 n = 110,560	Observational studies of at least 100 women with ovarian cancer (40 cases in case of cohort study)	ever use hormonal contraception versus never use	Ovarian cancer incidence	**RR: 0.73** **95%CI: 0.70-0.76**
			hormonal contraception for ≥ 15 y versus never use	Ovarian cancer incidence	**RR: 0.42** **95%CI: 0.36-0.49**

The studies by Hannaford showed, both in the entire cohort, as in the GP cohort, a decrease in the incidence of and mortality due to ovarian cancer (Hannaford 2007 and 2010). Also here, the incidence further decreases as afunction of the duration of the contraceptive use. The differences between users and non-users for cancer incidence remain significant for up to 15 years after stopping use.

Ovarian cancer: Use of hormonal contraception versus no use Hannaford 2007					
Design	**N/n**	**Population**	**Risk factor**	**Outcome**	**Results***
MA	- n = 45.950 -complete cohort: 1.084.066 person years -primary care cohort:555.666 person years	- Women 18-60y, mean 29y - married or with stable relation ship	ever use hormonal contraception versus never use	Ovarian cancer incidence	**- complete cohort:** **RR: 0,54** **95%CI: 0,40-0,71** **- primary care cohort:** **RR 0,51** **95%CI: 0,33-0,78**
			hormonal contraception for ≥ 15 y versus never use	Ovarian cancer incidence	**Primary care cohort:** **RR 0,38** **95%CI: 0,16-0,88**
*adjusted for age, parity, smoking, and social class					

Ovarian cancer mortality: Use of hormonal contraception versus no use Hannaford 2010					
Design	**N/n**	**Population**	**Risk factor**	**Outcome**	**Results***
Cohort	- n = 46.112 -complete cohort: 1.197.181 person years -primary care cohort: 579.752 person years	- Women 18-60y, mean 29y - married or with stable relation ship	ever use hormonal contraception versus never use	Ovarian cancer mortality	**- complete cohort:** **RR: 0,53** **95%CI: 0,38-0,72** **- primary care cohort:** **RR 0,43** **95%CI: 0,23-0,81**
			hormonal contraception for ≥ 8y versus never use	Ovarian cancer mortality	**- primary care cohort:** **RR 0,43** **95%CI: 0,12-0,98**
*adjusted for age, parity, smoking, and social class					

Also in an European prospective observational study , this protective effect is also seen. Again, the effect is greatest in women who take the pill for more than 10 years of use (Tsilidis 2011).

Ovarian cancer: Use of hormonal contraception versus no use Tsilidis 2011					
Design	**N/n**	**Population**	**Risk factor**	**Outcome**	**Results**
Retrospective cohort	n = 327,396 (±2900.000 person years)	- Women (mean age 50 y) without cancer at baseline - 23 centres in 10 European countries - FU: mean 9 y	ever use hormonal contraception versus never use	Ovarian cancer incidence	HR: 0.84 95%CI: 0.73-1.00
			hormonal contraception for ≥ 10 y versus never use or ≤1 y of use	Ovarian cancer incidence	**RR: 0.55** **95%CI: 0.41-0.75**

Although here the same remarks are to be made as above (overall cancer incidence) , there is the evidence that a protective effect of the pill against ovarian cancer is very high. This effect seems to increase with the duration of the pill and continues long after pill use.

Grade

Ovarian cancer and mortality risk decreased with use of combined hormonal contraception						
Quality -	Consistency -	Directness - 1	Imprecision -	Large effect? +1	Dose response? +1	Confounding? -
Grade assessment: *moderate quality of evidence*						

7.6. Reduced risk of colorectal carcinoma

A meta-analysis of observational studies confirms previous data associated with a protective effect of the pill against colorectal cancer: women who had taken the pill had a significantly lower risk of colorectal cancer than women who had never taken the pill (RR: 0.82: 95% BI: 0.74-0.92). Duration of use seemed to have no influence on the risk, but women who recently (less than ten years ago) stopped taking the pill showed a greater decrease in risk (RR: 0.46; 95% BI 0.30 to 0.71) (Fernandez 2001).

Colorectal cancer: Use of hormonal contraception versus no use Fernandez 2001					
Design	**N/n**	**Population**	**Risk factor**	**Outcome**	**Results**
MA (case control & cohort)	n = 327,396 (±2900.000 person years)	Observational studies on colorectal cancer that included quantitative information on contraceptive use	ever use hormonal contraception versus never use	Colorectal cancer incidence	**RR: 0.82** **95%CI: 0.74-0.92**
			Use <10 y vs never use	Colorectal cancer incidence	**RR: 0.46** **95%CI: 0.30-0.71**
			Use ≥10 y vs never use	Colorectal cancer incidence	**RR: 0.77** **95%CI: 0.67-0.89**

These data are confirmed in a meta-analysis of more recent date (Bosetti 2009).

Colorectal cancer: Use of hormonal contraception versus no use Bosetti 2009					
Design	**N/n**	**Population**	**Risk factor**	**Outcome**	**Results**
MA (case control & cohort)	N = 18	Observational studies on colorectal cancer that included quantitative information on contraceptive use	ever use hormonal contraception versus never use	Colorectal cancer incidence	**RR: 0.82** **95%CI: 0.69-0.97**
			Use <5 y vs never use	Colorectal cancer incidence	**RR: 0.84** **95%CI:0.75-0.94**
			Use ≥5 y vs never use	Colorectal cancer incidence	**RR: 0.83** **95%CI:0.74-0.94**

Hannaford's findings point in the same direction: in the entire cohort, the incidence of and mortality from colorectal cancer is lower among pill users than among non-users, in the GP cohort, the differences were not significant (Hannaford 2007 and 2010).

Colorectal Cancer: Use of hormonal contraception versus no use Hannaford 2007					
Design	**N/n**	**Population**	**Risk factor**	**Outcome**	**Results***
Cohort	- n = 45.950 -complete cohort: 1.084.066 person years -primary care cohort: 555.666 person years	- Women 18-60y, mean 29y - married or with stable relation ship	ever use hormonal contraception versus never use	Colorectal cancer incidence	**- complete cohort: RR: 0,72 95%CI: 0,58-0,90** - primary care cohort: RR 0,85 95%CI: 0,59-1,20
*adjusted for age, parity, smoking, and social class					

Colorectal Cancer mortality: Use of hormonal contraception versus no use Hannaford 2010					
Design	**N/n**	**Population**	**Risk factor**	**Outcome**	**Results***
Cohort	- n = 46.112 -complete cohort: 1.197.181 person years -primary care cohort: 579.752 person years	- Women 18-60y, mean 29y - married or with stable relation ship	ever use hormonal contraception versus never use	Colorectal cancer mortality	**- complete cohort: RR: 0,62 95%CI: 0,46-0,83** - primary care cohort: RR 0,70 95%CI: 0,41-1,20
*adjusted for age, parity, smoking, and social class					

Grade

Colorectal cancer and mortality risk decreased with use of combined hormonal contraception						
Quality -	Consistency -	Directness - 1	Imprecision -	Large effect? -	Dose response? +1	Confounding? -
Grade assessment: *low quality of evidence*						

7.7. Benign and malignant liver disease

There is little data on the risk of benign liver diseases and hormonal contraception. A systematic review (Cibula 2010) found some (old) case-control studies. Two old case-control studies from the 70's reported an increased risk of hepatocellular adenoma with oral contraceptives versus no use. A recent case-control study with lower doses of oral contraceptives found no significant difference.

Hepatocellular adenoma: Ever oral contraceptive use versus no use Cibula 2010			
Design	**Study**	**Comparison**	**Results**
SR of observational studies	Case-control USA (Edmondson 1976)	Ever use of OC vs control	RR= 1.3 for 1–3 years of OC use RR= 5.0 for 5-7 years RR=7.5 for 8–11years and RR= 25 for >11 years
	Case-control USA (Rooks 1979)	Ever use of OC vs control	RR= 9 for 13-36 months, RR=116 for 37–60 months, RR= 123 for 61-84 months, RR= 503 for ≥85months
	Case-control multicentre (Heinemann 1998)	Ever use of OC vs control	RR =1.25 (95% CI: 0.37–4.22) There was no relation between duration and age at first or last OC use and the prevalence of HA. The data mainly reflected recent low-dose OC

Two case-control studies suggest an association between oral contraceptive use and focal nodular hyperplasia with prolonged use (Cibula 2010). We have insufficient data to make a statement about this.

Focal nodular hyperplasia: Ever oral contraceptive use versus no use Cibula 2010			
Design	**Study**	**Comparison**	**Results**
SR of observational studies	"comparative study', n=216 (Mathieu 1998)	OC vs other OC	"OC use did not influence the size of FNH"
	Case-control multicentre (Heinemann 1998)	Ever use of OC vs control	1.96 (95% CI: 0.85-4.57). "The RR increased with longer duration and more recent usage"
	Case-control (Scalori 2002)	Ever use of OC vs control	RR= 2.8 (95% CI:0.8–9.4) for ever OC use RR=4.5 (95% CI: 1.2-16.9) for OC use lasting ≥3 years. "The trend in risk with duration was significant"

The same systematic review identified one meta-analysis of 12 case-control studies that evaluate the risk of hepatocellular carcinoma. A pooled relative risk is not significantly increased. When a recent European study was excluded, there was a significant association observed between OC use and hepatocellular carcinoma, while heterogeneity reduced.

Hepatocellular carcinoma: Ever use of oral contraceptive versus no use Cibula 2010			
Design	**Study**	**Comparison**	**Results**
SR of observational studies	MA of case-control studies N = 12 739 cases 5223 controls (Maheshwari 2007)	OC use versus no use	RR= 1.57 (95% CI: 0.96-2.54) "some evidence of duration-risk association in six studies" Exclusion of a recent multinational European study increased the pooled RR to **1.70 (95% to 1.12–2.59**) and decreased heterogeneity.

The large British cohort study by Hannaford showed no significant correlation between the use of hormonal contraception and cancer of the liver or gallbladder.

Cancer of gallbladder or liver. Use of hormonal contraception versus no use Hannaford 2007					
Design	**N/n**	**Population**	**Risk factor**	**Results***	
cohort	n = 45950 Full cohort: 1084066 person years GP cohort 555666 person years	- women (18-60 y, mean age at recruitment 29), - married or in a stable relationship - follow-up 36y	- ever use hormonal contraception versus never use	Cancer incidence - gallbladder or liver	Full cohort: 0.55 95%CI: 0.26 to 1.17 GP cohort RR=1.11 95%CI:0.37 to 3.30
			≥ 8 y hormonal contraception vs never use		GP cohort RR= 1.52 95%CI: 0.38 to 6.07
			Time since last OC use		NS
*adjusted for age, parity, smoking, and social class					

Grade

Benign liver tumours increase with use of combined hormonal contraception? *Hepatocellular carcinoma risk increase with use of combined hormonal contraception?*						
Quality	Consistency	Directness	Imprecision	Large effect?	Dose response?	Confounding?
- 1	- 1	- 1	-1	-	-	-
Grade assessment: *very low quality of evidence (insufficient evidence)*						

7.8. Increased risk of venous thromboembolism

7.8.1. Combined hormonal contraceptives

Meta-analysis

A meta-analysis of observational studies (cohort and case-control) calculates the risk of venous thromboembolism with the use of combined oral preparations. The risk of VTE is increased with use of combined oral preparations. The risk is higher in the first year of use. The risk remains when only the combination contraceptives containing ethinylestradiol <50µg are considered .

All the studied combination contraceptives (containing levonorgestrel, desogestrel, gestodene, drospirenone, and cyproterone acetate) are associated with an increased risk.

Compared with levonorgestrel-containing combination pills, the risk is higher with desogestrel, gestodene, drospirenone and cyproterone acetate.

Combined oral contraception vs no use of hormonal contraception
Combined oral contraception vs other combined oral contraception
(Manzoli 2012)

Design	N	Risk factor	Results OR (95%CI)	
MA of cohort and case/ control	329	Current use of OC vs no use	VTE	All studies: **OR= 3.41 (2.98 – 3.92)** Cohort design: **OR= 2.91 (2.33 - 3.62)**
	154	Current use of OC vs no use	idiopathic VTE	All studies: **OR= 4.94 (4.23, 5.78)** Cohort design: **OR= 4.47 (2.84, 7.03)**
	101	Current use of OC <1y vs no use	VTE	All studies: **OR= 5.28 (4.27, 6.55)** Cohort design: **OR= 4.17(3.73, 4.66)**
	101	Current use of OC ≥1y vs no use		All studies: **OR= 3.52 (2.83, 4.37)** Cohort design: **OR= 2.87 (2.70, 3.06)**
	92	Current use of OC (EE<50µg) vs no use		All studies: **OR= 3.59 (3.01, 4.27)** Cohort design: **OR= 3.23 (3.04, 3.45)**
	114	Current use of LNG/EE vs non OC use		All studies: **OR= 2.88 (2.26, 3.66)** Cohort design: **OR= 2.04 (1.79, 2.31)**
	71	Current use of DSG/EE vs non OC use		All studies: **OR= 4.88 (3.02, 7.88)** Cohort design: **OR= 2.09 (1.44,3.04**)
	51	Current use of GSD/EE vs non OC use		All studies: **OR= 4.41 (2.59, 7.51)** Cohort design: **OR= 2.25 (1.40, 3.61**)
	124	Current use of DSG/EE vs LNG/EE		All studies: **OR= 1.71 (1.46, 2.01)** Cohort design: **OR= 1.71 (1.02, 2.86)**
	94	Current use of GSD/EE vs LNG/EE		All studies: **OR= 1.36 (1.04, 1.77)** Cohort design: OR= 1.41 (0.66, 3.00)
	21	Current use of DRSP/EE vs LNG/EE		All studies: **OR= 1.65 (1.29, 2.10)** Cohort design: **OR= 1.64 (1.27, 2.10)**
	31	Current use of CPA/EE vs LNG/EE		All studies: **OR= 1.90 (1.55, 2.33)** Cohort design: **OR= 1.88 (1.47, 2.41)**

Later studies: Lidegaard 2011

The largest study by far is from Denmark (Lidegaard 2011). This study included all Danish women aged between 15 and 49 years without malignancy, cardiovascular disease or pregnancy. The first results from this study were published in 2009. This study covered the period 1995-2005 and is included in the above meta-analysis of Manzoli 2012. Some newer contraceptives (including drospirenone) were then only recently on the market.

In 2011, the Lidegaard study was updated and its design slightly modified to meet criticisms of its first publication: by running the study period from 2001 to 2009, with complete information on contraceptive use since 1995, more women were included who had used the newer contraceptives longer and the risk of "left censoring bias" was countered. The results of this new publication are fully in line with those of the first publication in 2009.
In 2011 the authors reported on more than 8,000,000 person-years . Venous thrombosis incidence was 8,2 / 10 000 person-years among pill users vs. 3.7 / 10 000 person-years among non-users, but no statistical analyses were performed for the group of all contraceptive users together.
In both publications there was a lower risk of VTE with pills with a lower oestrogen dose, but these differences were not always significant. When the pills were compared with each other on the basis of their progestin composition, the risk was lowest with norethisterone and levonorgestrel (in combination with an oestrogen dose of 30-40 ug). All third-generation progestogens and drospirenone and cyproterone, even if combined with a lower oestrogen dose (20 µg ethinyl estradiol) were associated with a significantly higher risk than levonorgestrel (in combination with an oestrogen dose of 30-40 µg). Note that combination pills containing norethisterone and norgestimate dit not present a higher risk than the combined pill containing levonorgestrel (Lidegaard 2009, Lidegaard 2011).

Current use of non-oral hormonal contraception vs no use (Lidegaard 2011)					
Design	**N/n Duration**	**Population**	**Risk factor**	**Results**	
cohort	8 010 290 person years	- all Danish women - 15-49 y - no malignant disease, cardiovascular disease or pregnancy	- Current use of hormonal contraception vs no use	VTE-incidence	8.2 vs 3.7 per 10 000 women years
			- Current use of specific COC vs no use of hormonal contraception		see table below
			- Current use of specific COC vs use of LNG/EE30-40		see table below

Combined oral contraception vs no use of hormonal contraception **Combined oral contraception vs other combined oral contraception** (Lidegaard 2011)							
COC with	NET	LNG	NGM	DSG	GSD	DRSP	CPA
50 µg EE - vs no use * - vs LNG**	**5.66 (3.12-10.3)** **-**	**3.54 (2.48-5.05)** **-**	- -	- -	- -	- -	- -
30-40 µg EE - vs no use * - vs LNG**	1.57 (0.84-2.92) 0.76 (0.36-1.60)	**2.19 (1.74-2.75)** 1 (reference)	**2.56 (2.18-3.01)** 1.18 (0.86-1.62)	**4.21 (3.63-4.87)** **2.24 (1.65-3.02)**	**4.23 (3.87-4.63)** **2.12 (1.61-2.78)**	**4.47 (3.81-5.11)** **2.09 (1.55-2.82)**	**4.10 (3.37-4.99)** **2.11 (1.51-2.95)**
20 µg EE - vs no use * - vs LNG**	- -	- -	- -	**3.26 (2.88-3.69)** **1.60 (1.20-2.14)**	**3.50 (3.09-3.97)** **1.70 (1.27-2.27)**	**4.84 (3.19-7.33)** **2.22 (1.27-3.89)**	- -
* rate ratios (95%-Confidence interval): First year of use, corrected for age and education level ** rate ratios (95%-Confidence interval): use for entire study duration , corrected for age, education level and duration of use							

Later studies: FDA 2011

A second study not included in the meta-analysis, is from FDA from 2011. The FDA conducted a retrospective observational study based on data from large databases of public and private health care programs. The data from over 800,000 women aged 10-55 years was collected for the period 2001-2007 and yielded a total of 898,250 person-years of exposure to oestroprogestative associations for contraception.

Compared with levonorgestrel (in association with 30 µg ethinyl estradiol), the risk of venous thromboembolism was significantly higher with pills containing drospirenone

Also when compared to pills with levonorgestrel, norethindrone or norgestimate as a progestin, the risk of venous thromboembolism was significantly higher with pills containing drospirenone (RR = 1.74, 95% CI :1,42-2, 14) (not in table). (FDA 2011)

Current use of hormonal contraception vs use of LNG150/EE30 (FDA 2011)					
Design	**N/n Duration**	**Population**	**Risk factor**	**Results Incidence rate ratio (95%CI)**	
Retrospective review databases	898250 women years	2001-2007 10-55y health databases	- Current use of COC with DRSP vs COC containing **LNG150/EE30**	VTE	**RR= 1.49 (1.19-1.87)**
			- Current use of combined contraceptive patch vs COC containing **LNG150/EE30**		RR=1.27 (0.93 – 1.72)
			- Current use of vaginal ring vs COC containing LNG/EE		RR=1.48 (0.96 - 2.27)
*Adjusted for age and site					

The FDA also compared the risk of thrombosis of the patch with that of older contraceptives (containing levonorgestrel, norethindrone or norgestimate as a progestin). When compared only to levonogestrel (in association with 30 micrograms ethinyl estradiol), the differences were not significant. A significantly increased risk of venous thromboembolism was observed with the patch compared to all older contraceptives (RR = 1.55, 95% CI: 1.17 to 2.07) (not in table) that remained significantly higher even after the first year (FDA 2011).

For the first time, a comparison was made of the vaginal ring to the older contraceptives (containing levonorgestrel, norethindrone or norgestimate as progestin). When only levonogestrel (in association with 30 µg ethinyl estradiol) was the comparator, the differences were not significant. A significantly increased risk of venous thromboembolism is observed with the vaginal ring, when compared to all older contraceptives (RR = 1 , 56, 95% BI: 1.02-2.37) (not in the table).

Later studies: Lidegaard 2012a

In 2012, Lidegaard published new data mostly concerning non oral hormonal contraception.
Here again there was no increased risk with norgestimate-containing combination pills as compared with levonorgestrel-containing pills.
Based on a limited number of women-years of observation, an increased risk of VTE is observed with the contraceptive patch and vaginal ring compared with no use.
In comparison with the combination pill with levonorgestrel the VTE risk with the patch is borderline significantly increased and the risk with the vaginal ring is significantly increased.

Current use of non-oral hormonal contraception vs no use
(Lidegaard 2012a)

Design	N/n Duration	Population	Risk factor	Results*	
Cohort	298 566 vs 231 675 women years	- all Danish women - 15-49 y - no malignant disease, cardiovascular disease or pregnancy 9 429 128 women years	- Current use of COC with norgestimate vs COC containing LNG/EE30-40	VTE confirmed events	Adjusted RR= 1.09 (95% CI 0.86 to 1.38); NS
	6178 women years		- Current use of combined contraceptive patch vs no use of hormonal contraception		9.7 vs 2.1 per 10 000 exposure years **Adjusted RR = 7.9** **(95% CI 3.5 to 17.7); SS**
	6178 vs 231 675 women years		- Current use of combined contraceptive patch vs COC containing LNG/EE30-40		Adjusted RR= 2.3 (95%CI 1.0 to 5.2);NS
	50 334 women years		- Current use of vaginal ring vs no use of hormonal contraception		7.8 vs 2.1 per 10 000 exposure years **Adjusted RR = 6.5** **(95%CI 4.7 to 8.9); SS**
	50 334 vs 231 675 women years		- Current use of vaginal ring vs COC containing LNG/EE30-40		**Adjusted RR= 1.9** **(95%CI 1.3 to 2.7)** **SS**

*Adjusted for age, year, length of use and level of education.

Grade

VTE risk increases with use of combined hormonal contraception *VTE risk is higher with gestodene, desogestrel, drospirenone and cyproterone –containing COC than for levonorgestrel-containing COC*						
Quality	Consistency	Directness	Imprecision	Large effect?	Dose response?	Confounding?
-	-	-	-	+1	-	-
Grade assessment: *moderate quality of evidence*						

VTE risk increases with higher content of ethinylestradiol						
Quality	Consistency	Directness	Imprecision	Large effect?	Dose response?	Confounding?
-	- 1	-	-	-	-	-
Grade assessment: *very low quality of evidence*						

7.8.2. Progestogen-only contraceptives

Current use of progestogen-only pill vs no use
(Lidegaard 2011)

Design	N/n Duration	Population	Risk factor	Results*	
cohort	29 187 women years	- all Danish women - 15-49 y - no malignant disease, cardiovascular disease or pregnancy	- Current use of progestogen-only desogestrel vs no use of hormonal contraception	VTE - incidence	Adjusted RR 0.64 (95% CI 0.29 to 1.42) NS
*Adjusted for age, year, and level of education.					

The study by Lidegaard on the VTE risk of hormonal contraceptives (Lidegaard 2011) also contained a very small group of users on the minipill. With desogestrel, there is no significant increase in the risk of VTE observed.

Current use of non-oral hormonal contraception vs no use
(Lidegaard 2012a)

Design	N/n Duration	Population	Risk factor	Results*	
cohort	29497 Women years	- all Danish women - 15-49 y - no malignant disease, cardiovascular disease or pregnancy	- Current use of subcutaneous implants vs no use of hormonal contraception	VTE	1.7 vs 2.1 per 10 000 exposure years Adjusted RR = 1.4 (95% CI 0.6 to 3.4); NS
	29 497 vs 231 675 Women years		- Current use of subcutaneous implants vs COC containing LNG/EE30-40		Adjusted RR=0.43 (95%CI 0.18 to 1.05); NS
	239841 Women years		- Current use of LNG- IUD vs no use of hormonal contraception		1.4 vs 2.1 per 10 000 exposure years Adjusted RR = 0.6 (95% CI 0.4 to 0.8); NS
	239841 vs 231 675 Women years		- Current use of LNG- IUD vs COC containing LNG/EE30-40		**Adjusted RR =0.18** **(95%CI 0.12 to 0.26)** **SS (lower with LNG-IUS)**
*Adjusted for age, year, length of use and level of education.					

The national cohort study of 2012a Lidegaard observed no increased risk of VTE with a progestogen implant, based on a limited number of women-years

With the levonorgestrel IUS also no increased risk of VTE is observed. Compared to pill users who take the combined pill containing levonorgestrel, the risk of VTE with the levonorgestrel-IUS is significantly lower.

There are no cohort studies that describe the risk of VTE with the progestogen-only injection (depot medroxyprogesterone acetate). A recent meta-analysis pooled the results of two smaller case-control studies that evaluated the risk of VTE using an injectable depot progestogen. An injectable depot progestin was associated with an increased risk of VTE compared with no use (Adjusted RR = 2.67, 95% BI 1.29-5.53) (Mantha 2012).

More and larger studies are needed to make a definitive statement.

Grade

VTE risk not increased with use of progestogen-only contraceptive methods						
Quality -	Consistency -	Directness -	Imprecision -	Large effect? -	Dose response? -	Confounding? -
Grade assessment: *low quality of evidence*						

7.9. Arterial hypertension

In women in their reproductive years, the absolute risk of cardiovascular disease is very small (risk of myocardial infarction in normotensive women aged 30-34 years: 1.7 / 1000000; risk of stroke in this population 34.1 / 1000000). Hypertension is a risk factor for cardiovascular disease and increases substantially this limited risk (risk of AMI: 10.2 / 1000000; risk of stroke: 185.3 / 1000000) (Curtis 2006). Two small observational studies of weak methodology suggest that pill users with hypertension have a higher blood pressure than non-users with hypertension (Curtis 2006)

7.10. Increased risk of myocardial infarction

7.10.1. Combined hormonal contraception

In a meta-analysis of 23 observational studies, the current use of oral contraceptives is associated with a significantly higher risk of myocardial infarction (OR: 2.48, 95% BI: 1.91-3.22). Use in the past was not associated with an increased risk (OR: 1.15, 95% BI: 0.98-1.35) (Khader 2003). Subgroup analyses showed that the risk of first and second generation progestogens are significantly increased in comparison with non-users, but with third-generation progestogens, it is not (borderline statistical significance) (no statistical data concerning direct comparison). Subgroup analyses also showed that the risk with higher dose oestrogen was greater compared to non-users, but not with the lowest dose (20 µg) (this latter finding is based on only two studies, there are no statistics concerning direct comparison). It also showed that the risk is significantly higher in smokers and in women with hypertension and / or hypercholesterolemia.

Use of combined oral contraceptives versus no use Khader 2003					
Design	**N/n**	**Population**	**Risk factor**	**Results**	
MA of observational studies (cohort and case-control)	N = 23 n = 60513	Observational study with - Adequate data concerning fatal/non-fatal MI - Current/previous use of COC - At least 20 cases of MI	current use COC vs never use	Incidence myocardial infarction	**OR: 2.48 (95%CI: 1.91-3.22)**
			previous use COC vs never use		OR: 1.15 95%CI: 0.98-1.35)
			Current use 1st gen vs never use		**OR: 2.21 95%CI: 1.30-3.76)**
			Current use 2nd gen vs never use		**OR: 2.17 95%CI: 1.76-2.69**
			Current use 3rd gen vs never use		OR: 1.27 95%CI: 0.96-1.67)
			Current use ≥50 µg EE vs never use		**OR: 3.62 95%CI: 2.22-5.90)**
			Current use 30-49µg EE vs never use		**OR: 1.97 95%CI: 1.43-2.71)**
			Current use 20 µg EE vs never use		OR: 0.90 95%CI: 0.21-4.08)
			Smoking and COC vs non- smoking and never COC		**OR: 9.52 95%CI: 5.41-16.72)**
			Hypertension and COC vs no hypertension and no COC		**OR: 9.30 95%CI: 3.89-22.23)**

A large Swedish prospective cohort study found, however, more recently, no increased risk of myocardial infarction due to current or past use of oral contraceptives (mainly low-dose oestrogens and 2nd and 3rd generation progestogens), even in the presence of other risk factors (smoking, hypertension, diabetes) (Margolis 2007).

This study was underpowered to find differences between the pills with a different composition.

Use of combined oral contraception versus no use Margolis 2007					
Design	**N/n**	**Population**	**Risk factor**	**Results**	
cohort	n = 48321	Women (30-49 y) years, randomly selected from the population of a certain region Average follow-up 11y	- current use COC vs never use	MI incidence	OR: 0.7 (95%CI: 0.4-1.4)
			- previous use COC vs never use		OR: 1.0 95%CI: 0.7-1.4)

A Danish retrospective cohort study included all Danish women, aged 15-49 without malignancies and cardiovascular disease and who were not pregnant, and followed them for for 15 years.

The risk of myocardial infarction and thrombotic stroke was evaluated with the use of hormonal contraceptives versus no use. The risk of myocardial infarction when no hormonal contraception was used, was 13.2 per 100,000 person-years.

All oral combination contraceptives were associated with an increased risk of myocardial infarction compared with no use. The risk was higher at higher doses of ethinyl estradiol.

No significant difference was found (versus no use) with the contraceptive patch, the vaginal ring, and with combination pills with cyproterone, drospirenone and gestodene +ethinyl estradiol 20µg. The rather small number of observation years in these comparisons will play a part in these findings. (Lidegaard 2012b)

Current use of non-oral hormonal contraception vs no use (Lidegaard 2012b)						
Design	**Women years**	**Population**	**Risk factor** **P + E (vs no use)**		**Results*** **Adjusted RR (95%CI)**	
cohort	126.984	- all Danish women - 15-49 y - no malignant disease, cardiovascular disease or pregnancy 14 251 063 person years	NET +	EE30-40µg	Myocardial infarction	**2.3 (1.3 to 3.9)**
	460.559		LNG +	EE30-40µg		**2.0 (1.6 to 2.5)**
	453.536		NGM +	EE30-40µg		1.3 (0.9 to 1.9)
	313.560 695.603		DSG +	EE 30-40µg EE 20µg		**2.1 (1.5 to 2.8)** **1.6 (1.1 to 2.1)**
	1,318,962 564.268		GSD +	EE 30-40µg EE 20µg		**1.9 (1.6 to 2.3)** 1.2 (0.8 to 1.9)
	286.770 23.056		DRSP +	EE 30-40µg EE 20µg		**1.7 (1.0 to 2.6)** 0.0
	187.145		CPA	EE 30-40µg		1.47 (0.83–2.61)
			COC with EE 50µg EE 30-40µg EE20µg			**3.73 (2.78 to 5.00)** **1.88 (1.66 to 2.13)** **1.40 (1.07 to 1.81)** **P<0.001 for trend**
	4.748		Patch			0.0
	38.246		Vaginal ring			2.1 (0.7 to 6.5)
*Adjusted for age, level of education, calendar year and risk factors						

Grade

Myocardial infarction risk increased with use of combined hormonal contraception						
Quality -	Consistency -	Directness -	Imprecision -	Large effect? -	Dose response? -	Confounding? -
Grade assessment: *low quality of evidence*						

7.10.2. Progestogen only contraception

The Danish retrospective cohort study of Lidegaard also examined the risk of myocardial infarction in users of progestogen-only methods. No significant difference is apparent with the mini-pill containing desogestrel, with the levonorgestrel intrauterine device and with the implant in comparison with no use of hormonal contraception. Because the number of observation years is limited, a definitive conclusion is difficult (Lidegaard 2012b).

Current use of non-oral hormonal contraception vs no use
(Lidegaard 2012b)

Design	**Women-years**	**Population**	**Risk factor** **P only vs no use**	**Results*** **Adjusted RR (95%CI)**	
cohort	29.185	- all Danish women - 15-49 y - no malignant disease, cardiovascular disease or pregnancy	Oral desogestrel	Myocardial infarction	1.46 (0.55–3.90)
	24.954		Implant		2.14 (0.69–6.65)
	184.875		LNG-IUD		1.02 (0.71–1.46)
*Adjusted for age, level of education, calendar year and risk factors					

A meta-analysis of six observational studies (Chaktoura 2012) found no increased incidence of myocardial infarction in women using progestogen-only contraception. These findings were independent of the route of administration (implant, injectable or oral). The authors of this meta-analysis concluded that on the basis of these limited findings, no definitive statement can be made.

Grade

Myocardial infarction risk not increased with use of progestogen only pill, implant or levonorgestrel-IUS						
Quality -	Consistency -	Directness -	Imprecision -1	Large effect? -	Dose response? -	Confounding? -
Grade assessment: *very low quality of evidence*						

7.11. Increased risk of stroke

7.11.1. Combined hormonal contraception

An older large meta-analysis of observational studies (N = 16, n = 1,101,199) shows an increased risk of stroke in women who use the contraceptive pill (OR: 1.92, 95% CI: 1.44-2.57). In the studies that specifically addressed the association with ischemic stroke, the risk was statistically significant (OR: 2.74, 95% BI: 2.24 to 3.35), in the studies that examined haemorrhagic stroke, the association was not significant (OR: 1.30, 95% BI: 0.99-1.71). The authors questionthat a clear association exists between stroke and pill use, because a meta-analysis of 4 cohort studies (n = 1,086,093) in the study seemed to show no association between stroke and OC use, while a meta-analysis of 12 case-control studies (n = 15 106) found a clear association. We must be aware that the predominance of a large cohort study (which showed significantly less haemorrhagic stroke in pill users), representing more than 80% of the patients in the meta-analysis, could have influenced a number of outcomes (such as the findings from the separate analysis of cohort studies and related haemorrhagic stroke).
Current users are at markedly increased risk, while those who have 'ever' taken the pill (no duration or time since last use specified) showed no increase risk of stroke.
Both use of pills with 50 micrograms EE or more as the use of "sub-50" pills was associated with a higher risk of stroke. The risk of second and third generation pills appeared similar.
Smoking and hypertension further increase the risk of stroke, but non-smoking and normotensive patients also had an increased stroke risk. (Chan 2004)

Stroke: Use of combined oral contraceptives versus no use Chan 2004					
Design	**N/n**	**Population**	**Risk factor**	**Results**	
MA of observational studies	N = 16 n = 1101199	- observational studies reporting risk of stroke with data on use of contraceptives	- ever use COC vs never use	Stroke	**OR: 1.92 95%CI: 1.44-2.57)**
				Ischemic stroke	**OR: 2.74 95%CI: 2.24-3.35)**
				Haemorrhagic stroke	OR: 1.30 95%CI: 0.99-1.71)
			- current use COC vs never use	Stroke	**OR: 1.99 95%CI: 1.40-2.83)**
			- previous use COC vs never use		OR: 1.21 (95%CI:0.86-1.71)
			Current use 50 µg EE vs never use		**OR: 1.79 (95%CI:1.39-2.30)**
			- EE ≥ 50 µg EE vs no use		**OR: 1.77 95%CI: 1.37-2.30)**
			- smoking and COC vs non-smoking and COC		**OR: 3.50 95%CI: 2.17-5.64)**
			- non smoking and COC vs non smoking and no COC		**OR: 1.86 95%CI: 1.46-2.37)**
			- hypertension and COC vs no hypertension and no COC		**OR: 9.82 95%CI: 6.97-13.84)**
			- no hypertension and COC vs no hypertension and no COC		**OR: 2.06 (95%CI:1.46-2.92)**

A Danish retrospective cohort study included all Danish women, aged 15-49 without malignancies and cardiovascular disease and who were not pregnant, and followed them for 15 years. The risk of myocardial infarction and thrombotic stroke was evaluated with the use of hormonal contraceptives versus no use. The risk of thrombotic stroke when no hormonal contraception was used, was 24.2 per 100,000 person-years.
All oral combination contraceptives were associated with an increased risk of thrombotic stroke compared with no use. There was no clear relationship between the dose of ethinylestradiol and the size of the risk.
No significant difference was observed (versus no use) with contraceptive pills with cyproterone, with the contraceptive patch and with drospirenone +20µg ethinylestradiol , however the number of observation years in these comparisons is (too) limited. (Lidegaard 2012b)

Stroke: Current use of non-oral hormonal contraception vs no use (Lidegaard 2012b)						
Design	**Women-years**	**Population**	**Risk factor** **P + E vs no use**		**Results***	**Adjusted RR (95%CI)**
cohort	126.984	- all Danish women - 15-49 y - no malignant disease, cardiovascular disease or pregnancy	NET +	EE30-40µg	Thrombotic stroke	**2.2 (1.5 to 3.2)**
	460.559		LNG +	EE30-40µg		**1.7 (1.4 to 2.0)**
	453.536		NGM +	EE30-40µg		**1.5 (1.2 to 1.9)**
	313.560 695.603		DSG +	EE 30-40µg EE 20µg		**2.2 (1.8 to 2.7)** **1.5 (1.3 to 1.9)**
	1,318,962 564.268		GSD +	EE 30-40µg EE 20µg		**1.8 (1.6 to 2.0)** **1.7 (1.4 to 2.1)**
	286.770 23.056		DRSP +	EE 30-40µg EE 20µg		**1.6 (1.2 to 2.2)** 0.9 (0.2 to 3.5)
	187.145		CPA	EE 30-40µ		1.40 (0.97–2.03)
			COC with EE 50µg EE 30-40µg EE20µg			**1.97 (1.45 to 2.66)** **1.75 (1.61 to 1.92)** **1.60 (1.37 to 1.86)** P=0.24 for trend
	4.748		Patch			3.2 (0.8 to 12.6)
	38.246		Vaginal ring			**2.5 (1.4 to 4.4)**
*Adjusted for age, level of education, calendar year and risk factors						

Grade

Thrombotic stroke risk increased with use of combined hormonal contraception						
Quality -	Consistency -	Directness -	Imprecision -	Large effect? -	Dose response? -	Confounding? -
Grade assessment: *low quality of evidence*						

7.11.2. Progestogen only contraception

The Danish retrospective cohort study by Lidegaard also examined the risk of thrombotic stroke in users of progestogen-only methods. No significant difference is observed with the mini-pill containing desogestrel, with the levonorgestrel intrauterine device and with the implant in comparison with no use of hormonal contraception. The fact that the number of observation years is limited, makes a definitive conclusion difficult (Lidegaard 2012b).

Stroke: Current use of non-oral hormonal contraception vs no use (Lidegaard 2012b)					
Design	**N/n Duration**	**Population**	**Risk factor** **P only vs no use**	**Results*** **Adjusted RR (95%CI)**	
cohort	29,185 person years	- all Danish women - 15-49 y - no malignant disease, cardiovascular disease or pregnancy	Oral desogestrel	Thrombotic stroke	088 (0.71-2.63)
	24,954 Women years		Implant		0.88 (0.28–2.72)
	184,875 Women years		LNG-IUD		0.73 (0.54–0.98)
*Adjusted for age, level of education, calendar year and risk factors					

A meta-analysis of six observational studies (Chaktoura 2009) found no increased incidence of stroke in women using a progestogen-only preparation. These findings were independent of the route of administration (implant, injectable or oral). The authors of this meta-analysis concluded that no definitive statement can be made on the basis of these limited findings.

Grade

Thrombotic stroke risk not increased with use of progestogen-only pill, implant or levonorgestrel-IUS						
Quality -	Consistency -	Directness -	Imprecision - 1	Large effect? -	Dose response? -	Confounding? -
Grade assessment: *very low quality of evidence*						

7.12. Cardiovascular mortality

Mortality data from the large British cohort study of Hannaford (see earlier in cancer incidence) does not give us a clear picture. In the entire cohort cardiovascular mortality was significantly lower among pill users, while in the general practitioner's cohort this was just significantly higher. The authors give no explanation. (Hannaford 2010)

Cardiovascular mortality: Use of hormonal contraception versus no use
Hannaford 2010

Design	N/n	Population	Risk factor	Results*	
cohort	n = 46112 Full cohort: 1 197 181 person years GP cohort 579 752 person years	- women (18-60 y, mean age at recruitment 29), - married or in a stable relationship - follow-up 39y	- ever use hormonal contraception versus never use	Cardiovascular mortality	**Full cohort:** **RR: 0.86** **95%CI: 0.77-0.96** **GP cohort** **RR 1.37** **95%CI: 1.07-1.75**

*adjusted for age, parity, smoking, and social class

7.13. Overall mortality

The mortality data from Hannaford suggest that hormonal contraceptives could have a beneficial effect on mortality. In the entire cohort mortality (all causes) was significantly lower in pill users than among non-users (RR 0.88, 95% BI 0.82 to 0.93) in the general practitioners' cohort, this was not the case (Hannaford 2010).

There was a large drop-out in this very long observational study (1/3 lost to follow-up). A bias may occur if a relationship exists between contraceptive use and mortality. The authors also mention the phenomenon of 'healthy survivorship': women with chronic diseases were not included in the cohort study. The studied cohort was healthier than the overall population.

All cause mortality: Use of hormonal contraception versus no use
Hannaford 2010

Design	N/n	Population	Risk factor	Results*	
cohort	n = 46112 Full cohort: 1 197 181 person years GP cohort 579 752 person years	- women (18-60 y, mean age at recruitment 29), - married or in a stable relationship - follow-up 39y	- ever use hormonal contraception versus never use	All cause mortality	**Full cohort:** **RR: 0.88** **95%CI: 0.82-0.93** **GP cohort** RR 0.98 95%CI: 0.88-1.10
*adjusted for age, parity, smoking, and social class					

Grade

All cause mortality decreased with use of combined hormonal contraception

Quality	Consistency	Directness	Imprecision	Large effect?	Dose response?	Confounding?
-	-	- 1	-	-	-	-

Grade assessment: *very low quality of evidence*

8. Adverse events of hormonal contraceptives

Source: Belgisch Centrum voor Farmacotherapeutische Informatie (BCFI),
Federal Agency for Medicines and Health Products (FAMHP),
European Medicines Agency (EMA),
Meyler's Side Effects of Drugs (15th edition),
Martindale: The complete drug reference (36th edition),
Farmacotherapeutisch Kompas

8.1. Adverse events of combined hormonal contraception (oestroprogestogens, CHCs)

8.1.1. All combined preparations

Attributed mainly to the oestrogen:

- Nausea and vomiting
- Headache, irritability, tiredness
- Spotting
- Oedema, painful breast engorgement
- Abdominal pain
- Enlargement of varices

Other adverse events of oestrogens:

- Water and salt retention with weight gain
- Venous thromboembolism (e.g.: deep vein thrombosis, pulmonary embolism)
- Increased tendency to develop gallstones with increased incidence of gallbladder disorders
- Increase in volume of fibroids
- Dysmenorrhoea and premenstrual syndrome
- Vertigo
- Skin rashes
- Changes in libido
- Endometrial hyperplasia

Attributed mainly to the progestogen:

- Depressed mood
- Dyspareunia, reduced libido
- Weight gain
- Acne
- Hypomenorrhoea

Other

- **Cholestasis and jaundice**
  (particularly in women who have had jaundice or pruritus in pregnancy in the past)
- **Benign liver tumours**
  (rare but sometimes hazardous due to their high level of vascularisation, with a risk of peritoneal haemorrhage)
- **Reduced carbohydrate tolerance**, not usually clinically significant
- **Effect on plasma lipids**
  (varies depending on the product used, the dose and the route of administration; the clinical significance is unclear)
- **Disturbances in certain thyroid and adrenal function tests**
- **Reversible increase in blood pressure**
- **Amenorrhoea** for more than 6 months after stopping the contraceptive
  (occurs more frequently if there were irregular periods beforehand)
- Slight increase in the **risk of stroke and myocardial infarction**;
  this increase in risk depends on the dose (mainly the oestrogen dose), age (especially above 35 years), the presence of cardiovascular risk factors and tobacco use;
  it has not been proven whether the risk of myocardial infarction is lower with third-generation contraceptives (containing desogestrel or gestodene)
- **Increased risk of deep vein thrombosis (and pulmonary embolism)**;

the risk increases with age, obesity, the presence of deep varices and a personal or family history of venous thromboembolism. It is generally assumed that this risk is higher where there is a high oestrogen content. The risk of venous thromboembolism is higher with third-generation contraceptives and contraceptives containing drospirenone than with second-generation contraceptives

- Probably **a slight increase in the risk of breast cancer**
  (particularly among women under 35 years old)
- **Premature closure of the epiphyseal disks and arrested growth in children**

8.1.2. Combined preparations containing drospirenone

Very common unwanted effects (occurring in more than 1% to 10% of cases) are low mood, headache, migraine, nausea, intermenstrual bleeding, breast tenderness, leukorrhoea and vaginal candidiasis.
The following serious side-effects have been reported in women using combined preparations: arterial and venous thromboembolism, hypertension, liver tumours and chloasma.
Conditions that may occur or may be exacerbated but where there is no clear proof of an association with the use of COCs are Crohn's disease, ulcerative colitis, epilepsy, uterine fibroids, porphyria, systemic lupus erythematosus, gestational herpes, Sydenham's chorea, haemolytic-uraemic syndrome and cholestatic jaundice.
In women with congenital angioedema, exogenous oestrogens may precipitate or exacerbate symptoms of angioedema.
Hyperkalaemia due to the anti-mineralocorticoid effect has been reported.

8.1.3. Combined oral contraceptives containing estradiol

Nomegestrol acetate + estradiol (Zoely®)
The most common adverse events (seen in more than 1 in 10 users) are acne and changes in menstruation (e.g. delayed menstruation or irregular menstruation). Other frequently occurring unwanted effects are reduced libido, depression, mood swings, headache, migraine, nausea, abdominal pain, breast tenderness and weight gain. (source: EMA, EPAR on Zoely)

Dienogest + estradiol, sequential preparation (Qlaira ®)
The following side effects have been associated with this preparation.
Common adverse events (between 1 and 10 out of 100 users) are headache, abdominal pain, nausea, acne, irregular periods, breast tenderness, dysmenorrhoea and weight gain.
Uncommon adverse events (between 1 and 10 in every 1000 users) are fungal vaginal infections, increased appetite, depression, emotional disturbance, sleeping problems, reduced interest in sex, mood swings, dizziness, migraine, hot flushes, high blood pressure, diarrhoea and vomiting, raised liver enzymes, alopecia, hyperhidrosis, itching, skin rash, muscle cramps, menorrhagia, mastodynia, cervical dysplasia, fibrocystic breast nodules, ovarian cysts, premenstrual syndrome, uterine fibroids, dyspareunia, tiredness, irritability and oedema.

8.1.4. Transdermal oestroprogestogens (Evra®)

Venous thrombosis (deep vein thrombosis and pulmonary embolism) particularly during the first year of use, and arterial thrombosis sometimes resulting in death. Particularly during the first few months of use, irregular vaginal blood loss. Breast sensitivity or tenderness, nipple discharge. Headache, migraine, change in libido, depressed mood. Nausea and vomiting. Changes in vaginal secretions.

Skin conditions such as rashes, erythema nodosum or multiforme and photosensitisation. Contact lens intolerance. Fluid retention, changes in body weight and hypersensitivity reactions. Irregular blood loss ('spotting' and breakthrough bleeding) and amenorrhoea, particularly on lower doses of oestrogen. Increases in Crohn's disease and increases in clinical manifestations of Dubin-Johnson syndrome and Rotor syndrome have been reported during use. Occasional (irreversible) melasma, particularly where there is a history of melasma gravidarum. Changes in serum lipid levels, including (occasionally persistent) hypertriglyceridaemia.
Also common (1-10%): patch site reactions such as itch, erythema, sometimes reactions such as discoloration and hypersensitivity.

8.1.5. Vaginal oestroprogestogens (Nuvaring®)

Common (1-10%): Headache, migraine, depression, emotional lability, reduced libido. Lower abdominal pain, nausea, weight gain. Breast tenderness, ring related problems (e.g. expulsion, problems during coitus and sensation of a foreign body), dysmenorrhoea, leukorrhoea, uncomfortable sensation in the vagina, vaginitis. Acne. Uncommon (0.1-1%): genital pruritus, skin rash. Diarrhoea, vomiting. Cystitis, urinary tract infections. Cervicitis, fibroadenomas of the breast. Abdominal distension, back pain.

8.1.6. Cyproterone + ethinylestradiol (Diane-35® etc.)

The main adverse events are adynamia, depressed mood, reduced libido, headache, hot flushes, liver toxicity and thromboembolic events.
Particularly during the first few months of use, irregular vaginal blood loss (spotting and breakthrough bleeding). Breast sensitivity or tenderness, nipple discharge. Migraine, nausea and vomiting. Changes in vaginal secretions. Skin conditions such as rashes, erythema nodosum or multiforme and photosensitisation. Occasionally melasma, particularly where there is a history of melasma gravidarum. Fluid retention, changes in body weight and hypersensitivity reactions. Exacerbation of Crohn's disease and increases in clinical manifestations of Dubin-Johnson syndrome and Rotor syndrome have been reported during use.

8.2. Adverse events of progestogen-only contraception

8.2.1. Mini pill (POP)

- Disorders of lipid and carbohydrate metabolism
- Nausea, vomiting and diarrhoea
- Reduced libido
- Headache, tiredness, tendency towards depression
- Oedema, weight gain
- Cholestatic jaundice and urticaria (rare)
- Acne, seborrhoea, alopecia and hirsutism on derivatives with androgenic effects

8.2.2. Depot injection (Depo-Provera® i.m.; Sayana® s.c.)

Injection of medoxyprogesterone to prevent menstruation, often results in irregular blood loss (spotting) during treatment and amenorrhoea persisting for a long or short time after stopping treatment.
A very common (>10%) unwanted effect is weight change.
Common (1-10%) effects are anorgasmia, depression, emotional disturbance, reduced libido, mood changes, irritability, headache, abdominal pain, acne, amenorrhoea, mastodynia and menometrorrhagia.
Long-term contraceptive effect. The median period of contraception for women who do conceive is ten months (4-31 months) after the last injection.

8.2.3. Implant (Implanon®)

When using etonogestrel s.c. changes will probably occur in the pattern of menstruation, which cannot be predicted beforehand. These include irregular periods (absent, less frequent, more frequent, constant) and changes in the intensity (heavier or lighter) and duration of periods. Amenorrhoea is reported by 1 in 5 women, while a further 1 in 5 women report repeated and/or long periods. Heavy periods are occasionally reported. In clinical studies, changes in the pattern of menstruation were the most common reason for stopping its use (approximately 11%). For many women, their pattern of menstruation during the first three months gives a good indication of the subsequent pattern.
Very common side effects (> 1/10) are vaginal infections, headache, acne, breast sensitivity or tenderness and weight gain.

8.2.4. Intra-uterine device (Mirena®)

Side effects occur mainly during the first few months after insertion and decline afterwards.
Very common (> 10%): uterine/vaginal bleeding ('spotting'), in 20%: oligomenorrhoea and amenorrhoea, benign ovarian cysts. Common (1-10%): abdominal pain, nausea, weight gain. Depressed mood, nervousness, reduced libido, headache. Acne. Back pain, pelvic pain, dysmenorrhoea, vaginal secretion, vulvovaginitis, breast sensitivity and tenderness, expulsion of the IUD. Uncommon (0.1-1%): mood swings, migraine, bloated sensation. Alopecia, hirsutism, pruritus, eczema. Pelvic inflammation, endometritis, cervicitis or pap smear normal, class II. Oedema. Rare (0.01-0.1%): rash, urticaria, uterine perforation (particularly at the time of insertion) which can cause inflammatory reactions. Microscopic endometrial polyps and cervical dysplasia have been reported. Occasionally, a brief period of loss of consciousness or slowing of the heart rate may occur when inserting or removing the IUD, and in epilepsy patients they may have a seizure.

8.3. Adverse events of emergency contraception (morning after pill)

8.3.1. Levonorgestrel (Norlevo®, Postinor®)

Very common side-effects (more than 10%) are dizziness, headache, nausea, lower abdominal pain, breast tightness, delayed menstruation or heavy periods and tiredness.
Common unwanted effects (between 1 and 10%) are diarrhoea and vomiting.
The side effects usually disappear within 48 hours after administration. Up to 30% of patients complain of spotting and irregular periods, and these symptoms can continue until the next period.

8.3.2. Ulipristal (Ellaone®)

The main unwanted effects of ulipristal are abdominal pain and menstrual disturbances. Common side effects (>1/100 to <1/10) are headache, dizziness, mood disturbances, nausea, vomiting, myalgia, back pain, breast sensitivity and tiredness.
Due to its affinity for corticosteroid receptors, ulipristal is not recommended for women with asthma which is severe and not adequately controlled by an oral corticosteroid. The effectiveness of ulipristal may be reduced if used concomitantly with CYP3A4 inducers or gastric acid secretion inhibitors.

References

(Abou-Setta 2006) Abou-Setta AM, Al-Inany HG, Farquhar C. Levonorgestrel-releasing intrauterine device (LNG-IUD) for symptomatic endometriosis following surgery. Cochrane Database of Systematic Reviews 2006, Issue 4. Art. No.: CD005072. DOI: 10.1002/14651858.CD005072.pub2.

(ACOG 2010 Emergency) The American College of Obstetricians and Gynecologists. Practice bulletin n° 112. Emergency contraception. Obstet gynecol 2010; 115: 1100-09

(ACOG 2010 Noncontraceptive) The American College of Obstetricians and Gynecologists. Practice bulletin n° 110. Noncontraceptive uses of hormonal contraceptives. Obstet gynecol 2010; 115: 206-18

(ACOG 2011) The American College of Obstetricians and Gynecologists. Practice bulletin n° 121. Long-acting Reversible contraception: Implants and Intrauterine Devices. Obstet gynecol 2011; 118: 184-96

(Affinito 1993) Affinito P, Monterubbianesi M, Primizia M, et al. Efficacy, cycle control and side-effects of two monophasic combination oral contraceptives: gestodene/ethinyl estradiol and norgestimate/ethinylestradiol. Gynecol Endocrinol 1993;7:259-266.

(Agoestina 1987) Agoestina T, Sulaeman M, Rarung M, Sabarudin U. Clinical evaluation of low dose pill triphasic (EE + estoden) versus monophasic (EE + desogestrel). Presented at the XIth Asian and Oceanic Congress of Obstetrics and Gynecology; 1987 Dec 6-12; Hongkong.

(Ahrendt 2006) Ahrendt H-J, Nisand I, Bastianelli C, et al.Efficacy, acceptability and tolerability of the combined contraceptive ring, NuvaRing, compared with an oral contraceptive containing 3 µg of ethinyl estradiol and 3 mg of drospirenone. Contraception 2006;74:451-7 + Milsom I, Lete I, Bjertnaes A et al.Effects on cycle control and bodyweight of the combined contraceptive ring, NuvaRing, versus an oral contraceptive containing 30 µg ethinyl estradiol and 3 mg drospirenone. Hum Reprod 2006;21:2304-11.

(Ahrendt 2009) Ahrendt HJ, Makalova D, Parke S, et al. Bleeding pattern and cycle control with an estradiolbased oral contraceptive: a seven-cycle, randomized comparative trial of estradiol valerate/dienogest and ethinyl estradiol/levonorgestrel. Contraception 2009;80:436-44.

(Akerlund 1993) Akerlund M, Rode A,Westergaard J. Comparative profiles of reliability, cycle control and side effects of two oral contraceptive formulations containing 150 µg desogestrel and either 30 µg or 20 µg ethinyl oestradiol. BJOG 1993;100:832-8.

(Anderson 2003) Anderson FD, Hait H, the Seasonale-301 Study Group. A multicenter, randomized study of an extended cycle oral contraceptive. Contraception 2003;68:89-96

(Andrade 1993) Andrade RP. Clinical comparison of a triphasic gestodene preparation and a monophasic desogestrel preparation. Gynecol Endocrinol 1993;7 Suppl:33-41.

(Anttila 2009) Anttila L, Kunz M, Marr J. Bleeding pattern with drospirenone 3 mg+ethinyl estradiol 20 mcg 24/4 combined oral contraceptive compared with desogestrel150 mcg+ ethinyl estradiol 20 mcg 21/7 combined oral contraceptive. Contraception 2009;80:445-51.

(Arowojolu 2012) Arowojolu AO, Gallo MF, Lopez LM, Grimes DA. Combined oral contraceptive pills for treatment of acne. Cochrane Database of Systematic Reviews 2012, Issue 7. Art. No.: CD004425. DOI: 10.1002/14651858.CD004425.pub6.

(Audet 2001) Audet MC, Moreau M, Koltun WD, et al.Evaluation of contraceptive efficacy and cycle control of a transdermal contraceptive patch vs an oral contraceptive: a randomized controlled trial. JAMA 2001;285:2347-54.

(Basdevant 1993) Basdevant A, Conard J, Pelissier C, et al.Hemostatic and metabolic effects of lowering the ethinyl-estradiol dose from 30 mcg to 20 mcg in oral contraceptives containing desogestrel. Contraception 1993;48:193-204.

(Baveja 1989) Baveja R, Bichille LK, Coyaji KJ, et al. Randomized clinical trial with intrauterine devices (levonorgestrel intrauterine device (LNG), CuT 380Ag, CuT 220C and CuT 200B). A 36-month study. Indian Council of Medical Research Task Force on IUD. Contraception 1989;39:37-52.

(Bayar 2005) Bayar Ü, Barut A, Ayo lu F. Diagnosis and management of simple ovarian cysts. Int J Gynaecol Obstet 2005;91:187-8.

(Bayer 2011) Bayer Schering Pharma AG. GA YAZ ACNE in China Phase III. http://clinicaltrials.gov/ct2/show/NCT00818519 (accessed 25 Aug 2011).

(BCSC 1997) Ballard-Barbash R, Taplin SH, Yankaskas BC, et al. Breast Cancer Surveillance Consortium: a national mammography screening and outcomes database. AJR Am J Roentgenol 1997;169:1001-8.

(Belzer 2005) Belzer M, Sanchez K, Olson J, et al. Advance supply of emergency contraception: A randomized trial in adolescent mothers. J Pediatr Adolesc Gynecol 2005;18:347-54.

(Bosetti 2009) Bosetti C, Bravi F, Negri E, La Vecchia C. Oral contraceptives and colorectal cancer risk: a systematic review and meta-analysis. Hum Reprod Update 2009;15:489-98.

(Brill 1991) Brill K, Muller C, Schnitker J, Albring M. The influence of different modern low-dose oral contraceptives on intermenstrual bleeding. Adv Contracept 1991;7:51-61.

(Brill 1996) Brill K, Then A, Beisiegel U, et al. Investigation of the influence of two lowdose monophasic oral contraceptives containing 20 µg ethinylestradiol/75 µg gestodene and 30 µg ethinylestradiol/75 µg gestodene, on lipid metabolism in an openrandomized trial. Contraception 1996;54:291-7.

(Brown 2012) Brown J, Kives S, Akhtar M. Progestagens and anti-progestagens for pain associated with endometriosis. Cochrane Database of Systematic Reviews 2012, Issue 3. Art. No.: CD002122. DOI: 10.1002/14651858.CD002122.pub2.

(Bruni 2000) Bruni V, Croxatto H, De La Cruz J, et al. A comparison of cycle control and effect on well-being of monophasic gestodene-, triphasic gestodene- and monophasic desogestrel-containing oral contraceptives. Gynecol Endocrinol 2000;14:90-8.

(Burbos 2011) Nikolaos Burbos and Edward P Morris. Menopausal symptoms. BMJ Clin Evid [online] 2011 [cited dec 2012]. http://clinicalevidence.bmj.com

(Cachrimandou 1993) Cachrimanidou AC, Hellberg D, Nilsson S, et al. Long-interval treatment regimen with a desogestrel-containing oral contraceptive. Contraception 1993;48:2015.

(Carlborg 1983) Carlborg L. Comparison of contraceptive acceptability of levonorgestrel and ethinyl oestradiol administered in one three-phasic (Trionetta) and one monophasic (Neovletta) version. Contraception 1983;27:439–52.

(Carlborg 1986) Carlborg L. Cyproterone acetate versus levonorgestrel combined with ethinyl estradiol in the treatment of acne. Acta Obstet Gynecol Scand 1986;134:29-32.

(CGESOC 2008) Collaborative Group on Epidemiological Studies of Ovarian Cancer. Ovarian cancer and oral contraceptives: collaborative reanalysis of data from 45 epidemiological studies including 23 257 women with ovarian cancer and 87 303 controls. Lancet 2008;371:303-14.

(Chaktoura 2009) Chakhtoura Z, Canonico M, Gompel A, et al. Progestogen-only contraceptives and the risk of stroke : a meta-analysis. Stroke. 2009;40:1059-62.

(Chaktoura 2011) Chakhtoura Z, Canonico M, Gompel A, et al. Progestogen-only contraceptives and the risk of acute myocardial infarction: a meta-analysis. J Clin Endocrinol Metab 2011;96:1169-74.

(Chan 2004) Chan WS, Ray J, Wai EK et al. Risk of stroke in women exposed to low-dose oral contraceptives. Arch Intern Med 2004;164:741-7.

(Chen 1987) Chen JK. A comparative clinical study of the effects of three types of low dose estrogen/progestogen oral contraceptives. Reprod Contracept 1987;7:11–6.

(Cheng 2012) Cheng L, Che Y, Gülmezoglu AM. Interventions for emergency contraception. Cochrane Database of Systematic Reviews 2012, Issue 8. Art. No.: CD001324. DOI: 10.1002/14651858.CD001324.pub4.

(Cibula 2010) Cibula D, Gompel A, Mueck AO, et al. Hormonal contraception and risk of cancer. Hum Reprod Update 2010;16:631-50.

(CKS POM) CKS (2007) Contraception – progestogen-only methods. Clinical Knowledge Summaries. http://www.cks.nhs.uk/contraception_progestogen_only_methods.

(Coenen 1996) Coenen CM, Thomas CM, Borm GF, et al. Changes in androgens during treatment with four low-dose contraceptives. Contraception 1996;53:171-6.

(Collaborative 1998) Collaborative Study Group on the Desogestrel-containing Progestogen-only Pill. A double-blind study comparing the contraceptive efficacy, acceptability and safety of two progestogen-only pills containing desogestrel 75 µg/day or levonorgestrel 30 µg/day. Eur J Contracept Reprod Health Care 1998;3:169-78.

(Coney 2001) Coney P, Washenik K, Langley RGB, et al. . Weight change and adverse event incidence with a low-dose oral contraceptive: two randomized, placebo-controlled trials. Contraception 2001;63:297-302.

(Coutinho 1995) Coutinho EM, O'Dwyer E, et al. Comparative study on intermittent versus continuous use of a contraceptive pill administered by vaginal route. Contraception 1995;51:355-8.

(Creinin 2006) Creinin MD, Schlaff W, Archer DF, et al. Progesterone receptor modulator for emergency contraception. A randomized controlled trial. Obstet Gynecol 2006;108:1089-97.

(Curis 2006) Curtis KM, Mohllajee AP, Martins SL, Peterson HB. Combined oral contraceptive use among women with hypertension: a systematic review. Contraception 2006;73:179-188.

(Davis 2007) Davis LJ, Kennedy SS, Moore J, Prentice A. Oral contraceptives for pain associated with endometriosis. Cochrane Database of Systematic Reviews 2007, Issue 3. Art. No.: CD001019. DOI: 10.1002/14651858.CD001019.pub2.

(Dieben 1984) Cullberg G. A comparative multicentre study on a triphasic, and a fixed low-dose oral contraceptive combination. Acta Obstet Gynecol Scand Supplement 1983;116:97 + Cullberg G, Samsioe G, Andersen RF, et al. Two oral contraceptives, efficacy, serum proteins, and lipid metabolism. A comparative multicentre study on a triphasic and a fixed dose combination. Contraception 1982;26:229–43 + Mattsson LA, Cullberg G. Clinical and metabolic effects of Marvelon: Scandinavian experience. Br J Fam Plann 1984;10:43–8.

(Domus Medica 2012) Peremans L, van Leeuwen E, Delvaux N, Keppens K, Yilkilkan H. Richtlijn voor goede medische praktijkvoering: Hormonale anticonceptie. Huisarts Nu 2012;41:S1-S32.

(Duckitt 2012) Kirsten Duckitt and Sally Collins. Menorrhagia. BMJ Clin Evid [online] 2012 [cited dec 2012]. http://clinicalevidence.bmj.com

(Duijkers 2004) Duijkers I, Killick S, Bigrigg A, Dieben TO. A comparative study on the effects of a contraceptive vaginal ring NuvaRing and an oral contraceptive on carbohydrate metabolism and adrenal and thyroid function. Eur J Contracept Reprod Health Care 2004;9:131-40.

(Dunson 1993) Dunson TR, McLaurin VL, Aguayo EL, et al. A multicenter comparative trial of triphasic and monophasic, low dose combined oral contraceptives. Contraception 1993;47:515–25.

(Edelman 2005) Edelman A, Gallo MF, Jensen JT, Nichols MD, Grimes DA. Continuous or extended cycle vs. cyclic use of combined hormonal contraceptives for contraception. *Cochrane Database of Systematic Reviews* 2005, Issue 3. Art. No.: CD004695. DOI: 10.1002/14651858.CD004695.pub2.

(Edelman 2010) Edelman A, Gallo MF, Jensen JT, Nichols MD, Grimes DA. Continuous or extended cycle vs. cyclic use of combined hormonal contraceptives for contraception. Cochrane Database of Systematic Reviews 2005, Issue 3. Art. No.: CD004695. DOI:10.1002/14651858.CD004695.pub2

(Edmondson 1976) Edmondson HA, Henderson B, Benton B. Liver-cell adenomas associated with use of oral contraceptives. N Engl J Med 1976;294:470–2.

(Ekstrand 2008) Ekstrand M, Larsson M, Darj E, Tyden T. Advance provision of emergency contraceptive pills reduces treatment delay: a randomized controlled trial among Swedish teenage girls. Acta Obstet Gynecol Scand 2008;8:354-9.

(Elkind-Hirsch 2007) Elkind-Hirsch KE, Darensbourg C, Ogden B, Ogden LF, Hindelang P. Contraceptive vaginal ring use for women has less adverse metabolic effects than an oral contraceptive. Contraception 2007;76:348-56.

(Endrikat 1997) Endrikat J, Muller U, Dusterberg B. A twelve-month comparative clinical investigation of two low-dose oral contraceptives containing 20 µg ethinylestradiol/75 µg gestodene and 30 µg ethinylestradiol/75 µg gestodene, with respect to efficacy, cycle control, and tolerance. Contraception 1997;55:131-7

(Endrikat 1999) Endrikat J, Dusterberg B, Ruebig A, et al. Comparison of efficacy, cycle control, and tolerability of two low-dose oral contraceptives in a multicenter clinical study. Contraception 1999;60:269-74.

(Endrikat 2001) Endrikat J, Hite R, Bannemerschult R, Gerlinger C, SchmidtW. Multicenter, comparative study of cycle control, efficacy and tolerability of two low-dose oral contraceptives containing 20 µg ethinylestradiol/100 µg levonorgestrel and 20 µg ethinylestradiol/500 µg norethisterone. Contraception 2001;64:3-10.

(Engebretsen 1987) Engebretsen T, Thorsen E, Smith CC, et al. . Triphasic versus monophasic p-pill. A comparative multicenter study [Trefasisk versus monofasisk p–pille: en sammenlignende multisenterstudie]. Tidsskr Nor Laegeforen 1987;107:941-3.

(Farquhar 2009) Farquhar C, Brown J. Oral contraceptive pill for heavy menstrual bleeding. Cochrane Database of Systematic Reviews 2009, Issue 4. Art. No.: CD000154. DOI: 10.1002/14651858.CD000154.pub2.

(FDA 2011) US Food and Drug Administration. Combined hormonal contraceptives (CHCs) and the risk of cardiovascular disease endpoints. FDA, 2011. http://www.fda.gov/downloads/Drugs/DrugSafety/UCM277384.pdf.

(Feldblum 2005) Feldblum PJ, Caraway J, Bahamondes L, et al. Randomized assignment to copper IUD or depotmedroxyprogesterone acetate: feasibility of enrollment, continuation and disease ascertainment. Contraception 2005;72:187-91.

(Fernandez 2001) Fernandez E, La Vecchia C, Balducci A et al. Oral contraceptives and colorectal cancer risk: a meta-analysis. Br J Cancer 2001;84:722-7.

(Ferrero 2010) Simone Ferrero, Valentino Remorgida, and Pier Luigi Venturini . Endometriosis. BMJ Clin Evid [online] 2010 [cited dec 2012]. http://clinicalevidence.bmj.com

(Foidart 2000) Foidart JM,WuttkeW, Bouw GM, Gerlinger C, Heithecker R. A comparative investigation of contraceptive reliability, cycle control and tolerance of two monophasic oral contraceptives containing either drospirenone or desogestrel. Eur J Contracept Reprod Health Care 2000;5:124-34.

(Fraser 2011) Fraser IS, Römer T, Parke S, et al. Effective treatment of heavy and/or prolonged menstrual bleeding with an oral contraceptive containing estradiol valerate and dienogest: a randomized, double-blind Phase III trial. Hum Reprod 2011;26:2698-708.

(Freeman 2001) Freeman EW, Kroll R, Rapkin A, Pearlstein T, et al. Evaluation of a unique oral contraceptive in the treatment of premenstrual dysphoric disorder. J Womens Health Gend Based Med 2001;10:561-9.

(French 2004) French R, Sorhaindo AM, Van Vliet HAAM,Mansour DD, Robinson AA, Logan S, Helmerhorst FM, Guillebaud J, Cowan FM. Progestogen-releasing intrauterine systems versus other forms of reversible contraceptives for contraception. Cochrane Database of Systematic Reviews 2004, Issue 3. Art. No.: CD001776. DOI: 10.1002/14651858.CD001776.pub2.

(FSRH 2009 POI) Faculty of Sexual and Reproductive Health Care (Royal College of Obstetricians and Gynaecologists). Progestogen-only implants. Clinical effectiveness unit guidance. April 2008 (updated January 2009). http://www.fsrh.org/pdfs/CEUGuidanceProgestogenOnlyImplantsApril08.pdf

(FSRH 2009 POInj) Faculty of Sexual and Reproductive Health Care (Royal College of Obstetricians and Gynaecologists). Progestogen-only injectable contraception. Clinical effectiveness unit guidance. November 2008 (updated june 2009). http://www.fsrh.org/pdfs/CEUGuidanceProgestogenOnlyInjectables09.pdf

(FSRH 2009 POP) Faculty of Sexual and Reproductive Health Care (Royal College of Obstetricians and Gynaecologists). Progestogen-only pills. Clinical Effectiveness Unit Guidance. November 2008 (Updated June 2009). http://www.fsrh.org/pdfs/CEUGuidanceProgestogenOnlyPill09.pdf.

(FSRH 2010 40+) Faculty of Sexual and Reproductive Health Care (Royal College of Obstetricians and Gynaecologists). Contraception for women aged over 40 years. Clinical Effectiveness Unit Guidance. July 2010: http://www.fsrh.org/pdfs/ContraceptionOver40July10.pdf

(FSRH 2010 Start) Faculty of Sexual and Reproductive Health Care (Royal College of Obstetricians and Gynaecologists). Quick starting Contraception. Clinical effectiveness unit guidance. September 2010. http://www.fsrh.org/pdfs/CEUGuidanceQuickStartingContraception.pdf

(FSRH 2010 Young) Faculty of Sexual and Reproductive Health Care (Royal College of Obstetricians and Gynaecologists). Contraceptive choices for young people. March 2010. http://www.fsrh.org/pdfs/ceuGuidanceYoungPeople2010.pdf

(FSRH 2011) Faculty of Sexual and Reproductive Health Care (Royal College of Obstetricians and Gynaecologists). Missed pill recommendations. CEU statement. May 2011. http://www.fsrh.org/pdfs/CEUStatementMissedPills.pdf

(FSRH 2012 Combined) Faculty of Sexual & Reproductive Healthcare. *Combined hormonal contraception.* 2011 (Updated august 2012). www.fsrh.org

(FSRH 2012 Drug interactions) Faculty of Sexual and Reproductive Health Care (Royal College of Obstetricians and Gynaecologists). Drug interactions with hormonal contraception. January 2011 (Updated January 2012). http://www.fsrh.org/pdfs/CEUGuidanceDrugInteractionsHormonal.pdf

(FSRH 2012 Emergency) Faculty of Sexual and Reproductive Health Care (Royal College of Obstetricians and Gynaecologists). Emergency contraception. Clinical effectiveness unit guidance. August 2011 (updated January 2012) http://www.fsrh.org/pdfs/CEUguidanceEmergencyContraception11.pdf

(Gaffield 2009) Gaffield ME, Culwell KR, Ravi A. Oral contraceptives and family history of breast cancer. Contraception 2009;80:372-80.

(Gallo 2011a) Gallo MF, Nanda K, Grimes DA, Lopez LM, Schulz KF. 20 µg versus >20 µg estrogen combined oral contraceptives for contraception. *Cochrane Database of Systematic Reviews* 2011, Issue 1. Art. No.: CD003989. DOI: 10.1002/14651858.CD003989.pub4.

(Gallo 2011b) Gallo MF, Lopez LM, Grimes DA, Schulz KF, Helmerhorst FM. Combination contraceptives: effects on weight. *Cochrane Database of Systematic Reviews* 2011, Issue 9. Art. No.: CD003987. DOI: 10.1002/14651858.CD003987.pub4.

(Glasier 2010) Glasier AF, Cameron ST, Fine PM, et al. Ulipristal acetate versus levonorgestrel for emergency contraception: a randomised non-inferiority trial and meta-analysis. Lancet 2010;37:555-62.

(Gold 2004) Gold MA, Woldford JE, Smith KA, Parker AM. The effects of advance provision of emergency contraception on adolescent women's sexual and contraceptive behaviors. J Pediatr Adolesc Gynecol 2004;17:87-96.

(Goyal 2011) Amit Goyal. Breast pain. BMJ Clin Evid [online] 2011 [cited dec 2012]. http://clinicalevidence.bmj.com

(Grimes 2010) Grimes DA, Lopez LM, O'Brien PA, Raymond EG. Progestin-only pills for contraception. Cochrane Database of Systematic Reviews 2010, Issue 1. Art. No.: CD007541. DOI: 10.1002/14651858.CD007541.pub2.

(Grimes 2011) Grimes DA, Jones LB, Lopez LM, SchulzKF.Oral contraceptives for functional ovarian cysts. Cochrane Database of Systematic Reviews 2011, Issue 9. Art. No.: CD006134. DOI: 10.1002/14651858.CD006134.pub4.

(Gruber 2006) Gruber DM, Huber JC, Melis GB, et al. A comparison of the cycle control, safety, and efficacy profile of a 21-day regimen of ethinylestradiol 20µg and drospirenone 3mg with a 21-day regimen of ethinylestradiol 20µg and desogestrel 150µg. Treat Endocrinol 2006;5:115–21.

(GSD Group 1999) Gestodene Study Group. Cycle control, safety and efficacy of a 24- day regimen of gestodene 60mcg/ethinylestradiol 15mcg and a 21-day regimen of desogestrel 150mcg/ ethinylestradiol 20mcg. Eur J Contracept Reprod Health Care 1999;4(Suppl 2):17–25.

(Guang-Sheng 2010) Guang-Sheng F, Mei-Lu B, Li-Nan C, et al. Efficacy and safety of the combined oral contraceptive ethinylestradiol/drospirenone (Yasmin) in healthy Chinese women. Clin Drug Invest 2010;30:387-96.

(Haile 2006) Haile RW, Thomas DC, McGuire V. BRCA1 and BRCA2 mutation carriers, oral contraceptive use and breast cancer before age 50. Cancer Epidemiol Biomarkers Prev 2006;15:1863-70.

(Halbe 1998) Halbe HW, de Melo NR, Bahamondes L, Petracco A, et al.Efficacy and acceptability of two monophasic oral contraceptives containing ethinylestradiol and either desogestrel or gestodene. Eur J Contracept Reprod Health Care 1998;3:113–20.

(Halpern 2010) Halpern V, Raymond EG, Lopez LM. Repeated use of pre- and postcoital hormonal contraception for prevention of pregnancy. Cochrane Database of Systematic Reviews 2010, Issue 1. Art. No.: CD007595. DOI: 10.1002/14651858.CD007595.pub2.

(Hannaford 2007) Hannaford PC, Selvaraj S, Elliott AM et al. Cancer risk among users of oral contraceptives: cohort data from the Royal College of General Practitioner's oral contraception study. BMJ 2007;335:651.

(Hannaford 2010) Hannaford PC, Iversen L, Macfarlane TV et al. Mortality among contraceptive pill users: cohort evidence from Royal College of General Practitioners' Oral Contraception Study. BMJ 2010;340:c927.

(Hazari 2000) Hazari K. Use of emergency contraception by women as a back-up method. Health Popul 2000;23: 115-122.

(Heinemann 1998) Heinemann LA, Weimann A, Gerken G, et al. Modern oral contraceptive use and benign liver tumours: the German Benign Liver Tumor Case–control Study. Eur J Contracept Reprod Health Care 1998;3:194–200.

(Hickey 2012) Hickey M, Higham JM, Fraser I. Progestogens with or without oestrogen for irregular uterine bleeding associated with anovulation. Cochrane Database of Systematic Reviews 2012, Issue 9. Art. No.: CD001895. DOI: 10.1002/14651858.CD001895.pub3.

(Hofmeyr 2010) Hofmeyr GJ, Singata M, Lawrie TA. Copper containing intra-uterine devices versus depot progestogens for contraception. *Cochrane Database of Systematic Reviews* 2010, Issue 6. Art. No.: CD007043. DOI: 10.1002/14651858.CD007043.pub2.

(Hu 2005) Hu X, Cheng L, Hua X, Glasier A. Advanced provision of emergency contraception to postnatal women in China makes no difference in abortion rates: a randomized controlled trial. Contraception 2005;72:111-6.

(Huber 2000) Huber J, Foidart JM, Wuttke W, et al. Efficacy and tolerability of a monophasic oral contraceptive containing ethinylestradiol and drospirenone. Eur J Contracept Reprod Health Care 2000;5:25–34.

(Hughes 2007) Hughes E, Brown J, Collins JJ, Farquhar C, Fedorkow DM, Vanderkerchove P. Ovulation suppression for endometriosis for women with subfertility. Cochrane Database of Systematic Reviews 2007, Issue 3. Art. No.: CD000155. DOI: 10.1002/14651858.CD000155.pub2.

(ICESCC 2007) International Collaboration of Epidemiological Studies of Cervical Cancer. Cervical cancer and hormonal contraceptives: collaborative reanalysis of individual data for 16 573 women with cervical cancer and 35 509 women without cervical cancer from 24 epidemiological studies. Lancet 2007;370:1609-21.

(Iodice 2010) Iodice S, Barile M, Rotmensz N et al. Oral contraceptive use and breast or ovarian cancer risk in BRCA1/2 carriers: a meta-analysis. Eur J Cancer 2010;46:2275-84.

(Ismail 1991) Ismail MTM. A randomised comparative study of Triquilar versus Marvelon: the Malaysian experience. Malays J Reprod Health 1991;9:9-17.

(Jackson 2003) Jackson RA, Schwarz EB, Freedman L, Darney P. Advance supply of emergency contraception: effect on use and usual contraception - a randomized trial. Obstet Gynecol 2003;102:8-16.

(Jensen 2011) Jensen JT, Parke S, Mellinger U, et al. Effective treatment of heavy menstrual bleeding with estradiol valerate and dienogest: a randomized controlled trial. Obstet Gynecol 2011;117:777-87.

(Kahlenborn 2006) Kahlenborn C, Modungo F, Potter DM, Severs WB. Oral contraceptive use as a risk factor for premenopausal breast cancer: a meta-analysis. Mayo Clin Proc 2006;81:1290-1302.

(Kashanian 2010) Kashanian M, Shahpourian F, Zare O. A comparison between monophasic levonorgestrel-ethinyl estradiol 150/30 and triphasic levonorgestrel-ethinyl estradiol 50-75-125/ 30-40-30 contraceptive pills for side effects and patient satisfaction: a study in Iran. Eur J Obstet Gynecol Reprod Biol 2010; 150:47-51.

(Kaunitz 2009) Kaunitz AM, Darney P, Ross D, et al. Subcutaneous DMPA vs. intramuscular DMPA: a 2-year randomized study of contraceptive efficacy and bone mineral density. Contraception 2009;80:7-17.

(Kelly 2010) Kelly S, Davies E, Fearns S, et al. Effects of oral contraceptives containing ethinyl estradiol with either drospirenone or levonorgestrel on various parameters associated with wellbeing in healthy women. Clin Drug Invest 2010;30:325-36.

(Khader 2003) Khader YS, Rice J, Lefante J, Abueita O. Oral contraceptive use and the risk of myocardial infarction: a meta-analysis. Contraception 2003;68:11-7.

(Kirkman 1994) Kirkman RJ, Pedersen JH, Fioretti P, Roberts HE. Clinical comparison of two low-dose oral contraceptives, Minulet and Mercilon, in women over 30 years of age. Contraception 1994;49:33–46 + Kirkman RJE. Clinical comparison of two low-dose oral contraceptives in women older than 30 years. Adv Contracept 1991;7:63–76.

(Klipping 2012a) Klipping C, Duijkers I, Fortier MP, et al. Contraceptive efficacy and tolerability of ethinylestradiol 20 µg/drospirenone 3 mg in a flexible extended regimen: an open-label, multicentre, randomised, controlled study. J Fam Plann Reprod Health Care 2012;38:73–83.

(Klipping 2012b) Klipping C, Duijkers I, Fortier MP, et al. Long-term tolerability of ethinylestradiol 20 µg/drospirenone 3 mg in a flexible extended regimen: results from a randomised, controlled, multicentre study. J Fam Plann Reprod Health Care 2012;38:84–93.

(Kluft 2008) Kluft C, Mayer G, Helmerhorst FM, Hall H, Creasy G. Comparison of the effects of a contraceptive patch and oral contraceptives on coagulation parameters [abstract no. FC2.30.04]. Int J Gynaecol Obstet 2000;70:77 + Kluft C, Meijer P, LaGuardia KD, Fisher AC. Comparison of a transdermal contraceptive patch vs. oral contraceptives on hemostasis variables. Contraception 2008;77:77-83.

(Koetsawang 1995) Koetsawang S, Charoenvisal C, Banharnsupawat L, et al. Multicenter trial of two monophasic oral contraceptives containing 30 mcg ethinylestradiol and either desogestrel or gestodene in Thai women. Contraception 1995;51:225-9.

(Koltun 2008) Koltun W, Lucky AW, Thiboutot D, et al.Efficacy and safety of 3 mg drospirenone/ 20 mcg ethinylestradiol oral contraceptive administered in 24/4 regimen in the treatment of acne vulgaris: a randomized, double-blind, placebo-controlled trial. Contraception 2008;77:249-56 + Lucky AW, Koltun W, et al. A combined oral contraceptive containing 3-mg drospirenone/ 20-µg ethinyl estradiol in the treatment of acne vulgaris: a randomized, double-blind, placebo-controlled study evaluating lesion counts and participant self-assessment. Cutis 2008;82:143-50.

(Kriplani 2010) Kriplani A, Periyasamy AJ, Agarwal N, Kulshrestha V, et al. Effect of oral contraceptive containing ethinyl estradiol combined with drospirenone vs. desogestrel on clinical and biochemical parameters in patients with polycystic ovary syndrome. Contraception 2010;82:139-146.

(Kwan 2010) Irene Kwan and Joseph Loze Onwude. Premenstrual syndrome. BMJ Clin Evid [online] 2010 [cited dec 2012]. http://clinicalevidence.bmj.com

(Kwiecien 2003) Kwiecien M, Edelman M, Nichols M, Jensen JT. Bleeding patterns and patient acceptability of standard or continuous dosing regimens of a low-dose oral contraceptive: a randomized trial. Contraception 2003;67:9-13.

(Lachnit-Fixson 1984) Lachnit-Fixson U. Fortschritte in der oralen kontrazeption: vorteille eines levonorgestrel–haltigen dreistufenpraparates gegenuber niedrigdosierten levonorgestrel– und desogestrel–haltigen monophasischen kombinationspraparaten. MMW Fortschr Med 1984;102:825-30.

(L-America 1994) Latin American Oral Contraceptive Study Group. Clinical comparison of monophasic oral contraceptive preparations of gestodene/ethinyl estradiol and desogestrel/ethinyl estradiol. Contraception 1994;50:201-14.

(Lawrie 2011) Lawrie TA, Helmerhorst FM,Maitra NK, Kulier R, Bloemenkamp K, Gülmezoglu AM. Types of progestogens in combined oral contraception: effectiveness and side-effects. Cochrane

Database of Systematic Reviews 2011, Issue 5. Art. No.: CD004861. DOI:10.1002/14651858.CD004861.pub2.

(Lethaby 2005) Lethaby A, Cooke I, Rees MC. Progesterone or progestogen-releasing intrauterine systems for heavy menstrual bleeding. Cochrane Database of Systematic Reviews 2005, Issue 4. Art. No.: CD002126. DOI: 10.1002/14651858.CD002126.pub2.

(Lethaby 2011) Anne Lethaby and Beverley Vollenhoven. Fibroids (uterine myomatosis, leiomyomas). BMJ Clin Evid [online] 2011 [cited dec 2012]. http://clinicalevidence.bmj.com

(Leyden 2002) Leyden J, Shalita A, Hordinsky M, et al. Efficacy of a low-dose oral contraceptive containing 20 µg of ethinyl estradiol and 100 µg of levonorgestrel for the treatment of moderate acne: a randomized placeb-controlled trial. J Am Acad Dermatol 2002;47:399-409.

(Lidegaard 2009) Lidegaard O, Lokkegaard E, Svendsen AL, Agger C. Hormonal contraception and risk of venous thromboembolism: national follow-up study. BMJ 2009;339:b2890.

(Lidegaard 2011) Lidegaard O, Hougaard L, Wessel Skovlund C et al. Risk of venous thromboembolism from use of oral contraceptives containing different progestogens and oestrogen doses: Danish cohort study 2001-9. BMJ 2011;343:d6423.

(Lidegaard 2012a) Lidegaard O, Hougaard Nielsen L, Wessel Skovlund C, Lokkegaard e. Venous thrombosis in users of non-oral hormonal contraception: follow-up study, Denmark 2001-10. *BMJ* 2012;344:e2990.

(Lidegaard 2012 b) Lidegaard O, Lokkegaard E, Jensen A, et al. Thrombotic stroke and myocardial infarction with Hormonal Contraception. N Engl J Med 2012;366:2257-66.

(Lo 2004) Lo SST, Fan SYS, Ho PC, Glasier AF. Effect of advanced provision of emergency contraception on women's contraceptive behavior: a randomized controlled trial. Human Reproduction 2004;19:2404-10.

(Lopez 2008) Lopez LM, Newmann SJ, Grimes DA, Nanda K, Schulz KF. Immediate start of hormonal contraceptives for contraception. *Cochrane Database of Systematic Reviews* 2008, Issue 2. Art. No.: CD006260. DOI: 10.1002/14651858.CD006260.pub2.

(Lopez 2010a) Lopez LM, Grimes DA, Gallo MF, Schulz KF. Skin patch and vaginal ring versus combined oral contraceptives for contraception. *Cochrane Database of Systematic Reviews* 2010, Issue 3. Art. No.: CD003552. DOI: 10.1002/14651858.CD003552.pub3.

(Lopez 2010b) Lopez LM, Grimes DA, Chen-Mok M, Westhoff C, Edelman A, Helmerhorst FM. Hormonal contraceptives for contraception in overweight or obese women. Cochrane Database of Systematic Reviews 2010, Issue 7. Art. No.: CD008452. DOI: 10.1002/14651858.CD008452.pub2.

(Lopez 2011) Lopez LM, EdelmanA,Chen-MokM,Trussell J,Helmerhorst FM. Progestin-only contraceptives: effects on weight. *Cochrane Database of Systematic Reviews* 2011, Issue 4. Art. No.: CD008815. DOI: 10.1002/14651858.CD008815.pub2.

(Lopez 2012) Lopez LM,Kaptein AA, Helmerhorst FM.Oral contraceptives containing drospirenone for premenstrual syndrome. Cochrane Database of Systematic Reviews 2012, Issue 2. Art. No.: CD006586. DOI: 10.1002/14651858.CD006586.pub4.

(Loudon 1990) Loudon NB, Kirkman RJE, Dewsbury JA. A double-blind comparison of the efficacy and acceptability of Femodene and Microgynon-30. Eur J Obstet Gynecol Reprod Biol 1990;34:257–66.

(Maheshwari 2007) Maheshwari S, Sarraj A, Kramer J, El-Serag HB. Oral contraception and the risk of hepatocellular carcinoma. J Hepatol 2007;506-13.

(Maloney 2008) Maloney JM, Dietze P, Watson D, et al.Treatment of acne using a 3-milligram drospirenone/ 20-microgram ethinyl estradiol oral contraceptive administered in a 24/4 regimen. Obstet Gynecol 2008;112:773-81.

(Mansour 2011) Mansour D, Verhoeven C, Sommer W, et al. Efficacy and tolerability of a monophasic combined oral contraceptive containing nomegestrol acetate and 17 β -oestradiol in a 24/4 regimen, in comparison to an oral contraceptive containing ethinylestradiol and drospirenone in a 21/7 regimen. Eur J Contracept Reprod Health Care 2011; 16: 430–443.

(Mantha 2012) Mantha S, Karp R, Raghavan V, et al. Assessing the risk of venous thromboembolic events in women taking progestin-only contraception: a meta-analysis. BMJ 2012;345:e4944.

(Manzoli 2012) Manzoli L, DE Vito C, Marzuillo C, et al; Oral contraceptives and venous thromboembolism: a systematic review and meta-analysis. Drug Saf 2012;35:191-205.

(Margolis 2007) Margolis KL, Adami HO, Luo J et al. A prospective study of oral contraceptive use and risk of myocardial infarction among Swedish women. Fertil Steril 2007;88:310-6.

(Mathieu 1998) Mathieu D, Kobeiter H, Cherqui D, et al. Oral contraceptive intake in women with focal nodular hyperplasia of the liver. Lancet 1998;352:1679-80.

(Miller 2001) Miller L, Notter KM. Menstrual reduction with extended use of combination oral contraceptive pills: randomized controlled trial. Obstet Gynecol 2001;98:771-8.

(Miller 2003) Miller L, Hughes J. Continuous combination oral contraceptive pills to eliminate withdrawal bleeding: a randomized trial. Obstet Gynecol 2003;101:653-61.

(Miller 2005) Miller L, Verhoeven C, in't Hout J. Extended regimens of the contraceptive vaginal ring. Obstet Gynecol 2005;106:473-82.

(Milsom 2006) Milsom I, Lete I, Bjertnaes A, Rokstad,et al. Effects on cycle control and bodyweight of the combined contraceptive ring, NuvaRin, versus an oral contraceptive containing 30 µg ethinyl estradiol and 3 mg drospirenone. Hum Reprod 2006;21:2304-11.

(Mohamed 2011) Mohamed AM, El-Sherbiny WS, Mostafa WA. Combined contraceptive ring versus combined oral contraceptive (30-µg ethinylestradiol and 3-mg drospirenone). Int J Gynecol Obstet 2011;114:145-8.

(Mueck 2010) Mueck AO, Seeger H, Rabe T. Hormonal contraception and risk of endometrial cancer: a systematic review. Endocr Relat Cancer 2010;17:R263-71.

(Narod 2002) Narod SA, Dubé MP, Klijn J et al. Oral Contraceptives and the Risk of Breast Cancer in BRCA1 and BRCA2 Mutation Carriers. J Natl Cancer Inst 2002;94:1773-9.

(Nelson 2012) Nelson HD, Zakher B, Cantor A, et al. Risk factors for breast cancer for women ages 40 to 49 years: a systematic review and meta-analysis. Ann Int Med 2012;156:635-48.

(Oddson 2005) Oddsson K, Leifels-Fischer B, de Melo NR, et al. Efficacy and safety of a contraceptive vaginal ring (NuvaRing) compared with a combined oral contraceptive: a 1-year randomized trial. Contraception 2005;71:176–82 + Oddsson K, Leifels-Fischer B, Wiel-Masson D, et al.Superior cycle control with a contraceptive vaginal ring compared with an oral contraceptive containing 30 µg ethinylestradiol and 150 µg levonorgestrel: a randomized trial. Hum Reprod 2005:20:557-62.

(Pallavi 2011)Pallavi M Latthe, Rita Champaneria, and Khalid S Khan. Dysmenorrhoea. BMJ Clin Evid [online] 2011 [cited dec 2012]. http://clinicalevidence.bmj.com

(Pearlstein 2005) Pearlstein TB, Bachmann GA, Zacur HA, Yonkers KA. Treatment of premenstrual dysphoric disorder with a new drospirenone-containing oral contraceptive formulation. Contraception 2005;72:414-21.

(Plewig 2009) Plewig G, Cunliffe WJ, Binder N,Höschen K. Efficacy of an oral contraceptive containing EE 0.03 mg and CMA 2 mg (Belara) in moderate acne resolution: a randomized, doubleblind, placebo-controlled Phase III trial. Contraception 2009;80,:25-33.

(Polis 2007) Polis CB, Grimes DA, Schaffer K, Blanchard K, Glasier A, Harper C. Advance provision of emergency contraception for pregnancy prevention. Cochrane Database of Systematic Reviews 2007, Issue 2. Art. No.: CD005497. DOI:10.1002/14651858.CD005497.pub2

(Power 2007) Power J, French R, Cowan FM. Subdermal implantable contraceptives versus other forms of reversible contraceptives or other implants as effective methods for preventing pregnancy. *Cochrane Database of Systematic Reviews* 2007, Issue 3. Art. No.: CD001326. DOI: 10.1002/14651858.CD001326.pub2.

(Rabe 1989) Rabe T, Runnebaum B, Kohlmeier M, et al. Clinical and metabolic effects of gestodene and levonorgestrel. Int J Fertil 1989;32:29-44.

(Raine 2005) Raine TR, Harper CC, Rocca CH, Fischer R, Padian N, Klausner JD, et al. Direct access to emergency contraception through pharmacies and effect on unintended pregnancy and STIs: a randomized controlled trial. JAMA 2005;293:54-62.

(Ramos 1989) Ramos R, Apelo R, Osteria T, Vilar E. A comparative analysis of three different dose combinations of oral contraceptives. Contraception 1989;39:165–77.

(Raymond 2006) Baecher L, Weaver MA, Raymond EG. Increased access to emergency contraception: why it may fail. Human Reproduction 2009;1:1-5+ Raymond EG, Stewart F, Weaver M, Monteith C, Van Der Pol B. Randomized trial to evaluate the impact of increased access to emergency contraceptive pills. Obstet Gynecol 2006;108:1098-106 + Raymond EG, Weaver MA. Effect of an emergency contraceptive pill intervention on pregnancy risk behavior. Contraception 2008;77(5):333–6 + Weaver MS, Raymond EG, Sander PM. Attitude and behavior effects in a randomized trial of increased access to emergency contraception. Obstet Gynecol 2009;113:107-16.

(RCOG 2010) Royal College of Obstetricians and Gynaecologists. Green-top Guideline no. 40. Venous thromboembolism and hormonal contraception. July 2010. http://www.rcog.org.uk/files/rcog-corp/GTG40VenousThromboEmbolism0910.pdf

(Reiter 1990) Reiter SL, Baer LJ. Initial selection of oral contraceptives. J Reprod Med 1990;35:547-8.

(Rickert 2007) Rickert V, Tiezzi L, Lipshutz J, et al. Depo Now: preventing unintended pregnancies among adolescents and young adults. J Adolesc Health 2007;40:22-8.

(Rooks 1979) Rooks JB, Ory HW, Ishak KG, Strauss LT, et al. Epidemiology of hepatocellular adenoma. The role of oral contraceptive use. J Am Med Assoc 1979;242:644–8.

(Sabatini 2006) Sabatini R, Cagiano R. Comparison profiles of cycle control, side effects and sexual satisfaction of three hormonal contraceptives. Contraception 2006;74:220-3.

(Sangthawan 2005) Sangthawan M, Taneepanichskul S. A comparative study of monophasic oral contraceptives containing either drospirenone 3 mg or levonorgestrel 150µg on premenstrual symptoms. Contraception 2005;71:1-7.

(Saxena 1992) Datey S, Gaur LN, Saxena BN. Vaginal bleeding patterns of women using different contraceptive methods (implants, injectables, IUDs, oral pills)-an Indian experience. Contraception 1995;51:155–65 + Saxena B. Randomised clinical trial with Triquilar-ED and low-dose combination pill. J Obstet Gynaecol India 1992;42:71–7.

(Scalori 2002) Scalori A, Tavani A, Gallus S, et al. Oral contraceptives and the risk of focal nodular hyperplasia of the liver: a case–control study. Am J Obstet Gynecol 2002;186:195–7.

(Schreiber 2009) Schreiber CA, Ratcliffe SJ, Barnhart KT. A randomized controlled trial of the effect of advanced supply of emergency contraception in postpartum teens: a feasibility study. Unpublished manuscript.

(Schwartz 2008) Schwarz EB, Gerbert B, Gonzales R. Computer-assisted Provision of Emergency Contraception: a randomized controlled trial. J Gen Int Med 2008; 23:794-9.

(Serfaty 1998) Serfaty D, Vree ML. A comparison of the cycle control and tolerability of two ultra low-dose oral contraceptives containing 20µg ethinyl estradiol and either 150µg desogestrel and 75µg gestodene. Eur J Contracept Reprod Health Care 1998;3:179-89.

(Seracchioli 2010a) Seracchioli R, Mabrouk M, Frasca C, et al. Long-term cyclic oral contraceptive therapy and endometria recurrence: a randomized controlled trial. Fertil Steril 2010;93:52-6.

(Seracchioli 2010b) Seracchioli R, mabrouk M, Frasca C, et al. Long-term oral contraceptive pills and postoperative pain management after laparoscopic excision of ovarian endometrioma: a randomized controlled trial. Fertil Steril 2010;94:464-71.

(Sesti 2007) Sesti F, Pietropolli A, Capozzolo T, et al. Hormonal suppression treatment of dietary therapy versus placebo in the control of painful symptoms after conservative surgery for endometriosis stage III-IV. A randomized controlled trial. Fertil Steril 2007;88:1541-7.

(Sesti 2009) Sesti F, Capozzolo T, Pietropolli A, et al. Recurrence rate of endometrioma after laparoscopic cystectomy: a comparative randomized trial between post-operative hormonal suppression treatment or dietary therapy vs. placebo. Eur J Obstet Gynecol Reprod Biol 2009;147:72-7.

(Shabaan 2011) Shabaan MM, Zakherah MS, El-Nashar SA, Sayed GH. Levonorgestrel-releasing intrauterine system compared to low dose combined oral contraceptive pills for idiopathic menorrhagia: a randomized clinical trial. Contraception 2011;83:48-54.

(Sheth 1982) Sheth A, Jain U, Sharma S et al. A randomized, double-blind study of two combined and two progestogen-only oral contraceptives. Contraception 1982; 25:243-52

(Sibai 2001) Sibai BM, Odlind V, Meador ML, et al. A comparative and pooled analysis of the safety and tolerability of the contraceptive patch (Ortho Evra/Evra). Fertil Steril 2002;77(Suppl 2):19-26.

(Sivin 1994) Sivin I, Stern J. Health during prolonged use of levonorgestrel 20 micrograms/d and the copper TCu 380Ag intrauterine contraceptive devices: a multicenter study. International Committee for Contraception Research (ICCR). Fertil Steril 1994;61:70-7.

(SOGC 2008) Society of Obstetricians and Gynaecologists of Canada. SOGC Clinical practice guideline no. 219. Missed hormonal contraceptives: new recommendations.
http://www.sogc.org/guidelines/documents/gui219ECO0811.pdf

(SOGC 2010) Society of Obstetricians and Gynaecologists of Canada. SOGC Clinical practice guideline no. 252. Oral contraceptives and the risk of venous thromboembolism: an update. J. Obstet Gynaecol Can. 2010; 32:1192-204.

(SOGC 2012) Society of Obstetricians and Gynaecologists of Canada. SOGC Clinical practice guideline no. 280. Emergency contraception.
http://www.sogc.org/guidelines/documents/gui280CPG1209E_000.pdf

(Stewart 2005) Stewart F, Kaunitz A, LaGuardia K, et al. Extended use of transdermal norelgestromin/ethinyl estradiol: a randomized trial. Obstet Gynecol 2005; 105:1389-96.

(Stringer 2007) Stringer EM, Kaseba C, Levy J, et al. A randomized trial of the intrauterine contraceptive device vs hormonal contraception in women who are infected with the human immunodeficiency virus. Am J Obstet Gynecol 2007;197:144.e1–8.

(Suthipongse 2004) Suthipongse W, Taneepanichskul S. An open-label randomized comparative study of oral contraceptives between medications containing 3 mg drospirenone/30µg ethinyl estradiol and 150µg levonorgestrel/30µg ethinyle stradiol inThai women. Contraception 2004;69:23-6.

(Suvisaari 1996) Suvisaari J, Lahteenmaki P. Detailed analysis of menstrual bleeding patterns after postmenopausal and postabortal insertion of a copper IUD or a levonorgestrel-releasing intrauterine system. Contraception 1996;54:201-8.

(Taneepanichskul 2002) Taneepanichskul S, Kriengsinyot R, Jaisamrarn U. A comparison of cycle control, efficacy, and side effects among healthy Thai women between two low-dose oral contraceptives containing 20 µg ethinylestradiol/75 µg gestodene (Meliane) and 30 µg ethinylestradiol/75 µg gestodene (Gynera). Contraception 2002;66:407-9.

(Tang 2012) Tang JH, Lopez LM, Mody S, Grimes DA. Hormonal and intrauterine methods for contraception for women aged 25 years and younger. Cochrane Database of Systematic Reviews 2012, Issue 11. Art. No.: CD009805. DOI: 10.1002/14651858.CD009805.pub2.

(Teichmann 1995) Teichmann AT, Brill K, Albring M, et al. The influence of the dose of ethinylestradiol in oral contraceptives on follicle growth. Gynecol Endocrinol 1995;9:299-305.

(Thiboutot 2001) Thiboutot D, Archer DF, Lemay A, et al. A randomized, controlled trial of a low-dose contraceptive containing 20 µg of ethinyl estradiol and 100 µg of levonorgestrel for acne treatment. Fertil Steril 2001;76:461-8.

(Tsilidis 2011)Tsilidis KK, Allen NE, Key TJ et al. Oral contraceptive use and reproductive factors and risk of ovarian cancer in the European Prospective Investigation into Cancer and Nutrition. Br J Cancer 2011;105:1436-42.

(UKMEC 2009) Faculty of Sexual and Reproductive Health Care (Royal College of Obstetricians and Gynaecologists). UK medical eligibility criteria for contraceptive use. November 2009. http://www.fsrh.org/pdfs/UKMEC2009.pdf.

(Urdl 2005) Hedon B, Helmerhorst FM, Cronje HS, et al. Comparison of efficacy, cycle control,compliance and safety in users of a contraceptive patch vs an oral contraceptive. Int J Gynecol Obstet 2000;70:78 + UrdlW, Apter D, Alperstein A, et al. Contraceptive efficacy, compliance and beyond: factors related to satisfaction with once-weekly transdermal compared with oral contraception. Eur J Obstet Gynecol Reprod Biol 2005;121:202-10.

(Van Vliet 2006a) Van Vliet HAAM, Grimes DA, Helmerhorst FM, Schulz KF, Lopez LM. Biphasic versus triphasic oral contraceptives for contraception. Cochrane Database of Systematic Reviews 2006, Issue 3. Art. No.: CD003283. DOI: 10.1002/14651858.CD003283.pub2.

(Van Vliet 2006b)Van Vliet HAAM, Grimes DA, Helmerhorst FM, Schulz KF, Lopez LM. Biphasic versus monophasic oral contraceptives for contraception. Cochrane Database of Systematic Reviews 2006, Issue 3. Art. No.: CD002032. DOI: 10.1002/14651858.CD002032.pub2

(Van Vliet 2011a) Van Vliet HAAM, Grimes DA, Lopez LM, Schulz KF, Helmerhorst FM. Triphasic versus monophasic oral contraceptives for contraception. *Cochrane Database of Systematic Reviews* 2011, Issue 11. Art. No.: CD003553. DOI: 10.1002/14651858.CD003553.pub3.

(Van Vliet 2011b)Van Vliet HAAM, Raps M, Lopez LM, Helmerhorst FM. Quadriphasic versus monophasic oral contraceptives for contraception. *Cochrane Database of Systematic Reviews* 2011, Issue 11. Art. No.: CD009038. DOI: 10.1002/14651858.CD009038.pub2.

(Van Vloten 2002) Van Vloten WA, Van Haselen CV, Van Zuuren EJ, et al. The effect of 2 combined oral contraceptives containing either drospirenone or cyproterone acetate on acne and seborrhea. Cutis 2002;69 Suppl 4:2-15.

(Vartiainen 2001) Vartiainen M, de Gezelle H, Broekmeulen CJ. Comparison of the effect on acne with a combiphasic desogestrelcontaining oral contraceptive and a preparation containing cyproterone acetate. Eur J Contracept Reprod Health Care 2001;6:46-53.

(Veres 2004) Veres S, Miller L, Burington B. A comparison between the vaginal ring and oral contraceptives. Obstet Gynecol 2004;104:555-63.

(Weber-Diehl 1993) Weber-Diehl F, Lehnert J, Lachnit U Comparison of two triphasic oral contraceptives containing either gestodene or norethidrone: a randomized controlled trial. Contraception 1993;48:291-301.

(Westhoff 2007) Westhoff C,Heartwell S, Edwards S, et al.Initiation of oral contraceptives using a quick start compared with a conventional start. Obstet Gynecol 2007;109:1270-6.

(Westhoff 2012) Westhoff C, Kaunitz AM, Korver T, et al. Efficacy, safety, and tolerability of a monophasic oral contraceptive containing nomegestrol acetate and 17β-estradiol. Obstet Gynecol 2012;119:989-99.

(WHO 1996) Collaborative Group on Hormonal Factors in Breast Cancer. Breast cancer and hormonal contraceptives: collaborative reanalysis of individual data on 53 297 women with breast cancer and 100 239 without breast cancer from 54 epidemiological studies. Lancet 1996;347:1713-27.

(Winkler 1996) Winkler UH, Schindler AE, Endrikat J, Dusterberg B. A comparative study of the effects of the hemostatic system of two monophasic gestodene oral contraceptives containing 20 µg and 30 µg ethinylestradiol. Contraception 1996;53:75-84.

(Winkler 2004) Winkler UH, Ferguson H, Mulders JAPA. Cycle control, quality of life and acne with two low-dose oral contraceptives containing 20µg ethinylestradiol. Contraception 2004;69:469-76.

(Wong 2009) Wong CL, Farquhar C, Roberts H, Proctor M. Oral contraceptive pill for primary dysmenorrhoea. Cochrane Database of Systematic Reviews 2009, Issue 4. Art. No.: CD002120. DOI: 10.1002/14651858.CD002120.pub3.

(Worret 2001) Worret I, Arp W, Zahradnik HP, Andreas JO, Binder N. Acne resolution rates: results of a single-blind, randomized, controlled, parallel phase III trial with EE/CMA (Belara) and EE/LNG (Microgynon). Dermatology 2001;203: 38-44.

(Yonkers 2005) Yonkers KA, Brown C, Pearlstein TB, et al. Efficacy of a new low-dose oral contraceptive with drospirenone in premenstrual dysphoric disorder. Obstet Gynecol 2005;106:492-501.

(Zador 1979) Lachnit-Fixson U. Fortschritte in der oralen kontrazeption: vorteille eines levonorgestrel–haltigen dreistufenpraparates gegenuber niedrigdosierten levonorgestrel– und desogestrel–haltigen monophasischen kombinationspraparaten. MMW Fortschr Med 1984;102:825–30. + Lachnit-Fixson U. Erstes dreistufenpraeparat zur hormonalen konzeptionsverhutung: klinische ergebnisse. MMW Munch Med Wochenschr 1979;121:1421-6.

(Zichella 1999) Zichella L, Sbrignadello C, Tomassini A, et al. Comparative study on the acceptability of two modern oral contraceptive preparations: 30mcg ethinyl estradiol combined with 150mcg desogestrel or 75mcg gestodene. Adv Contracept 1999;15:191-200.

ANNEX: UK Medical Eligibility Criteria for Contraceptive Use

Selected chapters

UK MEDICAL ELIGIBILITY CRITERIA FOR CONTRACEPTIVE USE

UKMEC 2009

The Department of Health (England) provided funding to the Faculty of Sexual and Reproductive Healthcare to assist them in the production of this guidance, the UK Medical Eligibility Criteria for Contraceptive Use (2009).

Published by the Faculty of Sexual and Reproductive Healthcare (FSRH)
Registered in England No. 2804213 and Registered Charity No. 1019969

UKMEC first published in July 2006

This document is also available on the Faculty website **www.fsrh.org.**

The FSRH would also like to acknowledge the Sexual and Reproductive Health Department of the World Health Organization for allowing access to the literature searches up to 2008.

Table of contents

SECTION A: Introduction

SECTION B: Contraceptive methods

SECTION C: Summary

SECTION A: Introduction

Contraceptive choice

Many factors determine the method of contraception a person chooses to use. Provided a woman or man is medically eligible to use a particular method, she or he should be free to choose the method which is most acceptable. To be effective, contraception must be used correctly and consistently, and for the long-acting methods (such as intrauterine devices) to be cost-effective, continuation rates must be high. Effective and continued use of a method is directly related to its acceptability to the user.

Women and men should be given accurate information about all methods for which they are medically eligible and helped to decide which might best suit their needs. Health professionals who give advice about contraception should be competent to give information about the efficacy, risks and side-effects, advantages and disadvantages, and non-contraceptive benefits of all available methods.

What are the Medical Eligibility Criteria?

Most contraceptive users are medically fit and can use any available contraceptive method safely. However, some medical conditions are associated with theoretical increased health risks when certain contraceptives are used, either because the method adversely affects the condition or because the condition, or its treatment, affects the contraceptive. For example the combined oral contraceptive pill may increase the risk of a woman with diabetes developing cardiovascular complications, while some anticonvulsants interfere with the efficacy of oral contraceptives. Since most trials of new contraceptive methods deliberately exclude subjects with chronic medical conditions, there is little direct evidence on which to base sound prescribing advice.

A set of internationally agreed norms for providing contraception to women and men with a range of medical conditions which may contraindicate one or more contraceptive methods was developed by The World Health Organisation (WHO). The WHO Medical Eligibility Criteria for Contraceptive Use (WHOMEC), third edition was published in 2004[1] and updated in 2008.[2] The WHO anticipated that the medical eligibility criteria would be used by international organisations for updating or developing their own contraceptive guidelines in line with national health policies, needs, priorities and resources.

The eligibility criteria are aimed to be used when contraceptive methods are used **primarily for contraceptive purposes** and not for other uses alone (eg. the management of menorrhagia) as the risk benefit profile may differ. Criteria relate to the SAFETY (in terms of direct health risks) of using a contraceptive method by women with certain medical conditions or using certain drugs.

The UK Medical Eligibility Criteria

The first UK Medical Eligibility Criteria (UKMEC)[3] was published in 2006 with a grant from the Department of Health (England). The document was widely distributed to clinicians throughout the United Kingdom with funding from the Department of Health (England), the Scottish Executive (Scotland) and the Faculty of Sexual and Reproductive Health (FSRH). The UKMEC was adapted from WHOMEC (third edition) using a formal consensus process, which was led by the Clinical Effectiveness Unit of the Faculty of Sexual and Reproductive Health (FSRH).[4] Formal consensus was used with the aim of making the best use of published evidence and to capture the collective knowledge of experts in the field of sexual and reproductive health and allied specialities.

UKMEC (2009) supersedes the first version (2006) and has taken account of new evidence including the WHOMEC (fourth edition).[2] This UKMEC update was guided by anonymous scoring and informal consensus at a face-to-face Consensus Group meeting where evidence and opinion could be openly discussed. The changes in UKMEC (second edition) are summarised and highlighted at the end of Section A.

Development Group

Ms Lisa Allerton
Dr Susan Brechin
Professor Anna Glasier
(Chair of Expert Consensus Group)

Expert Consensus Group (2009)

Ms Toni Belfield
Dr Alyson Elliman†
Professor Phil Hannaford
Ms Lynn Hearton
Dr Meera Kishen
Dr Ali Kubba
Dr Diana Mansour
Ms Shelley Mehigan
Dr Jane Thomas
Ms Sue Ward
Dr Anne Webb

†Dr Alyson Elliman was not present at the face-to-face Consensus Group meeting but provided input verbally and with written comments before and after the meeting.

Also present at the Consensus Group meeting but not involved in the final consensus decision on UKMEC Categories were: Dr Connie Smith (member of WHOMEC Expert Group); Dr Janet Nooney and Dr Kersti Oselin (Medicine and Healthcare products Regulatory Agency); Ms Amy Harvey (British National Formulary) and Ms Julie Craik (Faculty of Sexual and Reproductive Healthcare Clinical Effectiveness Unit).

How to use this document

The chapters in this document (Section B) list the UK categories given for all methods of contraception currently, or soon to be, available in the UK. The classification system (Categories 1 to 4) is used for all hormonal methods, intrauterine devices (copper IUD and levonorgestrel IUD), emergency contraception and barrier methods (Table A). As noted previously this classification system refers to **contraceptive methods being used for contraceptive purposes** and not for other indications where the eligibility criteria may differ. **Each UK category should be considered separately** (it is NOT appropriate to consider Category 1 and 2 safe and 3 and 4 unsafe). The definitions for each category are summarised in Table A. When an individual has multiple conditions all scoring UKMEC 3, use of the contraceptive may pose an unacceptable risk.

A **UK Category 1** indicates that there is no restriction for use. A **UK Category 2** indicates that the method can generally be used, but more careful follow-up may be required. A contraceptive method with a **UK Category 3** can be used, however this may require expert clinical judgement and/or referral to a specialist contraceptive provider, since use of the method is not usually recommended unless other methods are not available or not acceptable. A **UK Category 4** indicates that use poses an unacceptable health risk.

Table A: Definitions of UK categories

UKMEC	Definition of category
1	A condition for which there is **no restriction for the use** of the contraceptive method
2	A condition where the **advantages of using the method generally outweigh the theoretical or proven risks**
3	A condition where the theoretical or **proven risks usually outweigh the advantages** of using the method. The provision of a method requires expert clinical judgement and/or referral to a specialist contraceptive provider, since use of the method is not usually recommended unless other more appropriate methods are not available or not acceptable
4	A condition which represents an **unacceptable health** risk if the contraceptive method is used

Fertility awareness based methods (Table B) and male and female sterilisation (Table C) are classified differently. This is based on: whether it is acceptable to use the method (A); whether extra precautions, preparations or counselling are required (C); or whether use of the method should be delayed until circumstances change, for example until breastfeeding stops (D). For sterilisation a fourth category (S) denotes that special arrangements should be made for the procedure.

Table B: Definitions of UK categories for Fertility awareness based methods

UK Category		Fertility awareness based methods (FAB)
A	Accept	There is no medical reason to deny the particular FAB method to a woman in this circumstance.
C	Caution	The method is normally provided in a routine setting, but with extra preparation and precautions. For FAB methods, this usually means that special counselling may be needed to ensure correct use of the method by a woman in this circumstance.
D	Delay	Use of the method should be delayed until the condition is evaluated or changes. Alternative temporary methods of contraception should be offered.

Table C: Definitions of UK categories for Male and Female Sterilisation

UK Category		Sterilisation
A	Accept	There is no medical reason to deny sterilisation to a person with this condition.
C	Caution	The procedure is normally conducted in a routine setting, but with extra preparation, precautions and counselling.
D	Delay	The procedure is delayed until the condition is evaluated, treated and/or changes. Alternative temporary methods of contraception should be provided.
S	Special	The procedure should be undertaken in a setting with an experienced surgeon and staff, equipment needed to provide general anaesthesia, and other back-up medical support. For these conditions, the capacity to decide on the most appropriate procedure and anaesthesia method is also needed. Alternative temporary methods of contraception should be provided, if referral is required or there is otherwise any delay.

Section B includes individual sections of UK categories for groups of contraceptives: combined hormonal methods (combined oral contraceptive pill, patch and vaginal ring); progestogen-only methods (pills, injectables and implants); intrauterine devices (copper IUD and levonorgestrel IUD); sterilisation (male and female); emergency contraception (oral progestogen-only and copper IUD); barrier methods (male and female condoms, diaphragms and cervical caps); and fertility awareness based methods (cervical mucus assessment method and devices for measuring hormones).

In some cases **initiation** of a contraceptive method (I) and **continuation** of the method (C) are distinguished and classified differently (Table D).

Table D: Initiation and continuation of a contraceptive method by women with a medical condition

Initiation (I)	Starting a method of contraception by a woman with a specific medical condition.
Continuation (C)	Continuing with the method already being used by a woman who develops a new medical condition.

The duration of use of a method of contraception prior to the onset of a new medical condition may influence decisions regarding continued use. However, there is no set duration and clinical judgement will be required.

In the section tables the first column indicates the **CONDITION**. Each condition is defined as representing either an individual's characteristics (e.g. age, history of pregnancy) or a known pre-existing medical condition (e.g. diabetes, hypertension). Some conditions are subdivided to differentiate between varying degrees of the condition (e.g. migraine with or without aura). The second column classifies the condition into one of the four **CATEGORIES** (1 to 4, or A, C, D, or S).

For some conditions the third column is used to provide **CLARIFICATION** or to make comment on the **EVIDENCE** for the recommendation (Table E).

At the end of each method section additional comments can be found. References are listed at the end of each chapter.

Table E: Example of Tables in UKMEC

TYPE OF CONTRACEPTIVE		
CONDITION	**CATEGORY** I = Initiation or C = Continuation	**CLARIFICATIONS / EVIDENCE**
eg Diabetes	Category 1, 2, 3 or 4 Category A,C,D and S NA (not applicable) denotes a condition for which a ranking was not given but for which clarifications have been provided.	Clarifications and evidence regarding the classification

The summary sheets at the end of the document list the most common reversible methods of contraception, conditions and categories, and can be used as a quick reference in the clinic setting. In addition, these sheets and UK Category definitions are reproduced in a pull out section which can be used for photocopying and distribution in your own clinical setting.

In developing the fourth edition of WHOMEC a number of multinational expert groups were convened to review evidence in relation to liver diseases (viral hepatitis, cirrhosis and tumours), systemic lupus erythematosus, gestational trophoblastic disease and drug interactions. The categories given by WHO have been accepted in this UKMEC update. A summary of these and other changes in the UKMEC 2009 from the previous edition are summarised on pages eleven to fourteen. The UKMEC should be used as a guide to safe use of contraception however, this should not replace clinical judgment and evaluation in individual situations.

Commonly used abbreviations

AIDS	Acquired immune deficiency syndrome
BMI	Body mass index
CHC	Combined hormonal contraception
COC	Combined oral contraception
Cu-IUD	Copper intrauterine device
DMPA	Depot medroxyprogesterone acetate
DVT	Deep vein thrombosis
EE	Ethinylestradiol
HIV	Human immunodeficiency virus
IMP	Implant (progestogen-only)
LNG-IUD	Levonorgestrel releasing intrauterine device
NET-EN	Norethisterone enantate
PE	Pulmonary embolism
PID	Pelvic inflammatory disease
POC	Progestogen-only contraception
POEC	Progestogen-only emergency contraception
POP	Progestogen-only pill
STI	Sexually transmitted infection
SLE	Systemic lupus erythematosus
VTE	Venous thromboembolism

References

1. WHO Medical Eligibility Criteria for Contraceptive Use, 3rd edition, 2004. ISBN 92 4 156266 8. Publications of the World Health Organization.

2. WHO Medical Eligibility Criteria for Contraceptive Use, 4th edition, 2008 Edition.

3. UK Medical Eligibility Criteria (UKMEC 2005/06). www.fsrh.org

4. Stephen G, Brechin S, Glasier A. Using formal consensus methods to adapt World Health Organization Medical Eligibility Criteria for Contraceptive Use. *Contraception* 2008, Oct; **78** (4):300-308

SECTION B: CONTRACEPTIVE METHODS

Combined hormonal contraceptives (CHCs)

COMBINED HORMONAL CONTRACEPTIVES (CHCs) *Combined oral contraception (COC), combined transdermal patch and vaginal ring*	**These methods do not protect against STI/HIV. If there is risk of STI/HIV (including during pregnancy or postpartum), the correct and consistent use of condoms is recommended, either alone or with another contraceptive method. Male condoms reduce the risk of STI/HIV.**	
CONDITION	**CATEGORY** I=Initiation C=Continuation	**CLARIFICATIONS/EVIDENCE- Most evidence available relates to COC use. However, this evidence is also applied to patch and ring use.**
PERSONAL CHARACTERISTICS AND REPRODUCTIVE HISTORY		
PREGNANCY	NA	**Clarification:** Use is not required. There is no known harm to the woman, the course of her pregnancy, or the fetus if accidentally used during pregnancy.
AGE*		
a) Menarche to <40 years b) ≥40 years	1 2	**Clarification:** Guidance from the FSRH supports use of CHC up to age 50 years if there are no medical contraindications to use.[1]
PARITY		
a) Nulliparous b) Parous	1 1	
BREASTFEEDING*		
a) <6 weeks postpartum	4	**Clarification:** Use of combined hormonal methods <6 weeks postpartum has a detrimental effect on breastmilk volume.[2] Evidence on the effect of combined hormonal contraception on breastmilk quality or quantity >6 weeks postpartum is poor but there appears to be no effect on infant growth. Combined hormonal methods can be used safely but are unlikely to be required if women are fully or almost fully breastfeeding, amenorrhoeic and <6 months postpartum.[2]
b) ≥6 weeks to <6 months postpartum (fully or almost fully breastfeeding)	3	**Definition:** *Full and almost fully breastfeeding* includes *exclusive* with no other liquids or solids given; *almost exclusive*: vitamins, water or juice given infrequently in addition to breastfeeds; or *partial (high) breastfeeding* where the vast majority of feeds are breastfeeds.
c) ≥6 weeks to <6 months postpartum (partial breastfeeding medium to minimal)	2	*Partial or token breastfeeding includes: Medium* - about half feeds are breastfeeds; *Low* - vast majority of feeds are not breastfeeds; *Minimal* - occasional irregular breastfeeds cannot be relied upon as a contraceptive method.[3]
d) ≥6 months postpartum	1	
POSTPARTUM* (in non-breastfeeding women)		
a) <21 days b) ≥21 days	3 1	**Clarification:** This includes any births, including stillbirths from 24 weeks gestation

*See also additional comments at end of section

UKMEC	DEFINITION OF CATEGORY
CATEGORY 1	A condition for which there is no restriction for the use of the contraceptive method
CATEGORY 2	A condition where the advantages of using the method generally outweigh the theoretical or proven risks
CATEGORY 3	A condition where the theoretical or proven risks generally outweigh the advantages of using the method. The provision of a method requires expert clinical judgement and/or referral to a specialist contraceptive provider, since use of the method is not usually recommended unless other more appropriate methods are not available or not acceptable
CATEGORY 4	A condition which represents an unacceptable health risk if the contraceptive method is used

COMBINED HORMONAL CONTRACEPTIVES (CHCs) *Combined oral contraception (COC), combined transdermal patch and vaginal ring*	**These methods do not protect against STI/HIV. If there is risk of STI/HIV (including during pregnancy or postpartum), the correct and consistent use of condoms is recommended, either alone or with another contraceptive method. Male condoms reduce the risk of STI/HIV.**	
CONDITION	**CATEGORY** I=Initiation C=Continuation	**CLARIFICATIONS/EVIDENCE- Most evidence available relates to COC use. However, this evidence is also applied to patch and ring use.**
POST-ABORTION		
a) First trimester	1	**Clarification:** includes induced and spontaneous abortion <24 weeks gestation. Combined hormonal methods may be started immediately following surgical abortion or after the second part of a medical abortion.
b) Second trimester	1	
c) Immediate post-septic abortion	1	
PAST ECTOPIC PREGNANCY*	1	
HISTORY OF PELVIC SURGERY	1	
SMOKING		
a) Age <35 years	2	COC users who smoke are at an increased risk of cardiovascular disease (in particular myocardial infarction) compared to COC users who do not smoke.[4-11]
b) Age ≥35 years		
(i) <15 cigarettes/day	3	The risk of myocardial infarction increases as the number of cigarettes smoked increases. COC users who smoke >15 cigarettes per day (so called heavy smokers) have the greatest increase in risk of myocardial infarction.[9-11]
(ii) ≥15 cigarettes/day	4	
(iii) stopped smoking <1 year ago	3	
(iv) stopped smoking ≥1 year ago	2	The 35 year age cut off is identified because any excess mortality associated with smoking is only apparent from this age. The mortality rate from all causes (including cancers) decreases to that of a non-smoker within 20 years of smoking cessation. The cardiovascular disease risk associated with smoking decreases within one to five years of smoking cessation.[11-13]
OBESITY		The absolute risk of venous thromboembolism (VTE) in the women of reproductive age is low. The relative risk of VTE increases with combined hormonal contraceptive use. Nevertheless, the absolute risk of VTE in combined hormonal contraceptive users is still low. The risk of VTE rises as BMI increases over 30 and rises further with BMI over 35. Use of CHC raises this inherent increased risk further.[15-20]
a) ≥30 - 34 kg/m² body mass index	2	
b) ≥35 kg/m² body mass index	3	
CARDIOVASCULAR DISEASE		
MULTIPLE RISK FACTORS FOR CARDIOVASCULAR DISEASE (such as older age, smoking, diabetes, hypertension & obesity)	3/4	When multiple risk factors exist, risk of cardiovascular disease may increase substantially.

*See also additional comments at end of section

UKMEC	DEFINITION OF CATEGORY
CATEGORY 1	A condition for which there is no restriction for the use of the contraceptive method
CATEGORY 2	A condition where the advantages of using the method generally outweigh the theoretical or proven risks
CATEGORY 3	A condition where the theoretical or proven risks generally outweigh the advantages of using the method. The provision of a method requires expert clinical judgement and/or referral to a specialist contraceptive provider, since use of the method is not usually recommended unless other more appropriate methods are not available or not acceptable
CATEGORY 4	A condition which represents an unacceptable health risk if the contraceptive method is used

COMBINED HORMONAL CONTRACEPTIVES (CHCs) *Combined oral contraception (COC), combined transdermal patch and vaginal ring*	**These methods do not protect against STI/HIV. If there is risk of STI/HIV (including during pregnancy or postpartum), the correct and consistent use of condoms is recommended, either alone or with another contraceptive method. Male condoms reduce the risk of STI/HIV.**	
CONDITION	**CATEGORY** I=Initiation C=Continuation	**CLARIFICATIONS/EVIDENCE- Most evidence available relates to COC use. However, this evidence is also applied to patch and ring use.**
HYPERTENSION*		
For all categories of hypertension, classifications are based on the assumption that **no other risk factors for cardiovascular disease exist**. When multiple risk factors do exist, risk of cardiovascular disease may increase substantially. A single reading of blood pressure level is not sufficient to classify a woman as hypertensive. If elevated, the BP should be re-assessed at the end of the consultation. If blood pressure is increased it should be re-assessed on at least two subsequent clinic visits at monthly intervals.[21,22]		
a) Adequately controlled hypertension b) Consistently elevated blood pressure levels (properly taken measurements) (i) systolic >140 to 159 mmHg or diastolic >90 to 94mmHg (ii) systolic ≥160 or diastolic ≥95 mmHg	3 3 4	**Clarification:** Women adequately treated for hypertension are at reduced risk of acute myocardial infarction and stroke compared to untreated women. Although there are no data, COC users with adequately controlled and monitored hypertension should be at reduced risk of acute myocardial infarction and stroke compared with untreated hypertensive COC users. Guidelines from the British Hypertension Society suggest that although estrogen-containing contraception may be used for women with adequately controlled BP other methods may be more suitable.[21] **Evidence:** Among women with hypertension, COC users were at increased risk of stroke, acute myocardial infarction, and peripheral arterial disease compared with non-users.[5,6,9,23-42] **Clarification:** Anti-hypertensive therapy may be initiated when the BP is consistently 160/100 mmHg or greater.[21] Decisions about the initiation or continued use of combined hormonal contraception should be made at lower BP levels, and alternative contraception may be advised.
c) Vascular disease	4	**Clarification:** *Vascular disease* includes: coronary heart disease presenting with angina; peripheral vascular disease presenting with intermittent claudication; hypertensive retinopathy; and transient ischaemic attacks.
HISTORY OF HIGH BLOOD PRESSURE DURING PREGNANCY (where current blood pressure normal)	2	**Evidence:** Women with a history of gestational hypertension have a very small increase in the absolute risk of myocardial infarction and venous thromboembolism and use of COC increases this risk further. [9,16,28-30,43-48]

*See also additional comments at end of section

UKMEC	DEFINITION OF CATEGORY
CATEGORY 1	A condition for which there is no restriction for the use of the contraceptive method
CATEGORY 2	A condition where the advantages of using the method generally outweigh the theoretical or proven risks
CATEGORY 3	A condition where the theoretical or proven risks generally outweigh the advantages of using the method. The provision of a method requires expert clinical judgement and/or referral to a specialist contraceptive provider, since use of the method is not usually recommended unless other more appropriate methods are not available or not acceptable
CATEGORY 4	A condition which represents an unacceptable health risk if the contraceptive method is used

COMBINED HORMONAL CONTRACEPTIVES (CHCs) *Combined oral contraception (COC), combined transdermal patch and vaginal ring*	**These methods do not protect against STI/HIV. If there is risk of STI/HIV (including during pregnancy or postpartum), the correct and consistent use of condoms is recommended, either alone or with another contraceptive method. Male condoms reduce the risk of STI/HIV.**	
CONDITION	**CATEGORY** I=Initiation C=Continuation	**CLARIFICATIONS/EVIDENCE- Most evidence available relates to COC use. However, this evidence is also applied to patch and ring use.**
VENOUS THROMBOEMBOLISM (VTE)*		
a) History of VTE	4	Venous thromboembolism includes deep vein thrombosis and pulmonary embolism.
b) Current VTE (on anticoagulants)	4	
c) Family history of VTE		**A family history of VTE** may alert clinicians to women who may have an increased risk themselves but alone cannot identify with certainty an underlying thrombophillia.[49]
(i) first-degree relative age <45 years	3	
(ii) first-degree relative age ≥45 years	2	
d) Major surgery		**Major surgery** includes operations of >30 minutes duration. Procedures with high risk of VTE include: general or orthopaedic surgery, trauma and neurosurgery.[50] CHC should be discontinued at least 4 weeks prior to any major elective surgery and advice given on appropriate alternative methods.
(i) with prolonged immobilisation	4	
(ii) without prolonged immobilisation	2	
e) Minor surgery without immobilisation	1	**Minor surgery** includes operations lasting <30 minutes. Varicose vein surgery has a low risk of VTE.[50]
f) Immobility (unrelated to surgery) e.g. *wheelchair use, debilitating illness*	3	**Immobility** due to hospitalisation for acute trauma, acute illness, or paralysis, is associated with a high risk of VTE. Continuation of CHC should be reconsidered and alternative methods used until mobile.
KNOWN THROMBOGENIC MUTATIONS (e.g., Factor V Leiden, Prothrombin mutation, Protein S, Protein C, and Antithrombin deficiencies)	4	**Clarification:** Routine screening is not appropriate because of the rarity of the conditions and the high cost of screening.[51-53]
SUPERFICIAL VENOUS THROMBOSIS*		
a) Varicose veins	1	
b) Superficial thrombophlebitis	2	
CURRENT AND HISTORY OF ISCHAEMIC HEART DISEASE*	4	

*See also additional comments at end of section

UKMEC	DEFINITION OF CATEGORY
CATEGORY 1	A condition for which there is no restriction for the use of the contraceptive method
CATEGORY 2	A condition where the advantages of using the method generally outweigh the theoretical or proven risks
CATEGORY 3	A condition where the theoretical or proven risks generally outweigh the advantages of using the method. The provision of a method requires expert clinical judgement and/or referral to a specialist contraceptive provider, since use of the method is not usually recommended unless other more appropriate methods are not available or not acceptable
CATEGORY 4	A condition which represents an unacceptable health risk if the contraceptive method is used

COMBINED HORMONAL CONTRACEPTIVES (CHCs) *Combined oral contraception (COC), combined transdermal patch and vaginal ring*	**These methods do not protect against STI/HIV. If there is risk of STI/HIV (including during pregnancy or postpartum), the correct and consistent use of condoms is recommended, either alone or with another contraceptive method. Male condoms reduce the risk of STI/HIV.**	
CONDITION	**CATEGORY** I=Initiation C=Continuation	**CLARIFICATIONS/EVIDENCE- Most evidence available relates to COC use. However, this evidence is also applied to patch and ring use.**
STROKE* (history of cerebrovascular accident, including TIA)	4	
KNOWN HYPERLIPIDAEMIAS*	2/3	**Clarification:** Routine screening is not appropriate because of the rarity of the conditions and the high cost of screening. While some types of hyperlipidaemias are risk factors for vascular disease, the category should be assessed according to the type, its severity, and the presence of other cardiovascular risk factors. Lipid levels alone are poor predictors of risk of coronary heart disease. In the UK screening and treatment are aimed towards those at greatest risk of coronary heart disease, and this may also influence hormonal contraceptive use. Risk categories will vary depending on risk of premature coronary heart disease and the presence of other risk factors.[54] *Common hypercholesterolaemia* and *Familial combined hyperlipidaemia* are associated with an increased risk of coronary heart disease but usually this occurs over the age of 60 years.[54] *Familial hypercholesterolaemia* (autosomal dominant) has a prevalence of about 1 in 500. People with this condition have a four-fold increase in the risk of premature coronary heart disease.[54]
VALVULAR AND CONGENITAL HEART DISEASE*		
a) Uncomplicated	2	**Clarification:** *Valvular heart disease* occurs when any of the four heart valves are stenotic and/or incompetent (eg. aortic stenosis, mitral regurgitation; tricuspid valve abnormalities; pulmonary stenosis).[55] *Congenital heart disease* includes Aortic stenosis; Atrial septal defects; Atrio-ventricular septal defect; Cardiomyopathy (hypertrophic or dilated); Coarctation of the Aorta; Complex Transposition of the Great Arteries; Ebstein's Anomaly; Eisenmenger Syndrome: Patent Ductus Arteriosus; Pulmonary Atresia; Pulmonary Stenosis; Tetralogy of Fallot; Total Anomalous Pulmonary Venous Connection; Tricuspid Atresia; Truncus Arteriosus; Ventricular Septal Defect.[56] Surgical correction (prosthetic valve) and ongoing cardiac problems should be taken into account when considering contraceptive use.
b) Complicated *(eg. with pulmonary hypertension,atrial fibrillation, history of subacute bacterial endocarditis)*	4	

*See also additional comments at end of section

UKMEC	DEFINITION OF CATEGORY
CATEGORY 1	A condition for which there is no restriction for the use of the contraceptive method
CATEGORY 2	A condition where the advantages of using the method generally outweigh the theoretical or proven risks
CATEGORY 3	A condition where the theoretical or proven risks generally outweigh the advantages of using the method. The provision of a method requires expert clinical judgement and/or referral to a specialist contraceptive provider, since use of the method is not usually recommended unless other more appropriate methods are not available or not acceptable
CATEGORY 4	A condition which represents an unacceptable health risk if the contraceptive method is used

COMBINED HORMONAL CONTRACEPTIVES (CHCs) *Combined oral contraception (COC), combined transdermal patch and vaginal ring*	**These methods do not protect against STI/HIV. If there is risk of STI/HIV (including during pregnancy or postpartum), the correct and consistent use of condoms is recommended, either alone or with another contraceptive method. Male condoms reduce the risk of STI/HIV.**	
CONDITION	**CATEGORY** I=Initiation C=Continuation	**CLARIFICATIONS/EVIDENCE- Most evidence available relates to COC use. However, this evidence is also applied to patch and ring use.**
NEUROLOGIC CONDITIONS		
HEADACHES*	**I** / **C**	Headache is a common condition affecting women of reproductive age. Few studies have specifically assessed migraine in COC users. Classification depends on making an accurate diagnosis of those severe headaches that are migrainous and in addition those complicated by aura. **Symptoms** of aura include: homonymous hemianopia, unilateral paraesthesia and/or numbness; unilateral weakness and aphasia or unclassifiable speech disorder. Visual symptoms progress from fortification spectra (a starshaped figure near the point of fixation with scintillating edges) to scotoma (a bright shape which gradually increases in size). Flashing lights are not classified as aura. Aura occurs before the onset of headache.[57]
a) Non-migrainous (mild or severe)	1 / 2	
b) Migraine without aura, at any age	2 / 3	
c) Migraine with aura, at any age	4 / 4	
d) Past history (≥5 years ago) of migraine with aura, any age	3	Migraine without aura does not increase the risk of ischaemic stroke whilst migraine with aura does. Use of COC increases the risk of stroke however, the absolute risk remains very low. Women with migraine who use COC have a two to four fold increase in the risk of stroke compared to those not using COC.[57-59]
EPILEPSY	1	See section on drug interactions.
DEPRESSIVE DISORDERS		
DEPRESSIVE DISORDERS	1	**Clarification:** The classification is based on data for women with selected depressive disorders. No data on bipolar disorder or postpartum depression were available. There is a potential for drug interactions between certain antidepressant medications and hormonal contraceptives. **Evidence:** COC use did not increase depressive symptoms in women with depression compared to baseline or to non-users with depression.[60-61]
BREAST AND REPRODUCTIVE TRACT CONDITIONS		
VAGINAL BLEEDING PATTERNS*		
a) Irregular pattern without heavy bleeding	1	
b) Heavy or prolonged bleeding (includes regular and irregular patterns)	1	**Clarification:** Unusually heavy bleeding should raise the suspicion of a serious underlying condition.[62-65]

*See also additional comments at end of section

UKMEC	DEFINITION OF CATEGORY
CATEGORY 1	A condition for which there is no restriction for the use of the contraceptive method
CATEGORY 2	A condition where the advantages of using the method generally outweigh the theoretical or proven risks
CATEGORY 3	A condition where the theoretical or proven risks generally outweigh the advantages of using the method. The provision of a method requires expert clinical judgement and/or referral to a specialist contraceptive provider, since use of the method is not usually recommended unless other more appropriate methods are not available or not acceptable
CATEGORY 4	A condition which represents an unacceptable health risk if the contraceptive method is used

COMBINED HORMONAL CONTRACEPTIVES (CHCs) *Combined oral contraception (COC), combined transdermal patch and vaginal ring*	**These methods do not protect against STI/HIV. If there is risk of STI/HIV (including during pregnancy or postpartum), the correct and consistent use of condoms is recommended, either alone or with another contraceptive method. Male condoms reduce the risk of STI/HIV.**	
CONDITION	**CATEGORY** I=Initiation C=Continuation	**CLARIFICATIONS/EVIDENCE- Most evidence available relates to COC use. However, this evidence is also applied to patch and ring use.**
UNEXPLAINED VAGINAL BLEEDING* (suspicious for serious underlying condition) Before evaluation	2	**Clarification:** If pregnancy or an underlying pathological condition (such as pelvic malignancy) is suspected, it must be evaluated and the category adjusted after evaluation.
ENDOMETRIOSIS*	1	
BENIGN OVARIAN TUMOURS (including cysts)	1	
SEVERE DYSMENORRHOEA	1	**Evidence:** There was no increased risk of side-effects with COC use among women with dysmenorrhoea compared to women not using COCs. Some COC users had a reduction in pain and bleeding.[64-65]
GESTATIONAL TROPHOBLASTIC DISEASE (GTD)		**Clarification:** Gestational trophoblastic disease includes hydatidiform mole, invasive mole and placental site trophoblastic tumour. The use of a COC by women following evacuation of a molar pregnancy does not increase the risk of post-molar trophoblastic disease. Indeed there is some evidence that COC use by women in this situation is associated with a more rapid regression in serum β-hCG levels than in women not using a COC. [66-74] Advice should be sought from the specialist managing a woman's gestational trophoblastic disease as clinical guidelines vary within the UK.
a) Decreasing or undetectable β-hCG levels	1	
b) Persistently elevated β-hCG levels or malignant disease	1	
CERVICAL ECTROPION*	1	
CERVICAL INTRAEPITHELIAL NEOPLASIA (CIN)	2	**Evidence:** Among women with persistent human papilloma virus infection, long-term COC use (≥ 8 years) may increase the risk of carcinoma *in situ* and invasive carcinoma.[75,76]
CERVICAL CANCER* (awaiting treatment)	2	
BREAST DISEASE*	**I** / **C**	
a) Undiagnosed mass	3 / 2	**Clarification:** Evaluation should be pursued as early as possible.
b) Benign breast disease	1	
c) Family history of cancer	1	**Evidence:** Among COC users with a family history of breast cancer, there was no increased risk of breast cancer compared with non-COC users with a family history of breast cancer.[77-85] Among women with BRCA1 mutations, COC users may have a small increased risk of breast cancer compared with non-users.[86-88]
d) Carriers of known gene mutations associated with breast cancer (eg. BRCA1)	3	
e) Breast cancer		
(i) current	4	
(ii) past and no evidence of current disease for 5 years	3	

*See also additional comments at end of section

UKMEC	DEFINITION OF CATEGORY
CATEGORY 1	A condition for which there is no restriction for the use of the contraceptive method
CATEGORY 2	A condition where the advantages of using the method generally outweigh the theoretical or proven risks
CATEGORY 3	A condition where the theoretical or proven risks generally outweigh the advantages of using the method. The provision of a method requires expert clinical judgement and/or referral to a specialist contraceptive provider, since use of the method is not usually recommended unless other more appropriate methods are not available or not acceptable
CATEGORY 4	A condition which represents an unacceptable health risk if the contraceptive method is used

COMBINED HORMONAL CONTRACEPTIVES (CHCs) *Combined oral contraception (COC), combined transdermal patch and vaginal ring*	**These methods do not protect against STI/HIV. If there is risk of STI/HIV (including during pregnancy or postpartum), the correct and consistent use of condoms is recommended, either alone or with another contraceptive method. Male condoms reduce the risk of STI/HIV.**	
CONDITION	**CATEGORY** I=Initiation C=Continuation	**CLARIFICATIONS/EVIDENCE- Most evidence available relates to COC use. However, this evidence is also applied to patch and ring use.**
ENDOMETRIAL CANCER*	1	
OVARIAN CANCER*	1	
UTERINE FIBROIDS*		
a) Without distortion of the uterine cavity	1	
b) With distortion of the uterine cavity	1	
PELVIC INFLAMMATORY DISEASE (PID)*		
a) Past PID (assuming no current risk factors for STIs)	1	
b) PID Current	1	
SEXUALLY TRANSMITTED INFECTIONS (STIs*)		
a) Chlamydial infection		**Evidence:** Evidence suggests that there may be an increased risk of chlamydial cervicitis among COC users at high risk of STIs. For other STIs, there is either evidence of no association between COC use and STI acquisition or insufficient evidence from which to draw any conclusions.[89-165]
i) Symptomatic	1	
ii) Asymptomatic	1	
b) Current purulent cervicitis or gonorrhoea	1	
c) Other STIs (excluding HIV and hepatitis)	1	
d) Vaginitis (including *Trichomonas vaginalis* and bacterial vaginosis)	1	
e) Increased risk of STIs	1	
HIV/AIDS		
HIGH RISK OF HIV*	1	**Evidence:** Overall, evidence is inconsistent regarding whether or not there is any increased risk of HIV acquisition among COC users compared with non-users.

*See also additional comments at end of section

UKMEC	DEFINITION OF CATEGORY
CATEGORY 1	A condition for which there is no restriction for the use of the contraceptive method
CATEGORY 2	A condition where the advantages of using the method generally outweigh the theoretical or proven risks
CATEGORY 3	A condition where the theoretical or proven risks generally outweigh the advantages of using the method. The provision of a method requires expert clinical judgement and/or referral to a specialist contraceptive provider, since use of the method is not usually recommended unless other more appropriate methods are not available or not acceptable
CATEGORY 4	A condition which represents an unacceptable health risk if the contraceptive method is used

COMBINED HORMONAL CONTRACEPTIVES (CHCs) *Combined oral contraception (COC), combined transdermal patch and vaginal ring*	**These methods do not protect against STI/HIV. If there is risk of STI/HIV (including during pregnancy or postpartum), the correct and consistent use of condoms is recommended, either alone or with another contraceptive method. Male condoms reduce the risk of STI/HIV.**	
CONDITION	**CATEGORY** I=Initiation C=Continuation	**CLARIFICATIONS/EVIDENCE- Most evidence available relates to COC use. However, this evidence is also applied to patch and ring use.**
HIV-INFECTED		
a) Not using anti-retroviral therapy	1	
b) Using anti-retroviral therapy	1-3	See section on drug interactions.
AIDS (using antiretrovirals)	2	See section on drug interactions.
OTHER INFECTIONS		
SCHISTOSOMIASIS		
a) Uncomplicated	1	**Evidence:** Among women with uncomplicated schistosomiasis, COC use had no adverse effects on liver function.[166-173]
b) Fibrosis of liver (if severe, see cirrhosis)	1	
TUBERCULOSIS		
a) Non-pelvic	1	See section on drug interactions.
b) Known pelvic	1	
MALARIA	1	See section on drug interactions.

*See also additional comments at end of section

UKMEC	DEFINITION OF CATEGORY
CATEGORY 1	A condition for which there is no restriction for the use of the contraceptive method
CATEGORY 2	A condition where the advantages of using the method generally outweigh the theoretical or proven risks
CATEGORY 3	A condition where the theoretical or proven risks generally outweigh the advantages of using the method. The provision of a method requires expert clinical judgement and/or referral to a specialist contraceptive provider, since use of the method is not usually recommended unless other more appropriate methods are not available or not acceptable
CATEGORY 4	A condition which represents an unacceptable health risk if the contraceptive method is used

COMBINED HORMONAL CONTRACEPTIVES (CHCs) *Combined oral contraception (COC), combined transdermal patch and vaginal ring*	**These methods do not protect against STI/HIV. If there is risk of STI/HIV (including during pregnancy or postpartum), the correct and consistent use of condoms is recommended, either alone or with another contraceptive method. Male condoms reduce the risk of STI/HIV.**	
CONDITION	**CATEGORY** I=Initiation C=Continuation	**CLARIFICATIONS/EVIDENCE- Most evidence available relates to COC use. However, this evidence is also applied to patch and ring use.**
ENDOCRINE CONDITIONS		
DIABETES*		
a) History of gestational diabetes	1	
b) Non-vascular disease		
(i) non-insulin dependent	2	
(ii) insulin dependent	2	
c) Nephropathy/ retinopathy/neuropathy	3/4	**Clarification:** The category should be assessed according to the severity of the condition.
d) Other vascular disease	3/4	
THYROID DISORDERS		
a) Simple goitre	1	
b) Hyperthyroid	1	
c) Hypothyroid	1	
GASTROINTESTINAL CONDITIONS		
GALL-BLADDER DISEASE*		
a) Symptomatic		
(i) treated by cholecystectomy	2	
(ii) medically treated	3	
(iii) current	3	
b) Asymptomatic	2	
HISTORY OF CHOLESTASIS*		
a) Pregnancy-related	2	
b) Past COC-related	3	
VIRAL HEPATITIS*	**I** / **C**	The use of CHCs is not considered to exacerbate viral hepatitis. For carriers of viral hepatitis it appears that hormonal contraceptive use does not trigger liver failure or severe dysfunction. Acute or flare: this category should be assessed on the severity of the condition.[175-180]
a) Acute or flare	3/4 / 2	
b) Carrier	1 / 1	
c) Chronic	1 / 1	
CIRRHOSIS*		
a) Mild (compensated without complications)	1	**Clarification**:*Severe (decompensated) cirrhosis:* development of major complications (such as ascites, jaundice, encephalopathy, or gastrointestinal haemorrhage).[181]
b) Severe (decompensated)	4	

*See also additional comments at end of section

UKMEC	DEFINITION OF CATEGORY
CATEGORY 1	A condition for which there is no restriction for the use of the contraceptive method
CATEGORY 2	A condition where the advantages of using the method generally outweigh the theoretical or proven risks
CATEGORY 3	A condition where the theoretical or proven risks generally outweigh the advantages of using the method. The provision of a method requires expert clinical judgement and/or referral to a specialist contraceptive provider, since use of the method is not usually recommended unless other more appropriate methods are not available or not acceptable
CATEGORY 4	A condition which represents an unacceptable health risk if the contraceptive method is used

COMBINED HORMONAL CONTRACEPTIVES (CHCs) *Combined oral contraception (COC), combined transdermal patch and vaginal ring*	**These methods do not protect against STI/HIV. If there is risk of STI/HIV (including during pregnancy or postpartum), the correct and consistent use of condoms is recommended, either alone or with another contraceptive method. Male condoms reduce the risk of STI/HIV.**	
CONDITION	**CATEGORY** I=Initiation C=Continuation	**CLARIFICATIONS/EVIDENCE- Most evidence available relates to COC use. However, this evidence is also applied to patch and ring use.**
LIVER TUMOURS*		
a) Benign		CHCs do not appear to influence either resolution or progression of liver lesions. No evidence concerning the use of CHCs in those with malignant disease was found.[182-183]
(i) Focal nodular hyperplasia	2	
(ii) Hepatocellular (adenoma)	4	
b) Malignant (hepatoma)	4	
INFLAMMATORY BOWEL DISEASE (includes Crohn's disease and ulcerative colitis)	2	Continuation may need to be reviewed if the woman has an acute exacerbation, acute surgery or prolonged immobilisation (see section on VTE).[184] Absorption of oral contraception may be reduced if there is severe malabsorption due to small bowel involvement, but is unaffected by colectomy and ileostomy.
ANAEMIAS		
THALASSAEMIA*	1	
SICKLE CELL DISEASE	2	
IRON-DEFICIENCY ANAEMIA*	1	
RAYNAUD'S DISEASE*		
a) Primary	1	**Clarification:** Primary Raynaud's is not a contraindication to use of combined hormonal contraception. Secondary Raynaud's has an underlying cause such as scleroderma, rheumatoid arthritis, systemic lupus erythematosus. Systemic lupus erythematosus causes a tendency for increased coagulation if lupus anticoagulant is present.[1,185-189]
b) Secondary		
(i) without lupus anticoagulant	2	
(ii) with lupus anticoagulant	4	
RHEUMATIC DISEASES		
SYSTEMIC LUPUS ERYTHEMATOSUS		
a) Positive (or unknown) antiphospholipid antibodies	4	People with systemic lupus erythematosus are at an increased risk of ischaemic heart disease, stroke and venous thromboembolism. Categories are based on the assumption that no other risk factors for cardiovascular disease are present; these must be modified in the presence of such risk factors.[190-203]
b) Severe thrombocytopenia	2	
c) Immunosuppressive	2	
d) None of the above	2	

*See also additional comments at end of section

UKMEC	DEFINITION OF CATEGORY
CATEGORY 1	A condition for which there is no restriction for the use of the contraceptive method
CATEGORY 2	A condition where the advantages of using the method generally outweigh the theoretical or proven risks
CATEGORY 3	A condition where the theoretical or proven risks generally outweigh the advantages of using the method. The provision of a method requires expert clinical judgement and/or referral to a specialist contraceptive provider, since use of the method is not usually recommended unless other more appropriate methods are not available or not acceptable
CATEGORY 4	A condition which represents an unacceptable health risk if the contraceptive method is used

COMBINED HORMONAL CONTRACEPTIVES (CHCs) *Combined oral contraception (COC), combined transdermal patch and vaginal ring*	**These methods do not protect against STI/HIV. If there is risk of STI/HIV (including during pregnancy or postpartum), the correct and consistent use of condoms is recommended, either alone or with another contraceptive method. Male condoms reduce the risk of STI/HIV.**	
CONDITION	**CATEGORY** I=Initiation C=Continuation	**CLARIFICATIONS/EVIDENCE- Most evidence available relates to COC use. However, this evidence is also applied to patch and ring use.**
DRUG INTERACTIONS		
ANTIRETROVIRAL THERAPY: This section relates to the SAFETY of contraceptive use in women using antiretrovirals. EFFECTIVENESS may be reduced and pregnancy itself may have a negative impact on health for some women with certain medical conditions. [204–217]		
a) Nucleoside reverse transcriptase inhibitors b) Non-nucleoside reverse transcriptase inhibitors c) Ritonavir-boosted protease inhibitors	1 2 3	**Antiretroviral therapy and hormonal contraception:** Antiretroviral drugs have the potential to either decrease or increase the bioavailability of steroid hormones in hormonal contraceptives. Limited data suggest potential drug interactions between many antiretroviral drugs (particularly some non-nucleoside reverse transcriptase inhibitors and ritonavir-boosted protease inhibitors) and hormonal contraceptives. These interactions may alter the safety and effectiveness of both the hormonal contraceptive and the antiretroviral drug. Thus, **if a woman on antiretroviral treatment decides to initiate or continue combined hormonal contraceptive use, THE CONSISTENT USE OF CONDOMS IS RECOMMENDED**. This is for both preventing HIV transmission and to compensate for any possible reduction in the effectiveness of the hormonal contraceptive. When a COC is chosen, a preparation containing a minimum of 30mcgs EE should be used but usually a dose of 50mcgs EE is recommended.
ANTICONVULSANT THERAPY: This section relates to the SAFETY of contraceptive use in women using anticonvulsants. EFFECTIVENESS may be reduced and pregnancy itself may have a negative impact on health for some women with certain medical conditions. [218–255]		
a) Certain anticonvulsants (phenytoin, carbamazepine, barbiturates, primidone, topiramate, oxcarbazepine) b) Lamotrigine	3* 3*	**Certain anticonvulsants and combined oral contraception:** When a COC is chosen, a preparation containing a minimum of 30mcgs EE should be used. It is likely that interaction may reduce the effectiveness of CHC. **THE CONSISTENT USE OF CONDOMS IS RECOMMENDED*. Use of other contraceptives should be encouraged for women who are long-term users of any of these anticonvulsant drugs.** Use of DMPA is a Category 1 because its effectiveness is NOT decreased by the use of certain anticonvulsants. **Lamotrigine:** When a COC is chosen, a preparation containing a minimum of 30mcgs EE should be used. Anticonvulsant treatment regimens that combine lamotrigine and non-enzyme inducing antiepileptic drugs (such as sodium valproate) do not interact with COCs.
ANTIMICROBIAL THERAPY: This section relates to the SAFETY of contraceptive use in women using antimicrobials. EFFECTIVENESS may be reduced and pregnancy itself may have a negative impact on health for some women with certain medical conditions. [256–336]		
a) Broad spectrum antibiotics b) Antifungals c) Antiparasitics d) Rifampicin or rifabutin therapy	1* 1 1 3*	There is intermediate level evidence that the contraceptive effectiveness of COC is not affected by co-administration of most broad spectrum antibiotics. **Rifampicin or rifabutin therapy and combined oral contraception:** When a COC is chosen, a preparation containing a minimum of 30mcgs EE should be used. If a woman on rifampicin or rifabutin decides to use CHC **THE CONSISTENT USE OF CONDOMS IS RECOMMENDED*. Use of other contraceptives should be encouraged for women who are long-term users of rifampicIn or rifabutin**. Use of DMPA is a Category 1 because its effectiveness is unlikely to be decreased by the use of rifampicin or rifabutin.

UKMEC	DEFINITION OF CATEGORY
CATEGORY 1	A condition for which there is no restriction for the use of the contraceptive method
CATEGORY 2	A condition where the advantages of using the method generally outweigh the theoretical or proven risks
CATEGORY 3	A condition where the theoretical or proven risks generally outweigh the advantages of using the method. The provision of a method requires expert clinical judgement and/or referral to a specialist contraceptive provider, since use of the method is not usually recommended unless other more appropriate methods are not available or not acceptable
CATEGORY 4	A condition which represents an unacceptable health risk if the contraceptive method is used

Additional comments

AGE

Menarche to <40 years: Theoretical concerns about the use of combined hormonal contraceptives among young adolescents have not been substantiated.

≥**40 years:** The risk of cardiovascular disease increases with age and may also increase with combined hormonal contraceptive use. In the absence of other adverse clinical conditions, combined hormonal contraceptives can be used until menopause. Guidance suggests women can use combined methods until age 50 years if they have no other medical contraindications.[1]

POSTPARTUM

<21 days: There is some theoretical concern regarding the association between combined hormonal contraceptive use up to 3 weeks postpartum and risk of thrombosis in the mother. Blood coagulation and fibrinolysis are essentially normalised by 3 weeks postpartum.

PAST ECTOPIC PREGNANCY

The risk of future ectopic pregnancy is increased among women who have had an ectopic pregnancy in the past. Combined hormonal contraceptives provide protection against pregnancy in general, including ectopic gestation.

VENOUS THROMBOEMBOLISM (VTE)

Family history of VTE (first-degree relatives): Some conditions which increase the risk of VTE are heritable. For some young women it may not yet be possible to exclude a family history of VTE as first-degree relatives may still be aged under 45 years.

Major surgery: The degree of risk of VTE associated with major surgery varies depending on the length of time that a woman is immobilised. There is no need to stop combined hormonal contraceptives prior to female surgical sterilisation. Immobilisation due to non-surgical causes may increase risk of VTE.

SUPERFICIAL VENOUS THROMBOSIS

Varicose veins: Varicose veins are not risk factors for VTE.

HYPERTENSION, CURRENT AND HISTORY OF ISCHAEMIC HEART DISEASE, STROKE

Among women with these disorders, who are at increased risk of arterial thrombosis, the use of combined hormonal contraceptives should be avoided.

KNOWN HYPERLIPIDAEMIAS

Lipid levels alone are poor predictors of risk of coronary heart disease (CHD).

VALVULAR HEART DISEASE

Among women with valvular heart disease, combined hormonal contraceptive use may further increase the risk of arterial thrombosis; women with complicated valvular heart disease are at greatest risk.

CONGENITAL HEART DISEASE

Surgical correction, co-existing complications, and degree of cardiac disability will vary between individuals and should be taken into account when considering contraceptive use.

UNEXPLAINED VAGINAL BLEEDING

There are no conditions that cause vaginal bleeding that will be worsened in the short term by use of combined hormonal contraceptives.

ENDOMETRIOSIS

Combined hormonal contraceptives do not worsen, and may alleviate, the symptoms of endometriosis.

CERVICAL ECTROPION

Cervical ectropion is not a risk factor for cervical cancer, and there is no need for restriction of combined hormonal contraceptive use.

CERVICAL CANCER (awaiting treatment)

There is some theoretical concern that combined hormonal contraceptive use may affect prognosis of the existing disease. While awaiting treatment, women may use combined hormonal contraceptives. Treatment of this condition may render a woman sterile.

BREAST DISEASE

Family history of breast cancer: Women with BRCA1 or BRCA2 mutations have a much higher baseline risk of breast cancer than women who do not have these mutations. Most women with a family history of breast cancer do not have these mutations. Known carriers may consider use of combined hormonal contraception.

Breast cancer: Breast cancer is a hormonally sensitive tumour, and the prognosis of women with current or recent breast cancer may worsen with combined hormonal contraceptive use.

ENDOMETRIAL AND OVARIAN CANCER

COC use reduces the risk of developing endometrial cancer. While awaiting treatment, women may use COCs. In general, treatment of this condition renders a woman sterile.

UTERINE FIBROIDS

No evidence CHCs affect growth of fibroids.

STIs, HIGH RISK OF HIV, PELVIC INFLAMMATORY DISEASE (PID)
COCs may reduce the risk of PID among women with STIs, but do not protect against HIV or lower genital tract STIs.

DIABETES
Although carbohydrate tolerance may change with combined hormonal contraceptive use, the major concerns are vascular disease due to diabetes and additional risk of arterial thrombosis due to combined hormonal contraceptive use.

GALL-BLADDER DISEASE
COCs may cause a small increased risk of gall-bladder disease. There is also concern that COCs may worsen existing gall-bladder disease.

HISTORY OF CHOLESTASIS
Pregnancy-related: History of pregnancy-related cholestasis may predict an increased risk of developing COC-associated cholestasis.

Past COC-related: History of COC-related cholestasis predicts an increased risk with subsequent COC use.

VIRAL HEPATITIS
COCs are metabolised by the liver, and their use may adversely affect women whose liver function is compromised.

CIRRHOSIS
COCs are metabolised by the liver and their use may adversely affect women whose liver function is compromised.

LIVER TUMOURS
COCs are metabolised by the liver and their use may adversely affect women whose liver function is compromised. In addition, COC use may enhance the growth of tumours.

INFLAMMATORY BOWEL DISEASE (IBD)
There is no evidence that women with IBD have an inherent increased risk of VTE. Risk of VTE may increase if unwell, bed bound or undergoing acute surgery or with major surgery and prolonged immobilisation. Under these circumstances the use of combined methods should be avoided and alternative methods used.

THALASSAEMIA
There is anecdotal evidence from countries where thalassaemia is prevalent that COC use does not worsen the condition.

IRON-DEFICIENCY ANAEMIA
Combined hormonal contraceptive use may decrease menstrual blood loss.

RAYNAUD'S DISEASE
Combined hormonal methods may be used in 'Primary' disease but underlying cause of secondary disease may influence safety of use.

DRUG INTERACTIONS
Generally safety of using combined hormonal methods is unaffected. Nevertheless use of liver enzyme inducing medication may reduce contraceptive efficacy, increasing risk of unintended pregnancy. Contraceptive choice may depend on the likely duration of use of concurrent medications and need for additional or alternative methods.

REFERENCES: COMBINED HORMAL CONTRACEPTION

1. Faculty of Family Planning and Reproductive Healthcare Clinical Effectiveness Unit. Contraception for women aged over 40 years. *Journal of Family Planning and Reproductive Healthcare*. 2005;**31**:51-64.
2. FPRHC Guidance (July 2004) Contraceptive choices for breastfeeding women. Journal of Family Planning and Reproductive Health Care 2004;30(3):181-189.
3. Knight J, Pyper C. Postnatal contraception: What are the choices? *Nursing Practice*. 2002; **May**:23-25.
4. Vessey M, Painter R, Yeates D. Mortality in relation to oral contraceptive use and cigarette smoking. *Lancet.* 2003;**362**:185-191.
5. Khader YS, Rice J, John L, Abueita O. Oral contraceptives and the risk of myocardial infarction: a meta-analysis. *Contraception*. 2003;**68**:11-17.
6. Lawson DH, Davidson JF, Jick H. Oral contraceptive use and venous thromboembolism: absence of an effect of smoking. *British Medical Journal*. 1977;**2**:729-730.
7. Lidegaard O, Edstrom B, Kreiner S. Oral contraceptives and venous thromboembolism. A case-control study. *Contraception*. 1998;**57**:291-301.
8. Nightingale AL, Lawrenson RA, Simpson EL, Williams TJ, MacRae KD. The effects of age, body mass index, smoking and general health on the risk of venous thromboembolism in users of combined oral contraceptives. *European Journal of Contraception & Reproductive Health Care*. 2000;**5**:265-274.
9. Croft P, Hannaford P. Risk factors for acute myocardial infarction in women - evidence from RCGP Oral Contraceptive Study. *British Medical Journal*. 1989;**298**:165-168.
10. Dunn N, Faragher B, Thorogood M, de Caestecker L, MacDonald TM, McCollum C, et al. Oral contraceptives and myocardial infarction: results of the MICA case-control study. *British Medical Journal*. 1999;**318**:1579-1584.
11. Rosenberg R, Palmer JR, Shapiro S. Decline in the risk of myocardial infarction among women who stop smoking. *The New England Journal of Medicine*. 1990;**322**:213-217.
12. McElduff P, Dobson A, Beaglehole R, Jackson R. Rapid reduction in coronary risk for those who quit cigarette smoking. *Australian and New Zealand Journal of Public Health*. 1998;**22**:787-791.
13. Kenfield SA, Stampfer MJ, Rosner BA. Smoking and smoking cessation in relation to mortality in women. *Journal of the Medical Association*. 2008;**7**(299):2037-2047.
14. Abdollahi MC, Cushman M, Rosendaal FR. Obesity: risk of venous thrombosis and the interaction with coagulation factor levels and oral contraceptive use. *Thrombosis & Haemostasis*. 2003;**89**:493-498.
15. Sidney S, Petitti DB, Soff GA. Venous thromboembolic disease in users of low estrogen combined estrogen-progestin oral contraceptives. *Contraception*. 2004;**70**:3-10.
16. World Health Organization Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception. Venous thromboembolic disease and combined oral contraceptives: results of international multicentre case-control study. *Lancet*. 1995;346:1575-1582.
17. Lidegaard O, Edstrom B, Kreiner S. Oral contraceptives and venous thromboembolism: a five-year national case-control study. *Contraception*. 2002;**65**:187-196.
18. Pomp ER, le CS, Rosendaal FR, Doggen CJ. Risk of venous thrombosis: obesity and its joint effect with oral contraceptive use and prothrombotic mutations. *British Journal of Haematology*. 2007;**139**:289-296.
19. Nightingale AL, Lawrenson RA, Simpson EL, Williams TJ, MacRae KD. Farmer RD. The effects of age, body mass index, smoking and general health on the risk of venous thromboembolism in users of combined oral contraceptives. *European Journal of Contraception & Reproductive Health Care*. 2000;**5**:265-274.
20. Holt VL, Cushing-Haugen KL, Daling JR. Body weight and risk of oral contraceptive failure. *Obstetrics & Gynecology*. 2002;**99**:820-827.
21. Williams B, Poulter N, Brown MJ, Davies M, McInnes GT, Potter et al. The BHS Guidelines working Party Guidelines for Management of Hypertension: Report of the Fourth Working Party of the British Hypertension Society. *Journal of Human Hypertension*. 2004;**18**:139-185.
22. National Institute for Clinical Excellence. Hypertension. Management of hypertension in adults in primary care. 2004. London. http://www.nice.org.uk/nicemedia/pdf/HypertensionGuide.pdf
23. Gillum LA, Mamidipudi SK, Johnston SC. Ischemic stroke risk with oral contraceptives: a meta-analysis. *Journal of American Medical Association*. 2000;**284**:72-78.
24. Tanis BC, Van der Bosch MAAJ, Kemmeren JM, Cats VM, Helmerhorst FM, Algra A et al. Oral contraceptives and the risk of myocardial infarction. *New England Journal of Medicine*. 2001;**345**:1787-1793.

25. Van den Bosch MA, Kemmeren JM, Tannis BS, Mali WP, Helmerhorst FM, Rosendaal FR et al. The RATIO study: oral contraceptives and the risk of peripheral arterial disease in young women. *Journal of Thrombosis and Haemostasis*. 2003;**1**:439-444.

26. Heinemann LA, Lewis Ma, Spitzer WO, Thorogood M, Guggenmoos-Holzmann I, Bruppacher R. Thromboembolic stroke in young women. A European case-control study on oral contraceptives. Transnational Research Group on Oral Contraceptives and the Health of Young Women. *Contraception.* 1998;**57**:29-37.

27. Lewis MA, Heinemann La, Spitzer WO, MacRae KD, Bruppacher R. The use of oral contraceptives and the occurrence of acute myocardial infarction in young women. Results from the Transnational Study on Oral Contraceptives and the Health of Young Women. *Contraception*. 1997;**56**:129-140.

28. World Health Organization. Haemorrhagic stroke, overall stroke risk, and combined oral contraceptives: results of an international, multicentre, case-control study. WHO Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception. *Lancet.* 1996;**348**:505-510.

29. World Health Organization. Ischaemic stroke and combined oral contraceptives: results of an international, multicentre, case-control study. WHO Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception. *Lancet*. 1996;**348**:498-505.

30. World Health Organization. Acute myocardial infarction and combined oral contraceptives: results of an international multicentre case-control study. WHO Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception. *Lancet*. 1997;**349**:1202-1209.

31. Collaborative Group for the Study of Stroke in Young Women. Oral contraceptives and stroke in young women: associated risk factors. *Journal of the American Medical Association*. 1975;**231**:718-722.

32. D'Avanzo B, La Vecchia C, Negri E, Parazzini F, Franeschi S. Oral contraceptive use and risk of myocardial infarction: an Italian case-control study. *Journal of Epidemiology and Community Health*. 1994;**48**:324-325.

33. Dunn NR, Faragher B, Thorogood M, de Caestecker L, MacDonald TM, McCollum C, et al. Risk of myocardial infarction in young female smokers. *Heart (British Cardiac Society)*. 1999;**82**:581-583.

34. Hannaford PC, Croft PR, Kay CR. Oral contraception and stroke. Evidence from the Royal College of General Practitioners' Oral Contraception Study. *Stroke.* 1994;**25**:935-942.

35. Kemmeren JM, Tanis BS, Van der Bosch MA, Ballen EI, Helmerhost FM, Van der Graff Y et al.Risk of Arterial Thrombosis in Relation to Oral Contraceptives (RATIO) study: oral contraceptives and the risk of ischemic stroke. *Stroke*. 2002;**33**:1202-1208.

36. Lidegaard O. Oral contraception and risk of a cerebral thromboembolic attack: results of a case control study. *British Medical Journal.* 1993;**306**:956-963.

37. Lidegaard O. Oral contraceptives and risk of cerebral thrombosis: a five-year national case-control study. *Contraception*. 2002;**65**:197-205.

38. Lidegaard O. Oral contraceptives, pregnancy and the risk of cerebral thromboembolism: the influence of diabetes, hypertension, migraine and previous thrombotic disease. *British Journal of Obstetrics & Gynaecology*. 1995;**102**:153-159.

39. Lidegaard O, Kreiner S. Contraceptives and cerebral thrombosis: a five-year national case-control study. *Contraception*. 2002;**65**:197-205.

40. Lubianca JN, Faccin CS, Fuchs FD. Oral contraceptives: a risk factor for uncontrolled blood pressure among hypertensive women. Contraception. 2003;**67**:19-24.

41. Narkiewicz K, Graniero GR, D'este D, Mattarei M, Zonzin P, Palantini P. Ambulatory blood pressure in mild hypertensive women taking oral contraceptives. A case-control study. *American Journal of Hypertension*. 1995;**8**:249-253.

42. Siritho S, Thrift AG, McNeil JJ, You RY, Davis SM, Donnan GA. Risk of ischemic stroke among users of the oral contraceptive pill: The Melbourne Risk Factor Study (MERFS) Group. *Stroke*. 2003;**34**:1575-1580.

43. Aberg H, Karlsson L, Melander S. Studies on toxaemia of pregnancy with special reference to blood pressure. II. Results after 6-11 years' follow-up. Upsala Journal of Medical Sciences. 1978;**83**:97-102.

44. Carmichael SM, Taylor MM, Ayers CR. Oral contraceptives, hypertension, and toxemia. *Obstetrics & Gynecology*.1970;**35**:371-376.

45. Meinel H, Ihle R, Laschinski M. [Effect of hormonal contraceptives on blood pressure following pregnancy-induced hypertension]. [German]. *Zentralblatt für Gynäkologie*. 1987;**109**:527-531.

46. Pritchard JA, Pritchard SA. Blood pressure response to estrogen-progestin oral contraceptive after pregnancy-induced hypertension. *American Journal of Obstetrics & Gynecology*. 1977;**129**:733-739.

47. Sibai BM, Taslimi MM, El-Nazer A, Amon E, Mabie BC, Ryan GM. Maternal-perinatal outcome associated with the syndrome of hemolysis, elevated liver enzymes, and low platelets in severe preeclampsia-eclampsia. *American Journal of Obstetrics & Gynecology*. 1986;**155**:501-509.

48. Sibai BM, Ramadon M, Chari R, Friedman S. Pregnancies complicated by HELLP syndrome (hemolysis, elevated liver enzymes, and low platelets): subsequent pregnancy outcome and long-term prognosis. *American Journal of Obstetrics & Gynecology*. 1995;**172**:125-129.

49. Faculty of Family Planning and Reproductive Health Care Clinical Effectiveness Unit. First Prescription of the Combined Oral Contraceptive Pill. http://www.ffprhc.org.uk/admin/uploads/FirstPrescCombOralContJan06.pdf

50. Scottish Intercollegiate Guidelines Network Secretariat. Prophylaxis of venous thromboembolism. 2003;62: 1-47.http://www.sign.ac.uk/pdf/sign62.pdf

51. Wu O, Robertson L, Twaddle S, Lowe GDO, Clark P, Walker I, et al. Screening for thrombophilia in high-risk situations: a meta-analysis and cost-effectiveness analysis. *British Journal of Haematology.* 2005;**131**(1): 80-90.

52. Middledrop S, van Hylckama Vlieg A. Does thrombophillia testing help in the clinical management of patients? *British Journal of Haematology*. 2008;**143**(3):321-335.

53. Blickstein D, Blickstein I. Oral contraception and thrombophillia. *Current Opinion in Obstetrics and Gynacecology*. 2007;**19**(4):370-376.

54. NHS Clinical Knowledge Summaries. Lipid modification. Lipid modification - primary and secondary CVD prevention. http://cks.library.nhs.uk/lipid_modification_cvd_prevention/management/detailed_answers/secondary_prevention/when_to_refer#-336938.

55. British Heart Foundation. What is valvular heart disease? 2005. http://www.bhf.org.uk/hearthealth/index.asp?secID=1&secondlevel=77&thirdlevel=478.

56. British Heart Foundation. Living with congenital heart disease. 2005. http://www.bhf.org.uk/hearthealth/index.asp?secID=1&secondlevel=77&thirdlevel=362.

57. The International Headache Society Task Force on Combined Oral Contraceptives and hormone replacement therapy. Recommendations on the risk of ischemic stroke associated with the use of combined oral contraceptives and hormone replacement therapy in women with migraine. *Cephalagia*. 2000;***20***:155-156.

58. McGregor A. Migraine and use of combined hormonal contraceptive: a clinical review. *Journal of Family Planning and Reproductive Health Care*. 2007;**33**(3):155-169.

59. Chang CL, Donaghy M, Poulter N. Migraine and stroke in young women: case control study. The World Health Organisation Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception. BMJ 1999;318:13-18.

60. Deijen JB, Duyn KJ, Jansen WA, Kiltsen JW. Use of a monophasic, low-dose oral contraceptive in relation to mental functioning. *Contraception*.1992;**46**:359-367.

61. Herzberg BN, Droper KA, Johnson AL, Nicol GC. Oral contraceptives, depression, and libido. *British Medical Journal*. 1971;**3**:495-500.

62. National Institute of Clinical Excellence. Heavy Menstrual Bleeding. 2007. http://www.nice.org.uk/nicemedia/pdf/CG44FullGuideline.pdf

63. Faculty of Sexual and Reproductive Healthcare Clinical Effectiveness Unit. Unscheduled bleeding in women using hormonal contraception. 2009. [In Press]

64. Hendrix SL, Alexander NJ. Primary dysmenorrhea treatment with a desogestrel-containing low dose oral contraceptive. *Contraception*. 2002;**66**:393-399.

65. Proctor ML, Roberts H, Farquhar CM. Combined oral contraceptive pill (OCP) as treatment for primary dysmenorrhoea. *Cochrane Database of Systematic Reviews*. 2001.

66. Curry SL, Schlareth JB, Kohorn EI, Boyce JB, Gore H, Twiggs LB et al. Hormonal contraception and trophoblastic sequelae after hydatidiform mole (a Gynecologic Oncology Group Study). *American Journal of Obstetrics and Gynaecology*. 1989;**160**:850-859.

67. Adewole IF, Oladokun A, Fawole AO, Olawuyi JF, Adeleye JA. Fertility regulatory methods and devlopement of complications after evacuation of complete hydratidform mole. *Journal of Obstetrics & Gynaecology.* 2000;**20**:68-69.

68. Deicas RE, Miller DS, Rademaker EW, Lurain JR. The role of contraception in the development of postmolar trophoblastic tumour. *Obstetrics & Gynecology*.1991;**78**:221-226.

69. Berkowitz RS, Goldstein DP, Marean AR, Bernstein M. Oral contraceptives and post-molar trophoblastic disease. *Obstetrics & Gynecology*.1981;**58**:474-477.

70. Morrow P, Nakamura R, Schlaerth J, Gaddis O, Eddy G. The influence of oral contraceptives on the postmolar human chorionic gonadotrophin regression curve. *American Journal of Obstetrics and Gynecology*. 1985;**151**:906-914.

71. Ho Yuen B, Burch P. Relationship of oral contraceptives and the intrauterine contraceptive devices to the regression of concentration of the beta subunit of human chorionic gonadotrophin and invasive complications after molar pregnancy. *Journal of Obstetrics & Gynaecology*. 1983;**145**:241-17.

72. Stone M. Relationship of oral contraception to development of trophoblastic tumour after evacution of a hydatidform mole. *British Journal of Obstetrics and Gynaecology*. 1976;**83**:913-916.

73. Stone M, Bagshaw KD. An analysis of the influence of maternal age, gestational age, contraceptive method, and the mode of primary treatment of patients with hydatidiform moles on the incidence of subsequent chemotherapy. *British Journal of Obstetrics and Gynaecology.* 1979;**86**:782-792.

74. Eddy GL, Schlaerth JB, Natlick RH, Gaddis O, Nakamura RM, Morrow CP. Postmolar trophoblastic disease in women using hormonal contraception with and without estrogen. *Obstetrics & Gynecology.* 1983;**62**: 736-740.

75. Smith JS, Green J, de Gonzalez, A, Appleby P, Peto J. Cervical cancer and use of hormonal contraceptives: a systematic review. *Lancet.* 2003;**361**:1159-1167.

76. Hannaford P, Selvaraja S, Elliot, A, Angus V, Iversen L, Lee A. Cancer risk among users of oral contraceptives: cohort data from the royal College of General Practitioner's oral contraceptive study. *British Medical Journal.* 2007; online11th Sept:1-8

77. Collaborative Group on Hormonal Factors in Breast Cancer. Breast cancer and hormonal contraceptives: collaborative reanalysis of individual data on 53 297 women with breast cancer and 100 239 women without breast cancer from 54 epidemiological studies. *Lancet.* 1996;**347**:1713-1727.

78. Brinton LA, Gammond MD, Malone KE, Schonenberg JB, Dalling JR, Coates RJ. Modification of oral contraceptive relationships on breast cancer risk by selected factors among younger women. *Contraception.* 1997;**55**:197-203.

79. Colditz GA, Rosner BA, Speizer FE for the Nurses' Health Study Research Group. Risk factors for breast cancer according to family history of breast cancer. *Journal of the National Cancer Institute*. 1996;88:365-371.

80. Egan KM, Rosner BA, Speizser FE. Risk factors for breast cancer in women with a breast cancer family history. *Cancer Epidemiology, Biomarkers & Prevention*. 1998;**7**:359-364.

81. Grabrick DM, Hartman Lc, Cerhan JR, Vierkant RA, Therneau TM, Vachon CM et al. Risk of breast cancer with oral contraceptive use in women with a family history of breast cancer. *Journal of the American Medical Association*. 2000;**284**:1791-1798.

82. Harris RE, Zang EA, Wynder EL. Oral contraceptives and breast cancer risk: a case-control study. *International Journal of Epidemiology*. 1990;**19**:240-246.

83. Jick SS, Walker AM, Stergachis A, Jick H. Oral contraceptives and breast cancer. *British Journal of Cancer.* 1989;59:618-621.

84. Marchbanks PA, McDonald JA, Wilson HG, Folger SG, Mandel MG, Daling JR et al. Oral contraceptives and the risk of breast cancer. *New England Journal of Medicine*. 2002;**346**:2025-2032.

85. Rosenberg L, Palmer JR, Rao RS, Zauber AG, Strom BC, Warshauer ME et al. Case-control study of oral contraceptive use and risk of breast cancer. *American Journal of Epidemiology*. 1996;**143**:25-37.

86. Heimdal K, Skovlund E, Moller P. Oral contraceptives and risk of familial breast cancer. *Cancer Detection & Prevention.* 2002;**26**:23-27.

87. Narod SA, Dube MP, Klijn J, Lubinski J, Lynch HT, Ghadirian P et al. Oral contraceptives and the risk of breast cancer in BRCA1 and BRCA2 mutation carriers. *Journal of the National Cancer Institute.* 2002;**94**:1773-1779.

88. Ursin G, Henderson BE, Haile RW, Pike MC, Zhou N, Diep A et al. Does oral contraceptive use increase the risk of breast cancer in women with BRCA1/BRCA2 mutations more than in other women? *Cancer Research*. 1997;**57**:3678-3681.

89. The Italian MEGIC Group. Determinants of cervical Chlamydia trachomatis infection in Italy. *Genitourinary Medicine.* 1993;**69**:123-125.

90. Ackers JP, Lumsden WH, Catterall RD, Coyle R. Antitrichomonal antibody in the vaginal secretions of women infected with T. vaginalis. *British Journal of Venereal Disease*s. 1975;**51**:319-323.

91. Acosta-Cazares B, Ruiz-Maya L, Escobedo de la Pena J. Prevalence and risk factors for Chlamydia trachomatis infection in low-income rural and suburban populations of Mexico. *Sexually Transmitted Diseases*. 1996;**23**:283-288.

92. Addiss DG, Vaughn ML, Holzhueter MA, Bakken LL, Davis JP. Selective screening for Chlamydia trachomatis infection in nonurban family planning clinics in Wisconsin. *Family Planning Perspectives.* 1987;**19**:252-256.

93. Arya OP, Mallinson H, Goddard AD. Epidemiological and clinical correlates of chlamydial infection of the cervix. *British Journal of Venereal Diseases*. 1981;**57**:118-124.

94. Austin H, Louv WC, Alexander WJ. A case-control study of spermicides and gonorrhea. *Journal of the American Medical Association*. 1984;**251**:2822-2824.

95. Piot P, Avonts D, Sercu M, Heyerick P, Vandermeeran I, Meheus A. Incidence of uncomplicated genital infections in women using oral contraception or an intrauterine device: a prospective study. *Sexually Transmitted Diseases*. 1990;**17**:23-29.

96. Baeten JM, Nyange P, Richardson B, Lavreys L, Chohan B. Hormonal contraception and risk of sexually transmitted disease acquisition: results from a prospective study. *American Journal of Obstetrics & Gynecology*. 2001;**185**:380-385.

97. Barbone F, Austin H, Louv WC, Alexander WJ. A follow-up study of methods of contraception, sexual activity, and rates of trichomoniasis, candidiasis, and bacterial vaginosis. *American Journal of Obstetrics & Gynecology*. 1990;**163**:510-514.

98. Barnes RC, Katz BP, Rafs RT, Batteiger B, Caine V, Jones RB. Quantitative culture of endocervical Chlamydia trachomatis. *Journal of Clinical Microbiology*. 1990;**28**:774-780.

99. Berger GS, Keith L, Moss W. Prevalence of gonorrhoea among women using various methods of contraception. *British Journal of Venereal Diseases*. 1975;51:307-309.

100. Bhattacharyya MN, Jephcott AE. Diagnosis of gonorrhea in women - Influence of the contraceptive pill. *Journal of the American Venereal Disease Association*. 1976;**2**:21-24.

101. Blum M, Pery J, Kitai E. The link between contraceptive methods and Chlamydia trachomatis infection. *Advances in Contraception*. 1988;**4**:233-239.

102. Bontis J, Vavilis D, Paniclis D, Theodorisis T, Konstanindis T, Sidropulou A. Detection of Chlamydia trachomatis in asymptomatic women: relationship to history, contraception, and cervicitis. *Advances in Contraception.* 1994;**10**:309-315.

103. Bramley M, Kinghorn G. Do oral contraceptives inhibit Trichomonas vaginalis? *Sexually Transmitted Diseases.* 1979;**6**:261-263.

104. Bro F, Juul S. Predictors of Chlamydia trachomatis infection in women in general practice. *Family Practice.* 1990;**7**:138-143.

105. Burns DC, Darougar S, Thin RN, Lothian L, Nicol CS. Isolation of Chlamydia from women attending a clinic for sexually transmitted disease. *British Journal of Venereal Diseases*. 1975;**51**:314-318.

106. Ceruti M, Canestrelli M, Condemi V, Piantelli G, De Paolis P, Amone F et al. Methods of contraception and rates of genital infections. *Clinical & Experimental Obstetrics & Gynecology*. 1994;**21**:119-123.

107. Chacko MR, Lovchik JC. Chlamydia trachomatis infection in sexually active adolescents: prevalence and risk factors. *Pediatrics.* 1984;**73**:836-840.

108. Cottingham J, Hunter D. Chlamydia trachomatis and oral contraceptive use: a quantitative review. *Genitourinary Medicine*. 1992;**68**:209-216.

109. Crowley T. Hormonal factors and the laboratory detection of Chlamydia trachomatis in women: implications for screening? *International Journal of STD & AIDS*. 1997;**8**:25-31.

110. Edwards D, Phillips D, Stancombe S. Chlamydia trachomatis infection at a family planning clinic. *New Zealand Medical Journal*. 1985;**98**:333-335.

111. Evans BA, Kell PD, Bond RA, MacRae KD, Slomka MJ, Brown DW. Predictors of seropositivity to herpes simplex virus type 2 in women. *International Journal of STD & AIDS.* 2003;**14**:30-36.

112. Evans DL. Detection of Chlamydia trachomatis in adolescent females using direct immunofluorescence. *Clinical Pediatrics*. 1988;**27**:223-228.

113. Fish AN, Fairweather DV, Oriel JD, Ridgewater GL. Chlamydia trachomatis infection in a gynaecology clinic population: identification of high-risk groups and the value of contact tracing. *European Journal of Obstetrics, Gynecology, & Reproductive Biology*. 1989;**31**:67-74.

114. Fouts AC, Kraus SJ. Trichomonas vaginalis: reevaluation of its clinical presentation and laboratory diagnosis. *Journal of Infectious Diseases*. 1980;**141**:137-143.

115. Fraser JJ Jr., Rettig PJ, Kaplan DW. Prevalence of cervical Chlamydia trachomatis and Neisseria gonorrhoeae in female adolescents. *Pediatrics.* 1983;**71**:333-336.

116. Gertig DM. Risk factors for sexually transmitted diseases among women attending family planning clinics in Dar-es-Salaam, Tanzania. *Genitourinary Medicine.* 1997;**73**:39-43.

117. Green J. Human papillomavirus infection and use of oral contraceptives. *British Journal of Cancer.* 2003;**88**:1713-1720.

118. Griffiths M, Hindley D. Gonococcal pelvic inflammatory disease, oral contraceptives, and cervical mucus. *Genitourinary Medicine*. 1985;**61**:67.

119. Han Y, Lawrence CE, Murpy D, Hipps S. Risk profile for Chlamydia infection in women from public health clinics in New York State. *Journal of Community Health.* 1993;**18**:1-9.

120. Handsfield HH, Jasmann LL, Roberts PL, Hanson VW, Kothenbeutel RI, Stamm WE. Criteria for selective screening for Chlamydia trachomatis infection in women attending family planning clinics. *Journal of the American Medical Association.* 1986;**255**:1730-1734.

121. Hanna NF, Taylor-Robsinson D, Kalodiki-Karamanoli M, Harris JR, McFadyen IR. The relation between vaginal pH and the microbiological status in vaginitis. *British Journal of Obstetrics & Gynaecology.* 1985;**92**:1267-1271.

122. Harrison HR, Costin M, Meder JB, Bownds CM, Sim DA, Lewis M, et al. Cervical Chlamydia trachomatis infection in university women: relationship to history, contraception, ectopy, and cervicitis. *American Journal of Obstetrics & Gynecology*. 1985;**153**:244-251.

123. Hart G. Factors associated with genital chlamydial and gonococcal infection in females. *Genitourinary Medicine*. 1992;**68**:217-220.

124. Herrmann B, Espinoza F, Villegas RR, Smith GD, Ramos A, Egger M. Genital chlamydial infection among women in Nicaragua: validity of direct fluorescent antibody testing, prevalence, risk factors and clinical manifestations. *Genitourinary Medicine.* 1996;**72**:20-26.

125. Hewitt AB. Oral contraception among special clinic patients. With particular reference to the diagnosis of gonorrhoea. *British Journal of Venereal Diseases.* 1970;**46**:106-107.

126. Hilton AL, Richmond SJ, Milne JD, Hindley F, Clarke SK. Chlamydia A in the female genital tract. British Journal of Venereal Diseases. 1974;**50**:1-10.

127. Hiltunen-Back E, Jaikala O, Kautiainen H, Paavonen J, Reunala T. A nationwide sentinel clinic survey of chlamydia trachomatis infection in Finland. *Sexually Transmitted Diseases*. 2001;**28**:252-258.

128. Jacobson DL et al. Relationship of hormonal contraception and cervical ectopy as measured by computerized planimetry to chlamydial infection in adolescents. *Sexually Transmitted Diseases.* 2000;**27**:313-319.

129. Jaffe LR, Siqeria LM, Diamond SB, Diaz A, Speilsinger NA. Chlamydia trachomatis detection in adolescents. A comparison of direct specimen and tissue culture methods. J*ournal of Adolescent Health Care*. 1986;**7**: 401-404.

130. Jick H et al. Vaginal spermicides and gonorrhea. *Journal of the American Medical Association.* 1982;**248**:1619-1621.

131. Johannisson G, Karamustafa A, Brorson J. Influence of copper salts on gonococci. *British Journal of Venereal Diseases.* 1976;**52**:176-177.

132. Keith L, Berer GS, Moss W. Cervical gonorrhea in women using different methods of contraception. *Journal of the American Venereal Disease Association*. 1976;**3**:17-19.

133. Kinghorn GR, Waugh MA. Oral contraceptive use and prevalence of infection with Chlamydia trachomatis in women. *British Journal of Venereal Diseases*. 1981;**57**:187-190.

134. Lavreys, Chohan B, Ashley R, Richardson BA, Corey L, Mandaliya K, et al. Human herpesvirus 8: seroprevalence and correlates in prostitutes in Mombasa, Kenya. *Journal of Infectious Diseases.* 2003;**187**:359-363.

135. Lefevre JC, Averous S, Bauriaud R, Blanc C, Bertand Ma, Lareng MB, et al. Lower genital tract infections in women: comparison of clinical and epidemiologic findings with microbiology. *Sexually Transmitted Diseases.* 1988;**15**:110-113.

136. Louv WC, Austin H, Pelman J, Alexander WJ. Oral contraceptive use and the risk of chlamydial and gonococcal infections. *American Journal of Obstetrics & Gynecology.* 1989;**160**:396-402.

137. Lowe TL, Kraus SJ. Quantitation of Neisseria gonorrhoeae from women with gonorrhea. *Journal of Infectious Diseases*. 1976;**133**:621-626.

138. Lycke E, Lowhagen GB, Hallhagen G, Johannisson G, Ramsteadt K. The risk of transmission of genital Chlamydia trachomatis infection is less than that of genital Neisseria gonorrhoeae infection. *Sexually Transmitted Diseases.* 1980;**7**:6-10.

139. Macaulay ME, Riordan T, James JM, Leventhall PM, Morris EM, Neal BR, et al. A prospective study of genital infections in a family-planning clinic. 2. Chlamydia infection - the identification of a high-risk group. *Epidemiology & Infection*. 1990;**104**:55-61.

140. Magder LS, Harrison Hr, Ehret JM, Anderson TS, Judson FN. Factors related to genital Chlamydia trachomatis and its diagnosis by culture in a sexually transmitted disease clinic. *American Journal of Epidemiology*. 1988;**128**:298-308.

141. Magder LS, Kolntz KC, Bush LH, Barnes RC. Effect of patient characteristics on performance of an enzyme immunoassay for detecting cervical Chlamydia trachomatis infection. *Journal of Clinical Microbiology.* 1990;28:781-784.

142. Masse R, Laperrieve H, Rousseau H, Lefebvre J, Remis RS. Chlamydia trachomatis cervical infection: prevalence and determinants among women presenting for routine gynecologic examination. *Canadian Medical Association Journal*. 1991;**145**:953-961.

143. McCormack WM, Reynolds GH. Effect of menstrual cycle and method of contraception on recovery of Neisseria gonorrhoeae. *Journal of the American Medical Association*. 1982;**247**:1292-1294.

144. Nayyar KC, O'Neill JJ, Hambling WH, Waugh MA. Isolation of Chlamydia trachomatis from women attending a clinic for sexually transmitted diseases. *British Journal of Venereal Diseases*. 1976;**52**:396-398.

145. Oh MK, Feinstein RA, Soileau EJ, Cloud GA, Pass RF. Chlamydia trachomatis cervical infection and oral contraceptive use among adolescent girls. *Journal of Adolescent Health Care.* 1989;**10**:376-381.

146. Oriel JD. Infection of the uterine cervix with Chlamydia trachomatis. *Journal of Infectious Diseases.* 1978;**137**:443-451.

147. Paavonen J, Vesterinen E. Chlamydia trachomatis in cervicitis and urethritis in women. *Scandinavian Journal of Infectious Diseases – Supplementum*. 1982;32:45-54.

148. Park BJ, Stergachis A, Scholes D, Heiarich FE, Holmes KK, Stamm WE. Contraceptive methods and the risk of Chlamydia trachomatis infection in young women. *American Journal of Epidemiology*. 1995;**142**:771-778.

149. Pereira LH, Embil Ja, Haase DA, Manley KM. Cytomegalovirus infection among women attending a sexually transmitted disease clinic: association with clinical symptoms and other sexually transmitted diseases. *American Journal of Epidemiology.* 1990;**131**:683-692.

150. Reed BD, Huck W, Zazove P. Differentiation of Gardnerella vaginalis, Candida albicans, and Trichomonas vaginalis infections of the vagina. *Journal of Family Practice.* 1989;**28**:673-680.

151. Ripa KT, Svensson L, Mardh Pa, Westrom L. Chlamydia trachomatis cervicitis in gynecologic outpatients. *Obstetrics & Gynecology.* 1978;**52**:698-702.

152. Ruijs GJ, Kauer FM, Van Gjissel PM, Schirm J, Schroder FP. Direct immunofluorescence for Chlamydia trachomatis on urogenital smears for epidemiological purposes. *European Journal of Obstetrics, Gynecology & Reproductive Biology.* 1988;**27**:289-297.

153. Schachter J, Stoner E, Moncada J. Screening for chlamydial infections in women attending family planning clinics. *Western Journal of Medicine.* 1983;**138**:375-379.

154. Sellors JW, Karwalajtys TL, Kaczorowski J, Mahony JB, Lytwyh A, Chong S, et al. Incidence, clearance and predictors of human papillomavirus infection in women. *Canadian Medical Association Journal.* 2003; **168**:421-425.

155. Sessa R, Latino MA, Magliano EM, Nicosia R, Postorino R, Santino I, et al. Epidemiology of urogenital infections caused by Chlamydia trachomatis and outline of characteristic features of patients at risk. *Journal of Medical Microbiology.* 1994;**41**:168-172.

156. Shafer MA, Beck A, Blain B, Dole P, Irwin CE Jr, Sweet R, et al. Chlamydia trachomatis: important relationships to race, contraception, lower genital tract infection, and Papanicolaou smear. Journal of Pediatrics. 1984;**104**:141-146.

157. Smith JS, Herrero R, Munoz N, Eluf-Neto C, Ngelangel C, Bosch FX, et al. Prevalence and risk factors for herpes simplex virus type 2 infection among middle-age women in Brazil and the Philippines. *Sexually Transmitted Diseases*. 2001;**28**:187-194.

158. Staerfelt F, Gundersen TJ, Halos AM, Barlinn C, Johansen AG, norregarrd KM, et al. A survey of genital infections in patients attending a clinic for sexually transmitted diseases. *Scandinavian Journal of Infectious Diseases – Supplementum*. 1983;**40**:53-57.

159. Svensson L, Westrom L, Mardh PA. Chlamydia trachomatis in women attending a gynaecological outpatient clinic with lower genital tract infection. *British Journal of Venereal Diseases*. 1981;**57**:259-262.

160. Tait IA, Rees E, Hobson D, Byng RE, Tweedie MA. Chlamydial infection of the cervix in contacts of men with nongonococcal urethritis. *British Journal of Venereal Diseases*. 1980;**56**:37-45.

161. Willmott FE, Mair HJ. Genital herpesvirus infection in women attending a venereal diseases clinic. *British Journal of Venereal Diseases*. 1978;**54**:341-343.

162. Winer RL, Lee SK, Hughes JP, Adam DE, Kiviat NB, Koutsky LA. Genital human papillomavirus infection: incidence and risk factors in a cohort of female university students. *American Journal of Epidemiology.* 2003;**157**:218-226.

163. Winter L, Goldy AS, Baer C. Prevalence and epidemiologic correlates of Chlamydia trachomatis in rural and urban populations. *Sexually Transmitted Diseases.*1990;**17**:30-36.

164. Wolinska WH, Melamed MR. Herpes genitalis in women attending Planned Parenthood of New York City. *Acta Cytologica.* 1970;**14**:239-242.

165. Woolfitt JM, Watt L. Chlamydial infection of the urogenital tract in promiscuous and non-promiscuous women. *British Journal of Venereal Diseases*. 1977;**53**:93-95.

166. Mostad SB, Kreiss JK, Ryncarr AJ, Kishorchanidra M, Bhavna C, Achola J, et al. Cervical shedding of herpes simplex virus in human immunodeficiency virusinfected women: effects of hormonal contraception, pregnancy, and vitamin A deficiency. *Journal of Infectious Diseases*. 2000;**181**:58-63.

167. El-Raghy, Back DT, Osman F, Ormem L, Fathalla M. Contraceptive steroid concentrations in women with early active schistosomiasis: lack of effect of antischistosomal drugs. *Contraception.* 1986;**33**:373-377.

168. Gad-el-Mawla N, Abdallah A. Liver function in bilharzial females receiving contraceptive pills. Acta Hepato-Splenologica. 1969;**16**:308-310.

169. Gad-el-Mawla, El-Roubi O, Sabet S, Abdallah A. Plasma lipids and lipoproteins in bilharzial females during oral contraceptive therapy. *Journal of the Egyptian Medical Association*. 1972;**55**:137-147.

170. Shaaban MM, Hammad WA, Falthalla MF, Ghaneimah SA, El-Sharkawy MM, Salim TH, et al. Effects of oral contraception on liver function tests and serum proteins in women with active schistosomiasis. *Contraception.* 1982;**26**:75-82.

171. Shaaban MM, Ghaneimah SA, Mohamed MA, Abdel-Chani S, Mostafa SA. Effect of oral contraception on serum bile acid. *International Journal of Gynaecology & Obstetrics*. 1984;**22**:111-115.

172. Sy FS, Osteria TS, Opiniano V, Gler S. Effect of oral contraceptive on liver function tests of women with schistosomiasis in the Philippines. *Contraception.* 1986;**34**:283-294.

173. Tagy AH, Saker ME, Moussa AA, Kolgah A. The effect of low-dose combined oral contraceptive pills versus injectable contraceptive (Depot Provera) on liver function tests of women with compensated bilharzial liver fibrosis. *Contraception*. 2001;**64**:173-176.

174. Faculty of Family Planning and Reproductive Health Care Clinical Effectiveness Unit. Drug Interactions with Hormonal Contraception. *Journal of Family Planning and Reproductive Healthcare* 2005;**31**:139-150.

175. Schweitzer IL, Weiner JM, McPeak CM, Thursby MW. Oral contraceptives in acute viral hepatitis. J*ournal of the American Medical Association*. 1975;**1**:979-980.

176. Di Martino V, Lebray P, Myers RP, Pannier E, Paradis V, Charlotte F et al. Progression of liver fibrosis in women infected with hepatitis C: Long-term benefit of estrogen exposure. *Hepatology* 2008;**40**:1426-1433.

177. Libbrecht L, Craninx M, Nevens F, Desmet V, Roskams T. Predictive value of liver cell dysplasia for development of hepatocellular carcinoma in patients with non-cirrhotic and cirrhotic chronic viral hepatitis. *Histopathology*. 2001;**39**:66-73.

178. Peishan W, Zemin L, Jinlan T, Weili X, Xuewen M, Fengge M. Safety of hormonal steroid contraceptive use for hepatitis B virus carrier women. *Pharmacoepidemiology and Drug Safety.* 2000;**9**:245-6.

179. Shaaban MM, Hammad WA, Fathalla MF, Ghaneimah SA, El-Sharkawy MM, Salim TH, et al. Effects of oral contraception on liver function tests and serum proteins in women with past viral hepatitis. *Contraception.* 1982;**26**:65-74.

180. Eisalo A, Konttinen A, Hietala O. Oral contraceptives after liver disease. *British Medical Journal*. 1971;**4**: 561-562.

181. Gines P, Quintero E, Arroyo V, Teres J, Bruguera M, Rimola A, et al. Compensated cirrhosis: natural history and prognostic factors. *Hepatalogy.*1987;**7**(1):122-128.

182. Lam CM, Yong JL, Chan AO, Ng KK, Poon RT, Liu CL. Better survival in female patients with hepatocellular carcinoma: oral contraceptive pills related? *Journal Clinical Gastroenterology*. 2005;**39**:533-539.

183. Margolis KL, Adami HO, Luo J, Weimin Ye, Weiderpass E. A prospective study or oral contraceptive use and risk of myocardial infarction among Swedish women. *Fertility & Sterility*. 2007;**88**:310-316.

184. Faculty of Family Planning and Reproductive Health Care Clinical Effectiveness Unit. Contraceptive choices for women with inflammatory bowel disease. 2009 (update) www.fsrh.org.uk

185. Department of Health. Prodigy Guidance – Raynauds phenomenon. 2002. http://www/prodigy,nhs.uk/raynaud's-phenomenon.

186. Eastcott HH. Raynaud's disease and the oral contraceptive pill [Letter] *British Medical Journal.* 1976;**2**:477.

187. Altura BM. Sex and oestrogens and responsiveness of terminal arterioles to neurohypopyseal hormones and catecholamines. *Pharmocology and Experimental Theraputics*. 1975;**193**:403-412.

188. Greenstein D, Jeffcote N, Isley D. Kester RC. The menstrual cycle and Raynauds phenomenon. *Angiology.* 1996;**47**:427-436.

189. Bartelink ML, Wollersheim H, Vemer H, Thomas CM, de Boo T, Thien T. The effects of single oral doses of 17 beta-oestradiol and progesterone on finger circulation in healthy women and in women with primary Raynaud's phenomenon. *European Journal of Clinical Pharmocology.* 1994;**46**:557-560.

190. Sanchez-Guerrero J, Uribe AG, Jimenez-Santana L, Mestanza-Peralta M, Lara-Reyes P, Seuc AH, et al. A trial of contraceptive methods in women with systemic lupus erythematousus. *New England Journal of Medicine* 2005;**353**:2539-2542.

191. Petri M, Kim MY, Kalunian KC, Grossmann J, Hahn BH, Sammaritano LR, et al. Combined oral contraceptives in women with systemic lupus erythematosus. New England Journal of Medicine 2005;**353**:2550-2558.

192. Julkunen HA. Oral contraceptives in systemic lupus erythematosus: side-effects and influence on the activity of SLE. *British Journal of Rheumatology.* 1991;**32**:227-230.

193. Jungers P, Dougados M, Pelissier C, Kuttenn F, Tron F, Lesavre P et al. Influence of oral contraceptive therapy on the activity of systemic lupus erythematosus. *Arthritis and Rheumatism.* 1982;**25**:618-623.

194. Chopra N, Koren S, Greer WL, Fortin PR, Ruach J, Fortin I, et al. Factor V Leiden, prothrombin gene mutation, and thrombosis risk in SLE patients with postive antiphospholipid antibodies. *Journal of Rheumatology* 2002;**29**:1638-1688.

195. Choojitarom K, Verasertniyom O, Toemchokchyakarn K, Nantiruj K, Sumethkul V, Janwityanujit S. Lupus nephritis and Raynaud's phenonmenon are significant risk factors for vascular thrombosis on SLE patients with a postive antiphospholipid antibodies. *Clinical Rheumatology.* 2008;**24**:345-51.

196. McDonald J, Stewart J, Urowitz MB, Gladmann DD. Peripheral vascualr disease in pateints with systemic lupus erythematosus. *Ann Rheum Diseases*. 1992;**51**:56-60.

197. Julkunen HA, Kaaja R, Friman C. Contraceptive practice in women with systemic lupus erythematosus. *British Journal of Rheumatology.* 1993;**32**:227-230.

198. Petri M, Kim MY, Kalunian KC, Grossmann J, Sammaritano LR, Lockshin MM, et al. Musculoskeltal complications of systemic lupus erythmatosus in the Hopkins Lupus Cohort. *Arthritis Care Research.* 1995;**8**:137-145.

199. Ramsey-Goldman R, Dunn JE, Huang CF, Dunlop D, Rarie JE, Fitzgerald S, et al. Freqeuency of fractures in women with systemic lupus erythematosus: comparsion with United States population data. *Arthritis and Rheumatism*. 1999;**42**:882-890.

200. McAlidon T, Giannotta L, Taub N. Enviromental factors predicting nephritis in systemic lupus erythematosus. *Ann Rheum Diseases*. 1993;**51**:56-60.

201. Bernatsky S, Clarke A, Ramsey-Goldman R. Hormonal exposures and breast cancer in a sample of women with systemtic lupus erythematousus. *Rheumatology (Oxford)* 2004;**43**:1178-1781.

202. Bernatsky S, Ramsey-Goldman R, Gordon C. Factors associated with abnormal Pap results in systemic lupus erythematosus. *Rheumatology.* 2004;**43:**1386-1389.

203. Cosetenbader KH, Feskanich D, Stampfer MJ, Karlson EW. Reproductive and menopausal factors and risk of systemic lupus erythematosus in women. *Arthritis and Rheumatism*. 2007;**56**:1251-1262.

204. Aweeka FT, Rosenkranz SL, Segal Y, Coombs RW, Bardeguez A, thevanayagam L, et al. The impact of sex and contraceptive therapy on the plasma and intracellular pharmacokinetics of zidovudine. *AIDS*. 2006;**20**(14):1833-1841.

205. Clark RA, Theall K. Population-based study evaluating association between selected antiretroviral therapies and potential oral contraceptive failure. Journal Acquired Immune Deficiency Syndrome. 2004;**37**(1):1219-1220.

206. Ouellet D, Hsu A, Qian J, Locke CS, Eason CJ, Cavanaugh JH, et al. Effect of ritonavir on the pharmacokinetics of ethinyl oestradiol in healthy female volunteers. *British Journal of Clinical Pharmacology.* 1998;**46**(2):111-116.

207. Mildvan D, Yarrish R, Marshak A, Hutman Hw, Mc Donough M, Lamson M, et al. Pharmacokinetic interaction between nevirapine and ethinyl estradiol/norethindrone when administered concurrently to HIV-infected women. J*ournal of Acquired Immune Deficiency Syndromes*. 2002; **29**(5):471-477.

208. Schöller-Gyüre M, Debroye C, Aharchi F, Woodfall B, Peeters MVK, Hoetelmans R. No clinically relevant effect of TMC125 on the pharmacokinetics of oral contraceptives. 8th International Congress on Drug Therapy in HIV infection November 12–16, 2006, Glasgow, UK.

209. Sekar V, Lefebvre E, Spinosa-Guzman S et al. Pharmacokinetic interaction between ethinyl estradiol, norethindrone and TMC114, a new protease inhibitor. 46th Interscience Conference on Antimicrobial Agents and Chemotherapy, September 27–30, 2006, San Francisco, CA.

210. Tackett D, Child M, Agarwala S, Geiger M, Geraldes M, O'Mara E. Atazanavir: A Summary of Two Pharmacokinetic Drug Interaction Studies in Healthy Subjects. 10th Conference on Retroviruses and Opportunistic Infections. Abstract 543. Feb 10-14, 2003, Boston, MA.

211. Kearney BP, Isaacson E, Sayre J, Cheng AK. Tenofovir DF and Oral Contraceptives: Lack of a Pharmacokinetic Drug Interaction. 43rd Interscience Conference on Antimicrobial Agents and Chemotherapy. Abstract A-1618. September 14-17, 2003, Chicago, IL.

212. Abel S, Whitlock L, Ridgway C, Saifulanwar A, Bakhtyari A, Russell D. Effect of UK-427,857 on the pharmacokinetics of oral contraceptive steroids, and the pharmacokinetics of UK-427,857 in healthy young women. 43rd Interscience Conference on Antimicrobial Agents and Chemotherapy. September 14-17, 2003, Chicago, IL.

213. Anderson MS, Wenning L, Moreau A et al. Effect of raltegravir on the pharmacokinetics of oral contraceptives. 47th Interscience Conference on Antimicrobial Agents and Chemotherapy. September 17-20, 2007, Chicago, IL.

214. Joshi AS, Fiske WD, Benedek IH, White SJ, Joseph JL, Kornhauser DM. Lack of a pharmacokinetic interaction between efavirenz (DMP 266) and ethinyl estradiol in healthy female volunteers. 5th Conference on Retroviruses and Opportunistic Infections. Abstract 348. February 1-5, 1998, Chicago, IL

215. Sinicco A, Raiteri R, Rossati A, Savarino A, Di Perri G. Efavirenz interference in estradiol ELISA assay. Clinical Chemistry. 2000;**46**(5):734-735.

216. Chu JH, Gange SJ, Anastos K, Minkoff H, Cejtin H, Bacon M, et al. Hormonal contraceptive use and the effectiveness of highly active antiretroviral therapy. *American Journal of Epidemiology.* 2005;**161**(9):881-890.

217. Frohlich M, Burhenne J, Martin-Facklam M, Weiss J, von Wolff M, Strowitzki T. Oral contraception does not alter single dose saquinavir pharmacokinetics in women. *British Journal of Clinical Pharmacology.* 2004;**57**(3):244-252.

218. Christensen J, Petrenaite V, Atterman J, Petrenaite V, Otterman J, Sidenius P, Ohman I, Tomson T, et al. Oral contraceptives induce lamotrigine metabolism: evidence from a double-blind, placebo-controlled trial. *Epilepsia.* 2007;**48**:484-489.

219. Tomson T, Luef G, Sabers A, Luef G, Sabers A, Pittschieler S, Ohman I. Valproate effects on kinetics of lamotrigine in pregnancy and treatment with oral contraceptives. *Neurology*. 2006;**67**:1297-1299.

220. Dienel A, Klement S, Muller F. Influence of losigamone on the pharmacokinetics of a combined oral contraceptive in healthy female volunteers. *Arzneimittelforschung*. 2004;**54**:152-159.

221. Doose DR, Wang S, Padmanabhan M, Wang SS, Padmanabhan M, Schwabe S, Jacobs D, Bialer M. Effects of topiramate or carbamazepine on the pharmacokinetics of an oral contraceptive containing norethindrone and ethinyl estradiol in healthy obese and nonobese female subjects. *Epilepsia,*. 2003;**44**:540-549.

222. Griffith SG, Dai Y. Effect of Zonisamide on the pharmacokinetics and pharmacodynamics of a combination ethinyl estradiol-norethindrone oral contraceptive in health women. *Clinical Therapeutics.* 2004;**26**:2056-2064.

223. Sabers A, Buchholt JM, Uldall P, Thomson T. Lamotrigine plasma levels reduced by oral contraceptives. *Epilepsy Research*. 2001;**47**:151-154.

224. Contin M, Albani F, Ambrosetto G, Avoni P, Bisulli F, Riva R. Variation in lamotrigine plasma concentrations with hormonal contraceptive monthly cycles in patients with epilepsy. *Epilepsia*. 2006;47:1573-1575.

225. Galimberti CA, Mazzucchelli I, Arbasino C, Canevini MP, Fattore C, Perucca E, et al. Increased apparent oral clearance of valproic acid during intake of combined contraceptive steroids in women with epilepsy. *Epilepsia.* 2006;**47**:1569-1572.

226. Reimers A, Helde G, Brodtkorb E. Ethinyl estradiol, not progestogens, reduces lamotrigine serum concentrations. *Epilepsia*, 2005, **46**:1414-1417.

227. Schindlbeck C, Janni W, Friese K. Failure of Implanon contraception in a patient taking carbamazepine for epilepsia. *Archives of Gynecology & Obstetrics*. 2006;**273**:255-256.

228. Sidhu J, Job S, Singh S, Phillipson R. The pharmacokinetic and pharmacodynamic consequences of the co-administration of lamotrigine and a combined oral contraceptive in healthy female subjects. *British Journal of Clinical Pharmacology*. 2005;**61**:191-199.

229. Crawford P, Chadwick D, Cleland P et al. The lack of effect of sodium valproate on the pharmacokinetics of oral contraceptive steroids. *Contraception*, 1986, **33**:23-29.

230. Rosenfeld WE, Doose DR, Walker SA, Nayak R. Effect of topiramate on the pharmacokinetics of an oral contraceptive containing norethindrone and ethinyl estradiol in patients with epilepsy. *Epilepsia*. 1997;**38**: 317-323.

231. Sabers A, Ohman I, Christensen J, Tomson T. Oral contraceptives reduce lamotrigine plasma levels. *Neurology*. 2003;**61**:570-571.

232. Kenyon TE. Unplanned pregnancy in an epileptic. *British Medical Journal.* 1972;1:686-687.

233. Patsalos PN, Froscher W, Pisani F, van Rijn CM. The importance of drug interactions in epilepsy therapy. *Epilepsia*. 2002;**43**:365-385.

234. Venkatakrishnan K, Von Moltke LL, Greenblatt DJ. Human drug metabolism and the cytochromes P450: application and relevance of in vitro models. *Journal of Clinical Pharmacology.* 2001;**41**:1149-1179.

235. Wilbur K, Ensom MHH. Pharmacokinetic drug interactions between oral contraceptives and second-generation anticonvulsants. *Clinical Pharmacokinetics*, 2000, **38**:355-365.

236. Christensen J, Petrenaite V, Atterman J, Sibenius P, Ohman I, Thomson T, et al. Oral contraceptives induce lamotrigine metabolism: evidence from a double-blind, placebo-controlled trial. *Epilepsia.* 2007;**48**:484-489.

237. Tomson T, Luef G, Sabers A, Pittschieier S, Ohman I. Valproate effects on kinetics of lamotrigine in pregnancy and treatment with oral contraceptives.*Neurology.* 2006;**67**:1297-1299.

238. Bounds W, Guillebaud J. Observational series on women using the contraceptive Mirena concurrently with anti-epileptic and other enzyme-inducing drugs. *The Journal of Family Planning and Reproductive Health Care*. 2002;**28**:78-80.

239. Dienel A, Klement S, Muller F. Influence of losigamone on the pharmacokinetics of a combined oral contraceptive in healthy female volunteers. *Arzneimittelforschung.* 2004;**54**:152-159.

240. Griffith SG, Dai Y. Effect of Zonisamide on the pharmacokinetics and pharmacodynamics of a combination ethinyl estradiol-norethindrone oral contraceptive in health women. *Clinical Therapeutics.* 2004;26:2056-2064.

241. Contin M, Albani F, Ambrosetto G, Avoni P, Bisulli F, Riva R, et al. Variation in lamotrigine plasma concentrations with hormonal contraceptive monthly cycles in patients with epilepsy. *Epilepsia*. 2006;**47**:1573-1575.

242. Galimberti CA, Mazzucchelli I, Arbasino C, Canevini MP, Fattore C, Perucca E. Increased apparent oral clearance of valproic acid during intake of combined contraceptive steroids in women with epilepsy. *Epilepsia.* 2006;**47**:1569-1572.

243. Reimers A, Helde G, Brodtkorb E. Ethinyl estradiol, not progestogens, reduces lamotrigine serum concentrations. *Epilepsia*. 2005;**46**:1414-1417.

244. Schindlbeck C, Janni W, Friese K. Failure of Implanon contraception in a patient taking carbamazepine for epilepsia. *Archives of Gynecology & Obstetrics*. 2006;**273**:255-256.

245. Sidhu J, Job S, Singh S, Phillipson R. The pharmacokinetic and pharmacodynamic consequences of the co-administration of lamotrigine and a combined oral contraceptive in healthy female subjects. *British Journal of Clinical Pharmacology*. 2005;**61**:191-199.

246. Back DJ, Bates M, Bowden A, Breckenridge AM, Hall MJ, Jones H, et al. The interaction of Phenobarbital and other anticonvulsants with oral contraceptive steroid therapy. *Contraception.* 1980;**22**:495-503.

247. Crawford P, Chadwick D, Cleland P, Tjia j, Cowie A, Back DJ, et al. The lack of effect of sodium valproate on the pharmacokinetics of oral contraceptive steroids. *Contraception*. 1986;**33**:23-29.

248. Sabers A, Ohman I, Christensen J et al. Oral contraceptives reduce lamotrigine plasma levels. *Neurology,* 2003, **61**:570-571.

249. Haukkamaa M. Contraception by Norplant subdermal capsules is not reliable in epileptic patients on anticonvulsant treatment. *Contraception*. 1986;**33**:559-565.

250. Odlind V, Olsson S-E. Enhanced metabolism of levonorgestrel during phenytoin treatment in a woman with Norplant implants. *Contraception*. 1986;**33**:257-261.

251. Shane-McWhorter L, Cerven JD, MacFarlane LL, Osborne C, et al.. Enhanced metabolism of levonorgestrel during phenobarbital treatment and resultant pregnancy. *Pharmacotherapy.* 1998;**18**:1360-1364.

252. Bartoli A, Gatti G, Cipolla G, Barazaghi N, Vellz C, Fattore C, et al. A double-blind, placebo-controlled study on the effect of vigabatrin on in vivo parameters of hepatic microsomal enzyme induction and on the kinetics of steroid oral contraceptives in healthy female volunteers. *Epilepsia*. 1997;**38**:702-707.

253. Eldon MA, Underwood BA, Randinitis EJ, Sedmen AJ. Gabapentin does not interact with a contraceptive regimen of norethindrone acetate and ethinyl estradiol. *Neurology*. 1998;**50**:1146-1148.

254. Fattore C, Cipolla G, Gatti G, Limido GL, Strumm Y, Bernasconi C, et al. Induction of ethinylestradiol and levonorgestrel metabolism by oxcarbazepine in healthy women. *Epilepsia*. 1999;**40**:783-787.

255. Ragueneau-Majlessi I, Levy RH, Janik F. Levetiracetum does not alter the pharmacokinetics of an oral contraceptive in healthy women. *Epilepsia*. 2002;**43**:697-702.

256. Reimers D, Jezek A. [The simultaneous use of rifampicin and other antitubercular agents with oral contraceptives]. [German]. *Prax Pneumol*. 1971; **25**(5):255-62.

257. Nocke-Finck L, Breuer H, Reimers D. [Effects of rifampicin on the menstrual cycle and on oestrogen excretion in patients taking oral contraceptives]. [German]. *Dtsch Med Wochenschr.* 1973;**98**(33):1521-1523.

258. Hirsch A. [Letter: Sleeping pills]. [French]. *Nouv Presse Med*. 1973;***2***(44):2957.

259. Kropp R. [Rifampicin and oral contraceptives (author's transl)]. [German]. *Prax Pneumol.* 1974;**28**(5):270-272.

260. Piguet B, Muglioni JF, Chaline G. [Letter: Oral contraception and rifampicin]. [French]. *Nouv Presse Med.* 1975;**04**(2):115-116.

261. Hirschm A, Tillement JP, Chrentien J. Effets contrariants de la rifampicine sur les contraceptifsoraux: a propos de trois grossesses non desiree chez trois malades. *Rev. Franc. Mal. Resp*. 1975;**2**:174-82.

262. Skolnick JL, Stoler BS, Katz DB, Anderson WH. Rifampin, oral contraceptives, and pregnancy. *Journal of the American Medical Assocation*. 1976;**236**(12):1382.

263. Bessot JC, Petitjean R, Vandevenne A, Rempp M, Burghard G. [Rifampicin interference with oral contraceptives]. *J Med Strasb*.1977;**8**(3):131-3.

264. Gupta KC, Ali MY. Failure of oral contraceptive with rifampicin. *Medical Journal of Zambia*.1980-1981;**15**(1):23.

265. Szoka PR, Edgren RA. Drug interactions with oral contraceptives: compilation and analysis of an adverse experience report database. *Fertility & Sterility*. 1988;**49**(5 Suppl 2):31S-8S.

266. Bounds W, Guillebaud J. Observational series on women using the contraceptive Mirena concurrently with anti-epileptic and other enzyme-inducing drugs. *Journal of Family Planning and Reproductive Health Care.* 2002;**28**(2):78-80.

267. Bolt HM, Bolt M, Kappus H. Interaction of rifampicin treatment with pharmacokinetics and metabolism of ethinyloestradiol in man. *Acta Endocrinol* (Copenh) 1977;**85**(1):189-197.

268. Gelbke HP, Gethmann U, Knuppen R. Influence of rifampicin treatment on the metabolic fate of. *Hormonal Metabolim Research*. 1977;**9**(5):415-419.

269. Back DJ, Breckenridge AM, Crawford F, McIver M, Orme M, Park BK, et al. The effect of rifampicin on norethisterone pharmacokinetics. *European Journal Clinical Pharmacology.* 1979;**15**(3):193-7.

270. Back DJ, Breckenridge AM, Crawford FE, Hall JM, McIver M, Orme M, et al. The effect of rifampicin on the pharmacokinetics of ethynylestradiol in women. *Contraception*. 1980;**21**(2):135-143.

271. Joshi JV, Joshi UM, Sankolli GM, Gupta K, Rao AD, Hazari K, et al. A study of interaction of a low-dose combination oral contraceptive with anti-tubercular drugs. *Contraception*. 1980;**21**(6):617-29.

272. Meyer B, Muller F, Wessels P, Maree J. A model to detect interactions between roxithromycin and oral contraceptives. *Clinical Pharmacology & Therapeutics*. 1990; **47(**6):671-4.

273. LeBel M, Masson E, Guilbert E, Colborn D, Paquet F, Allard S, et al. Effects of rifabutin and rifampicin on the pharmacokinetics of ethinylestradiol and norethindrone. *Journal of Clinical Pharmacology*. 1998;**38(**11):1042-1050.

274. Barditch-Crovo P, Trapnell CB, Ette E, Zacur Ha, Coresh J, Rocco LE, et al. The effects of rifampin and rifabutin on the pharmacokinetics and pharmacodynamics of a combination oral contraceptive. *Clinical Pharmacology & Therapeutics.* 1999; **65**(4):428-38.

275. Trapnell CB, Connolly M, Pentikis H, Forbes WP, Bettenhausen DK. Absence of effect of oral rifaximin on the pharmacokinetics of ethinyl estradiol/norgestimate in healthy females. *Annalls of Pharmacotherapy.* 2007;**41**(2):222-228.

276. Chen YX, Cabana B, Kivel N, Pieniaszek H, Gilman S, Michaelis A. Lack of effect of rifalazil on ethinyl estradiol pharmacokinetics in healthy postmenopausal women. *International Journal of Clinical Pharmacolgy Therapy.* 2007;**45**(7):418-422.

277. Dosseter J. Drug interaction wtih oral contraceptives. *British Medical Journal*. 1994;**4**(5994):467-8.

278. Biron CR. Questions surface over whether antibiotics neutralized 'the pill,' resulting in pregnancy. RDH 1956;**16**(7):34-36.

279. Hempel E, Bohm W, Carol W, Klinger G. [Enzyme induction by drugs and hormonal contraception]. [German]. *Zentralbl Gynakol*. 1973;**95**(41):1451-7.

280. Bacon JF, Shenfield GM. Pregnancy attributable to interaction between tetracycline and oral contraceptives. *British Medical Journal*. 1980;**280**(6210):293.

281. Lequeux A. [Pregnancy under oral contraceptives after treatment with tetracycline]. *Louv Med.* 1980; **99**(6):413-414.

282. Driver J. Use of antibiotics during pregnancy [letter]. 1982.

283. Silber TJ. Apparent oral contraceptive failure associated with antibiotic administration. *Journal of Adolescent Health Care*. 1983;**4**(4):287-289.

284. van Dijke CP, Weber JC. Interaction between oral contraceptives and griseofulvin. *British Medical Journal* (Clin Res Ed). 1984;**288**(6424):1125-1126.

285. Bainton R. Interaction between antibiotic therapy and contraceptive medication. Oral Surgical, *Oral Medical and Oral Pathology*. 1986;**61**(5):453-455.

286. Cote J. Interaction of griseofulvin and oral contraceptives.[comment]. J*ournal of the American Academy of Dermatology*. 1990;**22**(1):124-125.

287. de Groot AC, Eshuis H, Stricker BH. [Inefficacy of oral contraception during use of minocycline]. *Ned Tijdschr Geneeskd* 1990;**134**(25):1227-1279.

288. Pillans PI, Sparrow MJ. Pregnancy associated with a combined oral contraceptive and itraconazole.[see comment]. *New Zealand Medical Journal*. 1993;**106**(965):436.

289. Bollen M. Use of antibiotics when taking the oral contraceptive pill.[comment]. *Australian Family Physician.* 1995;**24**(5):928-929.

290. Donley TG, Smith RF, Roy B. Reduced oral contraceptive effectiveness with concurrent antibiotic use: a protocol for prescribing antibiotics to women of childbearing age. *Compendium.* 1990;**11**(6):392-396.

291. Bacon L, Mina M. Unintended pregnancies with Implanon.[comment]. *Contraception*. 2006;**73**(1):111.

292. McDaniel PA, Caldroney RD. Oral contraceptives and griseofulvin interactions. *Drug Intelligence & Clinical Pharmacy.* 1986;**20**(5):384.

293. Back DJ, Grimmer SF, Orme ML, Proudlove C, Mann RD, Breckenridge AM. Evaluation of Committee on Safety of Medicines yellow card reports on oral contraceptive-drug interactions with anticonvulsants and antibiotics. *British Journal of Clinical Pharmacology.* 1988;**25**(5):527-532.

294. Sparrow MJ. Pill method failures. *New Zealand Medical Journal*. 1987;**100**(818):102-105.

295. Sparrow MJ. Pill method failures in women seeking abortion: fourteen years experience. *New Zealand Medical Journal.* 1998;**111**(1075):386-388.

296. Sparrow MJ. Pregnancies in reliable pill takers. New Zealand Medical Journal. 1989;**102**(879):575-577.

297. Kakouris H, Kovacs GT. How common are predisposing factors to pill failure among pill users? British Journal of Family Planning. 1994;**20**(2):33-35.

298. Kakouris H, Kovacs GT. Pill failure and nonuse of secondary precautions. British Journal of Family Planning. 1992;**18**:41-44.

299. Bromham DR, Cartmill RS. Knowledge and use of secondary contraception among patients requesting termination of pregnancy. British Medical Journal. 1993;**306**(6877):556-557.

300. Young LK, Farquhar CM, McCowan LM, Roberts HE, Taylor J. The contraceptive practices of women seeking termination of pregnancy in an Auckland clinic. *New Zealand Medical Journal.* 1994;**107**(978):189-192.

301. Kovacs GT, Riddoch G, Duncombe P et al. Inadvertent pregnancies in oral contraceptive users. *Medical Journal of Australia*. 1989;**150**(10):549-551.

302. DeSano EA Jr, Hurley SC. Possible interactions of antihistamines and antibiotics with oral contraceptive effectiveness. *Fertility & Sterility*. 1982;**37**(6):853-4.

303. Helms SE, Bredle DL, Zajic J, Jarjoura D, Brodell RT, Krishnarao I. Oral contraceptive failure rates and oral antibiotics. *Journal of the American Academy of Dermatology*. 1997;**36**(5 Pt 1):705-710.

304. Hughes BR, Cunliffe WJ. Interactions between the oral contraceptive pill and antibiotics.[comment]. *British Jounral of Dermatology.* 1990;**122**(5):717-718.

305. London BM, Lookingbill DP. Frequency of pregnancy in acne patients taking oral antibiotics and oral contraceptives. *Archives of Dermatology*. 1994;**130**(3):392-393.

306. Hetenyi G. Possible interactions between antibiotics and oral contraceptives. *Ther Hung*. 1989;**37**(2):86-89.

307. Hempel E, Zorn C, Graf K. [Effect of chemotherapy agents and antibiotics on hormonal contraception]. [German]. *Zeitschrift Fur Arztliche Fortbildung (Jena)* 1978; **72(**19):924-926.

308. Joshi JV, Joshi UM, Sankholi GM, Krishna U, Madlekar A, Chowdhury, et al. A study of interaction of low-dose combination oral contraceptive with Ampicillin and Metronidazole. *Contraception*. 1980;**22**(6):643-652.

309. Friedman CI, Huneke AL, Kim MH, Powell J. The effect of ampicillin on oral contraceptive effectiveness. *Obstetrics & Gynecology.* 1980;**55**(1):33-37.

310. Back DJ, Breckenridge AM, MacIver M, Orme M, Rowe Ph, Staiger PH, et al. The effects of ampicillin on oral contraceptive steroids in women. *British Journal of Clinical Pharmacology.* 1982;**14**(1):43-48.

311. Murphy AA, Zacur HA, Charache P, Burkman RT. The effect of tetracycline on levels of oral contraceptives. American Journal of Obstetrics and Gynecology. 1991; **164**(1 Pt 1):28-33.

312. Neely JL, Abate M, Swinker M, D'Angio R. The effect of doxycycline on serum levels of ethinyl estradiol, norethindrone, and endogenous progesterone. *Obstetrics & Gynecology*. 1991;**77**(3):416-20.

313. Dogterom P, van den Heuvel MW, Thomsen T. Absence of pharmacokinetic interactions of the combined contraceptive vaginal ring NuvaRing with oral amoxicillin or doxycycline in two randomised trials. *Clinical Pharmacokinet.* 2005;**44**(4):429-38.

314. Wermeling DP, Chandler MH, Sides GD, Collins D, Muse KN. Dirithromycin increases ethinyl estradiol clearance without allowing ovulation. *Obstetrics & Gynecology*. 1995;**86**(1):78-84.

315. Back DJ, Tjia J, Martin C, Millar E, Mant T, Morrison P, et al. The lack of interaction between temafloxacin and combined oral contraceptive steroids. *Contraception.* 1991;**43**(4):317-323.

316. Csemiczky G , Alvendal C, Landgren BM. Risk for ovulation in women taking a low-dose oral contraceptive (Microgynon) when receiving antibacterial treatment with a fluoroquinolone (ofloxacin). *Advances in Contraception*. 1996;**12**(2):101-109.

317. Scholten PC, Droppert RM, Zwinkels MG, Moesker HL, Nauta JJ, Hoepelman IM. No interaction between ciprofloxacin and an oral contraceptive. *Antimicrobial Agents & Chemotherapy*. 1998;**42**(12):3266-3268.

318. Maggiolo F, Puricelli G, Dottorini M, Caprioloi S, Bianchi W, Suter F. The effects of ciprofloxacin on oral contraceptive steroid treatments. *Drugs Exptl. Clinical Research*. 1991;**9**:451-454.

319. Grimmer SF, Allen WL, Back DJ, Breckenridge AM, Orme M, Tjia J. The effect of cotrimoxazole on oral contraceptive steroids in women. *Contraception*. 1983; **28**(1):53-59.

320. Meyboom RH, van Puijenbroek EP, Vinks MH, Lastdrager CJ. Disturbance of withdrawal bleeding during concomitant use of itraconazole and oral contraceptives. *New Zealand Medical Journal.* 1997;**110**(1049):300.

321. van Puijenbroek EP, Feenstra J, Meyboom RH. [Pill cycle disturbance in simultaneous use of itraconazole and oral contraceptives]. [Dutch]. *Ned Tijdschr Geneeskd.* 1998;**142**(3):146-149.

322. Van Puijenbroek EP, Egberts AC, Meyboom RH, Leufkens HG. Signalling possible drug-drug interactions in a spontaneous reporting system: delay of withdrawal bleeding during concomitant use of oral contraceptives and itraconazole. *British Journal of Clinical Pharmacology.* 1999;**47**(6):689-693.

323. Kovacs I, Somos P, Hamori M. Examination of the potential interaction between ketoconazole (Nizoral) and oral contraceptives with special regard to products of low hormone content (Rigevidon, anteovin). *Ther Hung.* 1986;**34**(3):167-170.

324. Devenport MH, Crook D, Wynn V, Lees LJ. Metabolic effects of low-dose fluconazole in healthy female users and non-users of oral contraceptives. *British Journal of Clinical Pharmacology.* 1989;**27**(6):851-859.

325. Rieth H, Sauerbrey N. [Interaction studies with fluconazole, a new triazole antifungal drug]. [German]. *Wien Med Wochenschr*. 1989;**139**(15-16):370-374.

326. Lunell NO, Pschera H, Zador G, Carlstrom K. Evaluation of the possible interaction of the antifungal triazole SCH 39304 with oral contraceptives in normal healthy women. *Gynecologic & Obstetric Investigation*. 1991;**32**(2):91-97.

327. Sinofsky FE, Pasquale SA. The effect of fluconazole on circulating ethinyl estradiol levels in women taking oral contraceptives. *American Journal of Obstetrics & Gynecology*. 1998;**178**(2):300-304.

328. Hilbert J, Messig M, Kuye O, Friedman H. Evaluation of interaction between fluconazole and an oral contraceptive in healthy women. *Obstetrics & Gynecology*. 2001;**98**(2):218-23.

329. Verhoeven CH, van den Heuvel MW, Mulders TM, Dieben TO. The contraceptive vaginal ring, NuvaRing, and antimycotic co-medication. *Contraception*. 2004;**69**(2):129-132.

330. Back DJ, Breckenridge AM, Grimmer SF, Orme ML, Purba HS. Pharmacokinetics of oral contraceptive steroids following the administration of the antimalarial drugs primaquine and chloroquine. *Contraception.* 1984;**30**(3):289-95.

331. el-Raghy I, Back DJ, Osman F, Orme ML, Fathalla M. Contraceptive steroid concentrations in women with early active schistosomiasis: lack of effect of antischistosomal drugs. *Contraception*. 1986;**33**(4):373-377.

332. Croft AM, Herxheimer A. Adverse effects of the antimalaria drug, mefloquine: due to primary liver damage with secondary thyroid involvement? BMC Public Health. 2:6, 2002 Mar 25 .

333. Karbwang J, Looareesuwan S, Back DJ, Migasana S, Bunnag D, Breckenridge AM. Effect of oral contraceptive steroids on the clinical course of malaria infection and on the pharmacokinetics of mefloquine in Thai women. *Bull World Health Organization.* 1988;**66**(6):763-767.

334. Wanwimolruk S, Kaewvichit S, Tanthayaphinant O, Suwannarach C, Oranratnachai A. Lack of effect of oral contraceptive use on the pharmacokinetics of quinine. *Br J Clin Pharmacol* 1991;**31**(2):179-181.

335. McGready R, Stepniewska K, Seaton E et al. Pregnancy and use of oral contraceptives reduces the biotransformation of proguanil to cycloguanil. Europena Journal of Clinical Pharmacology. 2003;59(7):553-557

336. Mulders TM, Dieben TO. The contraceptive vaginal ring, NuvaRing, and antimycotic co-medication. *Contraception.* 2004;**69**(2):129-132.

Progestogen-only contraceptives

PROGESTOGEN-ONLY CONTRACEPTIVES (POCs) *Includes progestogen-only pills (POP), progestogen-only injectables(depot medroxyprogesterone acetate [DMPA] and norethisterone enanthate [NET-EN]), and progestogen-only implants (IMP)*	**These methods do not protect against STI/HIV. If there is risk of STI/HIV (including during pregnancy or postpartum), the correct and consistent use of condoms is recommended, either alone or with another contraceptive method. Male condoms reduce the risk of STI/HIV.**			
CONDITION	**CATEGORY** I=Initiation, C=Continuation			**CLARIFICATIONS/EVIDENCE**
	POP	**DMPA/ NET-EN**	**IMP**	
PERSONAL CHARACTERISTICS AND REPRODUCTIVE HISTORY				
PREGNANCY	NA	NA	NA	**Clarification:** If a progestogen-only contraceptive is used accidentally during pregnancy there appears to be no known harm to the woman, the course of her pregnancy or to the fetus, although for the progestogen-only injectable this is perhaps less well documented.
AGE*				
a) Menarche to <18 years	1	2	1	A guideline from the National Institute for Health and Clinical Excellence recommends that women should be informed that use of DMPA is associated with a small reduction in bone mineral density but this usually recovers after discontinuation.[3] Evidence for the long term effects of DMPA on bone density in women aged <18 years is lacking. Evidence on long term fracture risk is sparse but women choosing to continue DMPA use should be reviewed every 2 years to assess individual situations and to discuss the risks and benefits.[2,4,5] Women should be supported in their choice of whether or not to continue. In women aged <18 years DMPA can be used as a first-line option after consideration of other methods.[2] Women may continue DMPA use to age 50 years. [2]
b) 18 to 45 years	1	1	1	
c) >45 years	1	2	1	
PARITY				
a) Nulliparous	1	1	1	
b) Parous	1	1	1	

*See also additional comments at end of section

UKMEC	DEFINITION OF CATEGORY
CATEGORY 1	A condition for which there is no restriction for the use of the contraceptive method
CATEGORY 2	A condition where the advantages of using the method generally outweigh the theoretical or proven risks
CATEGORY 3	A condition where the theoretical or proven risks generally outweigh the advantages of using the method. The provision of a method requires expert clinical judgement and/or referral to a specialist contraceptive provider, since use of the method is not usually recommended unless other more appropriate methods are not available or not acceptable
CATEGORY 4	A condition which represents an unacceptable health risk if the contraceptive method is used

PROGESTOGEN-ONLY CONTRACEPTIVES (POCs) *Includes progestogen-only pills (POP), progestogen-only injectables(depot medroxyprogesterone acetate [DMPA] and norethisterone enanthate [NET-EN]), and progestogen-only implants (IMP)*	**These methods do not protect against STI/HIV. If there is risk of STI/HIV (including during pregnancy or postpartum), the correct and consistent use of condoms is recommended, either alone or with another contraceptive method. Male condoms reduce the risk of STI/HIV.**			
CONDITION	**CATEGORY** I=Initiation, C=Continuation			**CLARIFICATIONS/EVIDENCE**
	POP	**DMPA/ NET-EN**	**IMP**	
BREASTFEEDING*				**Evidence:** There is no evidence that POCs have a detrimental effect on breast milk or infant growth.[7-31] FSRH suggest use before 6 weeks, but ideally delay until Day 21.[32,33]
a) <6 weeks postpartum	1	2	1	
b) ≥6 weeks to <6 months postpartum (fully or almost fully breastfeeding)	1	1	1	Women who are fully or almost fully breastfeeding, amenorrhoeic and <6 months postpartum can rely on lactational amenorrhoea method (LAM) for contraception unless breast feeding reduces or menstruation returns. **Definition:** *Fully and almost fully breastfeeding* includes exclusive with no other liquids or solids given; *almost exclusive:* vitamins, water or juice given infrequently in addition to breastfeeds; *partial* (high) where the vast majority of feeds are breastfeeds.
c) ≥6 weeks to <6 months postpartum (partial breastfeeding medium to minimal)	1	1	1	**Definition:** *Partial or token breastfeeding: Medium* – about half feeds are breastfeeds *Low* – vast majority of feeds are not breastfeeds *Minimal* – occasional irregular breastfeeds[33]
d) ≥6 months postpartum	1	1	1	
POSTPARTUM* (in non-breastfeeding women)				
a) <21 days	1	1	1	**Clarification:** This includes any births, including stillbirths from 24 weeks gestation
b) ≥21 days	1	1	1	
POST-ABORTION				
a) First trimester	1	1	1	**Clarification:** Includes spontaneous or induced abortion <24 weeks gestation. POCs can be commenced immediately following surgical abortion or following the second part of medical abortion.[34] **Evidence:** Limited evidence suggests that there are no adverse side-effects when Norplant or NET-EN are initiated after a first trimester abortion.[35-38]
b) Second trimester	1	1	1	
c) Immediate post-septic abortion	1	1	1	

*See also additional comments at end of section

UKMEC	DEFINITION OF CATEGORY
CATEGORY 1	A condition for which there is no restriction for the use of the contraceptive method
CATEGORY 2	A condition where the advantages of using the method generally outweigh the theoretical or proven risks
CATEGORY 3	A condition where the theoretical or proven risks generally outweigh the advantages of using the method. The provision of a method requires expert clinical judgement and/or referral to a specialist contraceptive provider, since use of the method is not usually recommended unless other more appropriate methods are not available or not acceptable
CATEGORY 4	A condition which represents an unacceptable health risk if the contraceptive method is used

PROGESTOGEN-ONLY CONTRACEPTIVES (POCs) *Includes progestogen-only pills (POP), progestogen-only injectables(depot medroxyprogesterone acetate [DMPA] and norethisterone enanthate [NET-EN]), and progestogen-only implants (IMP)*	**These methods do not protect against STI/HIV. If there is risk of STI/HIV (including during pregnancy or postpartum), the correct and consistent use of condoms is recommended, either alone or with another contraceptive method. Male condoms reduce the risk of STI/HIV.**			
CONDITION	**CATEGORY** I=Initiation, C=Continuation			**CLARIFICATIONS/EVIDENCE**
	POP	**DMPA/ NET-EN**	**IMP**	
PAST ECTOPIC PREGNANCY	1	1	1	All progestogen-only contraceptive methods reduce the risk of pregnancy (intrauterine and extrauterine). Methods which inhibit ovulation may be preferred in women with previous ectopic.
HISTORY OF PELVIC SURGERY	1	1	1	
SMOKING				
a) Age <35 years	1	1	1	Progestogen-only contraceptive methods do not appear to increase the risk of cardiovascular disease even in smokers.[39-42] The 35 year age cut off is identified because any excess mortality associated with smoking is only apparent from this age.[43] The mortality rate from all causes (including cancers) decreases to that of a non-smoker within 20 years of smoking cessation. The cardiovascular disease risk associated with smoking decreases within one to five years of smoking cessation.[42-45]
b) Age ≥35 years				
(i) <15 cigarettes per day	1	1	1	
(ii) ≥15 cigarettes per day	1	1	1	
(iii) stopped smoking <1 year ago	1	1	1	
(iv) stopped smoking ≥1 year ago	1	1	1	
OBESITY				Weight gain among women of reproductive age is common. Studies provide conflicting evidence regarding whether women are at increased risk of weight gain with DMPA use.[46-49] Results are also conflicting with regard to whether or not obese women are at an increased risk of weight gain with DMPA relative to non-obese women with DMPA use.[50-53]
a) ≥30 – 34 kg/m^2 body mass index	1	1	1	
b) ≥35 kg/m^2 body mass index	1	1	1	

UKMEC	DEFINITION OF CATEGORY
CATEGORY 1	A condition for which there is no restriction for the use of the contraceptive method
CATEGORY 2	A condition where the advantages of using the method generally outweigh the theoretical or proven risks
CATEGORY 3	A condition where the theoretical or proven risks generally outweigh the advantages of using the method. The provision of a method requires expert clinical judgement and/or referral to a specialist contraceptive provider, since use of the method is not usually recommended unless other more appropriate methods are not available or not acceptable
CATEGORY 4	A condition which represents an unacceptable health risk if the contraceptive method is used

PROGESTOGEN-ONLY CONTRACEPTIVES (POCs) *Includes progestogen-only pills (POP), progestogen-only injectables(depot medroxyprogesterone acetate [DMPA] and norethisterone enanthate [NET-EN]), and progestogen-only implants (IMP)*	**These methods do not protect against STI/HIV. If there is risk of STI/HIV (including during pregnancy or postpartum), the correct and consistent use of condoms is recommended, either alone or with another contraceptive method. Male condoms reduce the risk of STI/HIV.**			
CONDITION	**CATEGORY** I=Initiation, C=Continuation			**CLARIFICATIONS/EVIDENCE**
	POP	**DMPA/ NET-EN**	**IMP**	
CARDIOVASCULAR DISEASE				
MULTIPLE RISK FACTORS FOR CARDIOVASCULAR DISEASE (such as older age, smoking, diabetes, hypertension and obesity)	2	3	2	When multiple risk factors exist, risk of cardiovascular disease may increase substantially. The effects of DMPA and NET-EN may persist for some time after discontinuation.
HYPERTENSION				
For all categories of hypertension, classifications are based on the assumption **that no other risk factors for cardiovascular disease exist**. When multiple risk factors do exist, risk of cardiovascular disease may increase substantially. A single reading of blood pressure level is not sufficient to classify a woman as hypertensive. If elevated, the BP should be re-assessed at the end of the consultation. If blood pressure is increased it should be re-assessed on at least two subsequent clinic visits at monthly intervals.[54,55]				
a) Adequately controlled hypertension b) Consistently elevated blood pressure levels (properly taken measurements)	1	2	1	**Clarification:** Women adequately treated for hypertension are at reduced risk of acute myocardial infarction and stroke as compared with untreated women. Although there are no data, POC users with adequately controlled and monitored hypertension should be at reduced risk of acute myocardial infarction and stroke compared with untreated hypertensive POC users. Anti-hypertensive therapy may be initiated when the BP is consistently of 160/100 mmHg or greater.[55] **Evidence:** Limited evidence suggests that among women with hypertension, those who used POPs or progestogen-only injectables had a small increased risk of cardiovascular events compared with women who did not use these methods.[39]
(i) systolic >140-159 mmHg or diastolic >90-94 mmHg	1	1	1	
(ii) systolic >160 or diastolic >95 mmHg	1	2	1	
c) Vascular disease*	2	3	2	**Clarification:** *Vascular disease* includes: coronary heart disease presenting with angina; peripheral vascular disease presenting with intermittent claudication; hypertensive retinopathy; and transient ischaemic attacks.
HISTORY OF HIGH BLOOD PRESSURE DURING PREGNANCY (where current blood pressure is normal)	1	1	1	

*See also additional comments at end of section

UKMEC	DEFINITION OF CATEGORY
CATEGORY 1	A condition for which there is no restriction for the use of the contraceptive method
CATEGORY 2	A condition where the advantages of using the method generally outweigh the theoretical or proven risks
CATEGORY 3	A condition where the theoretical or proven risks generally outweigh the advantages of using the method. The provision of a method requires expert clinical judgement and/or referral to a specialist contraceptive provider, since use of the method is not usually recommended unless other more appropriate methods are not available or not acceptable
CATEGORY 4	A condition which represents an unacceptable health risk if the contraceptive method is used

PROGESTOGEN-ONLY CONTRACEPTIVES (POCs) *Includes progestogen-only pills (POP), progestogen-only injectables(depot medroxyprogesterone acetate [DMPA] and norethisterone enanthate [NET-EN]), and progestogen-only implants (IMP)*	**These methods do not protect against STI/HIV. If there is risk of STI/HIV (including during pregnancy or postpartum), the correct and consistent use of condoms is recommended, either alone or with another contraceptive method. Male condoms reduce the risk of STI/HIV.**			
CONDITION	**CATEGORY** I=Initiation, C=Continuation			**CLARIFICATIONS/EVIDENCE**
	POP	**DMPA/ NET-EN**	**IMP**	
VENOUS THROMBOEMBOLISM (VTE)				
a) History of VTE	2	2	2	Venous thromboembolism includes deep vein thrombosis and pulmonary embolism.
b) Current VTE (on anticoagulants)	2	2	2	Evidence is limited on the risk of VTE with progestogen-only contraceptives, however existing evidence is reassuring.[39,56,57,58]
c) Family history of VTE				
(i) first degree relative age <45 years	1	1	1	
(ii) first degree relative age ≥45 years	1	1	1	
d) Major surgery				**Major surgery** includes operations of >30 minutes duration. Procedures with high risk of VTE include: general or orthopaedic surgery, trauma and neurosurgery.[59]
(i) with prolonged immobilisation	2	2	2	
(ii) without prolonged immobilisation	1	1	1	
e) Minor surgery without immobilisation	1	1	1	**Minor surgery** includes operations lasting <30 minutes. Varicose vein surgery has a low risk of VTE.
f) Immobility (unrelated to surgery) e.g. *wheelchair use, debilitating illness*	1	1	1	**Immobility** due to hospitalisation for acute trauma, acute illness, or paralysis, is associated with a high risk of VTE.
KNOWN THROMBOGENIC MUTATIONS (e.g. Factor V Leiden, Prothrombin mutation, Protein S, Protein C, and Antithrombin deficiencies)	2	2	2	**Clarification:** Routine screening is not appropriate because of the rarity of the conditions and the high cost of screening.[60-62]
SUPERFICIAL VENOUS THROMBOSIS				
a) Varicose veins	1	1	1	
b) Superficial thrombophlebitis	1	1	1	

UKMEC	DEFINITION OF CATEGORY
CATEGORY 1	A condition for which there is no restriction for the use of the contraceptive method
CATEGORY 2	A condition where the advantages of using the method generally outweigh the theoretical or proven risks
CATEGORY 3	A condition where the theoretical or proven risks generally outweigh the advantages of using the method. The provision of a method requires expert clinical judgement and/or referral to a specialist contraceptive provider, since use of the method is not usually recommended unless other more appropriate methods are not available or not acceptable
CATEGORY 4	A condition which represents an unacceptable health risk if the contraceptive method is used

PROGESTOGEN-ONLY CONTRACEPTIVES (POCs) *Includes progestogen-only pills (POP), progestogen-only injectables(depot medroxyprogesterone acetate [DMPA] and norethisterone enanthate [NET-EN]), and progestogen-only implants (IMP)*	**These methods do not protect against STI/HIV. If there is risk of STI/HIV (including during pregnancy or postpartum), the correct and consistent use of condoms is recommended, either alone or with another contraceptive method. Male condoms reduce the risk of STI/HIV.**					
CONDITION	**CATEGORY** I=Initiation, C=Continuation					**CLARIFICATIONS/EVIDENCE**
	POP		**DMPA/ NET-EN**	**IMP**		
	I	**C**		**I**	**C**	
CURRENT AND HISTORY OF ISCHAEMIC HEART DISEASE*	2	3	3	2	3	The duration of use of POC in relation to the onset of disease should be carefully considered when deciding whether or not continuation of the method is appropriate.
STROKE* (history of cerebrovascular accident, including transient ischaemic attack)	2	3	3	2	3	The duration of use of POC in relation to the onset of disease should be carefully considered when deciding whether or not continuation of the method is appropriate.
KNOWN HYPERLIPIDAEMIAS	2		2	2		**Clarification:** Routine screening is not appropriate because of the rarity of the conditions and the high cost of screening. While some types of hyperlipidaemias are risk factors for vascular disease, the category should be assessed according to the type, its severity, and the presence of other cardiovascular risk factors. Lipid levels alone are poor predictors of risk of coronary heart disease. In the UK screening and treatment is aimed towards those at greatest risk of coronary heart disease, and this may also influence hormonal contraceptive use. Risk categories will vary depending on risk of premature coronary heart disease and the presence of other risk factors.[63] *Common hypercholesterolaemia* and *Familial combined hyperlipidaemia* are associated with an increased risk of coronary heart disease but usually this occurs over the age of 60 years.[63] *Familial hypercholesterolaemia* (autosomal dominant) has a prevalence of about 1 in 500. People with this condition have a four-fold increase in the risk of premature coronary heart disease.[63]

*See also additional comments at end of section

UKMEC	DEFINITION OF CATEGORY
CATEGORY 1	A condition for which there is no restriction for the use of the contraceptive method
CATEGORY 2	A condition where the advantages of using the method generally outweigh the theoretical or proven risks
CATEGORY 3	A condition where the theoretical or proven risks generally outweigh the advantages of using the method. The provision of a method requires expert clinical judgement and/or referral to a specialist contraceptive provider, since use of the method is not usually recommended unless other more appropriate methods are not available or not acceptable
CATEGORY 4	A condition which represents an unacceptable health risk if the contraceptive method is used

PROGESTOGEN-ONLY CONTRACEPTIVES (POCs) *Includes progestogen-only pills (POP), progestogen-only injectables(depot medroxyprogesterone acetate [DMPA] and norethisterone enanthate [NET-EN]), and progestogen-only implants (IMP)*	**These methods do not protect against STI/HIV. If there is risk of STI/HIV (including during pregnancy or postpartum), the correct and consistent use of condoms is recommended, either alone or with another contraceptive method. Male condoms reduce the risk of STI/HIV.**			
CONDITION	**CATEGORY** I=Initiation, C=Continuation			**CLARIFICATIONS/EVIDENCE**
	POP	**DMPA/ NET-EN**	**IMP**	
VALVULAR AND CONGENITAL HEART DISEASE				
a) Uncomplicated	1	1	1	**Clarification:** *Valvular heart disease* occurs when any heart valves are stenotic and/or incompetent (eg. Aortic stenosis, mitral regurgitation; tricuspid valve abnormalities; pulmonary stenosis).[64] *Congenital heart disease:* Aortic stenosis; Atrial septal defects; Atrio-ventricular septal defect; Cardiomyopathy (hypertrophic or dilated); Coarctation of the Aorta; Complex Transposition of the Great Arteries; Ebstein's Anomaly; Eisenmenger Syndrome: Patent Ductus Arteriosus; Pulmonary Atresia; Pulmonary Stenosis; Tetralogy of Fallot; Total Anomalous Pulmonary Venous Connection; Tricuspid Atresia; Truncus Arteriosus; Ventricular Septal Defect.[65] Surgical correction (prosthetic valve) and ongoing cardiac problems should be considered.
b) Complicated (eg. pulmonary hypertension, atrial fibrillation, history of subacute bacterial endocarditis)	1	1	1	

UKMEC	DEFINITION OF CATEGORY
CATEGORY 1	A condition for which there is no restriction for the use of the contraceptive method
CATEGORY 2	A condition where the advantages of using the method generally outweigh the theoretical or proven risks
CATEGORY 3	A condition where the theoretical or proven risks generally outweigh the advantages of using the method. The provision of a method requires expert clinical judgement and/or referral to a specialist contraceptive provider, since use of the method is not usually recommended unless other more appropriate methods are not available or not acceptable
CATEGORY 4	A condition which represents an unacceptable health risk if the contraceptive method is used

PROGESTOGEN-ONLY CONTRACEPTIVES (POCs) *Includes progestogen-only pills (POP), progestogen-only injectables(depot medroxyprogesterone acetate [DMPA] and norethisterone enanthate [NET-EN]), and progestogen-only implants (IMP)*	**These methods do not protect against STI/HIV. If there is risk of STI/HIV (including during pregnancy or postpartum), the correct and consistent use of condoms is recommended, either alone or with another contraceptive method. Male condoms reduce the risk of STI/HIV.**						
CONDITION	**CATEGORY** I=Initiation, C=Continuation						**CLARIFICATIONS/EVIDENCE**
	POP		**DMPA/ NET-EN**		**IMP**		
	I	**C**	**I**	**C**	**I**	**C**	
NEUROLOGIC CONDITIONS							
HEADACHES*							
a) Non-migrainous (mild or severe)	1	1	1	1	1	1	Headache is a common condition affecting women of reproductive age. Few studies have specifically assessed migraine in progestogen-only contraceptive users. Since there are no studies comparing active progestogen-only contraceptives with placebo, the true effect of progestogen-only methods on migraine is not clear. However, there is no evidence that the use of progestogen-only contraception is associated with an increased risk of ischaemic stroke.[66] Classification depends on making an accurate diagnosis of those severe headaches that are migrainous and in addition those complicated by aura. **Symptoms** of aura include: homonymous hemianopia, unilateral paraesthesia and/or numbness; unilateral weakness and aphasia or unclassifiable speech disorder. Visual symptoms progress from fortification spectra (a starshaped figure near the point of fixation with scintillating edges) to scotoma (a bright shape which gradually increases in size). Flashing lights are not classified as aura. Aura occurs before the onset of headache.[67]
b) Migraine without aura, at any age	1	2	2	2	2	2	
c) Migraine with aura, at any age	2		2		2		
d) Past history (≥5 years ago) of migraine with aura, any age	2		2		2		
EPILEPSY	1		1		1		See section on drug interactions.
DEPRESSIVE DISORDERS							
DEPRESSIVE DISORDERS	1		1		1		**Clarification:** The classification is based on data for women with selected depressive disorders. No data on bipolar disorder or postpartum depression were available. There is a potential for drug interactions between certain antidepressant medications and hormonal contraceptives. **Evidence:** Progestogen-only contraceptives do not increase depressive symptoms in women with depression compared to baseline.[68-71]

*See also additional comments at end of section

UKMEC	DEFINITION OF CATEGORY
CATEGORY 1	A condition for which there is no restriction for the use of the contraceptive method
CATEGORY 2	A condition where the advantages of using the method generally outweigh the theoretical or proven risks
CATEGORY 3	A condition where the theoretical or proven risks generally outweigh the advantages of using the method. The provision of a method requires expert clinical judgement and/or referral to a specialist contraceptive provider, since use of the method is not usually recommended unless other more appropriate methods are not available or not acceptable
CATEGORY 4	A condition which represents an unacceptable health risk if the contraceptive method is used

PROGESTOGEN-ONLY CONTRACEPTIVES (POCs) *Includes progestogen-only pills (POP), progestogen-only injectables(depot medroxyprogesterone acetate [DMPA] and norethisterone enanthate [NET-EN]), and progestogen-only implants (IMP)*	**These methods do not protect against STI/HIV. If there is risk of STI/HIV (including during pregnancy or postpartum), the correct and consistent use of condoms is recommended, either alone or with another contraceptive method. Male condoms reduce the risk of STI/HIV.**			
CONDITION	**CATEGORY** I=Initiation, C=Continuation			**CLARIFICATIONS/EVIDENCE**
	POP	**DMPA/ NET-EN**	**IMP**	
BREAST AND REPRODUCTIVE TRACT CONDITIONS				
VAGINAL BLEEDING PATTERNS a) Irregular pattern without heavy bleeding b) Heavy or prolonged bleeding (includes regular and irregular patterns)	2 2	2 2	2 2	Bleeding patterns in women using progestogen-only contraception are often altered particularly in the initial months of use and may not settle with time.[73] **Clarification:** Unusually heavy bleeding should raise the suspicion of a serious underlying condition.[72,73]
UNEXPLAINED VAGINAL BLEEDING (suspicious for serious underlying condition) Before evaluation	2	3	3	**Clarification:** If pregnancy or an underlying pathological condition (such as pelvic malignancy) is suspected, it must be evaluated and the category adjusted after evaluation.[73]
ENDOMETRIOSIS	1	1	1	
BENIGN OVARIAN TUMOURS (including cysts)	1	1	1	
SEVERE DYSMENORRHOEA	1	1	1	
GESTATIONAL TROPHOBLASTIC DISEASE (GTD) a) Decreasing or undetectable β-hCG levels b) Persistently elevated β-hCG levels or malignant disease	1 1	1 1	1 1	**Clarification:** Gestational trophoblastic disease (GTD) includes hydatidiform mole, invasive mole and placental site trophoblastic tumour. Advice should be sought from the specialist managing a woman's gestational trophoblastic disease as clinical guidelines vary within the UK.
CERVICAL ECTROPION	1	1	1	
CERVICAL INTRAEPITHELIAL NEOPLASIA (CIN)	1	2	1	**Evidence:** Among women with persistent HPV infection, long-term DMPA use (≥5 years) may increase the risk of carcinoma *in situ* and invasive carcinoma.[74]
CERVICAL CANCER (awaiting treatment)*	1	2	2	

*See also additional comments at end of table

UKMEC	DEFINITION OF CATEGORY
CATEGORY 1	A condition for which there is no restriction for the use of the contraceptive method
CATEGORY 2	A condition where the advantages of using the method generally outweigh the theoretical or proven risks
CATEGORY 3	A condition where the theoretical or proven risks generally outweigh the advantages of using the method. The provision of a method requires expert clinical judgement and/or referral to a specialist contraceptive provider, since use of the method is not usually recommended unless other more appropriate methods are not available or not acceptable
CATEGORY 4	A condition which represents an unacceptable health risk if the contraceptive method is used

PROGESTOGEN-ONLY CONTRACEPTIVES (POCs) *Includes progestogen-only pills (POP), progestogen-only injectables(depot medroxyprogesterone acetate [DMPA] and norethisterone enanthate [NET-EN]), and progestogen-only implants (IMP)*	**These methods do not protect against STI/HIV. If there is risk of STI/HIV (including during pregnancy or postpartum), the correct and consistent use of condoms is recommended, either alone or with another contraceptive method. Male condoms reduce the risk of STI/HIV.**			
CONDITION	**CATEGORY** I=Initiation, C=Continuation			**CLARIFICATIONS/EVIDENCE**
	POP	**DMPA/ NET-EN**	**IMP**	
BREAST DISEASE				
a) Undiagnosed mass	2	2	2	**Clarification:** Evaluation should be pursued as early as possible.
b) Benign breast disease	1	1	1	
c) Family history of breast cancer	1	1	1	
d) Carriers of known gene mutations associated with breast cancer (eg. BRCA1)	2	2	2	Breast cancer is a hormonally sensitive tumour and therefore the prognosis of women with current or recent breast cancer may worsen with progestogen-only contraceptive use.
e) Breast cancer				
(i) current	4	4	4	
(ii) past and no evidence of current disease for 5 years	3	3	3	
ENDOMETRIAL CANCER*	1	1	1	
OVARIAN CANCER*	1	1	1	
UTERINE FIBROIDS				
a) Without distortion of the uterine cavity	1	1	1	No evidence that progestogen-only contraceptives influence the growth of uterine fibroids.
b) With distortion of the uterine cavity	1	1	1	
PELVIC INFLAMMATORY DISEASE (PID)*				
a) Past PID (assuming no current risk factors for STIs)	1	1	1	
b) Current PID	1	1	1	

*See also additional comments at end of section

UKMEC	DEFINITION OF CATEGORY
CATEGORY 1	A condition for which there is no restriction for the use of the contraceptive method
CATEGORY 2	A condition where the advantages of using the method generally outweigh the theoretical or proven risks
CATEGORY 3	A condition where the theoretical or proven risks generally outweigh the advantages of using the method. The provision of a method requires expert clinical judgement and/or referral to a specialist contraceptive provider, since use of the method is not usually recommended unless other more appropriate methods are not available or not acceptable
CATEGORY 4	A condition which represents an unacceptable health risk if the contraceptive method is used

PROGESTOGEN-ONLY CONTRACEPTIVES (POCs) *Includes progestogen-only pills (POP), progestogen-only injectables(depot medroxyprogesterone acetate [DMPA] and norethisterone enanthate [NET-EN]), and progestogen-only implants (IMP)*	**These methods do not protect against STI/HIV. If there is risk of STI/HIV (including during pregnancy or postpartum), the correct and consistent use of condoms is recommended, either alone or with another contraceptive method. Male condoms reduce the risk of STI/HIV.**			
CONDITION	**CATEGORY** I=Initiation, C=Continuation			**CLARIFICATIONS/EVIDENCE**
	POP	**DMPA/ NET-EN**	**IMP**	
SEXUALLY TRANSMITTED INFECTIONS (STIs*)				
a) Chlamydial infection				**Evidence:** Limited evidence suggests that there may be an increased risk of chlamydial cervicitis among DMPA users at high risk of STIs. For other STIs, there is either evidence of no association between DMPA use and STI acquisition or too limited evidence to draw any conclusions. There is no evidence for other POCs.[75-81]
i) Symptomatic	1	1	1	
ii) Asymptomatic	1	1	1	
b) Current purulent cervicitis or gonorrhoea	1	1	1	
c) Other STIs (excluding HIV and hepatitis)	1	1	1	
d) Vaginitis (including *Trichomonas vaginalis* and bacterial vaginosis)	1	1	1	
e) Increased risk of STIs	1	1	1	
HIV/AIDS				
HIGH RISK OF HIV*	1	1	1	
HIV-INFECTED				
a) Not using anti-retroviral therapy	2	2	2	
b) Using anti-retroviral therapy	1-3	1-2	1-2	See section on drug interactions.
AIDS (using antiretrovirals)	2	2	2	See section on drug interactions.
OTHER INFECTIONS				
SCHISTOSOMIASIS				
a) Uncomplicated	1	1	1	**Evidence:** Among women with uncomplicated schistosomiasis, limited evidence showed that DMPA use had no adverse effects on liver function.[82]
b) Fibrosis of liver (if severe, see cirrhosis)	1	1	1	
TUBERCULOSIS				
a) Non-pelvic	1	1	1	
b) Known pelvic	1	1	1	See section on drug interactions.
MALARIA	1	1	1	**Clarification:** Doxycycline is increasingly used in the treatment and prevention of malaria[83] There is no interaction with POC.

*See also additional comments at end of section

UKMEC	DEFINITION OF CATEGORY
CATEGORY 1	A condition for which there is no restriction for the use of the contraceptive method
CATEGORY 2	A condition where the advantages of using the method generally outweigh the theoretical or proven risks
CATEGORY 3	A condition where the theoretical or proven risks generally outweigh the advantages of using the method. The provision of a method requires expert clinical judgement and/or referral to a specialist contraceptive provider, since use of the method is not usually recommended unless other more appropriate methods are not available or not acceptable
CATEGORY 4	A condition which represents an unacceptable health risk if the contraceptive method is used

PROGESTOGEN-ONLY CONTRACEPTIVES (POCs) *Includes progestogen-only pills (POP), progestogen-only injectables(depot medroxyprogesterone acetate [DMPA] and norethisterone enanthate [NET-EN]), and progestogen-only implants (IMP)*	**These methods do not protect against STI/HIV. If there is risk of STI/HIV (including during pregnancy or postpartum), the correct and consistent use of condoms is recommended, either alone or with another contraceptive method. Male condoms reduce the risk of STI/HIV.**			
CONDITION	**CATEGORY** I=Initiation, C=Continuation			**CLARIFICATIONS/EVIDENCE**
	POP	**DMPA/ NET-EN**	**IMP**	
ENDOCRINE CONDITIONS				
DIABETES*				
a) History of gestational diabetes	1	1	1	
b) Non-vascular disease				
(i) non-insulin dependent	2	2	2	
(ii) insulin dependent	2	2	2	
c) Nephropathy/ retinopathy/ neuropathy	2	3	2	
d) Other vascular disease	2	3	2	
THYROID DISORDERS				
a) Simple goitre	1	1	1	
b) Hyperthyroid	1	1	1	
c) Hypothyroid	1	1	1	
GASTROINTESTINAL CONDITIONS				
GALL-BLADDER DISEASE				
a) Symptomatic				
(i) treated by cholecystectomy	2	2	2	
(ii) medically treated	2	2	2	
(iii) current	2	2	2	
b) Asymptomatic	2	2	2	
HISTORY OF CHOLESTASIS*				
a) Pregnancy-related	1	1	1	
b) Past COC-related	2	2	2	
VIRAL HEPATITIS*				
a) Acute or flare	1	1	1	
b) Carrier	1	1	1	
c) Chronic	1	1	1	

*See also additional comments at end of section

UKMEC	DEFINITION OF CATEGORY
CATEGORY 1	A condition for which there is no restriction for the use of the contraceptive method
CATEGORY 2	A condition where the advantages of using the method generally outweigh the theoretical or proven risks
CATEGORY 3	A condition where the theoretical or proven risks generally outweigh the advantages of using the method. The provision of a method requires expert clinical judgement and/or referral to a specialist contraceptive provider, since use of the method is not usually recommended unless other more appropriate methods are not available or not acceptable
CATEGORY 4	A condition which represents an unacceptable health risk if the contraceptive method is used

PROGESTOGEN-ONLY CONTRACEPTIVES (POCs) *Includes progestogen-only pills (POP), progestogen-only injectables(depot medroxyprogesterone acetate [DMPA] and norethisterone enanthate [NET-EN]), and progestogen-only implants (IMP)*	**These methods do not protect against STI/HIV. If there is risk of STI/HIV (including during pregnancy or postpartum), the correct and consistent use of condoms is recommended, either alone or with another contraceptive method. Male condoms reduce the risk of STI/HIV.**			
CONDITION	**CATEGORY** I=Initiation, C=Continuation			**CLARIFICATIONS/EVIDENCE**
	POP	**DMPA/ NET-EN**	**IMP**	
CIRRHOSIS*				
a) Mild (compensated without complications)	1	1	1	**Clarification**: *Severe (decompensated) cirrhosis:* development of major complications (ascites, jaundice, encephalopathy, or gastrointestinal haemorrhage).[84]
b) Severe (decompensated)	3	3	3	
LIVER TUMOURS				
a) Benign				Progestogen-only contraceptives do not appear to influence either resolution or progression of liver lesions. No evidence concerning the use of Progestogen-only contraceptives in those with malignant disease was found[85].
i) Focal nodular hyperplasia	2	2	2	
ii) Hepatocellular adenoma	3	3	3	
b) Malignant (hepatoma)	3	3	3	
INFLAMMATORY BOWEL DISEASE* (Includes Crohn's disease, ulcerative colitis)	2	1	1	**Clarification:** Oral methods may be less reliable if there is significant malabsorption or small bowel resection (particularly with Crohn's disease). Oral methods are unaffected by colectomy and ileostomy.
ANAEMIAS				
THALASSAEMIA	1	1	1	
SICKLE CELL DISEASE	1	1	1	**Evidence:** Among women with sickle cell disease, POC use did not have adverse effects on haematological parameters and, in some studies, was beneficial with respect to clinical symptoms.[86-93]
IRON-DEFICIENCY ANAEMIA*	1	1	1	
RAYNAUD'S DISEASE				
a) Primary	1	1	1	**Clarification:** Secondary Raynaud's usually has an underlying disease such as scleroderma, rheumatoid arthritis, systemic lupus erythematosus. Progesterone has little effect but studies have not suggested an association with progestogens and Raynaud's.[94-97]
b) Secondary				
(i) without lupus anticoagulant	1	1	1	
(ii) with lupus anticoagulant	2	2	2	
RHEUMATIC DISEASES				
SYSTEMIC LUPUS ERYTHEMATOSUS (SLE)		**I**	**C**	People with SLE are at an increased risk of ischaemic heart disease, stroke and venous thromboembolism. Categories are based on the assumption that no other risk factors for cardiovascular disease are present; these must be modified in the presence of such risk factors.[98-100]
a) Positive (or unknown) antiphospholipid antibodies	3	3	3	3
b) Severe thrombocytopenia	2	3	2	2
c) Immunosuppressive treatment	2	2	2	2
d) None of the above	2	2	2	2

*See also additional comments at end of section

UKMEC	DEFINITION OF CATEGORY
CATEGORY 1	A condition for which there is no restriction for the use of the contraceptive method
CATEGORY 2	A condition where the advantages of using the method generally outweigh the theoretical or proven risks
CATEGORY 3	A condition where the theoretical or proven risks generally outweigh the advantages of using the method. The provision of a method requires expert clinical judgement and/or referral to a specialist contraceptive provider, since use of the method is not usually recommended unless other more appropriate methods are not available or not acceptable
CATEGORY 4	A condition which represents an unacceptable health risk if the contraceptive method is used

PROGESTOGEN-ONLY CONTRACEPTIVES (POCs) *Includes progestogen-only pills (POP), progestogen-only injectables(depot medroxyprogesterone acetate [DMPA] and norethisterone enanthate [NET-EN]), and progestogen-only implants (IMP)*	**These methods do not protect against STI/HIV. If there is risk of STI/HIV (including during pregnancy or postpartum), the correct and consistent use of condoms is recommended, either alone or with another contraceptive method. Male condoms reduce the risk of STI/HIV.**			
CONDITION	**CATEGORY** I=Initiation, C=Continuation			**CLARIFICATIONS/EVIDENCE**
	POP	**DMPA/ NET-EN**	**IMP**	
DRUG INTERACTIONS				
ANTIRETROVIRAL THERAPY: This section relates to the SAFETY of contraceptive use in women using these antiretrovirals. EFFECTIVENESS may be reduced and pregnancy itself may have a negative impact on health for some women with certain medical conditions.				
a) Nucleoside reverse transcriptase inhibitors	1	DMPA=1 NET-EN=2	1	**Antiretroviral therapy and hormonal contraception:** Antiretroviral drugs have the potential to either decrease or increase the bioavailability of steroid hormones in hormonal contraceptives. Limited data suggest potential drug interactions between many antiretroviral drugs (particularly some non-nucleoside reverse transcriptase inhibitors and ritonavir-boosted protease inhibitors) and hormonal contraceptives. These interactions may alter the safety and effectiveness of both the hormonal contraceptive and the antiretroviral drug. Thus, **if a woman on antiretroviral treatment decides to initiate or continue hormonal contraceptive use, the USE OF CONDOMS IS RECOMMENDED.** This is for both preventing HIV transmission and to compensate for any possible reduction in the effectiveness of the hormonal contraceptive.
b) Non-nucleoside reverse transcriptase inhibitors	2	DMPA=1 NET-EN=2	2	
c) Ritonavir-boosted protease inhibitors	3	DMPA=1 NET-EN=2	2	
ANTICONVULSANT THERAPY: This section relates to the SAFETY of contraceptive use in women using anticonvulsants. EFFECTIVENESS may be reduced and pregnancy itself may have a negative impact on health for some women with certain medical conditions.				
a) Certain anticonvulsants (phenytoin, carbamazepine, barbiturates, primidone, topiramate, oxcarbazepine)	3*	DMPA=1 NET-EN=2*	2*	**Certain anticonvulsants and progestogen-only contraception:** Although the interaction of certain anticonvulsants with POPs, NET-EN and implants is not harmful to women, it is likely to reduce the effectiveness of POPs, NET-EN and implants. Whether increasing the hormone dose of POPs alleviates this concern remains unclear. If a woman on certain anticonvulsants decides to use POP or implants **the USE OF CONDOMS IS RECOMMENDED*. Use of other contraceptives should be encouraged for women who are long-term users of any of these anticonvulsant drugs**. Use of DMPA is a Category 1 because its effectiveness is NOT decreased by the use of certain anticonvulsants.
b) Lamotrigine	1	1	1	**Lamotrigine:** There are no interactions with lamotrigine and progestogen-only contraceptives.

PROGESTOGEN-ONLY CONTRACEPTIVES (POCs) *Includes progestogen-only pills (POP), progestogen-only injectables(depot medroxyprogesterone acetate [DMPA] and norethisterone enanthate [NET-EN]), and progestogen-only implants (IMP)*	**These methods do not protect against STI/HIV. If there is risk of STI/HIV (including during pregnancy or postpartum), the correct and consistent use of condoms is recommended, either alone or with another contraceptive method. Male condoms reduce the risk of STI/HIV.**			
CONDITION	**CATEGORY** I=Initiation, C=Continuation			**CLARIFICATIONS/EVIDENCE**
	POP	**DMPA/ NET-EN**	**IMP**	
ANTIMICROBIAL THERAPY: **This section relates to the SAFETY of contraceptive use in women using antimicrobials. EFFECTIVENESS may be reduced and pregnancy itself may have a negative impact on health for some women with certain medical conditions.**				
a) Broad spectrum antibiotics	1	1	1	**Rifampicin or rifabutin therapy and progestogen-only contraception:** Although the interaction of rifampicin or rifabutin with POPs, NET-EN and implants is not harmful to women, it is likely to reduce the effectiveness of POPs, NET-EN and implants. Whether increasing the hormone dose of POPs alleviates this concern remains unclear. If a woman on rifampicin or rifabutin decides to use POP or implants **the consistent USE OF CONDOMS IS RECOMMENDED*. Use of other contraceptives should be encouraged for women who are long-term users of rifampicin or rifabutin**. Use of DMPA is a Category 1 because its effectiveness is unlikely to be decreased by the use of rifampicin or rifabutin.
b) Antifungals	1	1	1	
c) Antiparasitics	1	1	1	
d) Rifampicin or rifabutin therapy	3*	DMPA=1 NET-EN=2*	2*	

UKMEC	DEFINITION OF CATEGORY
CATEGORY 1	A condition for which there is no restriction for the use of the contraceptive method
CATEGORY 2	A condition where the advantages of using the method generally outweigh the theoretical or proven risks
CATEGORY 3	A condition where the theoretical or proven risks generally outweigh the advantages of using the method. The provision of a method requires expert clinical judgement and/or referral to a specialist contraceptive provider, since use of the method is not usually recommended unless other more appropriate methods are not available or not acceptable
CATEGORY 4	A condition which represents an unacceptable health risk if the contraceptive method is used

Additional comments

AGE

Menarche to <18 years: For women under 18 years of age, there are theoretical concerns regarding the hypo-estrogenic effects of DMPA use, including whether these women will achieve their appropriate peak bone mass.

45 years: DMPA can be continued to age 50 years and then stopped and a suitable alternative contraceptive used.[2]

BREASTFEEDING

<6 WEEKS POSTPARTUM: There is limited theoretical concern that the neonate may be at risk due to exposure to steroid hormones during the first 6 weeks postpartum. If used <6 weeks delay until Day 21.

POSTPARTUM

<21 days: Progestogen-only contraceptives may be safely used by non-breastfeeding women immediately postpartum, although they are not required for contraception until Day 21.

HYPERTENSION
There is no evidence that progestogen-only contraceptives affect blood pressure.

CARDIOVASCULAR DISEASE
Vascular disease, current and history of ischaemic heart disease and stroke: There is concern regarding hypo-estrogenic effects and reduced HDL levels, particularly among users of DMPA and NET-EN. However, there is little concern about these effects with regard to POPs or implants. The effects of DMPA and NET-EN may persist for some time after discontinuation.

CERVICAL CANCER (awaiting treatment)
There is some theoretical concern that progestogen-only contraceptive use may affect prognosis of the existing disease. While awaiting treatment, women may use progestogen-only contraceptives. In general, treatment of this condition renders a woman sterile.

ENDOMETRIAL AND OVARIAN CANCER
Whilst awaiting treatment, women may use progestogen-only contraceptives. In general, the treatment of this condition renders a woman sterile.

PELVIC INFLAMMATORY DISEASE (PID) AND SEXUALLY TRANSMITTED INFECTIONS (STI)
Whether progestogen-only-contraceptives, reduce the risk of PID among women with STIs is unknown, but they do not protect against HIV or lower genital tract STI.

DIABETES
Non-vascular disease: POCs may alter carbohydrate metabolism, but evidence is limited.
Nephropathy, retinopathy, neuropathy: There is concern regarding hypo-estrogenic effects and reduced HDL levels, particularly among users of DMPA and NET-EN. The effects of DMPA and NET-EN may persist for some time after discontinuation. Some POCs may increase the risk of thrombosis, although this increase is substantially less than with COCs.

Other vascular disease: There is concern regarding hypo-estrogenic effects and reduced HDL levels, particularly among users of DMPA and NET-EN. The effects of DMPA and NET-EN may persist for some time after discontinuation. Some POCs may increase the risk of thrombosis, although this increase is substantially less than with COCs.

HISTORY OF CHOLESTASIS
Theoretically, a history of COC-related cholestasis may predict subsequent cholestasis with POC use. However, this has not been documented.

VIRAL HEPATITIS & CIRRHOSIS
Active: POCs are metabolised by the liver and their use may adversely affect women whose liver function is compromised. This concern is similar to, but less than, that with COCs.

LIVER TUMOURS
Progestogen-only contraceptives are metabolised by the liver and use may adversely affect women whose liver function is compromised. Progestogen-only contraceptives may enhance the growth of benign adenoma and malignant tumours but less than with combined hormonal methods.

INFLAMMATORY BOWEL DISEASE
There is no evidence that women with IBD have an inherent increased risk of VTE. Risk of VTE may increase if unwell, bed bound or undergoing acute surgery or with major surgery and prolonged immobilisation. Under these circumstances POC can be continued. Absorption of oral methods may be reduced with malabsorption.

IRON-DEFICIENCY ANAEMIA
Changes in the menstrual pattern associated with POC use have little effect on haemoglobin levels.

DRUG INTERACTIONS
Generally safety of using progestogen-only contraception is unaffected. Nevertheless use of liver enzyme inducers or antibiotics may reduce contraceptive efficacy, increasing risk of unintended pregnancy. Contraceptive choice may depend on the likely duration of use of concurrent medications and need for additional or alternative methods. Progestogen-only injectables are unaffected by liver enzyme inducing drugs and injection intervals need not be reduced. POCs are unaffected by use of non-liver enzyme inducing antibiotics.

REFERENCES: PROGESTOGEN-ONLY CONTRACEPTIVES

1. Faculty of Sexual and Reproductive Healthcare Clinical Effectiveness Unit. Progestogen-only injectable contraception. http://www.ffprhc.org.uk/
2. Faculty of Family Planning and Reproductive Healthcare Clinical Effectiveness Unit. Contraceptive choices for women aged over 40 years. *Journal of Family Planning and Reproductive Health Care*. 2005;**31**(1):51–64
3. National Institute for Health and Clinical Excellence. Long acting-reversible contraception: the effective and appropriate use of long-acting reversible contraception. 2005. http://www.nice.org.uk/nicemedia/pdf/CG030fullguideline.pdf
4. Medicine and Healthcare products Regulatory Agency. Updated guidance on the use of Depo-provera contraception.http://www.mhra.gov.uk/Safetyinformation/Safetywarningsalertsandrecalls/Safetywarningsandmessagesformedicines/CON1004262.
5. Faculty of Family Planning and Reproductive Healthcare. Statement on MHRA Guidance on Depo-Provera. 2004. http://www.ffprhc.org.uk/
6. Faculty of Sexual and Reproductive Healthcare Clinical Guidance. Contraceptive Choices for Young People. *Journal of Family Planning and Reproductive Healthcare*, 2004:**30(4)**;29-42.
7. Abdel-Aleem H, Abol-Oyounel SM, Shaaban MM, el-Saeed M, Shoukry M, Makhlouf A et al. The use of nomegestrol acetate subdermal contraceptive implant, Uniplant, during lactation. *Contraception.* 1996;**54**:281-286.
8. Abdulla KA, Elwan SI, Salem HS, Shaaban MM. Effect of early postpartum use of the contraceptive implants, Norplant, on the serum levels of immunoglobulins of the mothers and their breastfed infants. *Contraception.* 1985;**32**:261-266.
9. Bjarnadottir RI, Gottfredsdottir H, Sigurdartdottir K, Gerisson R, Dieben TOM. Comparative study of the effects of a progestogen-only pill containing desogestrel and an intrauterine contraceptive device in lactating women. *British Journal of Obstetrics and Gynecology*. 2001;**108**:1174-1180.
10. Croxatto HB, Diaz S, Peralta O, Juez G, Casado ME, Salavatierra AM et al. Fertility regulation in nursing women. Comparative performance of progesterone implants versus placebo and copper T. *American Journal of Obstetrics & Gynecology*, 1982;**144**:201-8.
11. Diaz S, Paralta O, Juez G, Herreros C, Casada ME, Salvatierra AM et al. Fertility regulation in nursing women. VI. Contraceptive effectiveness of a subdermal progesterone implant. *Contraception*. 1984;**30**:311-325.
12. Halderman LD, Nelson AL. Impact of early postpartum administration of progestin-only hormonal contraceptives compared with nonhormonal contraceptives on short-term breast-feeding patterns. *American Journal of Obstetrics & Gynecology*. 2002;**186**:1250-1256.
13. Hannon PR, Duggan A, Serwint J, Vogelhurt J, Witter F. The influence of medroxyprogesterone on the duration of breast-feeding in mothers in an urban community. *Archives of Pediatrics & Adolescent Medicine.* 1997;**151**:490-496.
14. Jimenez J, Ochoa M, Soler MP, Portales P. Long-term follow-up of children breast-fed by mothers receiving depotmedroxyprogesterone acetate. *Contraception*. 1984;**30**:523-533.
15. Kamal I, Hefnawl F, Ghoneim M, Abdallah M, Razek SA. Clinical, biochemical, and experimental studies on lactation: clinical effects of steroids on the initiation of lactation. *American Journal of Obstetrics & Gynecology.* 1970;**108**:655-658.
16. Karim M, Ammar H, El-Mangoub S, El-Ganzoury B, Fikri F, Abdou I. Injected progestogen and lactation. *British Medical Journal*. 1971;**1**:200-203.
17. Massai R, Miranda P, Valdes P, Lavin P, Zepeda A, Casadom E, et al. Preregistration study on the safety and contraceptive efficacy of a progesteronereleasing vaginal ring in Chilean nursing women. *Contraception.* 1999;**60**:9-14.
18. McCann MF, Moggia AV, Higgins JE, Potts M, Becker C. The effects of a progestin-only oral contraceptive (levonorgestrel 0.03 mg) on breast-feeding. *Contraception*. 1989;**40**:635-648.
19. McEwan JA, Joyce DN, Tothill AU, Hawkins DF. Early experience in contraception with a new progestogen. *Contraception*. 1977;**16**:339-350.
20. Melis GB, Stringini F, Fruzzetti F, Paoletti AM, Rainer E, Dustenberg B et al. Norethisterone enanthate as an injectable contraceptive in puerperal and nonpuerperal women. *Contraception*. 1981;**23**:77-88.
21. Moggia AV, Harris GS, Dunsun TR, Diaz R, Moggia Ms, Ferrer Ma et al. A comparative study of a progestin-only oral contraceptive versus non-hormonal methods in lactating women in Buenos Aires, Argentina. A comparative study of a progestin-only oral contraceptive versus non-hormonal methods in lactating women in Buenos Aires, Argentina. *Contraception.* 1991;**44**:31-43.

22. Narducci U, Piatti N. [Use of Depo-Provera as a contraceptive during the puerperium]. *Minerva Ginecologic.* 1973;**2**:107-111.

23. Seth U, Aggrwal N, Laumas KR, Hingorani V. Effect of a subdermal silastic implant containing norethindrone acetate on human lactation. *Contraception*. 1977;**16**:383-398.

24. Shaaban MM, Salem HT, Abdullah KA. Influence of levonorgestrel contraceptive implants,Norplant, initiated early postpartum upon lactation and infant growth. *Contraception*. 1985;**32**:623-635.

25. haaban MM. Contraception with progestogens and progesterone during lactation. *Journal of Steroid Biochemistry & Molecular Biology*. 1991;**40**:705-710.

26. Shikary ZK, Bertrabet SS, Todaywalaw S, Patel DM, Datey S, Saxena BN. Pharmacodynamic effects of levonorgestrel (LNG) administered either orally or subdermally to early postpartum lactating mothers on the urinary levels of follicle stimulating hormone (FSH), luteinizing hormone (LH) and testosterone (T) in their breast-fed male infants. *Contraception*. 1986;**34**:403-412.

27. Sivin I, Diaz S, Croxatto HB, Miranda P, Shabban M, Sayed EH et al. Contraceptives for lactating women: a comparative trial of a progesterone-releasing vaginal ring and the copper T380 A IUD. Contraception. 1997;**55**:225-232.

28. Ginger Velasquez J, Cortes Gallegos V, Sotelo Lopez A, Bonadani GA. [Effect of daily oral administration of 0.350 mg of norethindrone on lactation and chemical composition of milk]. *Ginecologia y Obstetricia de Mexico.* 1976;**40**(237):31-39.

29. West CP. The acceptability of a progestagen-only contraceptive during breast-feeding. *Contraception.* 1983;**27**:563-569.

30. Zanartu J, Aguilera E, Munoz-Pinto G. Maintenance of lactation by means of continuous low-dose progestogen given post-partum as a contraceptive. *Contraception*. 1976;**13**:313-318.

31. Reinprayoon D, Taneepanichskul S, Bunyavejchevin S, Thaithumyanan P, Punnahitanda S, Tosukhowang P et al. Effects of the etonogestrel-releasing contraceptive implant (Implanon on parameters of breastfeeding compared to those of an intrauterine device. *Contraception*. 2000;**62**:239-246.

32. FPRHC Guidance (July 2004) Contraceptive choices for breastfeeding women. Journal of Family Planning and Reproductive Health Care 2004;30(3):181-18933. Knight J, Pyper C. Postnatal contraception: what are the choices? *Nursing in Practice* 2002; **May**:23-25

33. Faculty of Sexual and Reproductive Healthcare Clinical Guidance. Postnatal Sexual and reproductive Health (September 2009):**30**.www.fsrh.org.uk

34. Faculty of Family Planning and Reproductive Health Care Clinical Effectiveness Unit. The use of contraception outside the terms of the product licence. *Journal of Family Planning and Reproductive Health Care*. 2005;**31**:225-241

35. Kurunmaki H. Contraception with levonorgestrel-releasing subdermal capsules, Norplant, after pregnancy termination. *Contraception*. 1983;**27**:473-482.

36. Kurunmaki H, Tolvonen J, Lanteenmaki PI, Luukkainen T. Immediate postabortal contraception with Norplant: levonorgestrel, gonadotropin, estradiol, and progesterone levels over two postabortal months and return of fertility after removal of Norplant capsules. *Contraception*. 1984;**30**:431-442.

37. Lahteenmaki P, Toivonen J, Lahteenmaki PL. Postabortal contraception with norethisterone enanthate injections. *Contraception*. 1983;**27**:553-562.

38. Ortayli N, Bulut A, Sahin T, Sivin I. Immediate postabortal contraception with the levonorgestrel intrauterine device, Norplant, and traditional methods. *Contraception*. 2001;**63**:309-314.

39. World Health Organisation Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception. Cardiovascular Disease and Use of Oral and Injectable Progestogen-Only Contraceptives and Combined Injectable Contraceptives. *Contraception* 1998;**57**:315-24.

40. Dunn N, Faragher B, Thorogood M, de Caestecker L, MacDonald TM, McCollum C, et al. Oral contraceptives and myocardial infarction: results of the MICA case-control study. *British Medical Journal*. 1999;**318**:1579-1584

41. Croft P, Hannaford P. Risk factors for acute myocardial infarction in women - evidence from RCGP Oral Contraceptive Study. *British Medical Journal*. 1989;**298**:1651-168.

42. Rosenberg R, Palmer JR, Shapiro S. Decline in the risk of myocardial infarction among women who stop smoking. *The New England Journal of Medicine* 1990;**322**:213-217.

43. Vessey M, Painter R, Yeates D. Mortality in relation to oral contraceptive and cigarette smoking. *Lancet.* 2003;**362**:185-191.

44. McElduff P, Dobson A, Beaglehole R, Jackson R. Rapid reduction on coronary risk for those who quit cigarette smoking. *Australian and New Zealand Journal of Public Health*. 1998;**22**:787-791

45. Kenfield SA, Stampfer MJ, Rosner BA. Smoking and smoking Cessation in relation to mortality in women. *Journal of the American Medical Association*. 2008;**7**(299):2037-2047.

46. Clark MK, Dillon JS, Sowers M, Nichols S. Weight, fat mass, and central distribution of fat increase when women use depot-medroxyprogesterone acetate for contraception. *International Journal of Obesity.* 2005;**29**:1252-1258.

47. Bonny AE, Ziegler J, Harvey R, Debanne SM, Secic M, Cromer BA. Weight gain in obese and nonobese adolescent girls initiating depot medroxyprogesterone, oral contraceptive pills, or no hormonal contraceptive method. *Archives of Pediatric and Adolescent Medicine*. 2006;**160**:40-45.

48. Westhoff C, Jain JK, Milsom I, Ray A. Changes in weight with depot medroxyprogesterone acetate subcutaneous injection 104 mg/0.65 mL. *Contraception* 2007;**75**:261-267.

49. Berenson AB, Odom SD, Breitkopf CR, Rahman M. Physiologic and psychologic symptoms assocaited with use of injectbale contraception and 20µg oral contraceptive pills. *American Journal of Obstetrics and Gynaecology*. 2008;**199**:351.

50. Connor PD, Tavernier LA, Thomas SM, Gates D, Lytton SM. Determining risk between Depo-Provera use and increased uterine bleeding in obese and overweight women. *Journal of the American Board of Family Practice.* 2002;**15**:7-10.

51. Leiman G. Depo-medroyprogesterone acetate as a contraceptive agent: its effect on weight and blood pressure. American Journal of Obstetrics and Gynecology 1972;114:97-102.

52. Mangan SA, Larsen PG, Hudson S. Overweight teens at increased risk for weight gain while using depot medroxyprogesterone acetate. *Journal of Pediatric and Adolescent Gynecology*. 2002;**15**:79-82.

53. Risser WL, Gefter Lr, Barratt MS, Risser JM. Weight change in adolescents who used hormonal contraception. *Journal of Adolescent Health*, 1999;**24**:433-436.

54. Williams B, Poulter N, Brown MJ, Davies M, McInnes GT, Potter JP et al. The BHS Guidelines' Working Party Guidelines for Management of Hypertension: Report of the Fourth Working Party of the British Hypertension Society. *Journal of Human Hypertension*. 2004;**18**:139-185.

55. National Institute for Clinical Excellence. Hypertension. Management of hypertension in adults in primary care. 2004. London. http://www.nice.org.uk/nicemedia/pdf/HypertensionGuide.pdf

56. Heinemann LA, Assmann A, Dominh T, Barb E. Oral progestogen-only contraceptives and cardiovascular risk: results from the Transitional study on oral contraceptives and the health of young women. *European Journal of Contraception and Reproductive Health Care*. 1999;**4**:67-73.

57. Vasilakis C, jick H, Mar Melero-Montes M. Risk of idiopathic venous thromboembolism in users of progestogens alone. *Lancet*. 1999;**354**:1610-1611.

58. Sonmezer M, Atabekoglu C, Cengiz B, Dokmeci SD. Depot-medroyprogesterone acetate in anticoagulated patients with previous hemorrhagic corpus luteum. *European Journal of Contraception and Reproductive Health*. 2005;**10**:9-14.

59. Scottish Intercollegiate Guidelines Network Secretariat. Prophylaxis of venous thromboembolism. 2003;62:1-47.http://www.sign.ac.uk/pdf/sign62.pdf

60. Wu O, Robertson L, Twaddle S, Lowe GDO, Clark P, Walker I, et al. Screening for thrombophilia in high-risk situations: a meta-analysis and cost-effectiveness analysis. British Journal of Haematology. 2005;131(1):80-90.

61. Middledrop S, van Hylckama Vlieg A. Does thrombophillia testing help in the clinical management of patients? British Journal of Haematology. 2008;143(3):321-335.

62. Blickstein D, Blickstein I. Oral contraception and thrombophillia. Current Opinion in Obstetrics and Gynacecology. 2007;19(4):370-376.

63. NHS Clinical Knowledge Summaries. Lipid modification. Lipid modification - primary and secondary CVD prevention.http://cks.library.nhs.uk/lipid_modification_cvd_prevention/management/detailed_answers/secondary_prevention/when_to_refer#-336938.

64. British Heart Foundation. What is Valvular Heart Disease? 2005. http://www.bhf.org.uk/

65. British Heat Foundation. Living congenital heart disease. 2005. http://www.bhf.org.uk/

66. McGregor A. Migraine and use of combined hormonal contraceptive: a clinical review. Journal of Family Planning and Reproductive Health Care. 2007;33(3):15-169.

67. The International Headache Society and Task Force on Combined Oral Contraceptives and Hormone replacement therapy. Recommendations on the risk of ischemic stroke associated with use of oral contraceptives and hormone replacement therapy in women with migraine. *Cephalagia*. 2000;**20**:155-156.

68. Cromer BA, Smith RD, Dwyer J, Blair JM, Brown RT. A prospective study of adolescents who choose among levonorgestrel implant (Norplant), medroxyprogesterone acetate (Depo-Provera), or the combined oral contraceptive pill as contraception. *Pediatrics*. 1994;**94**:687-694.

69. Gupta N, O'Brien R, Jacobson LJ, Davis A, Zuckerman A, Supran S et al. Mood changes in adolescents using depot-medroxyprogesterone acetate for contraception: a prospective study. *Journal of Pediatric & Adolescent Gynecology*. 2001;**14**:71-76.

70. Westhoff C, Truman C, Kalmuss D, Cishman L, Rulin M, Heartwell S et al. Depressive symptoms and Norplant contraceptive implants. *Contraception*. 1998;**57**:241-245.

71. Westhoff C, Truman C, Kalmuss D, Cushman L, Davidson A, Rulin M et al. Depressive symptoms and Depo-Provera. *Contraception*. 1998;**57**:237-240.

72. National Institute of Clinical Excellence. Heavy Menstrual Bleeding. 2007. http://www.nice.org.uk/nicemedia/pdf/CG44FullGuideline.pdf

73. Faculty of Sexual and Reproductive Healthcare Clinical Guidance. Management of Unscheduled bleeding in women using hormonal contraception. Clinical Effcetiveness Unit: may 2009.

74. Smith JS, Green JS, Berrington de Gonzalez A, Appleby P, Peto J, Plummer M et al. Cervical cancer and use of hormonal contraceptives: a systematic review. *Lancet*. 2003;**361**:1159-1167.

75. Baeten JM, Nyaneg PM, Richardson BA, Lavreys L, Chohan B, Martin HL Jr. et al. Hormonal contraception and risk of sexually transmitted disease acquisition: results from a prospective study. *American Journal of Obstetrics & Gynecology*. 2001;**185**:380-385.

76. Giuliano AR, Papenfuss M, Abrahamsen M, Guernsey de Zapien J, Henze JLN et al. Human papillomavirus infection at the United States-Mexico border: implications for cervical cancer prevention and control. *Cancer Epidemiology, Biomarkers & Prevention*. 2001;**10**:1129-1136.

77. Jacobson DL, Peralta L, Farmer M, Grham Nm, Gaydos C, Zenilman. Relationship of hormonal contraception and cervical ectopy as measured by computerized planimetry to chlamydial infection in adolescents. *Sexually Transmitted Diseases*. 2000;**27**:313-319.

78. Lavreys L, Bhavna C, Rhonda A, Richardson B, Lawrence C et al. Human herpesvirus 8: seroprevalence and correlates in prostitutes in Mombasa, Kenya. *Journal of Infectious Diseases*, 2003, **187**:359-63.

79. Moscicki AB, Shilboski S, Powell K, Jay N, Hanson E et al. Risks for incident human papillomavirus infection and low-grade squamous intraepithelial lesion development in young females. *Journal of the American Medical Association*. 2001;**285**:2995-3002.

80. Nsofor BI, Bello CS, Ekwempu CC. Sexually transmitted disease among women attending a family planning clinic in Zaria, Nigeria. *International Journal of Gynaecology & Obstetrics*. 1989;**28**:365-367.

81. Ruijs GJ, Kaver FM, Van Gijssel PM, Schirm J, Schroder FP. Direct immunofluorescence for Chlamydia trachomatis on urogenital smears for epidemiological purposes. *European Journal of Obstetrics, Gynecology & Reproductive Biology*. 1988;**27**:289-297.

82. Tagy AH, Saker Me, Moussa AA, Kolgah A. The effect of low-dose combined oral contraceptive pills versus injectable contraceptive (Depot Provera) on liver function tests of women with compensated bilharzial liver fibrosis. *Contraception*. 2001;**64**:173-176.

83. Faculty of Family Planning and Reproductive Health Care Clinical Effectiveness Unit. Drug Interactions with hormonal contraception. *Journal of Family Planning and Reproductive Healthcare*. 2005;**31**:139-150

84. Gines P, Quintero E, Arroyo V, Teres J, Bruguera M, Rimola A et al. Compensated cirrhosis: natural history of prognostic factors. *Hepatology* 1987;**7**(1):122-128.

85. Lam CM, Yong JL, Chan AO, Ng KK, Poon RT, Liu CL. Better survival in female patients with hepatocellular carcinoma: oral contraceptive pills related? *Journal Clinical Gastroenterol* 2005;**39**:533-539.

86. Adadevoh BK, Isaacs WA. The effect of megestrol acetate on sick cell disease. *American Journal of the Medical Sciences*. 1973;**265**:367-370.

87. Barbosa IC, Ladipo O, De Lourdes M, Nascimento P, Athayde C, Hirsch C et al. Carbohydrate Metabolism in Sickle Cell Patients Using a Subdermal Implant Containing Nomegestrol Acetate (Uniplant). *Contraception*. 2001;**63**:263-265.

88. de Abood M, de Casteillo Z, Guerrero F, Espino M, Austin KL. Effects of Depo-Provera or Microgynon on the Painful Crises of Sickle Cell Anemia Patients. *Contraception*. 1997;**56**:313-316.

89. De Ceulaer K, Gruber C, Hayes R, Serjeant GR. Medroxyprogesterone acetate and homozygous sickle-cell disease. *Lancet*. 1982;**2**:229-231.

90. Howard RJ, Lillis C, Tuck SM. Contraceptives, Counselling, and Pregnancy in Women with Sickle Cell Disease. British Medical Journal. 1993;306:1735-1737.

91. Ladipo OA, Falusi AG, Feldblum Pj, Ostlorin EO, Ojengbede OA. Norplant use by women with sickle cell disease. *International Journal of Gynaecology and Obstetrics.* 1993;**41**:85-87.

92. Nascimento ML, Ladipo OA, Coutinho E. Nomegestrol acetate contraceptive implant use by women with sickle cell disease. *Clinical Pharmacology and Therapeutics*. 1998;**64**:433-438.

93. Yoong WC, Tuck SM, Yardumian A. Red cell deformability in oral contraceptive pill users with sickle cell anaemia. *British Journal of Haematology*. 1999;**104**:868-870.

94. NHS Clinical Knowledge Summary – Raynaud's-phenomenon. 2006. http://cks.library.nhs.uk/raynauds_phenomenon#-223261.

95. Eastcroft HH. Raynauds disease and the oral contraceptive pill [Letter]. *British Medical Journal*. 1976;477.

96. Altura BM. Sex and oestrogens and responsiveness or terminal arterioles to neurohypophyseal hormones and catecholamines. *Pharmacology and Experimental Theraputics.* 1975;**193**:403-412.

97. Greenstein D, Jeffcoate N, Iisley D, Lester RC. The menstrual cycle and Raynaud's phenomenon. *Angiology* 1996;**47**:427-436.

98. Sanchez-Guerrero J, Uribe, AG, Jimenez-Santana L, Messtanza-Peralta M, Lara-Reyes P, Seuc AH, et al. A trial of contraceptive methods in women with systemic lupus erythematousus. *New England Journal of Medicine*. 2005;**353**:2539-42.

99. Jungers P, Dougados M, Pelissier C, Kuttenn F, Tron F, Lesavre P et al. Influence of oral contraceptive therapy on the activity of systemic lupus erythematosus. *Arthritis and Rheumatism*. 1982;**25**:618-623.

100. Mintz G, Gutierrez G, Deleze M, Rodriquez E. Contraception with progestogens in systemic lupus erythematosus. *Contraception*. 1984;**30**:29-38.

101. Nanda K, Amaral E, Hays M, Viscola MA, Mehta N, Bahamondes L. Pharmacokinetic interactions between depotmedroxyprogesterone acetate and combination antiretroviral therapy. *Fertility and Sterility*. 2008;**90**: 956-971.

102. Cohn SE, Park JG, Watts DH, Stek A, Hitti J, Clax PA, et al. Depo-medroyprogesterone in women on antiretroviral therapy: Effective contraception and lack of clinically significant interactions. *Clinical Pharmacology and Threaputics*. 2007;**75**:37-39.

103. Matiluko AA, Soundararjan L, Hogston P. Early contraceptive failure of Implanon in an HIV-seropositive patient on triple antiretroviral therapy with zidovudine, lamivudine and efavirenz. *Journal of Family Planning and Reproductive Healthcare*. 2007;**33**:277-278.

104. Reimers A, Helde G, Broadtkrob E. Ethinyl estradiol, not progestogens, reduces lamotrigine serum concentrations. *Epilepsia.* 2005;**47**:1573-1574.

105. Schindlbeck C, Janni W, Friese K. Failure of Implanon contraception in a patient taking carbamazepine for epilespsia. *Archives of Gynecology and Obstetrics*. 2006;**273**:255-256.

106. Haukkamaa M. Contraception by Norplant subdermal capsules is not reliable in epileptic patients on anticonvulsant treatment. *Contraception*. 1986;**33**:559-565.

107. Odlind V, Olsson SE. Enhanced metabolism of levonorgestrel during phenytoin treatment in a woman with Norplant implants. *Contraception*. 1986;**33**:257-261.

108. Shane-McWhorter L, Cerveny JD, MacFarlane LL, Osborn C. Enhanced metabolism of levonorgestrel during phenobarbital treatment and resultant pregnancy. *Pharmacotherapy.* 1998;**18**:1360-1364.

Intrauterine devices

INTRAUTERINE DEVICES (IUDs) *Copper-bearing IUD (Cu-IUD)* *Levonorgestrel-releasing IUD (LNG-IUD)*	**IUDs do not protect against STI/HIV. If there is risk of STI/HIV (including the postpartum period), the correct and consistent use of condoms is recommended, either alone or with another contraceptive method. Male condoms reduce the risk of STI/HIV.**		
CONDITION	**CATEGORY** I=Initiation, C=Continuation		**CLARIFICATIONS/EVIDENCE**
	Cu-IUD	**LNG-IUD**	
PERSONAL CHARACTERISTICS AND REPRODUCTIVE HISTORY			
PREGNANCY	4	4	**Clarification:** Intrauterine methods are not indicated during pregnancy. Most pregnancies occurring in women using intrauterine contraception will be intrauterine, but ectopic pregnancy must be excluded. Women who become pregnant whilst using intrauterine contraception should be informed of increased risks of second trimester septic miscarriage, preterm delivery and infection if the intrauterine device is left *in situ*. Women who are pregnant with intrauterine contraception *in situ*, and who wish to continue with the pregnancy, should be informed that, when possible, device removal would reduce adverse outcomes. However, removal itself carries a small risk of miscarriage. Whether or not the intrauterine device is removed, pregnant women should be advised to seek medical care if they develop heavy bleeding, cramping pain, abnormal vaginal discharge or fever.[1-5]
AGE*			
a) Menarche to <20 years	2	2	
b) ≥20 years	1	1	
PARITY*			
a) Nulliparous	1	1	**Clarification:** There is no reduction in fertility associated with previous intrauterine method use. Risk of STI influences fertility, and sexual history taking is important.[6-16]
b) Parous	1	1	
POSTPARTUM* (breastfeeding or non-breastfeeding, including post-caesarean section)			This includes all deliveries including stillbirth from 24 weeks gestation. Due to increased risk of perforation insertion should be delayed until 4 weeks postpartum. Little LNG is absorbed systemically. No evidence was identified to suggest effects on breast milk.[17,18] Expulsion rates associated with intrauterine contraception are lower after interval insertion when compared to immediate postpartum insertion.[19,25]
a) 48 hours to <4 weeks	3	3	
b) ≥4 weeks	1	1	
c) Puerperal sepsis	4	4	
POST-ABORTION*			**Clarification:** Includes all induced or spontaneous abortions <24 weeks gestation. An IUD can be inserted immediately following surgical abortion or after the second part of medical abortion <24 weeks.[1-5,26-39]
a) First trimester	1	1	
b) Second trimester	2	2	
c) Immediate post septic abortion	4	4	
PAST ECTOPIC PREGNANCY*	1	1	

*See also additional comments at end of section

UKMEC	DEFINITION OF CATEGORY
CATEGORY 1	A condition for which there is no restriction for the use of the contraceptive method
CATEGORY 2	A condition where the advantages of using the method generally outweigh the theoretical or proven risks
CATEGORY 3	A condition where the theoretical or proven risks generally outweigh the advantages of using the method. The provision of a method requires expert clinical judgement and/or referral to a specialist contraceptive provider, since use of the method is not usually recommended unless other more appropriate methods are not available or not acceptable
CATEGORY 4	A condition which represents an unacceptable health risk if the contraceptive method is used

INTRAUTERINE DEVICES (IUDs) *Copper-bearing IUD (Cu-IUD)* *Levonorgestrel-releasing IUD (LNG-IUD)*	**IUDs do not protect against STI/HIV. If there is risk of STI/HIV (including the postpartum period), the correct and consistent use of condoms is recommended, either alone or with another contraceptive method. Male condoms reduce the risk of STI/HIV.**		
CONDITION	**CATEGORY** I=Initiation, C=Continuation		**CLARIFICATIONS/EVIDENCE**
	Cu-IUD	**LNG-IUD**	
HISTORY OF PELVIC SURGERY	1	1	
SMOKING			
a) Age <35 years	1	1	
b) Age ≥35 years			
(i) <15 cigarettes/day	1	1	
(ii) ≥15 cigarettes/day	1	1	
(iii) stopped smoking <1 year ago	1	1	
(iv) stopped smoking ≥1 year ago	1	1	
OBESITY			
a) ≥30 - 34 kg/m^2 body mass index	1	1	
b) ≥35 kg/m^2 body mass index	1	1	
CARDIOVASCULAR DISEASE			
MULTIPLE RISK FACTORS FOR CARDIOVASCULAR DISEASE (such as older age, smoking, diabetes, hypertension and obesity)	1	2	

UKMEC	DEFINITION OF CATEGORY
CATEGORY 1	A condition for which there is no restriction for the use of the contraceptive method
CATEGORY 2	A condition where the advantages of using the method generally outweigh the theoretical or proven risks
CATEGORY 3	A condition where the theoretical or proven risks generally outweigh the advantages of using the method. The provision of a method requires expert clinical judgement and/or referral to a specialist contraceptive provider, since use of the method is not usually recommended unless other more appropriate methods are not available or not acceptable
CATEGORY 4	A condition which represents an unacceptable health risk if the contraceptive method is used

INTRAUTERINE DEVICES (IUDs) *Copper-bearing IUD (Cu-IUD)* *Levonorgestrel-releasing IUD (LNG-IUD)*	**IUDs do not protect against STI/HIV. If there is risk of STI/HIV (including the postpartum period), the correct and consistent use of condoms is recommended, either alone or with another contraceptive method. Male condoms reduce the risk of STI/HIV.**		
CONDITION	**CATEGORY** I=Initiation, C=Continuation		**CLARIFICATIONS/EVIDENCE**
	Cu-IUD	**LNG-IUD**	
HYPERTENSION*			
For all categories of hypertension, classifications are based on the assumption that **no other risk factors for cardiovascular disease exist**. When multiple risk factors do exist, risk of cardiovascular disease may increase substantially. A single reading of blood pressure level is not sufficient to classify a woman as hypertensive. If elevated, the BP should be re-assessed at the end of the consultation. If blood pressure is increased it should be re-assessed on at least two subsequent clinic visits at monthly intervals.[40, 41]			
a) Adequately controlled hypertension	1	1	
b) Consistently elevated blood pressure levels (properly taken measurements)			
(i) systolic >140-159 mmHg or diastolic >90-94 mmHg	1	1	
(ii) systolic ≥160 or diastolic ≥95 mmHg	1	1	
c) Vascular disease	1	2	**Clarification:** *Vascular disease* includes: coronary heart disease presenting with angina; peripheral vascular disease presenting with intermittent claudication; hypertensive retinopathy, and transient ischaemic attacks.
HISTORY OF HIGH BLOOD PRESSURE DURING PREGNANCY (where current blood pressure is normal)	1	1	

*See also additional comments at end of section

UKMEC	DEFINITION OF CATEGORY
CATEGORY 1	A condition for which there is no restriction for the use of the contraceptive method
CATEGORY 2	A condition where the advantages of using the method generally outweigh the theoretical or proven risks
CATEGORY 3	A condition where the theoretical or proven risks generally outweigh the advantages of using the method. The provision of a method requires expert clinical judgement and/or referral to a specialist contraceptive provider, since use of the method is not usually recommended unless other more appropriate methods are not available or not acceptable
CATEGORY 4	A condition which represents an unacceptable health risk if the contraceptive method is used

INTRAUTERINE DEVICES (IUDs) *Copper-bearing IUD (Cu-IUD)* *Levonorgestrel-releasing IUD (LNG-IUD)*	**IUDs do not protect against STI/HIV. If there is risk of STI/HIV (including the postpartum period), the correct and consistent use of condoms is recommended, either alone or with another contraceptive method. Male condoms reduce the risk of STI/HIV.**		
CONDITION	**CATEGORY** I=Initiation, C=Continuation		**CLARIFICATIONS/EVIDENCE**
	Cu-IUD	**LNG-IUD**	
VENOUS THROMBOEMBOLISM (VTE)			Venous thromboembolism includes deep vein thrombosis and pulmonary embolism.
a) History of VTE	1	2	Systemic absorption of LNG from the LNG-IUD is low and is unlikely to be associated with an increased risk of VTE. Women who have current VTE may consider use of LNG-IUD or Cu-IUD but should perhaps consider delaying insertion until anti-coagulants have stopped, due to potential risk of bleeding during the insertion procedure.
b) Current VTE (on anticoagulants)	1	2	
c) Family history of VTE			
(i) first-degree relative aged <45 years	1	1	
(ii) first-degree relative aged ≥45 years	1	1	
d) Major surgery			**Major Surgery** includes operations of >30 minutes duration. Procedures with high risk of VTE include: general or orthopaedic surgery, trauma, neurosurgery.[42]
(i) with prolonged immobilisation	1	2	
(ii) without prolonged immobilisation	1	1	
e) Minor surgery without immobilisation	1	1	**Minor surgery** includes operations lasting <30 minutes (eg laparoscopic sterilisation), procedures such as knee arthroscopy. Varicose vein surgery has a low risk of VTE.
f) Immobility (unrelated to surgery) *e.g. wheelchair use, debilitating illness*	1	1	**Immobility** due to hospitalisation for acute trauma, acute illness, or paralysis is associated with a high risk of VTE.
KNOWN THROMBOGENIC MUTATIONS (e.g., Factor V Leiden, Prothrombin mutation, Protein S, Protein C, and Antithrombin deficiencies)	1	2	**Clarification:** Routine screening is not appropriate because of the rarity of the conditions and the high cost of screening.[43,44,45]
SUPERFICIAL VENOUS THROMBOSIS			
a) Varicose veins	1	1	
b) Superficial thrombophlebitis	1	1	

UKMEC	DEFINITION OF CATEGORY
CATEGORY 1	A condition for which there is no restriction for the use of the contraceptive method
CATEGORY 2	A condition where the advantages of using the method generally outweigh the theoretical or proven risks
CATEGORY 3	A condition where the theoretical or proven risks generally outweigh the advantages of using the method. The provision of a method requires expert clinical judgement and/or referral to a specialist contraceptive provider, since use of the method is not usually recommended unless other more appropriate methods are not available or not acceptable
CATEGORY 4	A condition which represents an unacceptable health risk if the contraceptive method is used

IINTRAUTERINE DEVICES (IUDs) *Copper-bearing IUD (Cu-IUD)* *Levonorgestrel-releasing IUD (LNG-IUD)*	**IUDs do not protect against STI/HIV. If there is risk of STI/HIV (including the postpartum period), the correct and consistent use of condoms is recommended, either alone or with another contraceptive method. Male condoms reduce the risk of STI/HIV.**		
CONDITION	**CATEGORY** I=Initiation, C=Continuation		**CLARIFICATIONS/EVIDENCE**
	Cu-IUD	**LNG-IUD**	
CURRENT AND HISTORY OF ISCHAEMIC HEART DISEASE*	1	I: 2 C: 3	**Clarification:** The method may be continued if women develop ischaemic heart disease while using the LNG-IUD. Clinical judgement and assessment of pregnancy risk and other factors required.
STROKE* (history of cerebrovascular accident, including TIA)	1	2	3	
KNOWN HYPERLIPIDAEMIAS	1	2	**Clarification:** Routine screening is not appropriate because of the rarity of the conditions and the high cost of screening. While some types of hyperlipidaemias are risk factors for vascular disease, the category should be assessed according to the type, its severity, and the presence of other cardiovascular risk factors. Lipid levels alone are poor predictors of risk of coronary heart disease. In the UK screening and treatment is aimed towards those at greatest risk of coronary heart disease. Risk categories will vary depending on risk of premature coronary heart disease and the presence of other risk factors.[46] *Common hypercholesterolaemia* and *Familial combined hyperlipidaemia* are associated with an increased risk of coronary heart disease but usually this occurs over the age of 60 years.[46] *Familial hypercholesterolaemia* (autosomal dominant) has a prevalence of about 1 in 500. People with this condition have a four-fold increase in the risk of premature coronary heart disease.[46]
VALVULAR AND CONGENTIAL HEART DISEASE a) Uncomplicated b) Complicated *(pulmonary hypertension, atrial fibrillation, history of subacute bacterial endocarditis)*	1 2	1 2	**Clarification:** *Valvular heart* disease occurs when any of the heart valves are stenotic and/or incompetent (eg. aortic stenosis, mitral regurgitation; tricuspid valve abnormalities; pulmonary stenosis).[47] *Congenital heart disease:* Aortic stenosis; Atrial septal defects; Atrio-ventricular septal defect; Cardiomyopathy (hypertrophic or dilated); Coarctation of the Aorta; Complex Transposition of the Great Arteries; Ebstein's Anomaly; Eisenmenger Syndrome: Patent Ductus Arteriosus; Pulmonary Atresia; Pulmonary Stenosis; Tetralogy of Fallot; Total Anomalous Pulmonary Venous Connection; Tricuspid Atresia; Truncus Arteriosus; Ventricular Septal Defect.[48] Prophylaxis against bacterial endocarditis is no longer indicated for women with artificial heart valves or previous endocarditis when inserting or removing Cu-IUD or LNG-IUD.[1,2]

*See also additional comments at end of section

UKMEC	DEFINITION OF CATEGORY
CATEGORY 1	A condition for which there is no restriction for the use of the contraceptive method
CATEGORY 2	A condition where the advantages of using the method generally outweigh the theoretical or proven risks
CATEGORY 3	A condition where the theoretical or proven risks generally outweigh the advantages of using the method. The provision of a method requires expert clinical judgement and/or referral to a specialist contraceptive provider, since use of the method is not usually recommended unless other more appropriate methods are not available or not acceptable
CATEGORY 4	A condition which represents an unacceptable health risk if the contraceptive method is used

INTRAUTERINE DEVICES (IUDs) *Copper-bearing IUD (Cu-IUD)* *Levonorgestrel-releasing IUD (LNG-IUD)*	**IUDs do not protect against STI/HIV. If there is risk of STI/HIV (including the postpartum period), the correct and consistent use of condoms is recommended, either alone or with another contraceptive method. Male condoms reduce the risk of STI/HIV.**		
CONDITION	**CATEGORY** I=Initiation, C=Continuation		**CLARIFICATIONS/EVIDENCE**
	Cu-IUD	**LNG-IUD**	
NEUROLOGIC CONDITIONS			
HEADACHES*			
a) Non-migrainous (mild or severe)	1	1	Headache is a common condition affecting women of reproductive age. No evidence was identified which specifically looked at migraine in women using an LNG-IUD.[49] Classification depends on making an accurate diagnosis of those severe headaches that are migrainous and in addition those complicated by aura. **Symptoms** of aura include: homonymous hemianopia, unilateral paraesthesia and/or numbness; unilateral weakness and aphasia or unclassifiable speech disorder. Visual symptoms progress from fortification spectra (a starshaped figure near the point of fixation with scintillating edges) to scotoma (a bright shape which gradually increases in size). Flashing lights are not classified as aura. Aura occurs before the onset of headache.[50]
b) Migraine without aura, at any age	1	2	
c) Migraine with aura, at any age	1	2	
d) Past history (≥5 years ago) of migraine with aura, any age	1	2	
EPILEPSY	1	1	See section on drug interactions.
DEPRESSIVE DISORDERS			
DEPRESSIVE DISORDERS	1	1	**Clarification:** The classification is based on data for women with selected depressive disorders. No data on bipolar disorder or postpartum depression were available. There is a potential for drug interactions between certain antidepressant medications and hormonal contraceptives.
BREAST AND REPRODUCTIVE TRACT CONDITIONS			
VAGINAL BLEEDING PATTERNS*		**I** / **C**	
a) Irregular pattern without heavy bleeding	1	1 / 1	
b) Heavy or prolonged bleeding (includes regular and irregular patterns)	2	1 / 2	**Clarification:** Unusually heavy bleeding should raise the suspicion of a serious underlying condition.[51-52] **Evidence:** Among women with heavy or prolonged bleeding, LNG-IUDs were beneficial in treating menorrhagia.[2,5;53-57]

*See also additional comments at end of section

UKMEC	DEFINITION OF CATEGORY
CATEGORY 1	A condition for which there is no restriction for the use of the contraceptive method
CATEGORY 2	A condition where the advantages of using the method generally outweigh the theoretical or proven risks
CATEGORY 3	A condition where the theoretical or proven risks generally outweigh the advantages of using the method. The provision of a method requires expert clinical judgement and/or referral to a specialist contraceptive provider, since use of the method is not usually recommended unless other more appropriate methods are not available or not acceptable
CATEGORY 4	A condition which represents an unacceptable health risk if the contraceptive method is used

INTRAUTERINE DEVICES (IUDs) *Copper-bearing IUD (Cu-IUD)* *Levonorgestrel-releasing IUD (LNG-IUD)*	**IUDs do not protect against STI/HIV. If there is risk of STI/HIV (including the postpartum period), the correct and consistent use of condoms is recommended, either alone or with another contraceptive method. Male condoms reduce the risk of STI/HIV.**		
CONDITION	**CATEGORY** I=Initiation, C=Continuation		**CLARIFICATIONS/EVIDENCE**
	Cu-IUD	**LNG-IUD**	
UNEXPLAINED VAGINAL BLEEDING (suspicious for serious underlying condition) Before evaluation	**I** 4 **C** 2	**I** 4 **C** 2	**Clarification:** If pregnancy or an underlying pathological condition (such as pelvic malignancy) is suspected, it must be evaluated and the category adjusted after evaluation. There is no need to remove the IUD before evaluation.
ENDOMETRIOSIS*	2	1	**Evidence:** LNG-IUD use among women with endometriosis decreased dysmenorrhoea and pelvic pain.[58-59]
BENIGN OVARIAN TUMOURS (including cysts)	1	1	
SEVERE DYSMENORRHOEA*	2	1	
GESTATIONAL TROPHOBLASTIC DISEASE (GTD)			Gestational trophoblastic disease (GTD) includes hydatidiform mole, invasive mole and placental site trophoblastic tumour.
a) Decreasing or undetectable β-hCG levels	1	1	Case-control studies do not show an increase in the risk of developing a GTD condition following the use of intrauterine contraception.[60-63] Avoid use due to the possible risks of perforation and irregular bleeding.[64]
b) Persistently elevated β-hCG levels or malignant disease	4	4	
CERVICAL ECTROPION	1	1	
CERVICAL INTRAEPITHELIAL NEOPLASIA (CIN)*	1	2	
CERVICAL CANCER* (awaiting treatment)	**I** 4 **C** 2	**I** 4 **C** 2	
BREAST DISEASE			
a) Undiagnosed mass	1	2	
b) Benign breast disease	1	1	
c) Family history of cancer	1	1	
d) Carriers of known gene mutations associated with breast cancer (eg. BRCA1)	1	2	
e) Breast cancer:			Breast cancer is a hormonally sensitive tumour and therefore the prognosis of women with current or recent breast cancer may worsen with progestogen-only contraceptive use.
(i) current	1	4	
(ii) past and no evidence of current disease for 5 years	1	3	
ENDOMETRIAL CANCER*	**I** 4 **C** 2	**I** 4 **C** 2	
OVARIAN CANCER*	3 **C** 2	3 **C** 2	

*See also additional comments at end of section

UKMEC	DEFINITION OF CATEGORY
CATEGORY 1	A condition for which there is no restriction for the use of the contraceptive method
CATEGORY 2	A condition where the advantages of using the method generally outweigh the theoretical or proven risks
CATEGORY 3	A condition where the theoretical or proven risks generally outweigh the advantages of using the method. The provision of a method requires expert clinical judgement and/or referral to a specialist contraceptive provider, since use of the method is not usually recommended unless other more appropriate methods are not available or not acceptable
CATEGORY 4	A condition which represents an unacceptable health risk if the contraceptive method is used

INTRAUTERINE DEVICES (IUDs) *Copper-bearing IUD (Cu-IUD)* *Levonorgestrel-releasing IUD (LNG-IUD)*	**IUDs do not protect against STI/HIV. If there is risk of STI/HIV (including the postpartum period), the correct and consistent use of condoms is recommended, either alone or with another contraceptive method. Male condoms reduce the risk of STI/HIV.**		
CONDITION	**CATEGORY** I=Initiation, C=Continuation		**CLARIFICATIONS/EVIDENCE**
	Cu-IUD	**LNG-IUD**	
UTERINE FIBROIDS			
a) Without distortion of the uterine cavity	1	1	**Evidence:** Among women with fibroids, there were no adverse health events with LNG-IUD use and there was a decrease in symptoms and size of fibroids for some women.[65-71]
b) With distortion of the uterine cavity	3	3	In women with a distorted uterine cavity it may be appropriate after counselling to attempt insertion of an intrauterine device
ANATOMICAL ABNORMALITIES			
a) Distorted uterine cavity (any congenital or acquired uterine abnormality distorting the uterine cavity in a manner that is incompatible with IUD insertion)	3	3	In women with a distorted uterine cavity it may be appropriate after counselling to attempt insertion of an intrauterine device.
b) Other abnormalities (including cervical stenosis or cervical lacerations) not distorting the uterine cavity or interfering with IUD insertion	2	2	
PELVIC INFLAMMATORY DISEASE (PID)*	**I** / **C**	**I** / **C**	
a) Past PID (assuming no current risk factors for STIs)	1 / 1	1 / 1	**Initiation:** For routine IUD/IUS insertion women with symptomatic pelvic infection should be tested, treated and insertion delayed until symptoms resolve. Appropriate counselling and provision of alternative contraception should be provided until the intrauterine device can be inserted.[1,5]
b) Current PID	4 / 2	4 / 2	**Continuation:** For women with symptomatic pelvic infection, treat the PID using appropriate antibiotics.[1,5] There is usually no need for removal of the IUD if the client wishes to continue its use.[3-4] Continued use of an IUD depends on the woman's informed choice and her current risk factors for STIs and PID. Among IUD users treated for PID there was no difference in clinical course if the IUD was removed of left in place.[72-74]

*See also additional comments at end of section

UKMEC	DEFINITION OF CATEGORY
CATEGORY 1	A condition for which there is no restriction for the use of the contraceptive method
CATEGORY 2	A condition where the advantages of using the method generally outweigh the theoretical or proven risks
CATEGORY 3	A condition where the theoretical or proven risks generally outweigh the advantages of using the method. The provision of a method requires expert clinical judgement and/or referral to a specialist contraceptive provider, since use of the method is not usually recommended unless other more appropriate methods are not available or not acceptable
CATEGORY 4	A condition which represents an unacceptable health risk if the contraceptive method is used

INTRAUTERINE DEVICES (IUDs) *Copper-bearing IUD (Cu-IUD)* *Levonorgestrel-releasing IUD (LNG-IUD)*	**IUDs do not protect against STI/HIV. If there is risk of STI/HIV (including the postpartum period), the correct and consistent use of condoms is recommended, either alone or with another contraceptive method. Male condoms reduce the risk of STI/HIV.**		
CONDITION	**CATEGORY** I=Initiation, C=Continuation		**CLARIFICATIONS/EVIDENCE**
	Cu-IUD	**LNG-IUD**	

SEXUALLY TRANSMITTED INFECTIONS (STIs*)	**I**	**C**	**I**	**C**	**Initiation:** There is no indication to routinely test for or treat other lower genital tract organisms (such as Group B streptococcus or bacterial vaginosis) in *asymptomatic* women considering intrauterine contraception.[1,5] **Evidence:** The real risk of pelvic infection following insertion of intrauterine contraception, even in the presence of infection, is unknown. Nevertheless, screening for STIs in advance of insertion (when indicated or requested) will allow infection to be treated before or at the time of insertion. If results are unavailable before insertion then prophylactic antibiotics should be considered for women at higher risk of STIs. The antibiotic regimen chosen should treat *C. trachomatis*. In addition, if local prevalence of *N. gonorrhoeae* is high then the regimen should also treat this infection.[1,5] If infection is identified, or if a woman is symptomatic at the time of routine insertion, the procedure should be delayed until appropriately treated. **Continuation:** Treat the STI using appropriate antibiotics. There is usually no need for removal of the IUD if the client wishes to continue use.
a) Chlamydial infection					
i) Symptomatic	4	2	4	2	
ii) Asymptomatic	4	2	4	2	
b) Current purulent cervicitis or gonorrhoea	4	2	4	2	
c) Other STIs excluding HIV and hepatitis	2	2	2	2	
d) Vaginitis (including *Trichomonas vaginalis* and bacterial vaginosis)	2	2	2	2	
e) Increased risk of STIs	2/3	2	2/3	2	
HIV/AIDS					
HIGH RISK OF HIV*	2		2		See section on drug interactions
HIV-INFECTED					
a) Not using anti-retroviral therapy	2		2		See section on drug interactions
b) Using anti-retroviral therapy	2-2/3		2-2/3		
AIDS (using antiretrovirals)	2		2		See section on drug interactions

*See also additional comments at end of section

UKMEC	DEFINITION OF CATEGORY
CATEGORY 1	A condition for which there is no restriction for the use of the contraceptive method
CATEGORY 2	A condition where the advantages of using the method generally outweigh the theoretical or proven risks
CATEGORY 3	A condition where the theoretical or proven risks generally outweigh the advantages of using the method. The provision of a method requires expert clinical judgement and/or referral to a specialist contraceptive provider, since use of the method is not usually recommended unless other more appropriate methods are not available or not acceptable
CATEGORY 4	A condition which represents an unacceptable health risk if the contraceptive method is used

INTRAUTERINE DEVICES (IUDs) *Copper-bearing IUD (Cu-IUD)* *Levonorgestrel-releasing IUD (LNG-IUD)*	**IUDs do not protect against STI/HIV. If there is risk of STI/HIV (including the postpartum period), the correct and consistent use of condoms is recommended, either alone or with another contraceptive method. Male condoms reduce the risk of STI/HIV.**		
CONDITION	**CATEGORY** I=Initiation, C=Continuation		**CLARIFICATIONS/EVIDENCE**
	Cu-IUD	**LNG-IUD**	
OTHER INFECTIONS			
SCHISTOSOMIASIS			
a) Uncomplicated	1	1	
b) Fibrosis of the liver (if severe, see cirrhosis)	1	1	
TUBERCULOSIS*	**I C**	**I C**	See section on drug interactions
a) Non-pelvic	1 1	1 1	
b) Known pelvic	4 3	4 3	
MALARIA	1	1	
ENDOCRINE CONDITIONS			
DIABETES*			
a) History of gestational diabetes	1	1	
b) Non-vascular disease			
(i) non-insulin dependent	1	2	
(ii) insulin dependent	1	2	
c) Nephropathy/retinopathy/ neuropathy	1	2	
d) Other vascular disease	1	2	
THYROID DISORDERS			
a) Simple goitre	1	1	
b) Hyperthyroid	1	1	
c) Hypothyroid	1	1	
GASTROINTESTINAL CONDITIONS			
GALL-BLADDER DISEASE			
a) Symptomatic			
(i) treated by cholecystectomy	1	2	
(ii) medically treated	1	2	
(iii) current	1	2	
b) Asymptomatic	1	2	
HISTORY OF CHOLESTASIS			
a) Pregnancy-related	1	1	
b) Past COC-related	1	2	
VIRAL HEPATITIS*			
a) Acute or flare	1	1	
b) Carrier	1	1	
b) Chronic	1	1	
CIRRHOSIS*			**Clarification:**
a) Mild (compensated without complications)	1	1	*Severe (decompensated) cirrhosis:* development of major complications (ascites, jaundice, encephalopathy, or gastrointestinal haemorrhage).[81]
b) Severe (decompensated)	1	3	

*See also additional comments at end of section

UKMEC	DEFINITION OF CATEGORY
CATEGORY 1	A condition for which there is no restriction for the use of the contraceptive method
CATEGORY 2	A condition where the advantages of using the method generally outweigh the theoretical or proven risks
CATEGORY 3	A condition where the theoretical or proven risks generally outweigh the advantages of using the method. The provision of a method requires expert clinical judgement and/or referral to a specialist contraceptive provider, since use of the method is not usually recommended unless other more appropriate methods are not available or not acceptable
CATEGORY 4	A condition which represents an unacceptable health risk if the contraceptive method is used

INTRAUTERINE DEVICES (IUDs) *Copper-bearing IUD (Cu-IUD)* *Levonorgestrel-releasing IUD (LNG-IUD)*	**IUDs do not protect against STI/HIV. If there is risk of STI/HIV (including the postpartum period), the correct and consistent use of condoms is recommended, either alone or with another contraceptive method. Male condoms reduce the risk of STI/HIV.**		
CONDITION	**CATEGORY** I=Initiation, C=Continuation		**CLARIFICATIONS/EVIDENCE**
	Cu-IUD	**LNG-IUD**	
LIVER TUMOURS*			
a) Benign			
i) Focal nodular hyperplasia	1	2	
ii) Hepatocellular adenoma	1	3	
b) Malignant (hepatoma)	1	3	
INFLAMMATORY BOWEL DISEASE* (includes Crohn's disease, ulcerative colitis)	1	1	
ANAEMIAS			
THALASSAEMIA*	2	1	
SICKLE CELL DISEASE*	2	1	
IRON-DEFICIENCY ANAEMIA*	2	1	
RAYNAUD'S DISEASE			
a) Primary	1	1	**Clarification:** Secondary Raynaud's usually has an underlying cause such as scleroderma, rheumatoid arthritis, systemic lupus erythematosus and other diseases. Systemic lupus erythematosus causes a tendency for increased coagulation if lupus coagulant is present.[82-83]
b) Secondary			
(i) without lupus anticoagulant	1	1	
(ii) with lupus anticoagulant	1	2	
RHEUMATIC DISEASES			
SYSTEMIC LUPUS ERYTHEMATOSUS (SLE)	**I** / **C**		People with SLE are at an increased risk of ischaemic heart disease, stroke and venous thromboembolism. Categories are based on the assumption that no other risk factors for cardiovascular disease are present; these must be modified in the presence of such risk factors. Severe thrombocytopenia increases the risk of menorrhagia. The category should be assessed according to the severity of thrombocytopenia and its clinical manifestations. In women with very severe thrombocytopenia who are at risk of spontaneous bleeding, consultation with a specialist and certain pre-treatments may be warranted.[84-85]
a) Positive (or unknown) antiphospholipid antibodies	1 / 1	3	
b) Severe thrombocytopenia	3 / 2	2	
c) Immunosuppressive treatment	2 / 1	2	
d) None of the above	1 / 1	2	

*See also additional comments at end of section

UKMEC	DEFINITION OF CATEGORY
CATEGORY 1	A condition for which there is no restriction for the use of the contraceptive method
CATEGORY 2	A condition where the advantages of using the method generally outweigh the theoretical or proven risks
CATEGORY 3	A condition where the theoretical or proven risks generally outweigh the advantages of using the method. The provision of a method requires expert clinical judgement and/or referral to a specialist contraceptive provider, since use of the method is not usually recommended unless other more appropriate methods are not available or not acceptable
CATEGORY 4	A condition which represents an unacceptable health risk if the contraceptive method is used

INTRAUTERINE DEVICES (IUDs) *Copper-bearing IUD (Cu-IUD)* *Levonorgestrel-releasing IUD (LNG-IUD)*	**These methods do not protect against STI/HIv. If there is a risk of STI/HI (including during pregnancy or postpartum), the correct and consistent use of condoms is recommended, either alone or with another contraceptive method. Male condoms reduce the risk of STI/HIV.**		
CONDITION	**CATEGORY** I=Initiation, C=Continuation		**CLARIFICATIONS/EVIDENCE – Most evidence available relates to COC use. However, this evidence is also applied to patch and ring use.**
	Cu-IUD	**LNG-IUD**	
DRUG INTERACTIONS			
ANTIRETROVIRAL THERAPY **This section relates to the SAFETY of contraceptive use in women using these antiretrovirals. EFFECTIVENESS may be reduced and pregnancy itself may have a negative impact on health for some women with certain medical conditions.**			
	I C	I C	
a) Nucleoside reverse transcriptase inhibitors	2/3 2	2/3 2	**Antiretroviral therapy and IUDs:** There is no known interaction between antiretroviral therapy and IUD use. However, AIDS as a condition is classified as Category 3 for insertion and Category 2 for continuation unless the woman is clinically well on antiretroviral therapy in which case, both insertion and continuation are classified as Category 2. (See AIDS condition).
b) Non-nucleoside reverse transcriptase inhibitors	2/3 2	2/3 2	
c) Ritonavir-boosted protease inhibitors	2/3 2	2/3 2	
ANTICONVULSANT THERAPY **This section relates to the SAFETY of contraceptive use in women using anticonvulsants. EFFECTIVENESS may be reduced and pregnancy itself may have a negative impact on health for some women with certain medical conditions.**			
a) Certain anticonvulsants (phenytoin, carbamazepine, barbiturates, primidone, topiramate, oxcarbazepine)	1	1	The effectiveness of the LNG-IUS is not reduced with liver enzyme-inducing anticonvulsants[88]
b) Lamotrigine	1	1	Lamotrigine concentrations in LNG-IUD users are similar to those of non-hormonal users.[89]
ANTIMICROBIAL THERAPY **This section relates to the SAFETY of contraceptive use in women using antimicrobials. EFFECTIVENESS may be reduced and pregnancy itself may have a negative impact on health for some women with certain medical conditions.**			
a) Broad spectrum antibiotics	1	1	
b) Antifungals	1	1	
c) Antiparasitics	1	1	
d) Rifampicin or rifabutin therapy	1	1	

Additional comments

AGE

Menarche to <20 years: There is concern both about the risk of expulsion due to nulliparity and risk of STIs due to sexual behaviour in younger age groups. Although young women rarely use intrauterine methods they may be suitable options for some.

PARITY

Nulliparous: Nulliparity is related to an increased risk of expulsion.

POSTPARTUM

<48 hours, 48 hours to <4 weeks, ≥4 weeks: Concern that the neonate may be at risk due to exposure to steroid hormones with LNG-IUD use during the first 6 weeks postpartum is the same as for other POCs. Risk of perforation is increased between 48 hours and 4 weeks, and insertion should be delayed.

Puerperal sepsis: Insertion of an IUD may substantially worsen the condition.

POST-ABORTION

Immediate post-septic abortion: Insertion of an IUD may substantially worsen the condition.

PAST ECTOPIC PREGNANCY

The absolute risk of ectopic pregnancy is extremely low due to the high effectiveness of IUDs. However, when a woman becomes pregnant during IUD use, the relative likelihood of ectopic pregnancy is greatly increased, and should be excluded.

HYPERTENSION, CURRENT & HISTORY OF ISCHAEMIC HEART DISEASE, STROKE

There is theoretical concern about the effect of LNG on lipids. There is no restriction for copper IUDs.

VAGINAL BLEEDING PATTERNS

LNG-IUD use frequently causes changes in menstrual bleeding patterns. Over time, LNG-IUD users are more likely than non-users to become amenorrhoeic, thus LNG-IUDs are sometimes used as a treatment to correct heavy bleeding.

ENDOMETRIOSIS

Copper IUD use may worsen dysmenorrhoea associated with the condition.

SEVERE DYSMENORRHOEA

Dysmenorrhoea may intensify with copper IUD use. LNG-IUD use has been associated with reduction of dysmenorrhoea.

GESTATIONAL TROPHOBLASTIC DISEASE (GTD)

There is an increased risk of perforation since the treatment for the condition may require multiple uterine curettages.

CERVICAL INTRAEPITHELIAL NEOPLASIA (CIN)

There is some theoretical concern that LNG-IUDs may enhance progression of CIN.

CERVICAL CANCER (awaiting treatment)

There is concern about the increased risk of infection and bleeding at insertion. The IUD may need to be removed at the time of treatment but, until then, the woman is at risk of pregnancy.

BREAST DISEASE

Breast cancer: Breast cancer is a hormonally sensitive tumour. Concerns about progression of the disease may be less with LNG-IUDs than with COCs or higher-dose POCs. The LNG-IUS may be considered individually, and in consultation with the woman's breast surgeon.

ENDOMETRIAL CANCER

There is concern about the increased risk of infection, perforation and bleeding at insertion. The IUD may need to be removed at the time of treatment but, until then, the woman is at risk of pregnancy.

OVARIAN CANCER

The IUD may need to be removed at the time of treatment but, until then, the woman is at risk of pregnancy.

ANATOMICAL ABNORMALITIES

Distorted uterine cavity: In the presence of an anatomical abnormality that distorts the uterine cavity, proper IUD placement may not be possible.

PELVIC INFLAMMATORY DISEASE (PID)

IUDs do not protect against STI/HIV/PID. In women at low risk of STIs, IUD insertion poses little risk of PID. Current risk of STIs and desire for future pregnancy are relevant considerations.

SEXUALLY TRANSMITTED INFECTIONS (STIs)

IUDs do not protect against STI/HIV/PID. Among women with Chlamydial infection or gonorrhoea, the potential increased risk of PID with IUD insertions should be considered carefully and insertion delayed where possible until swab results are available and any treatment has been given. The concern is less for other STIs.

TUBERCULOSIS

Known pelvic: Insertion of an IUD may substantially worsen the condition.

DIABETES

Whether the amount of LNG released by the IUD may slightly influence carbohydrate and lipid metabolism is unclear. Some progestogens may increase the risk of thrombosis, although this increase is substantially less than for COCs.

HISTORY OF CHOLESTASIS

There is concern that a history of COC-related cholestasis may predict subsequent cholestasis with LNG use. Whether there is any risk with use of an LNG-IUD is unclear.

VIRAL HEPATITIS, CIRRHOSIS, LIVER TUMOURS

Active: POCs are metabolised by the liver and their use may adversely affect women whose liver function is compromised. This concern is similar to, but less than, that with COCs.

INFLAMMATORY BOWEL DISEASE

There is no evidence that women with IBD have an inherent increased risk of VTE. Risk of VTE may increase if unwell, bed bound or undergoing acute surgery or with major surgery and prolonged immobilisation. Under these circumstances the use of the Cu-IUD or LNG-IUD is safe.

THALASSAEMIA, SICKLE CELL DISEASE, IRON-DEFICIENCY ANAEMIA

There is concern about an increased risk of blood loss with copper IUDs.

REFERENCES: INTRAUTERINE CONTRACEPTION

1. Faculty of Sexual & Reproductive Healthcare Clinical Effectiveness Unit. Intrauterine Contraception. Update 2007 (www.fsrh.org).
2. Faculty of Family Planning and Reproductive Healthcare Clinical Effectiveness Unit. The levonorgestrel-releasing intrauterine system (LNG-IUS) in contraception and reproductive health. *Journal of Family Planning and Reproductive Health 2004*;**(30)2**:99-109
3. World Health Organization. Selected Practice Recommendations for Contraceptive Use [Second Edition]. http://www.who.int./reproductive-health/publications/spr/2004
4. United Kingdom Selected Practice Recommendations for Contraceptive Use. http://www.ffprhc.org.uk/
5. Faculty of Family Planning and Reproductive Healthcare Guidance. The Copper Intra-uterine Device as Long-term Contraception. Journal of Family Planning and Reproductive Healthcare, 2004:**30(4)**;29-42
6. Cramer DW, Schiff I, Schoenbaum SC, Gibson M, Belisle S, Albreant B et al. Tubal infertility and the intrauterine device. *New England Journal of Medicine.* 1985;**312**:941-7.
7. Daling JR, Weiss NS, Chow WH, Soderstrom RM, Moore DE et al. Primary tubal infertility in relation to the use of an intrauterine device. *New England Journal of Medicine*, 1985;**312**:937-41.
8. Daling JR, Schiff I, Schoenbaum Sc, Gibson M, Belisle S, Albrecht B et al. The intrauterine device and primary tubal infertility. *New England Journal of Medicine*. 1992;326:203-4.
9. Delbarge W, Batar I, Bafort M, Bonnivert J, Colmont C, Dhont M, et al. Return to fertility in nulliparous and parous women after removal of the GyneFix intrauterine contraceptive system. *European Journal of Contraception & Reproductive Health Care*. 2002;**7**:24-30.
10. Doll H, Vessey M, Painter R. Return of fertility in nulliparous women after discontinuation of the intrauterine device: comparison with women discontinuing other methods of contraception. *BJOG: an International Journal of Obstetrics & Gynaecology*. 2001;**108**:304 14.
11. Hubacher D, Lara-Ricalde R, Taylor DJ, Guerra-Infonte F, Guzman-Rodriguez R. Use of copper intrauterine devices and the risk of tubal infertility among nulligravid women. *New England Journal of Medicine*. 2001;345:561-7.
12. Skjeldestad FE, Bratt H. Return of fertility after use of IUDs (Nova-T, MLCu250 and MLCu375). *Advances in Contraception*. 1987;**3**:139-45.
13. Urbach DR; Morrett LD, King R, Cohen MM. Association of perforation of the appendix with female tubal infertility. *American Journal of Epidemiology*. 2001;**153**:566-71.
14. Wilson JC. A prospective New Zealand study of fertility after removal of copper intrauterine contraceptive devices for conception and because of complications: a four-year study. *American Journal of Obstetrics & Gynecology*. 1989;**160**:391-6.
15. Hubacher D, Lara-Ricalde R, Taylor DJ, Guerra-Infante F, Guzman-Rodriguez R. Use of copper intrauterine devices and the risk of tubal infertility among nulligravid women. *The New England Journal of Medicine* 2001;**345**:561-567
16. Andersson K, Batar I, Rybo G. Return to fertility after removal of a levonorgestrel-releasing intrauterine device or a Nova-T. *Contraception* 1992;**46**:575-584

17. Faculty of Family Planning and Reproductive Healthcare Clinical Effectiveness Unit. Contraceptive choices for breastfeeding women. *Journal of Family Planning and Reproductive Health Care*. 2004;**30**(3):181–189.

18. Faculty of Sexual and Reproductive Heakthcare Clinical Guidance. Postnatal Sexual and Reproductive Health (September 2009):**30**.ww.fsrh.org

19. Brenner PF. A clinical trial of the Delta-T intrauterine device: immediate postpartum insertion. *Contraception*. 1983;**28**:135-47.

20. Chi IC, Wilkens L, Rogers S. Expulsions in immediate postpartum insertions of Lippes Loop D and Copper T IUDs and their counterpart Delta devices--an epidemiological analysis. *Contraception*. 1985;**32**:119-34.

21. El-Shafei M. Postpartum and postabortion intrauterine device insertion unmet needs of safe reproductive health: three year experience of Mansoura University Hospital. *European Journal of Contraception & Reproductive Health Care*. 2000;**26**:253-62.

22. Grimes D et al. Immediate post-partum insertion of intrauterine devices.[update of *Cochrane Database Systematic Reviews*, 2001, CD003036; PMID: 11406064]. [Review] [30 refs]. *Cochrane Database of Systematic Reviews*, 2003, CD003036.

23. Morrison C, Waszak C, Latz K, Diabate F, Mate EM. Clinical outcomes of two early postpartum IUD insertion programs in Africa. *Contraception*. 1996;**53**:17-21.

24. Thiery M, Van Kets H, Van Der Pas H, Vas Os W, Dombrowicz N. The ML Cu250; clinical experience in Belgium and The Netherlands. *British Journal of Obstetrics & Gynaecology*. 1982;**89**:51-3.

25. Thiery M, Delbeke L, Van Kets H. Comparative performance of two copper-wired IUDs (ML Cu 250 and T Cu 200): immediate postpartum and interval insertion. *Advances in Contraceptive Delivery Systems*. 1980;**1**: 27-35.

26. The World Health Organization's Special Programme of Research, Development and Research Training in Human Reproduction. Task Force on Intrauterine Devices for Fertility Regulation. The Alza T IPCS 52, a longer acting progesterone IUD: safety and efficacy compared to the TCu22OC and multiload 250 in two randomized multicentre trials. *Clinical Reproduction & Fertility*. 1983;**2**:113-28.

27. The World Health Organization's Special Programme of Research, Development and Research Training in Human Reproduction. Task Force on Intrauterine Devices for Fertility Regulation. IUD insertion following termination of pregnancy: a clinical trial of the TCu 220C, Lippes loop D, and copper 7. *Studies in Family Planning.* 1983;**14**:99-108.

28. The World Health Organization's Special Programme of Research, Development and Research Training in Human Reproduction. Task Force on Intrauterine Devices for Fertility Regulation. IUD insertion following spontaneous abortion: a clinical trial of the TCu 220C, Lippes loop D, and copper 7. *Studies in Family Planning*. 1983;**14**:109-14.

29. El Tagy A, Sakr E, Sokal DC, Issa AH. Safety and acceptability of post-abortal IUD insertion and the importance of counselling. *Contraception*. 2003;**67**:229-34.

30. Gillett PG, Lee NH, Yuzpe AA, Cerkus I. A comparison of the efficacy and acceptability of the Copper-7 intrauterine device following immediate or delayed insertion after first-trimester therapeutic abortion. *Fertility & Sterility*. 1980;**34**:121-4.

31. Grimes D, Schulz K, Stanwood N. Immediate postabortal insertion of intrauterine devices.[update of Cochrane Database Syst Rev. 2000;(2):CD001777; PMID: 10796820]. [Review] [28 refs]. *Cochrane Database of Systematic Reviews*, 2002, CD001777.

32. Gupta I, Devi PK. Studies on immediate post-abortion copper "T" device. *Indian Journal of Medical Research*. 1975;**63**:736-9.

33. Moussa A. Evaluation of postabortion IUD insertion in Egyptian women. *Contraception.* 2001;**63**:315-7.

34. Pakarinen P, Toivonen J, Luukkainen T. Randomized comparison of levonorgestrel- and copper releasing intrauterine systems immediately after abortion, with 5 years' follow-up. *Contraception*. 2003;**68**:31-4.

35. Stanwood NL, Grimes DA, Schulz KF. Insertion of an intrauterine contraceptive device after induced or spontaneous abortion: a review of the evidence. BJOG: an *International Journal of Obstetrics & Gynaecology*. 2001;**108**:1168-73.

36. Suvisaari J, Lahteenmaki P. Detailed analysis of menstrual bleeding patterns after postmenstrual and postabortal insertion of a copper IUD or a levonorgestrel-releasing intrauterine system. *Contraception*, 1996, **54**:201-8.

37. Timonen H, Luukkainen T. Immediate postabortion insertion of the copper-T (TCu-200) with eighteen months follow-up. *Contraception*. 1974;9:153-60.

38. Tuveng JM, Skjeldestad FE, Iversen T. Postabortal insertion of IUD. *Advances in Contraception*. 1986;**2**: 387-92.

39. Zhang PZ. Five years experience with the copper T 200 in Shanghai - 856 cases. *Contraception.* 1980;**22**: 561-71.

40. Williams B, Poulter N, Brown MJ, Davies M, McInnes GT, Potter JP et al The BHS Guidelines Working Party Guidelines for the Management of Hypertension: Report of the Fourth Working Party of the British Hypertension Society, 2004 – BHS IV. *Journal of Human Hypertension.* 2004;**18**:139-185

41. National Institute for Clinical Excellence. Hypertension. Management of hypertension in adults in primary care. 18. 2004. London, National Institute for Clinical Excellence.

42. Scottish Intercollegiate Guidelines Network Secretariat. Prophylaxis of venous thromoboembolism. 62, 1-47, 2003 http://www.sign.ac.uk/pdf/sign62.pdf

43. Wu O, Robertson L, Twaddle S, Lowe GDO, Clark P, Walker I, et al. Screening for thrombophilia in high-risk situations: a meta-analysis and cost-effectiveness analysis. *British Journal of Haematology*. 2005;**131**(1):80-90.

44. Middledrop S, van Hylckama Vlieg A. Does thrombophillia testing help in the clinical management of patients? *British Journal of Haematology*. 2008;**143**(3):321-335.

45. Blickstein D, Blickstein I. Oral contraception and thrombophillia. *Current Opinion in Obstetrics and Gynacecology*. 2007;**19**(4):370-376

46. Department of Health. Prodigy Guidance – Hyperlipidaemia. 2004. http://www/prodigy.nhs.uk/guidance/hyperlipidaemia

47. British Heart Foundation. What is valvular heart disease? 2005. http://www.bhf.org.uk/

48. British Heart Foundation. Living with congenital heart disease? 2005. http://www.bhf.org.uk/

49. McGregor A. Migraine and use of combined hormonal contraceptive: a clinical review. *Journal of Family Planning and Reproductive Health Care*. 2007;**33**(3):15-169.

50. The International Headache Society and Task Force on Combined Oral Contraceptives and Hormone replacement therapy. Recommendations on the risk of ischemic stroke associated with use of oral contraceptives and hormone replacement therapy in women with migraine. *Cephalagia*. 2000;**20**:155-156

51. National Institute of Clinical Excellence. Heavy Menstrual Bleeding. 2007. http://www.nice.org.uk/nicemedia/pdf/CG44FullGuideline.pdf

52. Faculty of Sexual and Reproductive Healthcare Clinical Effectiveness Unit. Unscheduled bleeding in women using hormonal contraception. 2009. [In Press]

53. Barrington JW, Arunkalaivanan AS, Abdel-Fattah. Comparison between the levonorgestrel intrauterine system (LNG-IUS) and thermal balloon ablation in the treatment of menorrhagia. *European Journal of Obstetrics, Gynecology & Reproductive Biology*. 2003;**108**:72-4.

54. Hurskainen R, Tepri J, Rissanen P, Aalito AM, Grehman S, Kivela A et al. Quality of life and cost-effectiveness of levonorgestrel-releasing intrauterine system versus hysterectomy for treatment of menorrhagia: a randomised trial. *Lancet*. 2001;**357**:273-7.

55. Istre O, Trolle B. Treatment of menorrhagia with the levonorgestrel intrauterine system versus endometrial resection. *Fertility & Sterility*. 2001;**76**:304-9.

56. Lethaby AE, Cooke I, Rees M. Progesterone/progestogen releasing intrauterine systems versus either placebo or any other medication for heavy menstrual bleeding. *Cochrane Database of Systematic Reviews*, 2000, CD002126.

57. Stewart A, Cummings C, Gold L, Jordon R, Phillips W. The effectiveness of the levonorgestrel-releasing intrauterine system in menorrhagia: a systematic review. *BJOG: an International Journal of Obstetrics & Gynaecology*. 2001;**108**:74-86.

58. Fedele L, Bianchi S, Zahconato G, Portuese A, Raffaelli R et al. Use of a levonorgestrel-releasing intrauterine device in the treatment of rectovaginal endometriosis. *Fertility & Sterility.* 2001;75:485-8.

59. Vercellini P, Aimi G, Panazza S, De Giorgi O, Pesole A, Crosignani PG. A levonorgestrel-releasing intrauterine system for the treatment of dysmenorrhea associated with endometriosis: a pilot study. *Fertility & Sterility.* 1999;**72**:505 8.

60. Deicas RE, Miller DS, Rademaker EW, Lurain JR. The role of contraception in the developement of postmolar trophoblastic tumour. *Obstetrics & Gynaecology*.1991;**78**:221-226.

61. Morrow P, Nakamura R, Schlaerth J, Gaddis O, Eddy G. The infleucene of oral contraceptives on the postmolar human chorionic gonadotrophin regression curve. *American Journal of Obstetrics and Gynecology*. 1985;**151**:906-914.

62. Ho Yuen B, Burch P. Relationship of oral contraceptives and the intrauterine contraceptive devices to the regression of concentration of the beta subunit of human chorionic gonadotrophin and invasive complications after molar pregnancy. *Journal of Obstetrics & Gynaecology.* 1983;**145**:241-17.

63. Stone M. Relationship of oral contraception to development of trophoblastic tumour after evacution of a hydatidform mole. *British Journal of Obstetrics and Gynaecology.* 1976;**83**:913-916.

64. Royal College of Obstetricians and Gynaecologists. The management of gestational trophoblastic neoplasia. 2004. http://www.rcog.org.uk/files/rcog-corp/uploaded-files/GT38GestationalTrophNeoplasia2004.pdf

65. Fedele L et al. Treatment of adenomyosis-associated menorrhagia with a levonorgestrel-releasing intrauterine device. *Fertility & Sterility*. 1997;**68**:426-9.

66. Grigorieva V, Chen-Mok M, Tarasova M, Mikhailov A. Use of a levonorgestrel-releasing intrauterine system to treat bleeding related to uterine leiomyomas. *Fertility & Sterility*. 2003;**79**:1194-8.

67. Mercorio F, De Simone R, Di Spiezieo Sardo A, Cerrota G, Bifiulco G, Vanacore T, Nappi C. The effect of a levonorgestrel-releasing intrauterine device in the treatment of myoma-related menorrhagia. *Contraception.* 2003;**67**:277-80.

68. Wildemeersch D, Schacht E, Wildemeersch P. Treatment of primary and secondary dysmenorrhea with a novel 'frameless' intrauterine levonorgestrel-releasing drug delivery system: a pilot study. *European Journal of Contraception & Reproductive Health Care*. 2001;**6**:192-8.

69. Wildemeersch D, Schacht E. The effect on menstrual blood loss in women with uterine fibroids of a novel "frameless" intrauterine levonorgestrel-releasing drug delivery system: a pilot study. *European Journal of Obstetrics, Gynecology & Reproductive Biology.* 2002;**102**:74-9.

70. Wildemeersch D, Schacht E, Wildemeersch P. Contraception and treatment in the perimenopause with a novel "frameless" intrauterine levonorgestrel-releasing drug delivery system: an extended pilot study. *Contraception*. 2002;**66**:93-99.

71. Wildemeersch D, Schacht E, Wildemeersch P. Performance and acceptability of intrauterine release of levonorgestrel with a miniature delivery system for hormonal substitution therapy, contraception and treatment in peri and postmenopausal women. *Maturitas*. 2003;**44**:237-45.

72. Larsson B, Wennergren M. Investigation of a copper-intrauterine device (Cu-IUD) for possible effect on frequency and healing of pelvic inflammatory disease. *Contraception*. 1977;**15**:143-9.

73. Soderberg G, Lindgren S. Influence of an intrauterine device on the course of an acute salpingitis. *Contraception*. 1981;**24**:137-43.

74. Teisala K. Removal of an intrauterine device and the treatment of acute pelvic inflammatory disease. *Annals of Medicine*. 1989;**21**:63-5.

75. Faundes A, Telles E, De Lourdes Cristo Foletti M, Faundes D, Castro S, Hardy E. The risk of inadvertent intrauterine device insertion in women carriers of endocervical Chlamydia trachomatis. *Contraception.* 1998;**58**:105-9.

76. Ferraz do Lago R, Simoes Ja, Bahamondes L, Camargo RPS, Perrotti M, Monterio I. Follow-up of users of intrauterine device with and without bacterial vaginosis and other cervicovaginal infections. Contraception. 2003;**68**:105-9.

77. Pap-Akeson M, Solheim F, Thorbert G, Akerlund M. Genital tract infections associated with the intrauterine contraceptive device can be reduced by inserting the threads into the uterine cavity. *British Journal of Obstetrics & Gynaecology*. 1992;99:676-9.

78. Sinei SK, Mapptey Pr, Grimes DA, Mati JK, Rosenthal SM et al. Preventing IUCD-related pelvic infection: the efficacy of prophylactic doxycycline at insertion. *British Journal of Obstetrics & Gynaecology.* 1990;**97**:412-9.

79. Skjeldestad FE, Halvorsen Le, Kahn H, Nordbo SA, Saake K. IUD users in Norway are at low risk for genital C. trachomatis infection. *Contraception*. 1996;**54**:209-12.

80. Walsh TL, Bernstein GS, Grimes Da, Frezieres R, Bernstein L, Coulson AH. IUD Study Group. Effect of prophylactic antibiotics on morbidity associated with IUD insertion: results of a pilot randomized controlled trial. *Contraception*. 1994;**50**:319-27.

81. Gines P, Quintero E, Arroyo V, Teres J, Bruguera M, Rimola A et al. Compensated cirrhosis: natural history and prognostic factors. *Hepatology*. 1987;**7**(1):122-128.

82. NHS Clinical Knowledge Summary – Raynaud's phenomenon. 2005. http://cks.library.nhs.uk/raynauds_phenomenon#-223261.

83. Greenstein D, Jeffcoate N, Ilsley D, Kester RC. The menstrual cycle and Raynaud's phenomenon. *Angiology* 1996;**47**:427-436.

84. Petri M, Kim MY, Kalunian KC, Grossmann J, Hahn BH, Sammaritano LR et al. Combined oral contraceptives in women with systemic lupus erythematosus. *New England Journal of Medicine* 2005;**353**:2550-8.

85. Julkunen HA, Kaaja R, Friman C. Contraceptive practice in women with systemic lupus erythematosus. *British Journal of Rheumatology* 1993;**32**:227-30.

86. Faculty of Sexual and Reproductive Healthcare Clinical Effectiveness Unit. Drug Interactions Hormonal Contraception. *Journal of Family Planning and Reproductive Health Care.* 2005;**31**:135-150.

87. Lehtovirta P, Paavonen J, Heikinheimo O. Experience with the levonorgestrel-releasing intrauterine system among HIV-infected women. *Contraception.* 2007;**81**:222-227.

88. Bounds W, Gulliebaud J. Observational series on women using the contraceptive Mirena concurrently with anti-epileptic and other enzyme-inducing drugs. *Journal of Family Planning and Reproductive Healthcare.* 2002;**28**:78-80.

89. Reimers A, Helde G, Broadtkorb E. Ethinyl estradiol, not progestogens, reduces lamotrigine plasma levels. *Neurology*. 2003:**61**:570-571.

Emergency contraception

EC

EMERGENCY CONTRACEPTION *(Progestogen-only emergency contraception, POEC, copper intrauterine contraceptive device, Cu-IUD)*	**POEC and Cu-IUDs do not protect against STI/HIV. If there is risk of STI/HIV (including during pregnancy or postpartum), the correct and consistent use of condoms is recommended, either alone or with another contraceptive method. Male condoms reduce the risk of STI/HIV.**		
CONDITION	**CATEGORY**		**CLARIFICATIONS/EVIDENCE**
	POEC	**Cu-IUD**	
PREGNANCY	NA	NA	**Clarification:** These methods are **not** abortifacient. Although not indicated for a woman with a known or suspected pregnancy, there is no known harm to the woman, the course of her pregnancy, or the fetus if POEC is accidentally used. An IUD can be inserted up to 5 days after the *first episode* of unprotected sex or if necessary up to 5 days after the *expected date of ovulation* (day 19 in a regular 28 day cycle) thus avoiding insertion after implantation is complete.[1]
POSTPARTUM (breastfeeding or not breastfeeding)			
a) <21 days	NA	NA	**Clarification:** Emergency contraception is not required if unprotected sex or barrier method failure occurs <21 days postpartum. The risks of inserting a Cu-IUD prior to 28 days (4 weeks) postpartum outweigh the benefits. POEC is indicated between 21 and 27 days postpartum, or an IUD after day 28 (≥4 weeks). Women who are fully or almost fully breastfeeding, amenhorroeic and <6 months postpartum can rely on lacational amenorrhea method (LAM) for contraception and therefore emergency contraception is not indicated unless frequency of breastfeeding decreases or menstruation returns.
b) ≥21 days	1	4	
c) ≥4 weeks	1	1	
HISTORY OF ECTOPIC PREGNANCY	1	1	**Clarification:** Women using contraception have a lower risk of ectopic pregnancy compared to women not using contraception. There does not appear to be an increased risk of ectopic pregnancy following use of POEC or Cu-IUD.

UKMEC	DEFINITION OF CATEGORY
CATEGORY 1	A condition for which there is no restriction for the use of the contraceptive method
CATEGORY 2	A condition where the advantages of using the method generally outweigh the theoretical or proven risks but more careful follow up is required
CATEGORY 3	A condition where the theoretical or proven risks usually outweigh the advantages of using the method. Provision of a method requires expert clinical judgement and/or referral ot a specialist contraceptive provider, since use of the method is not usually recommended unless other methods are not available or not acceptable
CATEGORY 4	A condition which represents an unacceptable health risk if the contraceptive method is used

EMERGENCY CONTRACEPTION *(Progestogen-only emergency contraception, POEC, copper intrauterine contraceptive device, Cu-IUD)*	**POEC and Cu-IUDs do not protect against STI/HIV. If there is risk of STI/HIV (including during pregnancy or postpartum), the correct and consistent use of condoms is recommended, either alone or with another contraceptive method. Male condoms reduce the risk of STI/HIV.**		
CONDITION	**CATEGORY**		**CLARIFICATIONS/EVIDENCE**
	POEC	**Cu-IUD**	
SMOKING			
a) Age <35 years	1	1	**Evidence:** Myocardial infarction is rare in women of reproductive age. Smoking is an important risk factor for cardiovascular disease. Overall mortality is strongly related to smoking. Excess mortality in heavy smokers is apparent from age 35 years.[4] Myocardial infarction risk increases as the number of cigarettes smoked per day increases and decreases when smoking stops.[5]
b) Age ≥35 years			
(i) <15 cigarettes/day	1	1	
(ii) ≥15 cigarettes/day	1	1	
(iii) stopped smoking <1 year ago	1	1	
(iv) stopped smoking ≥1 year ago	1	1	
HYPERTENSION			
For all categories of hypertension, classifications are based on the assumption that **no other risk factors for cardiovascular disease** exist. When multiple risk factors do exist, risk of cardiovascular disease may increase substantially. A single reading of blood pressure level is not sufficient to classify a woman as hypertensive. If elevated, the BP should be re-assessed at the end of the consultation. If blood pressure is increased it should be re-assessed on at least two subsequent clinic visits at monthly intervals.			
a) Adequately controlled hypertension	1	1	
b) Consistently elevated blood pressure levels (properly taken measurements)			
(i) systolic >140 to 159 mmHg or diastolic >90 to 94mmHg	1	1	
(ii) systolic ≥160 or diastolic ≥95 mmHg	1	1	
c) Vascular disease	1	1	

UKMEC	DEFINITION OF CATEGORY
CATEGORY 1	A condition for which there is no restriction for the use of the contraceptive method
CATEGORY 2	A condition where the advantages of using the method generally outweigh the theoretical or proven risks but more careful follow up is required
CATEGORY 3	A condition where the theoretical or proven risks usually outweigh the advantages of using the method. Provision of a method requires expert clinical judgement and/or referral ot a specialist contraceptive provider, since use of the method is not usually recommended unless other methods are not available or not acceptable
CATEGORY 4	A condition which represents an unacceptable health risk if the contraceptive method is used

EMERGENCY CONTRACEPTION *(Progestogen-only emergency contraception, POEC, copper intrauterine contraceptive device, Cu-IUD)*	**POEC and Cu-IUDs do not protect against STI/HIV. If there is risk of STI/HIV (including during pregnancy or postpartum), the correct and consistent use of condoms is recommended, either alone or with another contraceptive method. Male condoms reduce the risk of STI/HIV.**		
CONDITION	**CATEGORY**		**CLARIFICATIONS/EVIDENCE**
	POEC	**Cu-IUD**	
VENOUS THROMBOEMBOLISM (VTE)			Venous thromboembolism includes deep vein thrombosis and pulmonary embolism.
a) History of VTE	1	1	
b) Current VTE (on anticoagulants)	2	2	***Current VTE*** refers to disease for which anticoagulants are still being used. Evidence is limited on the risk of VTE with progestogen-only oral contraceptives, however existing evidence is reassuring.[6]
c) Family history of VTE			
(i) first-degree relative age <45 years	1	1	
(ii) first-degree relative ≥45 years	1	1	
d) Major surgery			***Major Surgery*** includes operations of >30 minutes duration. Procedures with high risk of VTE include: general or orthopaedic surgery, trauma, neurosurgery.[7]
(i) with prolonged immobilisation	1	1	
(ii) without prolonged immobilisation	1	1	
e) Minor surgery without immobilisation	1	1	***Minor surgery*** includes operations lasting <30 minutes (eg laparoscopic sterilisation), or procedures such as knee arthroscopy. Varicose vein surgery has a low risk of VTE.
f) Immobility (unrelated to surgery) e.g. *wheelchair bound, debilitating illness*	1	1	***Immobility*** due to hospitalisation for acute trauma, acute illness, or paralysis is associated with a high risk of VTE.
KNOWN HYPERLIPIDAEMIAS	1	1	**Clarification:** Routine screening is not appropriate because of the rarity of the conditions and the high cost of screening.
HEADACHES			Headache is a common condition affecting women of reproductive age.
a) Non-migrainous (mild or severe)	1	1	
b) Migraine without aura, at any age	1	1	Classification depends on making an accurate diagnosis of those severe headaches that are migrainous and in addition those complicated by aura. Symptoms of aura include: homonymous hemianopia, unilateral paraesthesia and/or numbness, unilateral weakness and aphasia or unclassifiable speech disorder. Visual symptoms progress from fortification spectra (star-shaped figure near the point of fixation with scintillating edges) to scotoma (a bright shape which gradually increases in size). Flashing lights are not classified as aura. Aura occurs before onset of the headache.
c) Migraine with aura, at any age	1	1	
d) Past history (≥5 years ago) of migraine with aura, any age	1	1	

UKMEC	DEFINITION OF CATEGORY
CATEGORY 1	A condition for which there is no restriction for the use of the contraceptive method
CATEGORY 2	A condition where the advantages of using the method generally outweigh the theoretical or proven risks but more careful follow up is required
CATEGORY 3	A condition where the theoretical or proven risks usually outweigh the advantages of using the method. Provision of a method requires expert clinical judgement and/or referral ot a specialist contraceptive provider, since use of the method is not usually recommended unless other methods are not available or not acceptable
CATEGORY 4	A condition which represents an unacceptable health risk if the contraceptive method is used

EMERGENCY CONTRACEPTION *(Progestogen-only emergency contraception, POEC, copper intrauterine contraceptive device, Cu-IUD)*	POEC and Cu-IUDs do not protect against STI/HIV. If there is risk of STI/HIV (including during pregnancy or postpartum), the correct and consistent use of condoms is recommended, either alone or with another contraceptive method. Male condoms reduce the risk of STI/HIV.		
CONDITION	**CATEGORY**		**CLARIFICATIONS/EVIDENCE**
	POEC	**Cu-IUD**	
GESTATIONAL TROPHOBLASTIC DISEASE (GTD)			**Clarification:** Gestational trophoblastic disease includes hydatidiform mole, invasive mole and placental site trophoblastic tumour. In the UK management depends on serum β-hCG concentrations and need for chemotherapy identified by measuring β-hCG concentrations.[10]
a) Decreasing or undetectable β-hCG levels	1	1	
b) Persistently elevated β-hCG levels or malignant disease	1	4	
BREAST DISEASE			
a) Undiagnosed mass	1	1	
b) Benign breast disease	1	1	
c) Family history of cancer	1	1	
d) Carriers of known gene mutations associated with breast cancer (eg. BRCA1)	1	1	
e) Breast cancer			
(i) current	2	1	
(ii) past and no evidence of current disease for 5 years	2	1	
UTERINE FIBROIDS			
a) Without distortion of the uterine cavity	1	1	In women with a distorted uterine cavity it may be appropriate after counselling to attempt insertion of an intrauterine device.
b) With distortion of the uterine cavity	1	3	
ANATOMICAL ABNORMALITIES			
a) Distorted uterine cavity (any congenital or acquired uterine abnormality distorting the uterine cavity in a manner that is incompatible with IUD insertion	1	3	In women with a distorted uterine cavity it may be appropriate after counselling to attempt insertion of an intrauterine device.
b) Other abnormalities (including cervical stenosis or cervical lacerations) not distorting the uterine cavity or interfering with IUD insertion	1	2	

UKMEC	DEFINITION OF CATEGORY
CATEGORY 1	A condition for which there is no restriction for the use of the contraceptive method
CATEGORY 2	A condition where the advantages of using the method generally outweigh the theoretical or proven risks but more careful follow up is required
CATEGORY 3	A condition where the theoretical or proven risks usually outweigh the advantages of using the method. Provision of a method requires expert clinical judgement and/or referral ot a specialist contraceptive provider, since use of the method is not usually recommended unless other methods are not available or not acceptable
CATEGORY 4	A condition which represents an unacceptable health risk if the contraceptive method is used

EMERGENCY CONTRACEPTION *(Progestogen-only emergency contraception, POEC, copper intrauterine contraceptive device, Cu-IUD)*	**POEC and Cu-IUDs do not protect against STI/HIV. If there is risk of STI/HIV (including during pregnancy or postpartum), the correct and consistent use of condoms is recommended, either alone or with another contraceptive method. Male condoms reduce the risk of STI/HIV.**		
CONDITION	**CATEGORY**		**CLARIFICATIONS/EVIDENCE**
	POEC	**Cu-IUD**	
INFLAMMATORY BOWEL DISEASE (includes Crohn's disease, ulcerative colitis)	2	1	**Clarification:** Oral methods may be less reliable if there is significant malabsorption or small bowel resection (particularly with Crohn's disease). Oral methods are unaffected by colectomy.
HISTORY OF SEVERE CARDIOVASCULAR COMPLICATIONS* (ischaemic heart disease, cerebrovascular attack, or other thromboembolic conditions)	1	1	**Clarification:** There is no evidence that POEC increases the risk of cardiovascular disease.
SEVERE LIVER DISEASE (including jaundice)*	1	1	
ACUTE INTERMITTENT PORPHYRIA	2	1	**Evidence:** Acute intermittent porphyria is a rare disorder characterised by acute attacks often precipitated by drugs. Estrogen and progestogens have been implicated. Around 1% of acute attacks are fatal. A third of female patients have cyclical symptoms in relation to the menstrual cycle but seldom proceed to an acute attack. In a population study almost half of women with porphyria had used hormonal contraception but only 4.5% had associated acute attacks. Combined hormonal contraception has been shown to reduce attacks for some women. Natural fluctuations in estrogen and progesterone appear to be associated with acute attacks more often than exogenous hormones. Women may use POEC following discussion of the risks and benefits and with clinical judgement.[11-15]
REPEATED USE OF POEC (in the same cycle)	1	NA	**Clarification:** Recurrent use of emergency contraception is an indication that the woman requires further counselling on other contraceptive options. POEC can be used more than once in a cycle if clinically indicated.[16] Alternatively a Cu-IUD can be inserted if repeated unprotected sex occurs up to 5 days after the first episode of unprotected sex **or** up to 5 days after expected date of ovulation.
RISK OF SEXUALLY TRANSMITTED INFECTIONS (STIs)	1	1	**Clarification:** Women thought to be at higher risk of STI from their sexual history (aged <25 years, or with a change in sexual partner or two or more partners in the last year) should be offered testing for STI.[1] A Cu-IUD can be inserted as emergency contraception, pending swab results. If deemed higher risk, prophylactic antibiotics (such as azithromycin or doxycycline) can be given to protect against *Chlamydia trachomatis* at the time of Cu-IUD insertion.[1]

UKMEC	DEFINITION OF CATEGORY
CATEGORY 1	A condition for which there is no restriction for the use of the contraceptive method
CATEGORY 2	A condition where the advantages of using the method generally outweigh the theoretical or proven risks but more careful follow up is required
CATEGORY 3	A condition where the theoretical or proven risks usually outweigh the advantages of using the method. Provision of a method requires expert clinical judgement and/or referral ot a specialist contraceptive provider, since use of the method is not usually recommended unless other methods are not available or not acceptable
CATEGORY 4	A condition which represents an unacceptable health risk if the contraceptive method is used

Additional comments

POSTPARTUM

The earliest ovulation postpartum is thought to be day 21 and therefore unprotected sex prior to day 21 is not an indication for emergency contraception. If unprotected sex occurs after day 21 emergency contraception can be considered. A Cu-IUD should not be inserted <4 weeks postpartum.

BREASTFEEDING

Although women who are fully or nearly fully breastfeeding, amenorrhoeic and <6 months postpartum can rely on this as an effective method of contraception, if breastfeeding frequency decreases or menstruation recurs emergency contraception may be indicted. POEC can be used from day 21 postpartum even if breastfeeding, and a Cu-IUD from 28 days postpartum.

HISTORY OF SEVERE CARDIOVASCULAR COMPLICATIONS, ANGINA PECTORIS

Use of POEC is not thought to increase the risk of cardiovascular complications.

MIGRAINE

Use of POEC is safe for women with a history of migraine with aura.

SEVERE LIVER DISEASE (including jaundice)

The duration of use of Emergency Contraceptive Pills is less than that of regular use of COCs or POPs and thus would be expected to have less clinical impact.

ACUTE INTERMITTENT PORPHYRIA

Cyclical symptoms have been found in relation to the menstrual cycle but seldom lead to acute attacks. Natural fluctuations in estrogen and progesterone appear to be associated with acute attacks more often than exogenous hormones. Women may use POEC following discussion of the risks and benefits and with clinical judgement.

REPEAT USE OF EMERGENCY CONTRACEPTION

POEC can be used more than once in a cycle if clinically indicated.

RISK OF SEXUALLY TRANSMITTED INFECTIONS (STIs)

Women who are thought to be at higher risk for STI based on a sexual history (age <25 years or age >25 years with a change in sexual partner or two or more partners in the last year) can be offered testing for STI and should be given prophylactic antibiotics to prevent *Chlamydia trachomatis* at the time of Cu-IUD insertion pending swab results.

DRUG INTERACTIONS

No category was scored by the Consensus Group on use of progestogen-only contraception by women using liver enzyme inducers. Current guidance from the FSRH recommends that women using liver enzyme inducers should be advised to use a Cu-IUD.[17] If progestogen-only emergency contraception is to be used it should be given as soon as possible and within 72 hours of unprotected sex. In women using liver enzyme inducing drugs two 1.5 milligram levonorgestrel tablets should be taken (3 milligrams) as a single dose. The efficacy of progestogen-only emergency contraception is not reduced by non-liver enzyme inducing antibiotics.

REFERENCES: EMERGENCY CONTRACEPTION

1. Faculty of Sexual & Reproductive Healthcare Clinical Effectiveness Unit. Intrauterine Contraception. Update 2007 (www.fsrh.org).
2. Faculty of Family Planning and Reproductive Health Care Clinical Effectiveness Unit. Contraceptive Choices for Breastfeeding Women. *Journal of Family Planning and Reproductive Health Care* 2004;**30**:181-9.
3. Knight J, Pyper C. Postnatal contraception: what are the choices? *Nursing in Practice* 2002;May:23-5.
4. Vessey M, Painter R, Yeates D. Mortality in relation to oral contraceptive use and cigarette smoking. *Lancet* 2003;362:185-91.
5. McElduff P, Dobson A, Beaglehole R, Jackson R. Rapid reduction in coronary risk for those who quit cigarette smoking. *Australian and New Zealand Journal of Public Health* 1998;**22**:787-91.
6. World Health Organization. Cardiovascular disease and use of oral and injectable progestagen only contraceptives and combine injectable contraceptives. Results of an international, multicentre, case control study. *Contraception* 1998;**57**:315-24.
7. Scottish Intercollegiate Guidelines Network Secretariat. Prophylaxis of venous thromboembolism. 62, 1-47. 2003.
8. American Council for Headache Education. How headaches differ. 2004. http://www.achenet.org/understanding/differ.php
9. The International Headache Society Task Force on Combined Oral Contraceptives and Hormone replacement Therapy. Recommendations on the risk of ischaemic stroke associated with use of combined oral contraceptives and hormone replacement therapy in women with migraine. *Cephalagia* 2000;**20**:155-6.
10. Royal College of Obstetricians and Gynaecologists. The Management of Gestational Trophoblastic Neoplasia. 2004.
11. Andersson C, Innala E, Bäckström T. Acute intermittant porphyria in women: clinical expression, use and experience of exogenous sex hormones. A population-based study in northern Sweden. *Journal of Internal Medicine* 2003;**254**:176-83.
12. Kauppinen, R and Mustajoki, Pj. Prognosis of acute porphyria: occurrence of acute attacks, precipitating factors, and associated diseases. *Medicine* 71(1), 1-13. 1992.
13. Gross, U, Honcamp, M, Daume, E, Frank, M, Dusterberg, B, and Doss, M O. Hormonal oral contraceptives, urinary porphyrin excretion and porphyrias. *Hormone & Metabolic Research* 27(8), 379-383. 1995.
14. Castelo-Branco C, Vicente JJ, Vanrell JA. Use of Gonadotropin-Releasing Hormone Analog With Tibolone to Prevent Cyclic Attacks of Acute Intermittent Porphyria. *Metabolism* 2001;**50**:995-6.
15. Thadani H, Deacon A, Peters T. Diagnosis and management of porphyria. *British Medical Journal* 2000;**320**:1647-51.
16. Faculty of Family Planning and Reproductive Health Care Clinical Effectiveness Unit. Emergency Contraception. *The Journal of Family Planning and Reproductive Health Care* 2003;**29**:9-16.
17. Faculty of Family Planning and Reproductive Health Care Clinical Effectiveness Unit. Emergency Contraception update (April 2006) *The Journal of Family Planning and Reproductive Health Care*. 2006; **32** (2): 121-128.