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Combination injectable contraceptives for contraception (Review)

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[Intervention Review]

Combination injectable contraceptives for contraception

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ABSTRACT

Background

Combination injectable contraceptives (CICs) provide a highly effective, reversible method of preventing pregnancy, and they do not require daily administration or use at the time of coitus. Although they are used in many countries, their acceptability could be limited by method characteristics, such as the need to obtain a monthly injection or bleeding pattern changes.

Objectives

To assess the contraceptive efficacy, bleeding patterns, discontinuation, user preferences, and side effects of CICs.

Search methods

In January and February 2013, we searched for randomized controlled trials (RCTs) of combination injectable contraceptives. Databases include MEDLINE, POPLINE, CENTRAL, EMBASE, and LILACS. We searched for current trials in ClinicalTrials.gov and ICTRP. Earlier searches also included AIM and IMEMR. For the initial review, we also assessed the references listed in review articles and in the eligible trial reports.

Selection criteria

RCTs were eligible if they compared a combination injectable contraceptive with any other contraceptive method (e.g., a second CIC, a progestin-only injectable contraceptive, another hormonal contraceptive or a barrier method) or a placebo. We limited the review to marketed CICs.

Data collection and analysis

Two authors independently extracted data on contraceptive efficacy, bleeding patterns, continuation, and side effects. We calculated the Peto odds ratio or mean difference with 95% confidence interval for dichotomous or continuous outcome, respectively. Survival analysis estimates for method discontinuation were presented where available.

Main results

Twelve trials met the inclusion criteria. Combination injectable contraceptives include depot medroxyprogesterone acetate (DMPA) 25 mg plus estradiol cypionate (E₂C) 5 mg, as well as norethisterone enanthate (NET-EN) 50 mg plus estradiol valerate (E₂V) 5 mg. These contraceptives resulted in lower rates of early study discontinuation due to amenorrhea or other bleeding problems than progestin-only contraceptives. However, rates were higher for overall discontinuation and discontinuation due to other medical reasons. Acceptability results favored the CIC in one study and the progestin-only in another.

Studies comparing two CICs found that NET-EN 50 mg plus E₂V 5 mg resulted in less overall discontinuation and less discontinuation due to amenorrhea or prolonged bleeding than DMPA 25 mg plus E₂C 5 mg. However, these differences were not detected in all trials. The NET-EN plus E₂V group also had more regular bleeding and fewer prolonged bleeding reference periods than the DMPA plus E₂C group. The groups did not differ in their amenorrhea rates.

Authors' conclusions

While discontinuation rates can be viewed as a measure of method acceptability, the findings should be interpreted with caution since discontinuation depends on many factors. Future research should be directed toward improving the acceptability of combination injectable contraceptives, such as providing injections in settings more convenient than clinics, methods for women to administer their own injections, and counseling about possible bleeding pattern changes.

PLAIN LANGUAGE SUMMARY

Injectable birth control with both progestin and estrogen

Birth control methods that can be injected may contain two hormones, a progestin and an estrogen. These combined injectable contraceptives (CICs) are effective in preventing pregnancy and can be stopped when a woman wants to get pregnant. This review looked at CICs for how well they prevented pregnancy and for the bleeding patterns and other side effects that may occur. We also studied whether women stopped using them early and whether women liked them.

In January and February 2013, we did computer searches to find randomized trials of combination injectable contraceptives. We included studies that compared a CIC with another birth control method. The other method could be another injectable contraceptive, either combined or having only a progestin. The CIC could also be compared to another hormonal method (like the pill) or to condoms, the diaphragm, or a placebo (or 'dummy').

We found 12 trials that studied four types of CICs. The combined methods required monthly injections. Four trials compared a CIC to 'depo', which has only a progestin. 'Depo' injections should be taken every three months. Five trials compared a CIC with a different combined injectable. Three trials compared a combined injectable with a different dose of the same hormones, with a progestin-only injectable, or with an intrauterine device (IUD).

More women using combined injectables had normal bleeding than women using progestin-only injectables like 'depo.' Also, fewer women using CICs stopped using them because of bleeding reasons than progestin-only users. However, users of combined injectables were more likely to stop using them overall and to stop for other medical reasons. Many factors can affect whether women keep using the method, including whether the women liked it.

BACKGROUND

Combined injectable contraceptives, which contain a progestin plus an estrogen, were developed to address troublesome side effects of progestin-only formulations. Negative effects of progestin-only injectables include disruption in bleeding patterns (Goldberg 2007), as well as the long duration of contraception. The median delay to conception after use of depot medroxyprogesterone acetate (DMPA) is 9 to 10 months after the last injection, which is longer than with other hormonal methods (Schwallie 1974; Pardthaisong 1980; Kaunitz 2000). Also, the drug takes months to be metabolized after the method is discontinued. This is a disadvantage for women who experience unpleasant side effects.

With an estrogen (such as estradiol cypionate) added to the long-acting progestin (such as depot medroxyprogesterone acetate), bleeding cycles are more regular than they are with injectable progestin-only methods (Goldberg 2007). In women not using hormonal contraceptives, bleeding occurs when serum estrogen and progesterone levels fall and the endometrium (lining of the uterus) is shed. Progestin-only contraceptives may produce a thin endometrium that can bleed irregularly and unpredictably. The estrogen component of a combined hormonal contraceptive may build up the endometrium and therefore regulate bleeding patterns. When women use combined oral contraceptives in a cyclical manner, bleeding occurs when the estrogen is withdrawn, and this mimics a typical menstrual period. Given monthly, combined injectable contraceptives allow the serum estrogen levels to fall in a similar manner, and this produces withdrawal bleeding (Kaunitz 2000).

The World Health Organization (WHO) supported the development of two combination injectables. For this review, nine formulations were considered that were marketed in Latin America, Asia, and Africa under various brand names (Newton 1994; IPPF 2010). Combination injectable contraceptives are given on a monthly basis, which is more convenient for some women than the daily oral contraception regimen. However, the monthly administration is more frequent than that for progestin-only injectables (every two or three months, depending on the progestin). The injections are usually provided in a clinical site or medical office. As with the progestin-only formulations, combination injectable contraceptives are discreet, and therefore they provide confidentiality. Combination injectables feature a more rapid return to fertility than progestin-only injectables (Bassol 1994; Bahamondes 1997a; Kaunitz 2000).

This review summarizes the randomized controlled trials that compared a combined injectable contraceptive with another contraceptive. Previously, little was known about the comparative efficacy and acceptability of combined injectable contraceptives. The focus of the review is on efficacy, continuation rates, and side effects.

OBJECTIVES

To assess the contraceptive efficacy, bleeding patterns, discontinuation, user preferences, and side effects of combination injectable contraceptives.

METHODS

Criteria for considering studies for this review

Types of studies

Randomized controlled trials reported in any language that compared a combination injectable to any other contraceptive method (e.g., a second combination injectable contraceptive, progestin-only injectable contraceptive, other hormonal contraceptive or barrier method) or placebo. Eligible combination injectable contraceptives were limited to formulations that were marketed at the time of this review.

Types of participants

Reproductive-age women without contraindications to combination injectable contraceptive use.

Types of interventions

Eligible interventions consisted of the combination injectable formulations that were marketed at the time of the review.

- Dihydroxyprogesterone acetophenide (also known as algeston acetophenide or alfasona) 75 mg and estradiol enanthate 5 mg
- Dihydroxyprogesterone acetophenide 120 mg and estradiol enanthate 10 mg
- Dihydroxyprogesterone acetophenide 150 mg and estradiol enanthate 10 mg
- Dihydroxyprogesterone acetophenide 150 mg and estradiol benzoate 10 mg
- Medroxyprogesterone acetate 25 mg and estradiol cypionate 5 mg
- Norethisterone enanthate 50 mg and estradiol valerate 5 mg
- Progesterone 50 mg and estradiol benzoate 5 mg

Nine formulations were available during the initial 2005 review. For the 2010 update, three were no longer available: dihydroxyprogesterone caproate 250 mg and estradiol valerate 5 mg; medroxyprogesterone acetate 25 mg and estradiol 3.5 mg; and megestrol acetate 25 mg and estradiol 3.5 mg. An additional formulation was marketed, i.e., progestin 50 mg and estradiol benzoate 5 mg for a new total of seven formulations.

Types of outcome measures

Measures of contraceptive efficacy, bleeding patterns, continuation, user preferences, and side effects were eligible. Side effects include reported medical or social events that possibly were related to the study treatment. However, rare events (e.g., thrombosis or cancer) could not be adequately studied in this review since randomized controlled trials generally do not have enough power for studying the risk of these events. Biochemical measures were not eligible.

Search methods for identification of studies

Electronic searches

In January and February 2013, we searched the computerized databases MEDLINE, Cochrane Central Register of Controlled Trials (CENTRAL), POPLINE, EMBASE, and LILACS for studies of combination injectable contraceptives. We also searched for trials via ClinicalTrials.gov and the search portal of the International

Clinical Trials Registry Platform (ICTRP). The most recent search strategies are shown in [Appendix 1](#). The 2010 searches are shown in [Appendix 2](#). The initial 2005 review and the 2008 update also included AIM and IMEMR ([Appendix 3](#)).

Searching other resources

For the initial review, we also assessed the references listed in review articles ([Koetsawang 1994](#); [Newton 1994](#); [Kaunitz 2001](#)) and in the eligible trial reports.

Data collection and analysis

One author evaluated all titles and abstracts located in the literature searches to identify the trial reports that met the inclusion criteria. Two authors independently extracted data from the eligible reports. We wrote to the researchers for clarifications or additional data when needed. Data were entered and analyzed with RevMan. We calculated the Peto odds ratios (OR) or mean difference (MD) with 95% confidence interval (CI) for each dichotomous or continuous outcome, respectively. Where available, survival analysis estimates for method discontinuation were also presented ([Table 1](#); [Table 2](#)). Some studies used 90-day reference periods for recording bleeding patterns ([Description of studies](#)). If outcomes were reported for multiple reference periods, we reported the outcomes for the first and last reference periods only. [Characteristics of included studies](#) has information on the length of each study.

The review was limited to the analytic method used in the trial report (e.g., intent to treat, per protocol, or a modification of either type). Studies were combined for meta-analysis only when identical drugs, dosages, and regimens were compared. We assessed the homogeneity of trials combined in meta-analysis using both fixed-effect and random-effects models. The alpha level was set at 0.10 since the χ^2 test for heterogeneity is a low power test. Sensitivity analysis was used to test the robustness of any results that appeared to be based on heterogeneous combinations by examining the effect of deleting each study. Trials were critically appraised by evaluating 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 yielded 185 unduplicated citations. These included 159 references from MEDLINE, CENTRAL, POPLINE, EMBASE, and LILACS, as well as 26 clinical trials from ClinicalTrials.gov and ICTRP. All were discarded based on review of the title or abstract or the trial summary. A trial previously listed as ongoing was excluded ([Kashanian 2013](#)), based on information from the investigator.

Included studies

The 12 trials that met the inclusion criteria evaluated four monthly combination injectable contraceptives:

- Medroxyprogesterone acetate (DMPA) 25 mg plus estradiol cypionate (E_2C) 5 mg was compared to a progestin-only injectable contraceptive containing DMPA 150 mg administered every three months in four trials ([Cuong 1996](#); [Piya-Anant 1998](#);

[Ruminjo 2005](#); [Simbar 2007](#)). Two trials had durations of 12 months: [Cuong 1996](#) randomized 600 women and [Ruminjo 2005](#) randomized 360 women. The other two studies lasted six months: [Piya-Anant 1998](#) randomized 100 women while [Simbar 2007](#) randomized 68 women. [Piya-Anant 1998](#) limited participation to women who were using DMPA for contraception for at least six months preceding study initiation and who had experienced amenorrhea (regardless of whether they reported dissatisfaction with the amenorrhea).

- One small trial ([Recio 1986](#)) of 16 women compared dihydroxyprogesterone acetophenide (DHPA) 150 mg plus estradiol enanthate (E_2EN) 10 mg to a combination injectable contraceptive with half-doses of the same progestin and estrogen. The women were followed for three treatment months.
- Norethisterone enanthate (NET-EN) 50 mg plus estradiol valerate (E_2V) 5 mg was compared to DMPA 25 plus E_2C 5 mg in five trials ([WHO 1988](#); [Mostafa 1994a](#); [Sang 1995](#); [WHO 1997](#); [Hassan 1999](#)). Three of the trials were large (2252 to 2707 randomized women) and 12 treatment months in duration ([WHO 1988](#); [Sang 1995](#); [Hassan 1999](#)). The remaining two trials randomized fewer women (300 to 370) and followed them for 9 ([WHO 1997](#)) or 12 treatment months ([Mostafa 1994a](#)).
- The combination injectable NET-EN 50 mg plus E_2V 5 mg also was compared to a progestin-only injectable contraceptive containing NET-EN 200 mg administered every two months in a 12-month trial of 1112 women ([Indian Council 1990](#)) and to a copper intrauterine device (IUD) in a 24-month trial of 148 women ([Von Kesseru 2000](#)).

Outcome measure limitations

Five trials ([WHO 1988](#); [Indian Council 1990](#); [Mostafa 1994a](#); [Sang 1995](#); [Cuong 1996](#)) used modified World Health Organization (WHO) guidelines for reporting bleeding patterns ([Belsey 1986](#)). The WHO recommended that trials divide menstrual diaries into 90-day reference periods and then calculate summary outcomes for the reference periods. Recommended summary outcomes included amenorrhea, infrequent bleeding, frequent bleeding, irregular bleeding, and prolonged bleeding. Three trials used identical definitions for these summary measures ([Mostafa 1994a](#); [Sang 1995](#); [Cuong 1996](#)), and two trials used similar definitions ([WHO 1988](#); [Simbar 2007](#)) (see [Characteristics of included studies](#)). [Indian Council 1990](#) and [Simbar 2007](#) did not specify the definitions used, although the latter used three-month reference periods. [Ruminjo 2005](#) also used three-month reference periods but had different criteria for assessing bleeding. The remaining five trials did not use reference periods, reported few bleeding-related outcomes, and did not define the bleeding-related outcomes.

Risk of bias in included studies

Allocation

Several trials described minimal details of the randomization method ([Sang 1995](#); [Cuong 1996](#); [WHO 1997](#); [Hassan 1999](#); [Von Kesseru 2000](#); [Ruminjo 2005](#)); [Simbar 2007](#) used a bag of marbles for randomizing women. None of the trials reported a method of allocation concealment.

Blinding

The trials were either open or did not describe any method of blinding.

Incomplete outcome data

Six trials excluded randomized women from the analysis for protocol violations (WHO 1988; Indian Council 1990; Sang 1995; Cuong 1996; WHO 1997; Hassan 1999), a practice that can lead to biased estimates. Most trials had less than 30% reduction in their samples due to exclusions, loss to follow up, or missing data. However, Indian Council 1990 excluded women from two centers (N=222) from the analysis since the centers had poor follow-up rates.

Effects of interventions

DMPA 25 mg plus E₂C 5 mg versus DMPA 150 mg

Four trials compared a combination to a progestin-only injectable contraceptive containing DMPA (Cuong 1996; Piya-Anant 1998; Ruminjo 2005; Simbar 2007). The larger trial of Cuong 1996 found no difference in overall early trial discontinuation between the two study groups (Table 1). The mid-sized study of Ruminjo 2005 had more discontinuation among the women assigned to the combination injectable compared to the progestin-only group (OR 2.24; 95% CI 1.43 to 3.50). The smaller trial of Piya-Anant 1998 also had higher odds of early discontinuation with the combination than the progestin-only group, but the effect estimate was imprecise (OR 8.41; 95% CI 1.82 to 38.77). In Cuong 1996, women in the progestin-only group were more likely to discontinue for amenorrhea or all bleeding problems (i.e., prolonged bleeding, heavy and prolonged bleeding, irregular bleeding, or spotting) than the combination group (Table 1). In contrast, the combination injectable users were more likely than the progestin-only group to discontinue early for other medical reasons (e.g., headache, not feeling well, or weight change) or personal reasons. However, in Ruminjo 2005, the study groups were similar for discontinuation due to menstrual changes as well as non-menstrual medical reasons.

The combination-injectable group was generally less likely to report bleeding irregularities. Piya-Anant 1998 measured amenorrhea as any occurrence during the study period (OR 0.06; 95% CI 0.03 to 0.13). Cuong 1996 and Ruminjo 2005 were combined in a meta-analysis for this outcome. Both trials measured amenorrhea during the first and fourth reference periods. The combination-injectable group was less likely than the progestin-only group to report amenorrhea; the ORs were 0.23 (95% CI 0.15 to 0.34) for the first reference period and 0.10 (95% CI 0.07 to 0.14) for the fourth. In Cuong 1996, the combination-injectable group was less likely to report infrequent bleeding measured during the first (OR 0.20; 95% CI 0.13 to 0.31) or fourth (OR 0.49; 95% CI 0.28 to 0.87) reference periods. In addition, the combination-injectable group had higher odds of regular (cyclical) bleeding patterns in the first (OR 4.93; 95% CI 3.48 to 7.00) and fourth (OR 6.14; 95% CI 4.19 to 9.00) reference periods than the progestin-only injectable group (Cuong 1996).

Differences in prolonged bleeding and irregular bleeding between the groups were less clear. The combination group was less likely to have prolonged bleeding during the first reference period (OR 0.34; 95% CI 0.23 to 0.50) but more likely during the fourth reference period than the progestin-only group (OR 3.60; 95% CI 1.09 to 11.89)

(Cuong 1996). In Ruminjo 2005, the combination-injectable group was more likely than the progestin-only group to have more than five days of bleeding during the first (OR 1.85; 95% CI 1.07 to 3.20) and fourth (OR 5.29; 95% CI 2.59 to 10.78) reference periods. Mean days of bleeding were similar for the groups in Simbar 2007 during the first reference period. For Cuong 1996, the combination group was more likely to have irregular bleeding in the fourth reference period than the progestin-only group (OR 2.75; 95% CI 1.41 to 5.36) but not in the first period. However, in Ruminjo 2005, the combination-injectable group was more likely to have moderate or severe intermenstrual bleeding during the first reference period (OR 0.14; 95% CI 0.03 to 0.65) but not during the fourth.

Women in the combination-injectable group in the Piya-Anant 1998 trial were more likely to report intention to continue their assigned method at the study end than those in the progestin-only group (OR 10.52; 95% CI 4.71 to 23.49). However, the wide confidence interval indicates imprecision in this finding. In contrast, somewhat fewer of the combination-injectable group in Ruminjo 2005 reported their experience with the method to have been 'very favorable' or 'somewhat favorable' (OR 0.48; 95% CI 0.23 to 1.02) than did those in the progestin-only group.

DHPA 150 mg plus E₂EN 10 mg versus DHPA 75 mg plus E₂EN 5 mg

The one trial (Recio 1986) that compared injectables containing DHPA was a small (N=16) trial with only one relevant outcome (i.e., number of bleeding or spotting days after injection), which did not significantly differ between groups.

NET-EN 50 mg plus E₂V 5 mg versus DMPA 25 mg plus E₂C 5 mg

Five trials compared the combination injectable contraceptive containing NET-EN plus E₂V to one with DMPA plus E₂C (WHO 1988; Mostafa 1994a; Sang 1995; Hassan 1999; WHO 1997). The NET-EN group was less likely to discontinue early than the DMPA group (OR 0.82; 95% CI 0.74 to 0.92). However, the results from three trials making this comparison were heterogeneous, and the statistical significance was dependent on the inclusion of Sang 1995. The three trials (WHO 1988; Mostafa 1994a; Hassan 1999) that reported life-table estimates found no difference in overall discontinuation between the groups (Table 2). The NET-EN group also was less likely to discontinue early due to amenorrhea (OR 0.32; 95% CI 0.22 to 0.44) or prolonged bleeding (OR 0.66; 95% CI 0.48 to 0.90) than the DMPA group. These differences, though, were not apparent with the life-table estimates. The only statistically significant life-table difference was the higher rate of discontinuation due to all bleeding problems for the NET-EN group versus the DMPA group in Mostafa 1994a and Hassan 1999 (Table 2).

Three trials reported bleeding patterns using the 90-day reference periods (WHO 1988; Mostafa 1994a; Sang 1995). Women using the combination injectable containing NET-EN were more likely to report regular (cyclical) bleeding patterns in the first (OR 1.68; 95% CI 1.48 to 1.90) or the fourth reference period (OR 1.39; 95% CI 1.19 to 1.62) than those assigned to the combination DMPA injectable contraceptive. The NET-EN group also reported less prolonged bleeding in the first (OR 0.41; 95% CI 0.32 to 0.53) and the fourth reference period (OR 0.49; 95% CI 0.35 to 0.69) than the DMPA group. The amenorrhea rates were not significantly different between the groups and other bleeding outcomes were mixed. The NET-EN group had less irregular bleeding, less infrequent bleeding and

more frequent bleeding patterns in the first reference period, but these differences were not apparent during the fourth reference period.

NET-EN 50 mg plus E₂V 5 mg versus NET-EN 200 mg

[Indian Council 1990](#) compared a combination to a progestin-only injectable contraceptive containing NET-EN. The combination injectable group had higher rates of overall discontinuation (OR 1.41; 95% CI 1.07 to 1.86) and discontinuation due to non-bleeding medical reasons (OR 2.24; 95% CI 1.23 to 4.07), due to other personal reasons (OR 1.93; 95% CI 1.26 to 2.97), or discontinuation due to being late for or lost to follow up (OR 1.76; 95% CI 1.05 to 2.95).

The combination group had higher rates of cyclical (regular) bleeding during both the first and fourth reference periods. The ORs were 3.17 (95% CI 2.14 to 4.71) and 1.59 (95% CI 1.08 to 2.34), respectively. They had lower rates of infrequent bleeding patterns than the progestin-only group in the first (OR 0.33; 95% CI 0.20 to 0.55) and fourth (OR 0.60; 95% CI 0.40 to 0.89) reference periods. The women using the combination injectable contraceptive had significantly less amenorrhea (OR 0.36; 95% CI 0.16 to 0.82) but more irregular bleeding (OR 2.80; 95% CI 1.56 to 5.01) in the fourth reference period than those assigned to the progestin-only injectable contraceptive.

NET-EN 50 mg plus E₂V 5 mg versus copper IUD

[Von Kesseru 2000](#) compared NET-EN plus E₂V injectable contraceptive to a copper IUD. The combination injectable group was 6.67 times (95% CI 2.08 to 21.41) more likely to discontinue early due to bleeding than the IUD group. The only other relevant outcome reported was pregnancy, which did not differ between the groups.

DISCUSSION

No differences were found in contraceptive effectiveness rates between the comparisons. Since injectable contraceptives are a highly effective method, though, the studies had insufficient power to study this outcome.

We did not include outcomes related to side effects that were reported during clinic visits with open-ended questioning. The combination injectable contraceptive users had more frequent clinic visits and, therefore, more opportunities to report these effects. Side effect data would have to be collected under comparable conditions in the study groups to avoid biased estimates.

The combination injectable contraceptive containing DMPA 25 mg plus E₂C 5 mg resulted in less amenorrhea and discontinuation due to amenorrhea or all bleeding problems than the contraceptive containing the same type of progestin (DMPA 150 mg) but without estrogen. However, the combination-injectable group was more likely to discontinue overall than the progestin-only group as well as due to other medical reasons (e.g., headache or not feeling well) or personal reasons. Similarly, the only other comparison between a combination and a progestin-only contraceptive with the same progestin type (NET-EN 50 mg plus E₂V 5 mg versus NET-EN 200 mg) found that the combination group had more cyclical (regular) bleeding and fewer infrequent bleeding reference periods than

the progestin-only contraceptive group. Again, the combination injectable group was more likely to discontinue for other reasons (i.e., overall, other medical reasons, personal reasons, late for or lost to follow up) than the progestin-only group. The higher rates of early discontinuation for reasons other than disruptions to bleeding patterns with the combination injectable contraceptives could be an indicator of poor acceptability of the requirement for more frequent clinic visits. In a demonstration project in California, established users of DMPA 150 mg could obtain re-injections from pharmacists ([PharmacyAccess 2005](#)). Early results suggest the program may be appropriate for women who can manage their injection cycle and do not need clinic attention ([Maderas 2007](#)). In Uganda, community-based health workers provided DMPA injections in a nonrandomized trial ([Stanback 2007](#)). Continuation to second injection was comparable to that for clinic-based clients, and the groups were similar for safety and acceptability measures. A study conducted in Brazil indicated that many women can be trained to self-administer a monthly injectable contraceptive ([Bahamondes 1997b](#)).

Studies comparing two combination injectable contraceptives found that NET-EN 50 mg plus E₂V 5 mg resulted in less overall early discontinuation and less discontinuation due to amenorrhea or prolonged bleeding than DMPA 25 mg plus E₂C 5 mg. The NET-EN plus E₂V group also had more regular (cyclical) bleeding and fewer prolonged bleeding reference periods than the DMPA plus E₂C group. The groups did not differ in their amenorrhea rates. However, the statistical significance of almost all of these findings was dependent on one trial conducted in China ([Sang 1995](#)), and the differences generally were not detected in the other populations studied.

The injectable contraceptive NET-EN 50 mg plus E₂V 5 mg led to more early discontinuation due to bleeding than a comparison copper IUD.

The acceptability of changes in bleeding patterns can vary across cultures as well as between individual women ([Glasier 2003](#)). For example, some women could perceive amenorrhea as a benefit of a contraceptive method, while others could be concerned due to uncertainty regarding possible pregnancy or cultural beliefs about regular menses. Also, the degree to which women are willing to tolerate bleeding pattern disruptions could be affected by other factors, such as the provision of counseling regarding these effects or the availability of other reliable and acceptable methods. Therefore, the results of these trials should be interpreted with caution since the discontinuation rates are dependent on many factors.

AUTHORS' CONCLUSIONS

Implications for practice

Combination injectable contraceptives (DMPA 25 mg plus E₂C 5 mg and NET-EN 50 mg plus E₂V 5 mg) led to more regular (cyclical) bleeding, less amenorrhea, and fewer infrequent bleeding patterns than the comparison progestin-only injectables (i.e., DMPA 150 mg and NET-EN 200 mg, respectively). The combination injectable contraceptives also resulted in lower rates of early study discontinuation due to amenorrhea or other bleeding problems. However, they had higher rates of discontinuation overall and due to non-bleeding reasons than the progestin-only contraceptives.

While discontinuation rates can be viewed as a measure of method acceptability, this acceptability is dependent on the population studied since perceptions of bleeding pattern changes can vary.

Implications for research

Future research should be directed toward interventions to improve the acceptability of combination injectable contraceptives. Such studies might include administering

injections in settings more convenient than the clinical sites in which they are currently provided. There could also be interventions for women to administer their own injections and for counseling about possible bleeding pattern changes.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Cuong 1996

Methods	Four sites in Vietnam. 12 treatment months. Randomized with computer-generated random table. Open trial.
Participants	600 healthy females aged 20 to 40 years with at least one living child. Excluded pregnancy, lactation, lack of at least one normal menstrual cycle following delivery or abortion, certain diseases or conditions, use of certain drugs.

Combination injectable contraceptives for contraception (Review)

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Cuong 1996 (Continued)

Interventions	Medroxyprogesterone acetate (DMPA) 25 mg / estradiol cypionate (E ₂ C) 5 mg given every 30 ±3 days (N=300) versus DMPA 150 mg given every 90 ± 5 days (N=300).
Outcomes	Used 90-day reference period for bleeding outcomes. Defined 'bleeding/spotting episode' as set of one or more bleeding or spotting days bounded at each end by at least two bleeding-free days. Defined outcomes: Amenorrhea - absence of bleeding or spotting throughout the reference period. Infrequent bleeding - fewer than two bleeding or spotting episodes. Frequent bleeding - more than four bleeding or spotting days. Irregular bleeding - a range of lengths of bleeding-free intervals exceeding 17 days. Prolonged bleeding - at least one bleeding or spotting episode lasting 10 days or more. Normal - all other reference periods.

Notes

Risk of bias

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

Hassan 1999

Methods	12 sites in Egypt. 12 treatment months. Computer-generated randomization scheme using blocks of eight.
Participants	2252 healthy women aged 20 to 35 years with regular menses and at least two children. Excluded pregnancy, lactation, certain diseases or conditions, use of certain drugs, use of DMPA in the prior six months.
Interventions	DMPA 25 mg and E ₂ C 5 mg given every 30 ±3 days versus NET-EN 50 mg and E ₂ V 5 mg every 30 ± 3 days
Outcomes	Discontinuation due to bleeding outcomes, pregnancy or other personal reasons.
Notes	Blinding not mentioned.

Risk of bias

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

Indian Council 1990

Methods	10 sites in India. 12 treatment months. Open trial.
Participants	1112 healthy women aged 18 to 35 years of proven fertility with regular menses. Excluded contraindications to steroidal hormones, steroidal hormone use within prior three months.

Indian Council 1990 (Continued)

Interventions	NET-EN 50 mg / E ₂ V 5 mg given every 30 ± 2 days versus NET-EN 200 mg given every 60 ± 5 days. 1112 women randomized but initial number randomized to each study group not reported.
Outcomes	Used 90-day reference period for bleeding outcomes. Did not define bleeding outcomes.
Notes	Randomization method not reported. Excluded 41 women (3.7%) from the analysis for protocol violations and 222 women from two sites (20.0%) from the analysis due to high loss to follow up.

Risk of bias

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

Mostafa 1994a

Methods	1 site in Egypt. 12 treatment months.
Participants	300 healthy, fertile women less than 35 years of age with at least two children, at risk of pregnancy, and willing to use only study method for contraception. Excluded pregnancy, lactation, irregular menses, without at least one menses following delivery or abortion, history of abnormal genital bleeding, recent injectable contraceptive use, contraindications to hormonal contraceptives.
Interventions	DMPA 25 mg / E ₂ C 5 mg given every 30 ± 3 days (N=150) versus NET-EN 50 mg / E ₂ V 5 mg given every 30 ± 3 days (N=150).
Outcomes	Used 90-day reference period for bleeding outcomes. Used same definitions for bleeding outcomes as Cuong 1996 .
Notes	Randomization method not reported. Blinding not mentioned.

Risk of bias

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

Piya-Anant 1998

Methods	One site in Thailand. Six treatment months. Open trial.
Participants	100 women currently using DMPA for contraception with amenorrhea for at least six months preceding study initiation. (Dissatisfaction with amenorrhea was not a criterion for participation.) Excluded pregnancy, lactation, certain diseases or conditions.

Piya-Anant 1998 (Continued)

Interventions	DMPA 25 mg / E ₂ C 5 mg given every 30 ± 3 days (N=50) versus DMPA 150 mg given every 90 ± 5 days (N=50).	
Outcomes	Amenorrhea was sole bleeding outcome.	
Notes	Randomization method not reported.	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	No information

Recio 1986

Methods	One site in Mexico. Three treatment months. Open trial.	
Participants	16 healthy women of reproductive age with regular menses without contraindications to hormonal contraception. Excluded hormonal contraceptive use in prior six months.	
Interventions	Dihydroxyprogesterone acetophenide (DHPA) 150 mg / estradiol enanthate (E ₂ EN) 10 mg given on days 1 to 5, 28 and 56 (N=9) versus DHPA 75 mg / E ₂ EN 5 mg given on days 1 to 5, 28 and 56 (N=7).	
Outcomes	Number of bleeding and spotting days following injection was sole bleeding outcome.	
Notes	Randomization method not reported.	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	No information

Ruminjo 2005

Methods	Three family planning clinics in Kenya (Nairobi, Riruta, and Thika). Duration: 12 months. Randomization method: permuted-block randomization. Intent-to-treat analysis used.	
Participants	Women seeking family planning services at the sites. Inclusion criteria: no contraindications to study contraceptive methods and gave informed consent.	
Interventions	Medroxyprogesterone acetate (DMPA) 25 mg / estradiol cypionate (E ₂ C) 5 mg given every 30 ± 3 days (N=180) versus DMPA 150 mg given every 90 ± 14 days (N=180). Injections provided in first 5 days of menstrual cycle.	
Outcomes	Bleeding patterns per 3-mo reference period:	

Combination injectable contraceptives for contraception (Review)

Ruminjo 2005 (Continued)

flow duration (amenorrhea, 1 to 4 or > 5 days bleeding, spotting); intermenstrual bleeding (none, staining or spotting, moderate, severe); no further definitions. Continuation rates, reasons for discontinuation, and satisfaction (favorable experience with study method).

Notes
No mention of blinding. No a priori sample size estimation. Losses to follow up: 15% in each group.

Risk of bias

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

Sang 1995

Methods
15 sites in China.
12 treatment months.
Randomization with random number tables.

Participants
1937 healthy, fertile women aged 18 to 35 years with regular menses and at least one normal cycle since any delivery or abortion.
Excluded pregnancy, lactation, certain diseases or conditions, use of certain drugs, recent injectable or oral contraception.

Interventions
NET-EN 50 mg / E₂V 5 mg given every 30 ± 3 days (N= 972) versus DMPA 25 mg / E₂C 5 mg given every 30 ± 3 days (N=965) versus dihydroxyprogesterone caproate (DHPC) 250 mg / E₂V 5 mg every 30 ± 3 days (N=770).
Due to a high pregnancy rate, the injection schedule was changed for the DHPC / E₂V group and 357 women in this group opted to terminate the study. Additional women were recruited to the study at this point. Therefore, we reported the results from the first two groups only.

Outcomes
Used 90-day reference period for bleeding outcomes.
Used same definitions for bleeding outcomes as [Cuong 1996](#).

Notes
Blinding not mentioned.
Excluded 3 women (0.2%) from the analysis for protocol violations.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	High risk	Not used

Simbar 2007

Methods
Family planning clinic in Tehran, Iran.
Duration - 6 months
Randomization method: 68 marbles placed in a bag; women selected either a red (N=38) or yellow (N=30 marble). A priori, the researchers made the group with the combination injectable larger due to expecting more drop outs.

Simbar 2007 (Continued)

Participants	68 healthy women, 18 to 39 years old, with regular menstrual cycles and seeking long-term contraception.
Interventions	Medroxyprogesterone acetate (MPA) 25 mg / estradiol cypionate (E ₂ C) 5 mg injected monthly versus DMPA 150 mg injected every 3 months.
Outcomes	Number of bleeding and spotting days per 3-month reference period: Bleeding - any bloody vaginal discharge requiring use of sanitary protection; Spotting - any bloody vaginal discharge that is not enough to require use of sanitary protection.
Notes	No mention of blinding. Losses: overall 37% (25/68), but this apparently included method discontinuation and problems with specimens. Author provided sample sizes for bleeding data for second reference period and noted where standard deviations were reported in text (rather than standard errors of mean).

Risk of bias

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

Von Kesseru 2000

Methods	Six sites in Argentina. 24 treatment months. Randomization with list at a ratio of 1:2. Open trial.
Participants	148 healthy women aged 38 to 50 years with normal menses. Excluded certain abnormal biochemical values.
Interventions	NET-EN 50 mg / E ₂ V 5 mg given every 30 ± 3 days (N=49) versus Nova T IUD (N=99).
Outcomes	Discontinuation related to bleeding was sole bleeding outcome.
Notes	

Risk of bias

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

WHO 1988

Methods	17 sites in Egypt, Thailand, Mexico, Guatemala, Cuba, Indonesia, Pakistan, USSR, the Philippines, Italy, Hungary, and Chile. 12 treatment cycles.
Participants	2328 healthy women aged 18 to 35 years with regular menses and proven fertility and at least one normal cycle following delivery for postpartum women.

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WHO 1988 (Continued)

Excluded pregnancy, lactation, certain diseases and conditions, use of certain drugs, DMPA or NET-EN use within the prior six or four months, respectively.

Interventions	NET-EN 50 mg / E ₂ V 5 mg given every 30 ±3 days versus DMPA 25 mg / E ₂ C 5 mg given every 30 ±3 days. 2328 women randomized but initial number randomized to each study group not reported.
Outcomes	Used 90-day reference period for bleeding outcomes. Defined outcomes: Amenorrhea - absence of bleeding or spotting throughout the reference period. Infrequent bleeding - one or two bleeding or spotting episodes. Frequent bleeding - more than five bleeding or spotting days. Irregular bleeding - three to five bleeding or spotting episodes and less than three bleeding or spotting episodes intervals of 14 days or more. Prolonged bleeding - at least one bleeding or spotting episode lasting more than 14 days. Normal - all other reference periods.
Notes	Randomization and allocation concealment methods not reported. Blinding not mentioned. Excluded 8 women (0.3%) from the analysis for protocol violations.

Risk of bias

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

WHO 1997

Methods	Four sites in China, Cuba and Indonesia. Nine treatment cycles. Randomization with random number table.
Participants	370 healthy women aged 18 to 35 years with at least two regular menstrual cycles since stopping their last contraceptive method and for postpartum or postabortion women at least six months since delivery or abortion with at least one normal cycle afterwards. Excluded pregnancy, lactation, nulliparity, certain diseases and conditions, obesity, smoking, use of certain drugs, oral contraceptive or injectable contraceptive use within prior three or six months, respectively.
Interventions	NET-EN 50 mg / E ₂ V 5 mg given every 30 days versus DMPA 25 mg / E ₂ C 5 mg given every 30 days. 370 women randomized but initial number randomized to each study group not reported.
Outcomes	Discontinuation related to bleeding was only bleeding outcome.
Notes	Blinding not mentioned. Excluded 13 women (3.5%) from the analysis, 10 of whom were excluded for protocol violations.

Risk of bias

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

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

Study	Reason for exclusion
Baweja 1985	Compared one marketed to three unmarketed combination injectable contraceptives. A fifth (progesterin-only) group was not randomized.
Benagiano 1997	Did not report relevant outcome data.
Brucker 2001	Did not report relevant outcome data.
Coutinho 1997	Compared one marketed to one unmarketed combination injectable contraceptive.
Garza-Flores 1987	Did not report relevant outcome data.
Jain 2000	Did not report relevant outcome data.
Karim 1971	Compared two unmarketed combination injectable contraceptives.
Kashanian 2013	Investigator communicated that she could not finish the study because of problems in the policy of the MOH [ministry of health].
Kesseru 1988	Compared one marketed to one unmarketed combination injectable contraceptive.
Khalaf 1994	Abstract without sufficient data.
Meng 1990	Did not report relevant outcome data.
Mostafa 1994b	Did not report relevant outcome data.
Werawatgoompa 1980	Did not study a marketed combination injectable contraceptive.
WHO 2003	Did not report relevant outcome data.

DATA AND ANALYSES

Comparison 1. DMPA 25 mg / E₂C 5 mg versus DMPA 150 mg

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Discontinuation - overall at 6 months	1	100	Peto Odds Ratio (Peto, Fixed, 95% CI)	8.41 [1.82, 38.77]
2 Discontinuation - overall at 12 months	1	360	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.24 [1.43, 3.50]
3 Discontinuation - amenorrhea	1	100	Peto Odds Ratio (Peto, Fixed, 95% CI)	7.39 [0.15, 372.38]
4 Discontinuation - menstrual changes	1	360	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.00 [0.71, 5.62]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5 Discontinuation - non-menstrual medical reasons	1	360	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.19 [0.80, 5.95]
6 Amenorrhea - any time during 6-month study	1	99	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.06 [0.03, 0.13]
7 Amenorrhea - first reference period	2	841	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.23 [0.15, 0.34]
8 Infrequent bleeding - first reference period	1	561	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.20 [0.13, 0.31]
9 Frequent bleeding - first reference period	1	561	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.16 [0.48, 2.77]
10 Prolonged bleeding - first reference period	1	561	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.34 [0.23, 0.50]
11 Irregular bleeding - first reference period	1	561	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.88 [0.62, 1.25]
12 Normal bleeding - first reference period	1	561	Peto Odds Ratio (Peto, Fixed, 95% CI)	4.93 [3.48, 7.00]
13 Amenorrhea - fourth reference period	2	609	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.10 [0.07, 0.14]
14 Infrequent bleeding - fourth reference period	1	421	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.49 [0.28, 0.87]
15 Frequent bleeding - fourth reference period	1	421	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.67 [0.37, 19.12]
16 Prolonged bleeding - fourth reference period	1	421	Peto Odds Ratio (Peto, Fixed, 95% CI)	3.60 [1.09, 11.89]
17 Irregular bleeding - fourth reference period	1	421	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.75 [1.41, 5.36]
18 Normal bleeding - fourth reference period	1	421	Peto Odds Ratio (Peto, Fixed, 95% CI)	6.14 [4.19, 9.00]
19 Bleeding > 5 days - first reference period	1	280	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.85 [1.07, 3.20]
20 Bleeding > 5 days - fourth reference period	1	188	Peto Odds Ratio (Peto, Fixed, 95% CI)	5.29 [2.59, 10.78]
21 Intermenstrual bleeding, moderate or severe - first reference period	1	280	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.14 [0.03, 0.65]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
22 Intermenstrual bleeding, moderate or severe - fourth reference period	1	188	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.44 [0.14, 1.36]
23 Mean days of bleeding and spotting - first reference period	1	43	Mean Difference (IV, Fixed, 95% CI)	-6.0 [-17.22, 5.22]
24 Mean days of bleeding and spotting - second reference period	1	43	Mean Difference (IV, Fixed, 95% CI)	-2.0 [-8.29, 4.29]
25 Weight gain (kg)	1	442	Mean Difference (IV, Fixed, 95% CI)	-0.20 [-0.63, 0.23]
26 Intention to continue method at study end	1	100	Peto Odds Ratio (Peto, Fixed, 95% CI)	10.52 [4.71, 23.49]
27 Experience with study method: very favorable or somewhat favorable	1	306	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.48 [0.23, 1.02]

Analysis 1.1. Comparison 1 DMPA 25 mg / E₂C 5 mg versus DMPA 150 mg, Outcome 1 Discontinuation - overall at 6 months.

Analysis 1.2. Comparison 1 DMPA 25 mg / E₂C 5 mg versus DMPA 150 mg, Outcome 2 Discontinuation - overall at 12 months.

Analysis 1.3. Comparison 1 DMPA 25 mg / E₂C 5 mg versus DMPA 150 mg, Outcome 3 Discontinuation - amenorrhea.

Analysis 1.4. Comparison 1 DMPA 25 mg / E₂C 5 mg versus DMPA 150 mg, Outcome 4 Discontinuation - menstrual changes.

Analysis 1.5. Comparison 1 DMPA 25 mg / E₂C 5 mg versus DMPA 150 mg, Outcome 5 Discontinuation - non-menstrual medical reasons.

Analysis 1.6. Comparison 1 DMPA 25 mg / E₂C 5 mg versus DMPA 150 mg, Outcome 6 Amenorrhea - any time during 6-month study.

Analysis 1.7. Comparison 1 DMPA 25 mg / E₂C 5 mg versus DMPA 150 mg, Outcome 7 Amenorrhea - first reference period.

Analysis 1.8. Comparison 1 DMPA 25 mg / E₂C 5 mg versus DMPA 150 mg, Outcome 8 Infrequent bleeding - first reference period.

Analysis 1.9. Comparison 1 DMPA 25 mg / E₂C 5 mg versus DMPA 150 mg, Outcome 9 Frequent bleeding - first reference period.

Analysis 1.10. Comparison 1 DMPA 25 mg / E₂C 5 mg versus DMPA 150 mg, Outcome 10 Prolonged bleeding - first reference period.

Analysis 1.11. Comparison 1 DMPA 25 mg / E₂C 5 mg versus DMPA 150 mg, Outcome 11 Irregular bleeding - first reference period.

Analysis 1.12. Comparison 1 DMPA 25 mg / E₂C 5 mg versus DMPA 150 mg, Outcome 12 Normal bleeding - first reference period.

Analysis 1.13. Comparison 1 DMPA 25 mg / E₂C 5 mg versus DMPA 150 mg, Outcome 13 Amenorrhea - fourth reference period.

Analysis 1.14. Comparison 1 DMPA 25 mg / E₂C 5 mg versus DMPA 150 mg, Outcome 14 Infrequent bleeding - fourth reference period.

Analysis 1.15. Comparison 1 DMPA 25 mg / E₂C 5 mg versus DMPA 150 mg, Outcome 15 Frequent bleeding - fourth reference period.

Analysis 1.16. Comparison 1 DMPA 25 mg / E₂C 5 mg versus DMPA 150 mg, Outcome 16 Prolonged bleeding - fourth reference period.

Analysis 1.17. Comparison 1 DMPA 25 mg / E₂C 5 mg versus DMPA 150 mg, Outcome 17 Irregular bleeding - fourth reference period.

Analysis 1.18. Comparison 1 DMPA 25 mg / E₂C 5 mg versus DMPA 150 mg, Outcome 18 Normal bleeding - fourth reference period.

Analysis 1.19. Comparison 1 DMPA 25 mg / E₂C 5 mg versus DMPA 150 mg, Outcome 19 Bleeding > 5 days - first reference period.

Analysis 1.20. Comparison 1 DMPA 25 mg / E₂C 5 mg versus DMPA 150 mg, Outcome 20 Bleeding > 5 days - fourth reference period.

Analysis 1.21. Comparison 1 DMPA 25 mg / E₂C 5 mg versus DMPA 150 mg, Outcome 21 Intermenstrual bleeding, moderate or severe - first reference period.

Analysis 1.22. Comparison 1 DMPA 25 mg / E₂C 5 mg versus DMPA 150 mg, Outcome 22 Intermenstrual bleeding, moderate or severe - fourth reference period.

Analysis 1.23. Comparison 1 DMPA 25 mg / E₂C 5 mg versus DMPA 150 mg, Outcome 23 Mean days of bleeding and spotting - first reference period.

Analysis 1.24. Comparison 1 DMPA 25 mg / E₂C 5 mg versus DMPA 150 mg, Outcome 24 Mean days of bleeding and spotting - second reference period.

Analysis 1.25. Comparison 1 DMPA 25 mg / E₂C 5 mg versus DMPA 150 mg, Outcome 25 Weight gain (kg).

Analysis 1.26. Comparison 1 DMPA 25 mg / E₂C 5 mg versus DMPA 150 mg, Outcome 26 Intention to continue method at study end.

**Analysis 1.27. Comparison 1 DMPA 25 mg / E₂C 5 mg versus DMPA 150 mg,
Outcome 27 Experience with study method: very favorable or somewhat favorable.**

Comparison 2. DHPA 150 mg / E₂EN 10 mg versus DHPA 75 mg / E₂EN 5 mg

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Bleeding or spotting days after third injection	1	16	Mean Difference (IV, Fixed, 95% CI)	-4.50 [-9.01, 0.01]

Analysis 2.1. Comparison 2 DHPA 150 mg / E₂EN 10 mg versus DHPA 75 mg / E₂EN 5 mg, Outcome 1 Bleeding or spotting days after third injection.

Comparison 3. NET-EN 50 mg / E₂V 5 mg versus DMPA 25 mg / E₂C 5 mg

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Discontinuation - overall	3	6592	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.82 [0.74, 0.92]
2 Discontinuation - pregnancy	2	6235	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.49 [0.76, 8.12]
3 Discontinuation - amenorrhea	2	6235	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.32 [0.22, 0.44]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4 Discontinuation - heavy bleeding	2	6235	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.79 [0.42, 1.45]
5 Discontinuation - prolonged bleeding	2	6235	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.66 [0.48, 0.90]
6 Discontinuation - irregular bleeding	2	6235	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.00 [0.66, 1.53]
7 Discontinuation - spotting	2	6235	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.96 [0.52, 1.74]
8 Discontinuation - other bleeding problems	2	6235	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.62 [0.37, 1.03]
9 Discontinuation - any bleeding problem	1	357	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.88 [0.67, 5.28]
10 Discontinuation - other medical reason	3	6592	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.07 [0.83, 1.37]
11 Discontinuation - other personal reason	2	6235	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.09 [0.90, 1.33]
12 Discontinuation - late for or lost to follow-up	2	6235	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.99 [0.80, 1.22]
13 Amenorrhea - first reference period	3	4070	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.69 [0.20, 2.37]
14 Infrequent bleeding - first reference period	3	4073	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.45 [0.32, 0.64]
15 Frequent bleeding - first reference period	3	4076	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.58 [1.27, 1.98]
16 Prolonged bleeding - first reference period	3	4085	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.41 [0.32, 0.53]
17 Irregular bleeding - first reference period	3	4072	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.69 [0.59, 0.81]
18 Normal bleeding - first reference period	3	4095	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.68 [1.48, 1.90]
19 Amenorrhea - fourth reference period	3	3100	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.91 [0.51, 1.62]
20 Infrequent bleeding - fourth reference period	3	3106	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.73 [0.55, 0.97]
21 Frequent bleeding - fourth reference period	3	3102	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.12 [0.79, 1.60]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
22 Prolonged bleeding - fourth reference period	3	3328	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.49 [0.35, 0.69]
23 Irregular bleeding - fourth reference period	3	3102	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.83 [0.66, 1.05]
24 Normal bleeding - fourth reference period	3	3095	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.39 [1.19, 1.62]
25 Weight at 12th month (kg)	1	134	Mean Difference (IV, Fixed, 95% CI)	1.10 [-2.75, 4.95]

Analysis 3.1. Comparison 3 NET-EN 50 mg / E₂V 5 mg versus DMPA 25 mg / E₂C 5 mg, Outcome 1 Discontinuation - overall.

Analysis 3.2. Comparison 3 NET-EN 50 mg / E₂V 5 mg versus DMPA 25 mg / E₂C 5 mg, Outcome 2 Discontinuation - pregnancy.

Analysis 3.3. Comparison 3 NET-EN 50 mg / E₂V 5 mg versus DMPA 25 mg / E₂C 5 mg, Outcome 3 Discontinuation - amenorrhea.

Analysis 3.4. Comparison 3 NET-EN 50 mg / E₂V 5 mg versus DMPA 25 mg / E₂C 5 mg, Outcome 4 Discontinuation - heavy bleeding.

Analysis 3.5. Comparison 3 NET-EN 50 mg / E₂V 5 mg versus DMPA 25 mg / E₂C 5 mg, Outcome 5 Discontinuation - prolonged bleeding.

Analysis 3.6. Comparison 3 NET-EN 50 mg / E₂V 5 mg versus DMPA 25 mg / E₂C 5 mg, Outcome 6 Discontinuation - irregular bleeding.

Analysis 3.7. Comparison 3 NET-EN 50 mg / E₂V 5 mg versus DMPA 25 mg / E₂C 5 mg, Outcome 7 Discontinuation - spotting.

Analysis 3.8. Comparison 3 NET-EN 50 mg / E₂V 5 mg versus DMPA 25 mg / E₂C 5 mg, Outcome 8 Discontinuation - other bleeding problems.

Analysis 3.9. Comparison 3 NET-EN 50 mg / E₂V 5 mg versus DMPA 25 mg / E₂C 5 mg, Outcome 9 Discontinuation - any bleeding problem.

Analysis 3.10. Comparison 3 NET-EN 50 mg / E₂V 5 mg versus DMPA 25 mg / E₂C 5 mg, Outcome 10 Discontinuation - other medical reason.

Analysis 3.11. Comparison 3 NET-EN 50 mg / E₂V 5 mg versus DMPA 25 mg / E₂C 5 mg, Outcome 11 Discontinuation - other personal reason.

Analysis 3.12. Comparison 3 NET-EN 50 mg / E₂V 5 mg versus DMPA 25 mg / E₂C 5 mg, Outcome 12 Discontinuation - late for or lost to follow-up.

Analysis 3.13. Comparison 3 NET-EN 50 mg / E₂V 5 mg versus DMPA 25 mg / E₂C 5 mg, Outcome 13 Amenorrhea - first reference period.

Analysis 3.14. Comparison 3 NET-EN 50 mg / E₂V 5 mg versus DMPA 25 mg / E₂C 5 mg, Outcome 14 Infrequent bleeding - first reference period.

Analysis 3.15. Comparison 3 NET-EN 50 mg / E₂V 5 mg versus DMPA 25 mg / E₂C 5 mg, Outcome 15 Frequent bleeding - first reference period.

Analysis 3.16. Comparison 3 NET-EN 50 mg / E₂V 5 mg versus DMPA 25 mg / E₂C 5 mg, Outcome 16 Prolonged bleeding - first reference period.

Analysis 3.17. Comparison 3 NET-EN 50 mg / E₂V 5 mg versus DMPA 25 mg / E₂C 5 mg, Outcome 17 Irregular bleeding - first reference period.

Analysis 3.18. Comparison 3 NET-EN 50 mg / E₂V 5 mg versus DMPA 25 mg / E₂C 5 mg, Outcome 18 Normal bleeding - first reference period.

Analysis 3.19. Comparison 3 NET-EN 50 mg / E₂V 5 mg versus DMPA 25 mg / E₂C 5 mg, Outcome 19 Amenorrhea - fourth reference period.

Analysis 3.20. Comparison 3 NET-EN 50 mg / E₂V 5 mg versus DMPA 25 mg / E₂C 5 mg, Outcome 20 Infrequent bleeding - fourth reference period.

Analysis 3.21. Comparison 3 NET-EN 50 mg / E₂V 5 mg versus DMPA 25 mg / E₂C 5 mg, Outcome 21 Frequent bleeding - fourth reference period.

Analysis 3.22. Comparison 3 NET-EN 50 mg / E₂V 5 mg versus DMPA 25 mg / E₂C 5 mg, Outcome 22 Prolonged bleeding - fourth reference period.

Analysis 3.23. Comparison 3 NET-EN 50 mg / E₂V 5 mg versus DMPA 25 mg / E₂C 5 mg, Outcome 23 Irregular bleeding - fourth reference period.

Analysis 3.24. Comparison 3 NET-EN 50 mg / E₂V 5 mg versus DMPA 25 mg / E₂C 5 mg, Outcome 24 Normal bleeding - fourth reference period.

Analysis 3.25. Comparison 3 NET-EN 50 mg / E₂V 5 mg versus DMPA 25 mg / E₂C 5 mg, Outcome 25 Weight at 12th month (kg).

Comparison 4. NET-EN 50 mg / E₂V 5 mg versus NET-EN 200 mg

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Discontinuation - overall	1	849	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.41 [1.07, 1.86]
2 Discontinuation - pregnancy	1	849	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.30 [0.05, 1.75]
3 Discontinuation - amenorrhea	1	849	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.54 [0.28, 1.05]
4 Discontinuation - heavy and prolonged bleeding	1	849	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.57 [0.31, 1.07]
5 Discontinuation - irregular bleeding or spotting	1	849	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.97 [0.56, 1.67]
6 Discontinuation - other medical reasons	1	849	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.24 [1.23, 4.07]
7 Discontinuation - other personal reasons	1	849	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.93 [1.26, 2.97]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
8 Discontinuation - late for, or lost to, follow up	1	849	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.76 [1.05, 2.95]
9 Infrequent bleeding - first reference period	1	430	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.33 [0.20, 0.55]
10 Frequent bleeding - first reference period	1	430	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.66 [0.35, 1.26]
11 Prolonged bleeding - first reference period	1	430	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.02 [0.31, 3.41]
12 Irregular bleeding - first reference period	1	430	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.81 [0.54, 1.21]
13 Normal bleeding - first reference period	1	430	Peto Odds Ratio (Peto, Fixed, 95% CI)	3.17 [2.14, 4.71]
14 Amenorrhea - fourth reference period	1	430	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.36 [0.16, 0.82]
15 Infrequent bleeding - fourth reference period	1	430	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.60 [0.40, 0.89]
16 Frequent bleeding - fourth reference period	1	430	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.62 [0.17, 2.34]
17 Prolonged bleeding - fourth reference period	1	430	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.82 [0.14, 4.81]
18 Irregular bleeding - fourth reference period	1	430	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.80 [1.56, 5.01]
19 Normal bleeding - fourth reference period	1	430	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.59 [1.08, 2.34]

Analysis 4.1. Comparison 4 NET-EN 50 mg / E₂V 5 mg versus NET-EN 200 mg, Outcome 1 Discontinuation - overall.

Analysis 4.2. Comparison 4 NET-EN 50 mg / E₂V 5 mg versus NET-EN 200 mg, Outcome 2 Discontinuation - pregnancy.

Analysis 4.3. Comparison 4 NET-EN 50 mg / E₂V 5 mg versus NET-EN 200 mg, Outcome 3 Discontinuation - amenorrhea.

Analysis 4.4. Comparison 4 NET-EN 50 mg / E₂V 5 mg versus NET-EN 200 mg, Outcome 4 Discontinuation - heavy and prolonged bleeding.

Analysis 4.5. Comparison 4 NET-EN 50 mg / E₂V 5 mg versus NET-EN 200 mg, Outcome 5 Discontinuation - irregular bleeding or spotting.

Analysis 4.6. Comparison 4 NET-EN 50 mg / E₂V 5 mg versus NET-EN 200 mg, Outcome 6 Discontinuation - other medical reasons.

Analysis 4.7. Comparison 4 NET-EN 50 mg / E₂V 5 mg versus NET-EN 200 mg, Outcome 7 Discontinuation - other personal reasons.

Analysis 4.8. Comparison 4 NET-EN 50 mg / E₂V 5 mg versus NET-EN 200 mg, Outcome 8 Discontinuation - late for, or lost to, follow up.

Analysis 4.9. Comparison 4 NET-EN 50 mg / E₂V 5 mg versus NET-EN 200 mg, Outcome 9 Infrequent bleeding - first reference period.

Analysis 4.10. Comparison 4 NET-EN 50 mg / E₂V 5 mg versus NET-EN 200 mg, Outcome 10 Frequent bleeding - first reference period.

Analysis 4.11. Comparison 4 NET-EN 50 mg / E₂V 5 mg versus NET-EN 200 mg, Outcome 11 Prolonged bleeding - first reference period.

Analysis 4.12. Comparison 4 NET-EN 50 mg / E₂V 5 mg versus NET-EN 200 mg, Outcome 12 Irregular bleeding - first reference period.

Analysis 4.13. Comparison 4 NET-EN 50 mg / E₂V 5 mg versus NET-EN 200 mg, Outcome 13 Normal bleeding - first reference period.

Analysis 4.14. Comparison 4 NET-EN 50 mg / E₂V 5 mg versus NET-EN 200 mg, Outcome 14 Amenorrhea - fourth reference period.

Analysis 4.15. Comparison 4 NET-EN 50 mg / E₂V 5 mg versus NET-EN 200 mg, Outcome 15 Infrequent bleeding - fourth reference period.

Analysis 4.16. Comparison 4 NET-EN 50 mg / E₂V 5 mg versus NET-EN 200 mg, Outcome 16 Frequent bleeding - fourth reference period.

Analysis 4.17. Comparison 4 NET-EN 50 mg / E₂V 5 mg versus NET-EN 200 mg, Outcome 17 Prolonged bleeding - fourth reference period.

Analysis 4.18. Comparison 4 NET-EN 50 mg / E₂V 5 mg versus NET-EN 200 mg, Outcome 18 Irregular bleeding - fourth reference period.

Analysis 4.19. Comparison 4 NET-EN 50 mg / E₂V 5 mg versus NET-EN 200 mg, Outcome 19 Normal bleeding - fourth reference period.

Comparison 5. NET-EN 50 mg / E₂V 5 mg versus nonhormonal IUD

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Discontinuation - bleeding	1	148	Peto Odds Ratio (Peto, Fixed, 95% CI)	6.67 [2.08, 21.41]
2 Pregnancy	1	148	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.22 [0.02, 2.47]

Analysis 5.1. Comparison 5 NET-EN 50 mg / E₂V 5 mg versus nonhormonal IUD, Outcome 1 Discontinuation - bleeding.

Analysis 5.2. Comparison 5 NET-EN 50 mg / E₂V 5 mg versus nonhormonal IUD, Outcome 2 Pregnancy.

ADDITIONAL TABLES

Table 1. One-year life-table discontinuation rates: DMPA 25 mg / E₂C 5 mg versus DMPA 150 mg

Study ID	Discontinue reason	Study group	Rate	SE
Cuong 1996	Overall	DMPA 25 mg / E ₂ C 5 mg	25.7	2.5
		DMPA 150 mg	27.0	2.6
	Amenorrhea	DMPA 25 mg / E ₂ C 5 mg	3.5	1.2
		DMPA 150 mg	7.8	1.6
	Prolonged bleeding	DMPA 25 mg / E ₂ C 5 mg	1.2	0.7
		DMPA 150 mg	2.1	0.9
	Heavy and prolonged bleeding	DMPA 25 mg / E ₂ C 5 mg	1.1	0.6
		DMPA 150 mg	2.4	1.0
	Irregular bleeding	DMPA 25 mg / E ₂ C 5 mg	0.8	0.5
		DMPA 150 mg	0.8	0.6
	Spotting	DMPA 25 mg / E ₂ C 5 mg	4.6	1.3
		DMPA 150 mg	10.0	1.8
	All bleeding problems	DMPA 25 mg / E ₂ C 5 mg	7.4	1.6
		DMPA 150 mg	14.9	2.1
	Other medical reasons	DMPA 25 mg / E ₂ C 5 mg	3.4	1.1
		DMPA 150 mg	2.2	0.9
	Other personal reasons	DMPA 25 mg / E ₂ C 5 mg	10.0	1.8
		DMPA 150 mg	3.0	1.1
	Loss to follow up	DMPA 25 mg / E ₂ C 5 mg	1.0	0.6
		DMPA 150 mg	1.3	0.7

Table 2. Life-table discontinuation rate per 100 women-years: NET-EN 50 mg / E₂V 5 mg versus DMPA 25 mg / E₂C 5 mg

Study ID	Discontinue reason	Study group	Rate	SE	Difference in rates	(95% CI)
Hassan 1999	Overall	NET-EN 50 mg / E ₂ V 5 mg	38.0	1.5	-0.9	---
		DMPA 25 mg / E ₂ C 5 mg	38.9	2.9		
	Pregnancy	NET-EN 50 mg / E ₂ V 5 mg	0.4	0.2	0.2	---
		DMPA 25 mg / E ₂ C 5 mg	0.2	0.1		
	Amenorrhea	NET-EN 50 mg / E ₂ V 5 mg	1.4	0.4	-1.3	---
		DMPA 25 mg / E ₂ C 5 mg	2.7	0.6		
	Heavy bleeding	NET-EN 50 mg / E ₂ V 5 mg	1.9	0.5	0.6	---
		DMPA 25 mg / E ₂ C 5 mg	1.3	0.4		
	Prolonged bleeding	NET-EN 50 mg / E ₂ V 5 mg	2.0	0.5	0.5	---
		DMPA 25 mg / E ₂ C 5 mg	1.5	0.4		
	Irregular bleeding	NET-EN 50 mg / E ₂ V 5 mg	2.4	0.5	0.8	---
		DMPA 25 mg / E ₂ C 5 mg	1.6	0.4		
	Spotting	NET-EN 50 mg / E ₂ V 5 mg	1.0	0.3	0.6	---
		DMPA 25 mg / E ₂ C 5 mg	0.4	0.2		
	All bleeding problems	NET-EN 50 mg / E ₂ V 5 mg	11.5	1.1	4.1	---
		DMPA 25 mg / E ₂ C 5 mg	7.4	0.9		
	Other medical reasons	NET-EN 50 mg / E ₂ V 5 mg	4.7	0.7	-3.1	---
		DMPA 25 mg / E ₂ C 5 mg	7.8	3.8		
	All personal reasons	NET-EN 50 mg / E ₂ V 5 mg	12.8	1.1	0.4	---
		DMPA 25 mg / E ₂ C 5 mg	12.4	1.1		
	Loss to follow-up	NET-EN 50 mg / E ₂ V 5 mg	2.7	0.6	-1.4	---
		DMPA 25 mg / E ₂ C 5 mg	4.1	0.7		

Table 2. Life-table discontinuation rate per 100 women-years: NET-EN 50 mg / E₂V 5 mg versus DMPA 25 mg / E₂C 5
mg (Continued)

Mostafa 1994a	Overall	NET-EN 50 mg / E ₂ V 5 mg	59.2	4.1	5.2	---
		DMPA 25 mg / E ₂ C 5 mg	54.0	5.0		
	Pregnancy	NET-EN 50 mg / E ₂ V 5 mg	0.7	0.7	0.7	---
		DMPA 25 mg / E ₂ C 5 mg	0.0	0.0		
	Amenorrhea	NET-EN 50 mg / E ₂ V 5 mg	3.5	2.0	-0.9	---
		DMPA 25 mg / E ₂ C 5 mg	4.4	1.9		
	Heavy bleeding	NET-EN 50 mg / E ₂ V 5 mg	2.5	1.4	-0.3	---
		DMPA 25 mg / E ₂ C 5 mg	2.8	1.7		
	Prolonged bleeding	NET-EN 50 mg / E ₂ V 5 mg	0.0	0.0	-1.5	---
		DMPA 25 mg / E ₂ C 5 mg	1.5	1.0		
	Irregular bleeding	NET-EN 50 mg / E ₂ V 5 mg	6.3	2.6	4.5	---
		DMPA 25 mg / E ₂ C 5 mg	1.8	1.3		
	Spotting	NET-EN 50 mg / E ₂ V 5 mg	0.8	0.8	0.8	---
		DMPA 25 mg / E ₂ C 5 mg	0.0	0.0		
	All bleeding problems	NET-EN 50 mg / E ₂ V 5 mg	19.1	4.0	5.3	---
		DMPA 25 mg / E ₂ C 5 mg	13.8	3.3		
	Other medical reasons	NET-EN 50 mg / E ₂ V 5 mg	15.9	3.7	-0.5	---
		DMPA 25 mg / E ₂ C 5 mg	16.4	6.4		
	All personal reasons	NET-EN 50 mg / E ₂ V 5 mg	24.4	4.3	-0.4	---
		DMPA 25 mg / E ₂ C 5 mg	24.8	4.1		
	Loss to follow up	NET-EN 50 mg / E ₂ V 5 mg	14.9	3.7	4.7	---
		DMPA 25 mg / E ₂ C 5 mg	10.2	3.0		
WHO 1988	Overall	NET-EN 50 mg / E ₂ V 5 mg	36.8	1.5	1.3	(-2.6 to 5.4)
		DMPA 25 mg / E ₂ C 5 mg	35.5	1.4		

Table 2. Life-table discontinuation rate per 100 women-years: NET-EN 50 mg / E₂V 5 mg versus DMPA 25 mg / E₂C 5 mg (Continued)

Pregnancy	NET-EN 50 mg / E ₂ V 5 mg	0.2	0.1	0.2	(0.0 to 0.4)
	DMPA 25 mg / E ₂ C 5 mg	0			
Amenorrhea	NET-EN 50 mg / E ₂ V 5 mg	1.6	0.4	-0.5	(-1.8 to 0.7)
	DMPA 25 mg / E ₂ C 5 mg	2.1	0.5		
Bleeding irregularities	NET-EN 50 mg / E ₂ V 5 mg	7.5	0.9	1.2	(-1.1 to 3.5)
	DMPA 25 mg / E ₂ C 5 mg	6.3	0.8		

APPENDICES

Appendix 1. Searches 2013

MEDLINE via PubMed (01 Apr 2010 to 28 Jan 2013)

((Acefil OR Agurin OR Anafertin OR Ciclofem OR Ciclofemina OR Ciclomes OR Ciclovar OR Cliclovular OR Clinomin OR Cyclofem OR Cyclofemina OR Cyclo-Provera OR Cycloven OR Deproxone OR Ginestest OR Gynomes OR Listen OR Lunelle OR Mesigyna OR Neogestar OR Norigynon OR Normagest OR Novafem OR Novular OR Oterol OR Ovoginal OR Perlutal OR Perlutan OR Perlutin-Unifarma OR Permisil OR Proter OR Segurames OR Soluna OR Topasel OR Unigalen OR Uno Ciclo OR Vagital OR Yectames OR Yectuna) OR (dihydroxyprogesterone acetophenide OR algestone acetophenide OR medroxyprogesterone 17-acetate OR norethisterone oenanthate OR norethindrone OR injectable) AND contraceptive agents, female NOT postmenopaus*[tiab])

Filter: Clinical trials

CENTRAL (01 Jan 2010 to 28 Jan 2013)

(dihydroxyprogesterone acetophenide OR algestone acetophenide OR medroxyprogesterone 17-acetate OR norethisterone oenanthate OR norethindrone OR injectable) in title abstract keywords
AND contracept* in title abstract keywords

POPLINE (01 Jan 2010 to 04 Feb 2013)

Contraceptive agents AND inject*

Filter by keywords: Research report

EMBASE (01 Jan 2010 to 14 Feb 2013)

contracept* AND (inject* OR 'intradermal'/exp) AND ([controlled clinical trial]/lim OR [randomized controlled trial]/lim) AND [obstetrics and gynecology]/lim AND [female]/lim AND [humans]/lim

LILACS (2010 through 04 Feb 2013)

(injectable or injectables or injection or injections or injetavel or inyectable or medroxiprogesterona or medroxyprogesterone or norethisterone or algestone acetophenide or acetofenida de algestona) and (contraceptive agents, female or contraceptive or contraceptives or agents anticonceptivos femininos or anticoncepcionais femininos) [words]

ClinicalTrials.gov (01 Jul 2010 to 13 Feb 2013)

Search terms: injectable OR injection OR injections OR injected

Condition: NOT (endometriosis OR HIV OR dysmenorrhea OR amenorrhea OR cancer OR in vitro OR lupus OR turner)

Intervention: contraceptive OR contraception

Study type: interventional studies

Gender: studies with female participants

ICTRP (01 Jul 2010 to 13 Feb 2013)

Condition: contraceptive OR contraception

Intervention: injectable OR injection OR injections OR injected

Appendix 2. Searches 2010

MEDLINE via PubMed (2008 to 30 Sep 2010)

((Acefil OR Agurin OR Anafertin OR Ciclofem OR Ciclofemina OR Ciclomes OR Ciclovar OR Clivovular OR Clinomin OR Cyclofem OR Cyclofemina OR Cyclo-Provera OR Cycloven OR Deproxone OR Ginestest OR Gynomes OR Listen OR Lunelle OR Mesigyna OR Neogestar OR Norigynon OR Normagest OR Novafem OR Novular OR Oterol OR Ovoginal OR Perlutal OR Perlutan OR Perlutin-Unifarma OR Permisil OR Proter OR Seguralmes OR Soluna OR Topasel OR Unigalen OR Uno Ciclo OR Vagital OR Yectames OR Yectuna) OR (dihydroxyprogesterone acetophenide OR algestone acetophenide OR medroxyprogesterone 17-acetate OR norethisterone oenanthate OR norethindrone OR injectable) AND contraceptive agents, female NOT postmenopaus*[tiab]) AND (randomized controlled trial [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 OR evaluation study 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]))

CENTRAL (2007 to 17 Sep 2010)

(dihydroxyprogesterone acetophenide OR algestone acetophenide OR medroxyprogesterone 17-acetate OR norethisterone oenanthate OR norethindrone OR injectable) in Title, Abstract or Keywords AND contracept* in Title, Abstract or Keywords

EMBASE (2008 to 01 Nov 2010)

((((hormonal contraception OR contraceptives) AND (intradermal(W)drug(W) administration OR intramuscular(W)drug(W)administration)) OR (inject?(W)contracept?)) NOT (male OR men) AND human AND clinical trial

POPLINE (2007 to 30 Sep 2010)

(random* / blind* / placebo* / crossover*) & contraceptive agents & (inject* / Acefil / Agurin / Anafertin / Chinese injectable / Ciclofem / Ciclovlar / Ciconor / Ciclofemina / Ciclomes / Ciclovular / Clivovular / Clinomin / Cyclofem / Cyclofemina / Cyclo-Provera / Cycloprovera / Cycloven / Damix / Deladroxate / Deproxone / Exuna / Ginestest / Gynomes / HRP 3 / HRP 4 / HRP 102 / HRP 112 / Listen / Lunelle / Mesigyna / Neogestar / Neolutin / Nonestrol / Norigynon / Normagest / Novafem / Novular / Oterol / Ovoginal / Patector / Perlutal / Perlutale / Perlutan / Perlutin-Unifarma / Permisil / Progestrol / Proter / Segutalmes / Soluna / Topasel / Unalmes / Unigalen / Unijab / Uno Ciclo / Vagital / Yectames / Yectuna / alfasona / algeston acetophenide / algestone acetophenide / dihydroxyprogesterone acetophenide / dihydroxyprogesterone caproate / medroxyprogesterone 17-acetate / norethisterone)

LILACS (2008 to 30 Sep 2010)

(injectable or injectables or injection or injections or injetavel or inyectable or medroxiprogesterona or medroxyprogesterone or norethisterone or algestone acetophenide or acetofenida de algestona) and (contraceptive agents, female or contraceptive or contraceptives or agents anticonceptivos femininos or anticoncepcionais femininos) [words]

ClinicalTrials.gov (through 20 Sep 2010)

Search terms: injectable OR injection OR injections OR injected

Condition: NOT (endometriosis OR HIV OR dysmenorrhea OR amenorrhea OR cancer OR in vitro OR lupus OR turner)

Intervention: contraceptive OR contraception

Study type: interventional studies

Gender: studies with female participants

ICTRP (through 20 Sep 2010)

Condition: contraceptive OR contraception

Intervention: injectable OR injection OR injections OR injected

Appendix 3. Searches 2005 and 2008

MEDLINE, EMBASE, POPLINE, and LILACS

See 2010 strategies in [Appendix 2](#).

AIM

{injectable} or {injectables} or {injection} or {injections} or {alfasona} or {algestone acetophenide} or {dihydroxyprogesterone} or {medroxyprogesterone} or {norethisterone}

IMEMR

injectable or injectables or injection or injections or alfasona or algestone acetophenide or dihydroxyprogesterone or medroxyprogesterone or norethisterone

WHAT'S NEW

Date	Event	Description
19 February 2013	New search has been performed	Searches were updated. We did not find any eligible new trials. A trial previously listed as ongoing was excluded (Kashanian 2013).

HISTORY

Protocol first published: Issue 1, 2004

Review first published: Issue 3, 2005

Date	Event	Description
1 November 2010	New search has been performed	Searches were updated, and searches were added for ClinicalTrials.gov and ICTRP. An ongoing trial was added (Kashanian 2010). No other new trials met the inclusion criteria.
14 April 2008	Amended	Converted to new review format.
28 January 2008	New citation required but conclusions have not changed	Two new trials were found and incorporated (Ruminjo 2005 ; Simbar 2007).
28 January 2008	New citation required and conclusions have changed	Substantive amendment
23 January 2008	New search has been performed	The searches were updated in Dec 2007 and Jan 2008.

CONTRIBUTIONS OF AUTHORS

M Gallo developed the idea, extracted the data for the original review, conducted the analyses, and wrote the initial review. D Grimes did the second data extraction. C d'Arcangues consulted on the content of the review. K Schultz provided statistical consultation. L Lopez conducted the updates through 2013, incorporated new trials when applicable, and edited the review.

DECLARATIONS OF INTEREST

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

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- National Institute of Child Health and Human Development, USA.

For conducting the review: MFG (2003 to 2004); DAG and KFS (2003 to 2010); LML (2005 to 2013)

- U.S. Agency for International Development, USA.

For conducting the review: MFG (2003 to 2004); DAG and KFS (2003 to 2010); LML (2005 to 2013)

INDEX TERMS**Medical Subject Headings (MeSH)**

Algestone [administration & dosage]; Contraception [*methods]; Contraceptive Agents, Female [*administration & dosage] [adverse effects]; Drug Combinations; Estradiol [administration & dosage] [analogs & derivatives]; Injections; Medication Adherence; Medroxyprogesterone [administration & dosage]; Megestrol Acetate [administration & dosage]; Norethindrone [administration & dosage] [analogs & derivatives]; Randomized Controlled Trials as Topic

MeSH check words

Female; Humans