Combination injectable contraceptives for contraception

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Compared with progestogen-only injectables, combination injectable contraceptives are associated with more regular bleeding patterns, lower risk of amenorrhea, and less likelihood of infrequent bleeding.

**RHL Commentary by Hassan EO and El-Gibaly OM**

1. INTRODUCTION

In under-resourced settings and in low-income countries, women usually prefer contraceptives that do not change the rhythm of their menstrual cycle. Both amenorrhea as well as infrequent, excessive, prolonged or irregular bleeding patterns are not acceptable. Amenorrhea raises the suspicion of pregnancy or induction of a menopausal state and bleeding may interfere with sexual relations and religious duties. For those reasons, many women in these settings choose combined contraceptive pills over progestogen-only injectable contraceptives, even though overall women express the desire for long-acting contraception. In under-resourced settings many women lack formal education and have problems complying with the requirement of taking the pill daily, resulting in irregular pill intake and a high contraceptive failure. Combined injectable contraceptives offer the advantage of preserving a regular bleeding pattern and there is no need to remember to take the pill daily. Thus, these methods have been considered to be an addition to the contraceptive choices available to those women. The most appropriate candidates for once-a-month injectable contraceptives are women who are satisfied with combined oral contraceptives pills, but are having problems with compliance.

The most important determinants of use discontinuation of once-a-month injectable contraceptives are young age, large family size, first time contraceptive use, previous experience with menstrual problems that led to termination of a previous method and poor quality of services (i.e. lack of appropriate counselling and social support) (1). The focus of this updated review (2) with two new trials is to assess efficacy, continuation rates, and side-effects of once-a-month combination injectables.

2. METHODS OF THE REVIEW

This is a systematic review of randomized controlled trials that compared a combination injectable to any other contraceptive method (e.g. a second combination injectable contraceptive, a progestogen-only injectable contraceptive, another hormonal contraceptive or a barrier method). The reviewers did a comprehensive search using standard search strategies to identify eligible randomized controlled trials in any language in the following electronic databases; Cochrane Central Register, MEDLINE, EMBASE, POPLINE, LILACS, AIM, IMEMR from the inception of each database to December 2007. They also
assessed the references listed in three review articles (3, 4, 5) and in eligible trial reports. Eligible combination injectable contraceptives were limited to nine formulations that were marketed at the time of this review: dihydroxyprogesterone caproate 250 mg and estradiol valerate 5 mg; dihydroxyprogesterone acetophenide (DHPA) (also known as algeston acetophenide or alfasona) 75 mg and estradiol enantate (E2EN) 5 mg; DHPA 120 mg and (E2EN) 10 mg; (DHPA) 150 mg and (E2-EN) 10 mg; DHPA 150 mg and estradiol benzoate 10 mg; medroxyprogesterone acetate (MPA) 25 mg and estradiol cypionate (E2C) 5 mg; MPA 25 mg and estradiol 3.5 mg; megestrol acetate 25 mg and estradiol 3.5 mg; and norethisterone enantate (NET-EN) 50 mg and estradiol valerate (E2V) 5 mg. The trials were limited to women in the reproductive age without contraindications to combination contraception use. Outcome measures sought were contraceptive efficacy, bleeding patterns, use continuation, user preferences, and side-effects (reported medical or social events that possibly were related to the study treatment).

The authors report that two authors independently extracted data from the eligible trials and the trial data were combined for meta-analysis only when identical drugs, dosages, and regimens had been compared in individual trials. Critical appraisal of the trial data was done by evaluating the potential for bias resulting from the study design, blinding, randomization method, group allocation concealment, and loss to follow up.

3. RESULTS OF THE REVIEW

Out of 35 identified studies, only 12 fulfilled the required eligibility criteria. Among those 12, several threats to validity were reported, notably that none of the trials reported a method of concealing the allocation process or blinding. In some the randomization process was minimally described, intention to treat was violated in 6 trials, there was up to 30% loss to follow-up in the sample of most of the trials, and bleeding patterns definitions were not standardized across all studies. The 12 available trials had evaluated four 'monthly combination injectable contraceptives', namely DMPA 25 mg plus E2C 5 mg, DHPA 150 mg plus E2EN10 mg, DHPA 75 mg and E2EN 5 mg, and NET-EN 50 mg plus E2V 5 mg.

**DMPA 25 mg plus E2C 5 mg versus DMPA 150 mg administered every 3 months**

Four trials involving 1128 women compared DMPA 25 mg plus E2C 5 mg with DMPA 150 mg. The durations studied were 12 months in two trials and 6 months in the other two. The data were not combined for analysis. The trials reported inconsistent findings, with the largest study among the four reporting no differences between the study groups. In two other studies there were high numbers of early discontinuations for the combined injectable contraceptive. In the fourth, relatively small study, there were more discontinuations among DMPA users compared with the combined injectable.

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

There was only one small trial of 16 women for this comparison, which did not show any difference between the study groups.

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

Five trials with 7187 women were available for this comparison. Three were large trials (2252–2707 woman) and two were small (300–370 women) and the duration of treatment varied between 9 months and12 months. Women in the NET-EN group were less likely to discontinue early than the women in theDMPA group [Peto odds ratio (OR) 0.82; 95% confidence interval (CI) 0.74–0.92]. Moreover, the NET-EN group was also less likely to discontinue early owing to amenorrhea (Peto OR 0.32; 95% CI 0.22 –0.44) or prolonged bleeding (Peto OR 0.66; 95% CI 0.48–0.90) than the DMPA group.

**NET-EN 50 mg plus E2V 5 mg versus a progestogen-only injectable contraceptive**
containing NET-EN 200 mg

One trial involving 1112 women had made this comparison over a 12-month period. The overall early discontinuation rate was higher for the combined injectable contraceptive (Peto OR 1.41; 95% CI 1.07–1.86).

**NET-EN 50 mg plus E2V 5 mg versus copper intrauterine device (IUD)**

This comparison was made in a single trial which lasted for 24 months and involved 148 women. Women using the NET-EN 50 mg plus E2V 5 mg injectable were 6.67 times more likely to discontinue early due to bleeding compared with those in the IUD group (95% CI 2.08–21.41).

**Collective summary of results**

Overall, compared with progestogen-only injectables (DMPA 150 mg and NET-EN 200 mg), combination injectable contraceptives (DMPA 25 mg plus E2C 5 mg and NET-EN 50 mg plus E2V 5 mg) were associated with more regular (cyclical) bleeding, lower risk of amenorrhea, and less likelihood of infrequent bleeding patterns. Women using combination injectable contraceptives (DMPA 25 mg plus E2C 5 mg or NET-EN 50 mg plus E2V 5 mg) were more likely to discontinue due to non-bleeding reasons (medical, personal, others) compared with the progestogen-only group (DMPA 150 mg or NET-EN 200 mg). Women in the progestogen-only group were more likely to discontinue due to amenorrhea or bleeding problems.

The trials that compared DMPA 25 mg plus E2C 5 mg with NET-EN 50 mg plus E2V 5 mg found that, overall, the latter resulted in lower rates of early discontinuation (Peto OR 0.82; 95% CI 0.74–0.92) and discontinuation due to amenorrhea (Peto OR 0.32; 95% CI 0.22–0.44) or prolonged bleeding (Peto OR 0.66; 95% CI 0.48–0.90). Moreover, women in the NET-EN plus E2V group were more likely to report regular (cyclical) bleeding and fewer prolonged bleeding reference periods. The amenorrhea rate did not differ in the two groups. However, the statistical significance of almost all of these findings was dependent on one trial conducted in China and the differences generally were not detected in the other populations studied.

4. DISCUSSION

4.1 Applicability of the results

We see no objection to the applicability of the findings of this review to under-resourced settings since a large number of the studies were conducted in such settings in Africa, Asia, and South America. Combined injectable contraceptives are an additional option to the method-mix for family planning programmes. They are less likely to produce bleeding problems and amenorrhea than progestogen-only injectables. However, their acceptability is lower as measured by the overall early discontinuation rate.

4.2 Implementation of the findings

Adding combined injectable contraceptives to the available contraceptive options requires that health-care systems strengthen their capacity for patient counselling as they introduce these methods into the method mix. This can help to improve the acceptability of the new methods.

4.3 Future research

Studies are needed to advance the understanding of non-medical reasons for discontinuation of combination injectable contraceptives. Trials could be conducted to determine whether providing women with three months' supply of a combined injectable contraceptive improves continuation rates. Studies to understand cultural barriers to acceptability of combination injectables are also required. Another needed dimension is to look carefully at the provider–client interaction as this may be the reason behind some discontinuations that may add a significant proportion to the overall discontinuation rates. In a study in South Africa, or
example, more than one third of clients in Eastern Cape who arrived late, but within the two weeks' grace period, were denied re-injections by providers (6).

References


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