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## Effectiveness and acceptability of progestogens in combined oral contraceptives – a systematic review

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### Abstract

**Background:** The progestogen component of oral contraceptives (OCs) has undergone changes since it was recognized that their chemical structure can influence the spectrum of minor adverse and beneficial effects.

**Methods:** The objective of this review was to evaluate currently available low-dose OCs containing ethinylestradiol and different progestogens in terms of contraceptive effectiveness, cycle control, side effects and continuation rates. The Cochrane Controlled Trials Register, MEDLINE and EMBASE databases were searched. Randomized trials reporting clinical outcomes were considered for inclusion and were assessed for methodological quality and validity.

**Results:** Twenty-two trials were included in the review. Eighteen were sponsored by pharmaceutical companies and in only 5 there was an attempt for blinding. Most comparisons between different interventions included one to three trials, involving usually less than 500 women. Discontinuation was less with second-generation progestogens compared to first-generation (RR 0.79; 95% CI 0.69–0.91). Cycle control appeared to be better with second-compared to first-generation progestogens for both, mono- and triphasic preparations (RR 0.69; 95% CI 0.52–0.91) and (RR 0.61; 95% CI 0.43–0.85), respectively. Intermenstrual bleeding was less with third-compared to second-generation pills (RR 0.71; 95% CI 0.55–0.91).

Contraceptive effectiveness of gestodene (GSD) was comparable to that of levonorgestrel (LNG), and had similar pattern of spotting, breakthrough bleeding and absence of withdrawal bleeding). Drospirenone (DRSP) was similar compared to desogestrel (DSG) regarding contraceptive effectiveness, cycle control and side effects.

**Conclusion:** The third- and second-generation progestogens are preferred over first generation in all indices of acceptability. Current evidence suggests that GSD is comparable to LNG in terms of contraceptive effectiveness and for most cycle control indices. GSD is also comparable to DSG. DRSP is comparable to DSG. Future research should focus on independently conducted well designed randomized trials comparing particularly the third- with second-generation progestogens.

**Table 1: Progestogens [1]**

Pregnanes	Estranes	Gonanes	
		2 <sup>nd</sup> generation	3 <sup>rd</sup> generation
Chlormadinone acetate	Norethindrone acetate	dl-Norgestrel	Desogestrel
Cyproterone acetate	Ethinodiol diacetate	Levonorgestrel	Gestodene
Nomegestrol, Nestorone	Lynestrenol		Norgestimate
	Norethynodrel		

**Background**

Combined oral contraceptives (OCs) were first introduced for clinical use in the 1960's. Ethinylestradiol (EE) has been the most commonly used estrogen component. In order to reduce the side effects and increase the acceptability, the EE dose was gradually reduced to 30 micrograms (mcg) or less and the biochemical structure of the progestogens was changed. The progestogen dose, though, cannot be reduced nowadays since further reduction may not prevent the LH-surge and thus allow ovulation. The different progestogens can be classified according to their steroid structure and to their timing of market introduction. All contraceptive progestogens have a similar steroid skeleton with 4 rings and can be categorized into three tetracyclic structures: the pregnanes (derived from the progesterone molecule), the estranes (derivatives of testosterone) and the gonanes [1] (table 1).

Estranes correspond to first generation progestogens, such as norethisterone (NE), norethindrone (NE), ethinodiol diacetate, lynestrenol (LYN) and norethynodrel as well as dienogest. Dienogest is derived from NE and is claimed to have no androgenic activity and lesser effect on glucocorticoids than mifepristone [1]. Gonane progestogens are divided into two classes: the second-generation progestogens levonorgestrel (LNG) and norgestrel (NG) and third-generation progestogens desogestrel (DSG), gestodene (GSD) and norgestimate (NGM). Examples of pregnanes in OCs are cyproterone acetate (CPA), chlormadinone acetate and nomegestrol.

Although norethynodrel was the progestogen component in the very first OC, norethisterone (as known in Europe) or norethindrone (NE) can be considered as the most important substances in the early period of oral contraception. The first-generation progestogens norethynodrel, norethisterone acetate, and lynestrenol are all metabolized to NE and were nearly always combined with 50 µg of EE or more. The synthesis of norgestrel (NG) in 1963 by Smith [2] was followed by the isolation of the biologically active component, levonorgestrel (LNG) [3]. These second-generation progestogens entered the market in the

1970s. Currently, LNG is probably the most widely used progestogen and predominantly combined with 30 µg EE. During the 1980s, three new progestogens forming the third-generation progestogens, desogestrel (DSG), gestodene (GSD) and norgestimate (NGM) were developed by three different pharmaceutical companies. DSG and NGM are both pro-drugs. DSG is activated in the body by conversion into 3-keto-DSG, whereas NGM is converted by biotransformation into several metabolites, one of which is LNG. Unclassified in generations are such progestogens as CPA (listed in the pregnane classification, not introduced into the US market) and drospirenone (DRSP), a recently introduced progestogen derived from 17-α-spironolactone that might possess antimineralecorticoid and mild antiandrogenic activity.

**Methods**

**Outcomes**

The objective of the review was to compare the various currently available low dose OCs containing different progestogens and assess their acceptability according to the following indicators:

1. Effectiveness (pregnancy rates)
2. Discontinuation rates
3. Reasons for discontinuation
4. Cycle control
5. Side-effects

Trials had to report clinical outcomes to be eligible for inclusion. Trials focusing on biochemical changes only were not eligible for the review. The primary outcome of interest in this review is acceptability.

*Contraceptive effectiveness*

For contraceptive effectiveness (incidence of pregnancy) we used the authors' definition and did not differentiate between method and user failure. The failure rate of

combined oral contraceptives varies with age, race and marital status in typical users of OCs. The lowest expected failure rate is thought to be around 0.1% with perfect use (theoretical efficacy) and the higher failure rates observed in typical users (effectiveness) are largely attributed to problems with compliance [4].

**Discontinuation**

Data on discontinuation rate and the reasons for discontinuation are important measures of acceptability.

**Cycle control**

Women's acceptance of a hormonal contraceptive method depends largely on the degree of cycle control and side effects [5]. In fact, a diminishing compliance due to poor cycle control will also affect the effectiveness of the method. Lack of standardization in the reporting and analysis of intermenstrual bleeding patterns prevents meaningful comparisons of the new formulations from one study to another [6]. The changes in cycle patterns were analysed separately from side-effects, according to the type of change, if possible (e.g. breakthrough bleeding, intermenstrual bleeding, spotting, absence of withdrawal bleeding).

**Common side-effects**

The common side-effects associated with OC use are reported as breast tenderness, headache, migraine, nausea, nervousness, vomiting, dizziness, weight gain, tiredness, decline of libido and increase in blood pressure. The side-effects can be due to estrogen, progestogen or androgen effects and can decrease after a few months of use [7]. It is not always possible to attribute a side-effect to the estrogen or to the progestogen component.

**Rare adverse events**

Both estrogen and progestogen component of combined OCs are believed to be responsible for cardiovascular events associated with OC use. Venous events have often been associated with the estrogen component. Association of acute myocardial infarction, stroke and venous thromboembolism with OC use has been studied extensively generating considerable controversy. These rare long term adverse events are not amenable to study through randomized controlled trials, hence, these events are not the focus of this review.

**Types of interventions**

1. Any monophasic low-dose estrogen (<50 mcg) combined OC containing a third-generation progestogen versus any monophasic low-dose estrogen combined OC containing a second-generation progestogen (same for multiphasic preparations)

2. Any monophasic low-dose estrogen combined OC containing a third generation progestogen versus any monophasic low-dose estrogen combined OC containing a first-generation progestogen (same for multiphasic preparations)

3. Any monophasic low-dose estrogen combined OC containing a second-generation progestogen versus any monophasic low-dose estrogen combined OC containing a first-generation progestogen (same for multiphasic preparations)

4. Comparisons between low-dose estrogen OCs containing a certain type of progestogen.

**Search strategy**

1. We searched the Cochrane Controlled Trials Register, MEDLINE and EMBASE with the following search strategy:

CONTRACEPTIVES-ORAL\*:ME  
 LEVONORGESTREL  
 NORETHISTERONE  
 norethynrone  
 NORETHINDRONE  
 NORGESTIMATE  
 DESOGESTREL  
 GESTODENE  
 ((((((#1 or #2) or #3) or #4) or #5) or #6) or #7) or #8)  
 MENOPAUS\*  
 NORPLANT  
 REPLACEMENT  
 ANIMAL  
 INJECT\*  
 CANCER  
 IUD  
 INTRAUTERINE  
 PROSTAT\*

(((((#10 or #11) or #12) or #13) or #14) or #15) or #16) or #17) or #18)

(#9 not #19)

2. Letters requesting information from pharmaceutical companies who have combined low-dose estrogen OCs containing different progestogens were sent.

3. Informal contacts with researchers in the field were made to identify any trials.

The reports identified with the electronic search were checked initially for two characteristics:

1. Random allocation to comparison groups
2. Clinical outcomes reported

If these characteristics were not clear from the title or the abstract the full report was retrieved. Reports that have met above criteria were assessed for other inclusion criteria, methodological quality and validity of the data. Both application of inclusion criteria and the data extraction were made by the reviewers independently and differences were resolved by discussion.

#### **Types of studies**

Randomized controlled trials comparing low-dose estrogen (<50 mcg) combined oral contraceptive (OC) formulations were eligible. Cross-over studies were not considered. Trials had to include women of reproductive age, using OCs for contraception, irrespective of the duration of past OC use, or being new starters or switchers. Trials enrolling volunteers for biochemical change assessments or women receiving OCs for non-contraceptive purposes (such as acne vulgaris) were not eligible. Comparisons between same phasic dosages were eligible. A trial comparing a monophasic OC with a multiphasic OC was not eligible even if the progestogens were within the scope of the review.

Interventions had to be applied for a minimum of six months for a trial to be considered for inclusion.

In addition to the clinical outcomes, systematic data extraction was carried out for each trial for the following variables:

#### **Methodology**

Random allocation techniques, blinding, post-randomization exclusions and loss to follow-up (intention-to-treat). Trials were given a quality score for the concealment of allocation as described in: Mulrow CD, Oxman AD (eds). Cochrane Collaboration Handbook [updated 1

March 1997]. In: The Cochrane Library [database on disk and CD ROM]. The Cochrane Collaboration. Oxford: Update Software; 1996-. Updated quarterly.

#### **Demographic characteristics**

Type of health care setting, city, country, total number of women included, and inclusion and exclusion criteria. Information on funding for the study and potential conflicts of interest were extracted if reported.

We used relative risk (RR) to report measures of effect and the random effects model.

Trials were excluded if there were unexplained imbalances of loss to follow-up in numbers between the comparison groups.

Trials were searched for, regardless of their language.

When there was more than one time period reported for an outcome (e.g. pregnancy after six months, one year) the longest follow-up data were extracted. The rest of the data are discussed in the text if warranted.

For cycle related side effects, stratification according to the dose of estrogen used was performed when possible.

#### **Definitions**

Low-dose OC refers to the EE content of <50 mcg.

Regarding cycle disturbances: definitions are used as they were made by the individual authors of the trials.

#### **Results**

Twenty-two trials were included in the review.

#### **Description of studies**

The trials were conducted in many diverse settings and some were multicenter trials including centers from several countries (table 2). The participants were usually described as women seeking contraception excluding those with medical conditions not suitable for OC use. Some trials reported selected outcomes such as cycle control but not other components of acceptability [8,9]. Thirteen studies clearly stated the inclusion and exclusion criteria. Both starters and switchers were included. Only one study [10] mentions a washout period of one cycle amongst the switchers prior to starting the study medication. In the study by Rossmannith [8], 40% of the switchers received the same OC before as after the randomization. The Zichella [11] trial recruited only starters, defined as women who had not used hormonal contraception for three months prior to study. Eleven trials were conducted in Europe, six in the United States and Canada, two in

**Table 2: Included studies and quality assessment**

Study	Sponsorship	Intervention	Methods			
			Randomization	Allocation concealment	Blinding	Intention to treat analysis
Affinito [18]	Pharmaceutical company	GSD vs NGM	unclear	unclear	not	unclear
Droegemüller [8]	No information	LNG vs NE	unclear	unclear	not	yes
Dunson [12]	Family Health International	NG vs NE	unclear	adequate	not	not
Endrikat [19]	Pharmaceutical company	GSD vs DSG	unclear	unclear	not	yes
Endrikat [20]	Pharmaceutical company	LNG vs NE	unclear	unclear	not	yes
Foidart [26]	Pharmaceutical company	DSG vs DRSP	unclear	unclear	not	unclear
GSD group [13]	Pharmaceutical company	GSD vs DSG	unclear	unclear	not	yes
Halbe [29]	Pharmaceutical company	GSD vs DSG	unclear	unclear	not	yes
Huber [10]	Pharmaceutical company	DSG vs DRSP	unclear	unclear	not	yes
Koetsawang [28]	Pharmaceutical company	GSD vs DSG	unclear	unclear	not	unclear
L. America [27]	Pharmaceutical company	GSD vs DSG	block randomisation	unclear	not	yes
Loudon [17]	No information	GSD vs LNG	unclear	unclear	double blind	unclear
Percival [23]	Pharmaceutical company	NG vs NE	random list	unclear	investigator blind	unclear
Rabe [14]	Pharmaceutical company	GSD vs LNG	unclear	unclear	not	yes
Ramos [22]	Pharmaceutical company and UNFPA	LNG vs NE	unclear	unclear	double blind	yes
Reiter [21]	Planned Parenthood Centers	NG vs NE	unclear	unclear	not	unclear
Rossmann [9]	Pharmaceutical company	DSG vs NE	unclear	unclear	double blind	yes
Serfaty [16]	Pharmaceutical company	GSD vs DSG	block randomisation	unclear	not	unclear
Shoupe [15]	Pharmaceutical company	DSG vs NE	computer generated random number tables	adequate	double blind	unclear
Singh [24]	Pharmaceutical company	DSG vs NE	unclear	unclear	not	yes
Weber-Diehl [25]	Pharmaceutical company	GSD vs NE	unclear	unclear	not	unclear
Zichella [11]	Pharmaceutical company	GSD vs DSG	unclear	unclear	unclear	yes

Latin America and two in South East Asia. The study by Dunson [12] was set across all major continents.

**Pill composition and regimen**

Eighteen trials used OCs distributed as 28-day cycles with 21 active pills and 7 days of no tablet taking. One trial [13] distributed one OC as a 24-day formulation with all active pills compared to a 21-day cycle. Another trial used 28-day packages for both groups, with 21 active hormone tablets and 7 iron tablets for one group and 7 inactive tablets for the other group [12]. We were unable to find information on the duration of OC dosing used for two trials [9,14].

The day of pill start varied within and between studies to either a first-day start, first-Sunday start or fifth-day start. Thirteen trials had no information on the day of pill start. Shoupe used first-Sunday start for both OCs [15]. Day-1 start for both pill types was used in six trials [13,16-20]. First Sunday and day 1 start for the two OC formulations was used in one trial [21]. Fifth day start for both OC types was advocated in the study by Ramos [22].

**Sponsorship**

Eighteen out of 22 trials were supported by pharmaceutical companies, one trial was jointly supported by a pharmaceutical company and an international organization (UNFPA) [22], whereas 2 studies were supported or conducted by international organizations, NGOs or university departments [12,21]. There is no information on funding for 2 trials [8,17].

**Comparisons**

Twenty-two trials were included in the review. The order in which the comparisons are arranged is based on the type of formulation (monophasic or triphasic) and type of progestogen (newer progestogens versus older progestogens) following the criteria given by Henzl [1]. Trials were only included if the difference of the total ethinylestradiol content did not exceed 105 mcg. Sixteen trials compared monophasic OCs and 6 compared triphasic OCs [8,15,21,23-25]. Except for two trials using drospirenone [10,26] all other trials included progestogens categorised as first-, second- or third-generation. No trials included other progestogens such as ethynodiol diacetate,

lynestrenol, norethynodrel, cyproterone acetate and dienogest.

#### **Methodological quality of included studies**

Methodological quality assessment was based on random allocation technique used, blinding, post-randomization exclusions and loss to follow-up. Each criterion was rated as met, unmet or unclear (table 2).

#### *Concealment of allocation*

Allocation concealment was found to be adequate in one trial [12] using sealed, opaque, sequentially numbered envelopes.

#### *Blinding*

Four trials reported to use 'double-blinding' but there was no mentioning of how this was achieved [9,15,17,22].

All trials randomized individuals. Two trials [16,27] randomized individuals in groups of 4 and 12, respectively. Randomization technique was clearly stated in 2 trials [15,28]. Twelve trials used analysis by intention to treat. Endrikat [19] reported both intention-to-treat as well as valid case analysis. The type of analysis was unclear in two studies [18,28]. Post randomization exclusions were not mentioned in fifteen trials. Thirteen studies reported loss to follow-up.

Some trials reported data on cycle control by describing the events per cycles rather than per subjects, or the data were given in graphical form. For the purpose of the review we did not include these data in the review. Generally there appears to be conformity between studies in the definitions of various cycle disturbances.

All trials except three have follow-up confined to the course of the study with the final assessment at the end of the concluding study cycle. Foidart [26] continued with follow-up for three months post study, Huber [10] for six weeks and Singh [24] for thirteen months in the desogestrel/ethinylestradiol (CTR-05) arm.

Seven studies were conducted over a study duration of twelve months, of which two [12,20] reported 18 pregnancies in 2438 participants. Three studies were conducted over a duration of thirteen to twenty six months; 17 pregnancies were reported in 2998 subjects recruited into the two trials reporting on it [10,26].

#### **Comparisons and outcomes**

##### *Third- versus second-generation progestogens (see additional file 1)*

Two trials were included in this comparison, comparing monophasic gestodene (GSD) with monophasic levonorgestrel (LNG) combined with 30 mcg EE [14,17]. No pregnancies were reported in a total of 817 women fol-

lowed for six cycles. Fewer women had intermenstrual bleeding with gestodene in the one trial reporting on it (RR 0.71 95% CI 0.55 – 0.91) [17]. Overall, the results between the 2 groups were similar for the following outcomes: discontinuation (RR 0.66; 95% CI 0.41–1.05), overall side effects (RR 1.44; 95% CI 0.68–3.04), spotting (RR 1.11; 95% CI 0.76–1.61), breakthrough bleeding (RR 0.66; 95% CI 0.33–1.34) and absence of withdrawal bleeding (RR 0.78; 95% CI 0.38–1.59).

##### *Third- versus first-generation progestogens (see additional file 1)*

Two trials used triphasic OCs [15,24]; and one used a monophasic preparation [9] Overall, 976 women were included in this comparison. Except for the two pregnancies in women receiving norethindrone (NE) in the Shoupe trial no other pregnancies were observed [15]. The number of women who had side effects, breakthrough bleeding or discontinued was similar for the comparison groups, for mono- and multiphasic preparations.

##### *Second- versus first-generation progestogens (see additional file 1)*

Six trials compared levonorgestrel (LNG) or norgestrel (NG) to norethindrone (NE) or norethisterone (NE); three monophasic and three triphasic preparations [8,12,20-23]. The number of women included in this comparison is 2709 for the monophasic and 581 for the triphasic preparations. Pregnancies occurred in one of the 2 trials reporting on it [12] with more pregnancies occurring in the group receiving a first-generation progestogen (RR 0.12, 95% CI 0.02–0.99) over a follow-up period of one year. In the monophasic group, fewer women in the second-generation group discontinued (RR: 0.76; 95% CI 0.67–0.86). Reported side effects and the number of women who discontinued due to side effects were similar in both groups for monophasic preparations; no data on these outcomes were available for the multiphasic preparations. Cycle control appeared to be better with second generation progestogens for both, mono- and triphasic preparations (RR: 0.69; 95% CI 0.52–0.91) and (RR: 0.61; 95% CI 0.43–0.85), respectively.

Dunson [12] used iron tablets during the 7 days hormone free interval in one group. The data from this trial on side effects such as headaches, nausea/vomiting and dizziness were therefore not included in the meta-analysis.

##### *Comparisons of specific preparations*

##### *Gestodene versus norethindrone (triphasic)*

One trial [25] with 229 women was included in this comparison. Fewer women had spotting in the GSD group (RR 0.59; 95% CI 0.35–0.99). Discontinuation and breakthrough bleeding were similar in the 2 groups (RR 0.60; 95% CI 0.34–1.05 and RR 0.65; 95% CI 0.41–1.04). No other data relevant for the review could be extracted.

*Gestodene versus desogestrel (monophasic) (see additional file 1)*

This comparison has the largest number of studies (seven) and number of women ( $n = 5624$ ) included [11,13,16,19,27-29]. The two groups were similar for the following outcomes: number of pregnancies; women who discontinued side effects and side effects leading to discontinuation. More women in the GSD group discontinued due to non-cycle related side effects (RR 1.81; 95% CI 1.01–3.23). Regarding cycle control, trials were further stratified according to their estrogen dose. In one trial [13] the estrogen dose was 15 mcg in GSD and 20 mcg in the DSG group. The data for cycle disturbances from this trial were therefore not included in the meta-analysis.

*Gestodene versus norgestimate (monophasic) (see additional file 1)*

This comparison is based on the single study by Affinito [18], including 174 women. No pregnancies were reported in either group at six months of OC use. Discontinuation, reasons for discontinuation and overall side effects were similar.

*Desogestrel versus norethisterone (monophasic)*

There is one trial included in this comparison [9]. No pregnancies were reported in either group after 6 cycles in a total of 118 women. Overall reported side effects were similar in both groups.

*Desogestrel versus norethindrone (triphasic)*

Two trials, with a total number 858 women were included [15,24]. No pregnancies occurred with desogestrel (0/430) as compared to 2/428 in the group receiving norethindrone. Both were described as user failures. Similar results for side effects, discontinuation and cycle disturbances were reported for both groups.

*Levonorgestrel versus norethindrone (monophasic)*

This comparison includes 1834 women from 2 trials [20,22]. No pregnancies occurred in either group at twelve months of OC use. Fewer women using LNG discontinued (RR 0.75; 95% CI 0.64–0.87).

*Levonorgestrel versus norethindrone (triphasic)*

This comparison is based on a single trial [8], including 96 women. There are no data on contraceptive effectiveness. Fewer women had spotting (RR 0.44; 95% CI 0.20–0.97), breakthrough bleeding (RR 0.45; 95% CI 0.24–0.85) and intermenstrual bleeding (RR 0.53; 95% CI 0.34–0.84) in the levonorgestrel (LNG) group.

*Norgestrel versus norethindrone (monophasic)*

One trial with 875 women was included in this comparison [12].

More pregnancies occurred with norethindrone (NE) (RR 0.12, 95% CI: 0.02–0.99) at twelve months of OC use.

Cycle disturbances as a reason for discontinuation were less frequent in the NG group (RR 0.27, 95% CI 0.12–0.61). Intermenstrual bleeding (RR 0.69, 95% CI 0.52–0.91), absence of withdrawal bleeding (RR 0.29, 95% CI 0.16–0.54) and other menstrual complaints (RR 0.37, 95% CI 0.25–0.55) were less often reported in the NG group compared to NE. Side effects were similar for both groups.

*Norgestrel versus norethindrone (triphasic)*

Two trials with 485 women were included in this comparison [21,23]. No data on contraceptive effectiveness were reported. A similar number of women was satisfied with the treatment, reported intermenstrual bleeding and absence of withdrawal bleeding in both groups.

*Drospirenone versus desogestrel (see additional file 1)*

Of the 2 trials included in this comparison, one was conducted over twenty six months [26] and another over thirteen months [10]. The total number of women randomized was 2985. At thirteen months and at 26 months the pregnancy rate was similar in both groups. A similar number of women in both groups reported side effects and discontinued with the treatment.

## Discussion

The aim of this systematic review was to evaluate the acceptability of progestogens used in low-dose oral contraceptives. In designing the protocol for this review, we have assumed that acceptability indices can be adequately assessed by means of contraceptive effectiveness, cycle control, discontinuation rates and side effects.

## Effectiveness

A clinically relevant difference in effectiveness among the different progestogens was not observed. Generally, trials with a follow-up period of up to one year or longer showed a failure rate ranging from 0.2 to 1.8% [12].

## Continuation

The overall discontinuation rate amongst different trials varied from 8.2% [27] to 17.9% [16] for trials using monophasic pills and had a follow-up of 6 cycles; and from 25.5% [12] to 28.7% [20] for trials conducted over a follow-up period of 12 cycles. Second-generation progestogens had higher discontinuation rates compared to third- and lower compared to first-generation preparations; which may be the reflection of a similar pattern seen with cycle disturbances.

The association between cycle disturbances and continuation has been demonstrated before. Data from longitudinal studies suggest that most of the women discontinuing OCs in the first year of use do so within the first two months and new starters are more likely to discontinue

than switchers. Most of the women who discontinued did not want to fall pregnant but continued with less effective contraceptive methods [5]. Apart from a Chlamydia trachomatis infection, uterine/cervical abnormalities, smoking and missing pills, low estrogenic efficacy on the endometrium might have a causal relationship with prolonged spotting and breakthrough bleeding [30]. Is the estradiol dose the sole important factor or should we consider the estradiol dose in combination with the progestogen type? Each progestogen steroid differs in its estrogenic, progestogenic and androgenic properties [31]. Spotting was reported in about 30% of women using a combination pill with an EE content of less than 30 mcg, as compared to about 7.5% in women using a pill with 30 mcg EE, regardless of the progestogen (GSD or DSG) content. Therefore, variation in estrogenic potential among progestogens may explain some clinical phenomena such as spotting and breakthrough bleeding. We were interested in the efficacy of preventing spotting and breakthrough bleeding by the combination of the estrogen/progestogen components, thus the progestogen together with the dose of ethinylestradiol.

One trial included in this review [13] used EE 15 mcg in one and EE 20 mcg in the other group. There was a trend that more women in the 15 mcg group reported breakthrough bleeding (RR 1.67, 95% CI 1.00–2.95), which may be related to the lower EE dose in that group. We were not able to lump data on spotting and breakthrough bleeding per cycle since a woman can experience the spotting during several cycles, but also several events of spotting per cycle. Clustering of these data might overestimate the outcome and distort the results.

#### Limitations of the review

1) There is a shortage of appropriately powered and independently conducted randomized trials. The majority of the trials were supported in full or partially by pharmaceutical companies. The methods of allocation concealment are unclear in most studies. 2) There is little information in all trials on other indicators of acceptability such as libido or sexual satisfaction scores: only one trial measured women's satisfaction with the treatment [21]. 3) Effectiveness: Failure rate – measured as pregnancies – was a rare outcome in all trials reporting on it. Therefore, trials with adequate sample sizes are required to determine the superiority of one method over the other. The included trials in this review did not have large enough sample sizes to detect rare outcomes. 4) Application: Assessment of user or method failures was unlikely to be blinded and could be biased. Most studies define user failure as two or more missed pills in a cycle.

Also, the day of pill start, recruitment of both starters and switchers, use of a washout period for the switchers and

the OC type received by switchers, particularly in double blind trials, all influence cycle control data and contraceptive outcomes.

Unfortunately, most of these factors do not appear to have been taken into account in these trials.

#### Conclusions

With 22 trials included, the total number of women involved in most comparisons was less than 500 and the data on the outcome variables are limited.

The third- and second-generation progestogens are preferred to first-generation progestogens in all acceptability indices. On the basis of data from one trial, pills containing GSD may be associated with less intermenstrual bleeding than LNG pills, but with similar patterns of spotting, breakthrough bleeding and absence of withdrawal bleeds. GSD is also comparable to DSG in contraceptive effectiveness in the standard low dose formulation. DRSP is comparable to DSG.

We have not come across acceptably controlled randomized comparisons on other progestogens used (e.g. cyproterone acetate). The major question as to whether the third-generation progestogen offers an improvement in performance over other low dose COCs, is still unanswered. Future research should focus on independently conducted, well designed randomized controlled trials with standardized inclusion criteria and outcome variables, particularly comparing the third-generation with second-generation progestogens.

#### Competing interests

None declared.

#### Authors' contributions

NM, AMG, FH had the idea and wrote the review protocol. RK wrote the manuscript and conducted the analysis. All authors contributed to the data extraction and writing up of the review.

#### Additional material

##### Additional File 1

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