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20 µg versus >20 µg estrogen combined oral contraceptives for contraception (Review)

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[Intervention Review]

20 µg versus >20 µg estrogen combined oral contraceptives for contraception

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ABSTRACT

Background

Concern about estrogen-related adverse effects has led to progressive reductions in the estrogen dose in combination oral contraceptives (COCs). However, reducing the amount of estrogen to improve safety could result in decreased contraceptive effectiveness and unacceptable changes in bleeding patterns.

Objectives

To test the hypothesis that COCs containing ≤ 20 µg ethinyl estradiol (EE) perform similarly as those containing > 20 µg in terms of contraceptive effectiveness, bleeding patterns, discontinuation, and side effects.

Search methods

In July 2013, we searched CENTRAL, MEDLINE, and POPLINE, and examined references of potentially eligible trials. We also searched for recent clinical trials using ClinicalTrials.gov and ICTRP. No new trials met the inclusion criteria. Previous searches included EMBASE. For the initial review, we wrote to oral contraceptive manufacturers to identify trials.

Selection criteria

English-language reports of randomized controlled trials were eligible that compare a COC containing ≤ 20 µg EE with a COC containing > 20 µg EE. We excluded studies where the interventions were designed to be administered for less than three consecutive cycles or to be used primarily as treatment for non-contraceptive conditions. Trials had to report on contraceptive effectiveness, bleeding patterns, trial discontinuation due to bleeding-related reasons or other side effects, or side effects to be included in the review.

Data collection and analysis

One author evaluated all titles and abstracts from literature searches to determine whether they met the inclusion criteria. Two authors independently extracted data from studies identified for inclusion. We wrote to the researchers when additional information was needed. Data were entered and analyzed with RevMan.

Main results

No differences were found in contraceptive effectiveness for the 13 COC pairs for which this outcome was reported. Compared to the higher-estrogen pills, several COCs containing 20 µg EE resulted in higher rates of early trial discontinuation (overall and due to adverse events such

as irregular bleeding) as well as increased risk of bleeding disturbances (both amenorrhea or infrequent bleeding and irregular, prolonged, frequent bleeding, or breakthrough bleeding or spotting).

Authors' conclusions

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

PLAIN LANGUAGE SUMMARY

Birth control pills with 20 µg estrogen versus more than 20 µg estrogen

Concerns about safety have led to making birth control pills with less of the hormone estrogen. Pills with less estrogen might not work as well to prevent pregnancy and could cause bleeding problems. This review looked at studies that compared pills with 20 µg ethinyl estradiol versus pills that have more estrogen.

In July 2013, we did computer searches for randomized trials of pills with 20 µg estrogen versus more estrogen. We did not find any new trials. For the initial review, we also wrote to researchers and makers of birth control pills to find other trials.

Studies had to be written in the English language, include at least three cycles, and focus on birth control. The trials had to report on pregnancy, bleeding problems, or stopping the pills early. We also looked at side effects.

More women taking the pills with less estrogen quit the studies early. The women on less estrogen also had more bleeding problems than those taking pills with more estrogen. Pregnancy rates seemed to be the same between groups, but the studies may not have been large enough to know for sure. This review did not focus on the rare events needed to test whether birth control pills with 20 µg estrogen were safer. Also, most trials compared pills with different types of the hormone progestin, which could also affect bleeding patterns. The high losses in many trials make the results hard to interpret.

BACKGROUND

Since the introduction of combined estrogen and progestin oral contraceptives (COCs) in the early 1960s, the dose of estrogen has been reduced progressively. COCs containing 50 µg of estrogen or more comprised over 99% of OC retail prescriptions in the United States (USA) in 1968 (Gerstman 1991). Twenty years later, less than 2% of these prescriptions were for 50-µg estrogen COCs. The reduction in the estrogen dose has been in response to two main discoveries. First, concern about estrogen-related adverse effects has driven the search for lower-dose estrogen COCs. COC use has been linked in epidemiological studies to breast cancer (CGHFBC 1996), and estrogen has been associated with a number of adverse events, including cerebrovascular complications, thromboembolic incidents, and myocardial infarction (Anonymous 2000). Low-estrogen COCs have been formulated in an attempt to reduce the risk of these rare events. Second, the discovery that estrogen and progestin act synergistically to inhibit ovulation revealed that contraceptive efficacy could be maintained with lower doses of each component. COCs with less than 50 µg estrogen contain ethinyl estradiol (EE) as the estrogenic component in combination with a progestin (Nelson 2007). Twenty-µg EE COCs (Table 1) first became available in the 1970s and, by 1998, accounted for about 8% of COC prescriptions in the USA (Wallach 2000). COC pills with 15 µg of estrogen contain the lowest estrogen dose available (Table 2) and have been approved for use in some countries in Europe, South America and elsewhere (IPPF 2013).

Reducing the estrogen dose to improve safety also could decrease contraceptive effectiveness and cycle control. Contraceptive effectiveness depends both on individual susceptibility and compliance. Determining the optimal estrogen dose required is complicated by high biological variation. The inter-individual variation in the blood levels of exogenous hormones has been estimated to vary tenfold (Guillebaud 1989) and intra-individual differences also occur. Consequently, the lowest estrogen dose needed to prevent pregnancy while also maintaining acceptable cycle control and minimal adverse side effects could vary substantially both among women and within an individual woman at different times. Also, the contraceptive effectiveness of low-estrogen COCs could be influenced more by missed pills or drug interactions (Elstein 1994).

Contraceptives with lower doses of estrogen also may compromise cycle control. Evaluating these concerns is difficult due to the lack of uniformity in the analyses of bleeding patterns. Recognizing the ambiguities in the interpretation of trial results and the comparison of contraceptive products, the World Health Organization (WHO) issued recommendations to standardize the collection and analysis of bleeding pattern data (Belsey 1986). Recently, Mishell 2007a reviewed methods used for collecting and analyzing bleeding data for trial reports of combined hormonal contraceptives. Mishell 2007b then developed recommendations for designing trials and for data collection and analysis of bleeding data. However, when this review was initially conducted, Belsey 1986 was considered the standard. 'Bleeding' was defined as a bloody vaginal discharge that requires sanitary protection whereas 'spotting' does not require protection. A 'bleeding or spotting episode' consists of one or more days with bleeding or spotting that is bounded by days without bleeding or spotting. The WHO advised that the woman, rather than the cycle, be used as the unit of analysis; this avoids disproportionate weight in the analysis from women who contribute more cycles and also prevents artificially precise confidence intervals (Belsey 1986). Outcomes should be measured using reference periods of at least 90 days, an amount of time that was sufficiently short to allow the identification of changes over time, while also long enough for bleeding patterns to be characterized properly. The reference period was modified to 84 days in a recent trial of COCs to correspond to the typical length of three pill cycles (Miller 2001). The WHO identified five bleeding outcomes to be included: the proportion of women with prolonged, frequent, infrequent, or irregular bleeding or spotting episodes and the proportion with amenorrhea during the reference period (Belsey 1986). They noted that the timing of bleeding is an additional issue particular to COC research and that terms for assessing bleeding associated with the pill-free interval (e.g., intermenstrual or breakthrough bleeding) should be defined and evaluated. However, the reporting of trial results often does not conform to the WHO recommendations. Instead many trials report only cyclical data for outcomes related to the control of the menstrual cycle, often without specifying precise definitions for the terms used.

Low-estrogen COCs have been attributed with more breakthrough bleeding and spotting (Nelson 2007). Although bleeding irregularities do not threaten health, sub-optimal cycle control impairs the acceptance of and adherence to the contraceptive. A large, six-month USA study found that 46% of pill users discontinued the method due to side effects or physician recommendations, and about 12% of these women identified bleeding irregularities as the primary reason for discontinuation (Rosenberg 1998). The progestin type and dosing regimen are also thought to affect cycle control. Reviews of COCs suggest that levonorgestrel results in better cycle control than norethindrone and that gestodene performs better than desogestrel and levonorgestrel (Rosenberg 1992; Maitra 2004). Given the possible relationship between progestin type and bleeding patterns, a meta-analysis of low-estrogen contraceptives should combine only trials that compare identical drugs, dosages, and regimens.

A secondary concern related to reducing the estrogenic component involves possible decreases in the non-contraceptive benefits of COCs. Combined oral contraception confers health benefits, such as the prevention of ovarian cancer and endometrial cancer and the reduction of acne (Nelson 2007), and the effect of reducing the estrogen level on these preventive benefits is unclear. Ness 2000 found that the reduction in the risk of ovarian cancer was similar for COCs containing less than 50 µg estrogen compared to those with 50 µg or more. Because 20-µg estrogen COCs were not analyzed separately from the other low-estrogen pills, the question remains as to whether this low dose is sufficient to maintain the protective effect. Contemporary low-estrogen COC pills may grant no protection against functional ovarian cysts, as was observed with COCs containing higher doses of estrogen (Holt 1992). As to acne reduction, a COC containing 20 µg estrogen and 100 µg levonorgestrel had better results than a placebo in Thiboutot 2001. However, whether the low-dose estrogen contraceptive is as effective in reducing acne as a higher-dose estrogen COC is unknown. Furthermore, low-estrogen contraceptives might vary in their ability to improve acne.

Combined contraceptives should have high contraceptive effectiveness, while maintaining cycle control and causing minimal adverse effects. The present review evaluates COCs containing 20

µg EE or less with those containing a higher dose of EE regarding these key outcomes. Rare adverse events, though, were not a focus because randomized controlled trials generally do not have sufficient power to study infrequent events, even when combined.

OBJECTIVES

To test the hypothesis that COCs containing ≤ 20 µg of EE perform similarly as those containing > 20 µg in terms of contraceptive effectiveness, bleeding patterns, discontinuation, and side effects.

METHODS

Criteria for considering studies for this review

Types of studies

Published or unpublished randomized controlled trials that compare a COC containing 20 µg of EE or less with a COC containing more than 20 µg EE were eligible. Trials were restricted to those reported in English (Higgins 2011).

Types of participants

Women of reproductive age without medical contraindications to COCs, irrespective of previous COC history were eligible.

Types of interventions

Eligible interventions included any COC containing ≤ 20 µg of EE that was compared with a COC containing > 20 µg EE. Trial interventions had to be designed to be administered for a minimum of three consecutive cycles to be eligible for inclusion. Studies were excluded if the interventions were used primarily as treatment for non-contraceptive conditions (e.g., acne, anovulation, dysmenorrhea, menorrhagia, pelvic pain, or endometriosis).

Types of outcome measures

To be included, trials had to report on contraceptive effectiveness, bleeding patterns, side effects, or trial discontinuation due to bleeding-related reasons or other side effects. Those that measured only biochemical changes were not eligible. The outcomes were measured as follows:

1) Contraceptive effectiveness

- Cumulative life-table or Kaplan-Meier pregnancy rate
- Pregnancy Pearl index
- Proportion of women pregnant

2) Discontinuation (overall, due to bleeding-related reasons, and due to other side effects)

- Cumulative life-table or Kaplan-Meier discontinuation rate
- Proportion of women who did not complete the trial
- Discontinuation Pearl index

3) Bleeding patterns

Cycle control during reference periods of 90 days (Belsey 1986) or 84 days (Miller 2001)

- Proportion of women with amenorrhea
- Proportion of women with prolonged (i.e., longer than 14 days) bleeding or spotting episodes
- Proportion of women with frequent (i.e., more than 5) bleeding or spotting episodes
- Proportion of women with infrequent (i.e., less than 3) bleeding or spotting episodes
- Proportion of women with irregular bleeding (i.e., 3 to 5 bleeding or spotting episodes and less than 3 bleeding or spotting-free intervals of at least 14 days)

Proportion of women with amenorrhea or breakthrough (also known as intermenstrual) bleeding or spotting for cycle three or cycle six, or if data for these cycles were not reported, for the last cycle of follow up

4) Side effects

Proportion of women experiencing any side effect reported

Search methods for identification of studies

Electronic searches

We searched the computerized databases the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, and POPLINE for eligible trials using a list of brand names of COCs containing 20 µg of EE or less (IPPF 2013). We also searched for trials via ClinicalTrials.gov and ICTRP. The strategies are shown in Appendix 1. Previous strategies, which also included EMBASE, can be found in Appendix 2.

Searching other resources

We assessed the references of eligible trials. For the initial review, we wrote to COC manufacturers to request information about any other published or unpublished trials not discovered in our search.

Data collection and analysis

One author evaluated the titles and abstracts located in the literature searches to determine whether they met the inclusion criteria. Two authors independently extracted data from the studies identified for inclusion. We wrote to the researchers when clarifications or additional data were needed. Data were entered and analyzed with RevMan. For trials that included more than two intervention groups, regardless of whether the authors identified a control group, we treated the ≤ 20 µg EE contraceptive as the referent and compared it to the other study groups.

We calculated Peto odds ratios (ORs) with 95% confidence intervals (CIs) for all dichotomous outcomes and mean differences using fixed-effect models with 95% CIs for all continuous outcomes. Contraceptive effectiveness and early discontinuation also were presented as Pearl indices or survival analysis estimates when these measures were available. Pearl indices are calculated by the number of events divided by the total person-time at risk of the event (Trussell 1998). Because contraceptive failure rates typically decrease with duration of use, the Pearl index rate tends to decline as the amount of person-time contributed by each woman increases. Thus, rates from two studies will not be comparable if the studies differed in duration. Although the Pearl method is a sub-optimal measurement, it was included in the review because its use remains prevalent. Survival analyses, which include life-table and Kaplan-Meier methods, are preferred measures. Because RevMan 4.2, used for the initial review, was not designed to include Pearl indices or measures of survival analysis, these estimates were presented in Table 3 and Table 4. Most of the studies that

included contraceptive effectiveness data simply reported the number of women who became pregnant, and we used these proportions of women to calculate ORs in RevMan. However, these measures potentially are biased in favor of OCs that result in higher discontinuation rates since women who discontinue the study treatment or study participation or who are lost to follow up were unlikely to have been followed to determine whether they became pregnant.

We included all bleeding-related outcomes reported in the eligible trials (e.g., WHO bleeding terms, breakthrough bleeding, spotting, and amenorrhea). Following WHO recommendations (Belsey 1986), we used women, rather than cycles, as the unit of analysis when possible. For studies that did not use the recommended 90- or 84-day reference period, we extracted bleeding-related data from the third and the sixth cycle, or when neither of these was available, from the last cycle of follow up. Although the choice of these cycles was arbitrary, the standardization in the data extraction facilitated comparisons across trials. Definitions of bleeding-related outcomes were described in Characteristics of included studies.

Interval estimation considers both the magnitude of the estimate and the width of the confidence intervals when assessing potential relationships (Rothman 1998). While all available data are presented in the tables, we highlighted the findings that suggest possible differences in COCs based on interval estimation as well as P values.

The review was limited to the analytic method (e.g., intent-to-treat, per-protocol, or a modification of either type) used in the trial report. We combined study results for meta-analysis only when identical drugs, dosages, and regimens were compared. Homogeneity was assessed by examining the results of both a fixed-effect model and a random-effects model. Because the chi-squared test for heterogeneity is a low-power test, the alpha-level was set at 0.10. We conducted sensitivity analyses by examining the effect of deleting each study in turn to test the robustness of any result that appeared to be based on heterogeneous combinations. We critically appraised validity of trials by assessing the potential for bias resulting from the study design, blinding, randomization method, group allocation concealment, and loss to follow up.

RESULTS

Description of studies

Results of the search

The 2013 search resulted in 201 unduplicated references: 162 from the main databases, 10 from other sources such as reference lists, and 29 ongoing or recent clinical trials. We did not find any RCTs that met our eligibility criteria for this review. One new study was excluded because it reported on pooled analysis from two uncontrolled trials (Marr 2012).

Included studies

The search strategy yielded 21 primary articles that were eligible for the review. Most trials recruited healthy, reproductive-age women without contraindications to COC use. Trials ranged in duration from 3 to 24 treatment cycles with most designed for 6 or 12 treatment cycles. The location was not described for 7 trials; the remaining 14 trials were conducted in North America, South America, Europe or Asia. The trials ranged from a single site (four trials) to 110 sites except for three trials with unspecified number of sites. Five trials included more than two eligible intervention arms. The trials compared 20 different COC pairs.

Risk of bias in included studies

The reporting of randomized clinical trials should include details on the participants, blinding, randomization method, group allocation concealment method, participant flow, and statistical methods (CONSORT 2009). One trial blinded only the study observer (Appel 1987). Three trials blinded the participants and either the clinic staff (Bounds 1979; WHO 1982) or the investigator (Endrikat 2001). Two articles described double-blinding but did not specify who was blinded (Akerlund 1993; Endrikat 1997). The remaining trials either were open (12 trials) or did not mention blinding (3 trials). Fourteen reports did not provide any details of the method of randomization. Reisman 1999 reported the use of sealed envelopes for allocation concealment; the remaining trials did not provide any details regarding attempts to conceal the allocation process. None of the articles described the person responsible for implementing the randomization process or the use of a centralized location for randomization.

The number of participants who were recruited, randomized, received treatment, lost to follow up, discontinued early, and excluded from the analysis should be reported in the details of the participant flow (CONSORT 2009). Only WHO 1982 reported the number of recruited women who were screened for trial participation. All trials reported the total number of women randomized, although these figures may have been the total numbers analyzed rather than randomized. The number of women reportedly randomized in the trials ranged from 20 to 2894. Four trials did not specify the number of women randomized to each study group (Bounds 1979; Appel 1987; Teichmann 1995; Endrikat 2001). Eleven trials reported excluding randomized women from the analysis, usually for protocol violations. Kluft 2006 used intent-to-treat analysis. Hampton 2001 reported using an intent-to-treat analysis for contraceptive effectiveness but did not specify the analytic method used for the remaining outcomes. Endrikat 2001 reported both modified intent-to-treat and per-protocol analyses without specifying which method was used for the results presented. Seven trials described using a per-protocol or modified per-protocol analysis based on the exclusion of women or treatment cycles from the analysis for failure to comply with the protocol (Akerlund 1993; Brill 1996; Winkler 1996; Chavez 1999; Kaunitz 2009; Reisman 1999; Skouby 2005). However, the decision to exclude the woman or the cycle was unclear in Chavez 1999 because different sections of the article reported conflicting procedures. Inauen 1991 had complete follow up and no early discontinuation. The remaining trials did not specify the analytic method used. Three trials did not report the proportion of women completing the study (Bounds 1979; Brill 1996; Winkler 1996), and the proportion ranged from 46% to 94% in the remaining trials.

Effects of interventions

Contraceptive effectiveness

No significant differences were found in contraceptive effectiveness for the 13 COC pairs for which this outcome was reported (Table 3).

Early Discontinuation

The COC containing EE 20 µg and norethindrone acetate 1 mg had higher life-table rates of early discontinuation (overall, due to medical reasons, and due to amenorrhea) than its five comparison COCs (Table 4), but P values were the only measure of variability provided for the estimates (WHO 1982). The remaining six comparisons with data for overall discontinuation found no significant differences between groups. Differences in bleeding-related discontinuations were apparent for three comparisons. Women in the EE 20 µg and desogestrel 150 µg group had an OR of discontinuation due to irregular bleeding 2.59 (95% CI 1.35 to 5.00) times that of the EE 30 µg and desogestrel 150 µg group (Akerlund 1993). Women assigned to use the COC with EE 20 µg and desogestrel 150 µg were 2.4 times as likely to discontinue due to metrorrhagia 2.35 (95% CI 1.16 to 4.77) than those in the EE 30 µg and gestodene 75 µg group (Kirkman 1994; Bruni 2000). In addition, women on EE 20 µg and norethindrone acetate 1 mg were more likely to discontinue due to bleeding than women on EE 30 µg and levonorgestrel 150 µg (Bounds 1979).

Bleeding Patterns

EE 20 mg and desogestrel COCs versus higher-estrogen COCs

Women in the EE 20 µg and desogestrel 150 µg group were more likely than those in the EE 30 µg and desogestrel 150 µg group to report irregular bleeding (OR 1.56; 95% CI 1.10 to 2.20) and a longer duration of irregular bleeding during the third cycle (mean difference 0.70 days; 95% CI 0.30 to 1.10) (Akerlund 1993). No significant differences in amenorrhea or the duration of irregular bleeding remained by the sixth cycle. The lower-dose estrogen group was also more likely to report the occurrence of irregular bleeding (OR 1.69; 95% CI 1.07 to 2.69) or prolonged withdrawal bleeding (OR 1.98; 95% CI 1.03 to 3.78) at least once throughout the trial than the higher-dose estrogen group. The EE 20 µg and desogestrel 150 µg group versus the EE 30 µg and gestodene 75 µg had an OR of irregular bleeding of 2.51 (95% CI 1.77 to 3.56) during the third cycle and 1.72 (95% CI 1.15 to 2.55) during the sixth cycle (Kirkman 1994). Women assigned to use EE 20 µg and desogestrel 150 µg were also more likely to report metrorrhagia (i.e., bleeding from the uterus that is not associated with menstruation) at least once during the trial than women using EE 30 µg and gestodene 75 µg (OR 1.67; 95% CI 1.05 to 2.66) (Brill 1996) or women using EE 30-40-30 µg and gestodene 50-70-100 µg (OR 2.28; 95% CI 1.39 to 3.73) (Bruni 2000).

Inauen 1991 compared a COC containing EE 20 µg and desogestrel to a second COC and also reported bleeding outcomes. However, the trial had insufficient power to detect major differences between the groups.

EE 20µg and gestodene COCs versus higher-estrogen COCs

Five trials compared the same gestodene dose (75 µg) but differing EE doses (20 µg versus 30 µg) with a standard (Brill 1996; Winkler 1996; Endrikat 1997; Taneepanichskul 2002) or an extended cycle length (Endrikat 2001). Limitations to assessing bleeding pattern changes included small sample sizes, insufficient data reported, and varying definitions.

EE 20 µg and levonorgestrel COCs versus higher-estrogen COCs

The trials comparing a low-estrogen and levonorgestrel COC to a triphasic norethindrone COC found no difference in amenorrhea between the groups at the third cycle (Chavez 1999; Reisman 1999).

EE 20 µg and drospirenone COC versus higher-estrogen COC

In Kaunitz 2009, the low dose group (EE 20 µg plus drospirenone) had more unscheduled bleeding days than the group with EE 25 µg and norgestimate 180-215-250 µg (mean difference 1.00; 95% CI 0.44 to 1.56).

EE 20 µg and norethindrone acetate COCs versus higher-estrogen COCs

The low-dose COC containing EE 20 µg and norethindrone acetate 1 mg fared worse than the COC EE 30 µg and levonorgestrel 150 µg for three bleeding outcomes during the first to third cycles: 1) frequent bleeding (OR 2.92; 95% CI 2.08 to 4.09); 2) infrequent bleeding (OR 2.84; 95% CI 1.80 to 4.46); and 3) irregular bleeding (OR 4.01; 95% CI 2.12 to 7.61) (WHO 1982). The low-dose COC also had worse bleeding outcomes during the first to third cycles when compared to a COC with the same norethindrone acetate dose (1 mg) but more estrogen (EE 50 µg): 1) frequent bleeding (OR 4.59; 95% CI 3.24 to 6.51); 2) infrequent bleeding (OR 3.08; 95% CI 1.95 to 4.86); 3) irregular bleeding (OR 5.33; 95% CI 2.74 to 10.34); and 4) prolonged bleeding (OR 3.11; 95% CI 1.83 to 5.27).

Similarly, EE 20 µg and norethindrone acetate 1 mg resulted in a longer duration of bleeding or spotting days during the third cycle when compared to three higher-dose COCs containing the same progestin type: 1) EE 30 µg and norethindrone acetate 1.5 µg (mean difference 1.10 days; 95% CI 0.37 to 1.83); 2) EE 50 µg and norethindrone acetate 1 mg (mean difference 1.20 days; 95% CI 0.43 to 1.97); and 3) EE 20-30-50 µg and norethindrone acetate 1-1.5-1 mg (mean difference 1.60 days; 95% CI 0.94 to 2.26) (Appel 1987). Women in the low-dose COC group (EE 20 µg and norethindrone acetate 1 mg) also were more likely to report frequent bleeding (OR 1.97; 95% CI 1.42 to 2.73), infrequent bleeding (OR 1.95; 95% CI 1.27 to 3.00), and irregular bleeding (OR 2.38; 95% CI 1.31 to 4.31) during the first to third cycles than those in the EE 50 µg and norethindrone acetate 1 mg group (WHO 1982). (The groups did not differ significantly in the frequency of prolonged bleeding during the first three cycles.) Likewise, women assigned to this low-dose COC reported more infrequent bleeding (OR 1.88; 95% CI 1.22 to 2.90) and irregular bleeding (OR 1.92; 95% CI 1.08 to 3.43) than those using EE 35 µg and norethindrone acetate 400 µg, but no difference in frequent or prolonged bleeding (WHO 1982).

The sole trial to compare EE 20 µg and norethindrone acetate 1 mg to mestranol 50 µg and norethindrone 1 mg found the low-dose COC group had a higher risk of frequent bleeding (OR 2.82; 95% CI 2.00 to 3.97), infrequent bleeding (OR 2.49; 95% CI 1.58 to 3.91), irregular bleeding (OR 4.85; 95% CI 2.49 to 9.43), and prolonged bleeding (OR 2.67; 95% CI 1.58 to 4.52) during the first to third cycles (WHO 1982). Finally, the COC with EE 20 µg and norethindrone acetate 1 mg resulted in more breakthrough bleeding during the third cycle (OR 2.79; 95% CI 2.09 to 3.74) and during the sixth cycle (OR 2.40; 95% CI 1.78 to 3.24) compared to the COC containing EE 25 µg and norgestimate 180-215-250 µg (Hampton 2001). When breakthrough spotting was included with the outcome breakthrough bleeding, the ORs were similar to those for breakthrough bleeding alone. The bleeding data were re-

analyzed with new criteria for a secondary article; the pattern was the same. However, the percentages with unscheduled bleeding at cycle six were 33.5% for EE 20 µg and norethindrone acetate 1 mg versus 21% for EE 25 µg and norgestimate 180-215-250 µg, while the earlier estimates of breakthrough bleeding or spotting were 22.2% and 10.3%, respectively.

Side effects

Side effects were measured as the proportion of women experiencing the event during the study. Three of the six COC pairs with side effects reported found differences. The ORs of headache (1.71; 95% CI 0.94 to 3.11), dizziness (7.65; 95% CI 1.54 to 38.08), mood changes (1.93; 95% CI 1.05 to 3.56), and weight gain (2.46; 95% CI 1.04 to 5.84) were higher for the COC EE 20 µg and desogestrel 150 µg group than the COC EE 30 µg and desogestrel 150 µg group (Akerlund 1993). However, women in the COC EE 20 µg and desogestrel 150 µg group were less likely to report breast pain (OR 0.70; 95% CI 0.47 to 1.05) and dizziness (OR 0.40; 95% CI 0.17 to 0.93), than those in the EE 30-40-30 µg and gestodene 50-70-100 µg group (Bruni 2000). Also, compared to women in the 35 µg and norethindrone 500-750-1000 µg, group women in the 20 µg and levonorgestrel 100 µg were less likely to report breast pain (OR 0.45; 95% CI 0.22 to 0.93) or vomiting (OR 0.33; 95% CI 0.11 to 0.96) (Chavez 1999).

Heterogeneity

Few comparisons could be combined in meta-analysis because most studies differed in the COC pairs that were compared. Only two of the comparisons that were eligible for meta-analyses appeared to combine heterogeneous estimates with either fixed-effect or random-effects models. The risk of headache differed in the two studies that compared COCs with gestodene 75 µg but different EE doses (Brill 1996; Endrikat 1997), but neither trial found significant ORs for this outcome. The increased rate of discontinuation due to adverse events in the EE 20 µg and levonorgestrel 100 µg group versus the EE 35 µg and norethindrone 500-750-1000 µg group was the result of Reisman 1999; Chavez 1999 did not show a difference in discontinuation for this reason between the two study groups.

DISCUSSION

Summary of main results

The included trials provide insufficient evidence to determine whether the contraceptive effectiveness of COCs containing 20 µg of EE differs from those with higher estrogen doses. Most studies were underpowered to study pregnancy as a primary outcome; larger sample sizes are required because COCs are highly effective and few pregnancies occurred. Furthermore, most pregnancy estimates could not be combined in meta-analysis because the study COCs contained different progestins. Research using ultrasonography to measure the growth of follicle-like structures suggests that low-estrogen pills could have a reduced margin of safety from missed pills or drug interactions (Teichmann 1995; Spona 1996). Increased risk of pregnancy from this possible lack of 'forgiveness' for missed pills among the low-dose estrogen users might not have been detected in the present review. Also, many studies excluded women from the analysis for protocol violations, including failure to adhere to the daily pill intake, which could have biased the results.

Early discontinuation from the trial can be considered a proxy measure of method acceptability. Overall discontinuation rates did not vary substantially for most COCs compared. Four comparisons showed higher rates of discontinuation due to adverse events for EE 20 µg pills than their higher-estrogen comparison COCs, and one trial found more medical-related discontinuations for the low-dose estrogen COC than its five high-dose estrogen counterparts. However, discontinuation due to adverse events or medical reasons provides limited information because this outcome can combine disparate reasons for quitting the trial early. For example, amenorrhea is different than excessive or irregular bleeding, and studies should separate these. On the other hand, the included trials might have been underpowered to detect differences between specific reasons for discontinuation. Few trials reported data for discontinuation due to specific adverse events.

Several COCs containing 20 µg EE resulted in higher rates of outcomes related to lack of bleeding (amenorrhea and infrequent bleeding) as well as changes in bleeding (irregular, prolonged, frequent, and breakthrough bleeding) than their higher-estrogen comparison pills. Comparing bleeding data from studies is complicated by lack of uniformity in the outcomes used. Also, determining the clinical importance of changes in bleeding patterns is difficult since women in different cultures may view menstrual patterns and assess the acceptability of any changes differently. For example, amenorrhea or infrequent bleeding may be more acceptable in certain cultural settings than others. Finally, the progestin type and dose as well as the ratio of the progestin and estrogen doses could also affect bleeding patterns. Research suggests that certain progestin types could result in better cycle control than others (Rosenberg 1992). While bleeding irregularities do not pose a health risk, they reduce method acceptability and adherence by users.

Overall completeness and applicability of evidence

The randomized controlled trial design, generally, is not suited for evaluating the risk of rare adverse events (e.g., thromboembolic events or myocardial infarction). Studies assessing various hemostatic outcomes as markers for these rare events indicate that the effects on these intermediate variables might be less with 20 µg pills (Basdevant 1993; Norris 1996; Winkler 1996). However, usual tests of hemostasis do not predict clinical events, so these intermediate outcomes have no clinical utility.

Quality of the evidence

Trials often failed to report a measure of variability for outcome data (e.g., reporting dichotomous outcomes in percentages, rather than absolute numbers, not including standard deviation or confidence interval for continuous outcomes). The lack of variability estimates severely constrains the interpretation of a point estimate and, consequently, prevented their inclusion in this review. A second limitation was that none of the trials described using adequate steps to conceal the allocation process during randomization. Failure to conceal the allocation sequence can lead to biased results (Schulz 2002). Furthermore, most trials were unblinded or did not report blinding of group assignment, and the knowledge of the group assignment could have introduced bias. Losses to follow up were high in many trials, which can bias the results (Strauss 2005). Finally, all of the trials appear to have been funded by pharmaceutical companies except for WHO 1982 and two that did not specify an industry relationship (Basdevant

1993; Teichmann 1995). Pharmaceutical sponsorship represents a potential conflict of interest and can introduce bias in terms of the study design, analysis or reporting of unfavorable results (Lexchin 2003).

AUTHORS' CONCLUSIONS

Implications for practice

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

Implications for research

Large randomized controlled trials comparing regimens with the same progestin type are needed to determine whether the contraceptive effectiveness of 20-µg EE COCs is similar to that of their higher-estrogen counterparts. Likewise, studies of bleeding patterns should compare pills containing the same progestin type but different estrogen doses. Trials should use standardized methods for collecting and analyzing bleeding data (Mishell 2007b). Trials should also employ better research methods, e.g., adequate allocation concealment (Schulz 2002), and follow CONSORT guidelines for reporting the results (CONSORT 2009). Higher follow-up rates are essential for meaningful interpretation of the results.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Akerlund 1993

Methods	Six sites in Norway, two in Sweden and one in Denmark. 12 treatment cycles. Double-blinded but did not specify who was blinded.
Participants	Women aged 18 to 35 (Norway sites) or 18 to 40 (Sweden and Denmark sites) years. Excluded heavy smoking among women 35 years of age; risk factors for or history of certain diseases; lactation; and certain antibiotics.
Interventions	EE 20 µg and desogestrel 150 µg (N=500) versus EE 30 µg and desogestrel 150 µg (N=500).
Outcomes	Contraceptive efficacy, cycle control, and side effects. 'Withdrawal' bleeding defined as bleeding that began within the pill-free period and did not exceed eight days. 'Irregular' bleeding defined as any other bleeding.
Notes	Allocated with simple random table. Excluded randomized women from the analysis. 67% (672/1000) completed study.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	Allocation concealment not reported.

Appel 1987

Methods	30 sites in unreported location(s). Four treatment cycles. Observer blinded. Tablets were supplied from manufacturer in standard, unmarked packs.

Appel 1987 *(Continued)*

Participants	Healthy women aged 18 to 36 years with regular menses. Excluded pregnancy; history of certain diseases; and certain drugs.
Interventions	EE 20 µg and norethindrone acetate 1.0 mg versus EE 30 µg and norethindrone acetate 1.5 µg versus EE 50 µg and norethindrone acetate 1.0 µg versus EE 20-30-50 µg and norethindrone acetate 1.0-1.5-1.0 mg. 564 women randomized; initial number assigned to each study group not reported.
Outcomes	Contraceptive efficacy, cycle control, side effects, blood pressure, body weight and hemoglobin. 'Breakthrough' bleeding or spotting defined as bleeding or spotting occurring during the pill-taking period.
Notes	Randomization method not reported. 76% (426/564) completed study.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	Not reported

Basdevant 1993

Methods	Number and location of sites not reported. Six treatment cycles. Blinding not described.
Participants	Healthy, non-obese women with regular menses. Excluded lactation; recent birth or abortion; recent steroid treatment; venous or arterial disease; diabetes; hyperlipidemia; eating disorders; smokers; hypertension; gynecological tumors; cancer; and certain drugs.
Interventions	EE 20 µg and desogestrel 150 µg (N=33) versus EE 30 µg and desogestrel 150 µg (N=25).
Outcomes	Plasma lipid levels, glucose tolerance, blood pressure, hemostatic values, and discontinuation. Did not report bleeding outcomes.
Notes	Randomization method not reported. 76% (426/564) completed study.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	Not reported

Bounds 1979

Methods	Seven initial sites in the U.K. planned but increased to 12 due to slow enrollment. 12 treatment cycles. Participants and clinic doctors blinded.

Bounds 1979 *(Continued)*

	Pre-coded, sealed envelopes with unmarked blister packs used for pills.
Participants	Sexually active women aged 16 to 39 years at risk for pregnancy with regular menses. Excluded contraindications to oral contraceptive use; lactation; and irregular bleeding and spotting.
Interventions	EE 20 µg and norethisterone acetate 1.0 mg versus EE 30 µg and levonorgestrel 150 µg. 143 women randomized; initial number assigned to each study group not reported.
Outcomes	Contraceptive efficacy, discontinuation, cycle control, and side effects. 'Menstrual' bleeding defined as any bleeding requiring sanitary protection regardless of timing in cycle.
Notes	Randomization method not reported. Excluded randomized women from the analysis. Number completing study was not reported.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	Not reported

Brill 1996

Methods	One site in unreported location. Three pill-free pretreatment and 13 treatment cycles. Unblinded.
Participants	Women aged 18 to 35 years with regular menses. Excluded smokers over 30 years of age; pregnancy; certain diseases; certain drugs; intrauterine device use; overweight or dieting; and heavy alcohol use.
Interventions	EE 20 µg and gestodene 75 µg (N=32) versus EE 30 µg and gestodene 75 µg (N=32).
Outcomes	Lipid metabolism, cycle control, and adverse events. Did not report bleeding outcomes.
Notes	Randomization method not reported. Excluded randomized women from the analysis. Number completing study was not reported.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	Not reported

Bruni 2000

Methods	Unreported number of sites in 18 nations. 13 treatment cycles.

Bruni 2000 *(Continued)*

	Unblinded.
Participants	Women 'over the legal age of consent' and less than 42 years of age with regular menses. Excluded estrogen or progestogen hypersensitivity; pregnancy; lactation; and certain disorders.
Interventions	EE 20 µg and desogestrel 150 µg (N=805) versus EE 30 µg and gestodene 75 µg (N=806) versus EE 30-40-30 µg and gestodene 50-70-100 µg (N=808).
Outcomes	Cycle control and effect on well-being. Bleeding terms not defined.
Notes	Randomization method not reported. Excluded randomized women from the analysis. 71% (1721/2419) completed study.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	Not reported

Chavez 1999

Methods	11 sites in the USA Four treatment cycles. Unblinded.
Participants	Healthy women at risk for pregnancy with regular menses. Excluded contraindications for oral contraceptive use; smokers aged 35 years or older; heavy smoking; recent oral injectable, implantable, or intrauterine contraceptive use; and drug or alcohol abuse.
Interventions	EE 20 µg and levonorgestrel 100 µg (N=169) versus EE 35 µg and norethindrone 500-750-1000 µg (N=173).
Outcomes	Cycle control. 'Withdrawal' bleeding or spotting defined as bleeding or spotting beginning in pill-free interval and stopping by fourth day of the next cycle. 'Intermenstrual' bleeding defined as all other bleeding.
Notes	Randomization method not reported. Excluded randomized women from the analysis. 56% (191/342) completed study.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	Not reported

Endrikat 1997

Methods	10 sites in Germany. 12 treatment cycles.

Endrikat 1997 *(Continued)*

	Double-blinded but did not specify who was blinded.
Participants	Healthy, sexually active women aged 18 to 39 years who wanted contraception for at least 12 months. Excluded recent depot-contraceptives; certain diseases; and contraindications for oral contraceptive use.
Interventions	EE 20 µg and gestodene 75 µg (N=428) versus EE 30 µg and gestodene 75 µg (N=221).
Outcomes	Contraceptive efficacy, cycle control, and tolerance. 'Intermenstrual' bleeding was defined as either spotting or breakthrough bleeding. The definition for 'intermenstrual' bleeding did not specify cycle days.
Notes	Randomization method not reported. Excluded randomized women from the analysis. 75% (488/649) completed study.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	Not reported

Endrikat 2001

Methods	Two sites in The Netherlands. Six treatment cycles. Participants and investigators blinded.
Participants	Healthy women aged 18 to 35 years who wanted contraception for at least six months. Excluded contraindications to oral contraceptive use; recent depot contraceptive use; genital bleeding; and menses-related migraines.
Interventions	EE 20 µg and gestodene 75 µg (23 pill days; N=35) versus EE 30 µg and gestodene 75 µg (21 pill days; N=34). 70 women randomized; the group assignment for one woman was not specified.
Outcomes	Hemostatic values, lipids, carbohydrate metabolism, and tolerability. 'Intracyclic' bleeding defined as any bleeding during cycle days 4 to 21 for the 21-day regimen and cycle days 6 to 23 for the 23-day regimen.
Notes	Randomization method not reported. 94% (66/70) completed study.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	Not reported

Hampton 2001

Methods	100 sites in USA and 10 in Canada.

Hampton 2001 *(Continued)*

	First 1/3 of participants were to have 13 treatment cycles and the remaining 2/3 were to have 6 treatment cycles. Allocated in block sizes of 11; blinded.
Participants	Sexually active, healthy women aged 18 to 45 years at risk for pregnancy with regular menses. Excluded recent pregnancy; recent lactation; contraindications to oral contraceptives; certain diseases; smokers aged 35 or more years; certain drugs or devices; recent DMPA use; and recent alcohol or substance abuse.
Interventions	EE 20 µg and norethindrone acetate 1.0 mg with 75 mg ferrous fumarate on days 22-28 (N=853 for 6 cycles / 318 for 13 cycles) versus EE 25 µg and norgestimate 180-215-250 µg (N=1236 for 6 cycles / 487 for 13 cycles).
Outcomes	Contraceptive efficacy, cycle control, and safety. 'Breakthrough' bleeding or spotting defined as bleeding or spotting that occurred during active pill days unless contiguous with menses. 'Amenorrhea' defined as two consecutive cycles without any bleeding or spotting. Secondary report (Burkman 2007) included weight change. Secondary report (Hampton 2009) re-analyzed bleeding data with new criteria (Mishell 2007b); unscheduled bleeding data presented here.
Notes	Cyclophasic regimens discontinued early and not reported. 74% (2130/2894) completed study.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	Allocation concealment methods not reported.

Inauen 1991

Methods	Number and location of sites not reported. Cross-over trial with 3 treatment cycles on each oral contraceptive. Blinding not described.
Participants	Healthy women aged 18 to 30 years without oral contraceptive use during prior four months. Excluded blood coagulation disorders.
Interventions	EE 20 µg and desogestrel 150 µg (N=20) versus EE 50 µg and desogestrel 125 µg (N=20).
Outcomes	Blood coagulation, thrombogenesis, and side effects. Bleeding terms were not defined.
Notes	Randomization method not reported. 100% completed study.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	Not reported

Kaunitz 2009

Methods	RCT at 20 centers in the USA. Computer-generated randomization schedule; stratified by center and recent hormonal contraceptive use (new user or switcher). 3 treatment cycles. Open label. Sample size based on prior studies for total bleeding days for cycles 1 to 3; 90% power to detect difference between groups.
Participants	334 healthy women, nonpregnant, non-lactating, sexually active, aged 18 to 45 years. Inclusion criteria: nonsmokers, regular menstrual cycles, negative Chlamydia test, normal Pap test in past 12 months. Exclusion criteria: contraindication to hormonal therapy, untreated thyroid disorder, body mass index (BMI) > 40 kg/m^2, previously discontinued one of the treatments due to breakthrough bleeding; received injectable contraceptive in past 6 months, implant in past 60 days, or hormonal IUD in past 3 months.
Interventions	EE 20 µg and drospirenone 3 mg (24/4-day regimen) (N=167) versus EE 25 µg and norgestimate 180-215-250 µg (21/7-day regimen) (N=167)
Outcomes	Bleeding data were recorded daily via a voice-response system. Bleeding and unscheduled bleeding (days) defined as per Mishell 2007b. Unscheduled bleeding episode was defined as per Belsey 1986.
Notes	Of 355 randomized, 21 were screen failures (10 EE 20 µg and 11 EE 25 µg). The remaining 334 women who received study drug were included in safety analysis. Completed study: EE 20 µg group, (156/167) 93%; EE 25 µg group, 154/167 (92%)

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	No information

Kirkman 1994

Methods	66 sites in Denmark, Italy, New Zealand and the UK. Six treatment cycles. Unblinded.
Participants	Healthy women over 30 years of age with regular menses. Excluded smokers over 34 years of age, select drug use, and lactation.
Interventions	EE 20 µg and desogestrel 150 µg (N=501) versus EE 30 µg and gestodene 75 µg (N=505).
Outcomes	Cycle control, discontinuation, body weight, blood pressure, and adverse events. 'Withdrawal' bleeding episode was defined as a sequence of one or more days of bleeding or spotting that began during the pill-free period and was bounded by two consecutive days without bleeding. Results, though, were reported for 'irregular' bleeding (with and without withdrawal bleeding), which was never defined.
Notes	Allocated with pre-distributed schedules. Excluded randomized women from the analysis. 87% (874/1006) completed study.

Risk of bias

Kirkman 1994 *(Continued)*

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	Not reported

Kluft 2006

Methods	Open-label, randomized trial at one center in The Netherlands from 1992 to 1993.
Participants	75 healthy women, 18 to 35 years. Inclusion criteria: desiring contraception for at least 6 cycles, new OC users or switchers with at least 2 OC-free cycles before study. Exclusion criteria: contraindications to OC use, family history of coagulation disorders, use of parenteral depot contraceptive in past 6 months, concomitant diseases (not specified in report), diagnostically unclassified genital bleeding, history of migraine with menstruation.
Interventions	Drospirenone 3 mg + EE 30 µg or drospirenone 3 mg + EE 20 µg versus desogestrel + EE 30 µg (N=25 in each group); 6 treatment cycles.
Outcomes	For pregnancy and serious adverse events, the researchers reported none occurred.
Notes	No information on method of randomization. No losses reported; N=75 in per protocol analysis.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	Not reported

Reisman 1999

Methods	11 sites in the USA Four treatment cycles. Unblinded.
Participants	Healthy women over aged 18 years at risk for pregnancy with regular menses. Excluded smokers over age 35 years; contraindications for oral contraceptive use; and recent oral contraceptive, intrauterine device, injectable, or implantable estrogens, progestins, or androgens.
Interventions	EE 20 µg and levonorgestrel 100 µg (N=192) versus EE 35 µg and norethindrone 500-750-1000 µg (N=195).
Outcomes	Cycle control and safety. 'Withdrawal' bleeding or spotting was defined as bleeding or spotting beginning in pill-free interval and stopping by fourth day of the next cycle. 'Intermenstrual' bleeding was defined as all other bleeding.
Notes	Excluded randomized women from the analysis. 57% (220/387) completed study.

Risk of bias

Reisman 1999 *(Continued)*

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	Allocated with sequentially numbered, sealed envelopes.

Rosenberg 1999

Methods	15 sites in US. Six-month wash-out period for injectable or implant contraceptive users. Six treatment cycles. Unblinded.
Participants	Sexually active, normal weight women aged 18 to 50 years with regular menses. Excluded contraindications to oral contraceptive use; smokers over 35 years of age; heavy alcohol use; and lactation.
Interventions	EE 20 µg and levonorgestrel 100 µg (N=154) versus EE 20 µg and desogestrel 150 µg (N=154) versus EE 35 µg and norgestimate 180-215-250 µg (N=155).
Outcomes	Cycle control. 'Unscheduled' bleeding was defined as bleeding not continuous with withdrawal bleeding. 'Withdrawal bleeding' was not defined.
Notes	Allocated with masked randomization lists at each site generated with block size of six. 86% (398/463) completed study.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	Not reported

Skouby 2005

Methods	Open-label, randomized trial at one center in Denmark
Participants	70 healthy women, 18 to 35 years. Inclusion criteria: desiring contraception for at least 13 cycles, new OC users or switchers with at least 2 OC-free cycles before study. Exclusion criteria: contraindications to OC use, parenteral depot contraceptive in past 6 months, co-existing diseases (not specified in report), diagnostically unclassified genital bleeding, history of migraine with menstruation.
Interventions	Levonorgestrel 100 µg + EE 20 µg (N=35) versus levonorgestrel 150 µg + EE 30 µg (N=35); 13 treatment cycles.
Outcomes	Pregnancy and adverse events.
Notes	No information on method of randomization. Losses: 1 took no study medication (excluded) and 7 discontinued early (8/70 = 11%); no information about which groups these women were assigned to. Full analysis reportedly had N=69; 49 in per protocol analysis (22 in EE 20 µg group and 27 in 30 µg).

Risk of bias

Skouby 2005 *(Continued)*

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	Not reported

Taneepanichskul 2002

Methods	One site in Thailand. Three-month wash-out period for OC users. 12 treatment cycles. Unblinded.
Participants	Women aged 18 to 35 years, willing to use contraception for over 12 complete cycles with at least a three-month washout period. Excluded contraindications to OC use; liver, vascular or metabolic diseases; tumor; pregnancy; unclassified and genital bleeding.
Interventions	EE 20 µg and gestodene 75 µg (N=76) versus EE 30 µg and gestodene 75 µg (N=74).
Outcomes	Contraceptive efficacy, cycle control, and side effects. 'Regular' cycle was defined as periodic withdrawal bleeding every 28±7days. 'Breakthrough bleeding' was defined as intermenstrual bleeding that did not require sanitary protection.
Notes	Randomization method not reported. 76% (114/150) completed study.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	Not reported

Teichmann 1995

Methods	One site in Poland. Two pretreatment and 12 treatment cycles. Blinding not described.
Participants	Healthy, normal-weight, sexually active women aged 19 to 40 years seeking oral contraception with regular menses. Excluded recent hormonal medication and certain other drugs; smokers; and contraindications to oral contraception.
Interventions	EE 20 µg and desogestrel 150 µg versus EE 30 µg and gestodene 75 µg. 500 women randomized; initial number assigned to each study group not reported.
Outcomes	Contraceptive efficacy, discontinuation, adverse events, and follicle growth. Bleeding terms not defined.
Notes	Allocated according to a randomization list in chronological order. Excluded randomized women from the analysis. 63% (314/500) completed study.

Teichmann 1995 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	Not reported

WHO 1982

Methods	10 sites in unreported location(s). 24 treatment cycles. Clinic staff and participants blinded. Pills were repackaged in packets and identified only by random number.
Participants	Healthy women aged 18 to 38 with regular menses. Excluded contraindications for oral contraceptive use; postpartum; lactation; and recent oral or injectable contraception.
Interventions	EE 20 µg and norethisterone acetate 1.0 mg (N=448) versus EE 35 µg and norethisterone acetate 400 µg (N=434) versus EE 50 µg and levonorgestrel 150 µg (N=435) versus EE 30 µg and levonorgestrel 150 µg (N=430) versus mestranol 50 µg and norethisterone 1.0 mg (N=436) versus EE 50 µg and norethisterone acetate 1.0 mg (N=431).
Outcomes	Contraceptive efficacy, discontinuation, and cycle control. 'Segments' were defined as the start of one menstrual-like bleeding episode to the start of the next. 'Infrequent' bleeding defined as when the longest menstrual segment was greater than 35 days and not over 60 days. 'Frequent' bleeding defined as when the shortest complete menstrual segment was less than 24 days. 'Irregular' bleeding defined as when the shortest complete segment was less than 24 days and the longest segment was greater than 35 days. 'Prolonged' bleeding defined as when bleeding or spotting episode was longer than 7 days.
Notes	Randomization method not reported. Excluded randomized women from the analysis. 46% (1196/2614) completed study.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	Not reported

Winkler 1996

Methods	One site in unreported location. Duration: 2 pretreatment cycles, 6 treatment cycles, and 1 post-treatment cycle. Unblinded.
Participants	Healthy women aged 18 to 30 with regular menses. Excluded contraindications to oral contraceptive use; smoking; and certain drugs.
Interventions	EE 20 µg and gestodene 75 µg (N=20) versus EE 30 µg and gestodene 75 µg (N=20).
Outcomes	Hemostatic values.

Winkler 1996 *(Continued)*

	Did not report bleeding outcomes.
Notes	Randomization method not reported. Number completing study not reported.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	Not reported

EE = ethinyl estradiol
OC = oral contraceptive

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Bassol 2000	The sum of the percentages of women completing the study and withdrawing appears to be greater than 100%.
Lawson 1979	Initiated as randomized controlled trial but some participants were re-assigned treatments in a nonrandom manner during the trial.
Marr 2012	Not an RCT; analysis involved pooling data from two uncontrolled trials.
Rosenberg 1996	Reported bleeding and spotting outcomes by percentages without providing absolute numbers.
Westhoff 2005	Ring released EE < 20 mcg; OC contained EE 25 mcg
Wiegratz 2003	Reported relevant outcomes by percentages without providing absolute numbers.

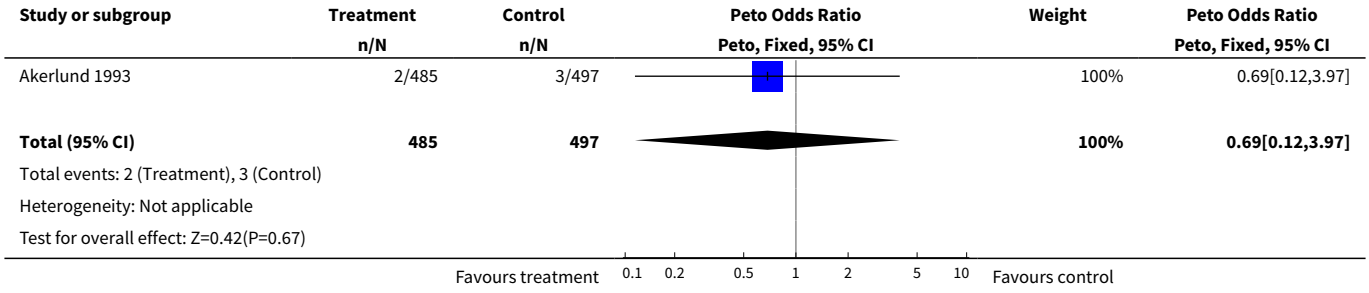
DATA AND ANALYSES

Comparison 1. EE 20 µg and desogestrel 150 µg versus EE 30 µg and desogestrel 150 µg

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pregnancy per woman	1	982	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.69 [0.12, 3.97]
2 Discontinuation - overall	1	1000	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.20 [0.92, 1.56]
3 Discontinuation - mood changes	1	1000	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.51 [0.68, 3.33]
4 Discontinuation - irregular bleeding	1	1000	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.59 [1.35, 5.00]
5 Discontinuation - nausea	1	58	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.75 [0.04, 12.64]

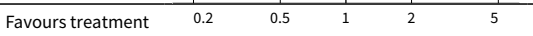
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6 Amenorrhea - cycle 3	1	778	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.49 [0.75, 2.97]
7 Amenorrhea - cycle 6	1	721	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.43 [0.65, 3.12]
8 Irregular bleeding - cycle 3	1	778	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.56 [1.10, 2.20]
9 Duration of irregular bleeding in days - cycle 3	1	778	Mean Difference (IV, Fixed, 95% CI)	0.70 [0.30, 1.10]
10 Duration of irregular bleeding in days - cycle 6	1	721	Mean Difference (IV, Fixed, 95% CI)	-0.10 [-0.46, 0.26]
11 Dizziness	1	982	Peto Odds Ratio (Peto, Fixed, 95% CI)	7.65 [1.54, 38.08]
12 Dysmenorrhea	1	982	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.46 [0.70, 3.06]
13 Headache	1	982	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.71 [0.94, 3.11]
14 Increased weight	1	982	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.46 [1.04, 5.84]
15 Irregular bleeding	1	982	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.69 [1.07, 2.69]
16 Mood change	1	982	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.93 [1.05, 3.56]
17 Nausea, diarrhea, vomiting	1	982	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.42 [0.74, 2.72]
18 Prolonged withdrawal bleeding	1	982	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.98 [1.03, 3.78]

Analysis 1.1. Comparison 1 EE 20 µg and desogestrel 150 µg versus EE 30 µg and desogestrel 150 µg, Outcome 1 Pregnancy per woman.



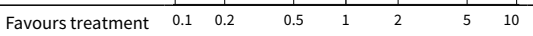
Analysis 1.2. Comparison 1 EE 20 µg and desogestrel 150 µg versus EE 30 µg and desogestrel 150 µg, Outcome 2 Discontinuation - overall.

Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Akerlund 1993	174/500	154/500		100%	1.2[0.92,1.56]
Total (95% CI)	**500**	**500**		**100%**	**1.2[0.92,1.56]**
Total events: 174 (Treatment), 154 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.35(P=0.18)					



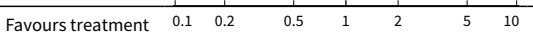
Analysis 1.3. Comparison 1 EE 20 µg and desogestrel 150 µg versus EE 30 µg and desogestrel 150 µg, Outcome 3 Discontinuation - mood changes.

Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Akerlund 1993	15/500	10/500		100%	1.51[0.68,3.33]
Total (95% CI)	**500**	**500**		**100%**	**1.51[0.68,3.33]**
Total events: 15 (Treatment), 10 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.01(P=0.31)					



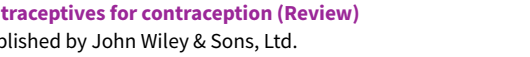
Analysis 1.4. Comparison 1 EE 20 µg and desogestrel 150 µg versus EE 30 µg and desogestrel 150 µg, Outcome 4 Discontinuation - irregular bleeding.

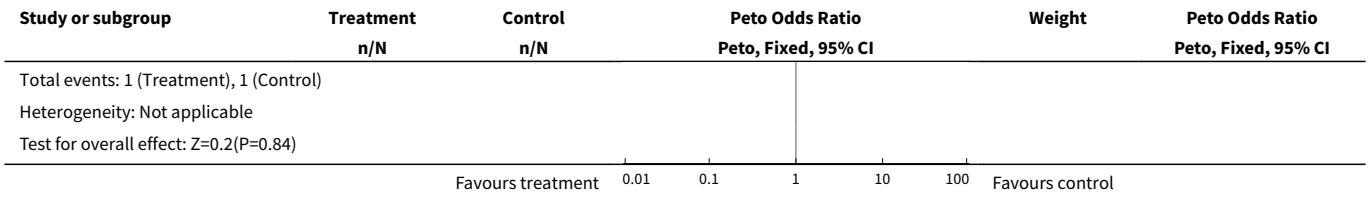
Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Akerlund 1993	27/500	10/500		100%	2.59[1.35,5]
Total (95% CI)	**500**	**500**		**100%**	**2.59[1.35,5]**
Total events: 27 (Treatment), 10 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=2.85(P=0)					



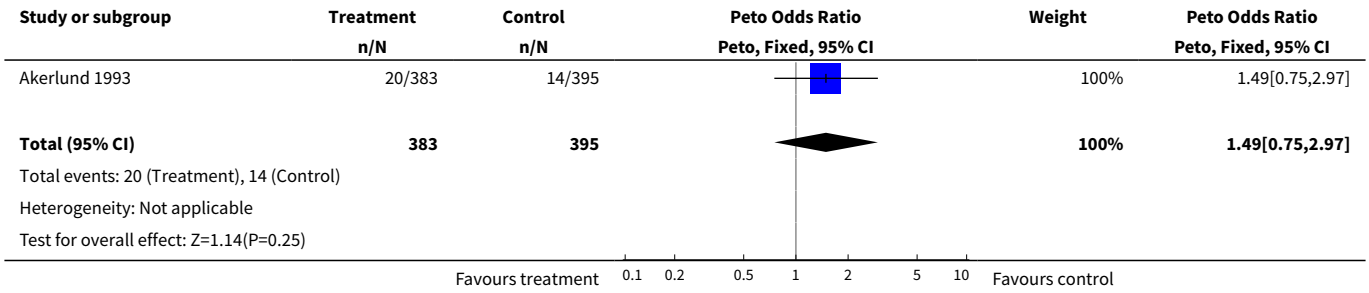
Analysis 1.5. Comparison 1 EE 20 µg and desogestrel 150 µg versus EE 30 µg and desogestrel 150 µg, Outcome 5 Discontinuation - nausea.

Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Basdevant 1993	1/33	1/25		100%	0.75[0.04,12.64]
Total (95% CI)	**33**	**25**		**100%**	**0.75[0.04,12.64]**

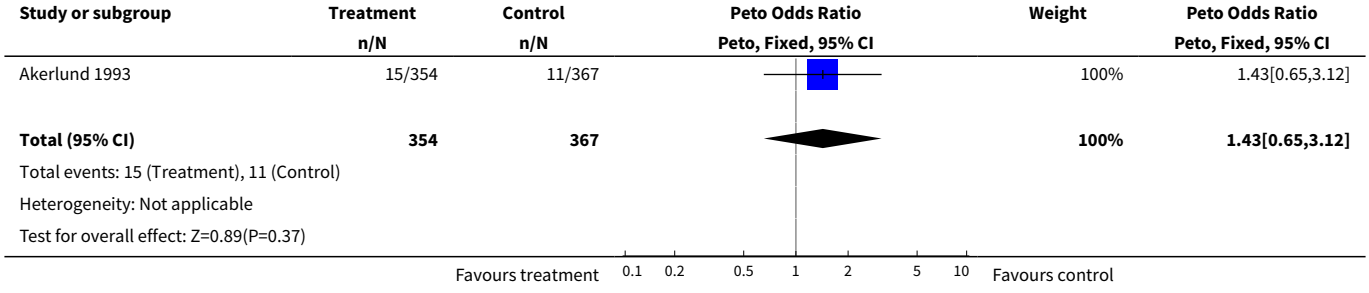




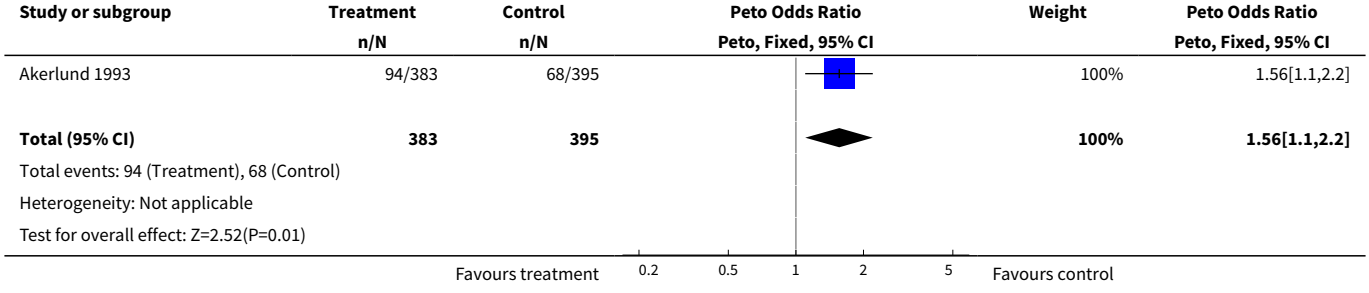
Analysis 1.6. Comparison 1 EE 20 µg and desogestrel 150 µg versus EE 30 µg and desogestrel 150 µg, Outcome 6 Amenorrhea - cycle 3.



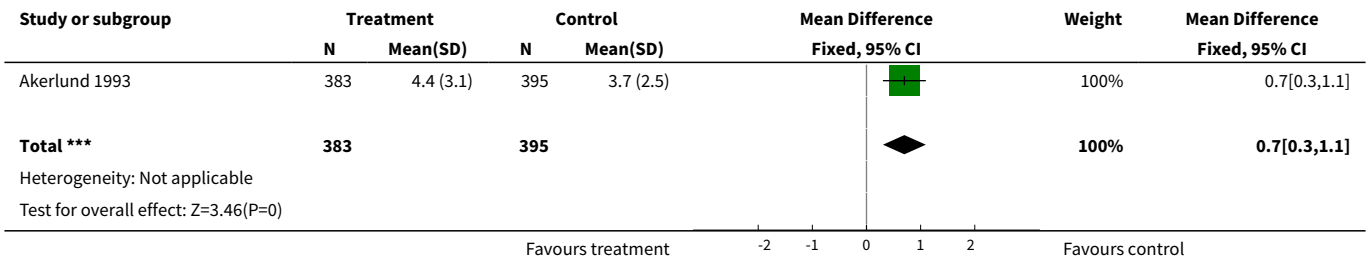
Analysis 1.7. Comparison 1 EE 20 µg and desogestrel 150 µg versus EE 30 µg and desogestrel 150 µg, Outcome 7 Amenorrhea - cycle 6.



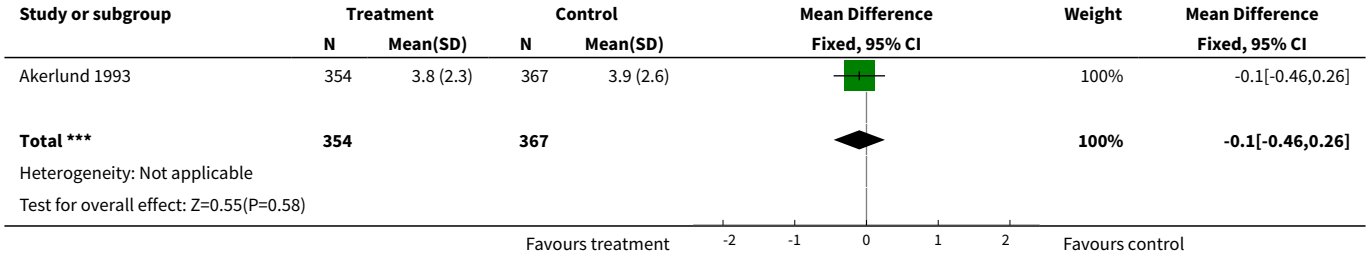
Analysis 1.8. Comparison 1 EE 20 µg and desogestrel 150 µg versus EE 30 µg and desogestrel 150 µg, Outcome 8 Irregular bleeding - cycle 3.



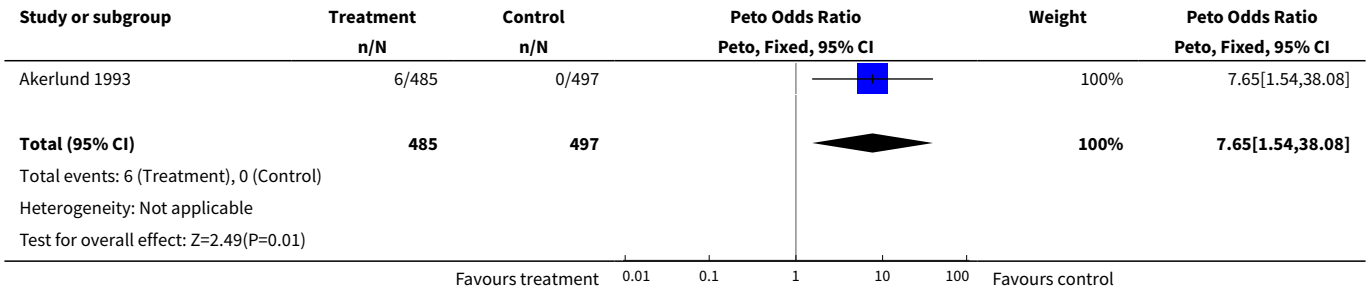
Analysis 1.9. Comparison 1 EE 20 µg and desogestrel 150 µg versus EE 30 µg and desogestrel 150 µg, Outcome 9 Duration of irregular bleeding in days - cycle 3.



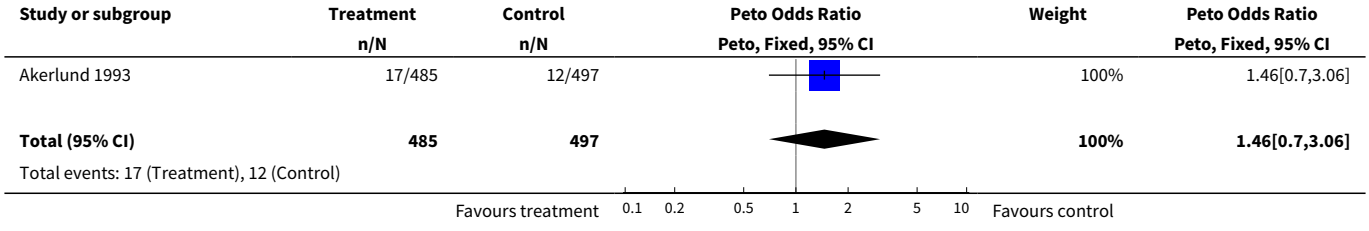
Analysis 1.10. Comparison 1 EE 20 µg and desogestrel 150 µg versus EE 30 µg and desogestrel 150 µg, Outcome 10 Duration of irregular bleeding in days - cycle 6.

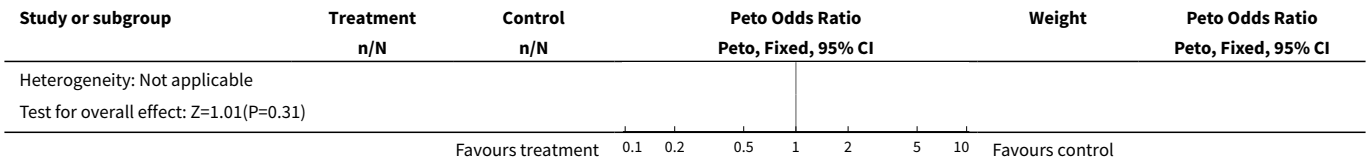


Analysis 1.11. Comparison 1 EE 20 µg and desogestrel 150 µg versus EE 30 µg and desogestrel 150 µg, Outcome 11 Dizziness.

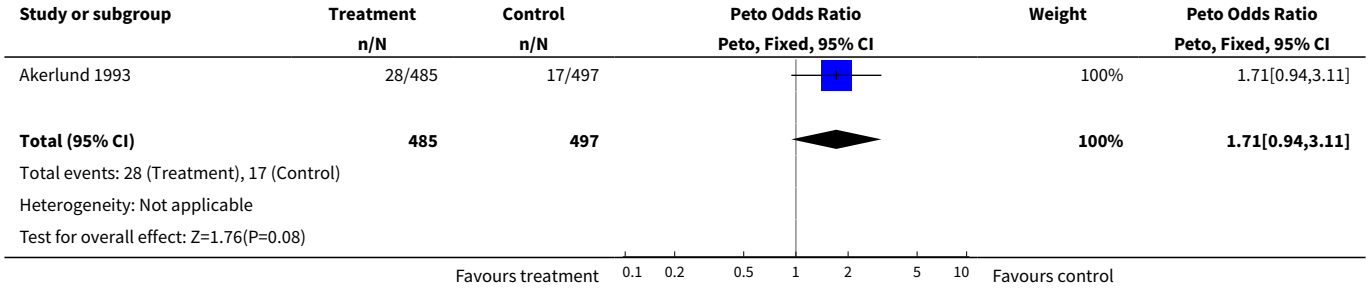


Analysis 1.12. Comparison 1 EE 20 µg and desogestrel 150 µg versus EE 30 µg and desogestrel 150 µg, Outcome 12 Dysmenorrhea.

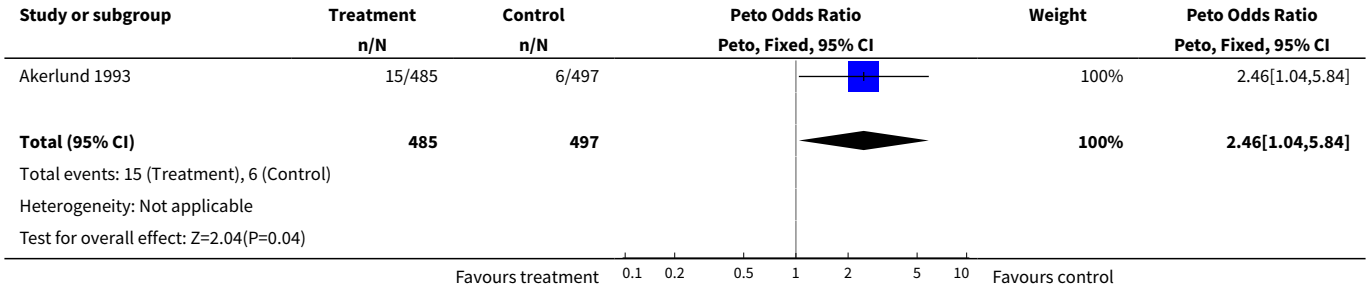




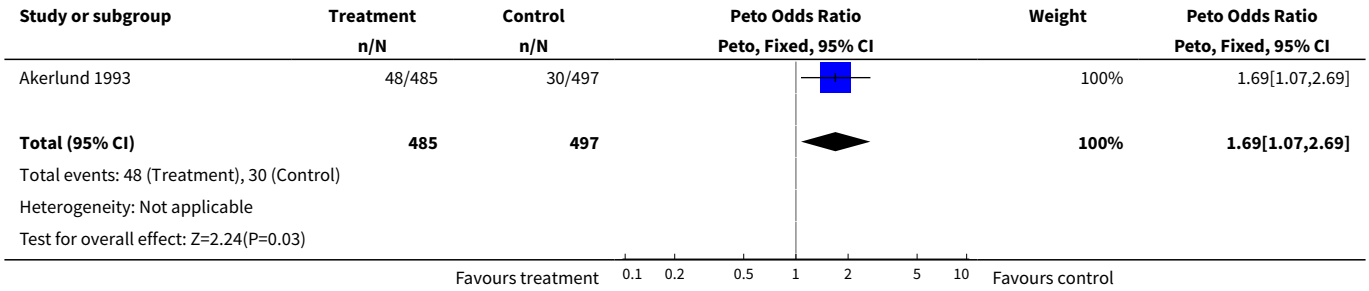
Analysis 1.13. Comparison 1 EE 20 µg and desogestrel 150 µg versus EE 30 µg and desogestrel 150 µg, Outcome 13 Headache.



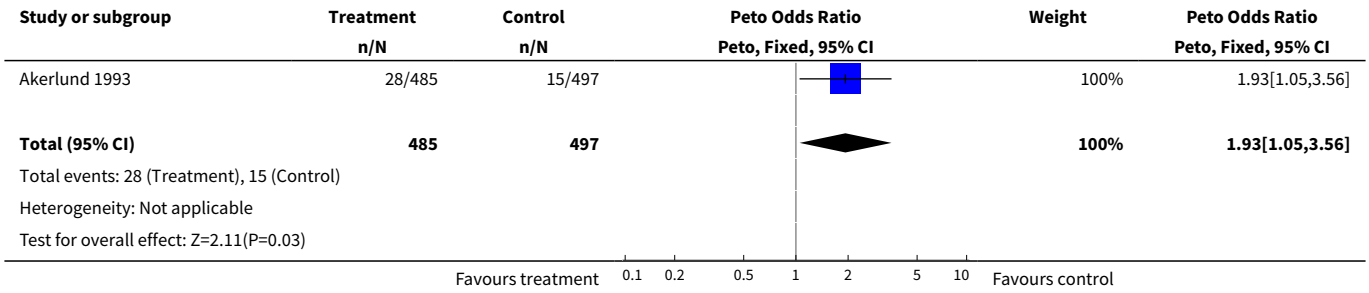
Analysis 1.14. Comparison 1 EE 20 µg and desogestrel 150 µg versus EE 30 µg and desogestrel 150 µg, Outcome 14 Increased weight.



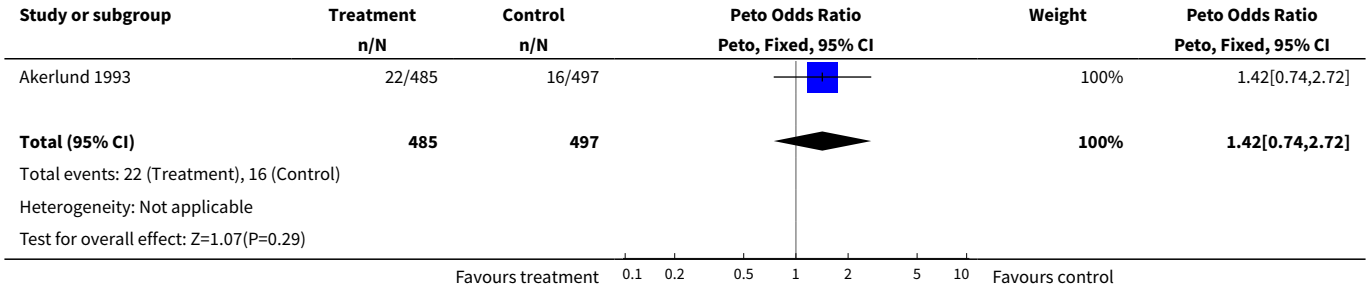
Analysis 1.15. Comparison 1 EE 20 µg and desogestrel 150 µg versus EE 30 µg and desogestrel 150 µg, Outcome 15 Irregular bleeding.



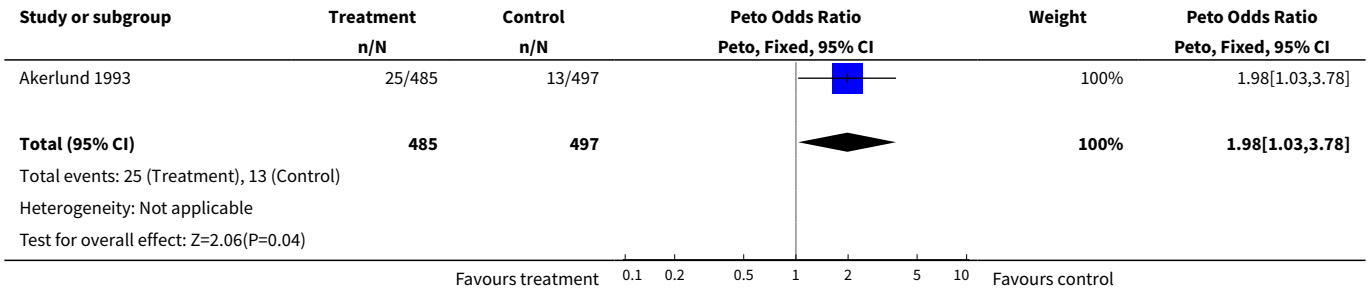
Analysis 1.16. Comparison 1 EE 20 µg and desogestrel 150 µg versus EE 30 µg and desogestrel 150 µg, Outcome 16 Mood change.



Analysis 1.17. Comparison 1 EE 20 µg and desogestrel 150 µg versus EE 30 µg and desogestrel 150 µg, Outcome 17 Nausea, diarrhea, vomiting.



Analysis 1.18. Comparison 1 EE 20 µg and desogestrel 150 µg versus EE 30 µg and desogestrel 150 µg, Outcome 18 Prolonged withdrawal bleeding.



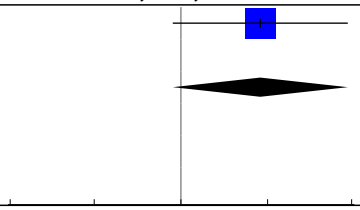
Comparison 2. EE 20 µg and desogestrel 150 µg versus EE 50 µg and desogestrel 125 µg

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Breakthough bleeding - cycles 1 to 3	1	40	Peto Odds Ratio (Peto, Fixed, 95% CI)	8.23 [0.81, 84.07]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2 Breakthrough spotting - cycles 1 to 3	1	40	Peto Odds Ratio (Peto, Fixed, 95% CI)	7.79 [0.47, 129.11]
3 Acne	1	40	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.13 [0.01, 2.13]
4 Breast tenderness	1	40	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.0 [0.13, 7.69]
5 Headache	1	40	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.14 [0.00, 6.82]
6 Weight gain	1	40	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.13 [0.01, 2.13]

Analysis 2.1. Comparison 2 EE 20 µg and desogestrel 150 µg versus EE 50 µg and desogestrel 125 µg, Outcome 1 Breakthough bleeding - cycles 1 to 3.

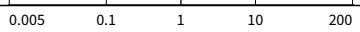
Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Inauen 1991	3/20	0/20		100%	8.23[0.81,84.07]
Total (95% CI)	**20**	**20**		**100%**	**8.23[0.81,84.07]**
Total events: 3 (Treatment), 0 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.78(P=0.08)					



Favours treatment — Favours control

Analysis 2.2. Comparison 2 EE 20 µg and desogestrel 150 µg versus EE 50 µg and desogestrel 125 µg, Outcome 2 Breakthrough spotting - cycles 1 to 3.

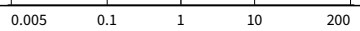
Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Inauen 1991	2/20	0/20		100%	7.79[0.47,129.11]
Total (95% CI)	**20**	**20**		**100%**	**7.79[0.47,129.11]**
Total events: 2 (Treatment), 0 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.43(P=0.15)					



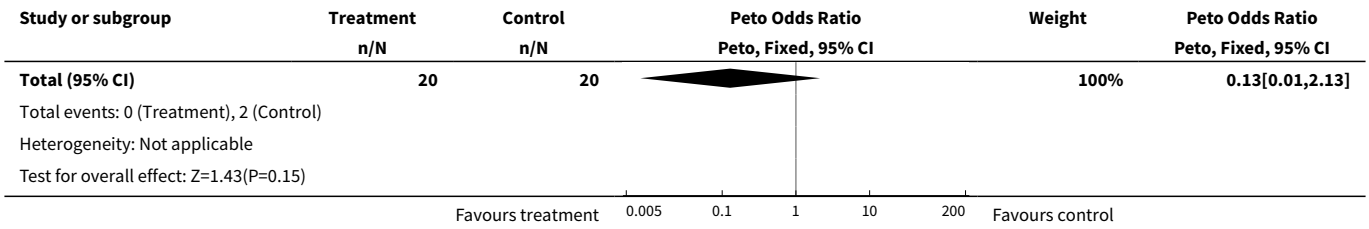
Favours treatment — Favours control

Analysis 2.3. Comparison 2 EE 20 µg and desogestrel 150 µg versus EE 50 µg and desogestrel 125 µg, Outcome 3 Acne.

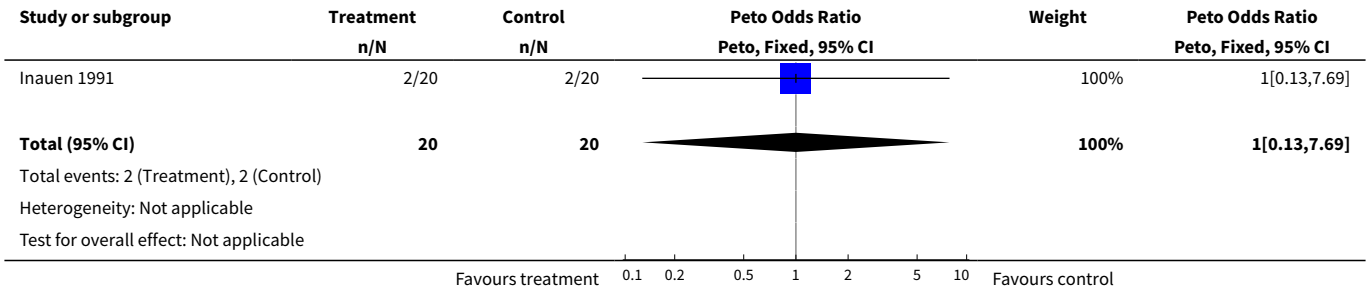
Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Inauen 1991	0/20	2/20		100%	0.13[0.01,2.13]



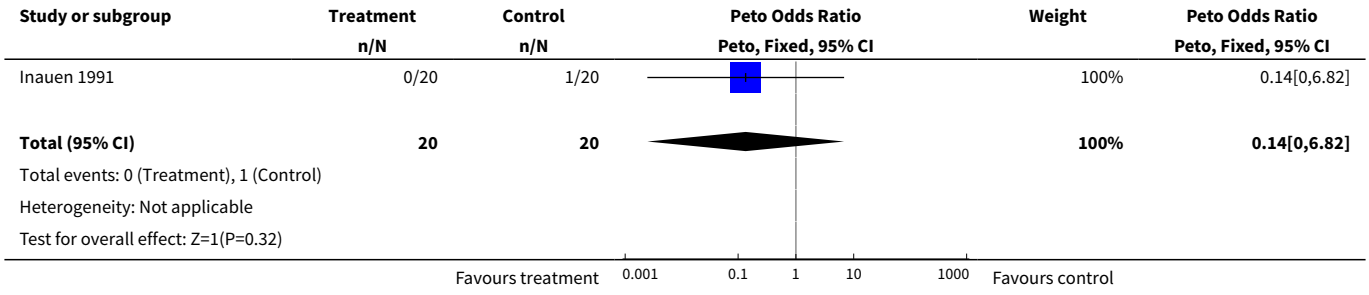
Favours treatment — Favours control



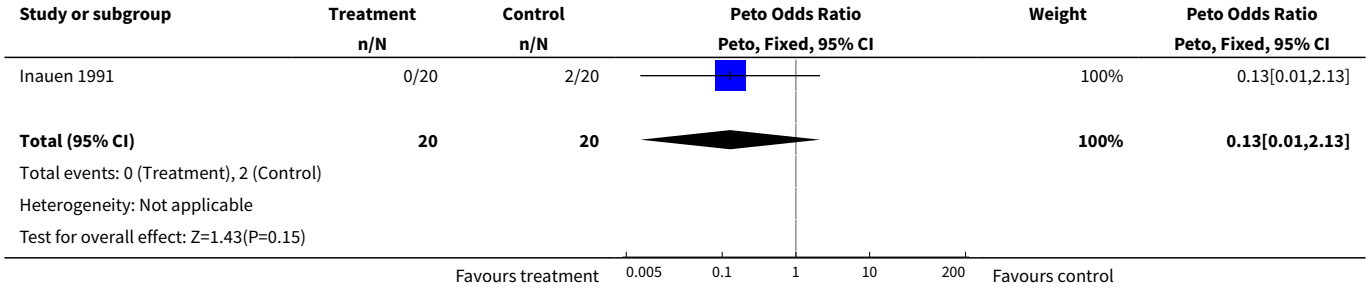
Analysis 2.4. Comparison 2 EE 20 µg and desogestrel 150 µg versus EE 50 µg and desogestrel 125 µg, Outcome 4 Breast tenderness.



Analysis 2.5. Comparison 2 EE 20 µg and desogestrel 150 µg versus EE 50 µg and desogestrel 125 µg, Outcome 5 Headache.



Analysis 2.6. Comparison 2 EE 20 µg and desogestrel 150 µg versus EE 50 µg and desogestrel 125 µg, Outcome 6 Weight gain.



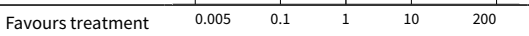
Comparison 3. EE 20 µg and desogestrel 150 µg versus EE 30 µg and gestodene 75 µg

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pregnancy per woman	2	2027	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.00 [0.20, 4.96]
2 Discontinuation - overall	3	3033	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.03 [0.85, 1.26]
3 Discontinuation - abdominal pain	1	416	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.49 [0.43, 5.22]
4 Discontinuation - adverse event	3	3033	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.28 [0.98, 1.68]
5 Discontinuation - breast tension	1	416	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.51 [0.05, 4.90]
6 Discontinuation - colpitis	1	416	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.99 [0.06, 15.89]
7 Discontinuation - depressive mood	1	416	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.51 [0.05, 4.90]
8 Discontinuation - dizziness	1	416	Peto Odds Ratio (Peto, Fixed, 95% CI)	7.43 [1.04, 53.09]
9 Discontinuation - headache	1	416	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.24 [0.33, 4.65]
10 Discontinuation - hypertension	1	416	Peto Odds Ratio (Peto, Fixed, 95% CI)	7.32 [0.15, 368.86]
11 Discontinuation - hypomenorrhea	1	1006	Peto Odds Ratio (Peto, Fixed, 95% CI)	7.46 [0.47, 119.49]
12 Discontinuation - intermenstrual bleeding	1	416	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.74 [0.17, 3.30]
13 Discontinuation - menorrhagia	1	1006	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.01 [0.14, 7.18]
14 Discontinuation - menstrual disorder	1	1006	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.52 [0.05, 4.98]
15 Discontinuation - metrorrhagia	2	2617	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.35 [1.16, 4.77]
16 Discontinuation - nausea	1	416	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.99 [0.24, 4.01]
17 Discontinuation - nervousness	1	416	Peto Odds Ratio (Peto, Fixed, 95% CI)	7.39 [0.76, 71.43]
18 Discontinuation - pruritus	1	416	Peto Odds Ratio (Peto, Fixed, 95% CI)	7.32 [0.15, 368.86]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
19 Discontinuation - vomiting	1	416	Peto Odds Ratio (Peto, Fixed, 95% CI)	3.82 [0.76, 19.10]
20 Irregular bleeding - cycle 3	1	910	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.51 [1.77, 3.56]
21 Irregular bleeding - cycle 6	1	823	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.72 [1.15, 2.55]
22 Amenorrhea - cycle 3	1	910	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.38 [0.83, 6.82]
23 Amenorrhea - cycle 6	1	823	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.37 [0.09, 1.47]
24 Abdominal pain	1	1611	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.19 [0.71, 2.01]
25 Acne	1	1611	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.94 [0.46, 1.91]
26 Breast pain	1	1611	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.85 [0.56, 1.30]
27 Decreased libido	1	1611	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.64 [0.25, 1.62]
28 Depression	1	1611	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.76 [0.40, 1.46]
29 Dizziness	1	1611	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.60 [0.23, 1.62]
30 Dysmenorrhea	1	1611	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.94 [0.48, 1.85]
31 Emotional lability	1	1611	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.72 [0.38, 1.38]
32 Flatulence	1	1611	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.59 [0.24, 1.45]
33 Headache	1	1611	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.08 [0.81, 1.42]
34 Menstrual disorder	1	1611	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.00 [0.41, 2.42]
35 Metrorrhagia	1	1611	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.67 [1.05, 2.66]
36 Migraine	1	1611	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.38 [0.83, 6.80]
37 Nausea	1	1611	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.16 [0.68, 1.95]
38 Pain	1	1611	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.37 [0.63, 2.97]
39 Vaginal moniliasis	1	1611	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.45 [0.62, 3.36]
40 Vomiting	1	1611	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.48 [0.19, 1.17]
41 Weight gain	1	1611	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.68 [0.34, 1.38]
42 Weight gain in kg	1	805	Mean Difference (IV, Fixed, 95% CI)	-0.20 [-0.40, -0.00]

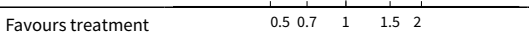
Analysis 3.1. Comparison 3 EE 20 µg and desogestrel 150 µg versus EE 30 µg and gestodene 75 µg, Outcome 1 Pregnancy per woman.

Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Bruni 2000	2/805	3/806		83.3%	0.67[0.12,3.88]
Teichmann 1995	1/209	0/207		16.7%	7.32[0.15,368.86]
Total (95% CI)	**1014**	**1013**		**100%**	**1[0.2,4.96]**
Total events: 3 (Treatment), 3 (Control)					
Heterogeneity: Tau^2=0; Chi^2=1.19, df=1(P=0.28); I^2=15.94%					
Test for overall effect: Z=0(P=1)					



Analysis 3.2. Comparison 3 EE 20 µg and desogestrel 150 µg versus EE 30 µg and gestodene 75 µg, Outcome 2 Discontinuation - overall.

Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Bruni 2000	132/805	129/806		56.55%	1.03[0.79,1.34]
Kirkman 1994	49/501	52/505		23.5%	0.94[0.63,1.42]
Teichmann 1995	54/209	48/207		19.94%	1.15[0.74,1.8]
Total (95% CI)	**1515**	**1518**		**100%**	**1.03[0.85,1.26]**
Total events: 235 (Treatment), 229 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0.42, df=2(P=0.81); I^2=0%					
Test for overall effect: Z=0.31(P=0.76)					



Analysis 3.3. Comparison 3 EE 20 µg and desogestrel 150 µg versus EE 30 µg and gestodene 75 µg, Outcome 3 Discontinuation - abdominal pain.

Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Teichmann 1995	6/209	4/207		100%	1.49[0.43,5.22]
Total (95% CI)	**209**	**207**		**100%**	**1.49[0.43,5.22]**
Total events: 6 (Treatment), 4 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.62(P=0.53)					

Analysis 3.4. Comparison 3 EE 20 µg and desogestrel 150 µg versus EE 30 µg and gestodene 75 µg, Outcome 4 Discontinuation - adverse event.

Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Bruni 2000	62/805	45/806		47.8%	1.41[0.95,2.08]
Kirkman 1994	43/501	37/505		35.25%	1.19[0.75,1.87]
Teichmann 1995	21/209	18/207		16.94%	1.17[0.61,2.26]
Total (95% CI)	**1515**	**1518**		**100%**	**1.28[0.98,1.68]**
Total events: 126 (Treatment), 100 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0.4, df=2(P=0.82); I^2=0%					
Test for overall effect: Z=1.81(P=0.07)					

Favours treatment — Favours control

Analysis 3.5. Comparison 3 EE 20 µg and desogestrel 150 µg versus EE 30 µg and gestodene 75 µg, Outcome 5 Discontinuation - breast tension.

Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Teichmann 1995	1/209	2/207		100%	0.51[0.05,4.9]
Total (95% CI)	**209**	**207**		**100%**	**0.51[0.05,4.9]**
Total events: 1 (Treatment), 2 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.59(P=0.56)					

Favours treatment — Favours control

Analysis 3.6. Comparison 3 EE 20 µg and desogestrel 150 µg versus EE 30 µg and gestodene 75 µg, Outcome 6 Discontinuation - colpitis.

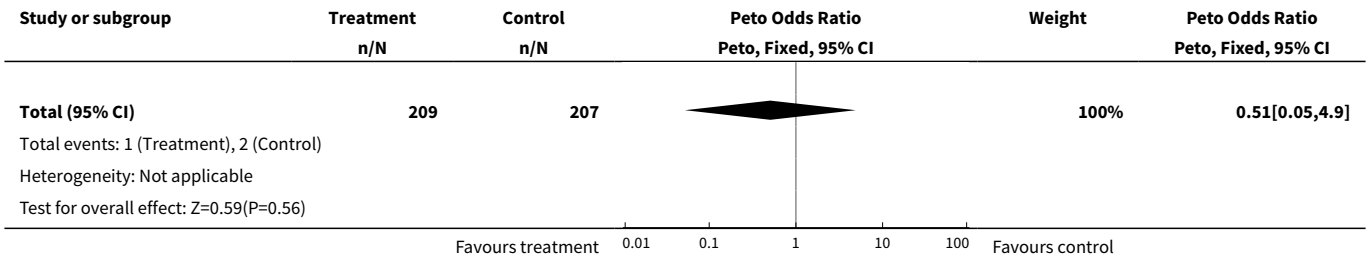
Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Teichmann 1995	1/209	1/207		100%	0.99[0.06,15.89]
Total (95% CI)	**209**	**207**		**100%**	**0.99[0.06,15.89]**
Total events: 1 (Treatment), 1 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.01(P=0.99)					

Favours treatment — Favours control

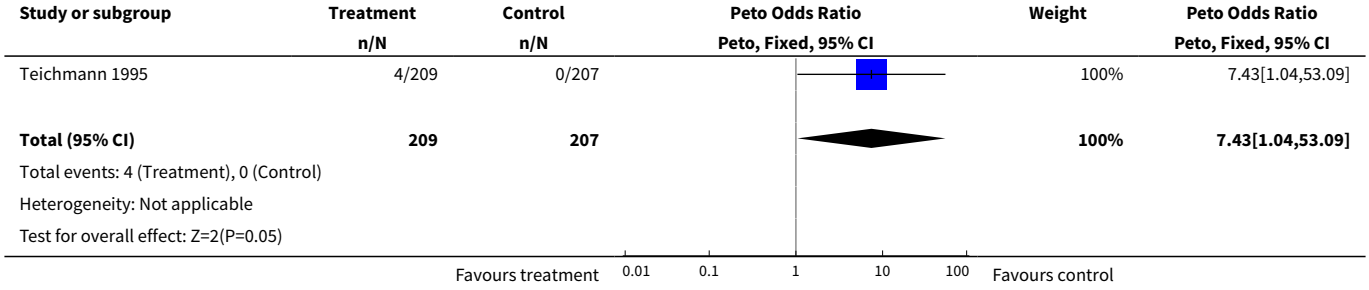
Analysis 3.7. Comparison 3 EE 20 µg and desogestrel 150 µg versus EE 30 µg and gestodene 75 µg, Outcome 7 Discontinuation - depressive mood.

Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Teichmann 1995	1/209	2/207		100%	0.51[0.05,4.9]

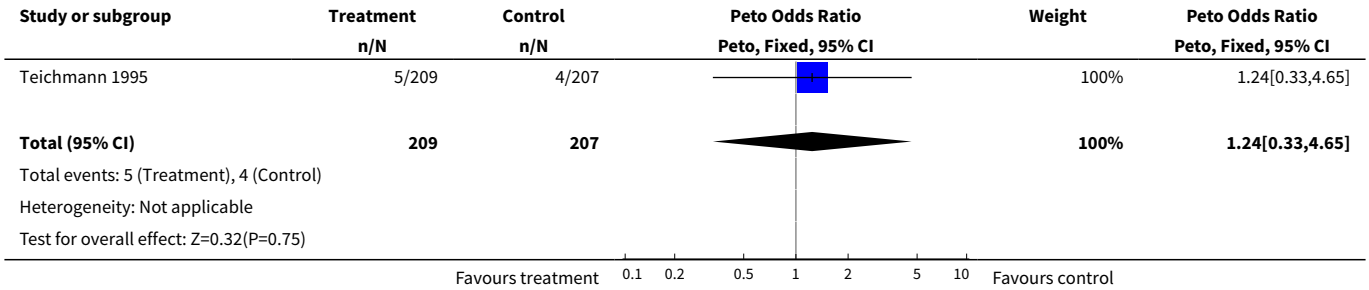
Favours treatment — Favours control



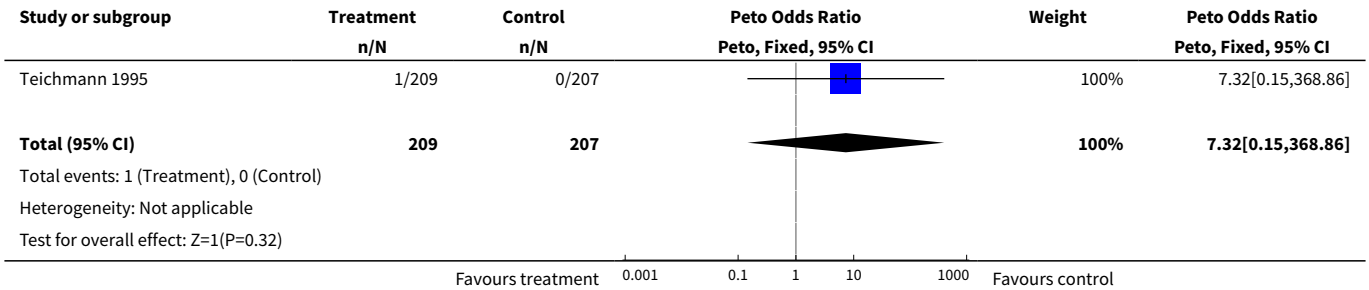
Analysis 3.8. Comparison 3 EE 20 µg and desogestrel 150 µg versus EE 30 µg and gestodene 75 µg, Outcome 8 Discontinuation - dizziness.



Analysis 3.9. Comparison 3 EE 20 µg and desogestrel 150 µg versus EE 30 µg and gestodene 75 µg, Outcome 9 Discontinuation - headache.

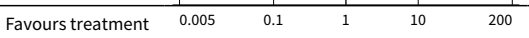


Analysis 3.10. Comparison 3 EE 20 µg and desogestrel 150 µg versus EE 30 µg and gestodene 75 µg, Outcome 10 Discontinuation - hypertension.



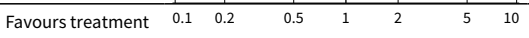
Analysis 3.11. Comparison 3 EE 20 µg and desogestrel 150 µg versus EE 30 µg and gestodene 75 µg, Outcome 11 Discontinuation - hypomenorrhea.

Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Kirkman 1994	2/501	0/505		100%	7.46[0.47,119.49]
Total (95% CI)	**501**	**505**		**100%**	**7.46[0.47,119.49]**
Total events: 2 (Treatment), 0 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.42(P=0.16)					



Analysis 3.12. Comparison 3 EE 20 µg and desogestrel 150 µg versus EE 30 µg and gestodene 75 µg, Outcome 12 Discontinuation - intermenstrual bleeding.

Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Teichmann 1995	3/209	4/207		100%	0.74[0.17,3.3]
Total (95% CI)	**209**	**207**		**100%**	**0.74[0.17,3.3]**
Total events: 3 (Treatment), 4 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.39(P=0.69)					

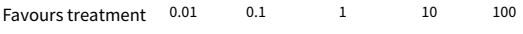


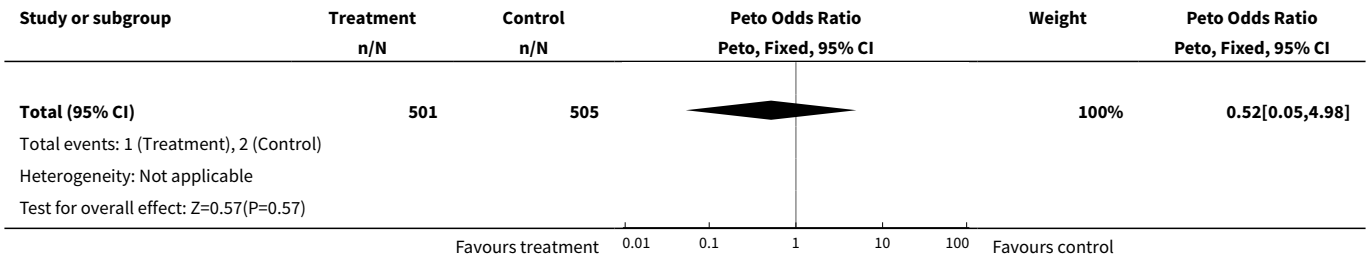
Analysis 3.13. Comparison 3 EE 20 µg and desogestrel 150 µg versus EE 30 µg and gestodene 75 µg, Outcome 13 Discontinuation - menorrhagia.

Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Kirkman 1994	2/501	2/505		100%	1.01[0.14,7.18]
Total (95% CI)	**501**	**505**		**100%**	**1.01[0.14,7.18]**
Total events: 2 (Treatment), 2 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.01(P=0.99)					

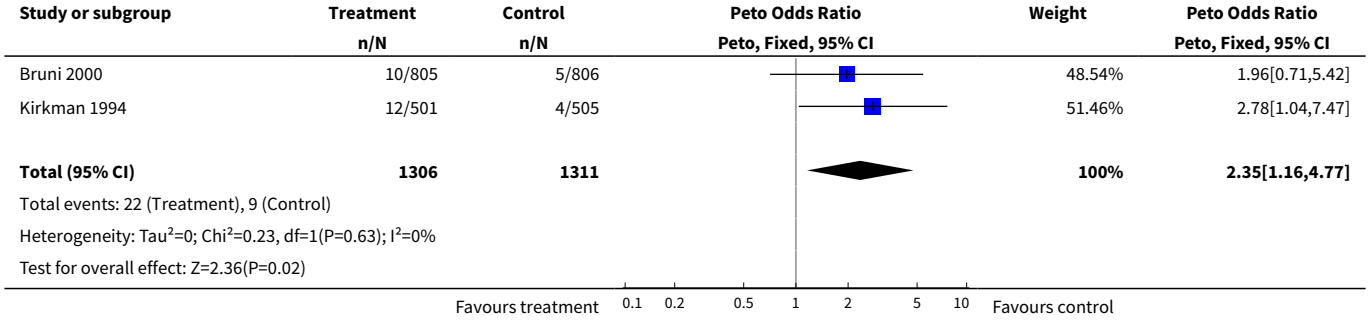
Analysis 3.14. Comparison 3 EE 20 µg and desogestrel 150 µg versus EE 30 µg and gestodene 75 µg, Outcome 14 Discontinuation - menstrual disorder.

Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Kirkman 1994	1/501	2/505		100%	0.52[0.05,4.98]

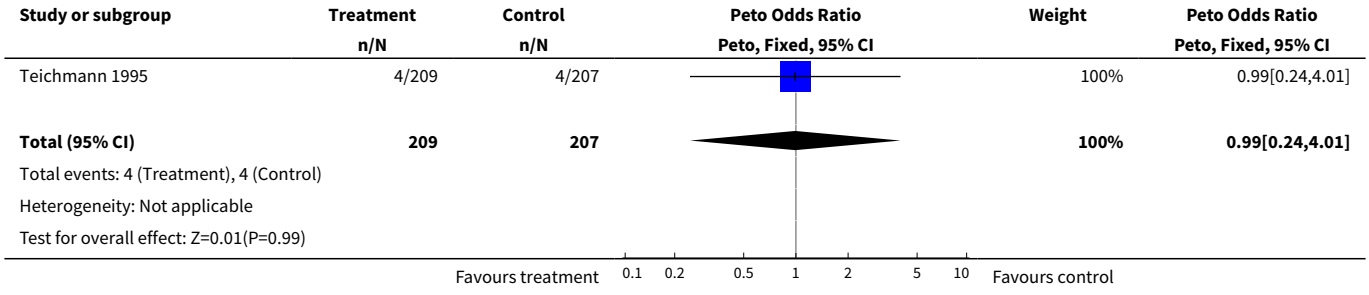




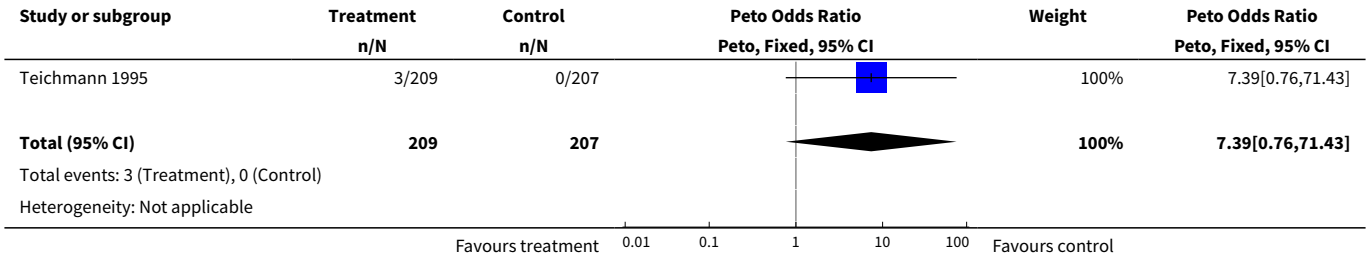
Analysis 3.15. Comparison 3 EE 20 µg and desogestrel 150 µg versus EE 30 µg and gestodene 75 µg, Outcome 15 Discontinuation - metrorrhagia.

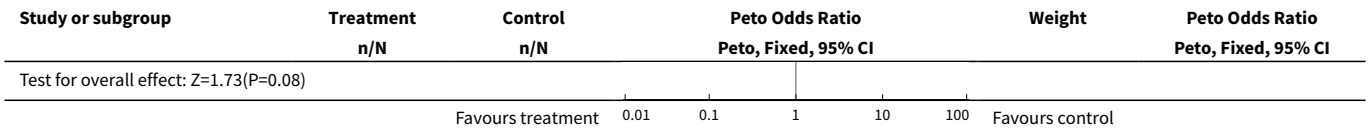


Analysis 3.16. Comparison 3 EE 20 µg and desogestrel 150 µg versus EE 30 µg and gestodene 75 µg, Outcome 16 Discontinuation - nausea.

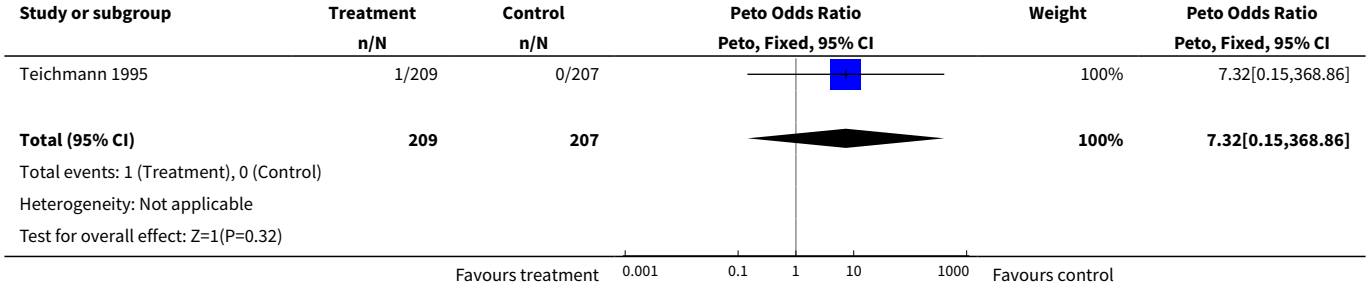


Analysis 3.17. Comparison 3 EE 20 µg and desogestrel 150 µg versus EE 30 µg and gestodene 75 µg, Outcome 17 Discontinuation - nervousness.

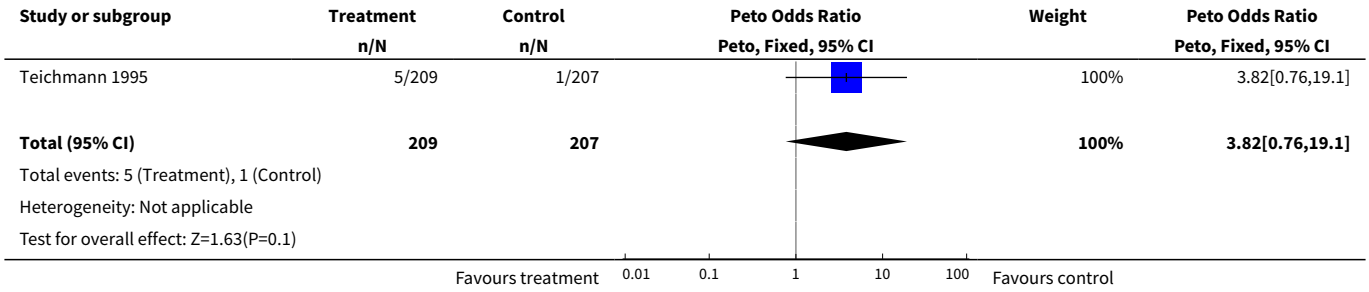




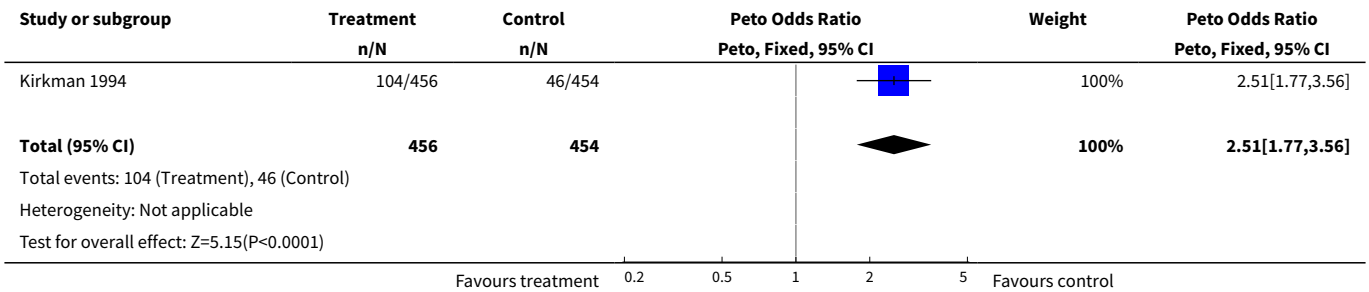
Analysis 3.18. Comparison 3 EE 20 µg and desogestrel 150 µg versus EE 30 µg and gestodene 75 µg, Outcome 18 Discontinuation - pruritus.



Analysis 3.19. Comparison 3 EE 20 µg and desogestrel 150 µg versus EE 30 µg and gestodene 75 µg, Outcome 19 Discontinuation - vomiting.

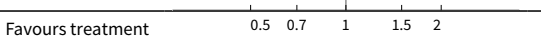


Analysis 3.20. Comparison 3 EE 20 µg and desogestrel 150 µg versus EE 30 µg and gestodene 75 µg, Outcome 20 Irregular bleeding - cycle 3.



Analysis 3.21. Comparison 3 EE 20 µg and desogestrel 150 µg versus EE 30 µg and gestodene 75 µg, Outcome 21 Irregular bleeding - cycle 6.

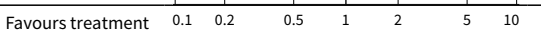
Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Kirkman 1994	69/411	43/412		100%	1.72[1.15,2.55]
Total (95% CI)	**411**	**412**		**100%**	**1.72[1.15,2.55]**
Total events: 69 (Treatment), 43 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=2.66(P=0.01)					



Favours treatment — Favours control

Analysis 3.22. Comparison 3 EE 20 µg and desogestrel 150 µg versus EE 30 µg and gestodene 75 µg, Outcome 22 Amenorrhea - cycle 3.

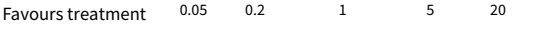
Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Kirkman 1994	10/456	4/454		100%	2.38[0.83,6.82]
Total (95% CI)	**456**	**454**		**100%**	**2.38[0.83,6.82]**
Total events: 10 (Treatment), 4 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.61(P=0.11)					



Favours treatment — Favours control

Analysis 3.23. Comparison 3 EE 20 µg and desogestrel 150 µg versus EE 30 µg and gestodene 75 µg, Outcome 23 Amenorrhea - cycle 6.

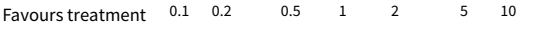
Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Kirkman 1994	2/411	6/412		100%	0.37[0.09,1.47]
Total (95% CI)	**411**	**412**		**100%**	**0.37[0.09,1.47]**
Total events: 2 (Treatment), 6 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.42(P=0.16)					



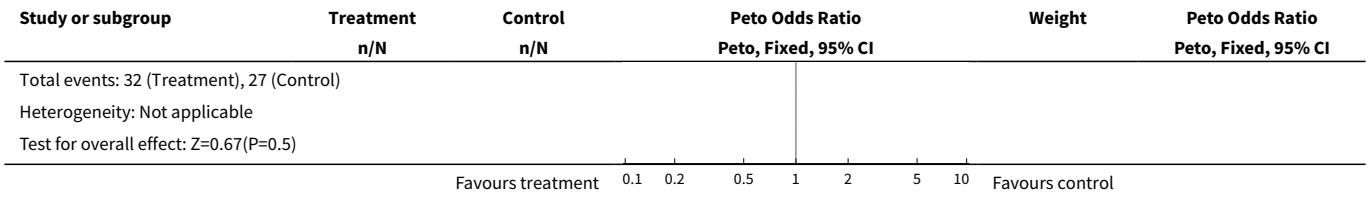
Favours treatment — Favours control

Analysis 3.24. Comparison 3 EE 20 µg and desogestrel 150 µg versus EE 30 µg and gestodene 75 µg, Outcome 24 Abdominal pain.

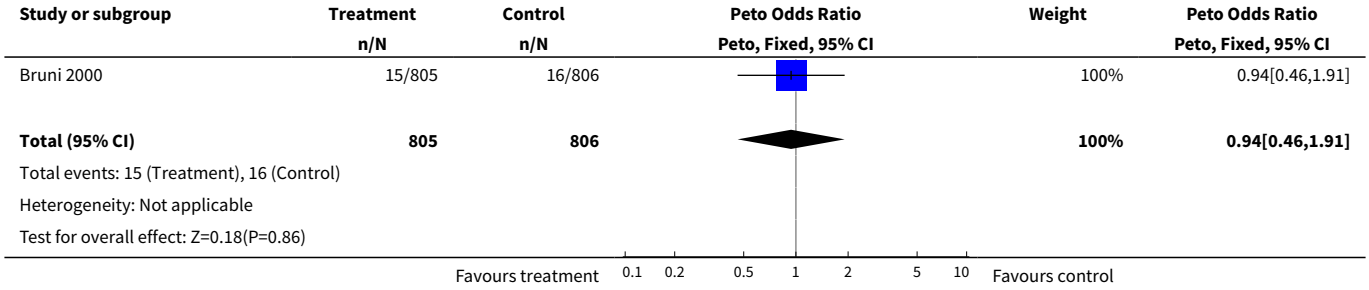
Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Bruni 2000	32/805	27/806		100%	1.19[0.71,2.01]
Total (95% CI)	**805**	**806**		**100%**	**1.19[0.71,2.01]**



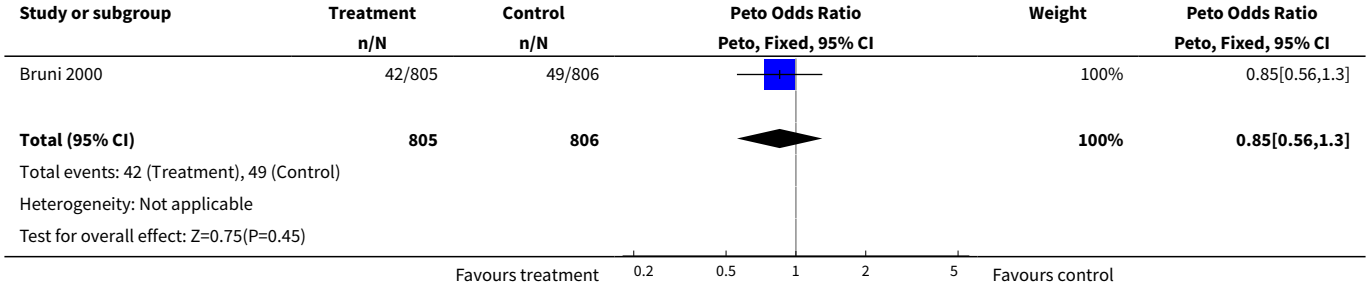
Favours treatment — Favours control



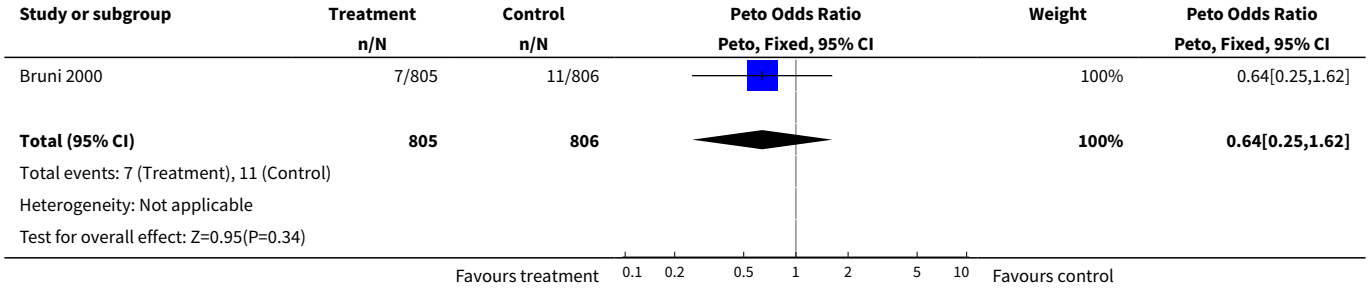
Analysis 3.25. Comparison 3 EE 20 µg and desogestrel 150 µg versus EE 30 µg and gestodene 75 µg, Outcome 25 Acne.



Analysis 3.26. Comparison 3 EE 20 µg and desogestrel 150 µg versus EE 30 µg and gestodene 75 µg, Outcome 26 Breast pain.

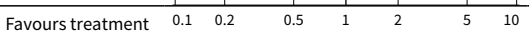


Analysis 3.27. Comparison 3 EE 20 µg and desogestrel 150 µg versus EE 30 µg and gestodene 75 µg, Outcome 27 Decreased libido.



Analysis 3.28. Comparison 3 EE 20 µg and desogestrel 150 µg versus EE 30 µg and gestodene 75 µg, Outcome 28 Depression.

Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Bruni 2000	16/805	21/806		100%	0.76[0.4,1.46]
Total (95% CI)	**805**	**806**		**100%**	**0.76[0.4,1.46]**
Total events: 16 (Treatment), 21 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.83(P=0.41)					



Analysis 3.29. Comparison 3 EE 20 µg and desogestrel 150 µg versus EE 30 µg and gestodene 75 µg, Outcome 29 Dizziness.

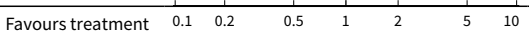
Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Bruni 2000	6/805	10/806		100%	0.6[0.23,1.62]
Total (95% CI)	**805**	**806**		**100%**	**0.6[0.23,1.62]**
Total events: 6 (Treatment), 10 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1(P=0.32)					

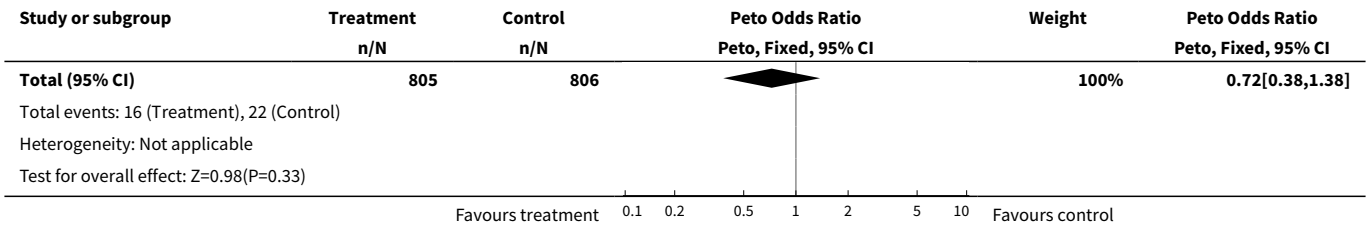
Analysis 3.30. Comparison 3 EE 20 µg and desogestrel 150 µg versus EE 30 µg and gestodene 75 µg, Outcome 30 Dysmenorrhea.

Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Bruni 2000	17/805	18/806		100%	0.94[0.48,1.85]
Total (95% CI)	**805**	**806**		**100%**	**0.94[0.48,1.85]**
Total events: 17 (Treatment), 18 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.17(P=0.87)					

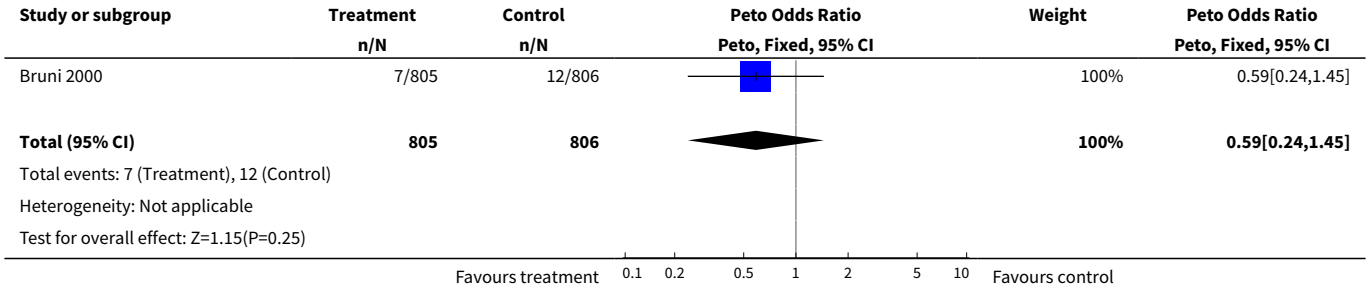
Analysis 3.31. Comparison 3 EE 20 µg and desogestrel 150 µg versus EE 30 µg and gestodene 75 µg, Outcome 31 Emotional lability.

Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Bruni 2000	16/805	22/806		100%	0.72[0.38,1.38]

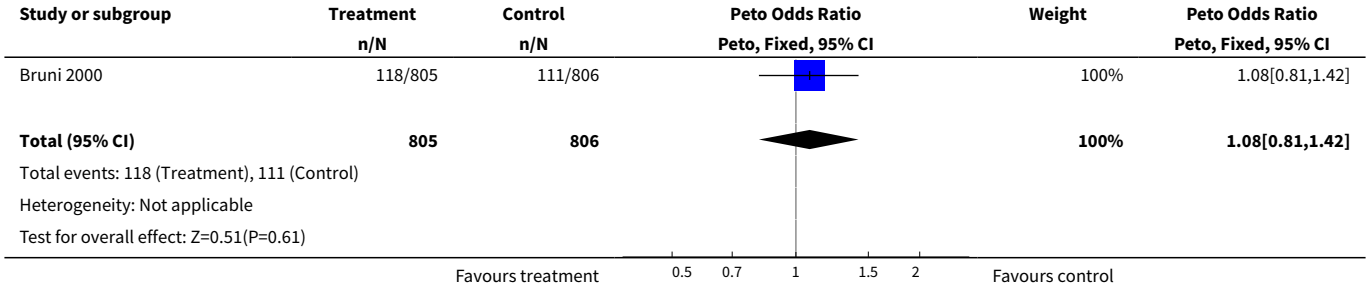




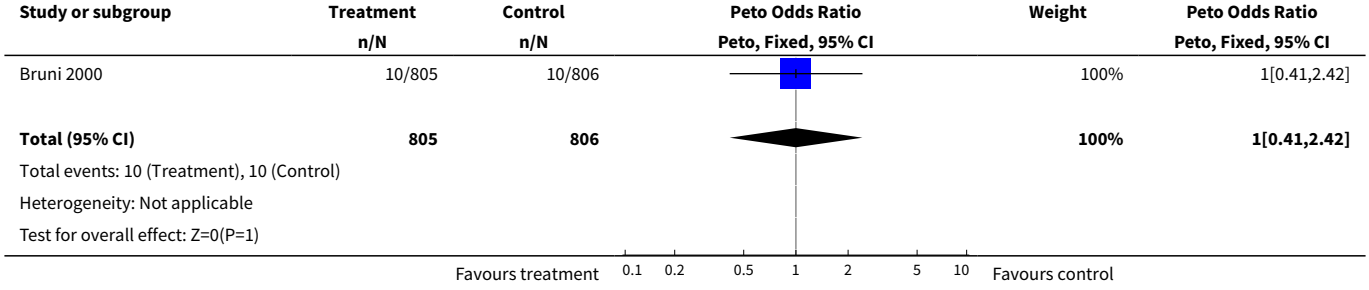
Analysis 3.32. Comparison 3 EE 20 µg and desogestrel 150 µg versus EE 30 µg and gestodene 75 µg, Outcome 32 Flatulence.



Analysis 3.33. Comparison 3 EE 20 µg and desogestrel 150 µg versus EE 30 µg and gestodene 75 µg, Outcome 33 Headache.

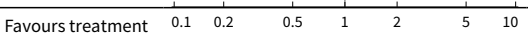


Analysis 3.34. Comparison 3 EE 20 µg and desogestrel 150 µg versus EE 30 µg and gestodene 75 µg, Outcome 34 Menstrual disorder.



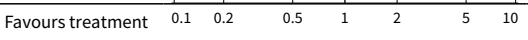
Analysis 3.35. Comparison 3 EE 20 µg and desogestrel 150 µg versus EE 30 µg and gestodene 75 µg, Outcome 35 Metrorrhagia.

Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Bruni 2000	46/805	28/806		100%	1.67[1.05,2.66]
Total (95% CI)	**805**	**806**		**100%**	**1.67[1.05,2.66]**
Total events: 46 (Treatment), 28 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=2.15(P=0.03)					



Analysis 3.36. Comparison 3 EE 20 µg and desogestrel 150 µg versus EE 30 µg and gestodene 75 µg, Outcome 36 Migraine.

Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Bruni 2000	10/805	4/806		100%	2.38[0.83,6.8]
Total (95% CI)	**805**	**806**		**100%**	**2.38[0.83,6.8]**
Total events: 10 (Treatment), 4 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.61(P=0.11)					

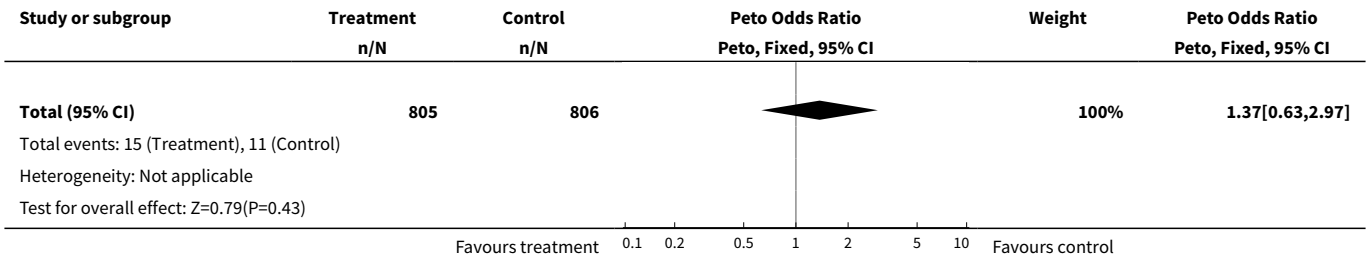


Analysis 3.37. Comparison 3 EE 20 µg and desogestrel 150 µg versus EE 30 µg and gestodene 75 µg, Outcome 37 Nausea.

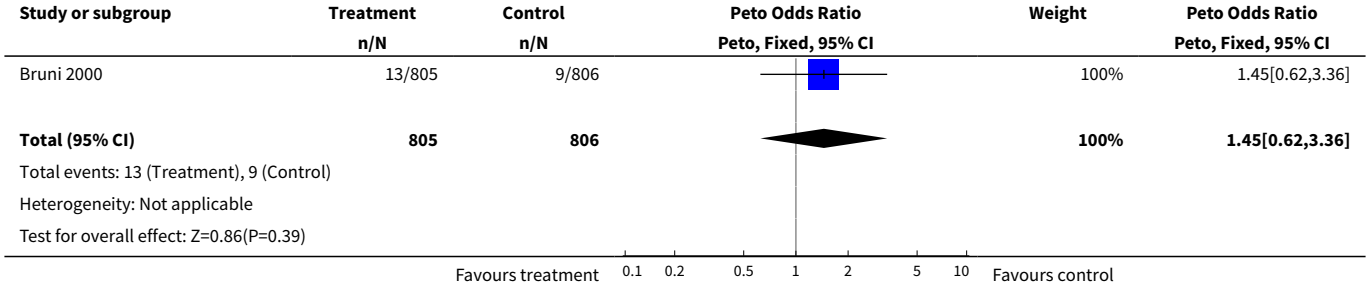
Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Bruni 2000	31/805	27/806		100%	1.16[0.68,1.95]
Total (95% CI)	**805**	**806**		**100%**	**1.16[0.68,1.95]**
Total events: 31 (Treatment), 27 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.54(P=0.59)					

Analysis 3.38. Comparison 3 EE 20 µg and desogestrel 150 µg versus EE 30 µg and gestodene 75 µg, Outcome 38 Pain.

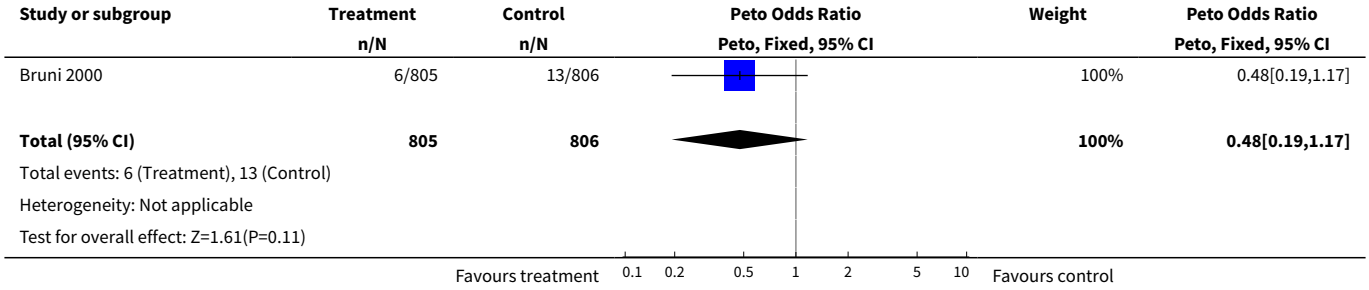
Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Bruni 2000	15/805	11/806		100%	1.37[0.63,2.97]



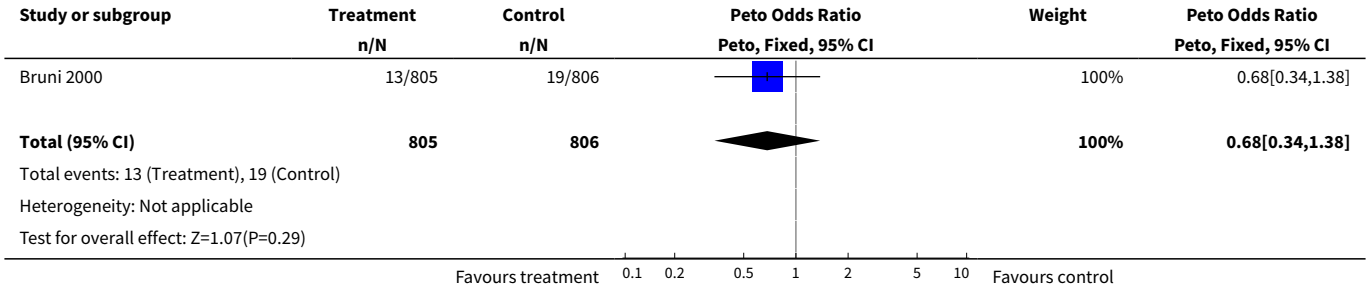
Analysis 3.39. Comparison 3 EE 20 µg and desogestrel 150 µg versus EE 30 µg and gestodene 75 µg, Outcome 39 Vaginal moniliasis.



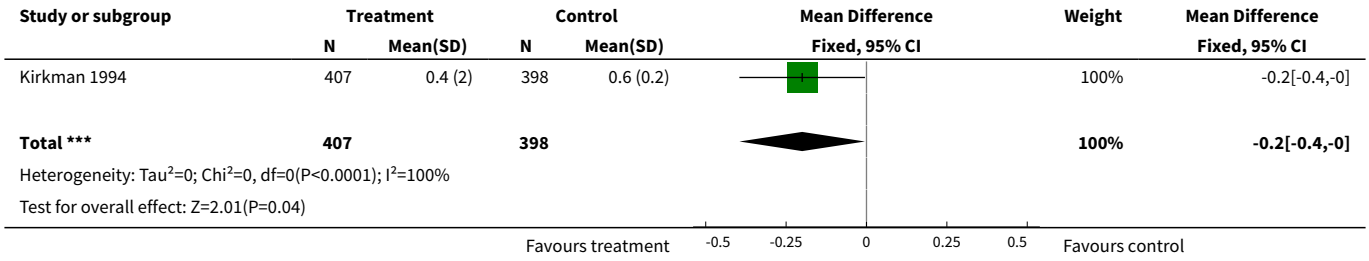
Analysis 3.40. Comparison 3 EE 20 µg and desogestrel 150 µg versus EE 30 µg and gestodene 75 µg, Outcome 40 Vomiting.



Analysis 3.41. Comparison 3 EE 20 µg and desogestrel 150 µg versus EE 30 µg and gestodene 75 µg, Outcome 41 Weight gain.



Analysis 3.42. Comparison 3 EE 20 µg and desogestrel 150 µg versus EE 30 µg and gestodene 75 µg, Outcome 42 Weight gain in kg.

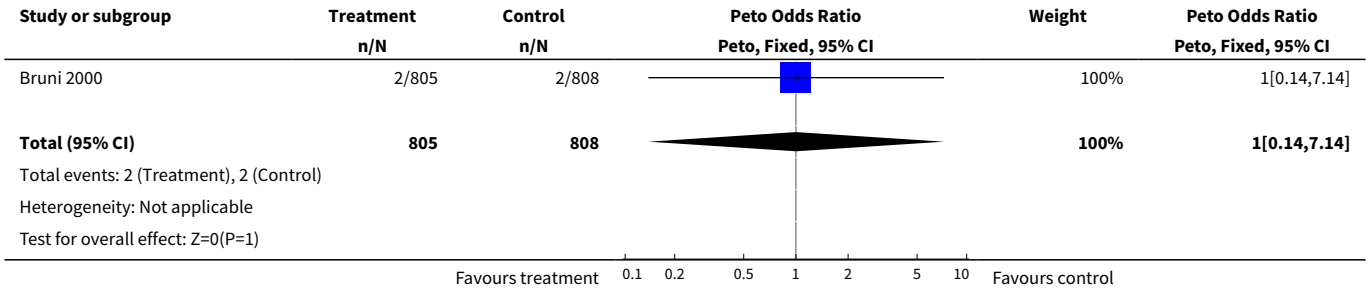


Comparison 4. EE 20 µg and desogestrel 150 µg versus EE 30-40-30 µg and gestodene 50-70-100 µg

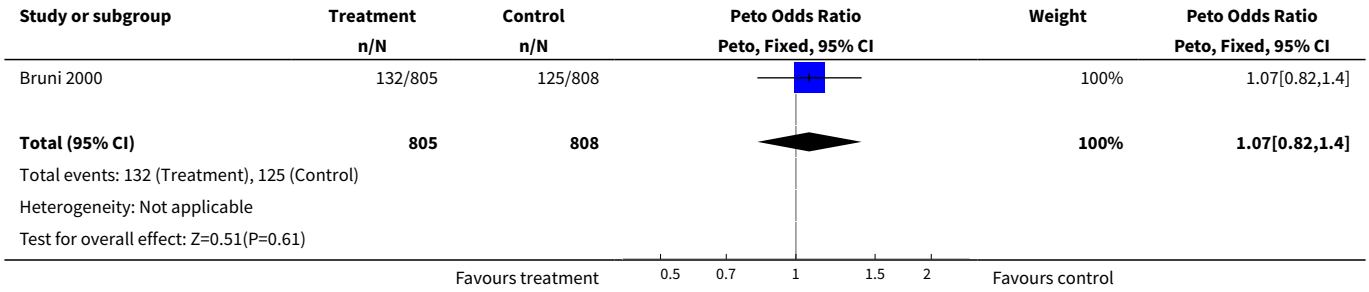
Outcome or sub-group title	No. of studies	No. of partici-pants	Statistical method	Effect size
1 Pregnancy per woman	1	1613	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.00 [0.14, 7.14]
2 Discontinuation - overall	1	1613	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.07 [0.82, 1.40]
3 Discontinuation - adverse reaction	1	1613	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.35 [0.91, 1.99]
4 Discontinuation - metrorrhagia	1	1613	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.97 [1.00, 8.85]
5 Abdominal pain	1	1613	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.20 [0.71, 2.01]
6 Acne	1	1613	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.75 [0.38, 1.46]
7 Breast pain	1	1613	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.70 [0.47, 1.05]
8 Decreased libido	1	1613	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.00 [0.35, 2.87]
9 Depression	1	1613	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.07 [0.53, 2.18]
10 Dizziness	1	1613	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.40 [0.17, 0.93]
11 Dysmenorrhea	1	1613	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.22 [0.60, 2.49]
12 Emotional lability	1	1613	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.89 [0.45, 1.76]
13 Flatulence	1	1613	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.17 [0.39, 3.49]
14 Headache	1	1613	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.04 [0.78, 1.37]
15 Menstrual disor-der	1	1613	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.43 [0.55, 3.73]
16 Metrorrhagia	1	1613	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.28 [1.39, 3.73]

Outcome or sub-group title	No. of studies	No. of partici-pants	Statistical method	Effect size
17 Migraine	1	1613	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.83 [0.36, 1.94]
18 Nausea	1	1613	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.73 [0.46, 1.17]
19 Pain	1	1613	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.10 [0.90, 4.86]
20 Vaginal moniliasis	1	1613	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.11 [0.86, 5.22]
21 Vomiting	1	1613	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.86 [0.29, 2.56]
22 Weight gain	1	1613	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.62 [0.31, 1.22]

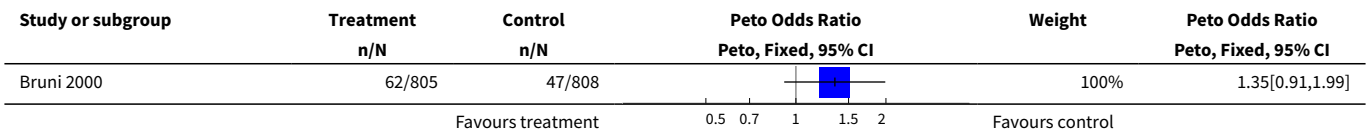
Analysis 4.1. Comparison 4 EE 20 µg and desogestrel 150 µg versus EE 30-40-30 µg and gestodene 50-70-100 µg, Outcome 1 Pregnancy per woman.

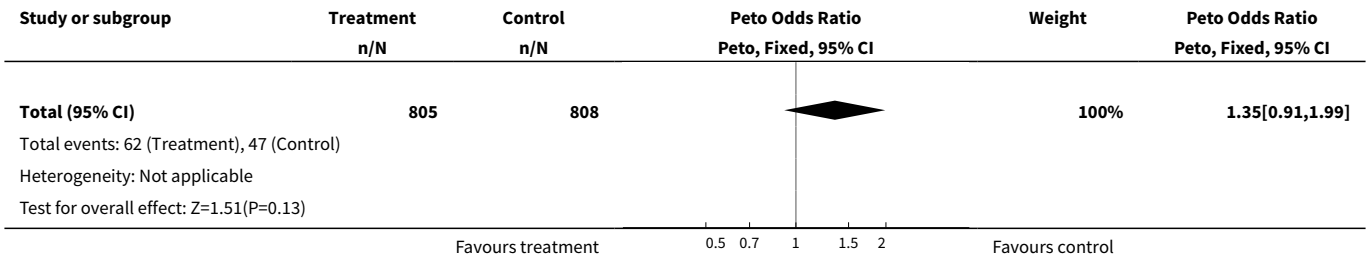


Analysis 4.2. Comparison 4 EE 20 µg and desogestrel 150 µg versus EE 30-40-30 µg and gestodene 50-70-100 µg, Outcome 2 Discontinuation - overall.

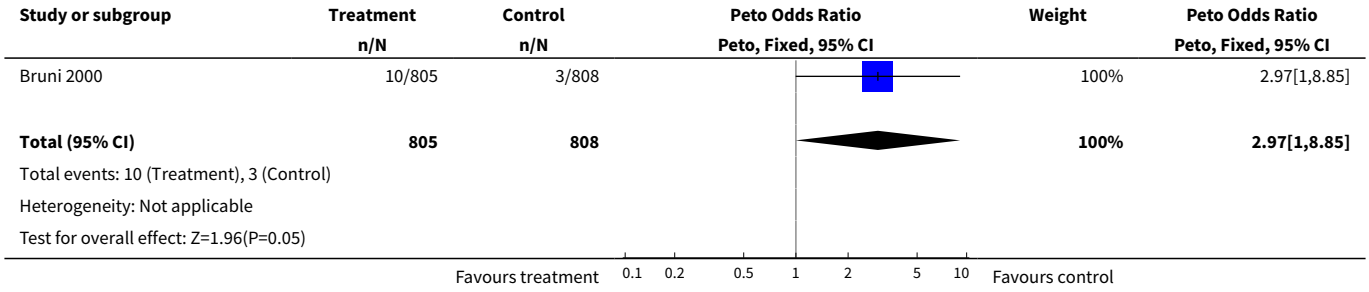


Analysis 4.3. Comparison 4 EE 20 µg and desogestrel 150 µg versus EE 30-40-30 µg and gestodene 50-70-100 µg, Outcome 3 Discontinuation - adverse reaction.

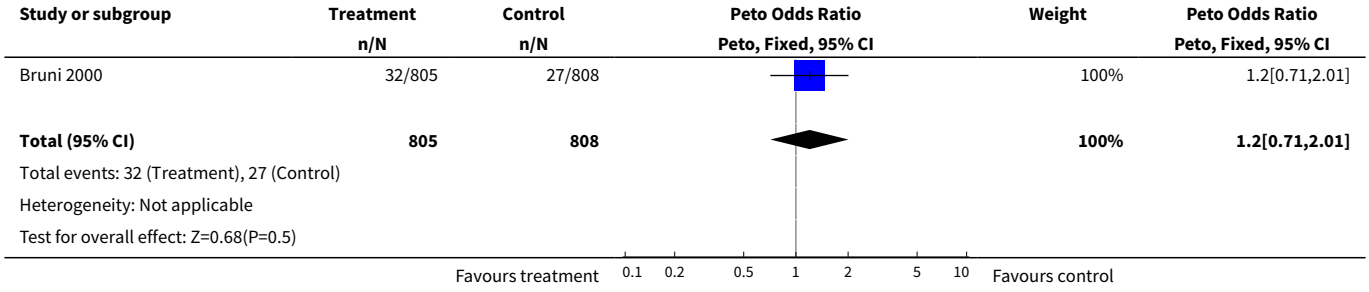




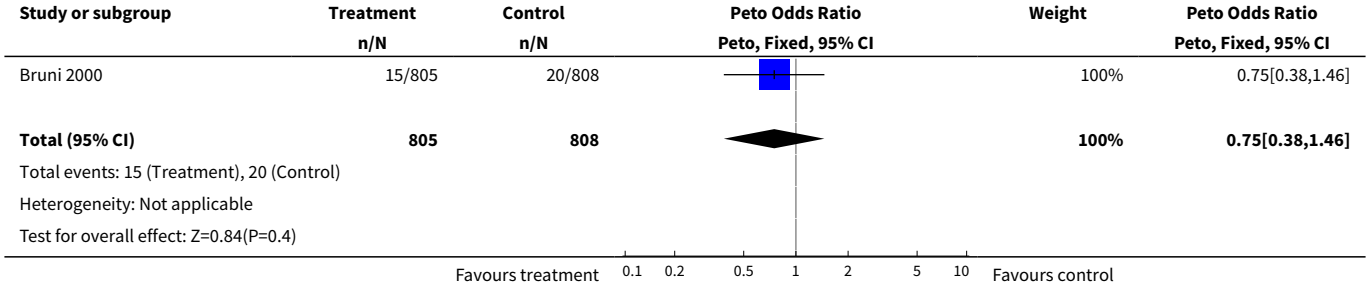
Analysis 4.4. Comparison 4 EE 20 µg and desogestrel 150 µg versus EE 30-40-30 µg and gestodene 50-70-100 µg, Outcome 4 Discontinuation - metrorrhagia.



Analysis 4.5. Comparison 4 EE 20 µg and desogestrel 150 µg versus EE 30-40-30 µg and gestodene 50-70-100 µg, Outcome 5 Abdominal pain.

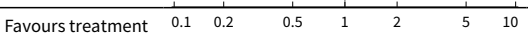


Analysis 4.6. Comparison 4 EE 20 µg and desogestrel 150 µg versus EE 30-40-30 µg and gestodene 50-70-100 µg, Outcome 6 Acne.



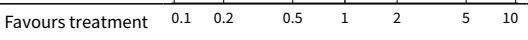
Analysis 4.7. Comparison 4 EE 20 µg and desogestrel 150 µg versus EE 30-40-30 µg and gestodene 50-70-100 µg, Outcome 7 Breast pain.

Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Bruni 2000	42/805	59/808		100%	0.7[0.47,1.05]
Total (95% CI)	**805**	**808**		**100%**	**0.7[0.47,1.05]**
Total events: 42 (Treatment), 59 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.73(P=0.08)					



Analysis 4.8. Comparison 4 EE 20 µg and desogestrel 150 µg versus EE 30-40-30 µg and gestodene 50-70-100 µg, Outcome 8 Decreased libido.

Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Bruni 2000	7/805	7/808		100%	1[0.35,2.87]
Total (95% CI)	**805**	**808**		**100%**	**1[0.35,2.87]**
Total events: 7 (Treatment), 7 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.01(P=0.99)					

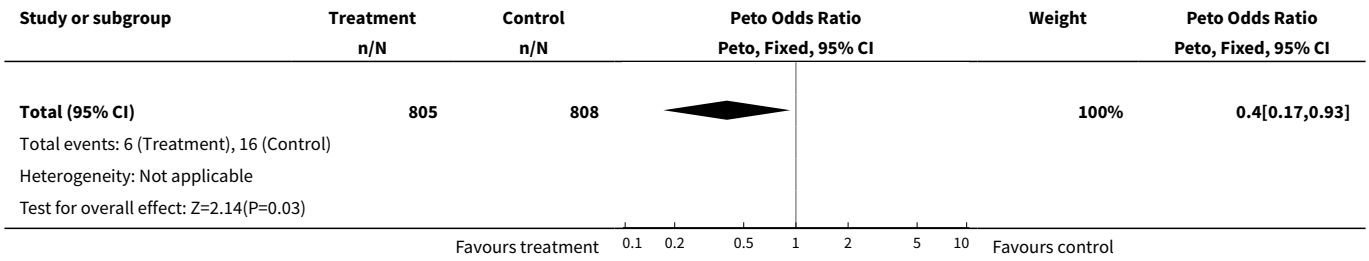


Analysis 4.9. Comparison 4 EE 20 µg and desogestrel 150 µg versus EE 30-40-30 µg and gestodene 50-70-100 µg, Outcome 9 Depression.

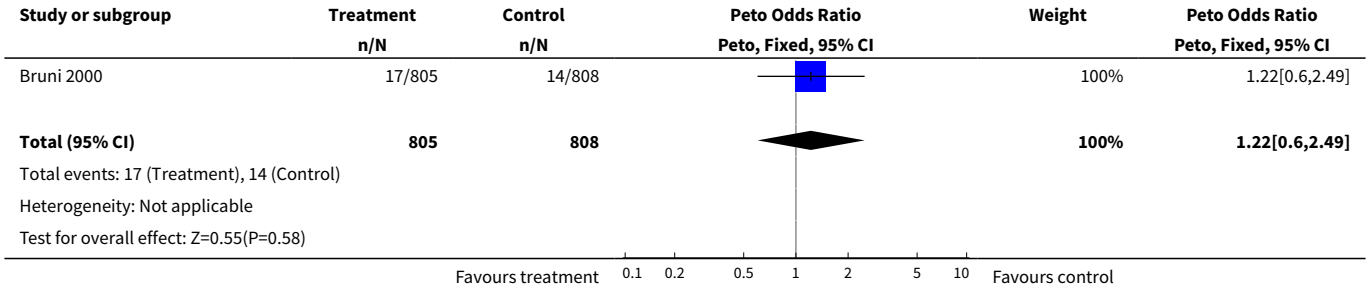
Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Bruni 2000	16/805	15/808		100%	1.07[0.53,2.18]
Total (95% CI)	**805**	**808**		**100%**	**1.07[0.53,2.18]**
Total events: 16 (Treatment), 15 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.19(P=0.85)					

Analysis 4.10. Comparison 4 EE 20 µg and desogestrel 150 µg versus EE 30-40-30 µg and gestodene 50-70-100 µg, Outcome 10 Dizziness.

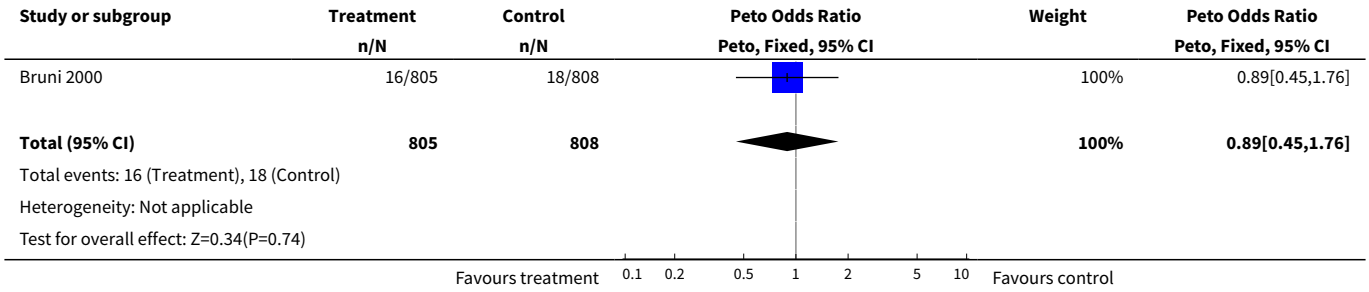
Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Bruni 2000	6/805	16/808		100%	0.4[0.17,0.93]



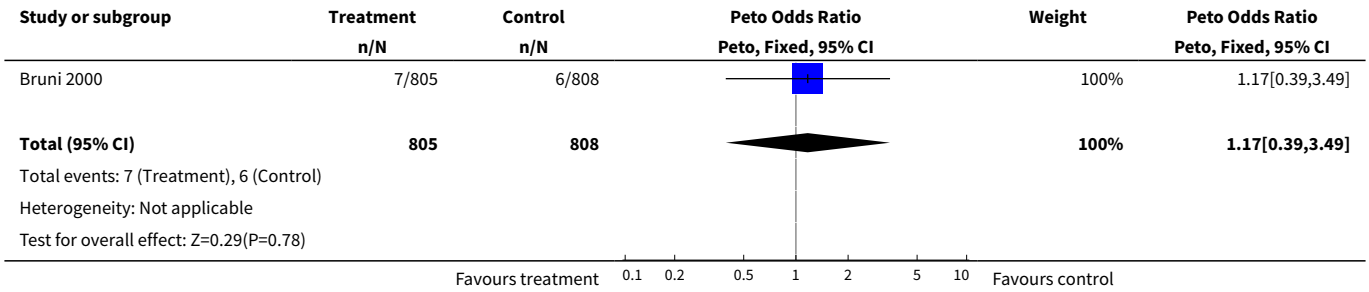
Analysis 4.11. Comparison 4 EE 20 µg and desogestrel 150 µg versus EE 30-40-30 µg and gestodene 50-70-100 µg, Outcome 11 Dysmenorrhea.



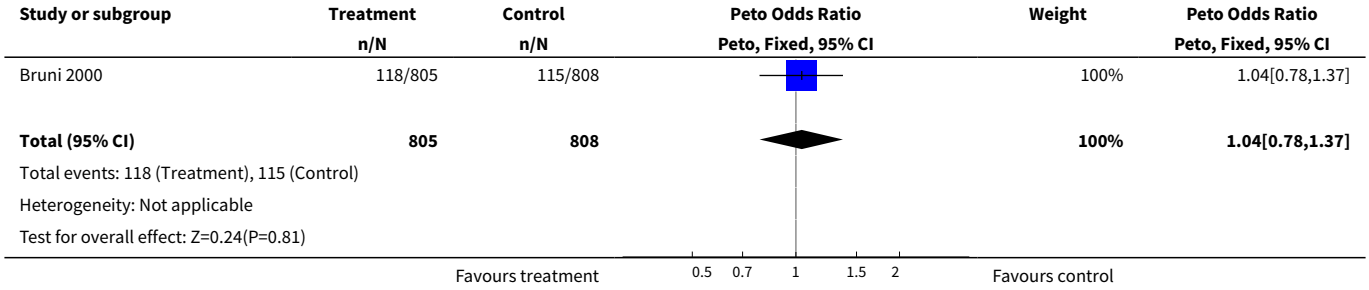
Analysis 4.12. Comparison 4 EE 20 µg and desogestrel 150 µg versus EE 30-40-30 µg and gestodene 50-70-100 µg, Outcome 12 Emotional lability.



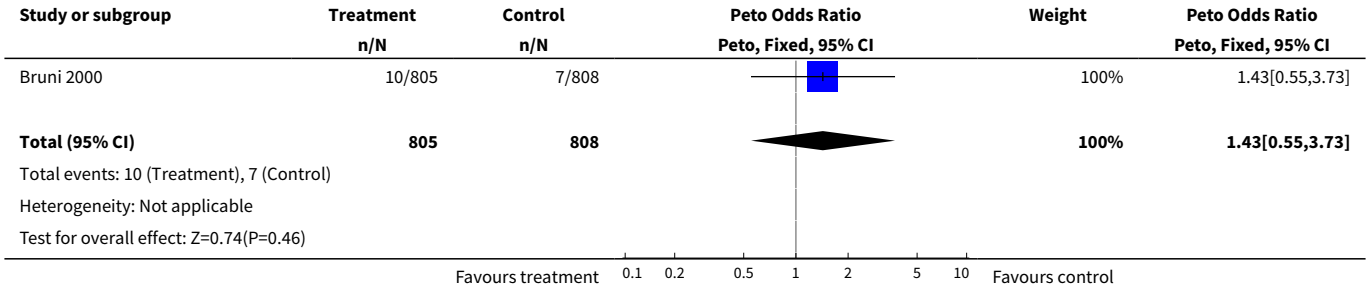
Analysis 4.13. Comparison 4 EE 20 µg and desogestrel 150 µg versus EE 30-40-30 µg and gestodene 50-70-100 µg, Outcome 13 Flatulence.



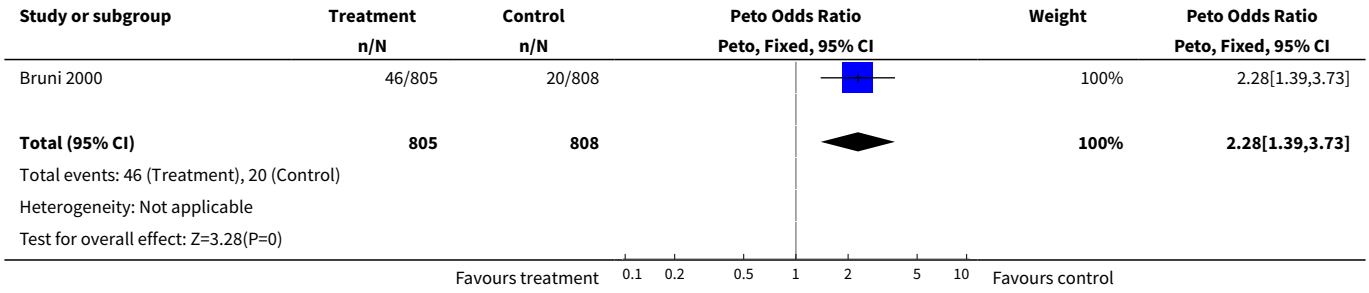
Analysis 4.14. Comparison 4 EE 20 µg and desogestrel 150 µg versus EE 30-40-30 µg and gestodene 50-70-100 µg, Outcome 14 Headache.



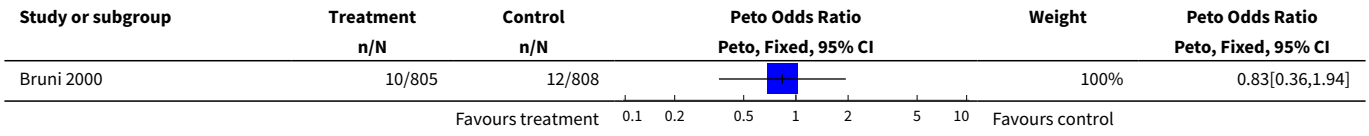
Analysis 4.15. Comparison 4 EE 20 µg and desogestrel 150 µg versus EE 30-40-30 µg and gestodene 50-70-100 µg, Outcome 15 Menstrual disorder.

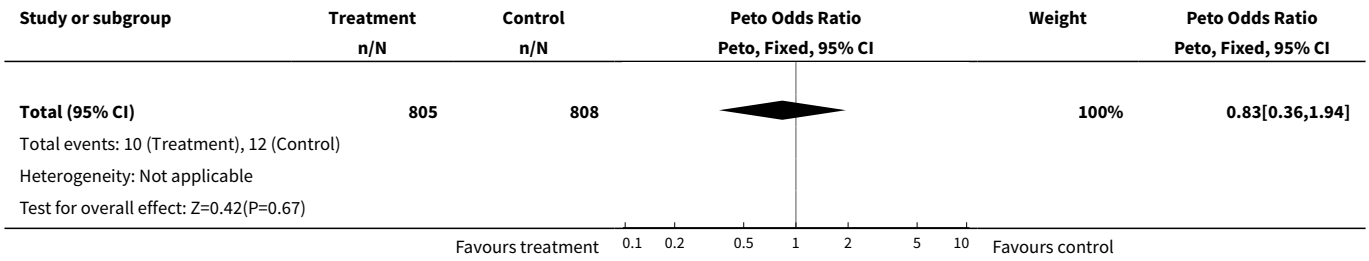


Analysis 4.16. Comparison 4 EE 20 µg and desogestrel 150 µg versus EE 30-40-30 µg and gestodene 50-70-100 µg, Outcome 16 Metrorrhagia.

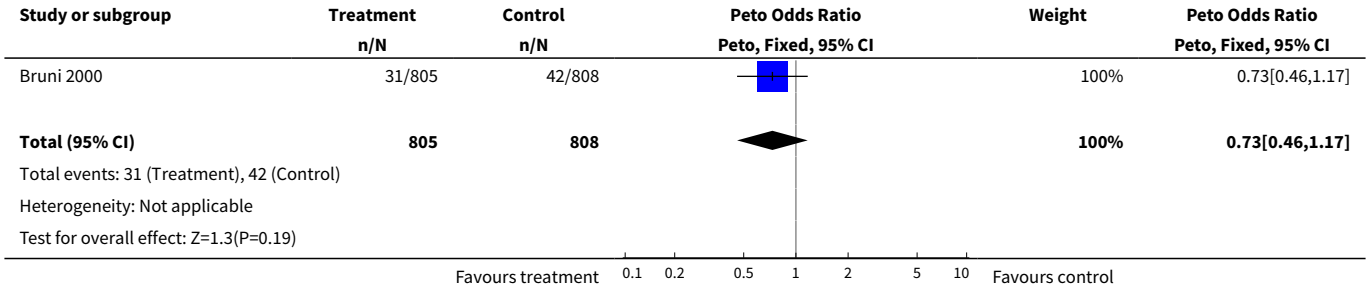


Analysis 4.17. Comparison 4 EE 20 µg and desogestrel 150 µg versus EE 30-40-30 µg and gestodene 50-70-100 µg, Outcome 17 Migraine.

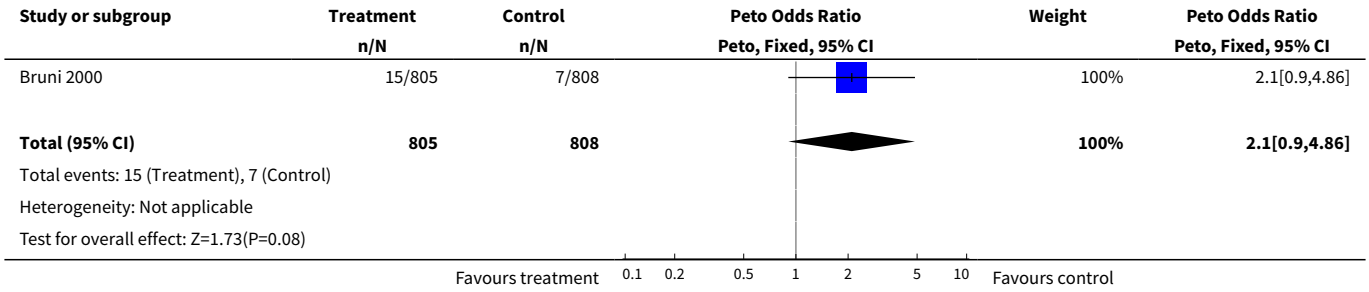




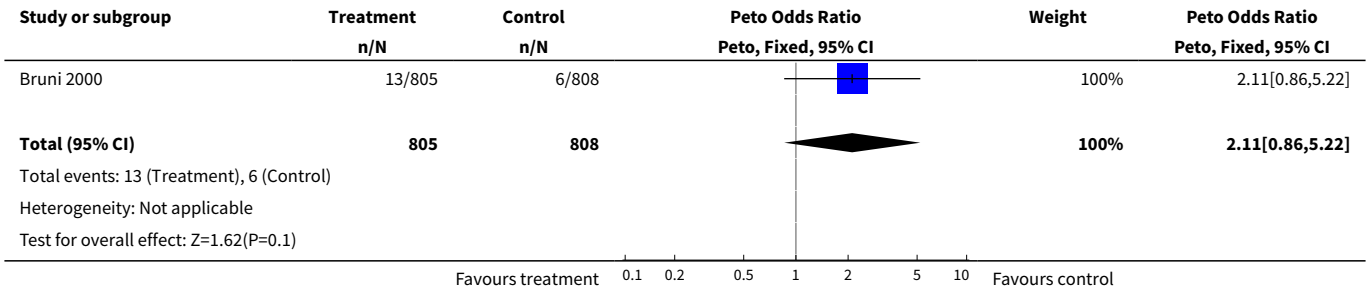
Analysis 4.18. Comparison 4 EE 20 µg and desogestrel 150 µg versus EE 30-40-30 µg and gestodene 50-70-100 µg, Outcome 18 Nausea.



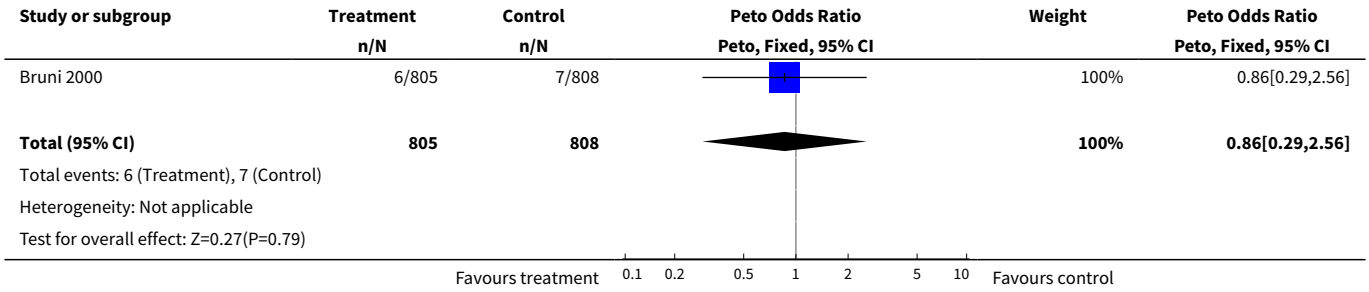
Analysis 4.19. Comparison 4 EE 20 µg and desogestrel 150 µg versus EE 30-40-30 µg and gestodene 50-70-100 µg, Outcome 19 Pain.



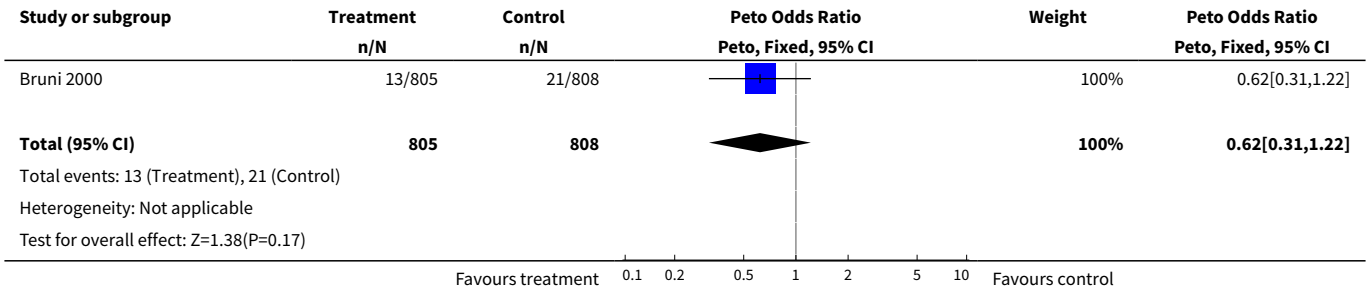
Analysis 4.20. Comparison 4 EE 20 µg and desogestrel 150 µg versus EE 30-40-30 µg and gestodene 50-70-100 µg, Outcome 20 Vaginal moniliasis.



Analysis 4.21. Comparison 4 EE 20 µg and desogestrel 150 µg versus EE 30-40-30 µg and gestodene 50-70-100 µg, Outcome 21 Vomiting.



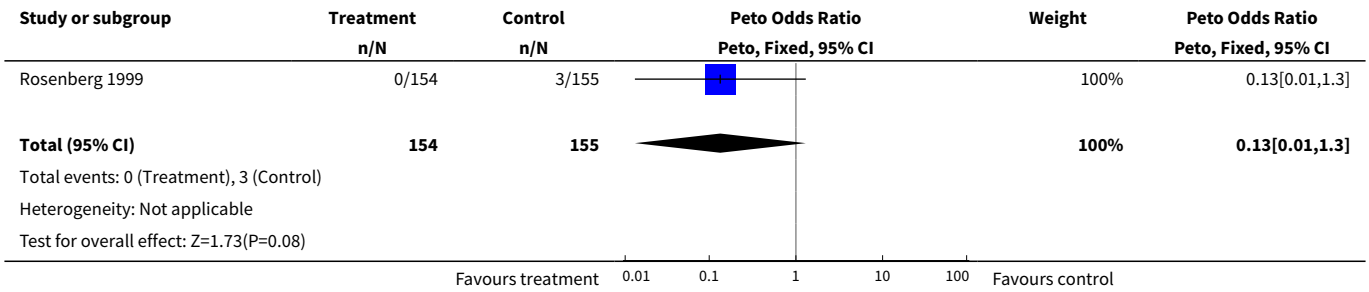
Analysis 4.22. Comparison 4 EE 20 µg and desogestrel 150 µg versus EE 30-40-30 µg and gestodene 50-70-100 µg, Outcome 22 Weight gain.



Comparison 5. EE 20 µg and desogestrel 150 µg versus EE 35 µg and norgestimate 180-215-250 µg

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pregnancy per woman	1	309	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.13 [0.01, 1.30]

Analysis 5.1. Comparison 5 EE 20 µg and desogestrel 150 µg versus EE 35 µg and norgestimate 180-215-250 µg, Outcome 1 Pregnancy per woman.



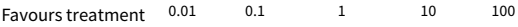
Comparison 6. EE 20 µg and gestodene 75 µg versus EE 30 µg and gestodene 75 µg

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pregnancy per woman	2	799	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.23 [0.02, 2.55]
2 Discontinuation - overall	2	799	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.14 [0.80, 1.63]
3 Discontinuation - adverse event	3	753	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.46 [0.86, 2.46]
4 Discontinuation - intermenstrual bleeding	1	64	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]
5 Discontinuation - metrorrhagia	1	40	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.14 [0.00, 6.82]
6 Breakthrough bleeding - cycle 3	1	114	Peto Odds Ratio (Peto, Fixed, 95% CI)	6.90 [0.14, 348.82]
7 Breakthrough bleeding - cycle 6	1	114	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.13 [0.00, 6.36]
8 Spotting - cycle 3	1	114	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.61 [0.10, 3.66]
9 Spotting - cycle 6	1	114	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.93 [0.06, 15.10]
10 Acne	2	707	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.35 [0.60, 3.08]
11 Breast tension or tenderness	3	821	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.18 [0.68, 2.05]
12 Change in libido	1	649	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.72 [0.64, 4.61]
13 Chloasma	1	114	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.93 [0.13, 6.79]
14 Depressive moods	2	707	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.12 [0.80, 5.66]
15 Diarrhea	1	114	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.33 [0.05, 2.43]
16 Dizziness	2	763	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.52 [0.57, 4.02]
17 Edema	1	649	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.49 [0.09, 2.66]
18 Headache	2	707	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.98 [0.60, 1.59]
19 Nausea	2	707	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.27 [0.66, 2.45]
20 Nausea and vomiting	1	114	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.84 [0.19, 18.04]
21 Nervousness	1	649	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.51 [0.59, 3.87]
22 Varicose conditions	1	649	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.86 [0.20, 3.72]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
23 Vomiting	2	707	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.68 [0.20, 2.25]
24 Weight gain >2 kg	1	452	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.06 [0.63, 1.81]
25 Weight gain in kg	1	114	Mean Difference (IV, Fixed, 95% CI)	-1.5 [-4.23, 1.23]

Analysis 6.1. Comparison 6 EE 20 µg and gestodene 75 µg versus EE 30 µg and gestodene 75 µg, Outcome 1 Pregnancy per woman.

Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Endrikat 1997	1/428	2/221		100%	0.23[0.02,2.55]
Taneepanichskul 2002	0/76	0/74			Not estimable
Total (95% CI)	**504**	**295**		**100%**	**0.23[0.02,2.55]**
Total events: 1 (Treatment), 2 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.19(P=0.23)					

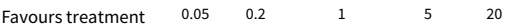


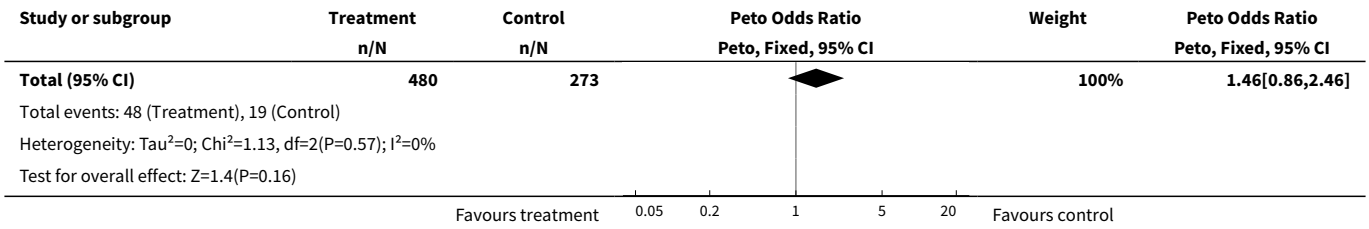
Analysis 6.2. Comparison 6 EE 20 µg and gestodene 75 µg versus EE 30 µg and gestodene 75 µg, Outcome 2 Discontinuation - overall.

Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Endrikat 1997	93/428	40/221		77.55%	1.25[0.84,1.87]
Taneepanichskul 2002	17/76	19/74		22.45%	0.84[0.4,1.76]
Total (95% CI)	**504**	**295**		**100%**	**1.14[0.8,1.63]**
Total events: 110 (Treatment), 59 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0.87, df=1(P=0.35); I^2=0%					
Test for overall effect: Z=0.73(P=0.46)					

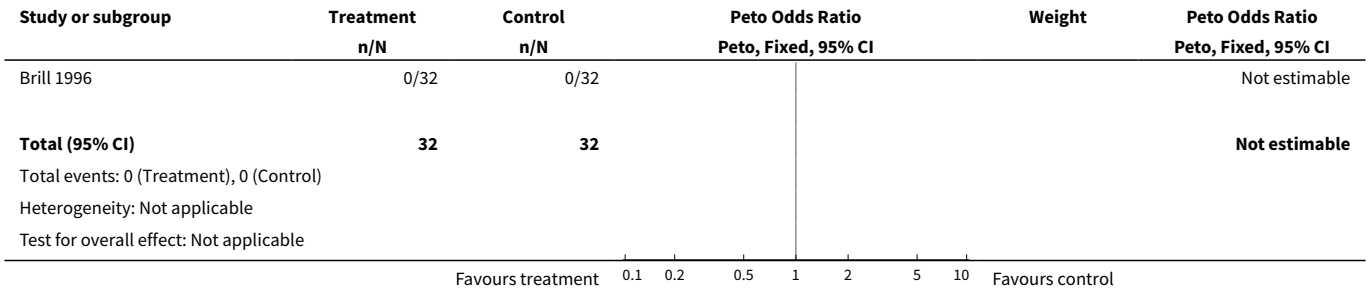
Analysis 6.3. Comparison 6 EE 20 µg and gestodene 75 µg versus EE 30 µg and gestodene 75 µg, Outcome 3 Discontinuation - adverse event.

Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Brill 1996	4/32	1/32		8.38%	3.6[0.59,22.04]
Endrikat 1997	42/428	16/221		85.02%	1.37[0.78,2.42]
Winkler 1996	2/20	2/20		6.61%	1[0.13,7.69]

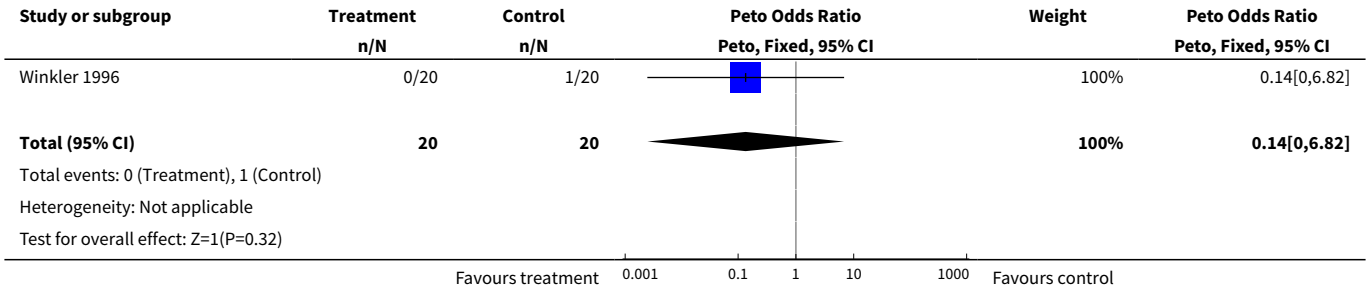




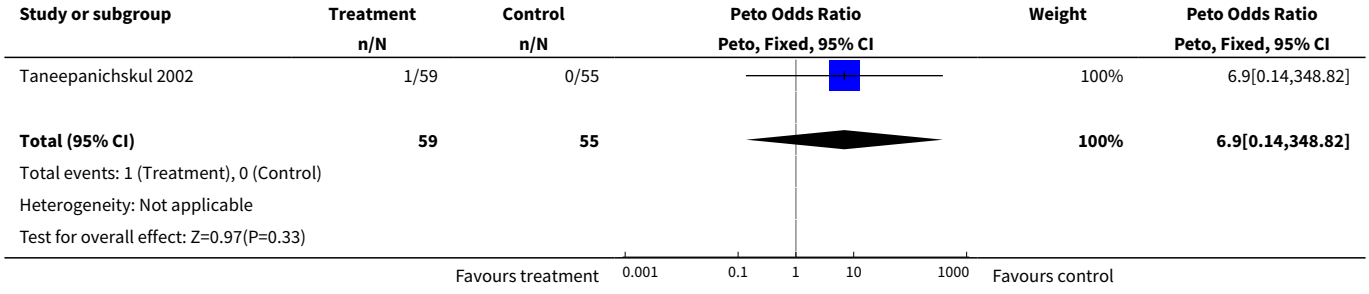
Analysis 6.4. Comparison 6 EE 20 µg and gestodene 75 µg versus EE 30 µg and gestodene 75 µg, Outcome 4 Discontinuation - intermenstrual bleeding.



Analysis 6.5. Comparison 6 EE 20 µg and gestodene 75 µg versus EE 30 µg and gestodene 75 µg, Outcome 5 Discontinuation - metrorrhagia.

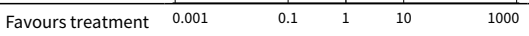


Analysis 6.6. Comparison 6 EE 20 µg and gestodene 75 µg versus EE 30 µg and gestodene 75 µg, Outcome 6 Breakthrough bleeding - cycle 3.



Analysis 6.7. Comparison 6 EE 20 µg and gestodene 75 µg versus EE 30 µg and gestodene 75 µg, Outcome 7 Breakthrough bleeding - cycle 6.

Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Taneepanichskul 2002	0/59	1/55		100%	0.13[0,6.36]
Total (95% CI)	**59**	**55**		**100%**	**0.13[0,6.36]**
Total events: 0 (Treatment), 1 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.04(P=0.3)					

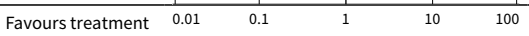


Analysis 6.8. Comparison 6 EE 20 µg and gestodene 75 µg versus EE 30 µg and gestodene 75 µg, Outcome 8 Spotting - cycle 3.

Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Taneepanichskul 2002	2/59	3/55		100%	0.61[0.1,3.66]
Total (95% CI)	**59**	**55**		**100%**	**0.61[0.1,3.66]**
Total events: 2 (Treatment), 3 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.54(P=0.59)					

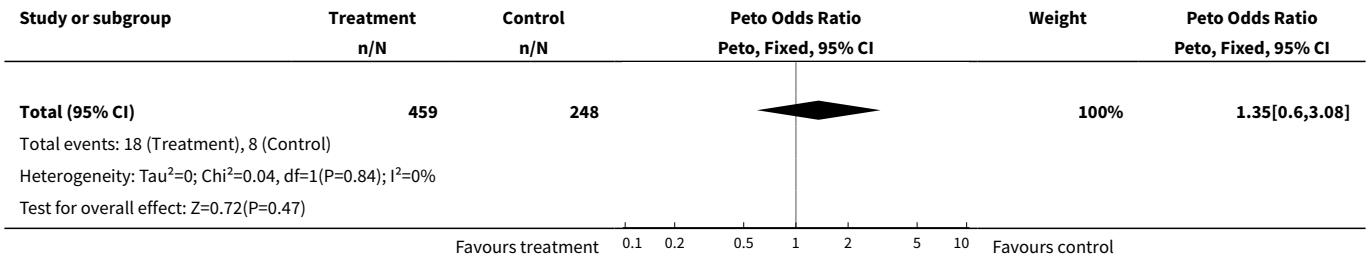
Analysis 6.9. Comparison 6 EE 20 µg and gestodene 75 µg versus EE 30 µg and gestodene 75 µg, Outcome 9 Spotting - cycle 6.

Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Taneepanichskul 2002	1/59	1/55		100%	0.93[0.06,15.1]
Total (95% CI)	**59**	**55**		**100%**	**0.93[0.06,15.1]**
Total events: 1 (Treatment), 1 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.05(P=0.96)					

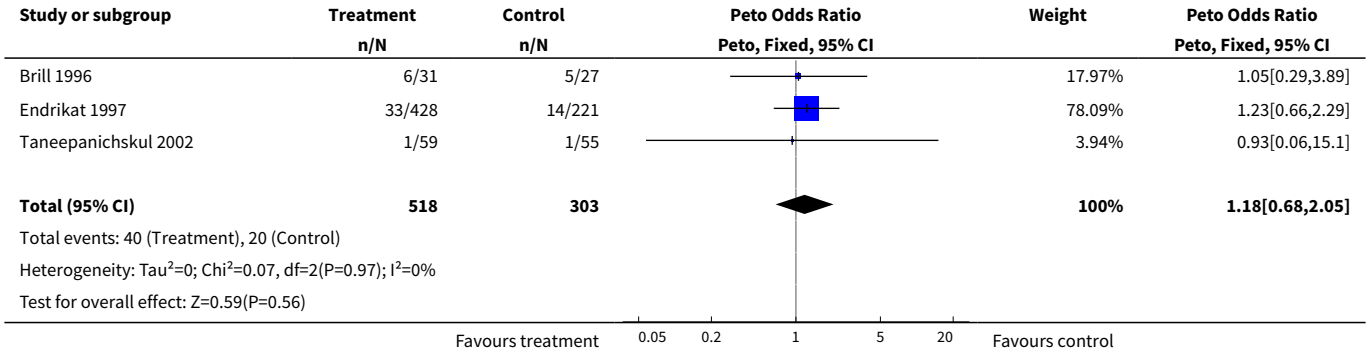


Analysis 6.10. Comparison 6 EE 20 µg and gestodene 75 µg versus EE 30 µg and gestodene 75 µg, Outcome 10 Acne.

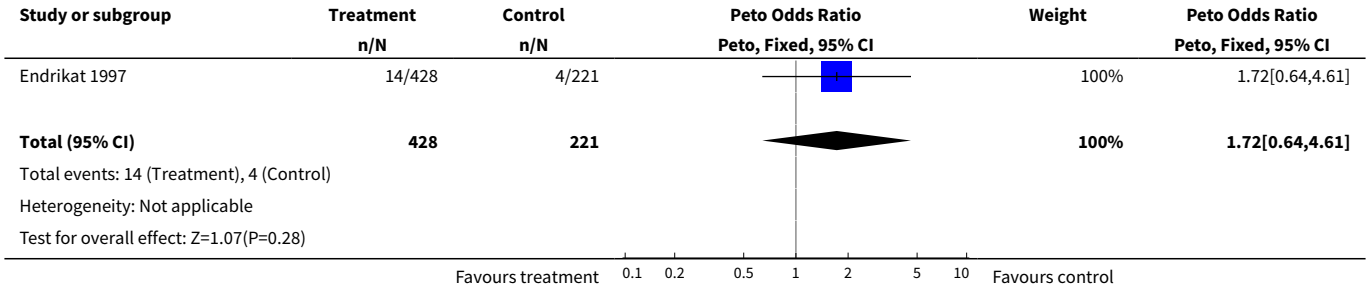
Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Brill 1996	4/31	3/27		27.31%	1.18[0.25,5.67]
Endrikat 1997	14/428	5/221		72.69%	1.43[0.54,3.73]



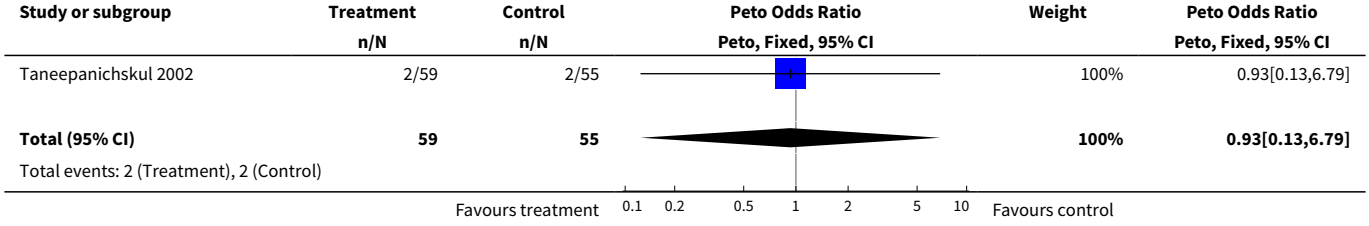
Analysis 6.11. Comparison 6 EE 20 µg and gestodene 75 µg versus EE 30 µg and gestodene 75 µg, Outcome 11 Breast tension or tenderness.

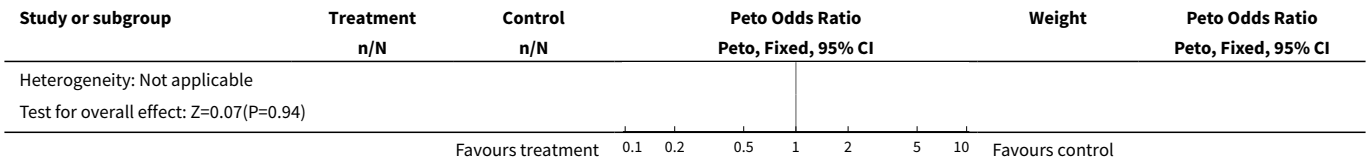


Analysis 6.12. Comparison 6 EE 20 µg and gestodene 75 µg versus EE 30 µg and gestodene 75 µg, Outcome 12 Change in libido.

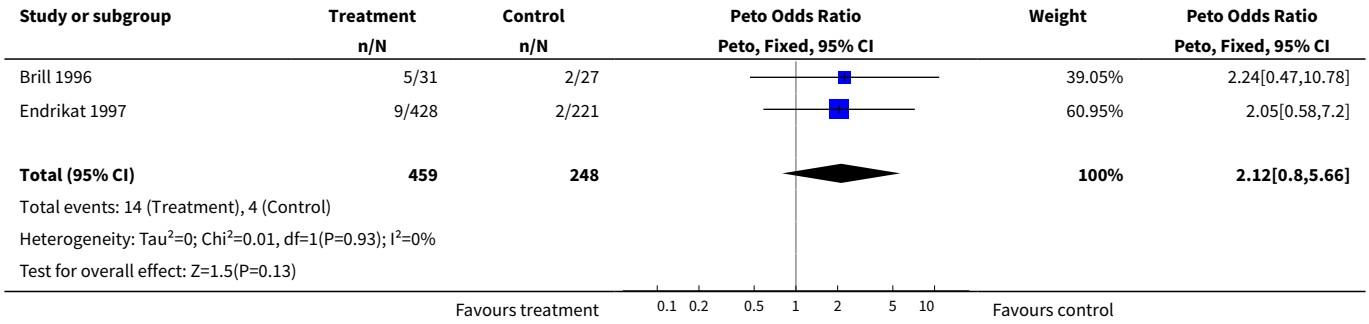


Analysis 6.13. Comparison 6 EE 20 µg and gestodene 75 µg versus EE 30 µg and gestodene 75 µg, Outcome 13 Chloasma.

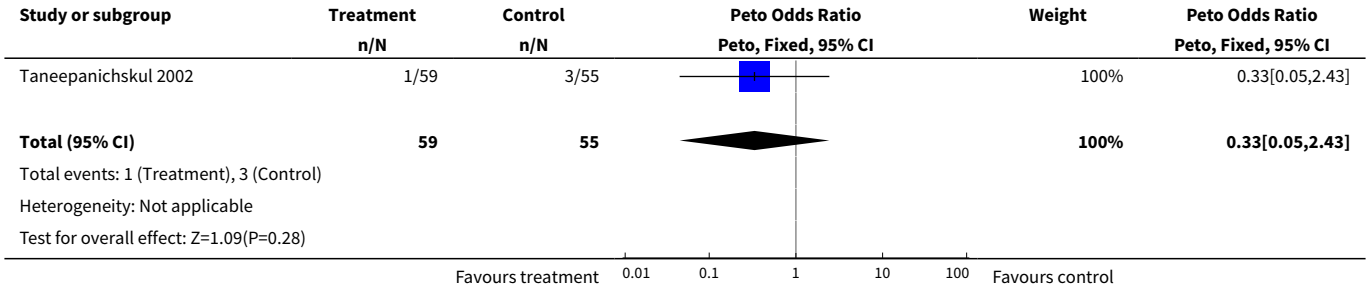




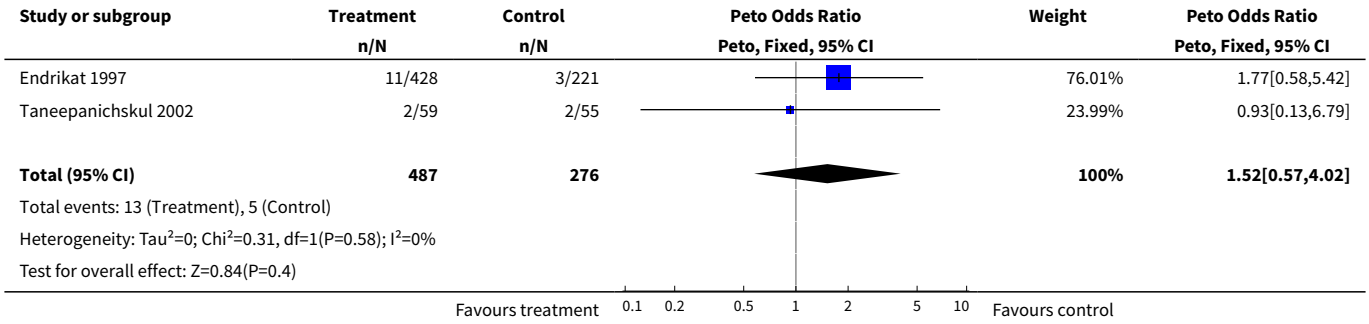
Analysis 6.14. Comparison 6 EE 20 µg and gestodene 75 µg versus EE 30 µg and gestodene 75 µg, Outcome 14 Depressive moods.



Analysis 6.15. Comparison 6 EE 20 µg and gestodene 75 µg versus EE 30 µg and gestodene 75 µg, Outcome 15 Diarrhea.

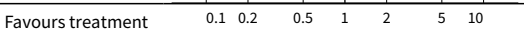


Analysis 6.16. Comparison 6 EE 20 µg and gestodene 75 µg versus EE 30 µg and gestodene 75 µg, Outcome 16 Dizziness.



Analysis 6.17. Comparison 6 EE 20 µg and gestodene 75 µg versus EE 30 µg and gestodene 75 µg, Outcome 17 Edema.

Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Endrikat 1997	3/428	3/221		100%	0.49[0.09,2.66]
Total (95% CI)	**428**	**221**		**100%**	**0.49[0.09,2.66]**
Total events: 3 (Treatment), 3 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.83(P=0.41)					



Favours treatment — Favours control

Analysis 6.18. Comparison 6 EE 20 µg and gestodene 75 µg versus EE 30 µg and gestodene 75 µg, Outcome 18 Headache.

Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Brill 1996	10/31	14/27		21.78%	0.45[0.16,1.28]
Endrikat 1997	44/428	19/221		78.22%	1.21[0.7,2.1]
Total (95% CI)	**459**	**248**		**100%**	**0.98[0.6,1.59]**
Total events: 54 (Treatment), 33 (Control)					
Heterogeneity: Tau^2=0; Chi^2=2.71, df=1(P=0.1); I^2=63.05%					
Test for overall effect: Z=0.09(P=0.93)					

Favours treatment — Favours control

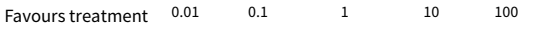
Analysis 6.19. Comparison 6 EE 20 µg and gestodene 75 µg versus EE 30 µg and gestodene 75 µg, Outcome 19 Nausea.

Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Brill 1996	9/31	8/27		34.33%	0.97[0.32,2.99]
Endrikat 1997	20/428	7/221		65.67%	1.46[0.65,3.29]
Total (95% CI)	**459**	**248**		**100%**	**1.27[0.66,2.45]**
Total events: 29 (Treatment), 15 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0.33, df=1(P=0.57); I^2=0%					
Test for overall effect: Z=0.71(P=0.48)					

Favours treatment — Favours control

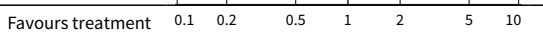
Analysis 6.20. Comparison 6 EE 20 µg and gestodene 75 µg versus EE 30 µg and gestodene 75 µg, Outcome 20 Nausea and vomiting.

Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Taneepanichskul 2002	2/59	1/55		100%	1.84[0.19,18.04]
Total (95% CI)	**59**	**55**		**100%**	**1.84[0.19,18.04]**
Total events: 2 (Treatment), 1 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.52(P=0.6)					



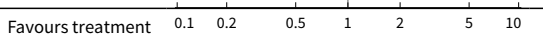
Analysis 6.21. Comparison 6 EE 20 µg and gestodene 75 µg versus EE 30 µg and gestodene 75 µg, Outcome 21 Nervousness.

Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Endrikat 1997	15/428	5/221		100%	1.51[0.59,3.87]
Total (95% CI)	**428**	**221**		**100%**	**1.51[0.59,3.87]**
Total events: 15 (Treatment), 5 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.87(P=0.39)					



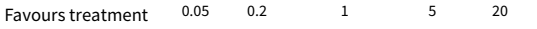
Analysis 6.22. Comparison 6 EE 20 µg and gestodene 75 µg versus EE 30 µg and gestodene 75 µg, Outcome 22 Varicose conditions.

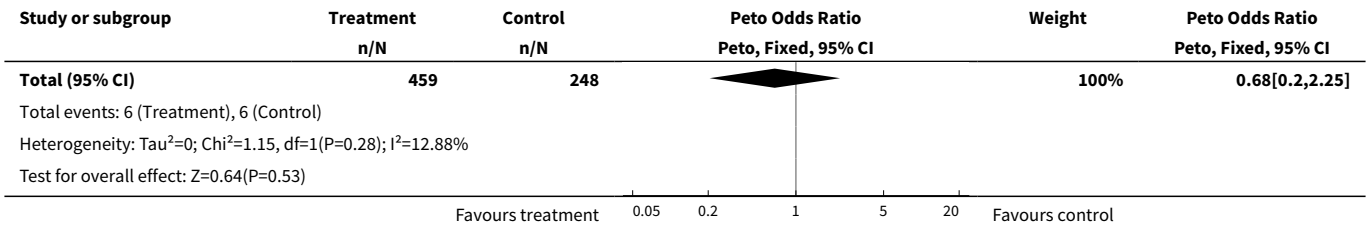
Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Endrikat 1997	5/428	3/221		100%	0.86[0.2,3.72]
Total (95% CI)	**428**	**221**		**100%**	**0.86[0.2,3.72]**
Total events: 5 (Treatment), 3 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.21(P=0.84)					



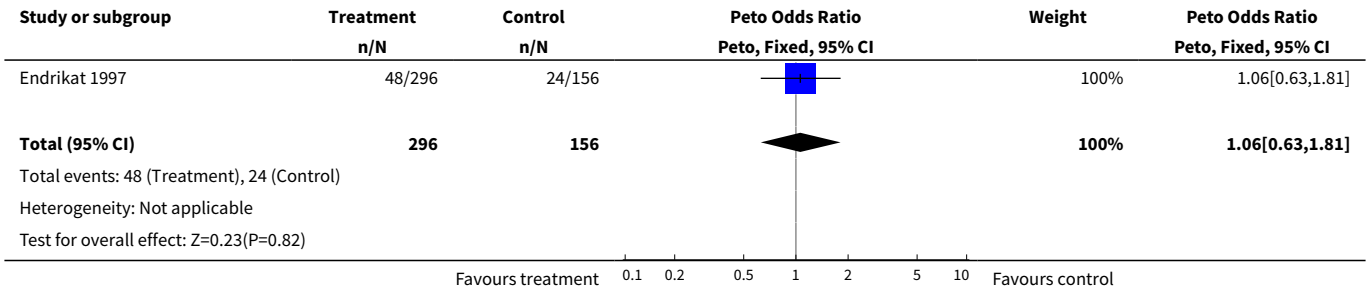
Analysis 6.23. Comparison 6 EE 20 µg and gestodene 75 µg versus EE 30 µg and gestodene 75 µg, Outcome 23 Vomiting.

Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Brill 1996	4/31	3/27		58.27%	1.18[0.25,5.67]
Endrikat 1997	2/428	3/221		41.73%	0.31[0.05,2]

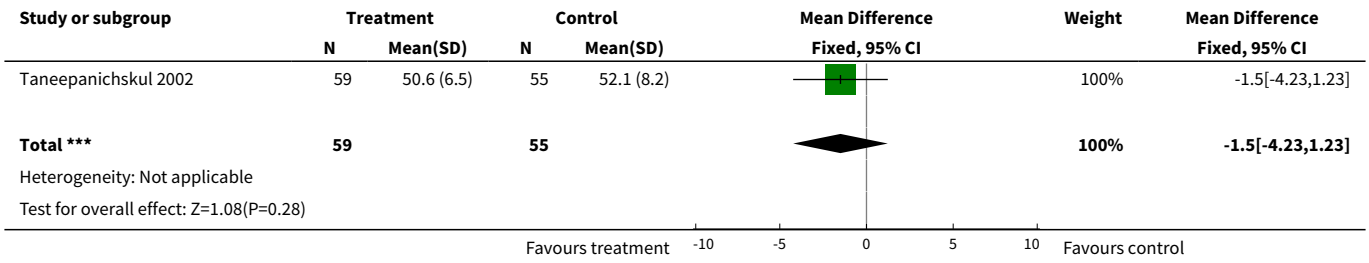




Analysis 6.24. Comparison 6 EE 20 µg and gestodene 75 µg versus EE 30 µg and gestodene 75 µg, Outcome 24 Weight gain >2 kg.



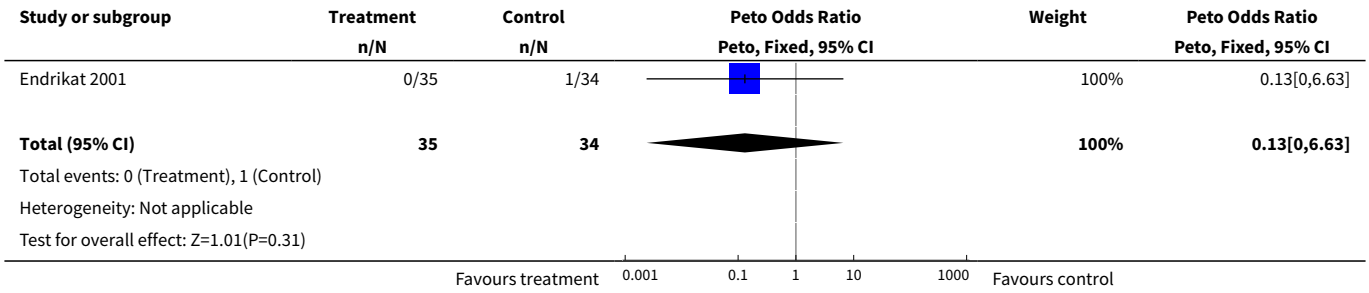
Analysis 6.25. Comparison 6 EE 20 µg and gestodene 75 µg versus EE 30 µg and gestodene 75 µg, Outcome 25 Weight gain in kg.



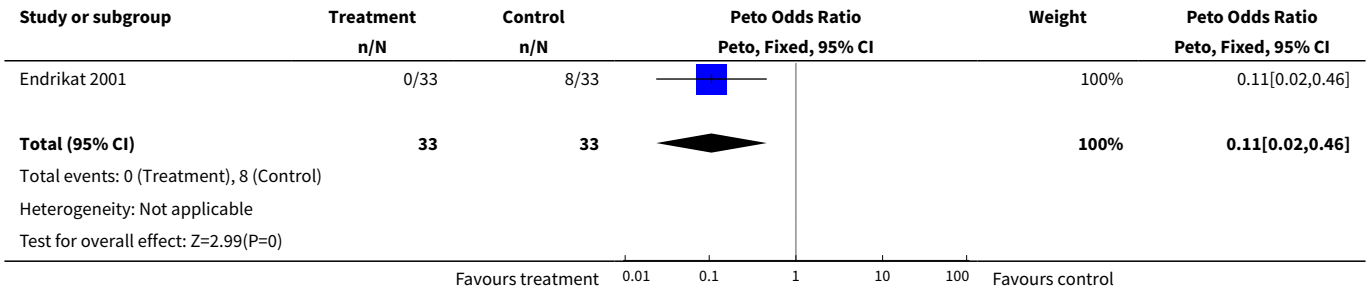
Comparison 7. EE 20 µg and gestodene 75 µg (23-day) versus EE 30 µg and gestodene 75 µg (21-day)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pregnancy per woman	1	69	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.13 [0.00, 6.63]
2 Intracyclic bleeding - cycle 1 and at least once during cycles 2 to 6	1	66	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.11 [0.02, 0.46]

Analysis 7.1. Comparison 7 EE 20 µg and gestodene 75 µg (23-day) versus EE 30 µg and gestodene 75 µg (21-day), Outcome 1 Pregnancy per woman.



Analysis 7.2. Comparison 7 EE 20 µg and gestodene 75 µg (23-day) versus EE 30 µg and gestodene 75 µg (21-day), Outcome 2 Intracyclic bleeding - cycle 1 and at least once during cycles 2 to 6.



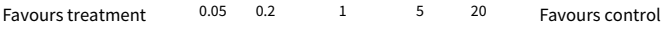
Comparison 8. EE 20 µg and levonorgestrel 100 µg versus EE 35 µg and norethindrone 500-750-1000 µg

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pregnancy per woman	2	729	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.52 [0.10, 2.60]
2 Discontinuation - overall	2	729	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.16 [0.78, 1.73]
3 Discontinuation - adverse events	2	729	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.44 [0.86, 2.41]
4 Discontinuation - breakthrough bleeding	1	387	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.78 [0.39, 19.91]
5 Discontinuation - headache	1	387	Peto Odds Ratio (Peto, Fixed, 95% CI)	3.42 [0.59, 19.90]
6 Discontinuation - nausea or vomiting	1	387	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.27 [0.34, 4.77]
7 Intermenstrual bleeding - cycle 3	2	420	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.85 [0.57, 1.26]
8 Amenorrhea - cycle 3	2	420	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.43 [0.32, 6.34]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
9 Breast pain	1	289	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.45 [0.22, 0.93]
10 Dysmenorrhea	1	289	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.82 [0.49, 1.36]
11 Headache	1	289	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.94 [0.57, 1.56]
12 Nausea	1	289	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.74 [0.40, 1.36]
13 Vomiting	1	289	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.33 [0.11, 0.96]

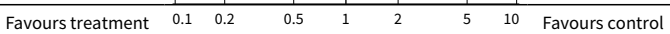
Analysis 8.1. Comparison 8 EE 20 µg and levonorgestrel 100 µg versus EE 35 µg and norethindrone 500-750-1000 µg, Outcome 1 Pregnancy per woman.

Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Chavez 1999	1/169	2/173		49.98%	0.52[0.05,5.07]
Reisman 1999	1/192	2/195		50.02%	0.52[0.05,5.03]
Total (95% CI)	**361**	**368**		**100%**	**0.52[0.1,2.6]**
Total events: 2 (Treatment), 4 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0, df=1(P=1); I^2=0%					
Test for overall effect: Z=0.79(P=0.43)					



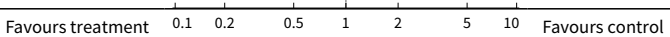
Analysis 8.2. Comparison 8 EE 20 µg and levonorgestrel 100 µg versus EE 35 µg and norethindrone 500-750-1000 µg, Outcome 2 Discontinuation - overall.

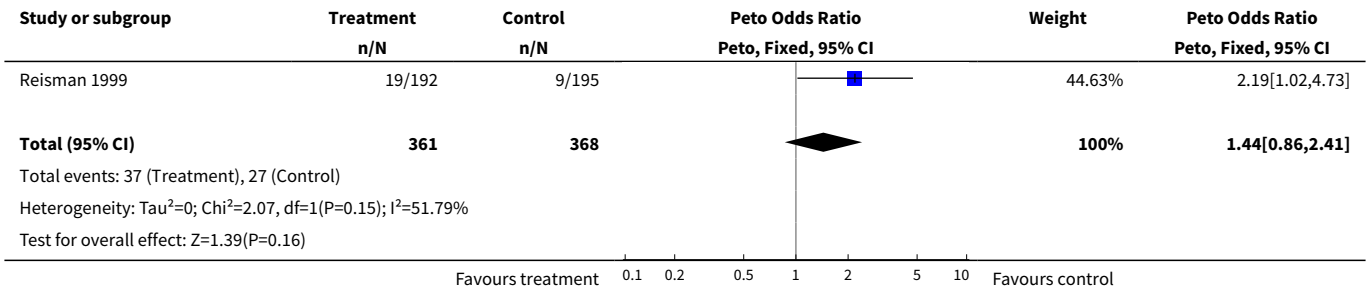
Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Chavez 1999	32/169	31/173		53.73%	1.07[0.62,1.85]
Reisman 1999	28/192	23/195		46.27%	1.28[0.71,2.3]
Total (95% CI)	**361**	**368**		**100%**	**1.16[0.78,1.73]**
Total events: 60 (Treatment), 54 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0.18, df=1(P=0.67); I^2=0%					
Test for overall effect: Z=0.73(P=0.47)					



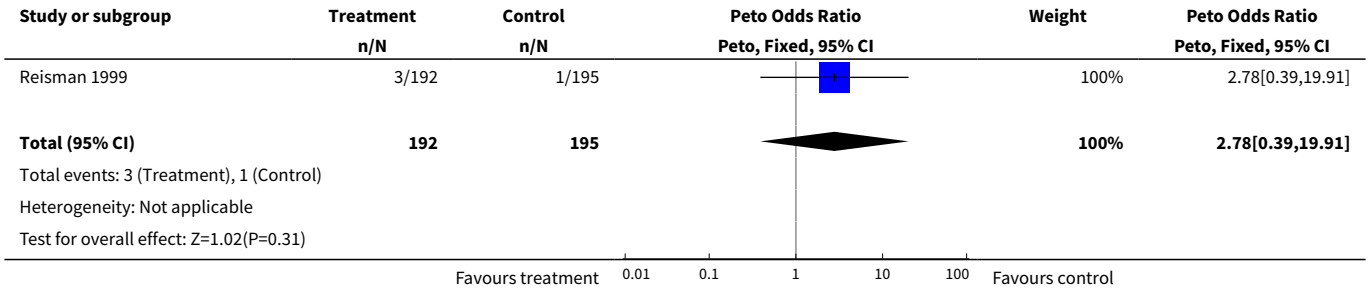
Analysis 8.3. Comparison 8 EE 20 µg and levonorgestrel 100 µg versus EE 35 µg and norethindrone 500-750-1000 µg, Outcome 3 Discontinuation - adverse events.

Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Chavez 1999	18/169	18/173		55.37%	1.03[0.51,2.05]

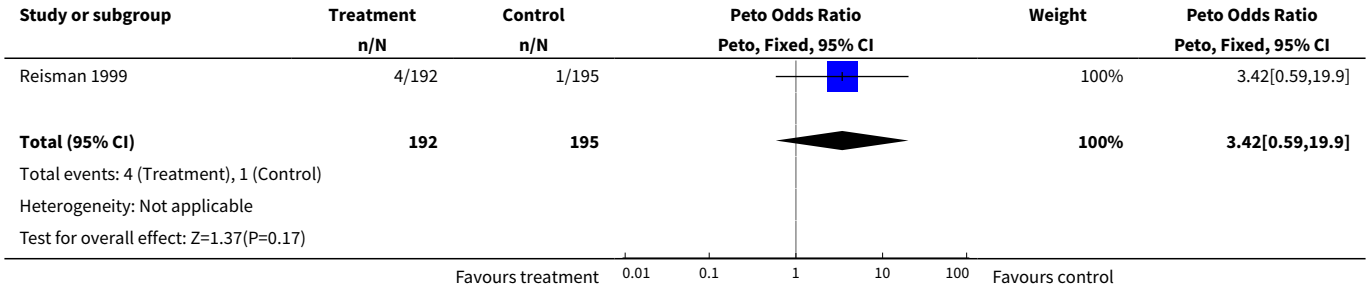




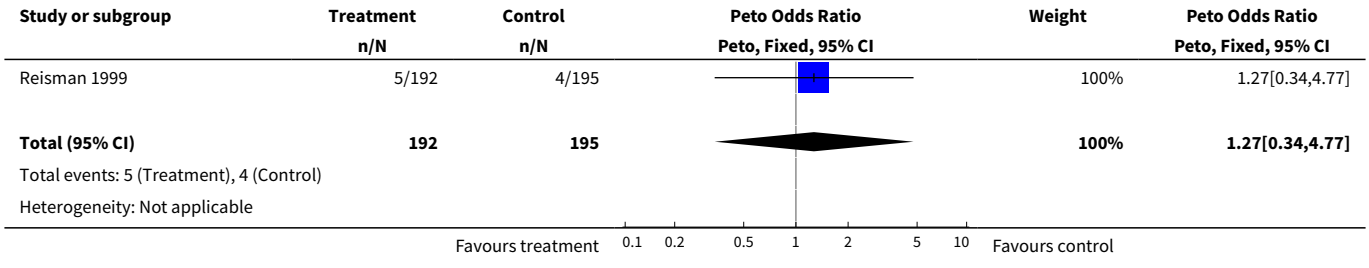
Analysis 8.4. Comparison 8 EE 20 µg and levonorgestrel 100 µg versus EE 35 µg and norethindrone 500-750-1000 µg, Outcome 4 Discontinuation - breakthrough bleeding.

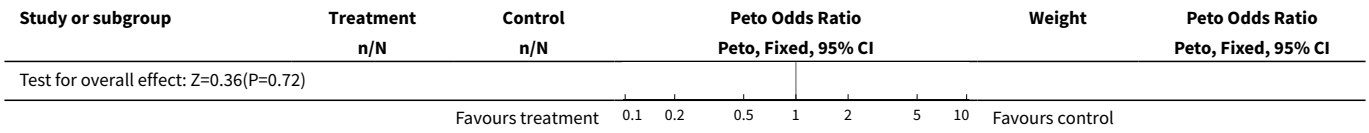


Analysis 8.5. Comparison 8 EE 20 µg and levonorgestrel 100 µg versus EE 35 µg and norethindrone 500-750-1000 µg, Outcome 5 Discontinuation - headache.

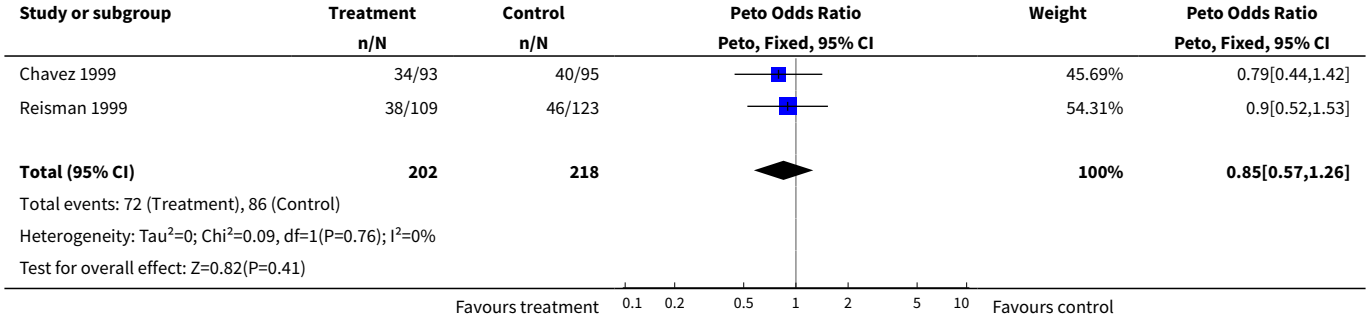


Analysis 8.6. Comparison 8 EE 20 µg and levonorgestrel 100 µg versus EE 35 µg and norethindrone 500-750-1000 µg, Outcome 6 Discontinuation - nausea or vomiting.

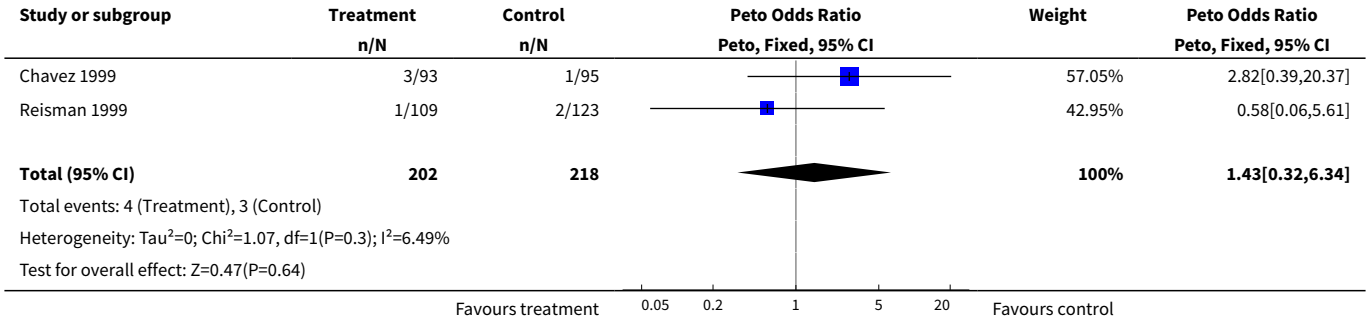




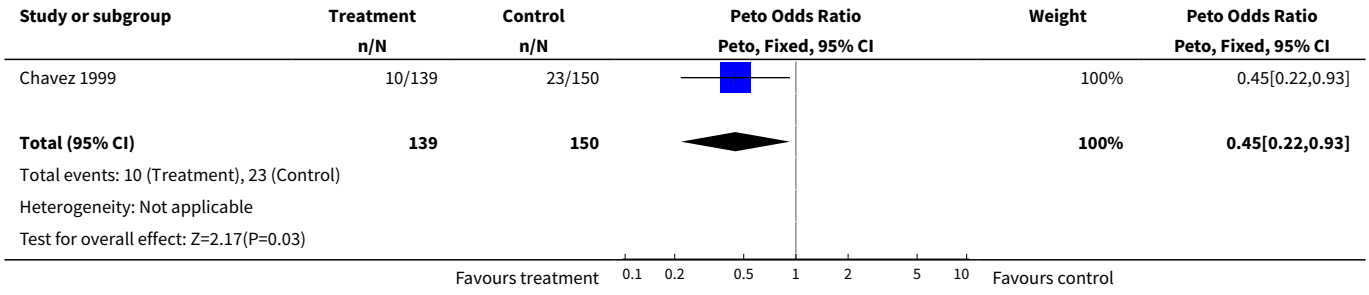
Analysis 8.7. Comparison 8 EE 20 µg and levonorgestrel 100 µg versus EE 35 µg and norethindrone 500-750-1000 µg, Outcome 7 Intermenstrual bleeding - cycle 3.



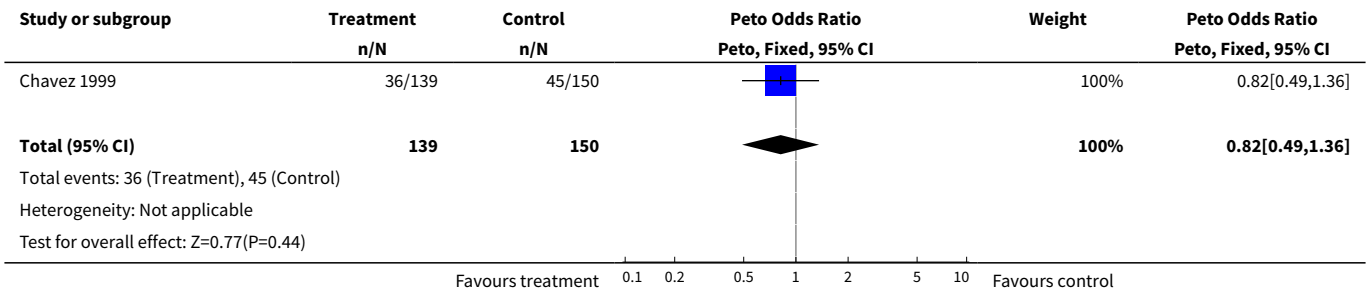
Analysis 8.8. Comparison 8 EE 20 µg and levonorgestrel 100 µg versus EE 35 µg and norethindrone 500-750-1000 µg, Outcome 8 Amenorrhea - cycle 3.



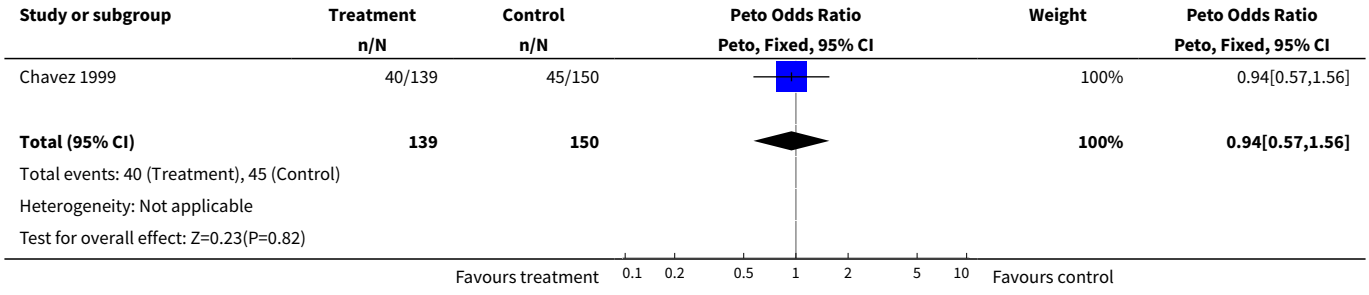
Analysis 8.9. Comparison 8 EE 20 µg and levonorgestrel 100 µg versus EE 35 µg and norethindrone 500-750-1000 µg, Outcome 9 Breast pain.



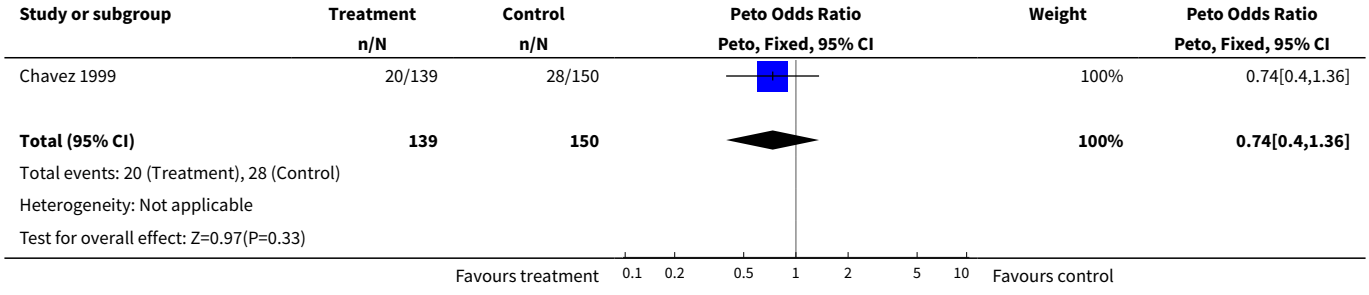
Analysis 8.10. Comparison 8 EE 20 µg and levonorgestrel 100 µg versus EE 35 µg and norethindrone 500-750-1000 µg, Outcome 10 Dysmenorrhea.



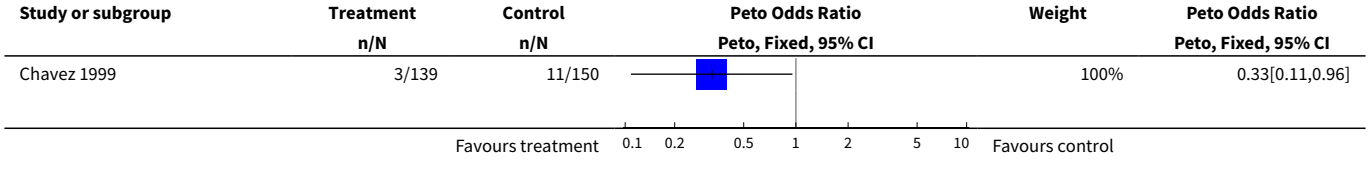
Analysis 8.11. Comparison 8 EE 20 µg and levonorgestrel 100 µg versus EE 35 µg and norethindrone 500-750-1000 µg, Outcome 11 Headache.

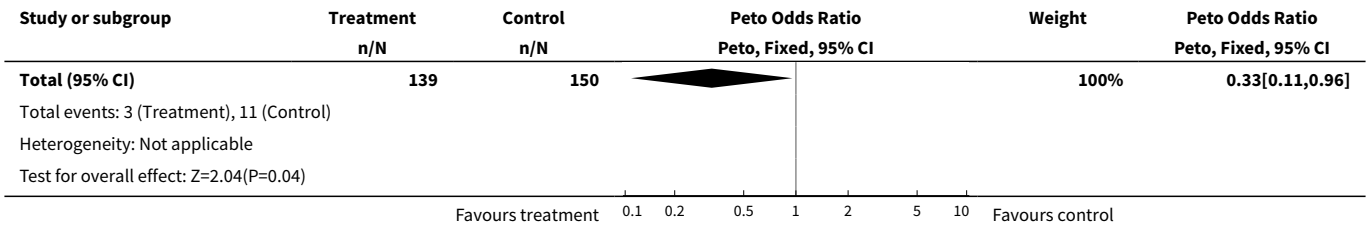


Analysis 8.12. Comparison 8 EE 20 µg and levonorgestrel 100 µg versus EE 35 µg and norethindrone 500-750-1000 µg, Outcome 12 Nausea.



Analysis 8.13. Comparison 8 EE 20 µg and levonorgestrel 100 µg versus EE 35 µg and norethindrone 500-750-1000 µg, Outcome 13 Vomiting.

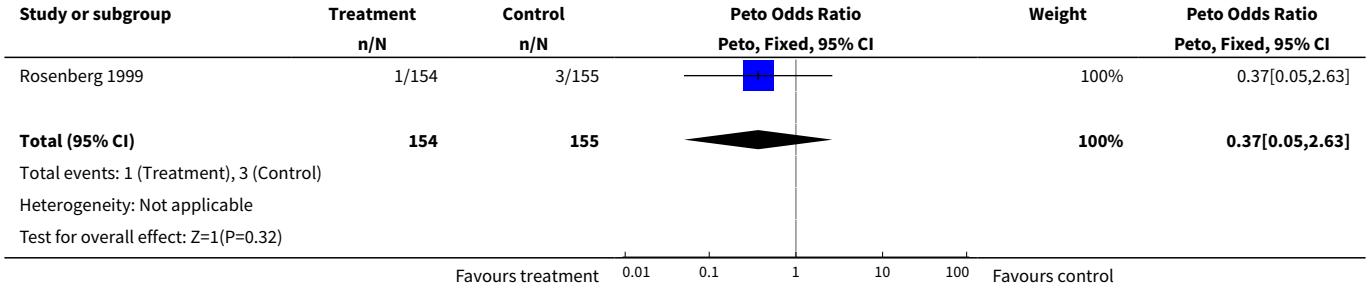




Comparison 9. EE 20 µg and levonorgestrel 100 µg versus EE 35 µg and norgestimate 180-215-250 µg

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pregnancy per woman	1	309	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.37 [0.05, 2.63]

Analysis 9.1. Comparison 9 EE 20 µg and levonorgestrel 100 µg versus EE 35 µg and norgestimate 180-215-250 µg, Outcome 1 Pregnancy per woman.



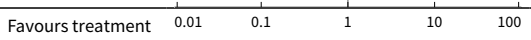
Comparison 10. EE 20 µg and norethindrone acetate 1 mg versus EE 30 µg and levonorgestrel 150 µg

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pregnancy per woman	1	110	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.80 [0.38, 20.41]
2 Discontinuation - bleeding	1	110	Peto Odds Ratio (Peto, Fixed, 95% CI)	5.38 [1.82, 15.91]
3 Frequent bleeding - cycles 1 to 3	1	629	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.92 [2.08, 4.09]
4 Infrequent bleeding - cycles 1 to 3	1	629	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.84 [1.80, 4.46]
5 Irregular bleeding - cycles 1 to 3	1	629	Peto Odds Ratio (Peto, Fixed, 95% CI)	4.01 [2.12, 7.61]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6 Prolonged bleeding - cycles 1 to 3	1	629	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.51 [0.94, 2.43]

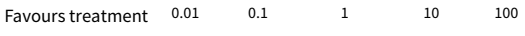
Analysis 10.1. Comparison 10 EE 20 µg and norethindrone acetate 1 mg versus EE 30 µg and levonorgestrel 150 µg, Outcome 1 Pregnancy per woman.

Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Bounds 1979	3/55	1/55		100%	2.8[0.38,20.41]
Total (95% CI)	**55**	**55**		**100%**	**2.8[0.38,20.41]**
Total events: 3 (Treatment), 1 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.01(P=0.31)					



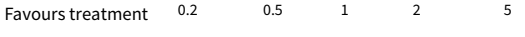
Analysis 10.2. Comparison 10 EE 20 µg and norethindrone acetate 1 mg versus EE 30 µg and levonorgestrel 150 µg, Outcome 2 Discontinuation - bleeding.

Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Bounds 1979	13/55	2/55		100%	5.38[1.82,15.91]
Total (95% CI)	**55**	**55**		**100%**	**5.38[1.82,15.91]**
Total events: 13 (Treatment), 2 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=3.04(P=0)					



Analysis 10.3. Comparison 10 EE 20 µg and norethindrone acetate 1 mg versus EE 30 µg and levonorgestrel 150 µg, Outcome 3 Frequent bleeding - cycles 1 to 3.

Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
WHO 1982	134/314	62/315		100%	2.92[2.08,4.09]
Total (95% CI)	**314**	**315**		**100%**	**2.92[2.08,4.09]**
Total events: 134 (Treatment), 62 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=6.22(P<0.0001)					

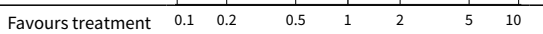


Analysis 10.4. Comparison 10 EE 20 µg and norethindrone acetate 1 mg versus EE 30 µg and levonorgestrel 150 µg, Outcome 4 Infrequent bleeding - cycles 1 to 3.

Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
WHO 1982	63/314	24/315		100%	2.84[1.8,4.46]
Total (95% CI)	**314**	**315**		**100%**	**2.84[1.8,4.46]**
Total events: 63 (Treatment), 24 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=4.52(P<0.0001)					

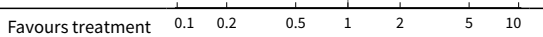
Analysis 10.5. Comparison 10 EE 20 µg and norethindrone acetate 1 mg versus EE 30 µg and levonorgestrel 150 µg, Outcome 5 Irregular bleeding - cycles 1 to 3.

Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
WHO 1982	33/314	7/315		100%	4.01[2.12,7.61]
Total (95% CI)	**314**	**315**		**100%**	**4.01[2.12,7.61]**
Total events: 33 (Treatment), 7 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=4.26(P<0.0001)					



Analysis 10.6. Comparison 10 EE 20 µg and norethindrone acetate 1 mg versus EE 30 µg and levonorgestrel 150 µg, Outcome 6 Prolonged bleeding - cycles 1 to 3.

Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
WHO 1982	46/314	32/315		100%	1.51[0.94,2.43]
Total (95% CI)	**314**	**315**		**100%**	**1.51[0.94,2.43]**
Total events: 46 (Treatment), 32 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.71(P=0.09)					

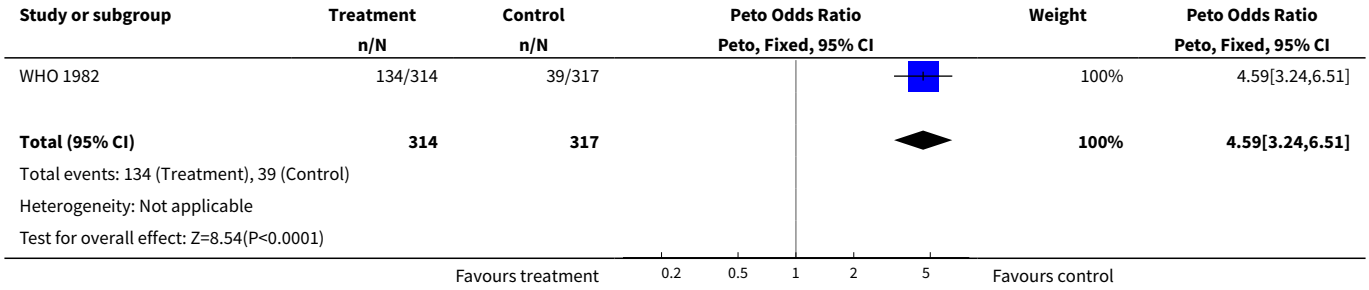


Comparison 11. EE 20 µg and norethindrone acetate 1 mg versus EE 50 µg and levonorgestrel 150 µg

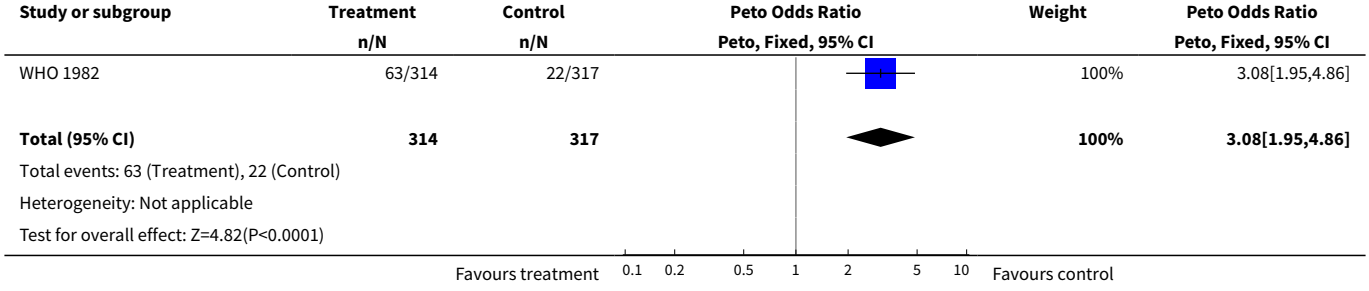
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Frequent bleeding - cycles 1 to 3	1	631	Peto Odds Ratio (Peto, Fixed, 95% CI)	4.59 [3.24, 6.51]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2 Infrequent bleeding - cycles 1 to 3	1	631	Peto Odds Ratio (Peto, Fixed, 95% CI)	3.08 [1.95, 4.86]
3 Irregular bleeding - cycles 1 to 3	1	631	Peto Odds Ratio (Peto, Fixed, 95% CI)	5.33 [2.74, 10.34]
4 Prolonged bleeding - cycles 1 to 3	1	631	Peto Odds Ratio (Peto, Fixed, 95% CI)	3.11 [1.83, 5.27]

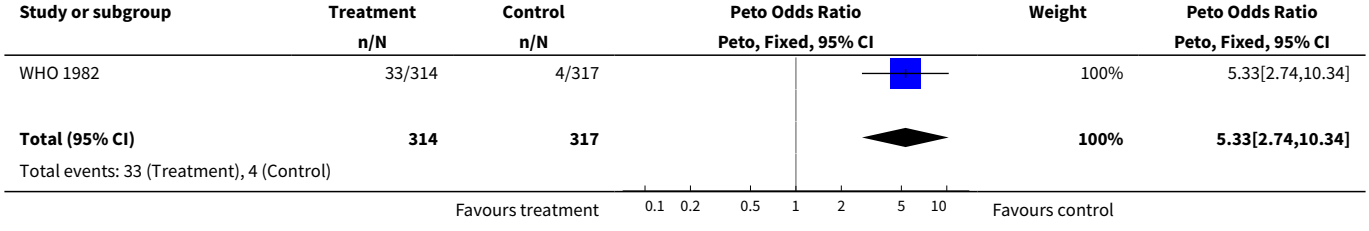
Analysis 11.1. Comparison 11 EE 20 µg and norethindrone acetate 1 mg versus EE 50 µg and levonorgestrel 150 µg, Outcome 1 Frequent bleeding - cycles 1 to 3.

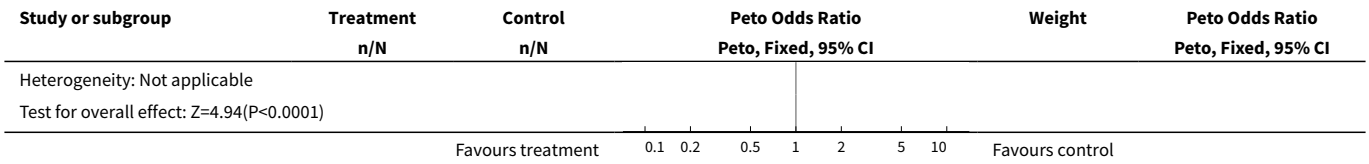


Analysis 11.2. Comparison 11 EE 20 µg and norethindrone acetate 1 mg versus EE 50 µg and levonorgestrel 150 µg, Outcome 2 Infrequent bleeding - cycles 1 to 3.

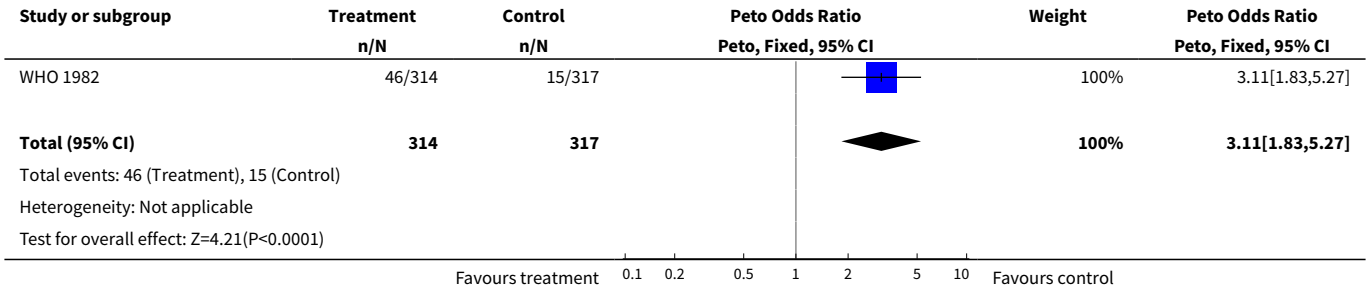


Analysis 11.3. Comparison 11 EE 20 µg and norethindrone acetate 1 mg versus EE 50 µg and levonorgestrel 150 µg, Outcome 3 Irregular bleeding - cycles 1 to 3.





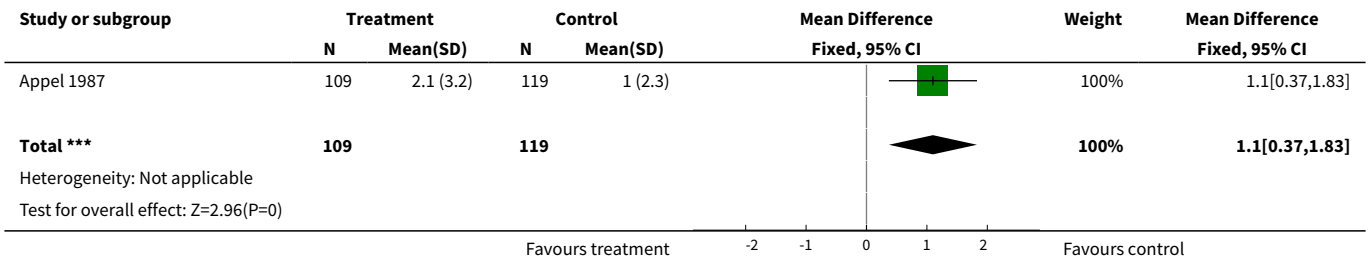
Analysis 11.4. Comparison 11 EE 20 µg and norethindrone acetate 1 mg versus EE 50 µg and levonorgestrel 150 µg, Outcome 4 Prolonged bleeding - cycles 1 to 3.



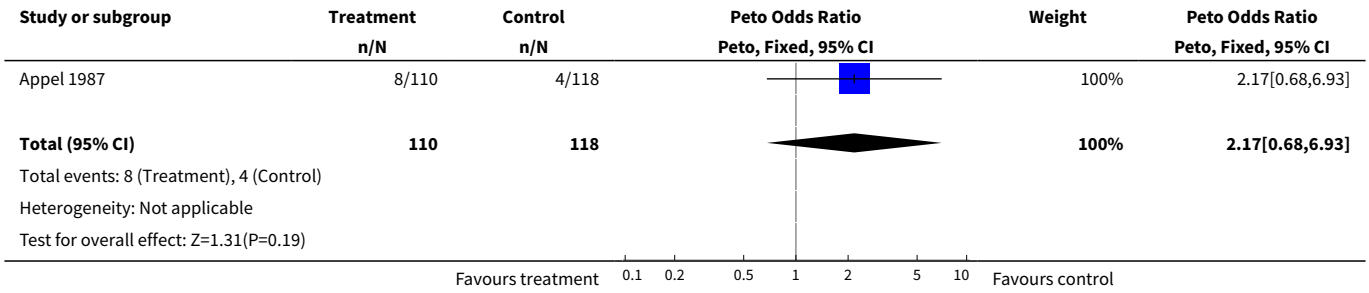
Comparison 12. EE 20 µg and norethindrone acetate 1 mg versus EE 30 µg and norethindrone acetate 1.5 mg

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Duration of breakthrough bleeding or spotting in days - cycle 3	1	228	Mean Difference (IV, Fixed, 95% CI)	1.1 [0.37, 1.83]
2 Amenorrhea - cycle 3	1	228	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.17 [0.68, 6.93]

Analysis 12.1. Comparison 12 EE 20 µg and norethindrone acetate 1 mg versus EE 30 µg and norethindrone acetate 1.5 mg, Outcome 1 Duration of breakthrough bleeding or spotting in days - cycle 3.



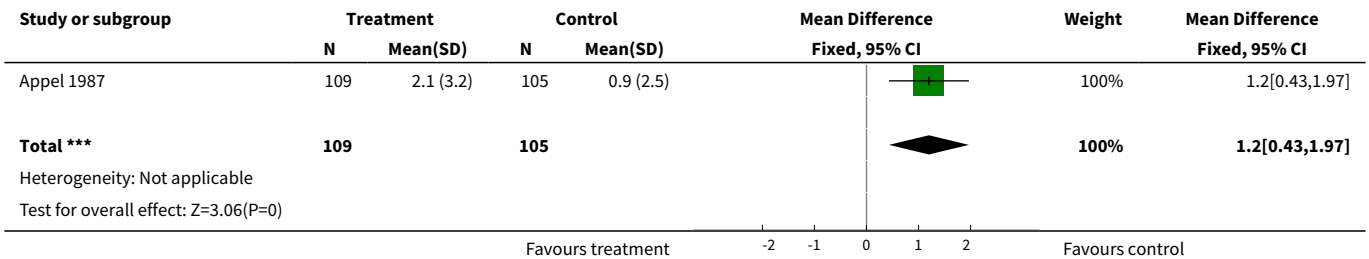
Analysis 12.2. Comparison 12 EE 20 µg and norethindrone acetate 1 mg versus EE 30 µg and norethindrone acetate 1.5 mg, Outcome 2 Amenorrhea - cycle 3.



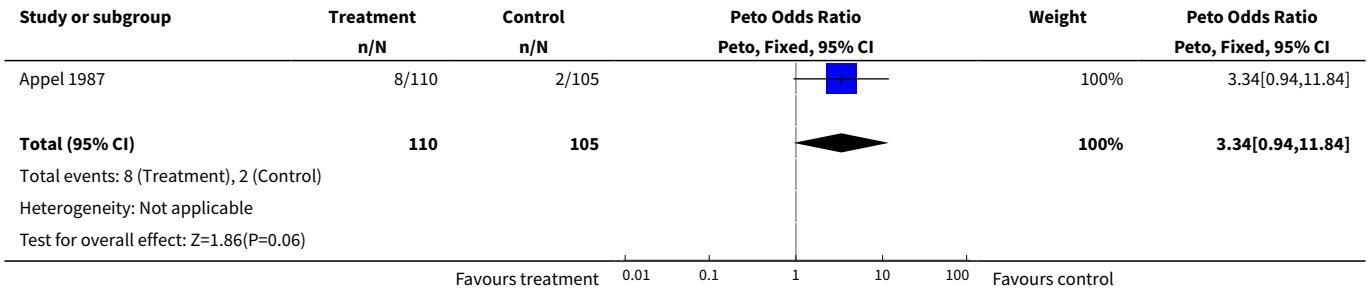
Comparison 13. EE 20 µg and norethindrone acetate 1 mg versus EE 50 µg and norethindrone acetate 1 mg

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Duration of breakthrough bleeding or spotting in days - cycle 3	1	214	Mean Difference (IV, Fixed, 95% CI)	1.20 [0.43, 1.97]
2 Amenorrhea - cycle 3	1	215	Peto Odds Ratio (Peto, Fixed, 95% CI)	3.34 [0.94, 11.84]
3 Frequent bleeding - cycles 1 to 3	1	626	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.97 [1.42, 2.73]
4 Infrequent bleeding - cycles 1 to 3	1	626	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.95 [1.27, 3.00]
5 Irregular bleeding - cycles 1 to 3	1	626	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.38 [1.31, 4.31]
6 Prolonged bleeding - cycles 1 to 3	1	626	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.27 [0.80, 2.02]

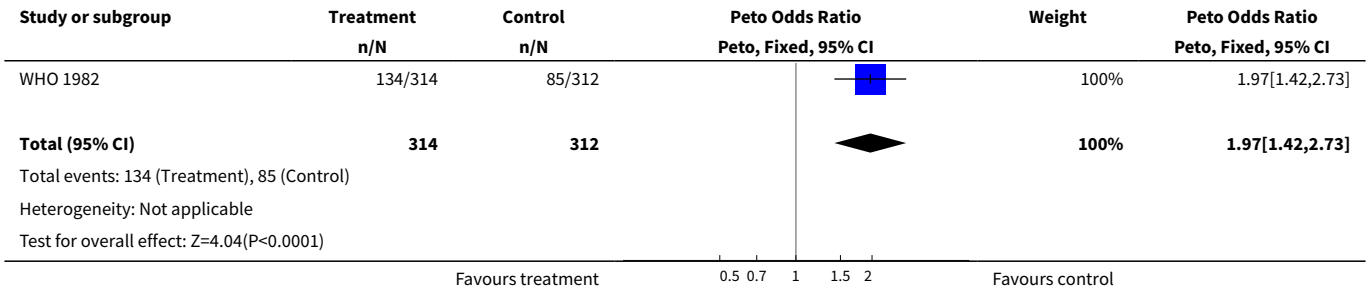
Analysis 13.1. Comparison 13 EE 20 µg and norethindrone acetate 1 mg versus EE 50 µg and norethindrone acetate 1 mg, Outcome 1 Duration of breakthrough bleeding or spotting in days - cycle 3.



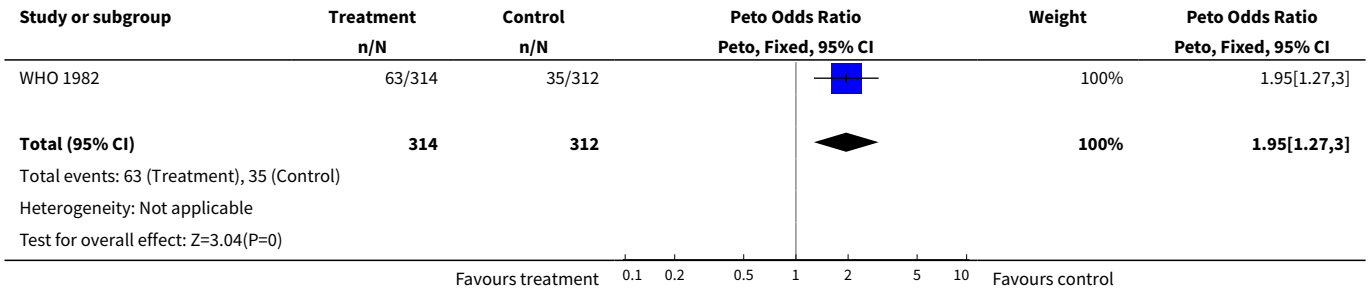
Analysis 13.2. Comparison 13 EE 20 µg and norethindrone acetate 1 mg versus EE 50 µg and norethindrone acetate 1 mg, Outcome 2 Amenorrhea - cycle 3.



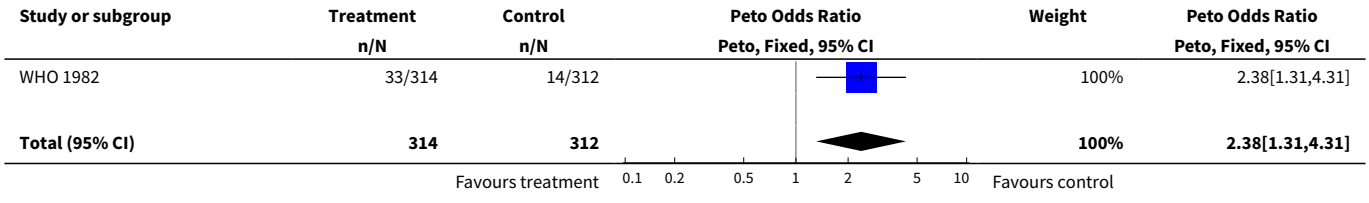
Analysis 13.3. Comparison 13 EE 20 µg and norethindrone acetate 1 mg versus EE 50 µg and norethindrone acetate 1 mg, Outcome 3 Frequent bleeding - cycles 1 to 3.

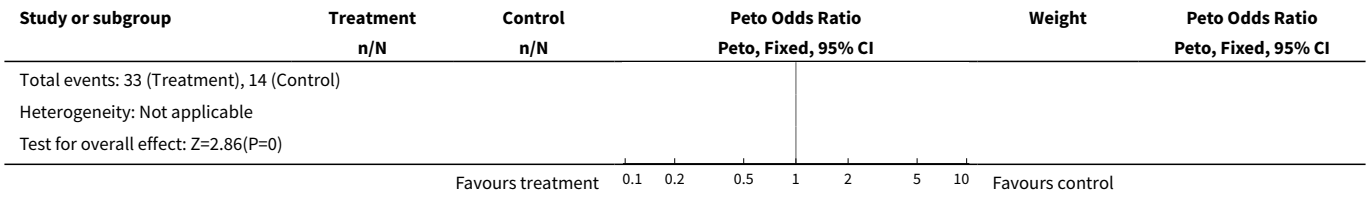


Analysis 13.4. Comparison 13 EE 20 µg and norethindrone acetate 1 mg versus EE 50 µg and norethindrone acetate 1 mg, Outcome 4 Infrequent bleeding - cycles 1 to 3.

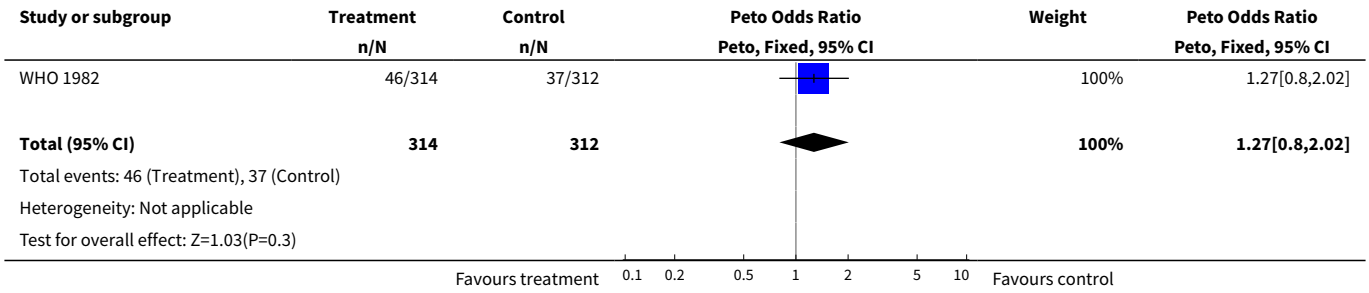


Analysis 13.5. Comparison 13 EE 20 µg and norethindrone acetate 1 mg versus EE 50 µg and norethindrone acetate 1 mg, Outcome 5 Irregular bleeding - cycles 1 to 3.





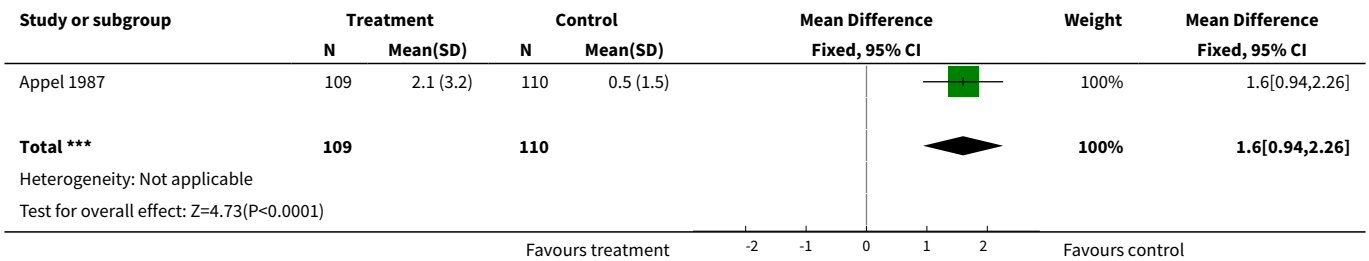
Analysis 13.6. Comparison 13 EE 20 µg and norethindrone acetate 1 mg versus EE 50 µg and norethindrone acetate 1 mg, Outcome 6 Prolonged bleeding - cycles 1 to 3.



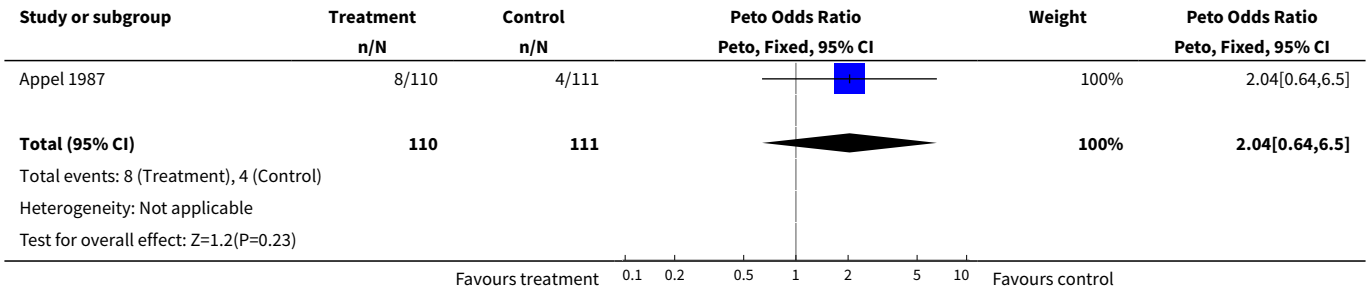
Comparison 14. EE 20 µg and norethindrone acetate 1 mg versus EE 20-30-50 µg and norethindrone acetate 1-1.5-1 mg

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Duration of bleeding or spotting in days - cycle 3	1	219	Mean Difference (IV, Fixed, 95% CI)	1.6 [0.94, 2.26]
2 Amenorrhea - cycle 3	1	221	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.04 [0.64, 6.50]

Analysis 14.1. Comparison 14 EE 20 µg and norethindrone acetate 1 mg versus EE 20-30-50 µg and norethindrone acetate 1-1.5-1 mg, Outcome 1 Duration of bleeding or spotting in days - cycle 3.



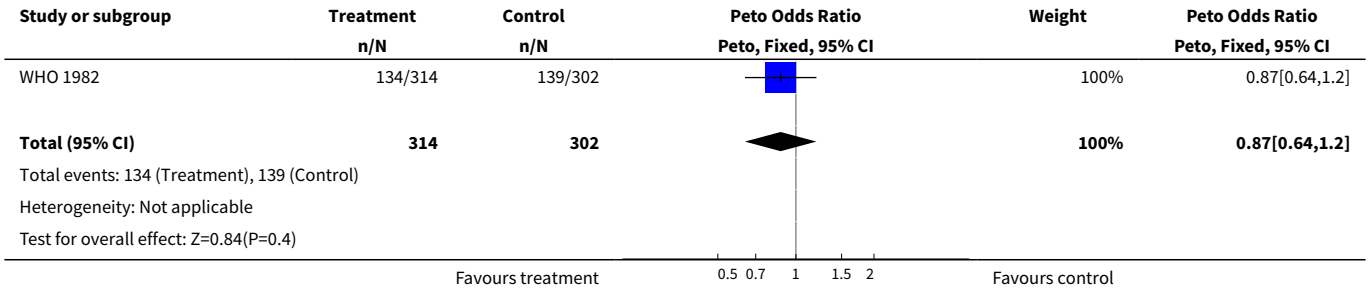
Analysis 14.2. Comparison 14 EE 20 µg and norethindrone acetate 1 mg versus EE 20-30-50 µg and norethindrone acetate 1-1.5-1 mg, Outcome 2 Amenorrhea - cycle 3.



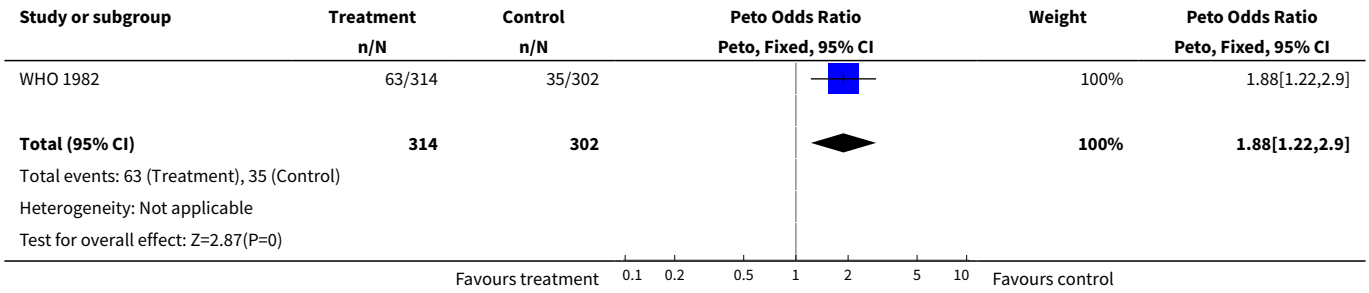
Comparison 15. EE 20 µg and norethindrone acetate 1 mg versus EE 35 µg and norethindrone acetate 400 µg

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Frequent bleeding - cycles 1 to 3	1	616	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.87 [0.64, 1.20]
2 Infrequent bleeding - cycles 1 to 3	1	616	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.88 [1.22, 2.90]
3 Irregular bleeding - cycles 1 to 3	1	616	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.92 [1.08, 3.43]
4 Prolonged bleeding - cycles 1 to 3	1	616	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.91 [0.59, 1.41]

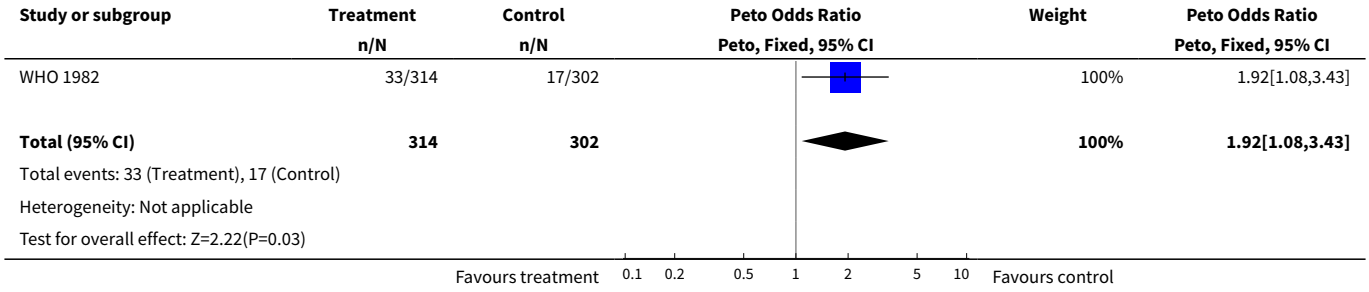
Analysis 15.1. Comparison 15 EE 20 µg and norethindrone acetate 1 mg versus EE 35 µg and norethindrone acetate 400 µg, Outcome 1 Frequent bleeding - cycles 1 to 3.



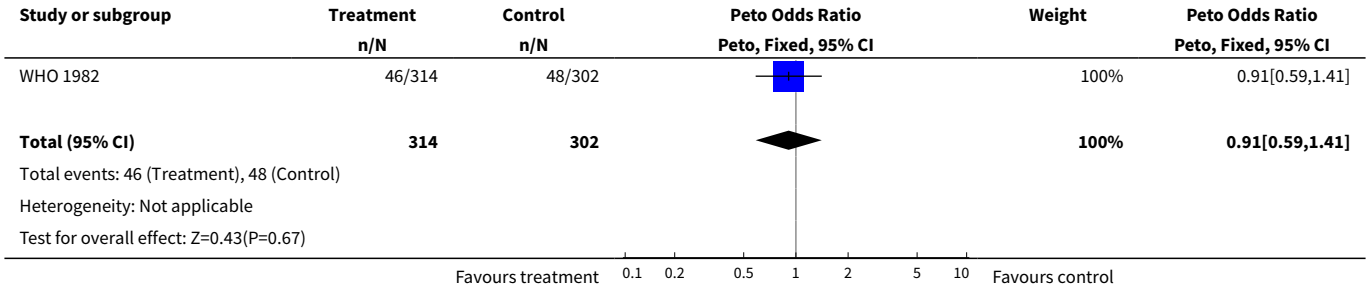
Analysis 15.2. Comparison 15 EE 20 µg and norethindrone acetate 1 mg versus EE 35 µg and norethindrone acetate 400 µg, Outcome 2 Infrequent bleeding - cycles 1 to 3.



Analysis 15.3. Comparison 15 EE 20 µg and norethindrone acetate 1 mg versus EE 35 µg and norethindrone acetate 400 µg, Outcome 3 Irregular bleeding - cycles 1 to 3.



Analysis 15.4. Comparison 15 EE 20 µg and norethindrone acetate 1 mg versus EE 35 µg and norethindrone acetate 400 µg, Outcome 4 Prolonged bleeding - cycles 1 to 3.

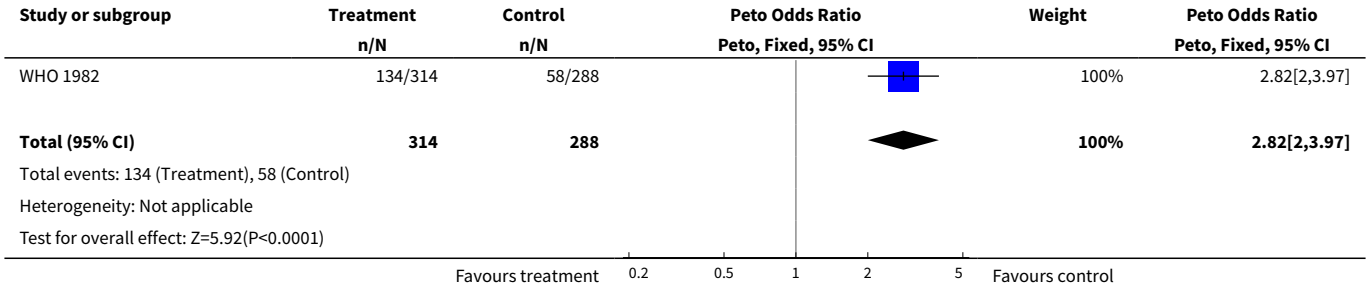


Comparison 16. EE 20 µg and norethindrone acetate 1 mg versus mestranol 50 µg and norethindrone 1 mg

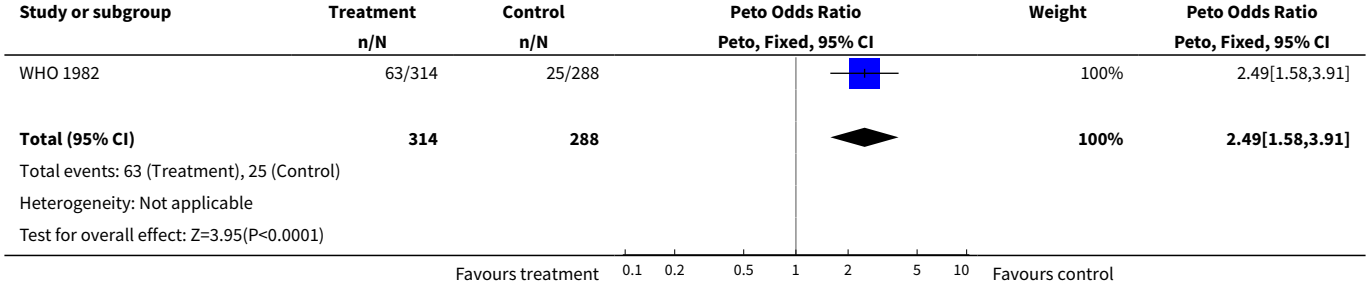
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Frequent bleeding - cycles 1 to 3	1	602	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.82 [2.00, 3.97]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2 Infrequent bleeding - cycles 1 to 3	1	602	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.49 [1.58, 3.91]
3 Irregular bleeding - cycles 1 to 3	1	602	Peto Odds Ratio (Peto, Fixed, 95% CI)	4.85 [2.49, 9.43]
4 Prolonged bleeding - cycles 1 to 3	1	602	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.67 [1.58, 4.52]

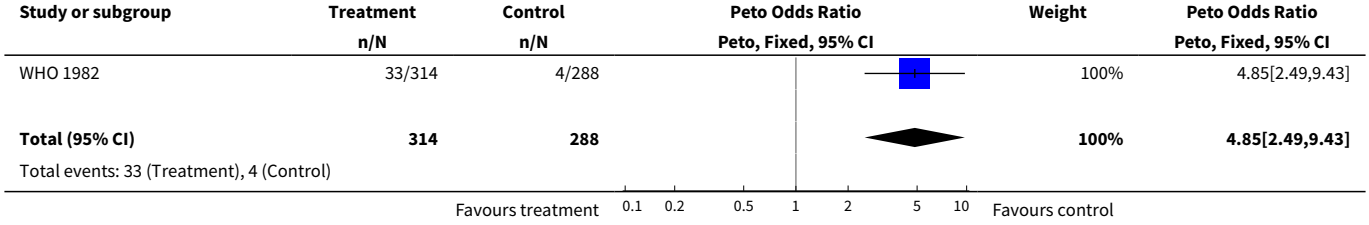
Analysis 16.1. Comparison 16 EE 20 µg and norethindrone acetate 1 mg versus mestranol 50 µg and norethindrone 1 mg, Outcome 1 Frequent bleeding - cycles 1 to 3.

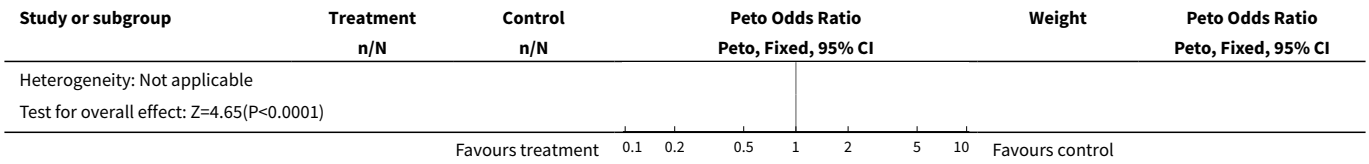


Analysis 16.2. Comparison 16 EE 20 µg and norethindrone acetate 1 mg versus mestranol 50 µg and norethindrone 1 mg, Outcome 2 Infrequent bleeding - cycles 1 to 3.

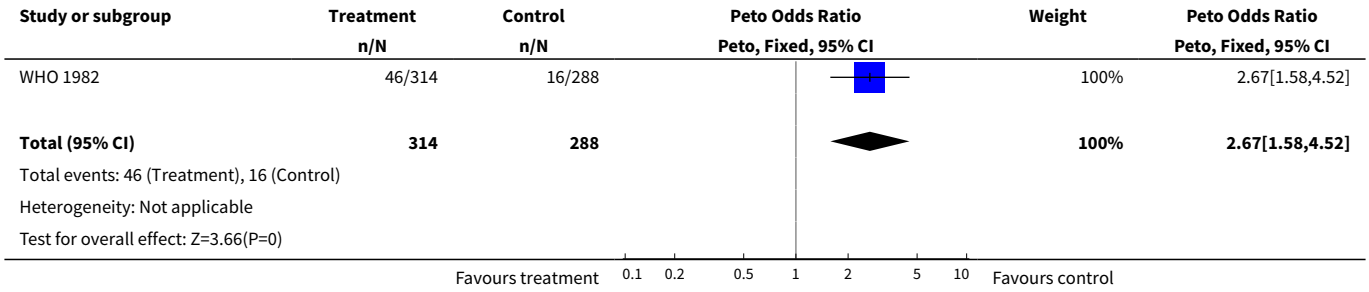


Analysis 16.3. Comparison 16 EE 20 µg and norethindrone acetate 1 mg versus mestranol 50 µg and norethindrone 1 mg, Outcome 3 Irregular bleeding - cycles 1 to 3.





Analysis 16.4. Comparison 16 EE 20 µg and norethindrone acetate 1 mg versus mestranol 50 µg and norethindrone 1 mg, Outcome 4 Prolonged bleeding - cycles 1 to 3.



Comparison 17. EE 20 µg and norethindrone acetate 1 mg versus EE 25 µg and norgestimate 180-215-250 µg

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pregnancy per woman	1	2814	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.41 [0.74, 2.68]
2 Discontinuation - overall	1	2894	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.98 [0.81, 1.18]
3 Discontinuation - adverse events	1	2894	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.79 [0.54, 1.16]
4 Breakthrough bleeding - cycle 3	1	2330	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.79 [2.09, 3.74]
5 Breakthrough bleeding - cycle 6	1	2118	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.40 [1.78, 3.24]
6 Breakthrough bleeding or spotting - cycle 3	1	2330	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.32 [1.85, 2.90]
7 Breakthrough bleeding or spotting - cycle 6	1	2118	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.51 [1.97, 3.20]
8 Unscheduled bleeding - cycle 3	1	2478	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.92 [1.61, 2.29]
9 Unscheduled bleeding - cycle 6	1	2222	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.91 [1.58, 2.32]

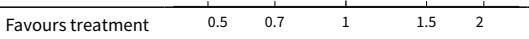
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
10 Weight loss, maintenance, or gain <5% - cycle 6	1	2157	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.16 [0.92, 1.46]

Analysis 17.1. Comparison 17 EE 20 µg and norethindrone acetate 1 mg versus EE 25 µg and norgestimate 180-215-250 µg, Outcome 1 Pregnancy per woman.

Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Hampton 2001	19/1141	20/1673		100%	1.41[0.74,2.68]
Total (95% CI)	**1141**	**1673**		**100%**	**1.41[0.74,2.68]**
Total events: 19 (Treatment), 20 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.05(P=0.3)					

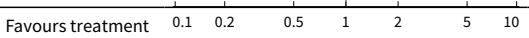
Analysis 17.2. Comparison 17 EE 20 µg and norethindrone acetate 1 mg versus EE 25 µg and norgestimate 180-215-250 µg, Outcome 2 Discontinuation - overall.

Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Hampton 2001	234/1171	350/1723		100%	0.98[0.81,1.18]
Total (95% CI)	**1171**	**1723**		**100%**	**0.98[0.81,1.18]**
Total events: 234 (Treatment), 350 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.22(P=0.83)					



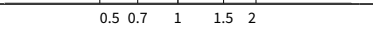
Analysis 17.3. Comparison 17 EE 20 µg and norethindrone acetate 1 mg versus EE 25 µg and norgestimate 180-215-250 µg, Outcome 3 Discontinuation - adverse events.

Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Hampton 2001	40/1171	74/1723		100%	0.79[0.54,1.16]
Total (95% CI)	**1171**	**1723**		**100%**	**0.79[0.54,1.16]**
Total events: 40 (Treatment), 74 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.19(P=0.23)					



Analysis 17.4. Comparison 17 EE 20 µg and norethindrone acetate 1 mg versus EE 25 µg and norgestimate 180-215-250 µg, Outcome 4 Breakthrough bleeding - cycle 3.

Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Hampton 2001	130/956	74/1374		100%	2.79[2.09,3.74]
Total (95% CI)	**956**	**1374**		**100%**	**2.79[2.09,3.74]**
Total events: 130 (Treatment), 74 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=6.9(P<0.0001)					



Favours treatment — Favours control

Analysis 17.5. Comparison 17 EE 20 µg and norethindrone acetate 1 mg versus EE 25 µg and norgestimate 180-215-250 µg, Outcome 5 Breakthrough bleeding - cycle 6.

Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Hampton 2001	117/858	79/1260		100%	2.4[1.78,3.24]
Total (95% CI)	**858**	**1260**		**100%**	**2.4[1.78,3.24]**
Total events: 117 (Treatment), 79 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=5.74(P<0.0001)					

Favours treatment — Favours control

Analysis 17.6. Comparison 17 EE 20 µg and norethindrone acetate 1 mg versus EE 25 µg and norgestimate 180-215-250 µg, Outcome 6 Breakthrough bleeding or spotting - cycle 3.

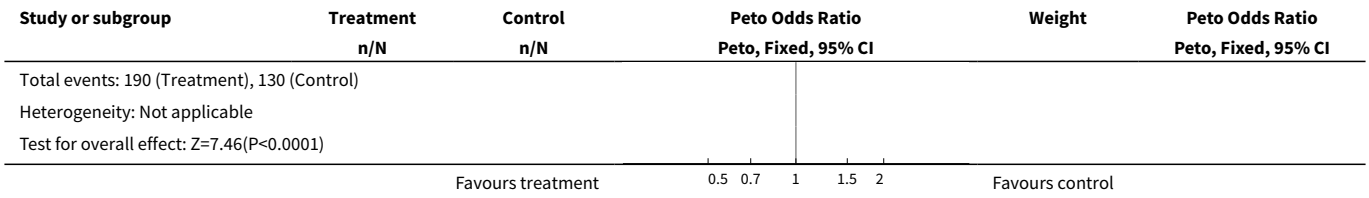
Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Hampton 2001	219/956	158/1374		100%	2.32[1.85,2.9]
Total (95% CI)	**956**	**1374**		**100%**	**2.32[1.85,2.9]**
Total events: 219 (Treatment), 158 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=7.35(P<0.0001)					

Favours treatment — Favours control

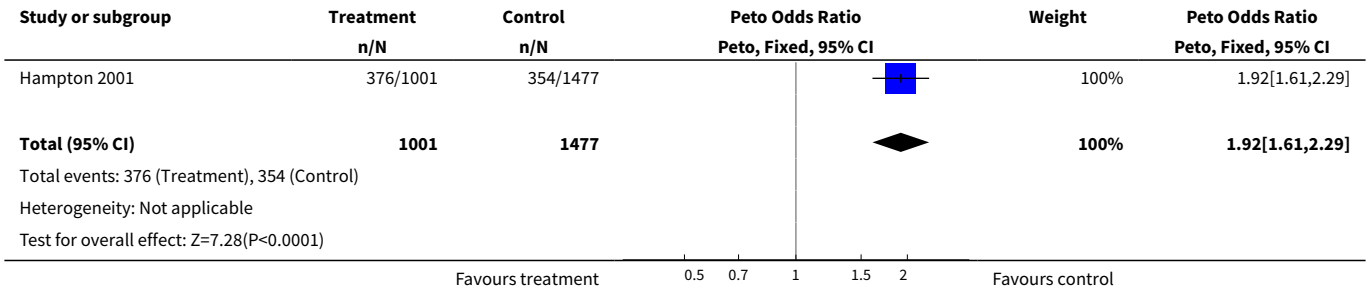
Analysis 17.7. Comparison 17 EE 20 µg and norethindrone acetate 1 mg versus EE 25 µg and norgestimate 180-215-250 µg, Outcome 7 Breakthrough bleeding or spotting - cycle 6.

Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Hampton 2001	190/858	130/1260		100%	2.51[1.97,3.2]
Total (95% CI)	**858**	**1260**		**100%**	**2.51[1.97,3.2]**

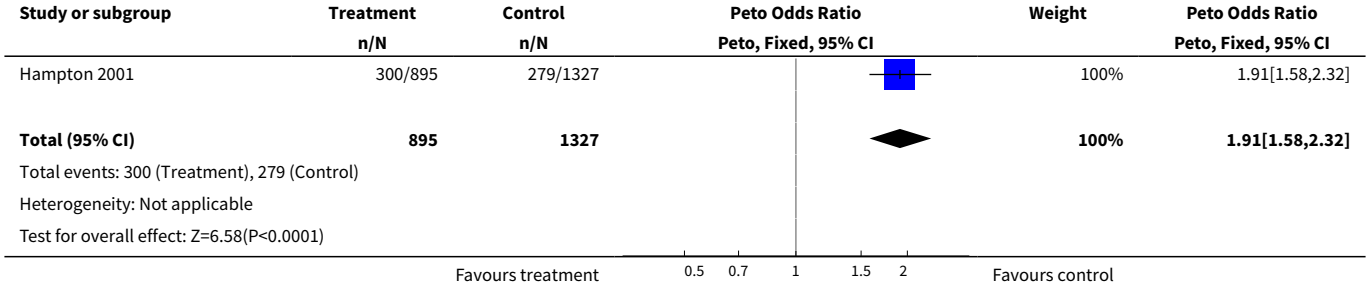
Favours treatment — Favours control



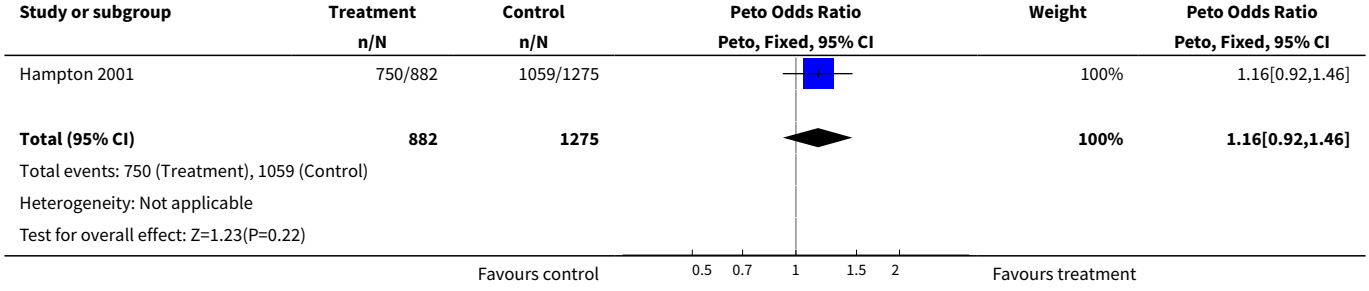
Analysis 17.8. Comparison 17 EE 20 µg and norethindrone acetate 1 mg versus EE 25 µg and norgestimate 180-215-250 µg, Outcome 8 Unscheduled bleeding - cycle 3.



Analysis 17.9. Comparison 17 EE 20 µg and norethindrone acetate 1 mg versus EE 25 µg and norgestimate 180-215-250 µg, Outcome 9 Unscheduled bleeding - cycle 6.



Analysis 17.10. Comparison 17 EE 20 µg and norethindrone acetate 1 mg versus EE 25 µg and norgestimate 180-215-250 µg, Outcome 10 Weight loss, maintenance, or gain <5% - cycle 6.

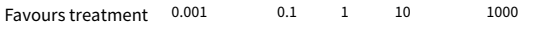


Comparison 18. EE 20 µg and drospirenone 3 mg versus EE 30 µg and drospirenone 3 mg

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pregnancy per woman	1	50	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]

Analysis 18.1. Comparison 18 EE 20 µg and drospirenone 3 mg versus EE 30 µg and drospirenone 3 mg, Outcome 1 Pregnancy per woman.

Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Kluft 2006	0/25	0/25			Not estimable
Total (95% CI)	**25**	**25**			**Not estimable**
Total events: 0 (Treatment), 0 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					

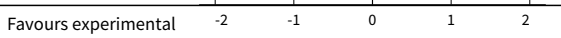


Comparison 19. EE 20 µg and drospirenone 3 mg versus EE 25 µg and norgestimate 180-215-250 µg

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Unscheduled bleeding days - cycle 3	1	332	Mean Difference (IV, Fixed, 95% CI)	1.0 [0.44, 1.56]

Analysis 19.1. Comparison 19 EE 20 µg and drospirenone 3 mg versus EE 25 µg and norgestimate 180-215-250 µg, Outcome 1 Unscheduled bleeding days - cycle 3.

Study or subgroup	Experimental N	Experimental Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Kaunitz 2009	167	2.4 (2.9)	165	1.4 (2.3)		100%	1[0.44,1.56]
Total ***	**167**		**165**			**100%**	**1[0.44,1.56]**
Heterogeneity: Not applicable							
Test for overall effect: Z=3.49(P=0)							



Comparison 20. EE 20 µg and levonorgestrel 100 µg versus EE 30 µg and levonorgestrel 150 µg

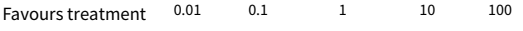
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pregnancy per woman	1	70	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 Adverse events	1	70	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.57 [0.62, 3.98]

Analysis 20.1. Comparison 20 EE 20 µg and levonorgestrel 100 µg versus EE 30 µg and levonorgestrel 150 µg, Outcome 1 Pregnancy per woman.

Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Skouby 2005	0/35	0/35			Not estimable
Total (95% CI)	**35**	**35**			**Not estimable**
Total events: 0 (Treatment), 0 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					

Analysis 20.2. Comparison 20 EE 20 µg and levonorgestrel 100 µg versus EE 30 µg and levonorgestrel 150 µg, Outcome 2 Adverse events.

Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Skouby 2005	19/35	15/35		100%	1.57[0.62,3.98]
Total (95% CI)	**35**	**35**		**100%**	**1.57[0.62,3.98]**
Total events: 19 (Treatment), 15 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.95(P=0.34)					



ADDITIONAL TABLES

Table 1. Twenty µg estrogen combination oral contraceptive

Formulation	Brand name	Manufacturer
150 µg desogestrel and 20 µg EE	Ciclidon 20	Lafi S.A.
	Cycleane-20	G D Searle & Co
	Dal	Osteolab
	Desmin 20	Grunenthal GmbH

Table 1. Twenty µg estrogen combination oral contraceptive *(Continued)*

	Desoren 20	Beta-Grunenthal
	Femilon	Organon International NV
	Lovelle	
	Marvelon 20	
	Mercilon	
	Mircette	
	Myralon	
	Securgin	
	Segurin	
	Suavuret	
	Femina	Ache Laboratorios Farmaceuticos S/A
	Gedarel 20/150	Consilient Health Ltd
	Gynostat-20	Pharmatrade S.A.
	Lovina 20	Hexal
	Midalet 20	Silesia
	Neolette	
	Novynette	Gedeon Richter
75 µg gestodene and 20 µg EE	Ciclomex 20	Pharmafina S.A.
	Diminut	Libbs
	Estinette 20	Effik Group
	Fedra	Schering AG
	Femiane	
	Femodette	
	Gynera 75/20	
	Gynovin 20	
	Logest	
	Meliane	
	Meloden	

Table 1. Twenty µg estrogen combination oral contraceptive *(Continued)*

	Melodene	
	Minigeste	
	Femadiol-Mepha 20	Mepha Pharma AG
	Feminol-20	Pharmatrade S.A.
	Gyselle 20	Spirig Pharma Ltd
	Harmonet	Wyeth-Ayerst International Inc
	Lerogin 20	Recalcine
	Lindynette 20	Gedeon Richter, Ltd
	Microgen	Silesia
	Millinette	Consilient Health Ltd
	Minifem	Urufarma
	Sunya	Stratgen Pharma SA
100 µg levonorgestrel and 20 µg EE	Alesse	Wyeth-Ayerst International Inc
	Leois	
	Loette	
	Loette 21	
	Lovette	
	Anulette 20	Silesia
	Aprll	Gador
	Elyfem 20	Berlis
	Femexin	Urufarma
	Levlite	Berlex Inc - subsidiary of Schering AG
	Microgynon 20	Schering AG
	Microgynon 20 ED	
	Microgynon Suave	
	Microlite	
	Miranova	
	Microlevlen	Bayer HealthCare

Table 1. Twenty µg estrogen combination oral contraceptive *(Continued)*

	Minisiston	
	Norvetal	Recalcine
500 µg norethisterone and 20 µg EE	Eve	Grunenthal
1000 µg norethisterone acetate and 20 µg EE	Loestrin	Pfizer Inc
	Loestrin 1/20	
	Loestrin 20	
	Loestrin 21 1/20	
	Loestrin Fe 1/20+	
	Minestril-20	
	Minestrin 1/20	
3 mg drospirenone and 20 µg EE	Aliane	Bayer HealthCare
	Beyaz	
	Dschess	
	Dzhess	
	Eloine	
	Jasminelle	
	Jasminellecontinu	
	Liofora	
	Yasmin 24/4	
	Yasminelle	
	Yasminique	
	YAZ	
	Diva	Urufarma

Table 2. Fifteen µg estrogen combination oral contraceptive

Formulation	Brand name	Manufacturer
60 µg gestodene and 15 µg EE	Arianna	Bayer HealthCare
	Careza	Silesia

Table 2. Fifteen µg estrogen combination oral contraceptive *(Continued)*

Meliane Light	Schering AG
Melodene 15	
Melodia	
Mirelle	
Minesse	Wyeth-Ayerst International Inc
Secret 28	Urufarma

Table 3. Pregnancy

Study ID	Effect measure	OC	Rate	95% CI	P value log rank test
Akerlund 1993	Pearl index (12 cycle)	EE 20 µg and desogestrel 150 µg	0.4	(0.0 to 1.5)	
		EE 30 µg and desogestrel 150 µg	0.6	(0.1 to 1.6)	
Hampton 2001	Kaplan-Meier (13 cycle)	EE 20 µg and norethindrone acetate 1 mg	2.6	(1.1 to 4.2)	
		EE 25 µg and norgestimate 180-215-250 µg	1.9	(0.8 to 2.9)	
WHO 1982	Life-table (676 days)	EE 20 µg and norethindrone acetate 1 mg	5.0		0.07
		EE 30 µg and levonorgestrel 150 µg	5.1		
		EE 50 µg and levonorgestrel 150 µg	4.2		
		Mestranol 50 µg and norethistrone 1 mg	1.0		
		EE 35 µg and norethindrone acetate 400 µg	6.0		
		EE 50 µg and norethindrone acetate 1 mg	4.2		

Table 4. Lifetable discontinuation at 676 days per 100 women (WHO 1982)

Effect estimate	OC	Rate	P value log rank test
Overall	EE 20 µg and norethisterone acetate 1 mg	68.8	0.04
	EE 30 µg and levonorgestrel 150 µg	62.0	
	EE 50 µg and levonorgestrel 150 µg	60.6	
	Mestranol 50 µg and norethistrone 1 mg	60.4	

Table 4. Lifetable discontinuation at 676 days per 100 women (WHO 1982) *(Continued)*

	EE 35 µg and norethisterone acetate 400 µg	63.5	
	EE 50 µg and norethindrone acetate 1 mg	64.9	
Due to medical reasons	EE 20 µg and norethisterone acetate 1 mg	46.4	0.00
	EE 30 µg and levonorgestrel 150 µg	35.0	
	EE 50 µg and levonorgestrel 150 µg	33.8	
	Mestranol 50 µg and norethistrone 1 mg	30.9	
	EE 35 µg and norethisterone acetate 400 µg	39.4	
	EE 50 µg and norethindrone acetate 1 mg	40.3	
Due to amenorrhea	EE 20 µg and norethisterone acetate 1 mg	13.7	0.00
	EE 30 µg and levonorgestrel 150 µg	1.5	
	EE 50 µg and levonorgestrel 150 µg	0.5	
	Mestranol 50 µg and norethistrone 1 mg	3.3	
	EE 35 µg and norethisterone acetate 400 µg	2.6	
	EE 50 µg and norethindrone acetate 1 mg	3.3	
Due to irregular bleeding	EE 20 µg and norethisterone acetate 1 mg	4.2	0.00
	EE 30 µg and levonorgestrel 150 µg	2.8	
	EE 50 µg and levonorgestrel 150 µg	2.6	
	Mestranol 50 µg and norethistrone 1 mg	2.8	
	EE 35 µg and norethisterone acetate 400 µg	8.5	
	EE 50 µg and norethindrone acetate 1 mg	6.2	
Due to prolonged bleeding	EE 20 µg and norethisterone acetate 1 mg	1.8	0.26
	EE 30 µg and levonorgestrel 150 µg	0.3	
	EE 50 µg and levonorgestrel 150 µg	0.7	
	Mestranol 50 µg and norethistrone 1 mg	0.3	
	EE 35 µg and norethisterone acetate 400 µg	1.5	
	EE 50 µg and norethindrone acetate 1 mg	1.2	

Table 4. Lifetable discontinuation at 676 days per 100 women (WHO 1982) *(Continued)*

Due to light bleeding	EE 20 µg and norethisterone acetate 1 mg	2.4	0.13
	EE 30 µg and levonorgestrel 150 µg	0.0	
	EE 50 µg and levonorgestrel 150 µg	1.2	
	Mestranol 50 µg and norethistrone 1 mg	2.2	
	EE 35 µg and norethisterone acetate 400 µg	1.6	
	EE 50 µg and norethindrone acetate 1 mg	2.0	
Due to spotting	EE 20 µg and norethisterone acetate 1 mg	5.3	0.00
	EE 30 µg and levonorgestrel 150 µg	2.8	
	EE 50 µg and levonorgestrel 150 µg	2.9	
	Mestranol 50 µg and norethistrone 1 mg	2.8	
	EE 35 µg and norethisterone acetate 400 µg	9.0	
	EE 50 mcg and norethindrone acetate 1 mg	6.8	

APPENDICES

Appendix 1. Search strategies 2013

OC BRAND LIST (used within MEDLINE and CENTRAL searches)
Adoless OR Alesse OR Aliane OR Allestra OR Anulette 20 OR April OR Arianna OR Beyaz OR Careza OR Ciclidon OR Ciclomex OR Ciclotab OR Cycleane-20 OR Dal OR Desmin OR Desorelle OR Desoren OR Diminut OR Diva OR Dschess OR Dzhess OR Eloine OR Elyfem OR Estinette OR Eve OR Fedra OR Femadiol-Mepha OR Femexin OR Femiane OR Femilon OR Femina OR Feminet OR Feminol-20 OR Femodette OR Gedarel OR Ginelea OR Ginesse OR Gynera OR Gynostat-20 OR Gynovin OR Gyselle OR Harmonet OR Jasminelle OR Jasminellecontinu OR Leois OR Lerogin OR Levlite OR Lindynette OR Liofora OR Loestrin OR Loette OR Logest OR Lovelle OR Lovette OR Lowette OR Marvelon OR Meliane OR Meloden OR Melodene OR Melodia OR Mercilon OR Microgen OR Microgynon OR Microlevlen OR Microlite OR Midalet OR Millinette OR Minesse OR Minestril-20 OR Minestrin OR Minian OR Minima OR Minifem OR Minigeste OR Minisiston OR Miranova OR Mirelle OR Myralon OR Neolette OR Norvetal OR Novinet OR Novynette OR Ortho Tri-cyclen Lo OR Primera OR Secret OR Securgin OR Siblima OR Suavuret OR Sunya OR Tamisa OR Vivelle OR Yasmin OR Yasminelle OR Yaz

MEDLINE via PubMed (01 Mar 2010 to 10 Jul 2013)

contraceptives, oral[MeSH] AND ("low dose" OR "low-dose"[title/abstract word] OR "ultra low dose" OR "ultra-low-dose"[title/abstract word] OR [**OC BRAND LIST**])
AND (Clinical Trial[ptyp])

CENTRAL (2010 to 10 Jul 2013)

Title, abstract, keywords: oral AND contracept*
AND Title, abstract, keywords: low dose OR low-dose OR ultra low dose OR ultra-low-dose OR [**OC BRAND LIST**]

POPLINE (2010 to 11 Jul 2013)

oral contraceptives, low-dose OR (contraceptive agents, female)
Filter by keywords: clinical trials, oral contraceptives combined

ClinicalTrials.gov (01 Sep 2010 to 08 Jul 2013)

Search terms: 20 µg OR 15 µg
Study type: Interventional studies
Condition: NOT (HIV OR acne OR PMDD OR post-menopausal OR postmenopausal OR polycystic OR PCOS OR dysmenorrhea OR cancer OR anorexia)
Intervention: oral AND (contraceptive OR contraception)
Gender: Studies with female participants

ICTRP (01 Sep 2010 to 08 Jul 2013)

Condition: contraceptive OR contraception
Intervention: 20 µg OR 15 µg

Appendix 2. Previous search strategies

OC BRAND LIST (used within database searches below)
Alesse OR Allestra OR Anulette OR April OR Arianna OR Careza OR Ciclidon OR Ciclomex OR Ciclotab OR Cycleane-20 OR Dal OR Desmin OR Desorelle OR Desoren OR Diminut OR Estrostep Eve OR Fedra OR Femexin OR Femiane OR Femilon OR Femina OR Feminet OR Feminol-20 OR Femodette OR Ginelea OR Ginesse OR Gynera OR Gynostat-20 OR Gynovin OR Harmonet OR Lamuna OR Leois OR Lerogin OR Levlite OR Lindynette OR Loestrin OR Leotte OR Logest OR Lovelle OR Lovette OR Lowette OR Lovina OR Marvelon OR Meliane OR Meloden OR Melodene OR Melodia OR Mercilon OR Microdosis OR Microgen OR Microgynon OR Microlevlen OR Microlite OR Midalet OR Minesse OR Minestril-20 OR Minestrin OR Minian OR Minima OR Minifem OR Minigeste OR Miranova OR Mircette OR Mirelle OR Myralon OR Neolette OR Norvetal OR Novinet OR Novynette OR Primera OR Secret OR Securgin OR Segurin OR Siblima OR Suavuret OR Tamisa OR YAZ

MEDLINE via PubMed (to 21 Sep 2010)

((randomized controlled trials [pt] OR controlled clinical trial [pt] OR randomized controlled trials [mh] OR random allocation [mh] OR double-blind method [mh] OR single-blind method [mh] OR clinical trial [pt] OR clinical trials [mh] OR ("clinical trial" [tw]) OR ((singl* [tw] OR doubl* [tw] OR trebl* [tw] OR tripl* [tw]) AND (mask* [tw] OR blind* [tw])) OR ("latin square" [tw]) OR placebos [mh] OR placebo* [tw] OR random* [tw] OR research design [mh:noexp] OR comparative study [mh] OR evaluation studies [mh] OR follow-up studies [mh] OR prospective studies [mh] OR cross-over studies [mh] OR control* [tw] OR prospectiv* [tw] OR volunteer* [tw]) NOT (animal [mh] NOT human [mh])) AND (eng [la] AND contraceptives, oral[MeSH] AND ("low dose" OR "low-dose"[title/abstract word] OR "ultra low dose" OR "ultra-low-dose"[title/abstract word] OR [**OC BRAND LIST**])

CENTRAL (to 21 Sep 2010)

(oral AND (contracept*) in Title, Abstract or Keywords AND (low dose OR low-dose OR ultra low dose OR ultra-low-dose OR [**OC BRAND LIST**]) in Title, Abstract or Keywords

EMBASE (to 03 Nov 2010)

((low dose oral contraceptive OR (oral contraceptive agent AND low(W)dose)) OR (oral contraceptive agent AND [**OC BRAND LIST**])) AND (clinical trial OR controlled study OR randomized controlled trial OR (controlled(W)clinical(W)trial) OR (random(W)allocation) OR multicenter study OR (comparative(W)study) OR (evidence(W)based(W)medicine) OR (research(W)design) OR (double(W)blind(W)procedure) OR (single(W)blind(W)procedure) OR random) AND human

POPLINE (to 01 Nov 2010)

(oral contraceptives, low-dose) / (contraceptive agents, female & [**OC BRAND LIST**])

ClinicalTrials.gov (to 28 Sep 2010)

Search terms: 20 µg OR 15 µg
Condition: NOT (HIV OR acne OR PMDD OR post-menopausal OR postmenopausal OR polycystic OR PCOS OR dysmenorrhea OR cancer OR anorexia)
Intervention: oral AND (contraceptive OR contraception)
Study type: Interventional studies
Gender: Studies with female participants

ICTRP (to 28 Sep 2010)

Condition: contraceptive OR contraception
Intervention: 20 µg OR 15 µg

WHAT'S NEW

Date	Event	Description
15 July 2013	New citation required but conclusions have not changed	Searches updated. No new trials were eligible for inclusion.

HISTORY

Protocol first published: Issue 1, 2003
Review first published: Issue 2, 2005

Date	Event	Description
3 November 2010	New citation required but conclusions have not changed	One new trial was included (Kaunitz 2009). A secondary report (Hampton 2009) from Hampton 2001 was also added.
3 November 2010	New search has been performed	Searches were updated; searches were added for ClinicalTrials.gov and ICTRP. In the original review, 37 studies did not have eligible outcomes and were listed as 'excluded.' Under our current procedures, we would consider them 'discarded' and not list them. Hence, we removed them for brevity.
14 April 2008	Amended	Converted to new review format.
6 February 2008	New citation required and conclusions have changed	Substantive amendment
6 February 2008	New citation required but conclusions have not changed	Two new trials were found (Skouby 2005; Kluft 2006. A secondary report was identified (Burkman 2007) from an earlier trial (Hampton 2001) and the relevant data were added.
31 January 2008	New search has been performed	Searches were updated in Dec 2007 and Jan 2008.

CONTRIBUTIONS OF AUTHORS

M Gallo extracted data for the initial review and drafted the original review. K Nanda developed the idea and extracted data for the initial review. K Nanda, D Grimes and K Schulz revised and approved the initial review. L Lopez conducted the updates from 2008 to 2013, extracted new data, and revised the review accordingly. D Grimes did the second data extraction for the 2008 and 2010 updates.

DECLARATIONS OF INTEREST

DA Grimes has consulted with the pharmaceutical companies Bayer Healthcare Pharmaceuticals and Merck & Co, Inc.

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Internal sources

- No sources of support supplied

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- US Agency for International Development, USA.

  Support for conducting the review at FHI 360

INDEX TERMS

Medical Subject Headings (MeSH)

Contraceptives, Oral, Combined [*administration & dosage] [adverse effects]; Contraceptives, Oral, Hormonal [*administration & dosage] [adverse effects]; Desogestrel [administration & dosage] [adverse effects]; Estrogens [*administration & dosage] [adverse effects]; Ethinyl Estradiol [*administration & dosage] [adverse effects]; Menstruation Disturbances [chemically induced]; Randomized Controlled Trials as Topic

MeSH check words

Female; Humans