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 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 combination injectable contraceptives.

Search strategy

We searched computerized databases for randomized controlled trials of combination injectable contraceptives.

Selection criteria

Randomized controlled trials were eligible if they compared a combination injectable with any other contraceptive method (e.g., a second combination injectable contraceptive, progestin-only injectable contraceptive, other hormonal contraceptive or barrier method) or placebo. We limited the review to currently marketed combination injectable contraceptives.

Data collection and analysis

One author evaluated all titles and abstracts from the literature searches to determine their eligibility. Two authors independently extracted data from the eligible trials. Data on contraceptive efficacy, bleeding patterns, continuation, and side effects were entered and analyzed with RevMan.

Main results

Combination injectable contraceptives include depot medroxyprogesterone acetate (DMPA) 25 mg plus estradiol cypionate (E_2C) 5 mg, as well as norethisterone enanthate (NET-EN) 50 mg plus estradiol valerate (E_2V) 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 combination injectable in one study and the progestin-only in another.

Studies comparing two combination injectable contraceptives found that NET-EN 50 mg plus E_2V 5 mg resulted in less overall discontinuation and less discontinuation due to amenorrhea or prolonged bleeding than DMPA 25 mg plus E_2C 5 mg. However, these differences were not detected in all trials. The NET-EN plus E_2V group also had more regular bleeding and fewer prolonged bleeding reference periods than the DMPA plus E_2C 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 interventions to improve 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 injectables are effective in preventing pregnancy and can be stopped when a woman wants to get pregnant. This review looked at combined injectables 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.

We did computer searches to find randomized trials of combined injectable methods of birth control. We included studies that compared a combined injectable with another birth control method. The other method could be another injectable contraceptive, either combined or having only a progestin. The combined injectable 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 4 types of combined injectable methods. The combined methods required monthly injections. Four trials compared a combined injectable to 'depo', which has only a progestin. 'Depo' injections should be taken every three months. Five trials compared a combined injectable 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 IUD.

More women using combined injectables had normal bleeding than women using progestin-only injectables like 'depo.' Also, fewer women using combined injectables 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 2002). 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).

Little is known about the comparative efficacy and acceptability of combined injectable contraceptives. Hence, this review summarizes the randomized controlled trials that compared a combined injectable contraceptive with another contraceptive. 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 nine combination injectable formulations that were marketed at the time of this review:

- Dihydroxyprogesterone caproate 250 mg and estradiol valerate 5 mg
- 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
- Medroxyprogesterone acetate 25 mg and estradiol 3.5 mg
- Megestrol acetate 25 mg and estradiol 3.5 mg
- Norethisterone enanthate 50 mg and estradiol valerate 5 mg

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

We searched computerized databases from their inception to December 2007 for eligible trials using the following search strategies:
Cochrane Central Register of Controlled Trials (CENTRAL)
injectable AND contraception
MEDLINE via PubMed
The recommended generic search strategy for identifying randomized controlled trials with PubMed (Robinson 2002) combined with the terms:
((Acefil OR Agurin OR Anafertin OR Ciclofem OR Ciclofemina OR Ciclomes OR Ciclovular 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 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]))

EMBASE

(((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

(random* / blind* / placebo* / crossover*) & contraceptive agents & (inject* / Acefil / Agurin / Anafertin / Chinese injectable / Ciclofem / Ciclovar / Cicnor / Ciclofemina / Ciclomes / Ciclovular / Cliclovular / 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

(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]

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

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 4.2. We calculated the Peto odds ratios (OR) or weighted mean difference (WMD) with 95% confidence interval (CI) for each dichotomous or continuous outcome, respectively. Survival analysis estimates for method discontinuation were presented in the section 'Additional tables.' Some studies used 90-day reference periods for recording bleeding patterns, as described in 'Methodological quality of included studies.' If outcomes were reported for multiple reference periods, we reported the outcomes for the first and last reference periods only. 'Description of 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-effect models. The alpha-level was set at 0.10 since the chi-square 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

See: Characteristics of included studies; Characteristics of excluded 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; Hassan 1999; WHO 1997). Three of the trials were large (2252 to 2707 randomized women) and 12 treatment months in duration (Sang 1995; Hassan 1999; WHO 1988). 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).

Risk of bias in included studies

The trials were either open or did not describe any method of blinding. 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 concealing the allocation process. Six trials (WHO 1988; Indian Council 1990; Sang 1995; Cuong 1996; WHO 1997; Hassan 1999) excluded randomized women from the analysis for protocol violations, 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, one trial (Indian Council 1990) excluded women from two centers (N=222) from the analysis since the centers had poor follow-up rates.

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 (Mostafa 1994a; Sang 1995; Cuong 1996) used identical definitions for these summary measures, and two trials (WHO 1988; Simbar 2007) used similar definitions (see Characteristics of included studies table). The 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.

Effects of interventions

DMPA 25 mg plus E_2C 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.

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

Study ID	Measure	Discontinue reason	Study group	Rate	SE
Cuong 1996	1-yr life-table discontinuation rate	Overall	DMPA 25 mg / E2C 5 mg	25.7	2.5

Table 1. DMPA 25 mg / E2C 5 mg versus DMPA 150 mg (*Continued*)

			DMPA 150 mg	27.0	2.6
		Amenorrhea	DMPA 25 mg / E2C 5 mg	3.5	1.2
			DMPA 150 mg	7.8	1.6
		Prolonged bleeding	DMPA 25 mg / E2C 5 mg	1.2	0.7
			DMPA 150 mg	2.1	0.9
		Heavy and prolonged bleeding	DMPA 25 mg / E2C 5 mg	1.1	0.6
			DMPA 150 mg	2.4	1.0
		Irregular bleeding	DMPA 25 mg / E2C 5 mg	0.8	0.5
			DMPA 150 mg	0.8	0.6
		Spotting	DMPA 25 mg / E2C 5 mg	4.6	1.3
			DMPA 150 mg	10.0	1.8
		All bleeding problems	DMPA 25 mg / E2C 5 mg	7.4	1.6
			DMPA 150 mg	14.9	2.1
		Other medical reasons	DMPA 25 mg / E2C 5 mg	3.4	1.1
			DMPA 150 mg	2.2	0.9
		Other personal reasons	DMPA 25 mg / E2C 5 mg	10.0	1.8
			DMPA 150 mg	3.0	1.1
		Loss to follow-up	DMPA 25 mg / E2C 5 mg	1.0	0.6

Table 1. DMPA 25 mg / E2C 5 mg versus DMPA 150 mg (*Continued*)

			DMPA 150 mg	1.3	0.7

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 E $_2$ EN 10 mg versus DHPA 75 mg plus E $_2$ EN 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 E $_2$ V 5 mg versus DMPA 25 mg plus E $_2$ C 5 mg

Five trials compared the combination injectable contraceptive containing NET-EN plus E_2V to one with DMPA plus E_2C (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 the Sang 1995 trial. 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 (0.32; 95% CI 0.22 to 0.44) or prolonged bleeding (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 the Mostafa 1994a and Hassan 1999 trials (Table 2).

Table 2. NET-EN 50 mg / E2V 5 mg versus DMPA 25 mg / E2C 5 mg

Study ID	Measure	Discontinue reason	Study group	Rate	SE	Difference in rates	(95% CI)
Hassan 1999	Life-table discontinuation rate per 100 women-yrs	Overall	NET-EN 50 mg / E2V 5 mg	38.0	1.5	-0.9	
			DMPA 25 mg / E2C 5 mg	38.9	2.9		
		Pregnancy	NET-EN 50 mg / E2V 5 mg	0.4	0.2	0.2	
			DMPA 25 mg / E2C 5 mg	0.2	0.1		
		Amenorrhea	NET-EN 50 mg / E2V 5 mg	1.4	0.4	-1.3	
			DMPA 25 mg / E2C 5 mg	2.7	0.6		
		Heavy bleeding	NET-EN 50 mg / E2V 5 mg	1.9	0.5	0.6	
			DMPA 25 mg / E2C 5 mg	1.3	0.4		
		Prolonged bleeding	NET-EN 50 mg / E2V 5 mg	2.0	0.5	0.5	
			DMPA 25 mg / E2C 5 mg	1.5	0.4		
		Irregular bleeding	NET-EN 50 mg / E2V 5 mg	2.4	0.5	0.8	

Table 2. NET-EN 50 mg / E2V 5 mg versus DMPA 25 mg / E2C 5 mg (*Continued*)

			DMPA 25 mg / E2C 5 mg	1.6	0.4		
		Spotting	NET-EN 50 mg / E2V 5 mg	1.0	0.3	0.6	
			DMPA 25 mg / E2C 5 mg	0.4	0.2		
		All bleeding problems	NET-EN 50 mg / E2V 5 mg	11.5	1.1	4.1	
			DMPA 25 mg / E2C 5 mg	7.4	0.9		
		Other medical reasons	NET-EN 50 mg / E2V 5 mg	4.7	0.7	-3.1	
			DMPA 25 mg / E2C 5 mg	7.8	3.8		
		All personal reasons	NET-EN 50 mg / E2V 5 mg	12.8	1.1	0.4	
			DMPA 25 mg / E2C 5 mg	12.4	1.1		
		Loss to follow-up	NET-EN 50 mg / E2V 5 mg	2.7	0.6	-1.4	
			DMPA 25 mg / E2C 5 mg	4.1	0.7		
Mostafa 1994	Life-table discontinuation rate per 100 women-yrs	Overall	NET-EN 50 mg / E2V 5 mg	59.2	4.1	5.2	

Table 2. NET-EN 50 mg / E2V 5 mg versus DMPA 25 mg / E2C 5 mg (*Continued*)

			DMPA 25 mg / E2C 5 mg	54.0	5.0		
		Pregnancy	NET-EN 50 mg / E2V 5 mg	0.7	0.7	0.7	
			DMPA 25 mg / E2C 5 mg	0.0	0.0		
		Amenorrhea	NET-EN 50 mg / E2V 5 mg	3.5	2.0	-0.9	
			DMPA 25 mg / E2C 5 mg	4.4	1.9		
		Heavy bleeding	NET-EN 50 mg / E2V 5 mg	2.5	1.4	-0.3	
			DMPA 25 mg / E2C 5 mg	2.8	1.7		
		Prolonged bleeding	NET-EN 50 mg / E2V 5 mg	0.0	0.0	-1.5	
			DMPA 25 mg / E2C 5 mg	1.5	1.0		
		Irregular bleeding	NET-EN 50 mg / E2V 5 mg	6.3	2.6	4.5	
			DMPA 25 mg / E2C 5 mg	1.8	1.3		
		Spotting	NET-EN 50 mg / E2V 5 mg	0.8	0.8	0.8	
			DMPA 25 mg / E2C 5 mg	0.0	0.0		

Table 2. NET-EN 50 mg / E2V 5 mg versus DMPA 25 mg / E2C 5 mg (*Continued*)

		All bleeding problems	NET-EN 50 mg / E2V 5 mg	19.1	4.0	5.3	
			DMPA 25 mg / E2C 5 mg	13.8	3.3		
		Other medical reasons	NET-EN 50 mg / E2V 5 mg	15.9	3.7	-0.5	
			DMPA 25 mg / E2C 5 mg	16.4	6.4		
		All personal reasons	NET-EN 50 mg / E2V 5 mg	24.4	4.3	-0.4	
			DMPA 25 mg / E2C 5 mg	24.8	4.1		
		Loss to follow-up	NET-EN 50 mg / E2V 5 mg	14.9	3.7	4.7	
			DMPA 25 mg / E2C 5 mg	10.2	3.0		
WHO 1988	Life-table discontinuation rate per 100 women-yrs	Overall	NET-EN 50 mg / E2V 5 mg	36.8	1.5	1.3	(-2.6-5.4)
			DMPA 25 mg / E2C 5 mg	35.5	1.4		
		Pregnancy	NET-EN 50 mg / E2V 5 mg	0.2	0.1	0.2	(0.0-0.4)
			DMPA 25 mg / E2C 5 mg	0			

Table 2. NET-EN 50 mg / E2V 5 mg versus DMPA 25 mg / E2C 5 mg (*Continued*)

		Amenorrhea	NET-EN 50 mg / E2V 5 mg	1.6	0.4	-0.5	(-1.8-0.7)
			DMPA 25 mg / E2C 5 mg	2.1	0.5		
		Bleeding irregularities	NET-EN 50 mg / E2V 5 mg	7.5	0.9	1.2	(-1.1-3.5)
			DMPA 25 mg / E2C 5 mg	6.3	0.8		

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 E_2 V 5 mg versus NET-EN 200 mg

One trial (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 nonbleeding 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 E_2 V 5 mg versus copper IUD

One trial compared a combination NET-EN plus E_2V injectable contraceptive to a copper IUD (Von Kesseru 2000). 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 E_2C 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 E_2V 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 (Bahamondes 1997b) indicated that many women can be trained to self-administer a monthly injectable contraceptive.

Studies comparing two combination injectable contraceptives found that NET-EN 50 mg plus E_2V 5 mg resulted in less overall early discontinuation and less discontinuation due to amenorrhea or prolonged bleeding than DMPA 25 mg plus E_2C 5 mg. The NET-EN plus E_2V group also had more regular (cyclical) bleeding and fewer prolonged bleeding reference periods than the DMPA plus E_2C 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 (Sang 1995) conducted in China and the differences generally were not detected in the other populations studied.

The injectable contraceptive NET-EN 50 mg plus E_2V 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, while some women could perceive amenorrhea as a benefit of a contraceptive method, others could view it with concern 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 provider 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 other factors.

AUTHORS' CONCLUSIONS

Implications for practice

Combination injectable contraceptives (DMPA 25 mg plus E_2C 5 mg and NET-EN 50 mg plus E_2V 5 mg) led to more regular (cyclical) bleeding, less amenorrhea, and fewer infrequent bleeding patterns than the progestin-only injectables with which they were compared (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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REFERENCES

References to studies included in this review

Cuong 1996 *{published data only}*

Cuong DT, My Huong NT. Comparative phase III clinical trial of two injectable contraceptive preparations, depot-medroxyprogesterone acetate and Cyclofem, in Vietnamese women. *Contraception* 1996;**54**:169–79.

Hassan 1999 *{published data only}*

Hassan EO, el-Nahal N, el-Hussein M. Acceptability of the once-a-month injectable contraceptives Cyclofem and Mesigyna in Egypt. *Contraception* 1994;**49**:469–88.

* Hassan EO, el-Nahal N, el-Hussinie M. Once-a-month injectable contraceptives, Cyclofem and Mesigyna, in Egypt. Efficacy, causes of discontinuation, and side effects. *Contraception* 1999;**60**:87–92.

Indian Council 1990 *{published data only}*

Datey S, Gaur LN, Saxena BN. Vaginal bleeding patterns of women using different contraceptive methods (implants, injectables, IUDs, oral pills)--an Indian experience. An ICMR Task Force Study. Indian Council of Medical Research. *Contraception* 1995;**51**:155–65.

* Indian Council of Medical Research Task Force on Hormonal Contraception. A multicentre phase III comparative study of two hormonal contraceptive preparations NET-OEN (50 mg) + E2 valerate (5 mg) given every month and NET-OEN (200 mg) given every 2 months as intramuscular injection--a report of 12-month study. *Contraception* 1990;**42**:179–90.

Mostafa 1994a *{published data only}*

Mostafa SAM, Sayed GH, Abdel-Hamid A, Abdullah SA, Saddeek OB, Newton JR, et al.Clinical evaluation of two once-a-month injectable contraceptives; Cyclofem and Mesigyna. *Assiut Medical Journal* 1994;**18**:41–9.

Piya-Anant 1998 *{published data only}*

Piya-Anant M, Koetsawang S, Patrasupapong N, Dinchuen P, d'Arcangues C, Piaggio G, et al.Effectiveness of Cyclofem in the treatment of depot medroxyprogesterone acetate induced amenorrhea. *Contraception* 1998;**57**:23–8.

Recio 1986 *{published data only}*

Recio R, Garza-Flores J, Schiavon R, Reyes A, Diaz-Sanchez V, Valles V, et al.Pharmacodynamic assessment of dihydroxyprogesterone acetophenide plus estradiol enanthate as a monthly injectable contraceptive. *Contraception* 1986;**33**:579–89.

Ruminjo 2005 *{published data only}*

Ruminjo JK, Sekadde-Kigondu CB, Karanja JG, Rivera R, Nasution M, Nutley T. Comparative acceptability of combined and progestin-only injectable contraceptives in Kenya. *Contraception* 2005; **72**:138–45.

Sang 1995 *{published data only}*

Sang GW, Shao QX, Ge RS, Ge JL, Chen JK, Song S, et al.A multicentred phase III comparative clinical trial of Mesigyna, Cyclofem and Injectable No. 1 given by intramuscular injection to Chinese women. I. Contraceptive efficacy and side effects. *Contraception* 1995;**51**:167–83.

* Sang GW, Shao QX, Ge RS, Ge JL, Chen JK, Song S, et al.A multicentred phase III comparative clinical trial of Mesigyna, Cyclofem and Injectable No. 1 given by intramuscular injection to Chinese women. II. The comparison of bleeding patterns. *Contraception* 1995;**51**:185–92.

Simbar 2007 *{published and unpublished data}*

Simbar M, Tehrani FR, Hashemi Z, Zham H, Fraser IS. A comparative study of Cyclofem® and depot medroxyprogesterone acetate (DMPA) effects on endometrial vasculature. *Journal of Family Planning and Reproductive Health Care* 2007;**33**:271–6.

Von Kesseru 2000 *{published only}*

von Kesseru E, Etchepareborda JJ, Wikinski R, Beier S. Premenopause contraception with monthly injectable Mesigyna with special emphasis on serum lipid and bone density patterns. *Contraception* 2000;**61**:317–22.

WHO 1988 *{published only}*

Gómez Alzugaray M, Romeo Gallardo J, Hernández ML, Mojena ML. Efficiency of two injectable contraceptives (cycloprovera and HRP-102) monthly administered by intramuscular via. *Revista Cubana de Obstetricia y Ginecología* 1989;**15**:45–53.

Kazi AI. Comparative evaluation of two once-a-month contraceptive injections. *Journal of the Pakistan Medical Association* 1989;**39**:98–102.

Lang Prieto J, Casas Fernández JA, Pérez García M, Reina Hernández A, Bustillo Tur C. Comparative study of 2 injectable contraceptives administered in monthly doses: cycloprovera and HRP-102. *Revista Cubana de Obstetricia y Ginecología* 1993;**19**:53–63.

Santoso SSI, Affandi B. Efficacy, acceptability and side-effects of two once-a-month injectable contraceptives [Abstract]. *Advances in Contraception* 1990;**6**:264.

* World Health Organization. Task Force on Long-Acting Systemic Agents for Fertility Regulation. A multicentred phase III comparative study of two hormonal contraceptive preparations given once-a-month by intramuscular injection: I. Contraceptive efficacy and side effects. *Contraception* 1988;**37**:1–20.

World Health Organization Task Force on Long-Acting Systemic Agents for Fertility Regulation. A multicentred phase III comparative study of two hormonal contraceptive preparations given once-a-month by intramuscular injection. II. The comparison of bleeding patterns. *Contraception* 1989;**40**:531–51.

WHO 1997 *{published only}*

* United Nations Development Programme/United Nations Population Fund/World Health Organization/World Bank, Special Programme of Research, Development and Research Training in Human Reproduction. Comparative study of the effects of two once-a-month injectable steroidal contraceptives (Mesigyna and Cyclofem) on lipid and lipoprotein metabolism. *Contraception* 1997;**56**:193–207.

United Nations Development Programme/United Population Fund/World Health Organization/World Bank, Special Programme of Research, Development and Research Training in Human Reproduction, Task Force on Long-acting Systemic Agents for Fertility Regulation. Comparative study of the effects of two once-a-month injectable steroidal contraceptives (Mesigyna® and Cyclofem®) on glucose metabolism and liver function. *Contraception* 1998;**57**:71–81.

References to studies excluded from this review

Aedo 1985 *{published data only}*

Aedo AR, Landgren BM, Johannisson E, Diczfalusy E. Pharmacokinetic and pharmacodynamic investigations with monthly injectable contraceptive preparations. *Contraception* 1985;**31**:453–69.

Aly 1984 *{published data only}*

Aly FA, El-genedi MM, Toppozada HK, El-abd M, Loutfi I. Acceptability study of the two versus three monthly injectable contraceptives. *Population Studies* 1984;**11**:27–39.

Bassol 1995 *{published data only}*

Bassol S, Hernandez C, Nava MP, Trujillo AM, Luz de la Cruz D. A comparative study on the return to ovulation following chronic use of once-a-month injectable contraceptives. *Contraception* 1995;**51**: 307–11.

Baweja 1985 *{published data only}*

Baweja R, Bhattacharya SK, Choudhury SD, Krishna U, Manuel M, Phillips FS, et al.Indian Council of Medical Research. Task Force on Hormonal Contraception. Phase II randomized clinical trial with norethisterone oenanthate 50 mg alone and in combination with 5 mg or 2.5 mg of either estradiol valerate or cypionate as a monthly injectable contraceptive. *Contraception* 1985;**32**:383–94.

Benagiano 1995 *{published data only}*

Benagiano G, Bianchi P. Carbohydrate metabolism comparative study with the new injectable mesigyna and a three-phasic oral contraceptive [Abstract]. *Advances in Contraception* 1995;**11**:39.

Benagiano 1997 *{published data only}*

Benagiano G, Primiero FM, Bastianelli C, Bianchi P, Medda E. Comparative clinical evaluation of the effect on carbohydrate and lipid metabolism of two norethisterone-containing hormonal contraceptives: Mesigyna and TriNovum. *Contraception* 1997;**55**:295–300.

Brucker 2001 *{published data only}*

Brucker C. Controlled trial with a monthly combination injectable contraceptive in Europe. *Gynecological Endocrinology* 2001;**15**:11–4.

Coutinho 1997 *{published data only}*

Coutinho EM, Spinola P, Barbosa I, Gatto M, Tomaz G, Morais K, et al.Multicenter, double-blind, comparative clinical study on the efficacy and acceptability of a monthly injectable contraceptive combination of 150 mg dihydroxyprogesterone acetophenide and 10 mg estradiol enanthate compared to a monthly injectable contraceptive combination of 90 mg dihydroxyprogesterone acetophenide and 6 mg estradiol enanthate. *Contraception* 1997;**55**:175–81.

Coutinho 2006 *{published data only}*

Coutinho EM, Spinola P, Athayde C, Noronha CF, de Melo NR, Cabral ZAF, et al.Comparison of two regimens of a monthly injectable contraceptive containing dihydroxyprogesterone acetophenide and estradiol enanthate. *Contraception* 2006;**73**:249–52.

De Souza 1972 *{published data only}*

De Souza JC, Coutinho EM. Control of fertility by monthly injections of a mixture of norgestrel and a long-acting estrogen. A preliminary report. *Contraception* 1972;**5**:395–9.

Garza-Flores 1987 *{published data only}*

Garza-Flores J, Rodriguez V, Perez-Palacios G, Virutamasen P, Tang-Keow P, Konsayreepong R, et al.A multicentered pharmacokinetic, pharmacodynamic study of once-a-month injectable contraceptives. I. Different doses of HRP112 and of DepoProvera. World Health Organization Task Force on Long-acting Systemic Agents for Fertility Regulation. *Contraception* 1987;**36**:441–57.

Haiba 1989 *{published data only}*

Haiba NA, el-Habashy MA, Said SA, Darwish EA, Abdel-Sayed WS, Nayel SE. Clinical evaluation of two monthly injectable contraceptives and their effects on some metabolic parameters. *Contraception* 1989;**39**:619–32.

Jain 2000 *{published data only}*

Jain JK, Ota F, Mishell DR Jr. Comparison of ovarian follicular activity during treatment with a monthly injectable contraceptive and a low-dose oral contraceptive. *Contraception* 2000;**61**:195–8.

Karim 1971 *{published data only}*

Karim M, el-Mahgoub S. Conception control by cyclic injections of norethisterone enanthate and estradiol unducelate. *American Journal of Obstetrics and Gynecology* 1971;**110**:740–2.

Kesseru 1988 *{published data only}*

Kesseru E, Tozzini R. Monthly injectable contraception with norethisterone enanthate plus estradiol valerate. In: Runnebaum B, Rabe T, Kiesel L editor(s). *Female contraception: update and trends*. Berlin: Springer-Verlag, 1988:221–6.

Khalaf 1994 *{published data only}*

Khalaf AA, Mostafa SA, Sayed GH, Saddeek OB, Abdullah SA. Monthly injectable contraceptives: are they a valuable addition to the birth control cafeteria [abstract]. *British Journal of Obstetrics and Gynaecology* 1994;**101**:269–74.

Meng 1990 *{published data only}*

Meng YX, Jiang HY, Chen AJ, Lu FY, Yang H, Zhang MY, et al.Hemostatic changes in women using a monthly injectable contraceptive for one year. *Contraception* 1990;**42**:455–66.

Mostafa 1994b *{published data only}*

Mostafa SAM, Abdel-Aleem H, Sayed GH, Abdullah SA, Saddeek OB, Newton JR, et al.Changes in serum lipids, lipoproteins and apolipoproteins during the use of two once-a-month injectable contraceptives; Cyclofem and Mesigyna. *Assiut Medical Journal* 1994; **18**:33–9.

Oyelola 1993 *{published data only}*

Oyelola OO. Fasting plasma lipids, lipoproteins and apolipoproteins in Nigerian women using combined oral and progestin-only injectable contraceptives. *Contraception* 1993;**47**:445–54.

Petta 2001 *{published data only}*

* Petta CA, Hays M, Brache V, Massai R, Hua Y, Alvarez-Sanchez F, et al.Delayed first injection of the once-a-month injectable contraceptive containing 25 mg medroxyprogesterone acetate and 5 mg estradiol-cypionate: effects on cervical mucus. *Contraception* 2001; **64**:363–8.

Petta CA, Hays M, Brache V, Massai R, Hua Y, Alvarez-Sanchez F, et al.Delayed first injection of the once-a-month injectable contraceptive containing 25 mg of medroxyprogesterone acetate and 5 mg of E(2)-cypionate: effects on ovarian function. *Fertility and Sterility* 2001;**75**:744–8.

Shulman 2001 *{published data only}*

Shulman LP. Controlled trial with a monthly combination injectable contraceptive in the USA. *Gynecological Endocrinology* 2001;**15**:15–8.

Werawatgoompa 1980 *{published data only}*

Werawatgoompa S, Vaivanijkul B, Leepipatpaiboon S, Channiyom K, Virutamasen P, Dusitsin N. The effect of injectable norethisterone oenanthate on ovarian hormones in Thai women. *Contraception* 1980;**21**:299–309.

WHO 2003 *{published data only}*

United Nations Development Programme/United Nations Population Fund/World Health Organization/World Bank Special Programme of Research, Development and Research Training in Human Reproduction, Task Force on Long-acting Systemic Agents for Fertility Regulation. Comparative study of the effects of two once-a-month injectable contraceptives (Cyclofem and Mesigyna) and one oral contraceptive (Ortho-Novum 1/35) on coagulation and fibrinolysis. *Contraception* 2003;**68**:159–76.

Additional references

Bahamondes 1997a

Bahamondes L, Lavin P, Ojeda G, Petta C, Diaz J, Maradiegue E, et al.Return of fertility after discontinuation of the once-a-month injectable contraceptive Cyclofem. *Contraception* 1997;**55**:307–10.

Bahamondes 1997b

Bahamondes L, Marchi NM, Nakagava HM, de Melo ML, Cristofoletti MdeL, Pellini E, et al.Self-administration with Uniject of the once-a-month injectable contraceptive Cyclofem. *Contraception* 1997;**56**:301–4.

Bassol 1994

Bassol S, Garza-Flores J. Review of ovulation return upon discontinuation of once-a-month injectable contraceptives. *Contraception* 1994;**49**:441–53.

Belsey 1986

Belsey EM, Machin D, d'Arcangues C. The analysis of vaginal bleeding patterns induced by fertility regulating methods. World Health Organization Special Programme of Research, Development and Research Training in Human Reproduction. *Contraception* 1986;**34**: 253–60.

Glasier 2003

Glasier AF, Smith KB, van der Spuy ZM, Ho PC, Cheng L, Dada K, et al.Amenorrhea associated with contraception-an international study on acceptability. *Contraception* 2003;**67**:1–8.

Goldberg 2007

Goldberg AB, Grimes DA. Injectable contraceptives. In: Hatcher RA, Trussell J, Nelson AL, Cates W, Stewart F, Kowal D editor(s). *Contraceptive Technology*. 19th Edition. New York: Ardent Media, Inc., 2007:157–179.

IPPF 2002

IPPF Directory of Hormonal Contraceptives. Available at http://contraceptive.ippf.org. Accessed September 2003.

Kaunitz 2000

Kaunitz AM. Injectable contraception. New and existing options. *Obstetrics and Gynecology Clinics of North America* 2000;**27**:741–80.

Kaunitz 2001

Kaunitz AM. Lunelle monthly injectable contraceptive. An effective, safe, and convenient new birth control option. *Archives of Gynecology and Obstetrics* 2001;**265**:119–23.

Koetsawang 1994

Koetsawang S. Once-a-month injectable contraceptives: efficacy and reasons for discontinuation. *Contraception* 1994;**49**:387–98.

Maderas 2007

Monastersky Maderas NJ, Landau SC. Pharmacy and clinic partnerships to expand access to injectable contraception. *Journal of the American Pharmacists Association (2003)* 2007;**47**:527–31.

Newton 1994

Newton JR, d'Arcangues C, Hall PE. A review of "once-a-month" combined injectable contraceptives. *Journal of Obstetrics and Gynaecology* 1994;**14 Suppl (1)**:1–34.

Pardthaisong 1980

Pardthaisong T, Gray RH, McDaniel EB. Return of fertility after discontinuation of depot medroxyprogesterone acetate and intra-uterine devices in Northern Thailand. *Lancet* 1980;**1**:509–12.

PharmacyAccess 2005

Pharmacy Access Partnership. Injectable Contraceptive (IC) Program. www.pharmacyaccess.org/ICProgram.htm (accessed 30 March 2005).

Robinson 2002

Robinson KA, Dickersin K. Development of a highly sensitive search strategy for the retrieval of reports of controlled trials using PubMed. *International Journal of Epidemiology* 2002;**31**:150–3.

Schwallie 1974

Schwallie PC, Assenzo JR. The effect of depo-medroxyprogesterone acetate on pituitary and ovarian function, and the return of fertility following its discontinuation: a review. *Contraception* 1974;**10**:181–202.

Stanback 2007

Stanback J, Mbonye AK, Bekiita M. Contraceptive injections by community health workers in Uganda: a nonrandomized community trial. *Bulletin of the World Health Organization* 2007;**85**:768–73.

* *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.
Interventions	Medroxyprogesterone acetate (DMPA) 25 mg / estradiol cypionate (E2C) 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	Allocation concealment method not described.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

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 E2C 5 mg given every 30 ±3 days versus NET-EN 50 mg and E2V 5 mg every 30 ±3 days

Hassan 1999 (*Continued*)

Outcomes	Discontinuation due to bleeding outcomes, pregnancy or other personal reasons.
Notes	Blinding not mentioned.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

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.
Interventions	NET-EN 50 mg / E2V 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 and allocation concealment methods 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

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

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.

Mostafa 1994a (*Continued*)

	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 / E2C 5 mg given every 30 ±3 days (N=150) versus NET-EN 50 mg / E2V 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 and allocation concealment methods not reported. Blinding not mentioned.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

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, though, was not a criterion for study participation.) Excluded pregnancy, lactation, certain diseases or conditions.
Interventions	DMPA 25 mg / E2C 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 and allocation concealment methods not reported.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

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 (E2EN) 10 mg given on days 1-5, 28 and 56 (N=9) versus DHPA 75 mg / E2EN 5 mg given on days 1-5, 28 and 56 (N=7).
Outcomes	Number of bleeding and spotting days following injection was sole bleeding outcome.
Notes	Randomization and allocation concealment methods not reported.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

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 (E2C) 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: 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 allocation concealment or blinding. No a priori sample size estimation. Losses to follow up: 15% in each group.

Risk of bias

Ruminjo 2005 (*Continued*)

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Sang 1995

Methods	15 sites in China. 12 treatment months. Randomization with random number tables. Allocation was not concealed.
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

Item	Authors' judgement	Description
Allocation concealment?	Unclear	D - 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.
Participants	68 healthy women, 18 to 39 years old, with regular menstrual cycles and seeking long-term contraception.

Simbar 2007 (*Continued*)

Interventions	Medroxyprogesterone acetate (MPA) 25 mg / estradiol cypionate (E2C) 5 mg injected monthly versus DMPA 150 mg injected every 3 months.
Outcomes	Number of bleeding and spotting days per 3-mo 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 allocation concealment or 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

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

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 / E2V 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	Allocation concealment method not described.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

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. 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 / E2V 5 mg given every 30 ±3 days versus DMPA 25 mg / E2C 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

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

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.

WHO 1997 (*Continued*)

Interventions	NET-EN 50 mg / E2V 5 mg given every 30 days versus DMPA 25 mg / E2C 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	Allocation concealment method not described. Blinding not mentioned. Excluded 13 women (3.5%) from the analysis, 10 of whom were excluded for protocol violations.

Risk of bias

Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	B - Unclear

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

Aedo 1985	Not a randomized controlled trial.
Aly 1984	Compared two progestin-only contraceptives.
Bassol 1995	Not a randomized controlled trial.
Baweja 1985	Compared one marketed to three unmarketed combination injectable contraceptives. A fifth (progestin-only) group was not randomized.
Benagiano 1995	Did not report relevant outcome data.
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.
Coutinho 2006	Study compared two different regimens of administering the same hormonal combination.
De Souza 1972	Single-arm trial.
Garza-Flores 1987	Did not report relevant outcome data.
Haiba 1989	Article does not mention randomization. Author did not respond to request for information regarding study design.
Jain 2000	Did not report relevant outcome data.
Karim 1971	Compared two unmarketed combination injectable contraceptives.
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.
Oyelola 1993	Not a randomized controlled trial.
Petta 2001	Compared day in menstrual cycle for administering combination injectable contraceptive.
Shulman 2001	Not a randomized controlled trial.

(*Continued*)

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]
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]

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]

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]

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]
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]
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]

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]
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]

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

Review: Combination injectable contraceptives for contraception

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

Outcome: 1 Discontinuation - overall at 6 months

Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
Piya-Anant 1998	7/50	0/50		100.0 %	8.41 [1.82, 38.77]
Total (95% CI)	**50**	**50**		**100.0 %**	**8.41 [1.82, 38.77]**
Total events: 7 (Treatment), 0 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.73 (P = 0.0063)					

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

Review: Combination injectable contraceptives for contraception

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

Outcome: 2 Discontinuation - overall at 12 months

Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
Ruminjo 2005	71/180	40/180		100.0 %	2.24 [1.43, 3.50]
Total (95% CI)	**180**	**180**		**100.0 %**	**2.24 [1.43, 3.50]**
Total events: 71 (Treatment), 40 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 3.53 (P = 0.00041)					

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

Review: Combination injectable contraceptives for contraception

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

Outcome: 3 Discontinuation - amenorrhea

Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
Piya-Anant 1998	1/50	0/50		100.0 %	7.39 [0.15, 372.38]
Total (95% CI)	**50**	**50**		**100.0 %**	**7.39 [0.15, 372.38]**
Total events: 1 (Treatment), 0 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.00 (P = 0.32)					

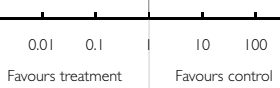
Analysis 1.4. Comparison 1 DMPA 25 mg / E2C 5 mg versus DMPA 150 mg, Outcome 4 Discontinuation - menstrual changes.

Review: Combination injectable contraceptives for contraception

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

Outcome: 4 Discontinuation - menstrual 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
Ruminjo 2005	10/180	5/180		100.0 %	2.00 [0.71, 5.62]
Total (95% CI)	**180**	**180**		**100.0 %**	**2.00 [0.71, 5.62]**
Total events: 10 (Treatment), 5 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.32 (P = 0.19)					



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

Review: Combination injectable contraceptives for contraception

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

Outcome: 5 Discontinuation - non-menstrual medical reasons

Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
Ruminjo 2005	11/180	5/180		100.0 %	2.19 [0.80, 5.95]
Total (95% CI)	**180**	**180**		**100.0 %**	**2.19 [0.80, 5.95]**
Total events: 11 (Treatment), 5 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.53 (P = 0.13)					

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

Review: Combination injectable contraceptives for contraception

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

Outcome: 6 Amenorrhea - any time during 6-month study

Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
Piya-Anant 1998	5/49	41/50		100.0 %	0.06 [0.03, 0.13]
Total (95% CI)	**49**	**50**		**100.0 %**	**0.06 [0.03, 0.13]**
Total events: 5 (Treatment), 41 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 7.12 (P < 0.00001)					

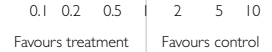
Analysis 1.7. Comparison 1 DMPA 25 mg / E2C 5 mg versus DMPA 150 mg, Outcome 7 Amenorrhea - first reference period.

Review: Combination injectable contraceptives for contraception

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

Outcome: 7 Amenorrhea - first reference period

Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
Cuong 1996	7/274	26/287		32.4 %	0.31 [0.15, 0.63]
Ruminjo 2005	22/132	80/148		67.6 %	0.20 [0.12, 0.33]
Total (95% CI)	**406**	**435**		**100.0 %**	**0.23 [0.15, 0.34]**
Total events: 29 (Treatment), 106 (Control)					
Heterogeneity: Chi^2 = 1.00, df = 1 (P = 0.32); I^2 =0.0%					
Test for overall effect: Z = 7.19 (P < 0.00001)					



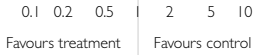
Analysis 1.8. Comparison 1 DMPA 25 mg / E2C 5 mg versus DMPA 150 mg, Outcome 8 Infrequent bleeding - first reference period.

Review: Combination injectable contraceptives for contraception

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

Outcome: 8 Infrequent bleeding - first reference period

Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
Cuong 1996	16/274	84/287		100.0 %	0.20 [0.13, 0.31]
Total (95% CI)	**274**	**287**		**100.0 %**	**0.20 [0.13, 0.31]**
Total events: 16 (Treatment), 84 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 7.24 (P < 0.00001)					



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

Review: Combination injectable contraceptives for contraception

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

Outcome: 9 Frequent bleeding - first reference period

Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
Cuong 1996	11/274	10/287		100.0 %	1.16 [0.48, 2.77]
Total (95% CI)	**274**	**287**		**100.0 %**	**1.16 [0.48, 2.77]**
Total events: 11 (Treatment), 10 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.33 (P = 0.74)					

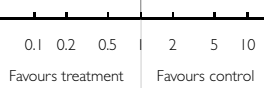
Analysis 1.10. Comparison 1 DMPA 25 mg / E2C 5 mg versus DMPA 150 mg, Outcome 10 Prolonged bleeding - first reference period.

Review: Combination injectable contraceptives for contraception

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

Outcome: 10 Prolonged bleeding - first reference period

Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
Cuong 1996	39/274	98/287		100.0 %	0.34 [0.23, 0.50]
Total (95% CI)	**274**	**287**		**100.0 %**	**0.34 [0.23, 0.50]**
Total events: 39 (Treatment), 98 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 5.48 (P < 0.00001)					



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

Review: Combination injectable contraceptives for contraception

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

Outcome: 11 Irregular bleeding - first reference period

Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
Cuong 1996	84/274	96/287		100.0 %	0.88 [0.62, 1.25]
Total (95% CI)	**274**	**287**		**100.0 %**	**0.88 [0.62, 1.25]**
Total events: 84 (Treatment), 96 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.71 (P = 0.48)					

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

Review: Combination injectable contraceptives for contraception

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

Outcome: 12 Normal bleeding - first reference period

Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
Cuong 1996	143/274	47/287		100.0 %	4.93 [3.48, 7.00]
Total (95% CI)	**274**	**287**		**100.0 %**	**4.93 [3.48, 7.00]**

Total events: 143 (Treatment), 47 (Control)

Heterogeneity: not applicable

Test for overall effect: Z = 8.95 (P < 0.00001)

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

Review: Combination injectable contraceptives for contraception

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

Outcome: 13 Amenorrhea - fourth reference period

Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
Cuong 1996	9/213	114/208		65.5 %	0.09 [0.06, 0.13]
Ruminjo 2005	16/79	77/109		34.5 %	0.13 [0.08, 0.24]
Total (95% CI)	**292**	**317**		**100.0 %**	**0.10 [0.07, 0.14]**

Total events: 25 (Treatment), 191 (Control)

Heterogeneity: Chi^2 = 1.43, df = 1 (P = 0.23); I^2 =30%

Test for overall effect: Z = 13.22 (P < 0.00001)

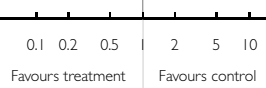
Analysis 1.14. Comparison 1 DMPA 25 mg / E2C 5 mg versus DMPA 150 mg, Outcome 14 Infrequent bleeding - fourth reference period.

Review: Combination injectable contraceptives for contraception

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

Outcome: 14 Infrequent bleeding - fourth reference period

Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
Cuong 1996	19/213	35/208		100.0 %	0.49 [0.28, 0.87]
Total (95% CI)	**213**	**208**		**100.0 %**	**0.49 [0.28, 0.87]**
Total events: 19 (Treatment), 35 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.42 (P = 0.015)					



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

Review: Combination injectable contraceptives for contraception

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

Outcome: 15 Frequent bleeding - fourth reference period

Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
Cuong 1996	3/213	1/208		100.0 %	2.67 [0.37, 19.12]
Total (95% CI)	**213**	**208**		**100.0 %**	**2.67 [0.37, 19.12]**
Total events: 3 (Treatment), 1 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.98 (P = 0.33)					

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

Review: Combination injectable contraceptives for contraception

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

Outcome: 16 Prolonged bleeding - fourth reference period

Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
Cuong 1996	9/213	2/208		100.0 %	3.60 [1.09, 11.89]
Total (95% CI)	**213**	**208**		**100.0 %**	**3.60 [1.09, 11.89]**
Total events: 9 (Treatment), 2 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.10 (P = 0.036)					

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

Review: Combination injectable contraceptives for contraception

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

Outcome: 17 Irregular bleeding - fourth reference period

Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
Cuong 1996	28/213	10/208		100.0 %	2.75 [1.41, 5.36]
Total (95% CI)	**213**	**208**		**100.0 %**	**2.75 [1.41, 5.36]**
Total events: 28 (Treatment), 10 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.98 (P = 0.0029)					

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

Review: Combination injectable contraceptives for contraception

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

Outcome: 18 Normal bleeding - fourth reference period

Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
Cuong 1996	150/213	52/208		100.0 %	6.14 [4.19, 9.00]
Total (95% CI)	**213**	**208**		**100.0 %**	**6.14 [4.19, 9.00]**
Total events: 150 (Treatment), 52 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 9.32 (P < 0.00001)					

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

Review: Combination injectable contraceptives for contraception

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

Outcome: 19 Bleeding > 5 days - first reference period

Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
Ruminjo 2005	40/132	28/148		100.0 %	1.85 [1.07, 3.20]
Total (95% CI)	**132**	**148**		**100.0 %**	**1.85 [1.07, 3.20]**
Total events: 40 (Treatment), 28 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.21 (P = 0.027)					

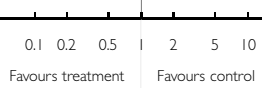
Analysis 1.20. Comparison 1 DMPA 25 mg / E2C 5 mg versus DMPA 150 mg, Outcome 20 Bleeding > 5 days - fourth reference period.

Review: Combination injectable contraceptives for contraception

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

Outcome: 20 Bleeding > 5 days - fourth reference period

Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
Ruminjo 2005	29/79	10/109		100.0 %	5.29 [2.59, 10.78]
Total (95% CI)	**79**	**109**		**100.0 %**	**5.29 [2.59, 10.78]**
Total events: 29 (Treatment), 10 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 4.58 (P < 0.00001)					



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.

Review: Combination injectable contraceptives for contraception

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

Outcome: 21 Intermenstrual bleeding, moderate or severe - first reference period

Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
Ruminjo 2005	0/132	7/148		100.0 %	0.14 [0.03, 0.65]
Total (95% CI)	**132**	**148**		**100.0 %**	**0.14 [0.03, 0.65]**
Total events: 0 (Treatment), 7 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.53 (P = 0.012)					

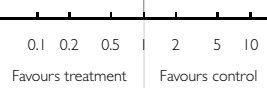
Analysis 1.22. Comparison 1 DMPA 25 mg / E2C 5 mg versus DMPA 150 mg, Outcome 22 Intermenstrual bleeding, moderate or severe - fourth reference period.

Review: Combination injectable contraceptives for contraception

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

Outcome: 22 Intermenstrual bleeding, moderate or severe - fourth reference period

Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
Ruminjo 2005	3/79	10/109		100.0 %	0.44 [0.14, 1.36]
Total (95% CI)	**79**	**109**		**100.0 %**	**0.44 [0.14, 1.36]**
Total events: 3 (Treatment), 10 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.43 (P = 0.15)					



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.

Review: Combination injectable contraceptives for contraception

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

Outcome: 23 Mean days of bleeding and spotting - first reference period

Study or subgroup	Treatment N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Simbar 2007	20	22 (14)	23	28 (23)		100.0 %	-6.00 [-17.22, 5.22]
Total (95% CI)	**20**		**23**			**100.0 %**	**-6.00 [-17.22, 5.22]**
Heterogeneity: not applicable							
Test for overall effect: Z = 1.05 (P = 0.29)							

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.

Review: Combination injectable contraceptives for contraception

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

Outcome: 24 Mean days of bleeding and spotting - second reference period

Study or subgroup	Treatment N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Simbar 2007	20	16 (9)	23	18 (12)		100.0 %	-2.00 [-8.29, 4.29]
Total (95% CI)	**20**		**23**			**100.0 %**	**-2.00 [-8.29, 4.29]**

Heterogeneity: not applicable

Test for overall effect: Z = 0.62 (P = 0.53)

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

Review: Combination injectable contraceptives for contraception

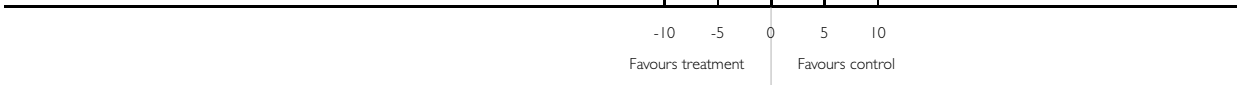
Comparison: 1 DMPA 25 mg / E2C 5 mg versus DMPA 150 mg

Outcome: 25 Weight gain (kg)

Study or subgroup	Treatment N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Cuong 1996	223	1.1 (2.2)	219	1.3 (2.4)		100.0 %	-0.20 [-0.63, 0.23]
Total (95% CI)	**223**		**219**			**100.0 %**	**-0.20 [-0.63, 0.23]**

Heterogeneity: not applicable

Test for overall effect: Z = 0.91 (P = 0.36)



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

Review: Combination injectable contraceptives for contraception

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

Outcome: 26 Intention to continue method at study end

Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
Piya-Anant 1998	45/50	17/50		100.0 %	10.52 [4.71, 23.49]
Total (95% CI)	**50**	**50**		**100.0 %**	**10.52 [4.71, 23.49]**
Total events: 45 (Treatment), 17 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 5.74 (P < 0.00001)					

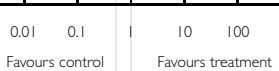
Analysis 1.27. Comparison 1 DMPA 25 mg / E2C 5 mg versus DMPA 150 mg, Outcome 27 Experience with study method: very favorable or somewhat favorable.

Review: Combination injectable contraceptives for contraception

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

Outcome: 27 Experience with study method: very favorable or somewhat favorable

Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
Ruminjo 2005	133/153	143/153		100.0 %	0.48 [0.23, 1.02]
Total (95% CI)	**153**	**153**		**100.0 %**	**0.48 [0.23, 1.02]**
Total events: 133 (Treatment), 143 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.92 (P = 0.055)					

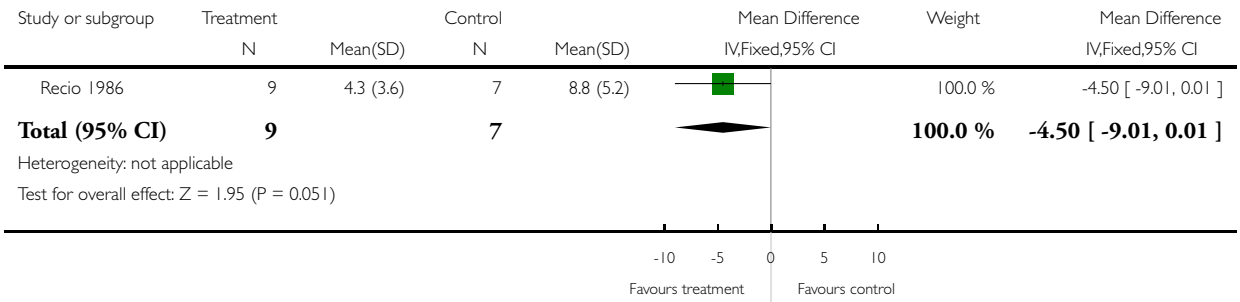


Analysis 2.1. Comparison 2 DHPA 150 mg / E2EN 10 mg versus DHPA 75 mg / E2EN 5 mg, Outcome 1 Bleeding or spotting days after third injection.

Review: Combination injectable contraceptives for contraception

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

Outcome: 1 Bleeding or spotting days after third injection

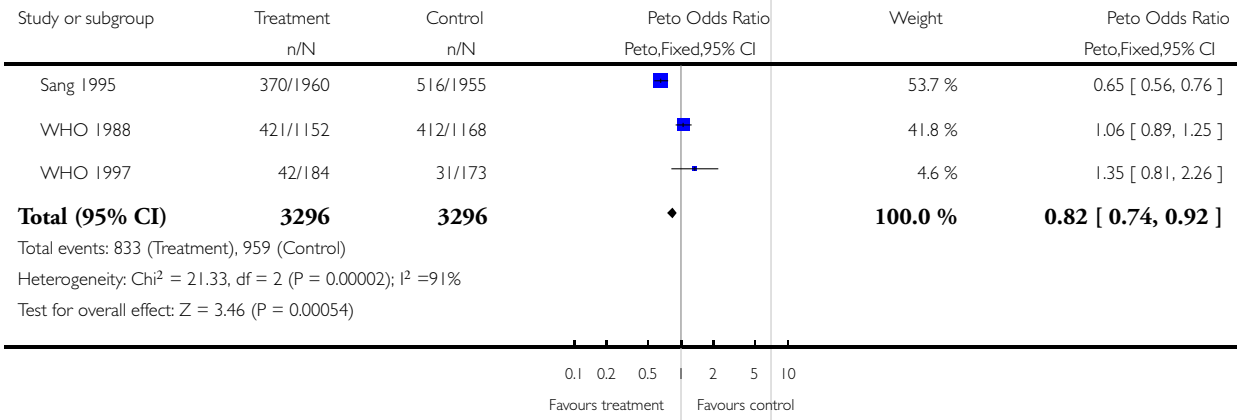


Analysis 3.1. Comparison 3 NET-EN 50 mg / E2V 5 mg versus DMPA 25 mg / E2C 5 mg, Outcome 1 Discontinuation - overall.

Review: Combination injectable contraceptives for contraception

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.

Review: Combination injectable contraceptives for contraception

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

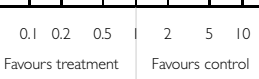
Outcome: 2 Discontinuation - pregnancy

Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
Sang 1995	6/1960	3/1955		81.8 %	1.95 [0.53, 7.20]
WHO 1988	2/1152	0/1168		18.2 %	7.50 [0.47, 119.97]
Total (95% CI)	**3112**	**3123**		**100.0 %**	**2.49 [0.76, 8.12]**

Total events: 8 (Treatment), 3 (Control)

Heterogeneity: $Chi^2 = 0.74$, df = 1 (P = 0.39); $I^2 = 0.0\%$

Test for overall effect: Z = 1.51 (P = 0.13)



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

Review: Combination injectable contraceptives for contraception

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

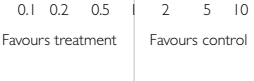
Outcome: 3 Discontinuation - amenorrhea

Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
Sang 1995	14/1960	87/1955		73.0 %	0.23 [0.15, 0.34]
WHO 1988	16/1152	21/1168		27.0 %	0.77 [0.40, 1.48]
Total (95% CI)	**3112**	**3123**		**100.0 %**	**0.32 [0.22, 0.44]**

Total events: 30 (Treatment), 108 (Control)

Heterogeneity: $Chi^2 = 9.98$, df = 1 (P = 0.002); $I^2 = 90\%$

Test for overall effect: Z = 6.71 (P < 0.00001)



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

Review: Combination injectable contraceptives for contraception

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

Outcome: 4 Discontinuation - heavy 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
Sang 1995	8/1960	17/1955		61.0 %	0.48 [0.22, 1.06]
WHO 1988	10/1152	6/1168		39.0 %	1.68 [0.63, 4.48]
Total (95% CI)	**3112**	**3123**		**100.0 %**	**0.79 [0.42, 1.45]**

Total events: 18 (Treatment), 23 (Control)

Heterogeneity: Chi^2 = 3.75, df = 1 (P = 0.05); I^2 =73%

Test for overall effect: Z = 0.77 (P = 0.44)

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

Review: Combination injectable contraceptives for contraception

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

Outcome: 5 Discontinuation - prolonged 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
Sang 1995	48/1960	74/1955		73.2 %	0.64 [0.45, 0.92]
WHO 1988	18/1152	26/1168		26.8 %	0.70 [0.39, 1.27]
Total (95% CI)	**3112**	**3123**		**100.0 %**	**0.66 [0.48, 0.90]**

Total events: 66 (Treatment), 100 (Control)

Heterogeneity: Chi^2 = 0.06, df = 1 (P = 0.81); I^2 =0.0%

Test for overall effect: Z = 2.66 (P = 0.0077)

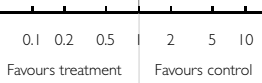
Analysis 3.6. Comparison 3 NET-EN 50 mg / E2V 5 mg versus DMPA 25 mg / E2C 5 mg, Outcome 6 Discontinuation - irregular bleeding.

Review: Combination injectable contraceptives for contraception

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

Outcome: 6 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
Sang 1995	31/1960	36/1955		76.0 %	0.86 [0.53, 1.39]
WHO 1988	13/1152	8/1168		24.0 %	1.64 [0.69, 3.87]
Total (95% CI)	**3112**	**3123**		**100.0 %**	**1.00 [0.66, 1.53]**
Total events: 44 (Treatment), 44 (Control)					
Heterogeneity: Chi^2 = 1.66, df = 1 (P = 0.20); I^2 =40%					
Test for overall effect: Z = 0.01 (P = 0.99)					



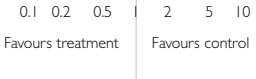
Analysis 3.7. Comparison 3 NET-EN 50 mg / E2V 5 mg versus DMPA 25 mg / E2C 5 mg, Outcome 7 Discontinuation - spotting.

Review: Combination injectable contraceptives for contraception

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

Outcome: 7 Discontinuation - spotting

Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
Sang 1995	14/1960	18/1955		74.4 %	0.78 [0.39, 1.55]
WHO 1988	7/1152	4/1168		25.6 %	1.75 [0.54, 5.73]
Total (95% CI)	**3112**	**3123**		**100.0 %**	**0.96 [0.52, 1.74]**
Total events: 21 (Treatment), 22 (Control)					
Heterogeneity: Chi^2 = 1.36, df = 1 (P = 0.24); I^2 =26%					
Test for overall effect: Z = 0.15 (P = 0.88)					



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.

Review: Combination injectable contraceptives for contraception

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

Outcome: 8 Discontinuation - other bleeding problems

Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
Sang 1995	15/1960	29/1955		75.8 %	0.52 [0.29, 0.95]
WHO 1988	7/1152	7/1168		24.2 %	1.01 [0.35, 2.90]
Total (95% CI)	**3112**	**3123**		**100.0 %**	**0.62 [0.37, 1.03]**
Total events: 22 (Treatment), 36 (Control)					
Heterogeneity: Chi^2 = 1.15, df = 1 (P = 0.28); I^2 =13%					
Test for overall effect: Z = 1.84 (P = 0.065)					

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.

Review: Combination injectable contraceptives for contraception

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

Outcome: 9 Discontinuation - any bleeding problem

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 1997	10/184	5/173		100.0 %	1.88 [0.67, 5.28]
Total (95% CI)	**184**	**173**		**100.0 %**	**1.88 [0.67, 5.28]**
Total events: 10 (Treatment), 5 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.20 (P = 0.23)					

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.

Review: Combination injectable contraceptives for contraception

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

Outcome: 10 Discontinuation - other medical reason

Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
Sang 1995	64/1960	58/1955		47.8 %	1.10 [0.77, 1.58]
WHO 1988	63/1152	62/1168		47.9 %	1.03 [0.72, 1.48]
WHO 1997	6/184	5/173		4.3 %	1.13 [0.34, 3.76]
Total (95% CI)	**3296**	**3296**		**100.0 %**	**1.07 [0.83, 1.37]**

Total events: 133 (Treatment), 125 (Control)

Heterogeneity: Chi^2 = 0.08, df = 2 (P = 0.96); I^2 =0.0%

Test for overall effect: Z = 0.53 (P = 0.59)

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.

Review: Combination injectable contraceptives for contraception

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

Outcome: 11 Discontinuation - other personal reason

Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
Sang 1995	89/1960	91/1955		44.0 %	0.97 [0.72, 1.31]
WHO 1988	131/1152	113/1168		56.0 %	1.20 [0.92, 1.56]
Total (95% CI)	**3112**	**3123**		**100.0 %**	**1.09 [0.90, 1.33]**

Total events: 220 (Treatment), 204 (Control)

Heterogeneity: Chi^2 = 1.02, df = 1 (P = 0.31); I^2 =2%

Test for overall effect: Z = 0.88 (P = 0.38)

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.

Review: Combination injectable contraceptives for contraception

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

Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
Sang 1995	51/1960	44/1955		27.7 %	1.16 [0.77, 1.74]
WHO 1988	132/1152	143/1168		72.3 %	0.93 [0.72, 1.19]
Total (95% CI)	**3112**	**3123**		**100.0 %**	**0.99 [0.80, 1.22]**

Total events: 183 (Treatment), 187 (Control)

Heterogeneity: Chi^2 = 0.84, df = 1 (P = 0.36); I^2 =0.0%

Test for overall effect: Z = 0.12 (P = 0.90)

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.

Review: Combination injectable contraceptives for contraception

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

Outcome: 13 Amenorrhea - first reference period

Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
Mostafa 1994a	2/125	0/140		19.9 %	8.40 [0.52, 135.58]
Sang 1995	0/902	3/903		30.0 %	0.14 [0.01, 1.30]
WHO 1988	2/1000	3/1000		50.0 %	0.67 [0.12, 3.87]
Total (95% CI)	**2027**	**2043**		**100.0 %**	**0.69 [0.20, 2.37]**

Total events: 4 (Treatment), 6 (Control)

Heterogeneity: Chi^2 = 5.09, df = 2 (P = 0.08); I^2 =61%

Test for overall effect: Z = 0.60 (P = 0.55)

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.

Review: Combination injectable contraceptives for contraception

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

Outcome: 14 Infrequent bleeding - first reference period

Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
Mostafa 1994a	6/128	8/140		10.5 %	0.81 [0.28, 2.38]
Sang 1995	5/902	30/903		27.2 %	0.23 [0.12, 0.46]
WHO 1988	29/1000	53/1000		62.3 %	0.54 [0.35, 0.85]
Total (95% CI)	**2030**	**2043**		**100.0 %**	**0.45 [0.32, 0.64]**

Total events: 40 (Treatment), 91 (Control)

Heterogeneity: Chi^2 = 5.56, df = 2 (P = 0.06); I^2 =64%

Test for overall effect: Z = 4.48 (P < 0.00001)

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.

Review: Combination injectable contraceptives for contraception

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

Outcome: 15 Frequent bleeding - first reference period

Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
Mostafa 1994a	6/128	1/143		2.2 %	4.85 [1.08, 21.75]
Sang 1995	70/902	45/903		34.2 %	1.59 [1.09, 2.32]
WHO 1988	134/1000	92/1000		63.6 %	1.52 [1.15, 2.00]
Total (95% CI)	**2030**	**2046**		**100.0 %**	**1.58 [1.27, 1.98]**

Total events: 210 (Treatment), 138 (Control)

Heterogeneity: Chi^2 = 2.22, df = 2 (P = 0.33); I^2 =10%

Test for overall effect: Z = 4.08 (P = 0.000045)

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.

Review: Combination injectable contraceptives for contraception

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

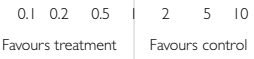
Outcome: 16 Prolonged bleeding - first reference period

Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
Mostafa 1994a	8/140	16/140		9.2 %	0.48 [0.21, 1.11]
Sang 1995	73/902	171/903		88.3 %	0.40 [0.30, 0.52]
WHO 1988	3/1000	3/1000		2.5 %	1.00 [0.20, 4.96]
Total (95% CI)	**2042**	**2043**		**100.0 %**	**0.41 [0.32, 0.53]**

Total events: 84 (Treatment), 190 (Control)

Heterogeneity: Chi^2 = 1.40, df = 2 (P = 0.50); I^2 =0.0%

Test for overall effect: Z = 6.85 (P < 0.00001)



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.

Review: Combination injectable contraceptives for contraception

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

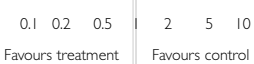
Outcome: 17 Irregular bleeding - first reference period

Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
Mostafa 1994a	21/127	35/140		7.1 %	0.60 [0.33, 1.08]
Sang 1995	141/902	176/903		41.7 %	0.77 [0.60, 0.98]
WHO 1988	167/1000	235/1000		51.2 %	0.65 [0.53, 0.82]
Total (95% CI)	**2029**	**2043**		**100.0 %**	**0.69 [0.59, 0.81]**

Total events: 329 (Treatment), 446 (Control)

Heterogeneity: Chi^2 = 1.14, df = 2 (P = 0.57); I^2 =0.0%

Test for overall effect: Z = 4.56 (P < 0.00001)



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.

Review: Combination injectable contraceptives for contraception

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

Outcome: 18 Normal bleeding - first reference period

Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
Mostafa 1994a	82/150	78/140		7.2 %	0.96 [0.60, 1.52]
Sang 1995	575/902	374/903		44.9 %	2.45 [2.03, 2.94]
WHO 1988	628/1000	568/1000		47.9 %	1.28 [1.07, 1.53]
Total (95% CI)	**2052**	**2043**		**100.0 %**	**1.68 [1.48, 1.90]**

Total events: 1285 (Treatment), 1020 (Control)

Heterogeneity: Chi² = 30.32, df = 2 (P<0.00001); I² =93%

Test for overall effect: Z = 8.21 (P < 0.00001)

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.

Review: Combination injectable contraceptives for contraception

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

Outcome: 19 Amenorrhea - fourth reference period

Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
Mostafa 1994a	6/59	4/75		19.8 %	2.00 [0.55, 7.30]
Sang 1995	2/787	5/740		15.0 %	0.40 [0.09, 1.75]
WHO 1988	14/700	17/739		65.2 %	0.87 [0.43, 1.77]
Total (95% CI)	**1546**	**1554**		**100.0 %**	**0.91 [0.51, 1.62]**

Total events: 22 (Treatment), 26 (Control)

Heterogeneity: Chi² = 2.65, df = 2 (P = 0.27); I² =24%

Test for overall effect: Z = 0.32 (P = 0.75)

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.

Review: Combination injectable contraceptives for contraception

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

Outcome: 20 Infrequent bleeding - fourth reference period

Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
Mostafa 1994a	1/59	6/75		3.4 %	0.28 [0.06, 1.30]
Sang 1995	10/787	30/740		20.1 %	0.34 [0.18, 0.63]
WHO 1988	80/714	87/731		76.4 %	0.93 [0.68, 1.29]
Total (95% CI)	**1560**	**1546**		**100.0 %**	**0.73 [0.55, 0.97]**
Total events: 91 (Treatment), 123 (Control)					
Heterogeneity: Chi^2 = 9.59, df = 2 (P = 0.01); I^2 =79%					
Test for overall effect: Z = 2.19 (P = 0.029)					

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.

Review: Combination injectable contraceptives for contraception

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

Outcome: 21 Frequent bleeding - fourth reference period

Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
Mostafa 1994a	3/59	0/75		2.3 %	10.03 [1.01, 99.75]
Sang 1995	50/787	39/740		67.2 %	1.22 [0.79, 1.87]
WHO 1988	17/708	22/733		30.5 %	0.80 [0.42, 1.50]
Total (95% CI)	**1554**	**1548**		**100.0 %**	**1.12 [0.79, 1.60]**
Total events: 70 (Treatment), 61 (Control)					
Heterogeneity: Chi^2 = 4.75, df = 2 (P = 0.09); I^2 =58%					
Test for overall effect: Z = 0.65 (P = 0.51)					

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.

Review: Combination injectable contraceptives for contraception

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

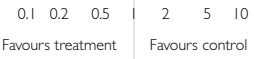
Outcome: 22 Prolonged bleeding - fourth reference period

Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
Mostafa 1994a	3/59	1/75		3.0 %	3.62 [0.49, 26.64]
Sang 1995	44/787	90/740		94.8 %	0.44 [0.31, 0.63]
WHO 1988	2/667	1/1000		2.2 %	3.04 [0.30, 30.66]
Total (95% CI)	**1513**	**1815**		**100.0 %**	**0.49 [0.35, 0.69]**

Total events: 49 (Treatment), 92 (Control)

Heterogeneity: Chi^2 = 6.60, df = 2 (P = 0.04); I^2 =70%

Test for overall effect: Z = 4.06 (P = 0.000050)



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.

Review: Combination injectable contraceptives for contraception

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

Outcome: 23 Irregular bleeding - fourth reference period

Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
Mostafa 1994a	14/59	14/75		7.4 %	1.36 [0.59, 3.13]
Sang 1995	26/787	55/740		26.0 %	0.44 [0.28, 0.69]
WHO 1988	117/713	118/728		66.6 %	1.01 [0.77, 1.34]
Total (95% CI)	**1559**	**1543**		**100.0 %**	**0.83 [0.66, 1.05]**

Total events: 157 (Treatment), 187 (Control)

Heterogeneity: Chi^2 = 11.04, df = 2 (P = 0.004); I^2 =82%

Test for overall effect: Z = 1.55 (P = 0.12)

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.

Review: Combination injectable contraceptives for contraception

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

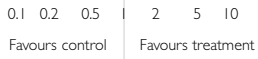
Outcome: 24 Normal bleeding - fourth reference period

Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
Mostafa 1994a	32/50	49/75		4.3 %	0.94 [0.45, 1.99]
Sang 1995	647/787	502/740		44.6 %	2.16 [1.71, 2.73]
WHO 1988	466/713	481/730		51.1 %	0.98 [0.79, 1.21]
Total (95% CI)	**1550**	**1545**		**100.0 %**	**1.39 [1.19, 1.62]**

Total events: 1145 (Treatment), 1032 (Control)

Heterogeneity: Chi^2 = 25.05, df = 2 (P<0.00001); I^2 =92%

Test for overall effect: Z = 4.16 (P = 0.000032)



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).

Review: Combination injectable contraceptives for contraception

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

Outcome: 25 Weight at 12th month (kg)

Study or subgroup	Treatment N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Mostafa 1994a	59	59.1 (11.2)	75	58 (11.4)		100.0 %	1.10 [-2.75, 4.95]
Total (95% CI)	**59**		**75**			**100.0 %**	**1.10 [-2.75, 4.95]**

Heterogeneity: not applicable

Test for overall effect: Z = 0.56 (P = 0.58)

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

Review: Combination injectable contraceptives for contraception

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

Outcome: 1 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
Indian Council 1990	186/423	152/426		100.0 %	1.41 [1.07, 1.86]
Total (95% CI)	**423**	**426**		**100.0 %**	**1.41 [1.07, 1.86]**
Total events: 186 (Treatment), 152 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.47 (P = 0.014)					

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

Review: Combination injectable contraceptives for contraception

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

Outcome: 2 Discontinuation - pregnancy

Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
Indian Council 1990	1/423	4/426		100.0 %	0.30 [0.05, 1.75]
Total (95% CI)	**423**	**426**		**100.0 %**	**0.30 [0.05, 1.75]**
Total events: 1 (Treatment), 4 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.34 (P = 0.18)					

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

Review: Combination injectable contraceptives for contraception

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

Outcome: 3 Discontinuation - amenorrhea

Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
Indian Council 1990	13/423	24/426		100.0 %	0.54 [0.28, 1.05]
Total (95% CI)	**423**	**426**		**100.0 %**	**0.54 [0.28, 1.05]**
Total events: 13 (Treatment), 24 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.83 (P = 0.068)					

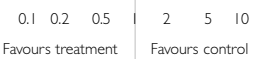
Analysis 4.4. Comparison 4 NET-EN 50 mg / E2V 5 mg versus NET-EN 200 mg, Outcome 4 Discontinuation - heavy and prolonged bleeding.

Review: Combination injectable contraceptives for contraception

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

Outcome: 4 Discontinuation - heavy and prolonged 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
Indian Council 1990	15/423	26/426		100.0 %	0.57 [0.31, 1.07]
Total (95% CI)	**423**	**426**		**100.0 %**	**0.57 [0.31, 1.07]**
Total events: 15 (Treatment), 26 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.74 (P = 0.082)					



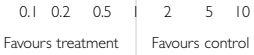
Analysis 4.5. Comparison 4 NET-EN 50 mg / E2V 5 mg versus NET-EN 200 mg, Outcome 5 Discontinuation - irregular bleeding or spotting.

Review: Combination injectable contraceptives for contraception

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

Outcome: 5 Discontinuation - irregular bleeding or spotting

Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
Indian Council 1990	27/423	28/426		100.0 %	0.97 [0.56, 1.67]
Total (95% CI)	**423**	**426**		**100.0 %**	**0.97 [0.56, 1.67]**
Total events: 27 (Treatment), 28 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.11 (P = 0.91)					



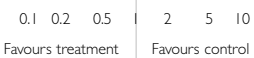
Analysis 4.6. Comparison 4 NET-EN 50 mg / E2V 5 mg versus NET-EN 200 mg, Outcome 6 Discontinuation - other medical reasons.

Review: Combination injectable contraceptives for contraception

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

Outcome: 6 Discontinuation - other medical reasons

Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
Indian Council 1990	31/423	14/426		100.0 %	2.24 [1.23, 4.07]
Total (95% CI)	**423**	**426**		**100.0 %**	**2.24 [1.23, 4.07]**
Total events: 31 (Treatment), 14 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.63 (P = 0.0086)					



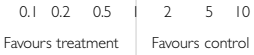
Analysis 4.7. Comparison 4 NET-EN 50 mg / E2V 5 mg versus NET-EN 200 mg, Outcome 7 Discontinuation - other personal reasons.

Review: Combination injectable contraceptives for contraception

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

Outcome: 7 Discontinuation - other personal reasons

Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
Indian Council 1990	60/423	33/426		100.0 %	1.93 [1.26, 2.97]
Total (95% CI)	**423**	**426**		**100.0 %**	**1.93 [1.26, 2.97]**
Total events: 60 (Treatment), 33 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 3.00 (P = 0.0027)					



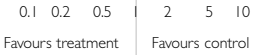
Analysis 4.8. Comparison 4 NET-EN 50 mg / E2V 5 mg versus NET-EN 200 mg, Outcome 8 Discontinuation - late for, or lost to, follow up.

Review: Combination injectable contraceptives for contraception

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

Outcome: 8 Discontinuation - late for, or lost to, follow up

Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
Indian Council 1990	39/423	23/426		100.0 %	1.76 [1.05, 2.95]
Total (95% CI)	**423**	**426**		**100.0 %**	**1.76 [1.05, 2.95]**
Total events: 39 (Treatment), 23 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.14 (P = 0.033)					



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

Review: Combination injectable contraceptives for contraception

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

Outcome: 9 Infrequent bleeding - first reference period

Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
Indian Council 1990	15/193	54/237		100.0 %	0.33 [0.20, 0.55]
Total (95% CI)	**193**	**237**		**100.0 %**	**0.33 [0.20, 0.55]**
Total events: 15 (Treatment), 54 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 4.21 (P = 0.000025)					

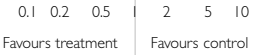
Analysis 4.10. Comparison 4 NET-EN 50 mg / E2V 5 mg versus NET-EN 200 mg, Outcome 10 Frequent bleeding - first reference period.

Review: Combination injectable contraceptives for contraception

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

Outcome: 10 Frequent bleeding - first reference period

Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
Indian Council 1990	15/193	27/237		100.0 %	0.66 [0.35, 1.26]
Total (95% CI)	**193**	**237**		**100.0 %**	**0.66 [0.35, 1.26]**
Total events: 15 (Treatment), 27 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.26 (P = 0.21)					



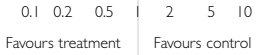
Analysis 4.11. Comparison 4 NET-EN 50 mg / E2V 5 mg versus NET-EN 200 mg, Outcome 11 Prolonged bleeding - first reference period.

Review: Combination injectable contraceptives for contraception

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

Outcome: 11 Prolonged bleeding - first reference period

Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
Indian Council 1990	5/193	6/237		100.0 %	1.02 [0.31, 3.41]
Total (95% CI)	**193**	**237**		**100.0 %**	**1.02 [0.31, 3.41]**
Total events: 5 (Treatment), 6 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.04 (P = 0.97)					



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

Review: Combination injectable contraceptives for contraception

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

Outcome: 12 Irregular bleeding - first reference period

Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
Indian Council 1990	57/193	81/237		100.0 %	0.81 [0.54, 1.21]
Total (95% CI)	**193**	**237**		**100.0 %**	**0.81 [0.54, 1.21]**
Total events: 57 (Treatment), 81 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.02 (P = 0.31)					

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

Review: Combination injectable contraceptives for contraception

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

Outcome: 13 Normal bleeding - first reference period

Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
Indian Council 1990	99/193	58/237		100.0 %	3.17 [2.14, 4.71]
Total (95% CI)	**193**	**237**		**100.0 %**	**3.17 [2.14, 4.71]**
Total events: 99 (Treatment), 58 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 5.74 (P < 0.00001)					

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

Review: Combination injectable contraceptives for contraception

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

Outcome: 14 Amenorrhea - fourth reference period

Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
Indian Council 1990	5/193	19/237		100.0 %	0.36 [0.16, 0.82]
Total (95% CI)	**193**	**237**		**100.0 %**	**0.36 [0.16, 0.82]**
Total events: 5 (Treatment), 19 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.44 (P = 0.015)					

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

Review: Combination injectable contraceptives for contraception

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

Outcome: 15 Infrequent bleeding - fourth reference period

Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
Indian Council 1990	56/193	97/237		100.0 %	0.60 [0.40, 0.89]
Total (95% CI)	**193**	**237**		**100.0 %**	**0.60 [0.40, 0.89]**
Total events: 56 (Treatment), 97 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.56 (P = 0.010)					

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

Review: Combination injectable contraceptives for contraception

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

Outcome: 16 Frequent bleeding - fourth reference period

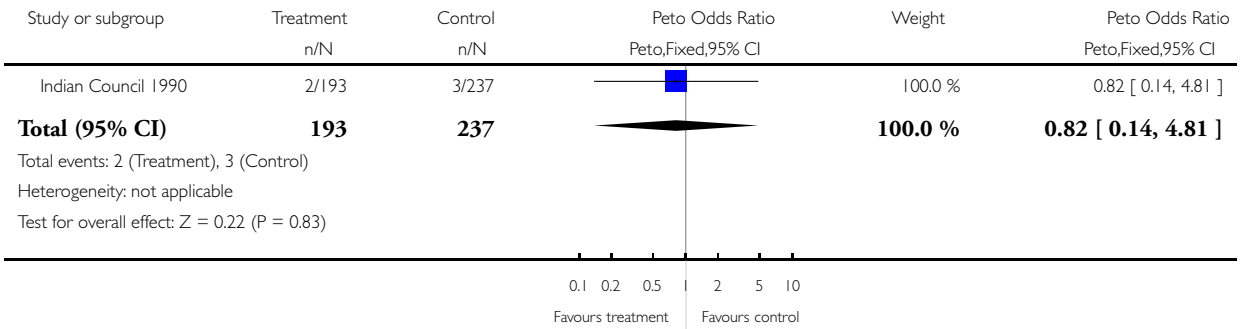
Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
Indian Council 1990	3/193	6/237		100.0 %	0.62 [0.17, 2.34]
Total (95% CI)	**193**	**237**		**100.0 %**	**0.62 [0.17, 2.34]**
Total events: 3 (Treatment), 6 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.70 (P = 0.48)					

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

Review: Combination injectable contraceptives for contraception

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

Outcome: 17 Prolonged bleeding - fourth reference period

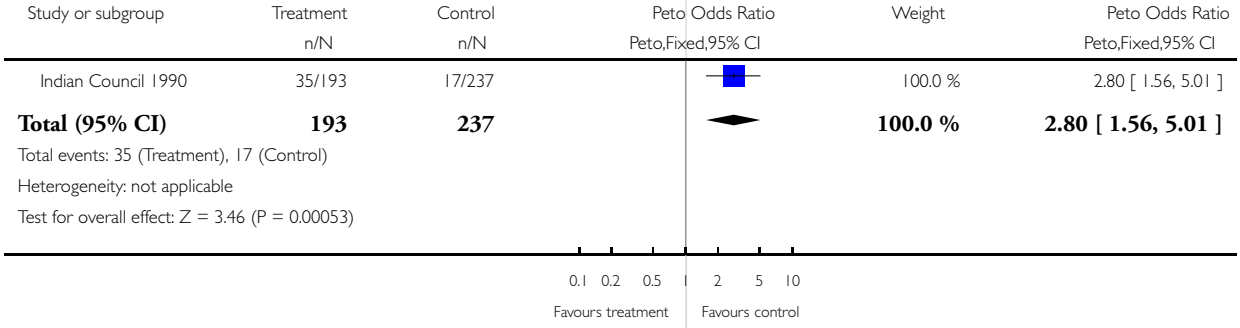


Analysis 4.18. Comparison 4 NET-EN 50 mg / E2V 5 mg versus NET-EN 200 mg, Outcome 18 Irregular bleeding - fourth reference period.

Review: Combination injectable contraceptives for contraception

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.

Review: Combination injectable contraceptives for contraception

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

Outcome: 19 Normal bleeding - fourth reference period

Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
Indian Council 1990	91/193	85/237		100.0 %	1.59 [1.08, 2.34]
Total (95% CI)	**193**	**237**		**100.0 %**	**1.59 [1.08, 2.34]**
Total events: 91 (Treatment), 85 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.36 (P = 0.018)					

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

Review: Combination injectable contraceptives for contraception

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

Outcome: 1 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
Von Kesseru 2000	10/49	4/99		100.0 %	6.67 [2.08, 21.41]
Total (95% CI)	**49**	**99**		**100.0 %**	**6.67 [2.08, 21.41]**
Total events: 10 (Treatment), 4 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 3.19 (P = 0.0014)					

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

Review: Combination injectable contraceptives for contraception

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

Outcome: 2 Pregnancy

Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
Von Kesseru 2000	0/49	3/99		100.0 %	0.22 [0.02, 2.47]
Total (95% CI)	**49**	**99**		**100.0 %**	**0.22 [0.02, 2.47]**
Total events: 0 (Treatment), 3 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.23 (P = 0.22)					

WHAT'S NEW

Last assessed as up-to-date: 27 January 2008.

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 and Simbar 2007). One new trial was excluded (Coutinho 2006).
23 January 2008	New search has been performed	The searches were updated in Dec 2007 and Jan 2008.

HISTORY

Protocol first published: Issue 1, 2004

Review first published: Issue 3, 2005

28 January 2008	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

Maria Gallo developed the idea, extracted the data for the original review, conducted the analyses, and wrote the initial review. David Grimes did the second data extraction. Catherine d'Arcangues consulted on the content of the review. Ken Schultz provided statistical consultation. Laureen Lopez extracted the primary data for the 2008 update, incorporated the results, and edited the review.

DECLARATIONS OF INTEREST

Dr. Grimes has consulted with or served on a speakers bureau for ALZA, Berlex Laboratories, Gynetics, GynoPharma, Mead Johnson, Organon, Ortho-McNeil, Parke-Davis, Pharmacia-Upjohn, Schering, Schmid, Searle and Wyeth-Ayerst.

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- National Institute of Child Health and Human Development, USA.
- U.S. Agency for International Development, USA.

INDEX TERMS

Medical Subject Headings (MeSH)

Algestone [administration & dosage]; Contraception [*methods]; Contraceptive Agents, Female [*administration & dosage; adverse effects]; Drug Combinations; Estradiol [administration & dosage]; Injections; Medication Adherence; Medroxyprogesterone [administration & dosage]; Megestrol Acetate [administration & dosage]; Norethindrone [administration & dosage]

MeSH check words

Female; Humans