Progestogens in combined oral contraceptives for contraception (Review)

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ABSTRACT

Background
The progestogen component of oral contraceptives (OC) has undergone changes since it was first recognised that their chemical structures could influence the spectrum of minor adverse and beneficial effects. The major determinants of OCs are effectiveness, cycle control and common side effects. The rationale of this review is to provide a systematic comparison of OCs containing the progestogens currently in use worldwide.

Objectives
The objective of this review is to compare currently available low-dose OCs containing ethinyl estradiol and different progestogens in terms of contraceptive effectiveness, cycle control, side effects and continuation rates.

Search strategy
The Cochrane Controlled Trials Register, MEDLINE and EMBASE databases have been searched systematically. Relevant pharmaceutical companies and the authors of articles included in this review have been contacted for clarification.

Selection criteria
Randomised trials reporting clinical outcomes were considered for inclusion. We excluded studies comparing mono- with multiphasic pills, and crossover trials with trials in which the difference in total content of ethinyl estradiol between preparations exceeded 105 μg.

Data collection and analysis
The methodological quality and validity of studies were assessed based on the above-mentioned inclusion criteria. Both application of inclusion criteria and data extraction were performed independently by the reviewers. Results are expressed as relative risk (RR) with 95% confidence interval (CI) using a random-effects model.

Main results
Twenty-two trials have been included in this review, thus generating 14 comparisons. Eighteen trials were sponsored by pharmaceutical companies and in only 5 cases had a blind trial been attempted. Most comparisons between different interventions included 1-3 trials. There was less discontinuation with second- compared to first-generation progestogens (RR: 0.79, 95% CI: 0.69-0.91). Cycle control appears to be better when using second- compared to first-generation progestogens for both mono- (RR: 0.69; 95% CI: 0.52-0.91) and triphasic (RR: 0.61; 95% CI: 0.43-0.85) preparations.

Contraceptive effectiveness, spotting, breakthrough bleeding and the absence of withdrawal bleeding was similar when using GSD compared to LNG, although there was less intermenstrual bleeding in the GSD group (RR: 0.71, 95% CI: 0.55, 0.91). Drospirenone (DRSP) appeared to be similar to DSG.

Authors' conclusions
Based on data from one trial, compared to pills containing LNG, those containing GSD may be associated with less intermenstrual bleeding although they show similar patterns of spotting, breakthrough bleeding and the absence of withdrawal bleeds. GSD is also comparable to DSG. Regarding acceptability, all the indices show that third- and second-generation progestogens are preferred over

first-generation preparations. Future research should focus on independently conducted, well-designed randomised trials that compare third- and second-generation progestogens in particular.

PLAIN LANGUAGE SUMMARY

Combined oral contraceptives (COC) have an oestrogen and a progestogen component. The oestrogen dose has gradually been reduced to 30 μg or less in order to minimise side effects. However, nowadays the progestogen dose cannot be decreased since further reduction could allow an oocyte to be released from the ovary, thus causing pregnancy. Furthermore, progestogens can be divided into several groups: first, second and third generation. The effectiveness of oral contraceptives (prevention of pregnancy) is not only dependent upon the steroid dosage but may also be controlled by whether the pill is found to be acceptable. Breakthrough bleeding, spotting, or the absence of monthly bleeding (together called cycle control) are factors that predominantly determine whether women consider the pill acceptable, although other complaints are also involved.

The type of progestogen and/or amount of estrogen or progestogen can vary per blister pack of oral contraceptive pills. The objective of this review is to compare currently available low-dose COCs containing different progestogens in terms of pregnancy prevention, cycle control, side effects and continuation rates.

Twenty-two trials have been included in this review. Based on data from one trial, in comparison pills containing levonorgestrel (LNG), those containing gestodene (GSD) may be associated with less intermenstrual bleeding but show similar patterns of spotting, breakthrough bleeding and the absence of withdrawal bleeds. Regarding contraceptive effectiveness, pills containing GSD are also comparable to those containing desogestrel (DSG) in the standard 30 μg oestrogen dosage. However, more pregnancies occurred when pills containing 20 μg ethinyl estradiol were used. In contrast to pills containing DSG, those with GSD render better cycle control, although the continuation rate was higher in women using DSG pills. The characteristics of pills containing drospirenone (DRSP) are similar to those with DSG with regard to pregnancy prevention, cycle control and side effects.

Regarding acceptability, all the indices show that third- and second-generation (LNG) progestogens are preferred over first-generation pills containing norethisterone, norethindrone-, ethynodiol diacetate-, lynestrenol- or norethynodrel.

BACKGROUND

Combined oral contraceptives (COC) were first introduced for clinical use in the 1960s. Ethinyl estradiol (EE) was the most commonly used oestrogen component during this era. Its dose has been gradually reduced to 30 μg or less in order to decrease side effects and, in turn, increase acceptability.

It was thought that a similar goal could be reached by changing the biochemical structure rather than dosage of the progestogen component in the COC. However, now that the progestogen dosage cannot be decreased because further reduction might not prevent the LH surge and thus allow the process of ovulation to develop. Different progestogens can be classified according to their steroid structure as well as to the timing of their introduction into the market.

All contraceptive progestogens have a similar 4-ring steroid skeleton and can be categorised according to three tetracyclic structures:
-pregnanes (derived from the progesterone molecule),
-estranes (derivatives of testosterone), and
-gonanes (Henzl 2000).

Estranes correspond to first-generation progestogens, such as norethisterone (NE), norethindrone (NE), ethynodiol diacetate, lynestrenol (LYN) and norethynodrel as well as dienogest. Dienogest which is derived from NE is claimed to lack any androgenic activity and supposedly may affect glucocorticoids to a lesser extent than mifepristone (Henzl 2000).

Gonane progestogens can be divided into two categories: i.e., the second-generation progestogens levonorgestrel (LNG) and norgestrel (NG) and the 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 used in the very first OC, norethisterone (as it is known in Europe) or norethindrone (NE) can be considered the most important substance used during the early period of oral contraception. The first-generation progestogens norethynodrel, norethisterone acetate, and lynestrenol which are all metabolised to NE were nearly always combined with at least 50 μg EE. After the synthesis of norgestrel (NG) in 1963 by Hershel Smith (Smith 1963), the biologically active component levonorgestrel (LNG) was isolated (Lachnit-Fixon 1991). These

second-generation progestogens were introduced into 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 third-generation progestogens (DSG, GSD and 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. Progestogens left unclassified according to generation are CPA (listed in the pregnane classification, not introduced into the US market) and drospirenone (DRSP), a recently introduced progestogen derived from 17-a spironolactone that might possess antimineralocorticoid and mild anti-androgenic activity.

OBJECTIVES

The objective of this review is to compare the various low-dose OCs currently available which contain different progestogens and to assess their acceptability according to the following indicators:

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

(1) Effectiveness as contraceptive:
The failure rate for COCs varies according to age, race and marital status in typical OC users. 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 (Hillard 1992).

(2/3) Discontinuation rates:
The rates and reasons for discontinuation related to the method which may cause unintended pregnancy are relevant to this review.

(4) Cycle control:
Whether a woman chooses to use a hormonal contraceptive method depends largely on the degree of cycle control and its side effects (Rosenberg 1999). In fact, a diminishing compliance due to poor cycle control will also affect the method's effectiveness. To date, large controlled trials comparing new with older progestogens have not been performed, and lack of standardisation during reporting and analysis of intermenstrual bleeding patterns prevents a meaningful comparison new compounds between studies (Speroff 1993).

(5) Side effects:
The common side effects associated with OC use are breast tenderness, headache, migraine, nausea, nervousness, vomiting, dizziness, weight gain, tiredness, decline of libido and an increase in blood pressure. This is due to the effects of estrogen, progestogen or androgen. However, it is not always possible to attribute a side effect to the estrogen or progestogen component. Some of these side effects decrease after few months use (ACOG 1995).

Some rare adverse events may be caused by both the estrogen and progestogen components of COCs which are believed to be responsible for cardiovascular events associated with OC use. Venous events have traditionally been associated with the estrogen component. The relationship between acute myocardial infarction, stroke and venous thromboembolism with OC use has been studied extensively, generating considerable controversy. However, because comparison of rare long-term adverse events is not amenable to studies using randomised controlled trials, such events are not the focus of this review and will not be discussed further.

CRITERIA FOR CONSIDERING STUDIES FOR THIS REVIEW

Types of studies

All relevant and acceptably controlled randomised trials comparing low-dose estrogen (< 50 mg) combined oral contraceptive (COC) compounds were considered eligible. The unit of randomisation in these trials is the individual woman. Crossover studies have not been included.

Types of participants

Participants are women of reproductive age irrespective of the duration of past OC use, or being new starters or switchers seeking contraception. Trials enrolling volunteers for biochemical change assessments or women for whom were prescribed OCs for non-contraceptive purposes (such as acne vulgaris) were not eligible.

Types of intervention

Only comparisons between the same phasic dosages are eligible. Trials comparing monophasic with multiphasic OCs are not eligible even if the progestogens fall within the scope of this review.

Interventions have to be applied for a minimum of 6 months before a trial is considered for inclusion.

Interventions are grouped as follows:

1. Any monophasic low-dose estrogen (<50 µg) COC containing a third-generation progestogen versus any monophasic low-dose oestrogen COC containing a second-generation progestogen (same for multiphasic preparations);

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

3. Any monophasic low-dose oestrogen COC containing a second-generation progestogen versus any monophasic low-dose oestrogen COC containing a first-generation progestogen (same for multiphasic preparations); and

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

Types of outcome measures

To be eligible, trials had to report clinical outcomes. Trials focusing only on biochemical changes were not eligible for this review. The primary outcome of interest in this review is acceptability. Indicators of acceptability are listed below as outcomes for this review. For contraceptive effectiveness (incidence of pregnancy) we used authors' definitions and did not differentiate between method and user failure.

1. Contraceptive effectiveness
- Incidence of pregnancy (within 6 months; within 1 year; overall)

2. Discontinuation rates and reasons for discontinuation
- Number of women discontinued within 6 months
- Number of women discontinued within 1 year
- Discontinued due to side effects (discontinuation due to specific side effects are recorded if reported)
- Discontinued due to cycle disturbances
- Discontinued due to the physician's recommendation

3. Cycle control: changes in cycle patterns are analysed separately from side effects, according to the type of change, if possible.
- Number of women with spotting or breakthrough bleeding (as defined by the trialists) within 6 months
- Number of women with spotting or breakthrough bleeding (as defined by the trialists) within 1 year
- Number of women with amenorrhoea (lack of withdrawal bleeding) within 6 months
- Number of women with amenorrhoea (lack of withdrawal bleeding) within 1 year

4. Side effects (reported during the course of the study but not necessarily causing discontinuation)
- Any side effect
- Breast tenderness
- Headache
- Migraine
- Nausea/vomiting
- Nervousness
- Dizziness
- Varicose veins
- Acne vulgaris
- Chloasma
- Edema
- Weight gain/weight loss

5. Women's satisfaction with the method

SEARCH METHODS FOR IDENTIFICATION OF STUDIES

See: methods used in reviews.

1. Cochrane Controlled Trials Register with the following search strategy:
CONTRACEPTIVES-ORAL*:ME
LEVONORGESTREL
NORETHISTERONE
norethyndrone
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 were sent requesting information from pharmaceutical companies which have combined low-dose estrogen OCs containing different progestogens.

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

METHODS OF THE REVIEW

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 either the title or abstract, the full report was retrieved. Reports that met the above-mentioned criteria were fully assessed for other inclusion criteria, methodological quality and data validity. Both application of inclusion criteria and data extraction were made independently by two reviewers, and differences were resolved by discussion and consultation with other reviewers if necessary.

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

- Methodology: Random allocation techniques, blinding, post-randomisation 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.

- We used relative risk (RR) to report measures of effect and the random-effects model. Because of the low baseline level, RR and Odds ratio (OR) were found to be very similar for all outcomes.
- 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.
- Trials were excluded if there were unexplained imbalances for 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 6 months, 1 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 oestrogen used was performed when possible.

Definitions:
Low-dose OC is referred to the EE content of <50 μg.
Regarding cycle disturbances: definitions are used as they have been given by the individual authors of the trials.

DESCRIPTION OF STUDIES

The trials were conducted in many diverse settings and some were multicenter trials including several countries. The participants were usually described as being women seeking contraception; those with medical conditions not suitable for OC use were excluded. Some trials reported selected outcomes such as cycle control but not other components of acceptability (Droegemüller (LNG-NE, Reiter (NG-NE); Rossmanith (DSG-NE).

Type of health-care setting, city, country, total number of women enrolled, inclusion and exclusion criteria were assessed. Most studies (except for 9) had clearly stated inclusion and exclusion criteria. Both starters and switchers were included. Only one study (Huber (DSG-DRSP)) mentions a washout period of one cycle amongst the switchers prior to starting the study medication. In the study by Rossmanith (DSG-NE), 40% of the switchers received the same OC that had been prescribed before due to double blinding and randomisation. The Zichella (GSD-DSG) trial only recruited starters defined as women who had not used hormonal contraception for 3 months prior to the study.

Eleven trials were conducted in Europe, six in the United States and Canada, two in Latin America and two in South East Asia. The study by Dunson (NG-NE) was set across all major continents.

PILL COMPOSITION & REGIMEN:
Eighteen trials used OCs distributed as 28-day cycles with 21 active pills and 7 days of no tablet taking. One trial (GSD Group (GSD-DSG)) distributed one OC as a 24-day preparation 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 inactive tablets for the other group (Dunson NG-NE). We have been unable to find information on the duration of OC dosing used for two trials (Rabe (GSD-LNG); Rossmanith (DSG-NE)).

The day for starting the pill varied within and between studies to either a first-day start, first-Sunday start or fifth-day start. Thirteen trials had no information about which day the pill was started. The Shoupe study used a first-Sunday start for both OCs (Shoupe (DSG-NE). Day-1 start for both pill types was used in 6 trials (Serfaty (GSD-DSG); Loudon (GSD-LNG); GSD Group (GSD-DSG); Affinito (GSD-NGM); Endrikat (GSD-DSG), Endrikat (LNG-NE)). First-Sunday and day-1 start for two OC preparations was used in one trial (Reiter (NG-NE)). Fifth-day start for both OC types was recommended in the study by Ramos (LNG-NE).

SPONSORSHIP
Eighteen out of 22 trials were supported by pharmaceutical companies, one trial (Ramos (LNG-NE)) was jointly supported by a pharmaceutical company and an international organization (UNFPA), whereas two studies (Dunson (NG-NE); Reiter (NG-NE)) were
supported or conducted by international organizations (WHO), NGOs or university departments. There is no information about funding for two trials (Droegemüller (LNG-NE), Loudon (GSD-LNG)).

COMPARISONS
Twenty-two trials have been included in this review. The order in which the comparisons are arranged is based on the type of preparation (monophasic or triphasic) and the type of progestogen (newer vs. older progestogens) as per the criteria given by Henzl (Henzl 2000). Trials were only included if the difference in the total content of ethinyl estradiol did not exceed 105 μg.

Sixteen trials compared monophasic OCs and six (Droegemüller (LNG-NE; Percival (NG-NE); Reiter (NG-NE); Shoupe (DSG-NE); Singh (DSG-NE), Weber-Diehl (GSD-NE)) compared triphasic OCs. Except for two trials using drospirenone (Foidart (DSG-DRSP); Huber (DSG-DRSP)) 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.

EXCLUDED TRIALS
See table of excluded studies.

METHODOLOGICAL QUALITY

The methodological quality of trials was assessed based on the random allocation technique used, blinding, post-randomisation exclusions and loss to follow up. Each criterion was rated as met, unmet or unclear, and decisions were made by consensus between the reviewers.

Concealment of allocation: Allocation concealment was found to be adequate in one trial (Dunson (NG-NE) using sealed, opaque, sequentially numbered envelopes.

Blinding: Four trials are reported to be 'double-blinded' but there is no mention of how this was achieved (Loudon (GSD-LNG); Ramos (LNG-NE); Rossmanith (DSG-NE); Shoupe (DSG-NE)).

All trials randomised individuals. The Serfaty (GSD-DSG) and L. America (GSD-DSG) trials randomised individuals in groups of 4 and 12, respectively. Randomisation technique was clearly stated in two trials (Koetsawang (GSD-DSG); Shoupe (DSG-NE)). Twelve trials used analysis by intention to treat. Endrikat (GSD-DSG) reported both intention to treat as well as valid case analysis. The type of analysis was unclear in two studies (Affinito (GSD-NGM); Koetsawang (GSD-DSG)). There were no post-randomisation exclusions reported in 15 trials. Thirteen studies have clearly stated data on loss to follow-up.

Some trials reported data on cycle control in terms of cycles rather than subjects, or the data were given graphically. For the purpose of this review, we have entered the data on cycle control only where it has been given as subject numbers and excluded data when reported as number of cycles. Generally there appears to be conformity between studies in the definitions of various cycle disturbances.

All but three trials have follow-up confined to the course of the study with the final assessment at the end of the concluding study cycle. Foidart (DSG-DRSP) continued with follow-up for 3 months post-study, Huber (DSG-DRSP) for 6 weeks and Singh (DSG-NE) for 13 months in the desogestrel/ethinyl estradiol (CTR-05) arm.

Seven studies were conducted over a duration of 12 months, of which two (Dunson (NG-NE); Endrikat (GSD-DSG)) reported 18 pregnancies in 2438 participants (0.73%). Three studies were conducted over a period of 13-26 months; 17 pregnancies were reported in 2998 subjects recruited into two trials reporting on it (Huber (DSG-DRSP); Foidart (DSG-DRSP)).

Further details on the methodological quality of individual studies is given in the notes section of the characteristics of included studies.

RESULTS

Twenty -two trials were included in this review.

01. THIRD- VS. SECOND-GENERATION PROGESTOGENS

Two trials have been included which compare monophasic gestodene (GSD) with monophasic levonorgestrel (LNG) combined with 30 µg EE (Loudon (GSD-LNG); Rabe (GSD-LNG)) [see also 04]. No pregnancies were reported within a total of 817 women followed for 6 cycles. Overall, the results between the two groups regarding reasons for discontinuation, overall side effects, spotting, breakthrough bleeding and the absence of withdrawal bleeding were similar. Fewer women had intermenstrual bleeding when using GSD in the one trial reporting on it (Loudon GSD-LNG) (RR 0.71 95% CI 0.55-0.91).

02. THIRD- VS. FIRST-GENERATION PROGESTOGENS

Two trials used triphasic OCs (Shoupe (DSG-NE); Singh (DSG-NE) [see also 09]; one trial used a monophasic preparation (Rossmanith (DSG-NE)) [see also 08]. Overall, 976 women were included in this comparison. Except for two pregnancies in women receiving norethindrone (NE) in the Shoupe (DSG-NE) trial, no other pregnancies were observed. The number of women who had side effects, breakthrough bleeding or discontinued usage was similar for the comparison groups, for mono- and multiphasic preparations.

03. SECOND- VS. FIRST-GENERATION PROGESTOGENS

Six trials compared levonorgestrel (LNG) or norgestrel (NG) to norethindrone (NE) or norethisterone (NE): monophasic LNG vs. NE [see also 10], monophasic NG vs NE [see also 12], triphasic LNG vs. NE [see also 11] and triphasic NG vs. NE [see also 13]. 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 two trials reporting on it (Dunson (NG-NE)) with more pregnancies occurring in the group receiving first-generation progestogen (RR 0.12, 95% CI: 0.02-0.99) over a follow-up period of 1 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. Dunson (Dunson NG-NE) used iron tablets during the 7-day 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. Cycle control appeared to be better when using second-generation progestogens for both mono- (RR: 0.69; 95% CI: 0.52-0.91) and triphasic (RR: 0.61; 95% CI: 0.43-0.85) preparations.

04. GESTODENE VS. LEVONORGESTREL (MONOPHASIC)

See above-mentioned third- vs. second-generation comparison (01).

05. GESTODENE VS. NORETHINDRONE (TRIPHASIC)

One trial (229 women) was included in this comparison. Fewer women had spotting in the GSD group (RR 0.59; 95%CI 0.35-0.99).

06. GESTODENE VS. DESOGESTREL (MONOPHASIC)
This comparison has the largest number of studies (7) and number of women (5624) included. The number of pregnancies, women who discontinued, side effects and side effects leading to discontinuation were similar in the two groups. 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 (GSD Group (GSD-DSG)) the estrogen dose was 15 µg in GSD and 20 µg in the DSG group. The data for cycle disturbances from this trial were therefore not included in the meta-analysis.

07. GESTODENE VS. NORGESTIMATE (MONOPHASIC)
This comparison is based on the single study by Affinito (GSD-NGM), including 174 women. No pregnancies were reported in either group after 6 months of OC use. Discontinuation, reasons for discontinuation and overall side effects were similar.

08. DESOGESTREL VS. NORETHISTERONE (MONOPHASIC)
There is one trial included in this comparison (Rossmanith (DSG-NE)). 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.

09. DESOGESTREL VS. NORETHINDRONE (TRIPHASIC)
Two trials, with a total number 858 women were included (Singh (DSG-NE); Shoupe (DSG-NE)). No pregnancies occurred with desogestrel (0/430) 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.

10. LEVONORGESTREL VS. NORETHINDRONE(MONOPHASIC)
This comparison includes 1834 women from two trials (Ramos (LNG-NE), Endrikat (LNG-NE)). No pregnancies occurred in either group at 12 months of OC use. Fewer women using LNG discontinued (RR: 0.75; 95% CI: 0.64-0.87).

11. LEVONORGESTREL VS. NORETHINDRONE (TRIPHASIC)
This comparison is based on a single trial (Droegemüller (LNG-NE), 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.

12. NORGESTREL VS. NORETHINDRONE (MONOPHASIC)
One trial with 875 women was included in this comparison (Dunson (NG-NE)). More pregnancies occurred with norethindrone (NE) (RR 0.12, 95% CI: 0.02-0.99) at 12 months of OC use. Cycle disturbances as a reason for discontinuation was 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 reported less frequently in the NG group compared to NE. Side effects were similar in both groups.

13. NORGESTREL VS. NORETHINDRONE (TRIPHASIC)
Two trials with 485 women were included in this comparison (Reiter (NG-NE); Percival (NG-NE)). No data on contraceptive effectiveness were reported. A similar number of women was satisfied with the treatment, reported intermenstrual bleeding and the absence of withdrawal bleeding in both groups.

14. DROSPIRENONE VS. DESOGESTREL
Of the two trials included in this comparison, one was conducted over a period of 26 months (Foidart (DSG-DRSP) and the other over 13 months (Huber (DSG-DRSP). The total number of women randomised was 2985. At 13 and at 26 months, the pregnancy rates were 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 review was to evaluate the acceptability of progestogens used in low-dose oral contraceptives.

Effectiveness:
A clinically relevant difference in effectiveness among the different progestogens was not observed. Generally, trials with a follow-up period of up to 1 year or longer showed a failure rate ranging from 0.2 to 1.8%.

Continuation:
The association between cycle disturbances and continuation has been previously demonstrated. Data from longitudinal studies suggest that most women who discontinue OCs during the first year of use do so within the first 2 months, and new starters are more likely to discontinue than switchers. Most of the women who discontinued did not want to become pregnant and continued using less effective contraceptive methods (Rosenberg 1999).

Apart from a Chlamydia trachomatis infection, uterine/cervical abnormalities, smoking and missing pills, low oestrogenic efficacy on the endometrium might have a causal relationship with prolonged spotting and breakthrough bleeding (Thorneycroft 1999). Should the oestradiol dosage be considered the sole important factor or should it be considered in combination with the type of progestogen? Each progestogen steroid differs in its oestrogenic, progestogenic and androgenic properties (Speroff 2001) and thus variation in oestrogenic potential among progestogens may explain some clinical phenomena such as spotting and breakthrough bleeding. Therefore we were interested in the efficacy of prevent-

ing spotting and breakthrough bleeding by considering the combination of oestrogen/progestogen components, thus progestogen together with the ethinyl estradiol dosage. One trial included in this review (GSD Group (GSD-DSG)) used 15 µg EE and 20 µg EE in the two groups. A trend showed that more women in the 15 µg group reported breakthrough bleeding (RR 1.67, 95% CI 1.00-2.95) which may be related to the lower dosage of EE in that group.

The overall discontinuation rate amongst the different trials varied from 8.2% (L. America GSD-DSG) to 17.9% (Serfaty GSD-DSG) for trials using monophasic pills and had a follow-up of 6 cycles and from 25.5% (Dunson NG-NE) to 28.7% (Endrikat LNG-NE) for trials conducted over a follow-up period of 12 cycles.

Use of second-generation progestogens showed higher discontinuation rates compared to third-generation and lower rates compared to first-generation preparations which may reflect a similar pattern seen with cycle disturbances.

Shortcomings:
We were not able to lump together data on spotting and breakthrough bleeding per cycle since a woman can experience spotting during several cycles, but also several events of spotting per cycle. Clustering of such data might overestimate the outcome and distort results.

Shortcomings of the review:

(1) We realised that there is a shortage of properly sized and independently conducted randomised trials, 19 out of 22 being supported in full or partially by pharmaceutical companies. The methods of randomisation are unclear in most studies. In all the trials, there is little information on other indicators of acceptability such as libido, sexual performance, satisfaction scores: only one trial measured women's satisfaction with the treatment (Reiter NG-NE). In designing the protocol for this review, we have assumed (perhaps erroneously?) that acceptability indices can be adequately assessed by means of contraceptive efficacy, cycle control, discontinuation rates and side effects. Further research using well-designed randomised trials with standardised definitions and outcomes is needed. The major question as to whether third-generation progestogen offers an improvement in performance over other low-dose COCs is still unanswered.

(2) Effectiveness: Failure rate - measured as pregnancies - was a rare outcome in all trials reporting it. Therefore, trials using adequate sample sizes are required to determine the superiority of one method over the other. The trials included in this review did not have large enough sample sizes to detect rare outcomes.

(3) Application: Assessment of user or method failures was unlikely to be blinded and could be biased. Most studies defined user failure as two or more missed pills during one cycle. Also, the day on which the pill was started, recruitment of both starters and switchers, use of a washout period for the switchers, and the type of OC received by switchers, particularly in double-blind trials, all influence cycle control data and contraceptive outcomes. Unfortunately, it appears that most of these factors were not taken into account in these trials.

AUTHORS' CONCLUSIONS

Implications for practice

Current evidence suggests that GSD is comparable to LNG in terms of contraceptive effectiveness, spotting, breakthrough bleeding and the absence of withdrawal bleeding, but may be associated with less intermenstrual bleeding. GSD is also comparable to DSG in contraceptive effectiveness in the standard low-dose formulation. All acceptability indices indicate that third- and second-generation progestogens are preferred to norethisterone acetate, norethindrone acetate and norethindrone. DRSP is similar to DSG.

Implications for research

With 14 comparisons from 22 included trials, the total number of women included in most comparisons was less than 500 and the data on the outcome variables are limited. We have not come across acceptably controlled randomised comparisons on other progestogens used (e.g., cyproterone acetate).

Future research should focus on independently conducted, well-designed randomised controlled trials with standardised inclusion criteria and outcome variables, particularly comparing third- with second-generation progestogens.

POTENTIAL CONFLICT OF INTEREST

None known.

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* *Indicates the major publication for the study*

TABLES

Characteristics of included studies

Study	**Affinito (GSD-NGM)**
Methods	Randomized trial. Total enrolled 189, no exclusions. Intention to treat analysis not clear. No blinding.
Participants	189 women in the age group 16 to 38 using standard inclusion criteria, history of at least 3 regular cycles, if smokers then less than 35 years. Study location: Italy. Setting not mentioned. Exclusion criteria: excessive alcohol consumption, PAP smear > grade 3, SBP > 140 mm Hg, DBP > 90, drug abuse, abnormal blood tests. Work-up at admission included gynecological history, breast and cervical smear examination, medical and gynecological examination.
Interventions	A) Monophasic gestodene 75 mcg+ EE 30 mcg versus B) monophasic norgestimate 250 mcg+ EE 35 mcg. Duration of study: 6 cycles.
Outcomes	Contraceptive effectiveness, discontinuation rate and reasons for discontinuation, cycle control analysis overall side-effects.
Notes	Sponsored by WYETH-AYERST laboratories. Cycle control analysis is not includede in the review as it usese^the number of cycles in the denominator.
Allocation concealment	B – Unclear

Study	**Droegemüller (LNG-NE**
Methods	Randomized multicentre open label study on 157 subjects with three triphasic OCs. Technique of allocation concealment unclear. Analysis by intention to treat.
Participants	157 women in outpatient setting were randomized to three groups. Age group, inclusion and exclusion criteria are not mentioned. It is not clear how many of these subjects were starters or switchers and which day the pill was started.
Interventions	A) triphasic LNG 50/75/125 +EE 30/40/30 (Trilevlen) versus B) triphasic norethindrone 500/1000/500 +EE35 mcg (Trinorinyl) versus C) triphasic norethindrone 500/750/1000 + EE 35 mcg (OrthoNovum7/7/7). Both formulations were given in 28 day packs with 21 active tablets and 7 placebos. Study duration 6 months.
Outcomes	Study mentions only cycle control analysis. There is no information on contraceptive effectiveness, discontinuation rate and side effects.
Notes	
Allocation concealment	B – Unclear

Study	**Dunson (NG-NE)**
Methods	Randomisation by use of pre- printed sealed envelopes . No blinding. Analysis not by intention to treat. There were no post randomisation exclusions.
Participants	892 women 18-35 years age group, in good health, desiring to use OCs, > 42 days post-partum, no known contraindications to OC use, if breast feeding, then at least >4 months post-partum, at least one normal period since termination of pregnancy. 42% had past history of OC use. The study was conducted across various centres in Malaysia, Egypt, Thailand and Mexico.
Interventions	A) Monophasic norgestrel 0.3 mg/EE 30 mcg (Lo-femenal) vs B) monophasic norethindrone acetate 1.5 mg/ EE 30 mcg (Lo-estrin).
Outcomes	Contraceptive effectiveness, discontinuation rate and reasons for discontinuation

Characteristics of included studies (*Continued*)

	cycle control analysis overall side-effects.
Notes	User failure defined as missing 2 or more pills. In norgestrel group, 4 pregnancies due to method failure, 4 due to user failure. In norethindrone group pregnancy was due to user failure. Trial organised by FHI
Allocation concealment	A – Adequate

Study	**Endrikat (GSD-DSG)**
Methods	Randomized trial, no blinding; allocation concealment unclear. Analysis both by intention to treat and valid case analysis. 1,563 enrolled and 87 excluded for protocol violations therefore not included in efficacy analysis.
Participants	1,563 women age group 18 to 35 years willing for contraception for at least 12 months. Conducted in 123 centres across 6 European countries. 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.
Interventions	A) Monophasic gestodene 75 mcg+EE20 mcg versus B) monophasic desogestrel 150 mcg+EE20 mcg; studied over 12 cycles of treatment.
Outcomes	Contraceptive effectiveness, discontinuation rate, cycle control analysis and side-effects.
Notes	Supported by SCHERING AG.
Allocation concealment	B – Unclear

Study	**Endrikat (LNG-NE)**
Methods	Multicentre randomized trial; no blinding was used; intention to treat analysis 3 arms - 2 arms included in the review
Participants	767 women between 18 and 35 years; exclusion criteria: use of depot contraception 6 months before study begin, concurrent diseases, contraindications for oral contraceptives, unexplained vaginal bleeding, menstruation associated with migraine
Interventions	A) Monophasic levonorgestrel 100 mcg+EE 20 mcg B) Monophasic norethisterone 500 mcg+EE 20 mcg
Outcomes	Discontinuation rate, side effects
Notes	Sponsored by SCHERING AG.
Allocation concealment	B – Unclear

Study	**Foidart (DSG-DRSP)**
Methods	Randomized open label multicentre trial across 26 study centres. Allocation concealment unclear. Analysis was not by intention to treat. There were 13 post randomisation exclusions.
Participants	900 women between 18 to 35 years, healthy, menstruating and seeking OC use. Both starters and switchers were included. Women were recruited from outpatient clinics across 26 centres in Europe (Belgium, Germany, NL). Exclusion Criteria: obesity, liver, vascular and metabolic disease, genital infection, use of diuretics or drugs known to affect hepatic enzymes. Regular follow-up during study and for 3 months after completion.
Interventions	A) Monophasic drospirenone 3 mg+EE30 mcg (Yasmin) versus B) monophasic desogestrel 150 mcg +EE30 mcg for 21 days days over 26 months.
Outcomes	Contraceptive effectiveness, cycle control, discontinuation rate and overall side effects.

Characteristics of included studies (*Continued*)

Notes	Cycle control is given in terms of cycles rather than subjects and has therefore not been included. Study supported by SCHERING
Allocation concealment	B – Unclear

Study	**GSD Group (GSD-DSG)**
Methods	Multicentre open label randomized trial on 1074 women. Allocation concealment is unclear. There were no post randomisation exclusions. Analysis was by intent to treat.
Participants	1074 women aged >18 years, healthy, menstruating regularly and not breast feeding were enrolled from 61 centers in Europe. 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. There is no mention of a washout period. Work up at admission involved medical, obstetric and gynae. history and examination, and pap smear testing.
Interventions	A) Monophasic gestodene 60 mcg/EE15 mcg given for 24 days versus B) monophasic desogestrel 150 mcg/ EE20 mcg (Mercilon) given for 21 days. Both pill types were started on day 1 of menses. Study duration 6 cycles.
Outcomes	Contraceptive effectiveness, cycle control, discontinuation rate and reasons, side effects.
Notes	Supported by WYETH AYERST. Cycle control for spotting and breakthrough bleeding is given in terms of cycles.
Allocation concealment	B – Unclear

Study	**Halbe (GSD-DSG)**
Methods	Randomized trial on 595 women over 6 cycles of OC use. Technique of allocation concealment is unclear. Analysis by intention to treat.
Participants	595 women at reproductive age and with regular menstrual cycles. Multicentre trial across centres in Brazil. Study setting is not mentioned. 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. Work-up at admission included detailed medical history and examination. Follow up was at 1, 3 and 6 cycles. No details available on day of starting the pill. No period of washout was given for the switchers.
Interventions	A) Monophasic desogestrel 150 mcg+EE 30 mcg vs B) monophasic gestodene 75 mcg+EE30 mcg given for 6 cycles.
Outcomes	Contraceptive effectiveness, cycle control and discontinuation rate, reasons for discontinuation.
Notes	Supported by Organon NV. 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.
Allocation concealment	B – Unclear

Study	**Huber (DSG-DRSP)**
Methods	Randomized open label multicentre trial. Allocation concealment unclear. There were 29 post randomisation exclusions. Analysis was by intention to treat.
Participants	2098 women aged 18 to 35 years were enrolled from 80 centres across 8 countries in Europe. Both starters and switchers were included with switchers being given one cycle of wash out. Exclusion criteria: pregnancy, lactation, liver disease, metabolic or vascular diseases, tumors, genital infections, drug/alcohol abuse, on medication such as diuretics or those causing interaction with OCs. Work up at admission included physical and gynaecological examination, cervical smear and general blood tests. The follow up was at 2 or 3, 6, 9 13 cycles and 6 weeks.

Characteristics of included studies (*Continued*)

Interventions	A) Monophasic drosperinone 3 mg/EE30 mcg (Yasmin) versus B) monophasic desogestrel 150 mcg/EE30 mcg (Marvelon) over 13 cycles. 1680 women were given drosperinone and 418 were given desogestrel containing OC. Pills were given in 28 day packs. There is no information on day of pill start.
Outcomes	Contraceptive effectiveness, cycle control, BP, body weight, side effects.
Notes	Supported by SCHERING AG.
Allocation concealment	B – Unclear

Study	**Koetsawang (GSD-DSG)**
Methods	Randomized trial; no post-randomization exclusions. Intention to treat analysis not clear. Allocation concealment unclear. No blinding.
Participants	783 women with mean age of 26 years, healthy women with regular menstrual cycles of at least 24 days. Study conducted across Family Health centres in Thailand. Exclusion criteria: known contraindications to OC use, use of medication and currently breast feeding. Work up included detailed medical history and physical exam. Follow-up at 1,3 and 6 cycles.
Interventions	A) Monophasic desogestrel 150 mcg+EE 30 mcg versus B) monophasic gestodene 75 mcg+EE 30 mcg. Duration of study 6 cycles.
Outcomes	Contraceptive effectiveness, discontinuation and reasons for discontinuation, cycle control, side-effects.
Notes	This study was sponsored by ORGANON.
Allocation concealment	B – Unclear

Study	**L. America (GSD-DSG)**
Methods	Randomized trial, allocation concealment unclear. Randomized in blocks of 12, analysis was by intention to treat. No post randomisation exclusions.
Participants	352 women 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. Location: Argentina, Brazil, Chile, Columbia, Venezuela. Exclusion criteria: women with thrombo-embolic disease, liver disease, estrogen dependant neoplasia, disorders of lipid metabolism, other known contraindication to OCs.
Interventions	A) monophasic gestodene 75mcg / EE 30 mcg vs B) monophasic desogestrel 150mcg/ EE 30 mcg. Follow-up at 6 months, check BP and weight at 3 and 6 cycles of treatment. Also 20 women randomly selected for laboratory tests. Study duration 6 cycles.
Outcomes	effectiveness, discontinuation rate and reasons for discontinuation cycle control, side effects and side-effects leading to discontinuation.
Notes	The study was supported by grants from WYETH-AYERST. Some of the side-effects have been mentioned in graphical format (figure 3) and these have not been included in the analysis.
Allocation concealment	B – Unclear

Study	**Loudon (GSD-LNG)**
Methods	Randomized double blind trial, 456 were randomised, 31 post randomization exclusions. Analysis was not by intention to treat.
Participants	Women 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.

Characteristics of included studies (*Continued*)

	Exclusion criteria: women less than 16 years, DBP > 90 mm amenorrhea, medical contraindications to OC use. This study was conducted in Family Planning centres in the UK.
Interventions	A) Monophasic gestodene 75mcg / EE 30mcg (Femodene) vs B) monophasic levonorgestrel 150mcg /EE 30mcg (Microgynon). Study duration 6 cycles.
Outcomes	Contraceptive effectiveness discontinuation rate and reasons for discontinuation, cycle control, side-effects.
Notes	
Allocation concealment	B – Unclear

Study	**Percival (NG-NE)**
Methods	Randomized trial on 469 women. Randomization was based on randomized code list provided by Parke-Davis. Allocation concealment adequate. Analysis not by intention to treat. Intervention giver was blinded to the medication given.
Participants	469 women in the age group 15 to 35 years, menstruating regularly for at least 2 months prior to enrollment and with no known contraindication to OC use. Classified into prestudy users and nonusers. 53% were non-users. Study conducted across 4 University centres in Canada. Exclusion criteria not clearly elucidated.
Interventions	A) triphasic Norgestrel 0.1/.15/25+EE 30/40/30 (Triphasil) vs B) triphasic Norethindrone500/750/1000+ EE 35mcg (Ortho7/7/7) over a duration of 6 cycles. Work-up at admission included a history and physical exam. Follow-up was at 3 and 6 months.
Outcomes	Discontinuation rate, reasons for discontinuation, cycle control, side-effects Intermenstrual bleeding recorded as cycles and not subjects.
Notes	Supported by PARKE-DAVIS division of Warner-Lambert, Canada.
Allocation concealment	B – Unclear

Study	**Rabe (GSD-LNG)**
Methods	Randomized clinical trial. No blinding used. Allocation concealment unclear. Analysis by intention to treat. There were no post randomisation exclusions.
Participants	361 women randomized to either gestodene or LNG containing pill for 6 cycles. Characteristics of participants, inclusion and exclusion criteria not mentioned. Study conducted across 5 European countries.
Interventions	A) Monophasic gestodene 75 mcg/EE30 mcg vs B) monophasic levonorgestrel 150 mcg/EE30 mcg. Study was conducted in three phases A, B, and C. In phase A, cycle control and contraceptive efficacy was evaluated over 6 cycles. In phase B 707 women including those from phase A were given the gestodene pill over 24 cycles. In phase C 30 women from either group on gestodene and LNG were studied for metabolic effects. Only Study A is included for purpose of this review.
Outcomes	Contraceptive effectiveness, cycle control.
Notes	Sponsored by SCHERING AG. Data for spotting and break through bleeding is presented according to cycles.
Allocation concealment	B – Unclear

Study	**Ramos (LNG-NE)**
Methods	Randomized trial, double-blind. Allocation concealment unclear. Analysis by intent to treat. No post randomization exclusions.

Characteristics of included studies (*Continued*)

Participants	1800 women seeking family planning, with a mean age of 26 years were enrolled from Health centres and Family Planning clinics in thePhilippines. Inclusion and exclusion criteria not stated. Physical and pelvic exam prior to study. Follow up was at 1, 4, 7 and 11 months.
Interventions	A) monophasic NE 0.4 mg + EE 35mcg vs B) monophasic LNG 150mcg+ EE 30mcg.
Outcomes	Contraceptive effectiveness, cycle control, side-effects leading to discontinuation
Notes	Project was supported by UNFPA. Some OC pills were provided by WYETH.
Allocation concealment	B – Unclear

Study	**Reiter (NG-NE)**
Methods	Randomized trial across 3 pill groups over 12 months, allocation concealment unclear, analysis was not by intention to treat, post randomisation exclusions are not mentioned.
Participants	477 women > 18 years of age were enrolled from Planned Parenthood Centres in the US. Mean age was 20.3 years. Inclusion and exclusion criteria are not clearly stated. No information is available on the work up at admission. Follow- up every 2/3 months.
Interventions	A) triphasic norethindrone 500/750/1000+ EE 35mcg (Ortho Novum 7/7/7) vs B) triphasic norgestrel 0.1/0.15/0.25 mg +EE 30/40/30 mcg(Triphasil) . Pills were given in 28 day packs. Ortho Novum had a Sunday start whereas Triphasil had a first day start.
Outcomes	Cycle control.
Notes	.
Allocation concealment	B – Unclear

Study	**Rossmanith (DSG-NE)**
Methods	Randomized multicentre trial, double blind, allocation concealment unclear. Analysis was by intent to treat.
Participants	Women aged 18 to 35, both starters and switchers were included. Pre trial work-up included physical and gynaecological. examination and biochemical tests. Inclusion and exclusion criteria not clearly stated. Study conducted across 10 centres in Germany.
Interventions	A) monophasic norethisterone 500 mcg/ EE20 mcg (EVE 20) vs B) monophasic desogestrel 150 mcg/ EE20 mcg (Lovelle). Study duration 6 cycles. For first 3 treatment cycles participants underwent estimation of LH, FSH, sex steroids and vaginal US for ovarian follicular activity.
Outcomes	Contraceptive effectiveness, cycle control, side-effects.
Notes	Original paper in German. Study supported by GRUNENTHAL GmBH Ltd. Data on cycle control analysis given in cycles. There was an unequal number of women who had switched preparations and those who were starters. Forty % of women on desogestrel were assigned the same preparation.
Allocation concealment	B – Unclear

Study	**Serfaty (GSD-DSG)**
Methods	Randomized trial, randomization in blocks of 4. Multicentre trial. Analysis not by intent to treat, 10 post randomisation exclusions.
Participants	1026 sexually active healthy women aged 18-45, with regular cycles, with normal lipid and carbohydrate profiles and a 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. Study conducted across 52 centres in France.
Interventions	A) monophasic desogestrel 150 mcg/ EE20mcg (Mercilon) vs B) monophasic gestodene 75 mcg/ EE20mcg (Harmonet.).

Characteristics of included studies (*Continued*)

	Study duration 6 cycles. Follow-up was at 3 and 6 cycles.
Outcomes	Contraceptive efficacy and cycle control analysis. This data on cycle control is in graphical format from which it is not possible to deduce figures.
Notes	Sponsored by ORGANON. Only data on contraceptive efficacy included in review.
Allocation concealment	B – Unclear

Study	**Shoupe (DSG-NE)**
Methods	Multicentre randomized trial using computer generated random number tables. 23 post-randomisation exclusions, Double blinding. Analysis not by intention to treat.
Participants	812 women aged 18 to 35, healthy volunteers, sexually active. Both starters and switchers included. Inclusion criteria not specified. Exclusion criteria : known contraindication to OC, on medication, BMI > 95 th percentile, breast feeding, use of progestogen containing IUD in past 3 months, injectable contraceptive within 12 months., irregular cycles. Setting: FP and Ob-Gyn. clinics, across USA and Canada. Work-up included complete physical exam, pap smears and biochemical tests. Follow-up at 3 and 6 months.
Interventions	A) Triphasic desogestrel 50/100/150 mcg+ EE 35/30/30 mcg versus B) triphasic norethindrone 500/750/1000 mcg+ EE 35 mcg. Duration 6 cycles.
Outcomes	Contraceptive efficacy, discontinuation rate, side-effects and cycle- control analysis.
Notes	Study supported by ORGANON and FHI. Cycle control figures given as % in graphic form, therefore not used.
Allocation concealment	B – Unclear

Study	**Singh (DSG-NE)**
Methods	Randomized trial, allocation concealment unclear. Analysis was by intention to treat.
Participants	46 healthy sexually active women aged 19 to 35 years, study setting (in New York) not mentioned. Exclusion Criteria: known contraindications to OC use, <80% or >130% of ideal body weight, pregnancy, current breast feeding, irregular menstrual cycles, diabetes, hypertension, alcohol/drug abuse, abnormal breast or physical examination, on medication known to interact with OCs. At work up a complete physical examination, pap smear, blood tests were performed. The women in CTR-05 group were followed for additional 13 cycles. No information on starters and switchers.
Interventions	A) Triphasic desogestrel 50/100/150 +EE 35/30/30 mcg (CTR-05) versus B) triphasic norethindrone 500/750/1000 mcg +EE35/35/35 mcg (Ortho Novum 7/7/7). Both pill types were supplied as 28 day packets with 21 active pills and 7 placebos. Study duration 6 cycles.
Outcomes	Contraceptive effectiveness, cycle control, discontinuation rate and reasons for discontinuation, side effects.
Notes	This study was funded by a grant from ORGANON.
Allocation concealment	B – Unclear

Study	**Weber-Diehl (GSD-NE)**
Methods	Randomized study, allocation concealment unclear, analysis not by intention to treat. No blinding used.
Participants	254 women aged 16 to 50 years were enrolled. Inclusion, exclusion criteria not mentioned. Total randomised 229, with 25 post-randomisation exclusions. Study location: Germany.
Interventions	A) Triphasic Gestodene 50/70/100 mcg+EE 30/40/30mcg vs B) triphasic Norethindrone 500/750/1000 mcg+ EE 35/35/35 mcg.Total duration of treatment 12 cycles.
Outcomes	Contraceptive effectiveness, discontinuation and reasons for discontinuation; cycle control, side-effects.

Notes	Study sponsored by SCHERING AG. Figures for side-effects given as % in graphic form.
Allocation concealment	B – Unclear

Study	**Zichella (GSD-DSG)**
Methods	Randomized open parallel group study, allocation concealment is unclear. Analysis was by intention to treat.
Participants	241 women aged 18 to 40 were enrolled in a University setting across 5 centres in Italy. The women had regular cycles with no contraindication to OC use. All women were starters. Exclusion Criteria: history of thromboembolic disease, thrombophlebitis, jaundice in pregnancy, estrogen 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. Follow up was at 1, 3 and 6 cycles.
Interventions	A) Monophasic desogestrel 150 mcg/EE30mcg (Marvelon) versus B) monophasic gestodene 75 mcg/ EE30mcg (Femodene) over 6 cycles
Outcomes	Contraceptive effectiveness, cycle control, discontinuation rate and reasons for discontinuation, side effects leading to discontinuation.
Notes	Study was supported by ORGANON NV. The data on cycle control is 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.
Allocation concealment	B – Unclear

Characteristics of excluded studies

Study	**Reason for exclusion**
Akerlund 1993	This study compares two monophasic OCs containing one progestogen desogestrel with oestrogen in two doses of 30 and 20 mcg.
Anstee 1993	This study compares two monophasic contraceptives NET 500/EE 35 mcg and LNG 150/EE 30 mcg. There appear to be some problems in the study methodology. 1) Of the 240 women enrolled, 140 only were available for follow-up between 1 and 16 months, giving a post randomisation exclusion rate of 42%. 2) Of these 140 women, at the end of 15 cycles, 34/80 and 14/60 respectively were available for follow up i.e. 46 women in either group discontinued for reasons that are not entirely clear. 3) Randomisation was performed according to hospital record numbers.
Ayangade 1989	This study compares a monophasic norethindrone 1mg + EE 35 mcg OC (Norinyl 1/35) with a norgestrel 0.3 mg + EE 30 mcg OC (Lo-Ovral) over a 12 cycle study period. Fifty subjects were enrolled in the study . Allocation concealment was by pre printed and sealed envelopes. The study was excluded due to an imbalance in loss to follow-up (26% vs 18%).
Bassol 2000	Compares a 30 mcg EE pill containing gestodene with a 20 mcg EE pill containing desogestrel. The difference in the oestrogen content of the two formulations is > than 105 mcg.
Benagiano (GSD-DSG)	This is an interim analysis of a multicenter study, and presents selected data, no data on follow up.
Boschitsch 2000	This is not an original study. This study was based on asking women who were involved in two major clinical trials how they felt after the trials had ended.
Bounds 1979	This is a randomised double blind trial of two combined OCs containing NE 1.0 mg +EE 20 mcg and LNG 150 mcg+EE 30 mcg. 133 sexually active women in the 16 to 39 age group studied over 12 cycles. There were 23 post randomisation exclusions. Study only mentions contraceptive efficacy with 2 /55 pregnancies in NE group and 1/55 in LNG group. No details obtained on number discontinued and reasons for discontinuation, cycle control and side-effects. Analysis not by intention to treat. Incomplete study data. Study supported by Parke-Davis. No correspondence with authors attempted.

Bruni 2000	This study compares three oral contraceptives: 1) monophasic gestodene + EE 30 mcg 2) triphasic gestodene + triphasic EE and monophasic desogestrel + EE 20 mcg. The monophasic pill is compared with triphasic pill. Also the two monophasic pills have 30 and 20 mcg EE respectively.
Carlborg 1983	Compares monophasic LNG containing OC with an LNG containing triphasic OC.
Cislo 1986	This paper in Polish compares two OC pills with an EE content of 50 mcg/pill.
Cullberg 1982	Compares monophasic desogestrel containing OC with triphasic LNG containing OC
Dickerson 1989	This is only a study design. There is no data available. Medline search did not reveal any other full text article.
Dunson 1993a	Compares triphasic LNG containing OC with monophasic LNG containing OC
Edgren (NG-NE)	unclear number of women included in the ananlysis; loss-to-follow up>60%
Garza Flores 1992	The data from this study appears to have been included in the multicentric trial of Dunson 1993. In this Dunson study 17% women were from Mexico (=151). We have excluded this study to avoid duplication of data. We had written to FHI and Dr. Garza-Flores for a clarification however there was no response.
Kaunitz 2000	This randomised trial compares two triphasic oral contraceptives. Cyclessa contains 25 mcg EE combined with desogestrel in a triphasic combination and Ortho-novum 7/7/7 contains 35 mcg EE with NET in a triphasic combination. The difference in the oestrogen content of the formulations is 210 mcg over 21 pill taking days.
Kirkman 1994	This is a randomised trial comparing a 30 mcg EE pill containing gestodene (Minulet) with a 20 mcg EE pill containing desogestrel (Mercilon).
Koetsawang 1977	This study compares the same progestin lynestrenol in two doses of 1 and 2 mg with 40 mcg ethinyl estradiol in 300 women at the Mahidol University, Bangkok.
Kovacs 1986	This study compares three oral contraceptives two of which contain EE in the standard dose of 50 mcg. The trial also looks only at Blood Pressure as major outcome variable which is not pertinent to the objectives of this review.
London 1992	This study set in USA compares two triphasic OCs containing either Norgestimate and fixed dose EE (35 mcg) or LNG. The study duration was 6 cycles. The trial studied 2115 women in the Norgestimate arm and 2132 women in the LNG arm. The outcomes studied were contraceptive efficacy, discontinuation rate and overall side effects. This trial was excluded due to high loss to follow-up rate of 32.23% (715/2115 and 654/2132 in each group respectively).
Otolorin (NG-NE)	The loss to follow up was 26% and 40% in the 2 groups.
Refn 1990	This study comparing a gestodene containing OC with another LNG containing OC looks predominantly at biochemical outcomes. Data on cycle control is scarce. This is a double publication (Am J Obstet Gynecol 1990;163:374-7 Two triphasic oral contraceptives containing levonorgestrel and gestodene are compared in this trial. The study looks at predominantly biochemical outcomes. There is scarce data on clinical outcomes. Double publication : (Am. J. Obstet gynecol 1990;163:374-7)
Rosenberg 1996	This is not an original study. It compares pooled data from two independent studies- one by G. Benagiano and the other paper is not referenced. We had written to Dr. Rosenberg seeking a clarification, but there has been no reply.
Sanhueza 1979	This study compares Norinyl 1+50 which contains 0.05 mg of mestranol with Ovral which contains 50 mcg of ethinyl estradiol.
Schilling 1989	This is a comparative study of three triphasic oral contraceptives given for 4 cycles, which does not fit into review protocol; the inclusion criteria for trials is 6 months minimum.
Vartiainen 2001	The pills in this study were given for therapeutic effects and not for contraceptive purposes. Also the study compares a combigesic pill with a monophasic pill.
WHO (LNG-NE)	unclear number of women included in the analysis; loss-to-follow-up >50%
Zrubek 1986	This article in Polish compares three OC preparations.

A) monophasic Mestranol 0.05 mg+Ethynodiol 1.0 mg in 21 tablets (Angravid).
B) monophasic EE 50 mcg + LNG 125 mcg in 21 tablets (Gravistat)
C) Triphasic LNG 50/75/125 mcg +EE30/40/30 mcg (Triquilar)

ADDITIONAL TABLES

Table 01. Methodological Assessment of Included Studies

Study ID	Allocation Concealm	Blinding	Post Rand. Excl.	Analysis by ITT	Loss to Follow-up
Affinito (GSD-NGM)	unclear	none	none	unclear	7.93%
Droegmueller (LNG-NE)	unclear	none	unknown	met	13.4%
Dunson (NG-NE)	adequate	none	17/892	unclear	9%
Endrikat (GSD-DSG)	unclear	none	87/1563	met	unclear
Endrikat (LNG-NE)	unclear	none	unknown	met	unclear
Foidart (DSG-DRSP)	unclear	none	13/900	unclear	unclear
GSD Study Group (GSD-DSG)	unclear	none	none	met	1.86%
Halbe (GSD-DSG)	unclear	none	none	met	2.68%
Huber (DSG-DRSP)	unclear	none	29/2098	met	0.9%
Koetsawang (GSD-DSG)	unclear	none	none	unclear	5.5%
L.America (GSD-DSG)	unclear	none	none	met	unclear
Loudon (GSD-LNG)	unclear	double-blinding	32/488	unclear	1.97%
Percival (NG-NE)	unclear	single - blinding (intervention giver)	78/469 (16%)	unclear	unclear
Rabe (GSD-LNG)	unclear	none	none	met	10.52%
Ramos (LNG-NE)	unclear	double-blind	none	met	2.08%
Reiter (NG-NE)	unclear	none	unclear	unclear	unclear
Rossmanith (DSG-NE)	unclear	double-blinding	none	met	unclear
Serfaty (GSD-DSG)	unclear	none	10/1026	unclear	unclear
Shoupe (DSG-NE)	adequate	double-blind	23/812	unclear	8.25%
Singh (DSG-NE)	unclear	none	none	met	3/23 and 7/23
Weber - Diehl (GSD - NE)	unclear	none	25/254	unclear	10.1% and 9.5%
Zichella (GSD-DSG)	unclear	none	none	met	unclear

Table 02. Classification of Progestogens

Pregnanes	Estranes	Gonanes	Gonanes	.

Medroxyprogesterone acetate	1st generation	2nd generation	3rd generation
Chlormadinone acetate	Norethindrone acetate	dl-Norgestrel	Desogestrel
Cyproterone acetate	Ethynodiol diacetate	Levonorgestrel	Gestodene
Nomegestrol, Nestorone	Lynestrenol		Norgestimate
	Norethynodrel		

ANALYSES

Comparison 01. Third versus second generation OCs

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 pregnancy	2	817	Relative Risk (Random) 95% CI	Not estimable
02 discontinuation			Relative Risk (Random) 95% CI	Subtotals only
03 discontinuation due to side-effects (cycle-unrelated)			Relative Risk (Random) 95% CI	Subtotals only
04 side effects (monophasic)			Relative Risk (Random) 95% CI	Subtotals only
05 side effects (multiphasic)	0	0	Relative Risk (Random) 95% CI	Not estimable
06 intermenstrual bleeding			Relative Risk (Random) 95% CI	Subtotals only
07 spotting			Relative Risk (Random) 95% CI	Subtotals only
08 breakthrough bleeding			Relative Risk (Random) 95% CI	Subtotals only
09 absence of withdrawal bleed			Relative Risk (Random) 95% CI	Subtotals only

Comparison 02. Third versus first generation OCs

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 pregnancy			Relative Risk (Random) 95% CI	Subtotals only
02 discontinuation			Relative Risk (Random) 95% CI	Totals not selected
03 discontinuation due to side-effects (cycle-unrelated)			Relative Risk (Random) 95% CI	Subtotals only
04 side effects (monophasic)			Relative Risk (Random) 95% CI	Subtotals only
05 side effects (multiphasic)			Relative Risk (Random) 95% CI	Subtotals only
06 intermenstrual bleeding			Relative Risk (Random) 95% CI	Subtotals only
07 spotting			Relative Risk (Random) 95% CI	Subtotals only
08 breakthrough bleeding			Relative Risk (Random) 95% CI	Subtotals only
09 absence of withdrawal bleed			Relative Risk (Random) 95% CI	Subtotals only

Comparison 03. Second versus first generation OCs

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 pregnancy			Relative Risk (Random) 95% CI	Subtotals only
02 discontinuation			Relative Risk (Random) 95% CI	Subtotals only
03 discontinuation due to side-effects (cycle-unrelated)			Relative Risk (Random) 95% CI	Subtotals only
04 side effects (monophasic)			Relative Risk (Random) 95% CI	Subtotals only
05 side effects (multiphasic)			Relative Risk (Fixed) 95% CI	Subtotals only

06 cycle disturbance		Relative Risk (Random) 95% CI	Subtotals only

Comparison 04. Gestodene vs Levonorgestrel (monophasic)

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Pregnancy	2	817	Relative Risk (Random) 95% CI	Not estimable
02 Discontinuation	2	817	Relative Risk (Random) 95% CI	0.66 [0.41, 1.05]
03 Reasons for discontinuation			Relative Risk (Random) 95% CI	Subtotals only
04 Cycle control			Relative Risk (Random) 95% CI	Subtotals only
05 Side-effects	1	456	Relative Risk (Random) 95% CI	1.44 [0.68, 3.04]

Comparison 05. Gestodene vs Norethindrone (triphasic)

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 pregnancy	1	229	Relative Risk (Random) 95% CI	Not estimable
02 Discontinuation	1	229	Relative Risk (Random) 95% CI	0.60 [0.34, 1.05]
03 Reasons for discontinuation			Relative Risk (Random) 95% CI	Subtotals only
04 Cycle control			Relative Risk (Random) 95% CI	Subtotals only
05 Side-effects	0	0	Relative Risk (Random) 95% CI	Not estimable

Comparison 06. Gestodene vs Desogestrel (monophasic)

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Pregnancy	7	5624	Relative Risk (Random) 95% CI	1.85 [0.64, 5.32]
02 Discontinuation	7	5624	Relative Risk (Random) 95% CI	1.11 [1.00, 1.24]
03 Reasons for discontinuation			Relative Risk (Random) 95% CI	Subtotals only
04 Cycle control			Relative Risk (Random) 95% CI	Subtotals only
05 Side-effects			Relative Risk (Random) 95% CI	Subtotals only
06 Side-effects leading to discontinuation			Relative Risk (Random) 95% CI	Subtotals only

Comparison 07. Gestodene vs Norgestimate (monophasic)

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Pregnancy	1	174	Relative Risk (Random) 95% CI	Not estimable
02 Discontinuation	1	174	Relative Risk (Random) 95% CI	0.61 [0.23, 1.64]
03 Reasons for discontinuation			Relative Risk (Random) 95% CI	Subtotals only
04 Cycle control			Relative Risk (Random) 95% CI	Subtotals only
05 Side-effects			Relative Risk (Random) 95% CI	Subtotals only

Comparison 08. Desogestrel vs Norethisterone (monophasic)

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Pregnancy	1	118	Relative Risk (Random) 95% CI	Not estimable
02 Discontinuation	0	0	Relative Risk (Random) 95% CI	Not estimable
03 Reasons for discontinuation			Relative Risk (Random) 95% CI	Subtotals only
04 Cycle control			Relative Risk (Random) 95% CI	Subtotals only

05 Side-effects	Relative Risk (Random) 95% CI	Subtotals only

Comparison 09. Desogestrel vs Norethindrone (triphasic).

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Pregnancy	2	858	Relative Risk (Random) 95% CI	0.20 [0.01, 4.13]
02 Discontinuation	2	858	Relative Risk (Random) 95% CI	1.17 [0.94, 1.47]
03 Reasons for discontinuation			Relative Risk (Random) 95% CI	Subtotals only
04 Cycle control			Relative Risk (Random) 95% CI	Subtotals only
05 Side-effects			Relative Risk (Random) 95% CI	Subtotals only
06 Side-effects leading to discontinuation			Relative Risk (Random) 95% CI	Subtotals only

Comparison 10. Levonorgestrel vs Norethindrone (monophasic)

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Pregnancy	1	1199	Relative Risk (Random) 95% CI	Not estimable
02 Discontinuation	2	1834	Relative Risk (Random) 95% CI	0.75 [0.64, 0.87]
03 Reasons for discontinuation			Relative Risk (Random) 95% CI	Subtotals only
04 Cycle control			Relative Risk (Random) 95% CI	Subtotals only
05 Side-effects			Relative Risk (Random) 95% CI	Subtotals only
06 Side-effects leading to discontinuation			Relative Risk (Random) 95% CI	Subtotals only

Comparison 11. Levonorgestrel vs Norethindrone (triphasic)

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Pregnancy	0	0	Relative Risk (Random) 95% CI	Not estimable
02 Discontinuation	0	0	Relative Risk (Random) 95% CI	Not estimable
04 Reasons for discontinuation			Relative Risk (Random) 95% CI	Subtotals only
05 Cycle control			Relative Risk (Random) 95% CI	Subtotals only
06 Side-effects			Relative Risk (Random) 95% CI	Subtotals only

Comparison 12. Norgestrel vs Norethindrone (monophasic)

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Pregnancy	1	875	Relative Risk (Random) 95% CI	0.12 [0.02, 0.99]
02 Discontinuation			Relative Risk (Random) 95% CI	Subtotals only
03 Reasons for discontinuation			Relative Risk (Random) 95% CI	Subtotals only
04 Cycle control			Relative Risk (Random) 95% CI	Subtotals only
05 Side-effects			Relative Risk (Random) 95% CI	Subtotals only
06 Side-effects leading to discontinuation			Relative Risk (Random) 95% CI	Subtotals only

Comparison 13. Norgestrel vs Norethindrone (triphasic)

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Pregnancy	0	0	Relative Risk (Random) 95% CI	Not estimable
02 Discontinuation	1	236	Relative Risk (Random) 95% CI	1.16 [0.82, 1.63]
03 Reasons for discontinuation			Relative Risk (Random) 95% CI	Subtotals only
04 Cycle control			Relative Risk (Random) 95% CI	Subtotals only
05 Side-effects			Relative Risk (Random) 95% CI	Subtotals only
06 women satisfied	1	249	Relative Risk (Fixed) 95% CI	1.02 [0.92, 1.14]

Comparison 14. Drospirenone vs Desogestrel

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Pregnancy	2	2725	Relative Risk (Random) 95% CI	1.43 [0.41, 5.03]
02 Discontinuation	2	2985	Relative Risk (Random) 95% CI	1.08 [0.93, 1.25]
03 Reasons for discontinuation			Relative Risk (Random) 95% CI	Subtotals only
04 Cycle control			Relative Risk (Random) 95% CI	Subtotals only
05 Side-effects			Relative Risk (Random) 95% CI	Subtotals only

INDEX TERMS

Medical Subject Headings (MeSH)

Contraception [*methods]; Contraceptives, Oral, Combined [*administration & dosage]; Progestins [*administration & dosage]; Randomized Controlled Trials

MeSH check words

Female; Humans

COVER SHEET

Title	Progestogens in combined oral contraceptives for contraception
Authors	Maitra N, Kulier R, Bloemenkamp KWM, Helmerhorst FM, Gülmezoglu AM
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GRAPHS AND OTHER TABLES

Analysis 01.01. Comparison 01 Third versus second generation OCs, Outcome 01 pregnancy

Review: Progestogens in combined oral contraceptives for contraception

Comparison: 01 Third versus second generation OCs

Outcome: 01 pregnancy

Study	3rd gen. n/N	2nd gen. n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
01 monophasic					
× Loudon (GSD-LNG)	0/229	0/227		0.0	Not estimable
× Rabe (GSD-LNG)	0/176	0/185		0.0	Not estimable
Subtotal (95% CI)	405	412		0.0	Not estimable
Total events: 0 (3rd gen.), 0 (2nd gen.)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					
02 multiphasic					
Subtotal (95% CI)	0	0		0.0	Not estimable
Total events: 0 (3rd gen.), 0 (2nd gen.)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					
Total (95% CI)	405	412		0.0	Not estimable
Total events: 0 (3rd gen.), 0 (2nd gen.)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					

Analysis 01.02. Comparison 01 Third versus second generation OCs, Outcome 02 discontinuation

Review: Progestogens in combined oral contraceptives for contraception

Comparison: 01 Third versus second generation OCs

Outcome: 02 discontinuation

Study	3rd gen. n/N	2nd gen. n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
01 monophasic					
Loudon (GSD-LNG)	28/229	35/227		61.4	0.79 [0.50, 1.26]
Rabe (GSD-LNG)	12/176	26/185		38.6	0.49 [0.25, 0.93]
Subtotal (95% CI)	405	412		100.0	0.66 [0.41, 1.05]
Total events: 40 (3rd gen.), 61 (2nd gen.)					
Test for heterogeneity chi-square=1.46 df=1 p=0.23 I^2 =31.4%					
Test for overall effect z=1.76 p=0.08					
02 multiphasic					
Subtotal (95% CI)	0	0		0.0	Not estimable
Total events: 0 (3rd gen.), 0 (2nd gen.)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					

Analysis 01.03. Comparison 01 Third versus second generation OCs, Outcome 03 discontinuation due to side-effects (cycle-unrelated)

Review: Progestogens in combined oral contraceptives for contraception

Comparison: 01 Third versus second generation OCs

Outcome: 03 discontinuation due to side-effects (cycle-unrelated)

Study	3rd gen. n/N	2nd gen. n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
01 monophasic					
Loudon (GSD-LNG)	16/229	18/227		100.0	0.88 [0.46, 1.68]
Subtotal (95% CI)	229	227		100.0	0.88 [0.46, 1.68]
Total events: 16 (3rd gen.), 18 (2nd gen.)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.38 p=0.7					
02 multiphasic					
Subtotal (95% CI)	0	0		0.0	Not estimable
Total events: 0 (3rd gen.), 0 (2nd gen.)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					

Analysis 01.04. Comparison 01 Third versus second generation OCs, Outcome 04 side effects (monophasic)

Review: Progestogens in combined oral contraceptives for contraception

Comparison: 01 Third versus second generation OCs

Outcome: 04 side effects (monophasic)

Study	3rd gen. n/N	2nd gen. n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
01 all					
Loudon (GSD-LNG)	16/229	11/227		100.0	1.44 [0.68, 3.04]
Subtotal (95% CI)	229	227		100.0	1.44 [0.68, 3.04]
Total events: 16 (3rd gen.), 11 (2nd gen.)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.96 p=0.3					

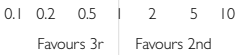
Analysis 01.06. Comparison 01 Third versus second generation OCs, Outcome 06 intermenstrual bleeding

Review: Progestogens in combined oral contraceptives for contraception

Comparison: 01 Third versus second generation OCs

Outcome: 06 intermenstrual bleeding

Study	3rd gen. n/N	2nd gen. n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
01 monophasic					
Loudon (GSD-LNG)	70/229	98/227		100.0	0.71 [0.55, 0.91]
Subtotal (95% CI)	229	227		100.0	0.71 [0.55, 0.91]
Total events: 70 (3rd gen.), 98 (2nd gen.)					
Test for heterogeneity: not applicable					
Test for overall effect z=2.75 p=0.006					
02 multiphasic					
Subtotal (95% CI)	0	0		0.0	Not estimable
Total events: 0 (3rd gen.), 0 (2nd gen.)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					



Analysis 01.07. Comparison 01 Third versus second generation OCs, Outcome 07 spotting

Review: Progestogens in combined oral contraceptives for contraception

Comparison: 01 Third versus second generation OCs

Outcome: 07 spotting

Study	3rd gen. n/N	2nd gen. n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
01 monophasic					
Loudon (GSD-LNG)	47/229	42/227		100.0	1.11 [0.76, 1.61]
Subtotal (95% CI)	229	227		100.0	1.11 [0.76, 1.61]
Total events: 47 (3rd gen.), 42 (2nd gen.)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.54 p=0.6					
02 multiphasic					
Subtotal (95% CI)	0	0		0.0	Not estimable
Total events: 0 (3rd gen.), 0 (2nd gen.)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					

Analysis 01.08. Comparison 01 Third versus second generation OCs, Outcome 08 breakthrough bleeding

Review: Progestogens in combined oral contraceptives for contraception

Comparison: 01 Third versus second generation OCs

Outcome: 08 breakthrough bleeding

Study	3rd gen. n/N	2nd gen. n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
01 monophasic					
Loudon (GSD-LNG)	12/229	18/227		100.0	0.66 [0.33, 1.34]
Subtotal (95% CI)	229	227		100.0	0.66 [0.33, 1.34]
Total events: 12 (3rd gen.), 18 (2nd gen.)					
Test for heterogeneity: not applicable					
Test for overall effect z=1.15 p=0.3					
02 multiphasic					
Subtotal (95% CI)	0	0		0.0	Not estimable
Total events: 0 (3rd gen.), 0 (2nd gen.)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					

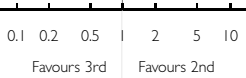
Analysis 01.09. Comparison 01 Third versus second generation OCs, Outcome 09 absence of withdrawal bleed

Review: Progestogens in combined oral contraceptives for contraception

Comparison: 01 Third versus second generation OCs

Outcome: 09 absence of withdrawal bleed

Study	3rd gen. n/N	2nd gen. n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
01 monophasic					
Loudon (GSD-LNG)	10/229	11/227		72.9	0.90 [0.39, 2.08]
Rabe (GSD-LNG)	3/176	6/185		27.1	0.53 [0.13, 2.07]
Subtotal (95% CI)	405	412		100.0	0.78 [0.38, 1.59]
Total events: 13 (3rd gen.), 17 (2nd gen.)					
Test for heterogeneity chi-square=0.43 df=1 p=0.51 I^2 =0.0%					
Test for overall effect z=0.69 p=0.5					
02 multiphasic					
Subtotal (95% CI)	0	0		0.0	Not estimable
Total events: 0 (3rd gen.), 0 (2nd gen.)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					



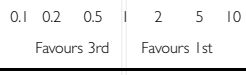
Analysis 02.01. Comparison 02 Third versus first generation OCs, Outcome 01 pregnancy

Review: Progestogens in combined oral contraceptives for contraception

Comparison: 02 Third versus first generation OCs

Outcome: 01 pregnancy

Study	3rd gen. n/N	1st gen. n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
01 monophasic					
× Rossmanith (DSG-NE)	0/59	0/59		0.0	Not estimable
Subtotal (95% CI)	59	59		0.0	Not estimable
Total events: 0 (3rd gen.), 0 (1st gen.)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					
02 multiphasic					
Shoupe (DSG-NE)	0/407	2/405		100.0	0.20 [0.01, 4.13]
× Singh (DSG-NE)	0/23	0/23		0.0	Not estimable
Subtotal (95% CI)	430	428		100.0	0.20 [0.01, 4.13]
Total events: 0 (3rd gen.), 2 (1st gen.)					
Test for heterogeneity: not applicable					
Test for overall effect z=1.04 p=0.3					

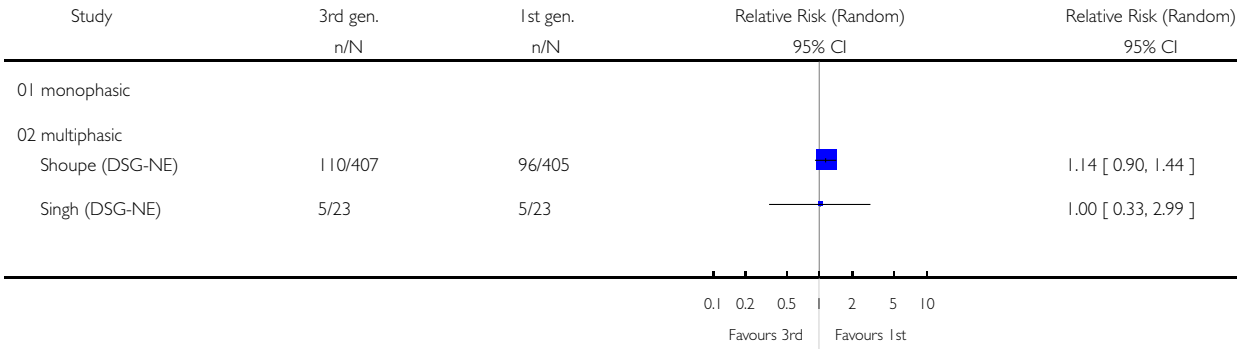


Analysis 02.02. Comparison 02 Third versus first generation OCs, Outcome 02 discontinuation

Review: Progestogens in combined oral contraceptives for contraception

Comparison: 02 Third versus first generation OCs

Outcome: 02 discontinuation

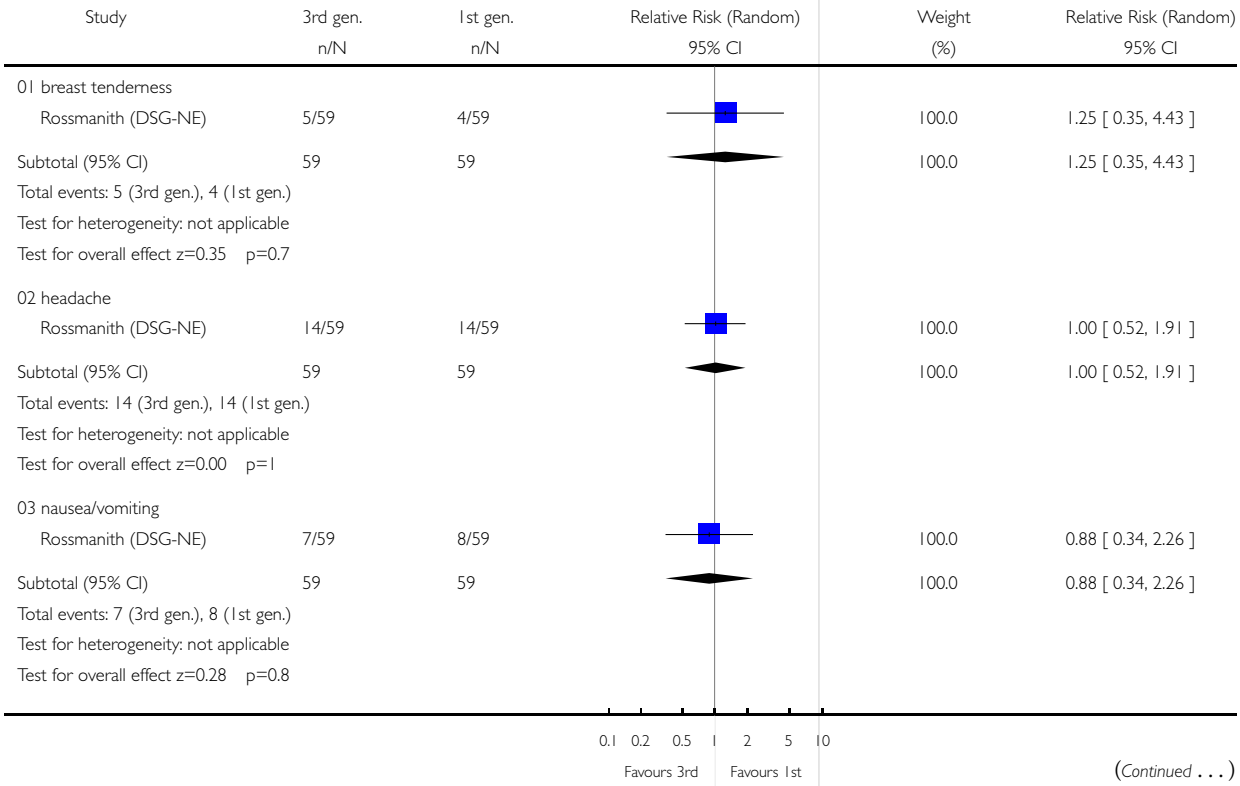


Analysis 02.04. Comparison 02 Third versus first generation OCs, Outcome 04 side effects (monophasic)

Review: Progestogens in combined oral contraceptives for contraception

Comparison: 02 Third versus first generation OCs

Outcome: 04 side effects (monophasic)



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Study	3rd gen. n/N	1st gen. n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
04 weight gain					
Rossmanith (DSG-NE)	1/59	0/59		100.0	3.00 [0.12, 72.18]
Subtotal (95% CI)	59	59		100.0	3.00 [0.12, 72.18]
Total events: 1 (3rd gen.), 0 (1st gen.)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.68 p=0.5					
05 other minor effects					
Rossmanith (DSG-NE)	11/59	10/59		100.0	1.10 [0.51, 2.39]
Subtotal (95% CI)	59	59		100.0	1.10 [0.51, 2.39]
Total events: 11 (3rd gen.), 10 (1st gen.)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.24 p=0.8					

Analysis 02.05. Comparison 02 Third versus first generation OCs, Outcome 05 side effects (multiphasic)

Review: Progestogens in combined oral contraceptives for contraception

Comparison: 02 Third versus first generation OCs

Outcome: 05 side effects (multiphasic)

Study	3rd gen. n/N	1st gen. n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
01 breast tenderness					
Shoupe (DSG-NE)	28/407	31/405		93.4	0.90 [0.55, 1.47]
Singh (DSG-NE)	2/16	2/20		6.6	1.25 [0.20, 7.92]
Subtotal (95% CI)	423	425		100.0	0.92 [0.57, 1.48]
Total events: 30 (3rd gen.), 33 (1st gen.)					
Test for heterogeneity chi-square=0.11 df=1 p=0.74 I^2 =0.0%					
Test for overall effect z=0.35 p=0.7					
02 headache					
Shoupe (DSG-NE)	55/407	49/405		85.5	1.12 [0.78, 1.60]
Singh (DSG-NE)	5/16	9/20		14.5	0.69 [0.29, 1.66]
Subtotal (95% CI)	423	425		100.0	1.04 [0.75, 1.45]
Total events: 60 (3rd gen.), 58 (1st gen.)					
Test for heterogeneity chi-square=0.98 df=1 p=0.32 I^2 =0.0%					
Test for overall effect z=0.25 p=0.8					

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Study	3rd gen. n/N	1st gen. n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
03 acne					
Singh (DSG-NE)	0/16	1/20		100.0	0.41 [0.02, 9.48]
Subtotal (95% CI)	16	20		100.0	0.41 [0.02, 9.48]
Total events: 0 (3rd gen.), 1 (1st gen.)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.55 p=0.6					
04 other minor					
Shoupe (DSG-NE)	60/407	59/405		92.2	1.01 [0.73, 1.41]
Singh (DSG-NE)	5/16	4/20		7.8	1.56 [0.50, 4.88]
Subtotal (95% CI)	423	425		100.0	1.05 [0.76, 1.44]
Total events: 65 (3rd gen.), 63 (1st gen.)					
Test for heterogeneity chi-square=0.52 df=1 p=0.47 I^2 =0.0%					
Test for overall effect z=0.28 p=0.8					

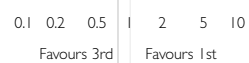
Analysis 02.08. Comparison 02 Third versus first generation OCs, Outcome 08 breakthrough bleeding

Review: Progestogens in combined oral contraceptives for contraception

Comparison: 02 Third versus first generation OCs

Outcome: 08 breakthrough bleeding

Study	3rd gen. n/N	1st gen. n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
01 monophasic					
Rossmanith (DSG-NE)	6/59	2/59		100.0	3.00 [0.63, 14.26]
Subtotal (95% CI)	59	59		100.0	3.00 [0.63, 14.26]
Total events: 6 (3rd gen.), 2 (1st gen.)					
Test for heterogeneity: not applicable					
Test for overall effect z=1.38 p=0.2					
02 multiphasic					
Subtotal (95% CI)	0	0		0.0	Not estimable
Total events: 0 (3rd gen.), 0 (1st gen.)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					



Analysis 03.01. Comparison 03 Second versus first generation OCs, Outcome 01 pregnancy

Review: Progestogens in combined oral contraceptives for contraception

Comparison: 03 Second versus first generation OCs

Outcome: 01 pregnancy

Study	2nd gen. n/N	1st gen. n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
01 monophasic					
Dunson (NG-NE)	1/438	8/437		100.0	0.12 [0.02, 0.99]
× Ramos (LNG-NE)	0/600	0/599		0.0	Not estimable
Subtotal (95% CI)	1038	1036		100.0	0.12 [0.02, 0.99]
Total events: 1 (2nd gen.), 8 (1st gen.)					
Test for heterogeneity: not applicable					
Test for overall effect z=1.97 p=0.05					
02 multiphasic					
Subtotal (95% CI)	0	0		0.0	Not estimable
Total events: 0 (2nd gen.), 0 (1st gen.)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					

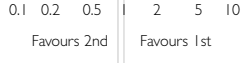
Analysis 03.02. Comparison 03 Second versus first generation OCs, Outcome 02 discontinuation

Review: Progestogens in combined oral contraceptives for contraception

Comparison: 03 Second versus first generation OCs

Outcome: 02 discontinuation

Study	2nd gen. n/N	1st gen. n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
01 monophasic					
Dunson (NG-NE)	99/438	124/437		30.7	0.80 [0.63, 1.00]
Ramos (LNG-NE)	151/600	192/599		49.1	0.79 [0.66, 0.94]
Endrikat (LNG-NE)	73/380	74/255		20.2	0.66 [0.50, 0.88]
Subtotal (95% CI)	1418	1291		100.0	0.76 [0.67, 0.86]
Total events: 323 (2nd gen.), 390 (1st gen.)					
Test for heterogeneity chi-square=1.21 df=2 p=0.55 I^2 =0.0%					
Test for overall effect z=4.21 p=0.00003					
02 multiphasic					
Percival (NG-NE)	46/119	39/117		100.0	1.16 [0.82, 1.63]
Subtotal (95% CI)	119	117		100.0	1.16 [0.82, 1.63]



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Study	2nd gen. n/N	1st gen. n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
Total events: 46 (2nd gen.), 39 (1st gen.)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.85 p=0.4					

Analysis 03.03. Comparison 03 Second versus first generation OCs, Outcome 03 discontinuation due to side-effects (cycle-unrelated)

Review: Progestogens in combined oral contraceptives for contraception

Comparison: 03 Second versus first generation OCs

Outcome: 03 discontinuation due to side-effects (cycle-unrelated)

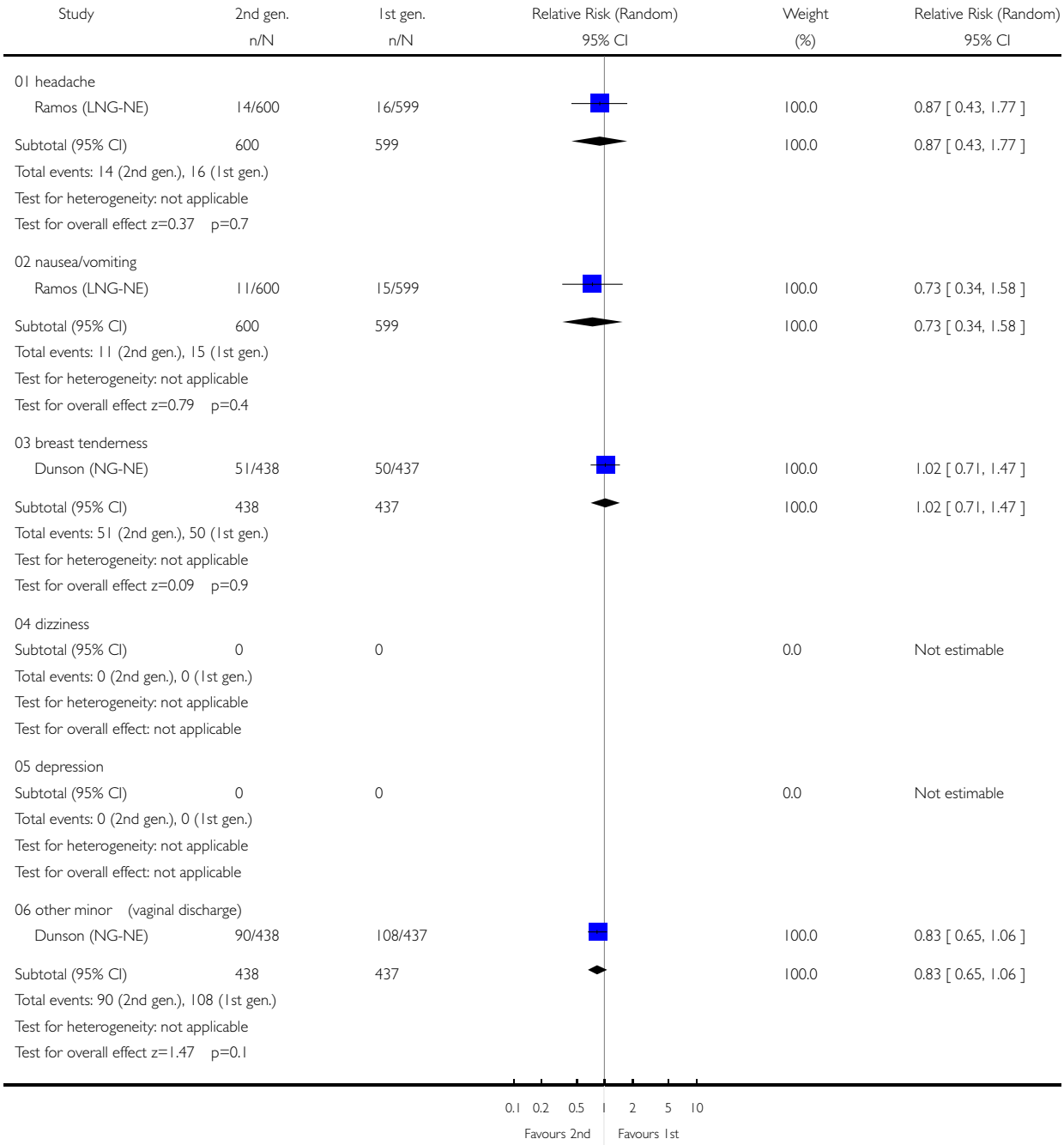
Study	2nd gen. n/N	1st gen. n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
01 monophasic					
Dunson (NG-NE)	17/438	20/437		29.0	0.85 [0.45, 1.60]
Ramos (LNG-NE)	25/600	31/599		34.0	0.81 [0.48, 1.35]
Endrikat (LNG-NE)	27/380	46/255		37.0	0.39 [0.25, 0.62]
Subtotal (95% CI)	1418	1291		100.0	0.63 [0.37, 1.05]
Total events: 69 (2nd gen.), 97 (1st gen.)					
Test for heterogeneity chi-square=5.79 df=2 p=0.06 I^2 =65.5%					
Test for overall effect z=1.76 p=0.08					
02 multiphasic					
Subtotal (95% CI)	0	0		0.0	Not estimable
Total events: 0 (2nd gen.), 0 (1st gen.)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					

Analysis 03.04. Comparison 03 Second versus first generation OCs, Outcome 04 side effects (monophasic)

Review: Progestogens in combined oral contraceptives for contraception

Comparison: 03 Second versus first generation OCs

Outcome: 04 side effects (monophasic)



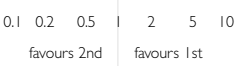
Analysis 03.06. Comparison 03 Second versus first generation OCs, Outcome 06 cycle disturbance

Review: Progestogens in combined oral contraceptives for contraception

Comparison: 03 Second versus first generation OCs

Outcome: 06 cycle disturbance

Study	2nd gen. n/N	1st gen. n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
01 Monophasic					
Dunson (NG-NE)	66/438	96/437		100.0	0.69 [0.52, 0.91]
Subtotal (95% CI)	438	437		100.0	0.69 [0.52, 0.91]
Total events: 66 (2nd gen.), 96 (1st gen.)					
Test for heterogeneity: not applicable					
Test for overall effect z=2.60 p=0.009					
02 Multiphasic					
Droegemüller (LNG-NE	16/48	30/48		56.2	0.53 [0.34, 0.84]
Reiter (NG-NE)	15/132	22/117		31.7	0.60 [0.33, 1.11]
Percival (NG-NE)	8/119	7/117		12.1	1.12 [0.42, 3.00]
Subtotal (95% CI)	299	282		100.0	0.61 [0.43, 0.85]
Total events: 39 (2nd gen.), 59 (1st gen.)					
Test for heterogeneity chi-square=1.86 df=2 p=0.39 I^2 =0.0%					
Test for overall effect z=2.86 p=0.004					



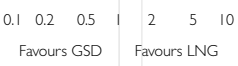
Analysis 04.01. Comparison 04 Gestodene vs Levonorgestrel (monophasic), Outcome 01 Pregnancy

Review: Progestogens in combined oral contraceptives for contraception

Comparison: 04 Gestodene vs Levonorgestrel (monophasic)

Outcome: 01 Pregnancy

Study	GSD n/N	LNG n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
× Loudon (GSD-LNG)	0/229	0/227		0.0	Not estimable
× Rabe (GSD-LNG)	0/176	0/185		0.0	Not estimable
Total (95% CI)	405	412		0.0	Not estimable
Total events: 0 (GSD), 0 (LNG)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					



Analysis 04.02. Comparison 04 Gestodene vs Levonorgestrel (monophasic), Outcome 02 Discontinuation

Review: Progestogens in combined oral contraceptives for contraception

Comparison: 04 Gestodene vs Levonorgestrel (monophasic)

Outcome: 02 Discontinuation

Study	GSD n/N	LNG n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
Loudon (GSD-LNG)	28/229	35/227		61.4	0.79 [0.50, 1.26]
Rabe (GSD-LNG)	12/176	26/185		38.6	0.49 [0.25, 0.93]
Total (95% CI)	405	412		100.0	0.66 [0.41, 1.05]
Total events: 40 (GSD), 61 (LNG)					
Test for heterogeneity chi-square=1.46 df=1 p=0.23 I^2 =31.4%					
Test for overall effect z=1.76 p=0.08					

Analysis 04.03. Comparison 04 Gestodene vs Levonorgestrel (monophasic), Outcome 03 Reasons for discontinuation

Review: Progestogens in combined oral contraceptives for contraception

Comparison: 04 Gestodene vs Levonorgestrel (monophasic)

Outcome: 03 Reasons for discontinuation

Study	GSD n/N	LNG n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
03 side-effects (other than cycle disturbances)					
Loudon (GSD-LNG)	16/229	18/227		100.0	0.88 [0.46, 1.68]
Subtotal (95% CI)	229	227		100.0	0.88 [0.46, 1.68]
Total events: 16 (GSD), 18 (LNG)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.38 p=0.7					
04 other medical reasons					
Loudon (GSD-LNG)	4/229	5/227		100.0	0.79 [0.22, 2.92]
Subtotal (95% CI)	229	227		100.0	0.79 [0.22, 2.92]
Total events: 4 (GSD), 5 (LNG)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.35 p=0.7					
05 lost to follow-up					
Loudon (GSD-LNG)	4/229	5/227		100.0	0.79 [0.22, 2.92]
Subtotal (95% CI)	229	227		100.0	0.79 [0.22, 2.92]
Total events: 4 (GSD), 5 (LNG)					

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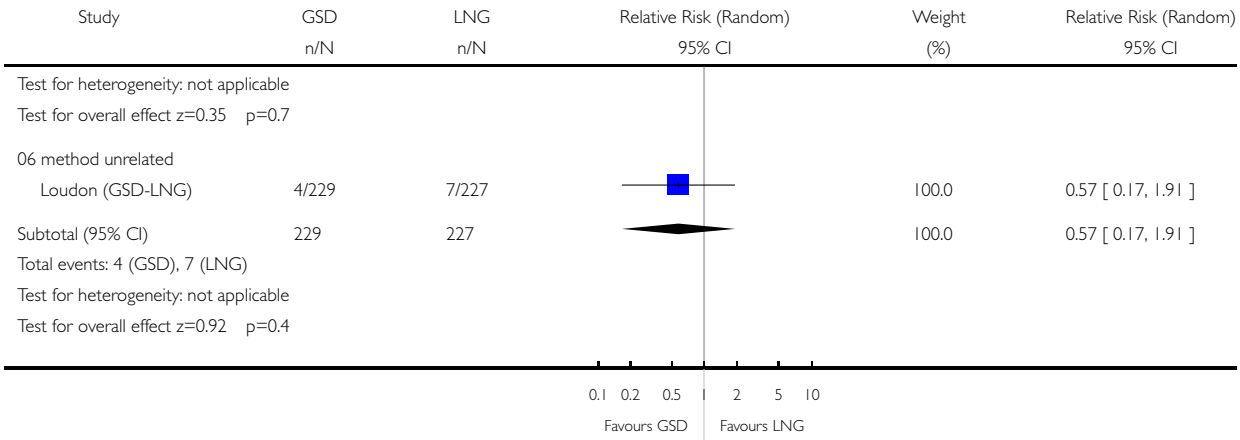
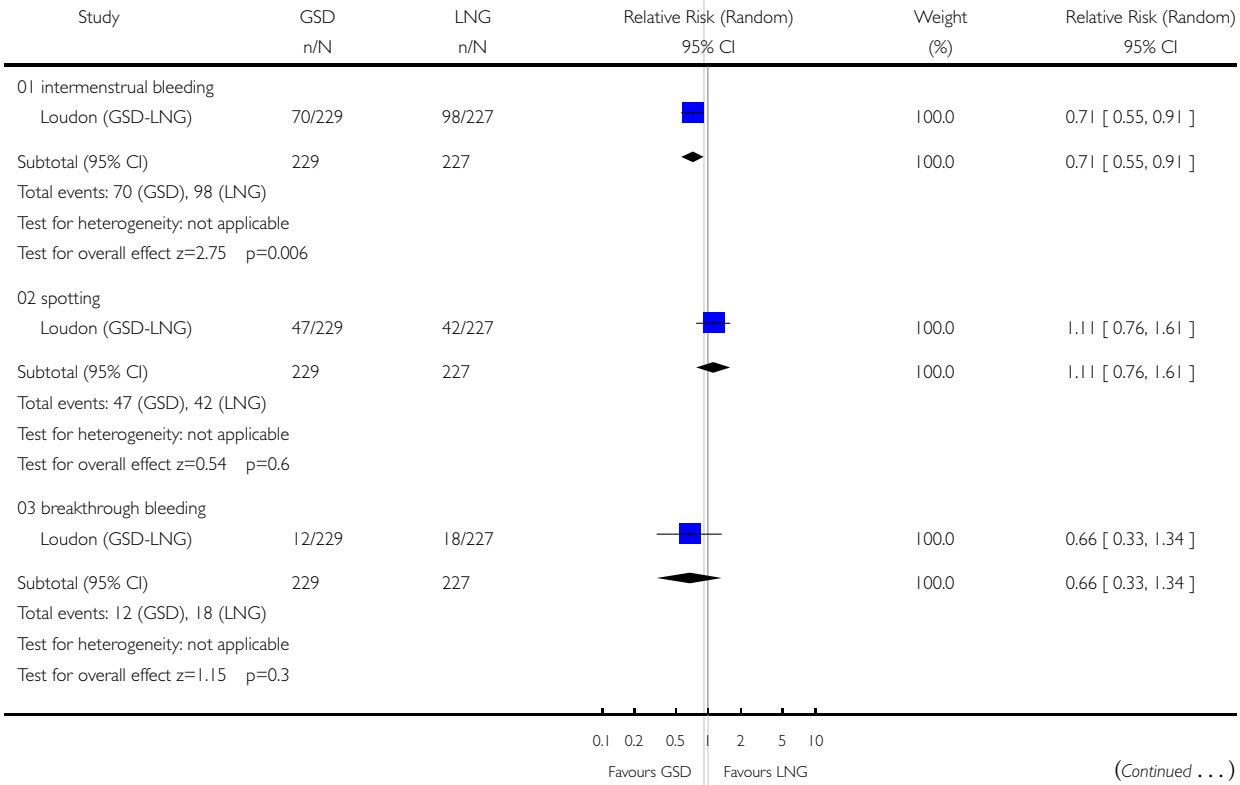


Analysis 04.04. Comparison 04 Gestodene vs Levonorgestrel (monophasic), Outcome 04 Cycle control

Review: Progestogens in combined oral contraceptives for contraception

Comparison: 04 Gestodene vs Levonorgestrel (monophasic)

Outcome: 04 Cycle control



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Study	GSD n/N	LNG n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
04 absence of withdrawal bleed					
Loudon (GSD-LNG)	10/229	11/227		72.9	0.90 [0.39, 2.08]
Rabe (GSD-LNG)	3/176	6/185		27.1	0.53 [0.13, 2.07]
Subtotal (95% CI)	405	412		100.0	0.78 [0.38, 1.59]
Total events: 13 (GSD), 17 (LNG)					
Test for heterogeneity chi-square=0.43 df=1 p=0.51 I^2 =0.0%					
Test for overall effect z=0.69 p=0.5					
05 abnormal cycles					
Loudon (GSD-LNG)	90/229	102/227		100.0	0.87 [0.70, 1.09]
Subtotal (95% CI)	229	227		100.0	0.87 [0.70, 1.09]
Total events: 90 (GSD), 102 (LNG)					
Test for heterogeneity: not applicable					
Test for overall effect z=1.22 p=0.2					

Analysis 04.05. Comparison 04 Gestodene vs Levonorgestrel (monophasic), Outcome 05 Side-effects

Review: Progestogens in combined oral contraceptives for contraception

Comparison: 04 Gestodene vs Levonorgestrel (monophasic)

Outcome: 05 Side-effects

Study	GSD n/N	LNG n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
01 acne					
Loudon (GSD-LNG)	16/229	11/227		100.0	1.44 [0.68, 3.04]
Total (95% CI)	229	227		100.0	1.44 [0.68, 3.04]
Total events: 16 (GSD), 11 (LNG)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.96 p=0.3					

Analysis 05.01. Comparison 05 Gestodene vs Norethindrone (triphasic), Outcome 01 pregnancy

Review: Progestogens in combined oral contraceptives for contraception

Comparison: 05 Gestodene vs Norethindrone (triphasic)

Outcome: 01 pregnancy

Study	GSD n/N	NE n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
× Weber-Diehl (GSD-NE)	0/114	0/115		0.0	Not estimable
Total (95% CI)	114	115		0.0	Not estimable
Total events: 0 (GSD), 0 (NE)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					

Analysis 05.02. Comparison 05 Gestodene vs Norethindrone (triphasic), Outcome 02 Discontinuation

Review: Progestogens in combined oral contraceptives for contraception

Comparison: 05 Gestodene vs Norethindrone (triphasic)

Outcome: 02 Discontinuation

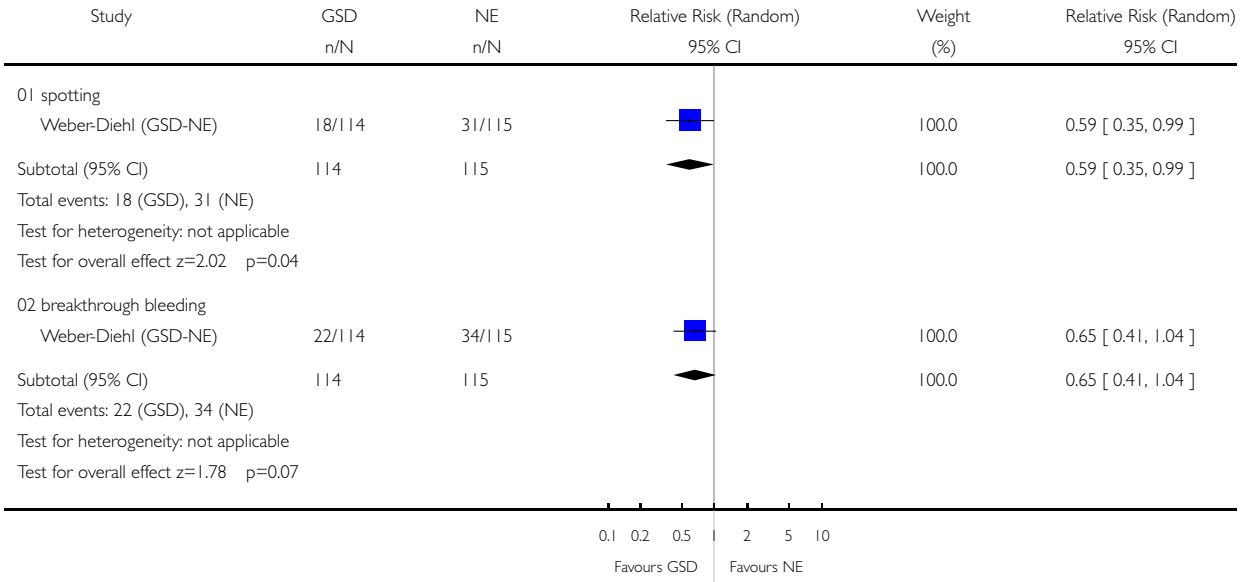
Study	GSD n/N	NE n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
Weber-Diehl (GSD-NE)	16/114	27/115		100.0	0.60 [0.34, 1.05]
Total (95% CI)	114	115		100.0	0.60 [0.34, 1.05]
Total events: 16 (GSD), 27 (NE)					
Test for heterogeneity: not applicable					
Test for overall effect z=1.80 p=0.07					

Analysis 05.04. Comparison 05 Gestodene vs Norethindrone (triphasic), Outcome 04 Cycle control

Review: Progestogens in combined oral contraceptives for contraception

Comparison: 05 Gestodene vs Norethindrone (triphasic)

Outcome: 04 Cycle control

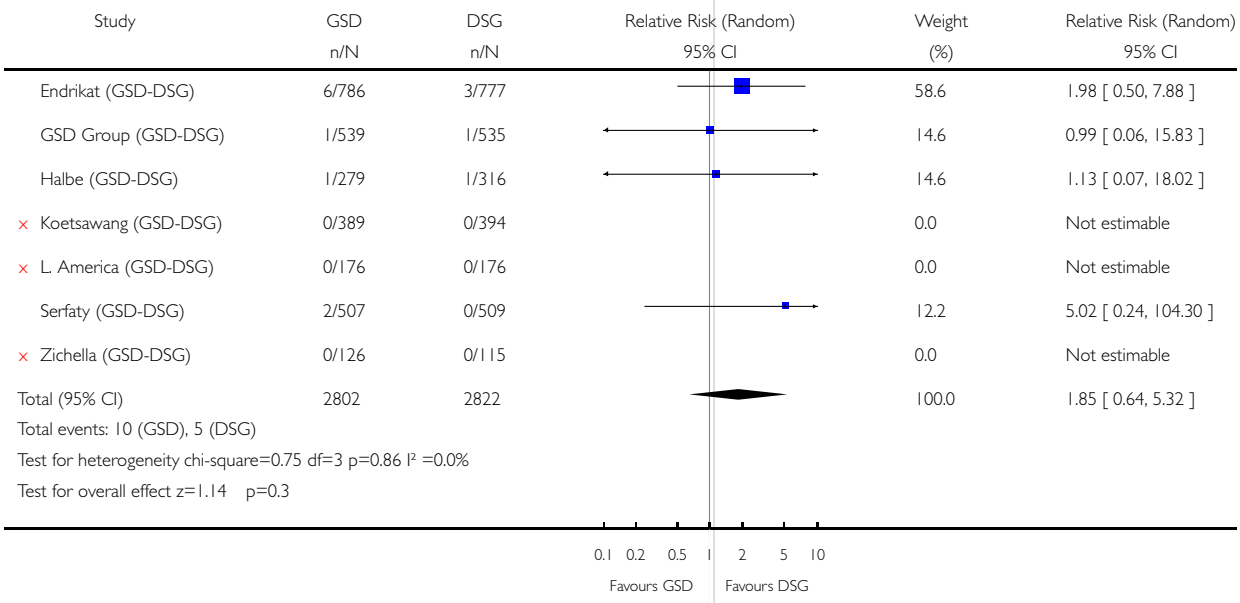


Analysis 06.01. Comparison 06 Gestodene vs Desogestrel (monophasic), Outcome 01 Pregnancy

Review: Progestogens in combined oral contraceptives for contraception

Comparison: 06 Gestodene vs Desogestrel (monophasic)

Outcome: 01 Pregnancy



Analysis 06.02. Comparison 06 Gestodene vs Desogestrel (monophasic), Outcome 02 Discontinuation

Review: Progestogens in combined oral contraceptives for contraception

Comparison: 06 Gestodene vs Desogestrel (monophasic)

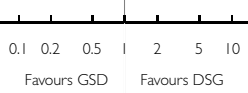
Outcome: 02 Discontinuation

Study	GSD n/N	DSG n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
Endrikat (GSD-DSG)	228/786	221/777		49.3	1.02 [0.87, 1.19]
GSD Group (GSD-DSG)	64/539	51/535		9.9	1.25 [0.88, 1.76]
Halbe (GSD-DSG)	52/279	42/316		8.6	1.40 [0.97, 2.04]
Koetsawang (GSD-DSG)	55/389	49/394		9.3	1.14 [0.79, 1.63]
L. America (GSD-DSG)	13/176	16/176		2.4	0.81 [0.40, 1.64]
Serfaty (GSD-DSG)	97/507	85/509		17.3	1.15 [0.88, 1.49]
Zichella (GSD-DSG)	25/126	13/115		3.1	1.76 [0.94, 3.27]
Total (95% CI)	2802	2822		100.0	1.11 [1.00, 1.24]

Total events: 534 (GSD), 477 (DSG)

Test for heterogeneity chi-square=6.00 df=6 p=0.42 I^2 =0.0%

Test for overall effect z=1.94 p=0.05



Analysis 06.03. Comparison 06 Gestodene vs Desogestrel (monophasic), Outcome 03 Reasons for discontinuation

Review: Progestogens in combined oral contraceptives for contraception

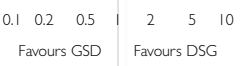
Comparison: 06 Gestodene vs Desogestrel (monophasic)

Outcome: 03 Reasons for discontinuation

Study	GSD n/N	DSG n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
01 cycle disturbances					
GSD Group (GSD-DSG)	2/539	2/535		11.7	0.99 [0.14, 7.02]
Halbe (GSD-DSG)	8/279	13/316		59.6	0.70 [0.29, 1.66]
Koetsawang (GSD-DSG)	1/389	1/394		5.8	1.01 [0.06, 16.14]
L. America (GSD-DSG)	1/176	1/176		5.9	1.00 [0.06, 15.86]
Zichella (GSD-DSG)	5/126	2/115		17.0	2.28 [0.45, 11.53]
Subtotal (95% CI)	1509	1536		100.0	0.93 [0.48, 1.81]

Total events: 17 (GSD), 19 (DSG)

Test for heterogeneity chi-square=1.62 df=4 p=0.81 I^2 =0.0%



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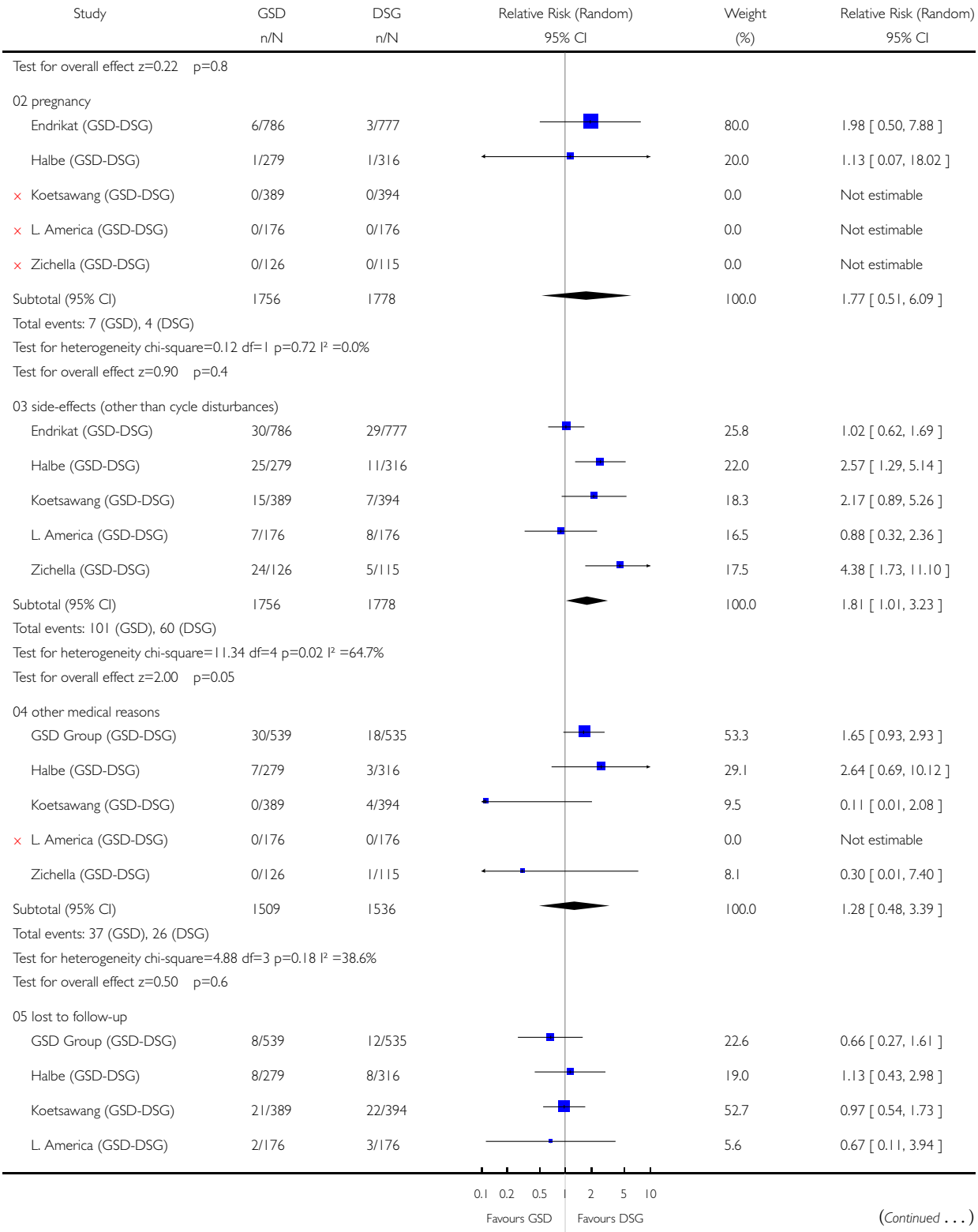

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Study	GSD n/N	DSG n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
Subtotal (95% CI)	1383	1421		100.0	0.90 [0.59, 1.37]
Total events: 39 (GSD), 45 (DSG)					
Test for heterogeneity chi-square=0.85 df=3 p=0.84 I^2 =0.0%					
Test for overall effect z=0.51 p=0.6					
06 method unrelated					
GSD Group (GSD-DSG)	26/539	21/535		42.7	1.23 [0.70, 2.16]
Halbe (GSD-DSG)	4/279	7/316		9.1	0.65 [0.19, 2.19]
Koetsawang (GSD-DSG)	18/389	15/394		30.1	1.22 [0.62, 2.38]
L. America (GSD-DSG)	4/176	5/176		8.0	0.80 [0.22, 2.93]
Zichella (GSD-DSG)	6/126	5/115		10.1	1.10 [0.34, 3.49]
Subtotal (95% CI)	1509	1536		100.0	1.10 [0.76, 1.59]
Total events: 58 (GSD), 53 (DSG)					
Test for heterogeneity chi-square=1.19 df=4 p=0.88 I^2 =0.0%					
Test for overall effect z=0.52 p=0.6					

Analysis 06.04. Comparison 06 Gestodene vs Desogestrel (monophasic), Outcome 04 Cycle control

Review: Progestogens in combined oral contraceptives for contraception

Comparison: 06 Gestodene vs Desogestrel (monophasic)

Outcome: 04 Cycle control

Study	GSD n/N	DSG n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
01 spotting EE< 30mcg					
Endrikat (GSD-DSG)	231/786	258/777		100.0	0.89 [0.76, 1.03]
Subtotal (95% CI)	786	777		100.0	0.89 [0.76, 1.03]
Total events: 231 (GSD), 258 (DSG)					
Test for heterogeneity: not applicable					
Test for overall effect z=1.62 p=0.1					
02 spotting EE = 30mcg					
Koetsawang (GSD-DSG)	7/389	6/394		27.6	1.18 [0.40, 3.48]
L. America (GSD-DSG)	21/176	37/176		72.4	0.57 [0.35, 0.93]
Subtotal (95% CI)	565	570		100.0	0.70 [0.37, 1.32]
Total events: 28 (GSD), 43 (DSG)					

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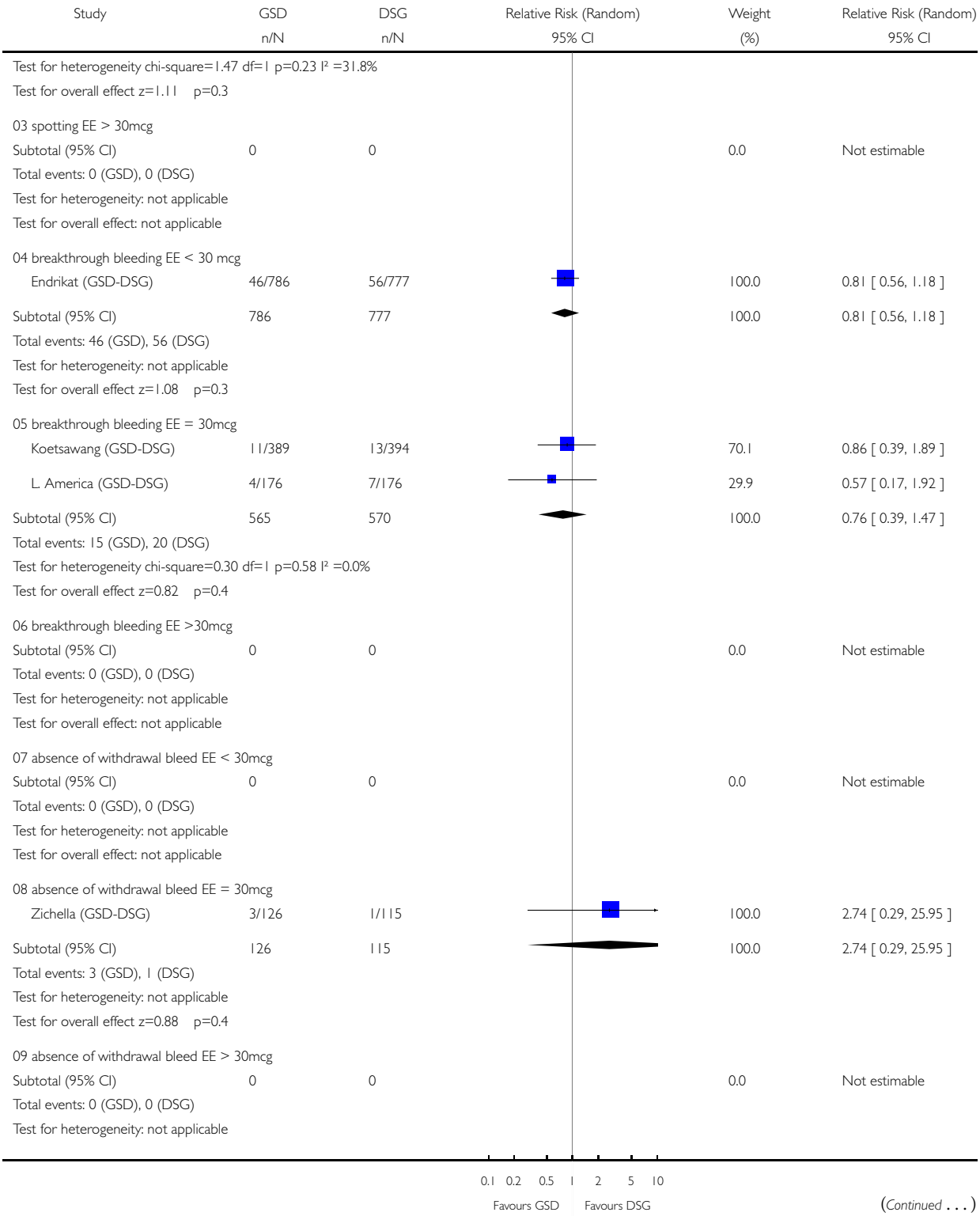

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Study	GSD n/N	DSG n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
Test for overall effect: not applicable					
10 other menstrual problems (dysmenorrhea)					
Endrikat (GSD-DSG)	59/786	69/777		54.7	0.85 [0.61, 1.18]
GSD Group (GSD-DSG)	41/539	28/535		45.3	1.45 [0.91, 2.31]
Subtotal (95% CI)	1325	1312		100.0	1.08 [0.64, 1.83]
Total events: 100 (GSD), 97 (DSG)					
Test for heterogeneity chi-square=3.45 df=1 p=0.06 I^2 =71.0%					
Test for overall effect z=0.29 p=0.8					

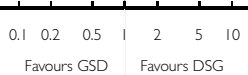
Analysis 06.05. Comparison 06 Gestodene vs Desogestrel (monophasic), Outcome 05 Side-effects

Review: Progestogens in combined oral contraceptives for contraception

Comparison: 06 Gestodene vs Desogestrel (monophasic)

Outcome: 05 Side-effects

Study	GSD n/N	DSG n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
01 breast tenderness					
Endrikat (GSD-DSG)	92/786	82/777		39.8	1.11 [0.84, 1.47]
GSD Group (GSD-DSG)	45/539	57/535		35.2	0.78 [0.54, 1.14]
Koetsawang (GSD-DSG)	1/389	4/394		3.5	0.25 [0.03, 2.26]
L. America (GSD-DSG)	11/176	24/176		21.5	0.46 [0.23, 0.91]
Subtotal (95% CI)	1890	1882		100.0	0.77 [0.50, 1.18]
Total events: 149 (GSD), 167 (DSG)					
Test for heterogeneity chi-square=7.73 df=3 p=0.05 I^2 =61.2%					
Test for overall effect z=1.20 p=0.2					
02 headache					
Endrikat (GSD-DSG)	144/786	122/777		38.8	1.17 [0.94, 1.45]
GSD Group (GSD-DSG)	166/539	162/535		57.6	1.02 [0.85, 1.22]
Koetsawang (GSD-DSG)	17/389	12/394		3.6	1.43 [0.69, 2.96]
Subtotal (95% CI)	1714	1706		100.0	1.09 [0.95, 1.25]
Total events: 327 (GSD), 296 (DSG)					
Test for heterogeneity chi-square=1.50 df=2 p=0.47 I^2 =0.0%					
Test for overall effect z=1.18 p=0.2					



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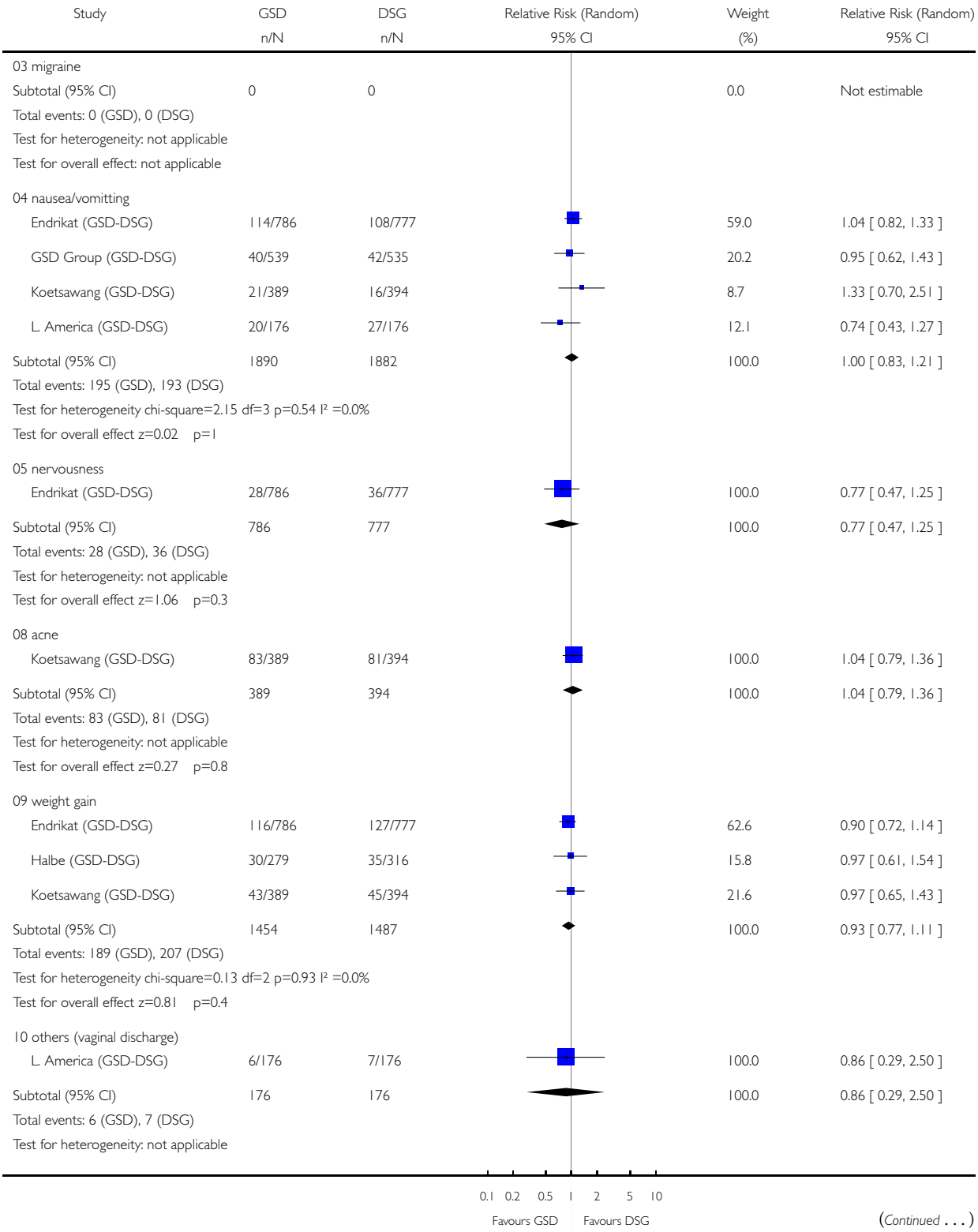

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Study	GSD n/N	DSG n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
Test for overall effect z=0.28 p=0.8					
11 depression					
Subtotal (95% CI)	0	0		0.0	Not estimable
Total events: 0 (GSD), 0 (DSG)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					

Analysis 06.06. Comparison 06 Gestodene vs Desogestrel (monophasic), Outcome 06 Side-effects leading to discontinuation

Review: Progestogens in combined oral contraceptives for contraception

Comparison: 06 Gestodene vs Desogestrel (monophasic)

Outcome: 06 Side-effects leading to discontinuation

Study	GSD n/N	DSG n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
01 breast tenderness					
GSD Group (GSD-DSG)	0/539	5/535		49.9	0.09 [0.01, 1.63]
Zichella (GSD-DSG)	8/126	0/115		50.1	15.53 [0.91, 266.04]
Subtotal (95% CI)	665	650		100.0	1.19 [0.01, 186.49]
Total events: 8 (GSD), 5 (DSG)					
Test for heterogeneity chi-square=6.21 df=1 p=0.01 I^2 =83.9%					
Test for overall effect z=0.07 p=0.9					
02 headache					
GSD Group (GSD-DSG)	2/539	6/535		33.9	0.33 [0.07, 1.63]
L. America (GSD-DSG)	2/176	2/176		22.8	1.00 [0.14, 7.02]
Zichella (GSD-DSG)	5/126	3/115		43.3	1.52 [0.37, 6.22]
Subtotal (95% CI)	841	826		100.0	0.82 [0.32, 2.10]
Total events: 9 (GSD), 11 (DSG)					
Test for heterogeneity chi-square=2.03 df=2 p=0.36 I^2 =1.6%					
Test for overall effect z=0.40 p=0.7					
03 migraine					
L. America (GSD-DSG)	1/176	0/176		100.0	3.00 [0.12, 73.14]
Subtotal (95% CI)	176	176		100.0	3.00 [0.12, 73.14]
Total events: 1 (GSD), 0 (DSG)					

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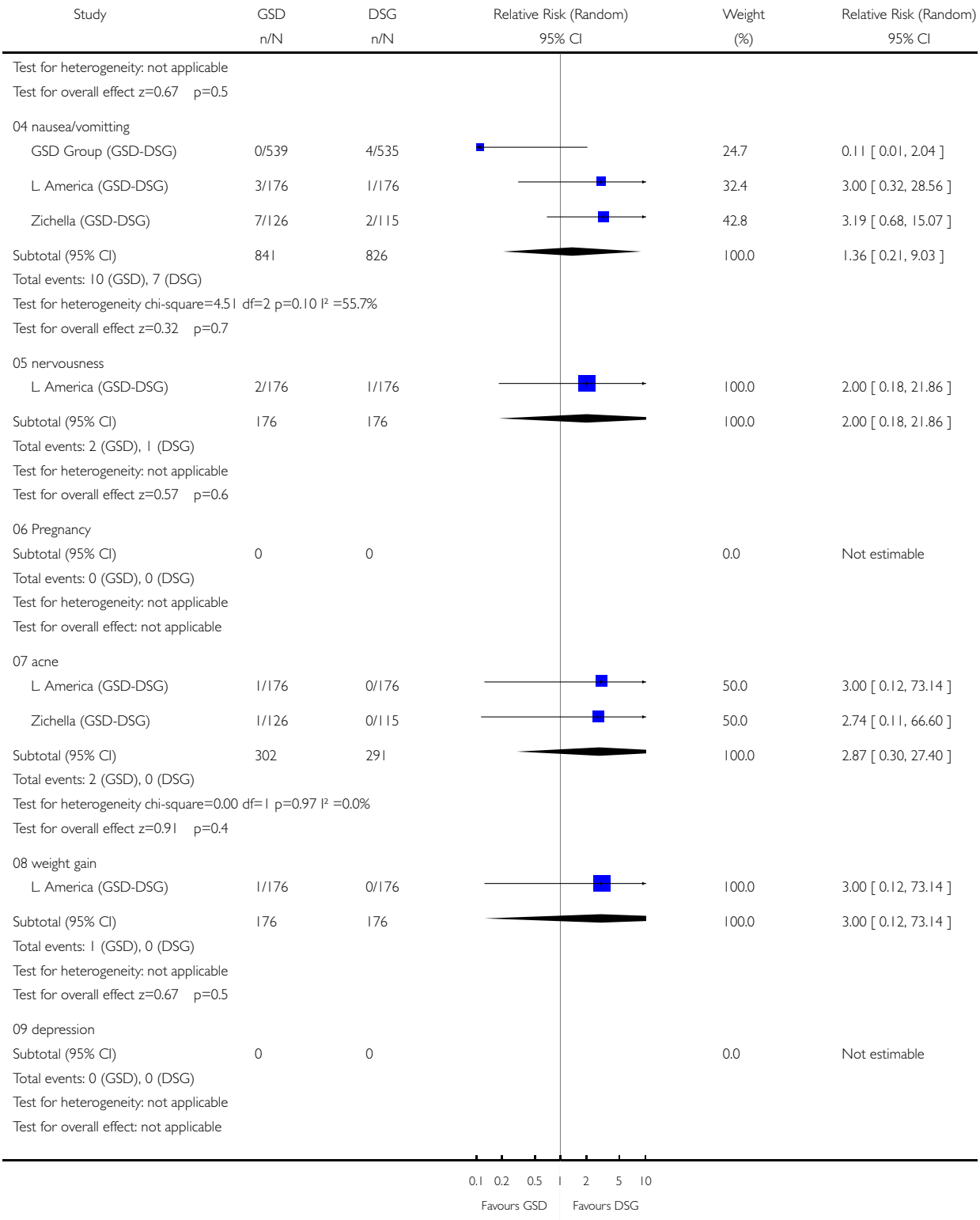


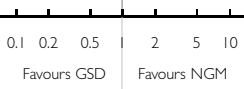
Analysis 07.01. Comparison 07 Gestodene vs Norgestimate (monophasic), Outcome 01 Pregnancy

Review: Progestogens in combined oral contraceptives for contraception

Comparison: 07 Gestodene vs Norgestimate (monophasic)

Outcome: 01 Pregnancy

Study	GSD n/N	NGM n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
× Affinito (GSD-NGM)	0/91	0/83		0.0	Not estimable
Total (95% CI)	91	83		0.0	Not estimable
Total events: 0 (GSD), 0 (NGM)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					



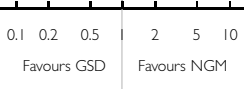
Analysis 07.02. Comparison 07 Gestodene vs Norgestimate (monophasic), Outcome 02 Discontinuation

Review: Progestogens in combined oral contraceptives for contraception

Comparison: 07 Gestodene vs Norgestimate (monophasic)

Outcome: 02 Discontinuation

Study	GSD n/N	NGM n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
Affinito (GSD-NGM)	6/91	9/83		100.0	0.61 [0.23, 1.64]
Total (95% CI)	91	83		100.0	0.61 [0.23, 1.64]
Total events: 6 (GSD), 9 (NGM)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.99 p=0.3					



Analysis 07.03. Comparison 07 Gestodene vs Norgestimate (monophasic), Outcome 03 Reasons for discontinuation

Review: Progestogens in combined oral contraceptives for contraception

Comparison: 07 Gestodene vs Norgestimate (monophasic)

Outcome: 03 Reasons for discontinuation

Study	GSD n/N	NGM n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
01 cycle disturbances					
× Affinito (GSD-NGM)	0/91	0/83		0.0	Not estimable
Subtotal (95% CI)	91	83		0.0	Not estimable
Total events: 0 (GSD), 0 (NGM)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					
02 pregnancy					
× Affinito (GSD-NGM)	0/91	0/83		0.0	Not estimable
Subtotal (95% CI)	91	83		0.0	Not estimable
Total events: 0 (GSD), 0 (NGM)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					
03 side-effects (other than cycle disturbances)					
Affinito (GSD-NGM)	3/91	2/83		100.0	1.37 [0.23, 7.99]
Subtotal (95% CI)	91	83		100.0	1.37 [0.23, 7.99]
Total events: 3 (GSD), 2 (NGM)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.35 p=0.7					
04 lost to follow-up					
× Affinito (GSD-NGM)	0/91	0/83		0.0	Not estimable
Subtotal (95% CI)	91	83		0.0	Not estimable
Total events: 0 (GSD), 0 (NGM)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					
05 other medical reasons					
× Affinito (GSD-NGM)	0/91	0/83		0.0	Not estimable
Subtotal (95% CI)	91	83		0.0	Not estimable
Total events: 0 (GSD), 0 (NGM)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					
06 method unrelated					
Affinito (GSD-NGM)	3/91	6/83		100.0	0.46 [0.12, 1.77]

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Study	GSD n/N	NGM n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
Subtotal (95% CI)	91	83		100.0	0.46 [0.12, 1.77]
Total events: 3 (GSD), 6 (NGM)					
Test for heterogeneity: not applicable					
Test for overall effect z=1.14 p=0.3					

Analysis 07.05. Comparison 07 Gestodene vs Norgestimate (monophasic), Outcome 05 Side-effects

Review: Progestogens in combined oral contraceptives for contraception

Comparison: 07 Gestodene vs Norgestimate (monophasic)

Outcome: 05 Side-effects

Study	GSD n/N	NGM n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
01 breast tenderness					
Affinito (GSD-NGM)	3/91	8/83		100.0	0.34 [0.09, 1.25]
Subtotal (95% CI)	91	83		100.0	0.34 [0.09, 1.25]
Total events: 3 (GSD), 8 (NGM)					
Test for heterogeneity: not applicable					
Test for overall effect z=1.63 p=0.1					
02 headache					
Affinito (GSD-NGM)	5/91	2/83		100.0	2.28 [0.45, 11.44]
Subtotal (95% CI)	91	83		100.0	2.28 [0.45, 11.44]
Total events: 5 (GSD), 2 (NGM)					
Test for heterogeneity: not applicable					
Test for overall effect z=1.00 p=0.3					
03 nausea/vomitting					
Affinito (GSD-NGM)	4/91	2/83		100.0	1.82 [0.34, 9.70]
Subtotal (95% CI)	91	83		100.0	1.82 [0.34, 9.70]
Total events: 4 (GSD), 2 (NGM)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.71 p=0.5					
04 other minor					
Affinito (GSD-NGM)	5/91	8/83		100.0	0.57 [0.19, 1.67]
Subtotal (95% CI)	91	83		100.0	0.57 [0.19, 1.67]
Total events: 5 (GSD), 8 (NGM)					
Test for heterogeneity: not applicable					
Test for overall effect z=1.02 p=0.3					

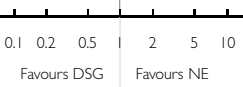
Analysis 08.01. Comparison 08 Desogestrel vs Norethisterone (monophasic), Outcome 01 Pregnancy

Review: Progestogens in combined oral contraceptives for contraception

Comparison: 08 Desogestrel vs Norethisterone (monophasic)

Outcome: 01 Pregnancy

Study	DSG n/N	NE n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
× Rossmanith (DSG-NE)	0/59	0/59		0.0	Not estimable
Total (95% CI)	59	59		0.0	Not estimable
Total events: 0 (DSG), 0 (NE)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					



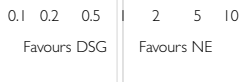
Analysis 08.05. Comparison 08 Desogestrel vs Norethisterone (monophasic), Outcome 05 Side-effects

Review: Progestogens in combined oral contraceptives for contraception

Comparison: 08 Desogestrel vs Norethisterone (monophasic)

Outcome: 05 Side-effects

Study	DSG n/N	NE n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
01 breast tenderness					
Rossmanith (DSG-NE)	5/59	4/59		100.0	1.25 [0.35, 4.43]
Subtotal (95% CI)	59	59		100.0	1.25 [0.35, 4.43]
Total events: 5 (DSG), 4 (NE)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.35 p=0.7					
02 headache					
Rossmanith (DSG-NE)	14/59	14/59		100.0	1.00 [0.52, 1.91]
Subtotal (95% CI)	59	59		100.0	1.00 [0.52, 1.91]
Total events: 14 (DSG), 14 (NE)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.00 p=1					
04 nausea/vomitting					
Rossmanith (DSG-NE)	7/59	8/59		100.0	0.88 [0.34, 2.26]
Subtotal (95% CI)	59	59		100.0	0.88 [0.34, 2.26]
Total events: 7 (DSG), 8 (NE)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.28 p=0.8					



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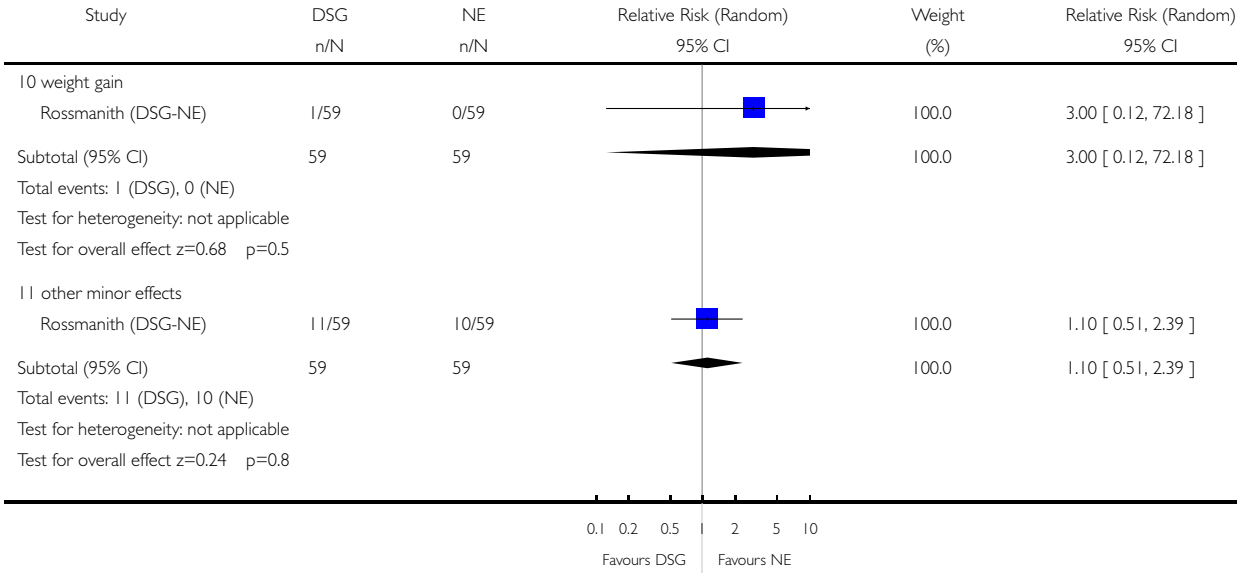
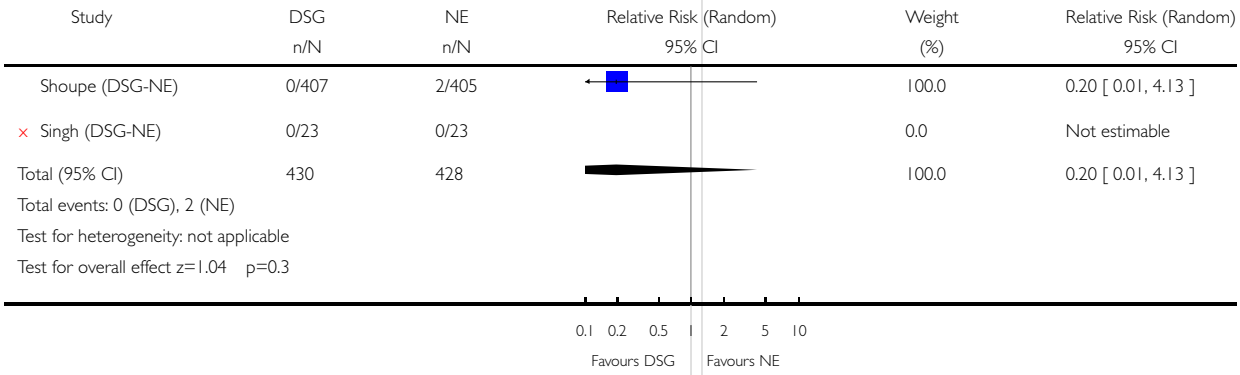


Analysis 09.01. Comparison 09 Desogestrel vs Norethindrone (triphasic)., Outcome 01 Pregnancy

Review: Progestogens in combined oral contraceptives for contraception

Comparison: 09 Desogestrel vs Norethindrone (triphasic).

Outcome: 01 Pregnancy



Analysis 09.02. Comparison 09 Desogestrel vs Norethindrone (triphasic)., Outcome 02 Discontinuation

Review: Progestogens in combined oral contraceptives for contraception

Comparison: 09 Desogestrel vs Norethindrone (triphasic).

Outcome: 02 Discontinuation

Study	DSG n/N	NE n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
Shoupe (DSG-NE)	110/407	96/405		89.3	1.14 [0.90, 1.44]
Singh (DSG-NE)	12/23	8/23		10.7	1.50 [0.76, 2.97]
Total (95% CI)	430	428		100.0	1.17 [0.94, 1.47]
Total events: 122 (DSG), 104 (NE)					
Test for heterogeneity chi-square=0.56 df=1 p=0.46 I^2 =0.0%					
Test for overall effect z=1.41 p=0.2					

Analysis 09.03. Comparison 09 Desogestrel vs Norethindrone (triphasic)., Outcome 03 Reasons for discontinuation

Review: Progestogens in combined oral contraceptives for contraception

Comparison: 09 Desogestrel vs Norethindrone (triphasic).

Outcome: 03 Reasons for discontinuation

Study	DSG n/N	NE n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
01 due to cycle disturbances					
Shoupe (DSG-NE)	6/407	8/405		100.0	0.75 [0.26, 2.13]
Subtotal (95% CI)	407	405		100.0	0.75 [0.26, 2.13]
Total events: 6 (DSG), 8 (NE)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.55 p=0.6					
02 pregnancy					
Shoupe (DSG-NE)	0/407	2/405		100.0	0.20 [0.01, 4.13]
× Singh (DSG-NE)	0/23	0/23		0.0	Not estimable
Subtotal (95% CI)	430	428		100.0	0.20 [0.01, 4.13]
Total events: 0 (DSG), 2 (NE)					
Test for heterogeneity: not applicable					
Test for overall effect z=1.04 p=0.3					
03 side-effects					
Shoupe (DSG-NE)	32/407	21/405		87.0	1.52 [0.89, 2.58]
Singh (DSG-NE)	4/23	3/23		13.0	1.33 [0.34, 5.30]

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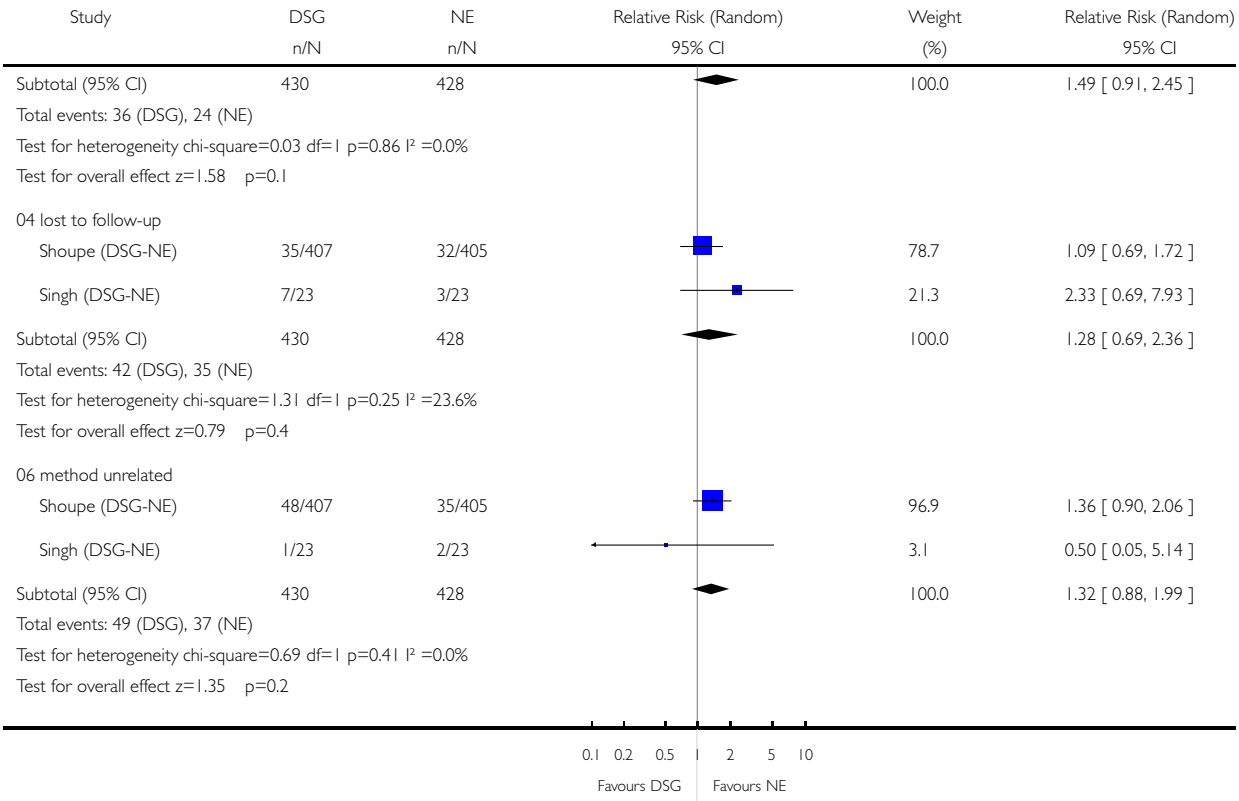


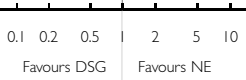
Analysis 09.05. Comparison 09 Desogestrel vs Norethindrone (triphasic)., Outcome 05 Side-effects

Review: Progestogens in combined oral contraceptives for contraception

Comparison: 09 Desogestrel vs Norethindrone (triphasic).

Outcome: 05 Side-effects

Study	DSG n/N	NE n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
01 breast tenderness					
Shoupe (DSG-NE)	28/407	31/405		93.5	0.90 [0.55, 1.47]
Singh (DSG-NE)	2/23	2/23		6.5	1.00 [0.15, 6.51]
Subtotal (95% CI)	430	428		100.0	0.91 [0.56, 1.46]
Total events: 30 (DSG), 33 (NE)					
Test for heterogeneity chi-square=0.01 df=1 p=0.91 I² =0.0%					
Test for overall effect z=0.41 p=0.7					
02 headache					
Shoupe (DSG-NE)	55/407	49/405		69.5	1.12 [0.78, 1.60]
Singh (DSG-NE)	5/23	9/23		30.5	0.56 [0.22, 1.41]
Subtotal (95% CI)	430	428		100.0	0.90 [0.48, 1.70]
Total events: 60 (DSG), 58 (NE)					
Test for heterogeneity chi-square=1.90 df=1 p=0.17 I² =47.2%					
Test for overall effect z=0.32 p=0.8					
04 nausea/vomitting					
Shoupe (DSG-NE)	41/407	37/405		87.6	1.10 [0.72, 1.68]
Singh (DSG-NE)	4/23	6/23		12.4	0.67 [0.22, 2.05]
Subtotal (95% CI)	430	428		100.0	1.04 [0.70, 1.54]
Total events: 45 (DSG), 43 (NE)					
Test for heterogeneity chi-square=0.67 df=1 p=0.41 I² =0.0%					
Test for overall effect z=0.18 p=0.9					
08 acne					
Singh (DSG-NE)	0/23	1/23		100.0	0.33 [0.01, 7.78]
Subtotal (95% CI)	23	23		100.0	0.33 [0.01, 7.78]
Total events: 0 (DSG), 1 (NE)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.68 p=0.5					
11 other minor					
Shoupe (DSG-NE)	60/407	59/405		92.7	1.01 [0.73, 1.41]
Singh (DSG-NE)	5/23	4/23		7.3	1.25 [0.38, 4.07]
Subtotal (95% CI)	430	428		100.0	1.03 [0.75, 1.41]
Total events: 65 (DSG), 63 (NE)					



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Study	DSG n/N	NE n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
Test for heterogeneity chi-square=0.11 df=1 p=0.74 I^2 =0.0%					
Test for overall effect z=0.17 p=0.9					
12 serious adverse events					
Shoupe (DSG-NE)	7/407	5/405		100.0	1.39 [0.45, 4.35]
Subtotal (95% CI)	407	405		100.0	1.39 [0.45, 4.35]
Total events: 7 (DSG), 5 (NE)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.57 p=0.6					

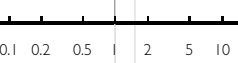
Analysis 09.06. Comparison 09 Desogestrel vs Norethindrone (triphasic)., Outcome 06 Side-effects leading to discontinuation

Review: Progestogens in combined oral contraceptives for contraception

Comparison: 09 Desogestrel vs Norethindrone (triphasic).

Outcome: 06 Side-effects leading to discontinuation

Study	DSG n/N	NE n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
01 breast tenderness					
Singh (DSG-NE)	1/23	0/23		100.0	3.00 [0.13, 70.02]
Subtotal (95% CI)	23	23		100.0	3.00 [0.13, 70.02]
Total events: 1 (DSG), 0 (NE)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.68 p=0.5					
02 headache					
Singh (DSG-NE)	1/23	3/23		100.0	0.33 [0.04, 2.97]
Subtotal (95% CI)	23	23		100.0	0.33 [0.04, 2.97]
Total events: 1 (DSG), 3 (NE)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.98 p=0.3					
04 nausea/vomitting					
Singh (DSG-NE)	1/23	1/23		100.0	1.00 [0.07, 15.04]
Subtotal (95% CI)	23	23		100.0	1.00 [0.07, 15.04]
Total events: 1 (DSG), 1 (NE)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.00 p=1					



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Study	DSG n/N	NE n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
11 other minor (vaginal dryness, dysmenorrhea)					
Singh (DSG-NE)	1/23	1/23		100.0	1.00 [0.07, 15.04]
Subtotal (95% CI)	23	23		100.0	1.00 [0.07, 15.04]
Total events: 1 (DSG), 1 (NE)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.00 p=1					

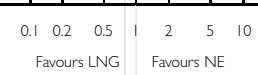
Analysis 10.01. Comparison 10 Levonorgestrel vs Norethindrone (monophasic), Outcome 01 Pregnancy

Review: Progestogens in combined oral contraceptives for contraception

Comparison: 10 Levonorgestrel vs Norethindrone (monophasic)

Outcome: 01 Pregnancy

Study	LNG n/N	NE n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
× Ramos (LNG-NE)	0/600	0/599		0.0	Not estimable
Total (95% CI)	600	599		0.0	Not estimable
Total events: 0 (LNG), 0 (NE)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					



Analysis 10.02. Comparison 10 Levonorgestrel vs Norethindrone (monophasic), Outcome 02 Discontinuation

Review: Progestogens in combined oral contraceptives for contraception

Comparison: 10 Levonorgestrel vs Norethindrone (monophasic)

Outcome: 02 Discontinuation

Study	LNG n/N	NE n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
Ramos (LNG-NE)	151/600	192/599		70.9	0.79 [0.66, 0.94]
Endrikat (LNG-NE)	73/380	74/255		29.1	0.66 [0.50, 0.88]
Total (95% CI)	980	854		100.0	0.75 [0.64, 0.87]
Total events: 224 (LNG), 266 (NE)					
Test for heterogeneity chi-square=1.00 df=1 p=0.32 I^2 =0.0%					
Test for overall effect z=3.76 p=0.0002					

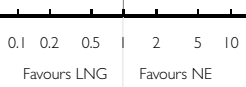
Analysis 10.03. Comparison 10 Levonorgestrel vs Norethindrone (monophasic), Outcome 03 Reasons for discontinuation

Review: Progestogens in combined oral contraceptives for contraception

Comparison: 10 Levonorgestrel vs Norethindrone (monophasic)

Outcome: 03 Reasons for discontinuation

Study	LNG n/N	NE n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
01 cycle disturbances					
Ramos (LNG-NE)	5/600	12/599		100.0	0.42 [0.15, 1.17]
Subtotal (95% CI)	600	599		100.0	0.42 [0.15, 1.17]
Total events: 5 (LNG), 12 (NE)					
Test for heterogeneity: not applicable					
Test for overall effect z=1.66 p=0.1					
02 pregnancy					
× Ramos (LNG-NE)	0/600	0/599		0.0	Not estimable
Subtotal (95% CI)	600	599		0.0	Not estimable
Total events: 0 (LNG), 0 (NE)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					
03 side-effects					
Ramos (LNG-NE)	25/600	31/599		100.0	0.81 [0.48, 1.35]
Subtotal (95% CI)	600	599		100.0	0.81 [0.48, 1.35]
Total events: 25 (LNG), 31 (NE)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.83 p=0.4					
04 other medical reasons					
Ramos (LNG-NE)	31/600	39/599		100.0	0.79 [0.50, 1.25]
Subtotal (95% CI)	600	599		100.0	0.79 [0.50, 1.25]
Total events: 31 (LNG), 39 (NE)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.99 p=0.3					
05 loss to follow up					
Ramos (LNG-NE)	16/600	9/599		100.0	1.77 [0.79, 3.98]
Subtotal (95% CI)	600	599		100.0	1.77 [0.79, 3.98]
Total events: 16 (LNG), 9 (NE)					
Test for heterogeneity: not applicable					
Test for overall effect z=1.39 p=0.2					
06 method unrelated					



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Study	LNG n/N	NE n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
Ramos (LNG-NE)	51/600	72/599		100.0	0.71 [0.50, 0.99]
Subtotal (95% CI)	600	599		100.0	0.71 [0.50, 0.99]
Total events: 51 (LNG), 72 (NE)					
Test for heterogeneity: not applicable					
Test for overall effect z=2.00 p=0.05					

Analysis 10.06. Comparison 10 Levonorgestrel vs Norethindrone (monophasic), Outcome 06 Side-effects leading to discontinuation

Review: Progestogens in combined oral contraceptives for contraception

Comparison: 10 Levonorgestrel vs Norethindrone (monophasic)

Outcome: 06 Side-effects leading to discontinuation

Study	LNG n/N	NE n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
01 headache					
Ramos (LNG-NE)	14/600	16/599		100.0	0.87 [0.43, 1.77]
Subtotal (95% CI)	600	599		100.0	0.87 [0.43, 1.77]
Total events: 14 (LNG), 16 (NE)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.37 p=0.7					
02 nausea/vomitting					
Ramos (LNG-NE)	11/600	15/599		100.0	0.73 [0.34, 1.58]
Subtotal (95% CI)	600	599		100.0	0.73 [0.34, 1.58]
Total events: 11 (LNG), 15 (NE)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.79 p=0.4					

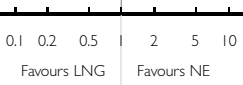
Analysis 11.05. Comparison 11 Levonorgestrel vs Norethindrone (triphasic), Outcome 05 Cycle control

Review: Progestogens in combined oral contraceptives for contraception

Comparison: 11 Levonorgestrel vs Norethindrone (triphasic)

Outcome: 05 Cycle control

Study	LNG n/N	NE n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
01 spotting					
Droegemüller (LNG-NE	7/48	16/48		100.0	0.44 [0.20, 0.97]
Subtotal (95% CI)	48	48		100.0	0.44 [0.20, 0.97]
Total events: 7 (LNG), 16 (NE)					
Test for heterogeneity: not applicable					
Test for overall effect z=2.04 p=0.04					
02 breakthrough bleeding					
Droegemüller (LNG-NE	10/48	22/48		100.0	0.45 [0.24, 0.85]
Subtotal (95% CI)	48	48		100.0	0.45 [0.24, 0.85]
Total events: 10 (LNG), 22 (NE)					
Test for heterogeneity: not applicable					
Test for overall effect z=2.45 p=0.01					
03 Intermenstrual bleeding					
Droegemüller (LNG-NE	16/48	30/48		100.0	0.53 [0.34, 0.84]
Subtotal (95% CI)	48	48		100.0	0.53 [0.34, 0.84]
Total events: 16 (LNG), 30 (NE)					
Test for heterogeneity: not applicable					
Test for overall effect z=2.70 p=0.007					



Analysis 12.01. Comparison 12 Norgestrel vs Norethindrone (monophasic), Outcome 01 Pregnancy

Review: Progestogens in combined oral contraceptives for contraception

Comparison: 12 Norgestrel vs Norethindrone (monophasic)

Outcome: 01 Pregnancy

Study	NG n/N	NE n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
Dunson (NG-NE)	1/438	8/437		100.0	0.12 [0.02, 0.99]
Total (95% CI)	438	437		100.0	0.12 [0.02, 0.99]
Total events: 1 (NG), 8 (NE)					
Test for heterogeneity: not applicable					
Test for overall effect z=1.97 p=0.05					

Analysis 12.02. Comparison 12 Norgestrel vs Norethindrone (monophasic), Outcome 02 Discontinuation

Review: Progestogens in combined oral contraceptives for contraception

Comparison: 12 Norgestrel vs Norethindrone (monophasic)

Outcome: 02 Discontinuation

Study	NG n/N	NE n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
Dunson (NG-NE)	99/438	124/437		100.0	0.80 [0.63, 1.00]
Subtotal (95% CI)	438	437		100.0	0.80 [0.63, 1.00]
Total events: 99 (NG), 124 (NE)					
Test for heterogeneity: not applicable					
Test for overall effect z=1.95 p=0.05					

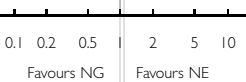
Analysis 12.03. Comparison 12 Norgestrel vs Norethindrone (monophasic), Outcome 03 Reasons for discontinuation

Review: Progestogens in combined oral contraceptives for contraception

Comparison: 12 Norgestrel vs Norethindrone (monophasic)

Outcome: 03 Reasons for discontinuation

Study	NG n/N	NE n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
01 cycle disturbances					
Dunson (NG-NE)	7/438	26/437		100.0	0.27 [0.12, 0.61]
Subtotal (95% CI)	438	437		100.0	0.27 [0.12, 0.61]
Total events: 7 (NG), 26 (NE)					
Test for heterogeneity: not applicable					
Test for overall effect z=3.13 p=0.002					
02 pregnancy					
Dunson (NG-NE)	1/438	8/437		100.0	0.12 [0.02, 0.99]
Subtotal (95% CI)	438	437		100.0	0.12 [0.02, 0.99]
Total events: 1 (NG), 8 (NE)					
Test for heterogeneity: not applicable					
Test for overall effect z=1.97 p=0.05					
03 side -effects (other than cycle disturbances)					
Dunson (NG-NE)	17/438	20/437		100.0	0.85 [0.45, 1.60]
Subtotal (95% CI)	438	437		100.0	0.85 [0.45, 1.60]
Total events: 17 (NG), 20 (NE)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.51 p=0.6					



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Study	NG n/N	NE n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
04 other medical reasons					
Dunson (NG-NE)	11/438	13/437		100.0	0.84 [0.38, 1.86]
Subtotal (95% CI)	438	437		100.0	0.84 [0.38, 1.86]
Total events: 11 (NG), 13 (NE)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.42 p=0.7					
05 method unrelated					
Dunson (NG-NE)	63/438	57/437		100.0	1.10 [0.79, 1.54]
Subtotal (95% CI)	438	437		100.0	1.10 [0.79, 1.54]
Total events: 63 (NG), 57 (NE)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.58 p=0.6					

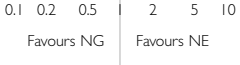
Analysis 12.04. Comparison 12 Norgestrel vs Norethindrone (monophasic), Outcome 04 Cycle control

Review: Progestogens in combined oral contraceptives for contraception

Comparison: 12 Norgestrel vs Norethindrone (monophasic)

Outcome: 04 Cycle control

Study	NG n/N	NE n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
01 Intermenstrual bleeding					
Dunson (NG-NE)	66/438	96/437		100.0	0.69 [0.52, 0.91]
Subtotal (95% CI)	438	437		100.0	0.69 [0.52, 0.91]
Total events: 66 (NG), 96 (NE)					
Test for heterogeneity: not applicable					
Test for overall effect z=2.60 p=0.009					
02 spotting					
Subtotal (95% CI)	0	0		0.0	Not estimable
Total events: 0 (NG), 0 (NE)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					
03 absence of withdrawal bleed					
Dunson (NG-NE)	13/438	44/437		100.0	0.29 [0.16, 0.54]
Subtotal (95% CI)	438	437		100.0	0.29 [0.16, 0.54]
Total events: 13 (NG), 44 (NE)					



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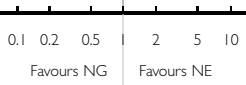
Study	NG n/N	NE n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
Test for heterogeneity: not applicable					
Test for overall effect z=3.96 p=0.00007					
04 other menstrual complaints					
Dunson (NG-NE)	31/438	83/437		100.0	0.37 [0.25, 0.55]
Subtotal (95% CI)	438	437		100.0	0.37 [0.25, 0.55]
Total events: 31 (NG), 83 (NE)					
Test for heterogeneity: not applicable					
Test for overall effect z=4.95 p<0.00001					



Analysis 12.05. Comparison 12 Norgestrel vs Norethindrone (monophasic), Outcome 05 Side-effects

Review: Progestogens in combined oral contraceptives for contraception

Comparison: 12 Norgestrel vs Norethindrone (monophasic)

Outcome: 05 Side-effects

Study	NG n/N	NE n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
01 breast tenderness					
Dunson (NG-NE)	51/438	50/437		100.0	1.02 [0.71, 1.47]
Subtotal (95% CI)	438	437		100.0	1.02 [0.71, 1.47]
Total events: 51 (NG), 50 (NE)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.09 p=0.9					
02 headache					
Subtotal (95% CI)	0	0		0.0	Not estimable
Total events: 0 (NG), 0 (NE)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					
03 nausea/vomitting					
Subtotal (95% CI)	0	0		0.0	Not estimable
Total events: 0 (NG), 0 (NE)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					
04 dizziness					
Subtotal (95% CI)	0	0		0.0	Not estimable
Total events: 0 (NG), 0 (NE)					

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Study	NG n/N	NE n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					
05 depression					
Subtotal (95% CI)	0	0		0.0	Not estimable
Total events: 0 (NG), 0 (NE)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					
06 others(vaginal discharge)					
Dunson (NG-NE)	90/438	108/437		100.0	0.83 [0.65, 1.06]
Subtotal (95% CI)	438	437		100.0	0.83 [0.65, 1.06]
Total events: 90 (NG), 108 (NE)					
Test for heterogeneity: not applicable					
Test for overall effect z=1.47 p=0.1					

Analysis 12.06. Comparison 12 Norgestrel vs Norethindrone (monophasic), Outcome 06 Side-effects leading to discontinuation

Review: Progestogens in combined oral contraceptives for contraception

Comparison: 12 Norgestrel vs Norethindrone (monophasic)

Outcome: 06 Side-effects leading to discontinuation

Study	NG n/N	NE n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
01 serious adverse events					
Dunson (NG-NE)	1/17	2/20		100.0	0.59 [0.06, 5.94]
Subtotal (95% CI)	17	20		100.0	0.59 [0.06, 5.94]
Total events: 1 (NG), 2 (NE)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.45 p=0.7					

Analysis 13.02. Comparison 13 Norgestrel vs Norethindrone (triphasic), Outcome 02 Discontinuation

Review: Progestogens in combined oral contraceptives for contraception

Comparison: 13 Norgestrel vs Norethindrone (triphasic)

Outcome: 02 Discontinuation

Study	NG n/N	NE n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
Percival (NG-NE)	46/119	39/117		100.0	1.16 [0.82, 1.63]
Total (95% CI)	119	117		100.0	1.16 [0.82, 1.63]
Total events: 46 (NG), 39 (NE)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.85 p=0.4					

Analysis 13.03. Comparison 13 Norgestrel vs Norethindrone (triphasic), Outcome 03 Reasons for discontinuation

Review: Progestogens in combined oral contraceptives for contraception

Comparison: 13 Norgestrel vs Norethindrone (triphasic)

Outcome: 03 Reasons for discontinuation

Study	NG n/N	NE n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
01 cycle disturbances					
Percival (NG-NE)	8/119	7/117		100.0	1.12 [0.42, 3.00]
Subtotal (95% CI)	119	117		100.0	1.12 [0.42, 3.00]
Total events: 8 (NG), 7 (NE)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.23 p=0.8					

Analysis 13.04. Comparison 13 Norgestrel vs Norethindrone (triphasic), Outcome 04 Cycle control

Review: Progestogens in combined oral contraceptives for contraception

Comparison: 13 Norgestrel vs Norethindrone (triphasic)

Outcome: 04 Cycle control

Study	NG n/N	NE n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
01 intermenstrual bleeding					
Reiter (NG-NE)	15/132	22/117		100.0	0.60 [0.33, 1.11]
Subtotal (95% CI)	132	117		100.0	0.60 [0.33, 1.11]
Total events: 15 (NG), 22 (NE)					
Test for heterogeneity: not applicable					
Test for overall effect z=1.63 p=0.1					
02 absence of withdrawal bleed					
Reiter (NG-NE)	0/132	4/117		100.0	0.10 [0.01, 1.81]
Subtotal (95% CI)	132	117		100.0	0.10 [0.01, 1.81]
Total events: 0 (NG), 4 (NE)					
Test for heterogeneity: not applicable					
Test for overall effect z=1.56 p=0.1					

Analysis 13.06. Comparison 13 Norgestrel vs Norethindrone (triphasic), Outcome 06 women satisfied

Review: Progestogens in combined oral contraceptives for contraception

Comparison: 13 Norgestrel vs Norethindrone (triphasic)

Outcome: 06 women satisfied

Study	NG n/N	NE n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Reiter (NG-NE)	112/132	97/117		100.0	1.02 [0.92, 1.14]
Total (95% CI)	132	117		100.0	1.02 [0.92, 1.14]
Total events: 112 (NG), 97 (NE)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.41 p=0.7					

Analysis 14.01. Comparison 14 Drospirenone vs Desogestrel, Outcome 01 Pregnancy

Review: Progestogens in combined oral contraceptives for contraception

Comparison: 14 Drospirenone vs Desogestrel

Outcome: 01 Pregnancy

Study	DRSP n/N	DSG n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
Foidart (DSG-DRSP)	3/310	3/317		62.4	1.02 [0.21, 5.03]
Huber (DSG-DRSP)	10/1680	1/418		37.6	2.49 [0.32, 19.38]
Total (95% CI)	1990	735		100.0	1.43 [0.41, 5.03]

Total events: 13 (DRSP), 4 (DSG)

Test for heterogeneity chi-square=0.46 df=1 p=0.50 I^2 =0.0%

Test for overall effect z=0.56 p=0.6

Analysis 14.02. Comparison 14 Drospirenone vs Desogestrel, Outcome 02 Discontinuation

Review: Progestogens in combined oral contraceptives for contraception

Comparison: 14 Drospirenone vs Desogestrel

Outcome: 02 Discontinuation

Study	DRSP n/N	DSG n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
Foidart (DSG-DRSP)	135/442	129/445		53.2	1.05 [0.86, 1.29]
Huber (DSG-DRSP)	361/1680	81/418		46.8	1.11 [0.89, 1.38]
Total (95% CI)	2122	863		100.0	1.08 [0.93, 1.25]

Total events: 496 (DRSP), 210 (DSG)

Test for heterogeneity chi-square=0.12 df=1 p=0.73 I^2 =0.0%

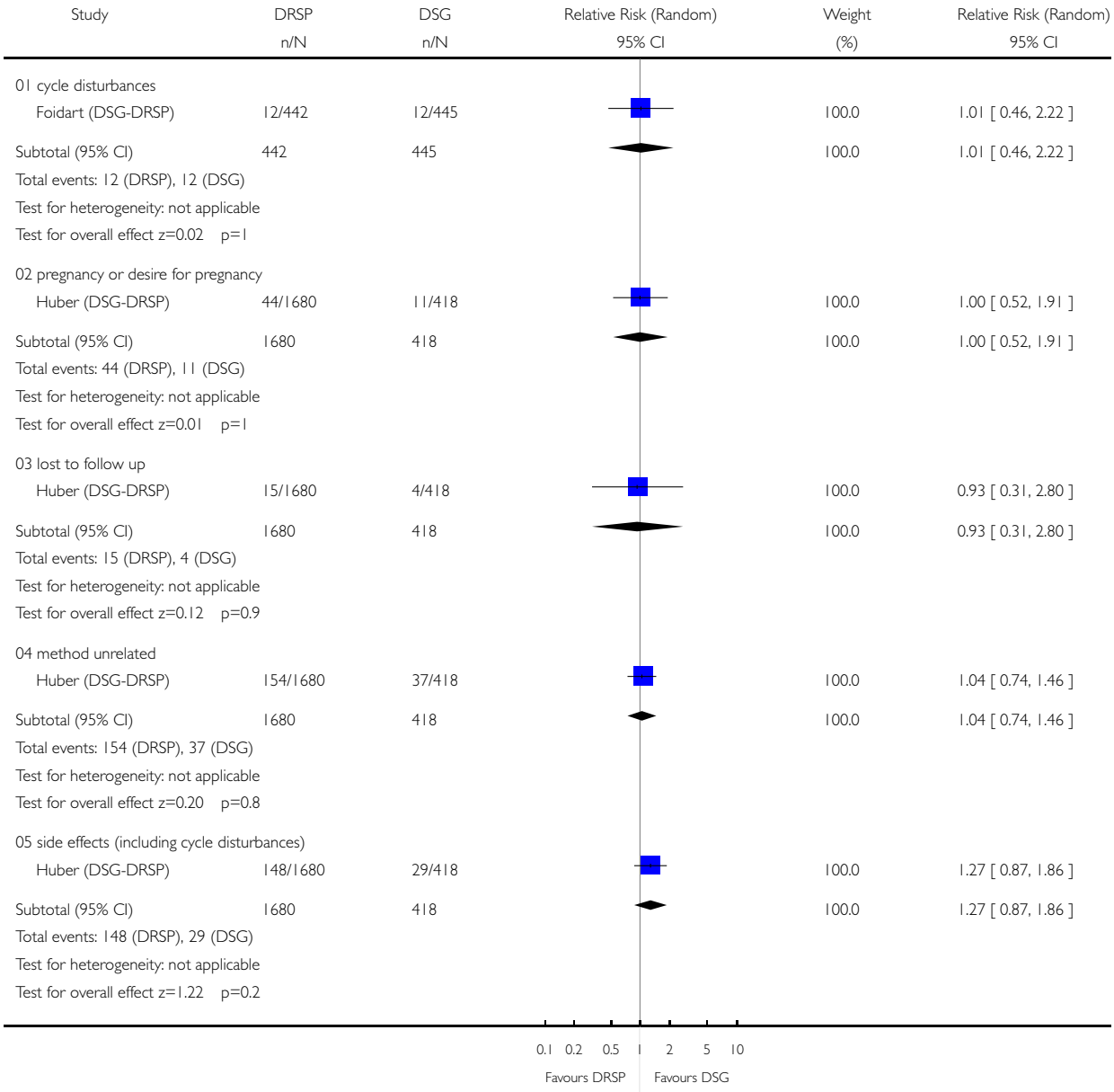
Test for overall effect z=1.01 p=0.3

Analysis 14.03. Comparison 14 Drospirenone vs Desogestrel, Outcome 03 Reasons for discontinuation

Review: Progestogens in combined oral contraceptives for contraception

Comparison: 14 Drospirenone vs Desogestrel

Outcome: 03 Reasons for discontinuation



Analysis 14.04. Comparison 14 Drospirenone vs Desogestrel, Outcome 04 Cycle control

Review: Progestogens in combined oral contraceptives for contraception

Comparison: 14 Drospirenone vs Desogestrel

Outcome: 04 Cycle control

Study	DRSP n/N	DSG n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
01 intermenstrual bleeding					
Huber (DSG-DRSP)	514/1680	131/418		100.0	0.98 [0.83, 1.14]
Subtotal (95% CI)	1680	418		100.0	0.98 [0.83, 1.14]
Total events: 514 (DRSP), 131 (DSG)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.30 p=0.8					

Analysis 14.05. Comparison 14 Drospirenone vs Desogestrel, Outcome 05 Side-effects

Review: Progestogens in combined oral contraceptives for contraception

Comparison: 14 Drospirenone vs Desogestrel

Outcome: 05 Side-effects

Study	DRSP n/N	DSG n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
01 breast tenderness					
Foidart (DSG-DRSP)	53/442	41/443		60.3	1.30 [0.88, 1.91]
Huber (DSG-DRSP)	108/1680	19/418		39.7	1.41 [0.88, 2.28]
Subtotal (95% CI)	2122	861		100.0	1.34 [0.99, 1.81]
Total events: 161 (DRSP), 60 (DSG)					
Test for heterogeneity chi-square=0.08 df=1 p=0.78 I^2 =0.0%					
Test for overall effect z=1.92 p=0.05					
02 headache					
Foidart (DSG-DRSP)	48/442	60/445		50.9	0.81 [0.56, 1.15]
Huber (DSG-DRSP)	165/1680	26/418		49.1	1.58 [1.06, 2.35]
Subtotal (95% CI)	2122	863		100.0	1.12 [0.58, 2.17]
Total events: 213 (DRSP), 86 (DSG)					
Test for heterogeneity chi-square=6.14 df=1 p=0.01 I^2 =83.7%					
Test for overall effect z=0.34 p=0.7					
03 migraine					
Foidart (DSG-DRSP)	9/442	9/445		36.6	1.01 [0.40, 2.51]
Huber (DSG-DRSP)	35/1680	10/418		63.4	0.87 [0.43, 1.74]

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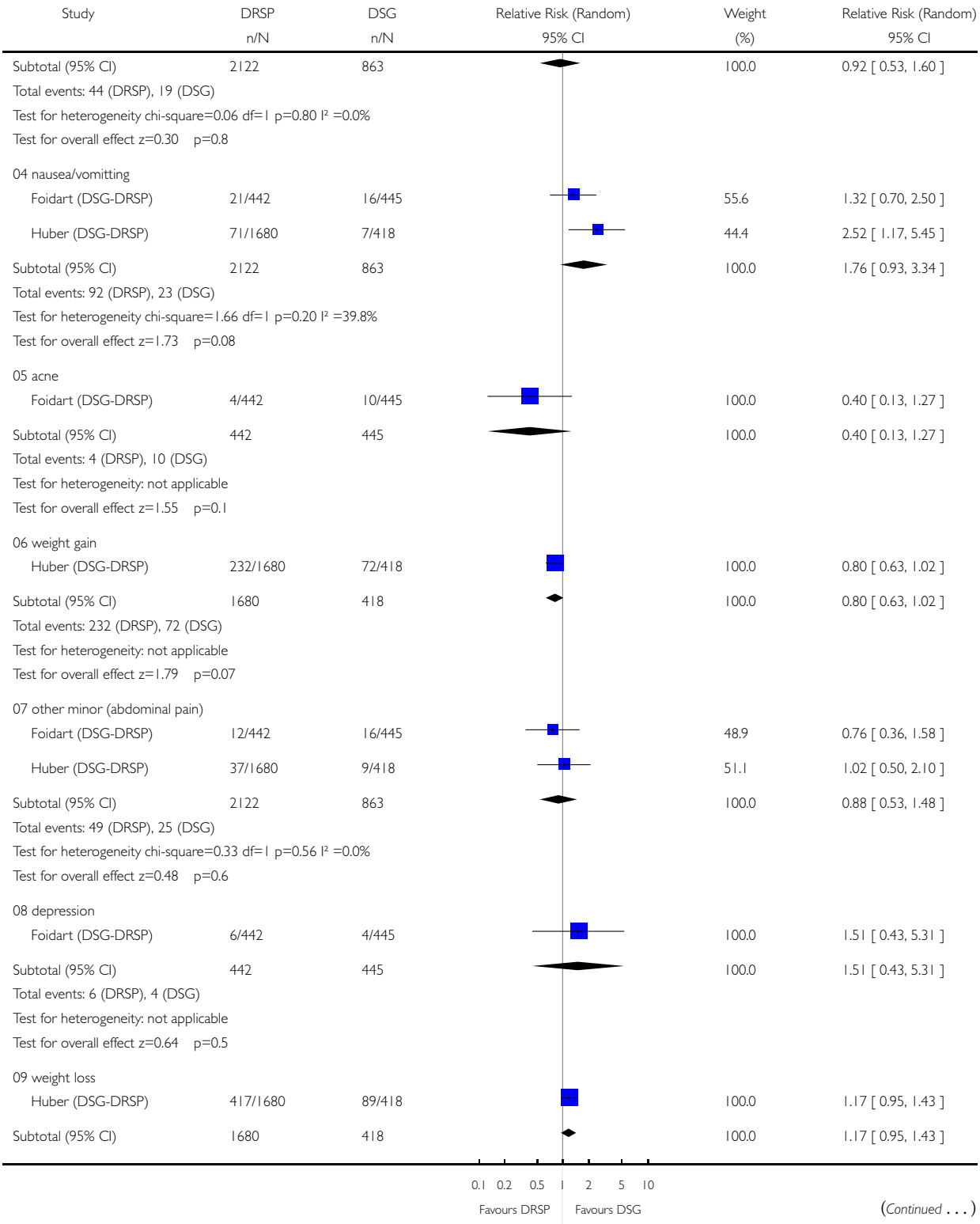

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Study	DRSP n/N	DSG n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
Total events: 417 (DRSP), 89 (DSG)					
Test for heterogeneity: not applicable					
Test for overall effect z=1.49 p=0.1