

Treatment of vaginal bleeding irregularities induced by progestin only contraceptives (Review)

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ABSTRACT

Background

Despite their high effectiveness, progestin-only contraceptives are considered less than ideal by the many women who experience irregular vaginal bleeding when using them. Current treatments to control these bleeding problems are not sufficiently effective.

Objectives

We evaluated preventive and therapeutic approaches to normalise bleeding irregularities associated with the use of progestin-only contraceptives.

Search strategy

Literature was identified through database searches, reference lists, organisations and individuals, covering the period until December 2006.

Selection criteria

Trials with random or alternate allocation, testing interventions for the prevention or treatment of bleeding irregularities associated with the use of progestin-only contraceptives were eligible.

Data collection and analysis

Results are expressed as relative risks (RR) with 95% confidence interval (CI) for categorical data and as weighted mean difference (WMD) with 95% CI for continuous data. When we encountered heterogeneity (visual or statistical) we used the random-effects model (quantitative) or did not produce a summary estimate (qualitative).

Main results

Twenty three randomised controlled trials enrolling 2674 participants were included. Seventy per cent were determined to reflect low to moderate risk of bias.

Estrogen treatments reduced the number of days of an ongoing bleeding episode in DMPA and Norplant users. However, treatment frequently led to study discontinuation due to gastrointestinal upset.

Combinations of oral ethinyl estradiol and levonorgestrel improved bleeding patterns in Norplant users, but method discontinuation rates were unchanged. One trial reported successful use of combined oral contraceptives in treating amenorrhea among DMPA users.

Norplant users, but not Implanon users, administered the anti-progestin mifepristone reported fewer days of bleeding than those given placebo. Mifepristone used monthly by new Norplant acceptors reduced bleeding, when compared to placebo.

A variety of NSAIDs have been evaluated for their ability to treat abnormal bleeding, with mixed results.

Norplant users receiving tamoxifen had less unacceptable bleeding after treatment and were more likely to continue using Norplant than those receiving placebo.

Tranexamic acid, mifepristone combined with an estrogen and doxycycline were more effective than placebo in terminating an episode of bleeding in women using progestin-only contraceptives, according to three small studies.

Authors' conclusions

Some women may benefit from the interventions described, particularly with cessation of current bleeding. Several regimens offer promise in regulating bleeding, but findings need to be reproduced in larger trials. The results of this review do not support routine clinical use of any of the regimens included in the trials, particularly for long-term effect.

PLAIN LANGUAGE SUMMARY

Plain language summary

As the use of progestin-only methods of contraception continues to increase worldwide, the problem of the vaginal bleeding disturbances these methods induce is becoming of increasing public health relevance. A number of approaches are used by clinicians to control these bleeding irregularities. Some women may benefit to some degree from the interventions tested particularly with regard to cessation of an ongoing bleeding episode. Several regimens offer promise in regulating bleeding, but positive results need to be reproduced in larger scale trials. Intermittent treatment with an agent may help some women to continue the use of a progestin-only contraceptive. However the evidence reviewed is not strong enough to recommend routine use of any of the regimens included in the trials, particularly for long-term effects.

BACKGROUND

Over the past 30 years, the number of users of progestin-only methods of contraception has been increasing steadily worldwide and is currently estimated to be over 20 million. The method most widely used is the injectable depot medroxy-progesterone acetate (DMPA), first registered in the late 1960s in some countries. Its approval for contraceptive use by the United States Food and Drug Administration in 1992 increased access to the method worldwide, through new registrations; approximately 13 million women worldwide currently use DMPA for contraception. The other progestin-only injectable contraceptive currently available, norethisterone enanthate, is estimated to be used by fewer than one million women.

Additional progestin-only contraceptive methods are based on several delivery systems: subcutaneous implants, intra-uterine systems, vaginal rings and oral preparations. Five implant systems are available to family planning programmes; the most widely-used of these is the six capsule levonorgestrel-releasing implantable system, Norplant. This method has been available since 1983, and is used by approximately six million women; post-registration studies have demonstrated that the method is highly effective over a period of seven years. The two-rod levonorgestrel-releasing implantable system, Jadelle, is effective for five years and was first registered for this length of use in the year 2000. Two generic products, designed to imitate the performance of these two implants, are made in China and are known as Sino-implant. A single-implant system

that has been available since 1997, Implanon releases etonogestrel and is effective for a period of 3 years. The levonorgestrel-releasing intra-uterine system, Mirena, has been available since 1990 and is currently used by several million women worldwide. The progesterone-releasing vaginal ring, Progering, designed for use by breast feeding women, has been available in limited markets since the late 1990s. Use of progestin-only oral preparations remains limited, despite being appropriate for women who are breast feeding. Other progestin-only methods are being developed, such as transdermal patches and new injectable, implantable and intra-uterine systems.

Progestin-only contraceptive methods are highly effective and their long-acting properties facilitate their use. However, despite differences in their primary mechanisms of action, all induce major uterine bleeding disturbances. Data from clinical trials demonstrate that, at one year of use, fewer than 10% of DMPA and Mirena users and only 25% of Norplant users experience regular monthly bleeding, while others experience a variety of patterns ranging from infrequent bleeding and amenorrhea to irregular, frequent or prolonged bleeding. These patterns are all classified as breakthrough bleeding and have been discussed in several publications (Newton 1994, Fan 1996, Suvisaari 1996, Affandi 1998, Fraser 1998). This side effect is the primary reason that women give for discontinuing use of these methods and accounts for 40-70% of termination from clinical trials (d'Arcangues 1992, Datey 1995). There seem to be great variations in the tolerance that women have for these disturbances. In a multicenter clinical trial of DMPA, for exam-

ple, users in Egypt, Jamaica and Thailand reported similar rates of amenorrhea. In Egypt, 27% of women discontinued DMPA use for this reason, while none did so in Thailand or Jamaica (Said 1987).

Individual women respond differently to the use of progestin-only methods. Bleeding effects may also vary according to the type of progestin and the dose. With Norplant use, prolonged and irregular breakthrough bleeding is usually at its worst during the first 12 months of use, becoming more regular thereafter. With DMPA, users also start by experiencing prolonged and irregular bleeding, but later on this pattern is replaced by increasing periods of amenorrhea. A reasonable clinical goal would be to provide an intervention to assist women in managing any irregularities in bleeding - thus continuing the use of their chosen contraceptive method - until the time when their bleeding becomes more regular or until they experience amenorrhea.

In the absence of complete understanding of the underlying mechanisms leading to vaginal bleeding irregularities, there are variations in clinical practice. In the early 1980s, a survey was conducted on the management of progestin-associated menstrual disturbances among physicians and organizations (Fraser 1983). There were 35 responses from 20 countries, most reporting experience with DMPA, and three with additional experience with NET-EN. Fourteen years later, another survey (Nutley 1997) was conducted among family planning providers and researchers on the treatment regimens they used for progestin-associated bleeding disturbances. Sixty four responses from 32 countries were received. The second survey collected information based on experience with injectable, implantable and oral progestin-only methods. Both surveys documented a wide variability of treatment regimens offered to women, ranging from estrogens, combined oral contraceptives, progestins, non-steroidal anti-inflammatory agents, to vitamins, iron and anxiolytic agents. This wide variation in treatments given to women, and the uncertainty about the potential benefits or risks of individual treatments, highlight the importance of conducting a rigorous and comprehensive review of the different treatments for vaginal bleeding irregularities associated with progestin-only contraceptives.

OBJECTIVES

The purpose of this review is to evaluate prophylaxis and treatment of bleeding irregularities associated with the use of progestin-only contraceptives.

CRITERIA FOR CONSIDERING STUDIES FOR THIS REVIEW

Types of studies

Trials designed to test regimens to treat or prevent bleeding irreg-

ularities associated with the use of progestin-only contraceptive methods were considered for inclusion. Studies were required to use random or systematic (i.e. alternation) methods of allocation. Studies employing a cross-over design were not eligible for inclusion.

Types of participants

Women using progestin-only contraceptives were the participants of the studies included in this review. These comprise:

1. Women experiencing vaginal bleeding irregularities i.e. bleeding/spotting, irregular bleeding, prolonged bleeding, frequent bleeding or amenorrhoea. The trialists' definitions of these conditions were accepted.
2. Women not experiencing vaginal bleeding irregularities but accepting prophylactic treatment. These women would be likely to be enrolled as they start using the progestin-only contraceptive method.

Types of intervention

Drugs used to prevent or treat bleeding irregularities in women using progestin-only contraceptives. These are likely to include:

1. Estrogens
2. Progestins
3. Combined oral contraceptives
4. Nonsteroidal anti-inflammatory drugs
5. Antioxidants
6. Antifibrinolytic agents
7. Antiprogestins
8. Selective estrogen receptor modulators
9. Antiangiogenesis agents
10. Others
11. Combinations of the above

The dose, duration and frequency of treatment and length of follow-up should be specified.

Types of outcome measures

The primary outcome of this review is the effectiveness of prophylactic or therapeutic interventions to prevent or treat bleeding irregularities, as defined by an improvement in irregular bleeding. Trials using objective or subjective methods for assessing bleeding were eligible.

Additional outcomes included:

1. Discontinuation of the contraceptive method
2. Discontinuation of the treatment
 - a. Discontinuation due to side-effects
 - b. Discontinuation due to lack of improvement
3. Any side-effect of treatment
4. Patient dissatisfaction with treatment
5. Blood loss during treatment

Outcome measures were assessed during treatment and/or at the end of treatment, to evaluate short-term effects, and at varying

intervals following discontinuation of treatment, to evaluate long-term effectiveness, according to the study design.

SEARCH METHODS FOR IDENTIFICATION OF STUDIES

See: methods used in reviews.

The search included:

1. ELECTRONIC DATABASES

- a. MEDLINE using OVID or SilverPlatter for the years 1966-2006; searches through PubMed and Popline were updated in December 2006.
- b. EMBASE using OVID for the years 1980-2006
The methodological search filter for high sensitivity in identifying randomised controlled trials in MEDLINE, parts I and II (11a.15 Appendix B, Cochrane Reviewers' Handbook 4.1, June 2000, p153) was added to the subject search strategy to identify reports of controlled trials in MEDLINE. This methodological search filter was adapted for use in searching EMBASE.
- c. The Cochrane Central Register of Controlled Trials (CENTRAL), which includes controlled trials identified from electronic databases as well as hand searching of relevant journals.
- d. The Spanish language database LILACS was searched with the same search terms.

The drug classes and individual names for progestin-only contraceptives, including their proprietary names used in different countries where known, were combined with terms describing vaginal bleeding irregularities in order to identify treatment interventions.

The following subject search terms were combined:

- #1 explode PROGESTATIONAL-HORMONES-SYNTHETIC
- #2 explode PROGESTERONE
- #3 explode CONTRACEPTIVES-ORAL-SYNTHETIC
- #4 CONTRACEPTIVES-ORAL-HORMONAL
- #5 PROGESTATIONAL-HORMONES
- #6 gestagen
- #7 progestogen only contracep* OR progestin only contracep*
- #8 progesterone OR progestogen* OR norgestrienone OR norgestrel OR ogylene OR microlut OR microval OR mirena OR norplant OR levonova OR microluton OR follistrel OR neogest OR norgeston OR postinor-2 OR ovrette OR levonorgestrel OR norgestimate OR nomegestrol acetate OR norethisterone acetate OR norethisterone enanthate OR norethisterone enantate OR micronovum OR primolut-nor OR locilan OR micronor OR noriday OR norlutate OR milligynon OR norfor OR noristerat OR norluten OR gestakadin OR sovel OR conludag OR nuristerate OR mini-pe OR menzol OR primolut-N OR sh420 OR utovlan OR aygestin OR nor-qd OR medroxyprogesterone acetate OR depo-provera OR depocon OR farluta OR prodaferm

- OR provera OR depo-ralovera OR ralovera OR depo-prodasone OR gestoral OR prodasone OR clinofem OR clinovir OR depo-clinovir OR g-farluta OR lutura OR perlutex OR petogen OR depo-progevera OR progevera OR cykrina OR gestapuran OR prodaferm OR amen OR curretab OR cyrcin OR lynoestrenol OR lynestrenol OR orgametril OR exluta OR exlutona OR exlutena OR gestodene OR etonogestrel OR implanon OR ethynodiol diacetate OR etynodiol diacetate OR lutometrodol OR luteonorm OR femulen OR drospirenone OR desogestrel OR dienogest OR demegestone OR lutionex OR cyproterone acetate OR andro-diane OR androcur OR cyprone OR cyprostat OR chlormadinone acetate OR luteran OR gestaforin OR prosta OR algestone acetophenide OR neolution depositum #9 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 #10 explode UTERINE-HEMORRHAGE
- #11 AMENORRHEA
- #12 vagina* NEAR (bleed* OR haemorrhag* OR hemorrhag* OR blood loss)
- #13 uter* NEAR (bleed* OR haemorrhag* OR hemorrhag* OR blood loss)
- #14 spotting
- #15 (irregular OR prolonged OR frequent OR persistent OR unpredictable OR unscheduled OR abnormal OR breakthrough) NEAR (bleed* OR menstrual* OR menses OR blood loss OR period OR periods OR haemorrhag* OR hemorrhag*)
- #16 menstrual disturbance*
- #17 #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 #18 #9 AND #17

(N.B. Upper case denotes controlled vocabulary, which comprise Thesaurus terms applied by the database indexers, and lower case denotes free-text terms, which are used by the authors of the studies).

2. Reference lists of trials identified and relevant review articles were scrutinized for any additional trials not retrieved with the database searches listed above.

3. Researchers active in the field were contacted for possible unpublished studies or data.

The searches included all languages.

METHODS OF THE REVIEW

Two reviewers (HAA and KV) initially assessed the results of the search by checking the titles and the abstracts where available. When unsure about the relevance or the methodology, they requested and reviewed full reports. Reports of studies using a random or quasi-random allocation and evaluating the interventions described here were critically appraised for inclusion.

A data extraction form was developed, as described in the Cochrane Handbook, for standardisation of the data extraction. Trials were

reviewed for methodological quality based on concealment of allocation, outcome assessment blinding and drop out rates. If all of the criteria were met, there was considered to be a low risk of bias (validity criteria score A). In cases where one or more criteria were partly met, for example if the trialists reported that the study was double blind, but didn't report any concealment approach, there was considered to be a moderate risk of bias (validity criteria score B). If one or more of the criteria was not met, if allocation concealment or outcome assessment were not blinded, or if the study participant drop-out rate was more than 10%, studies were given a validity criteria score of C.

There were no language restrictions for inclusion of trials. Abstracted data were entered into Review Manager software and analysed. Studies that enrolled women who were using different contraceptive methods were not combined, due to the different primary mechanisms of contraceptive action of the various methods, and their differing effects on bleeding patterns. Since the types and mechanisms of pharmaceutical agents used were different and the desired outcomes of treatment differed between trials (for example induction of regular menses or of amenorrhoea), different groups of agents were not combined in a single analysis. Therefore, three main variables were identified in the comparison plan: the contraceptive method, the intervention, and the prophylactic or therapeutic nature of the intervention. Few trials could be combined and we conducted the analyses with this consideration in mind.

Data regarding participant drop out rates, loss to follow up and reasons for early discontinuations were recorded and presented in the table of included studies. Study participant characteristics, treatment interventions, length of follow-up and outcome measures were recorded. Trial characteristics such as type of trial, study duration and setting where the trials were conducted were also recorded.

The data were entered separately by two reviewers (HAA and KV) and discrepancies or disagreements were resolved by discussion. The results are expressed as relative risks (RR) with 95% confidence interval (CI) in case of categorical data and as weighted mean difference (WMD) with 95% confidence interval (CI) for continuous data, using a fixed-effect approach where possible. When we encountered heterogeneity (visual or statistical) we used the random-effects model (quantitative) or did not produce a summary estimate (qualitative).

DESCRIPTION OF STUDIES

This review included 23 randomised (n=22) or systematic methods (n=1) controlled trials (RCTs), conducted in 17 countries (China, Indonesia, Iran, Pakistan, the Philippines and Thailand in Asia; Tunisia and Egypt in Africa; France, the Netherlands, Sweden, Switzerland and the United Kingdom in Europe; the United States

of America in North America; Chile and the Dominican Republic in Latin America; and Australia). Studies were conducted at family planning clinics, hospitals and university research centres.

Contraceptives used:

Eleven of the included studies enrolled women using Norplant as their contraceptive method. New Norplant users, as well as women using the method for one to 43 months were enrolled; most of the studies limited enrolment to women using the method for less than one year. Eight studies were conducted to evaluate interventions in women using the injectable DMPA, with the duration of use ranging from three to twelve months. In three trials, women used progestin-only pills; the duration of use was at least one month in one study and was not defined in the other two studies. One trial recruited women who had been using Implanon for a period of more than three months.

Characteristics of participants:

The age of women included in these trials generally was in the range of 20 and 30 years. Two studies (Subakir 2000, and Weisberg 2006) included women 18 to 40 years old. The parity of women recruited in the trials was reported in only six trials and ranged between 1.9 and 2.6 children. The body weight of study participants was reported in nine trials and was reported in the range between 44 and 62 kg. Height was not mentioned in the majority of the trials, but four studies reported the body mass index (Kaewrudee 1999, Nathirojanakun 2006, Phupong 2006 and Tantiwattanakul 2004).

Interventions:

There were twelve types of interventions tested in the trials. These included estrogens alone in various formulations (ethinyl estradiol, 17-beta estradiol, diethylstilbestrol, oestrone sulphate, quinesterol), as used therapeutically in six trials (Alvarez-Sanchez 1996, Boonkasemsanti 1996, Diaz 1990, Johannisson 1982, Said 1996, and Witjaksono 1996) and prophylactically in three trials (El-Habashy 1970, Goldberg 2002 and Parker 1980). Estrogen - progestin combinations were used therapeutically in three trials (Alvarez-Sanchez 1996, Sadeghi-Bazargani 2006, and Witjaksono 1996). A progestin was used therapeutically in a single trial (Diaz 1990). Anti-progestins were used therapeutically in two trials (Cheng 2000 and Weisberg 2006) and prophylactically in three trials (Gemzell-Danielsson 2002, Jain 2003 and Masai 2004). An antiprogestin was combined with an estrogen in one trial (Weisberg 2006). A capillary protecting venotonic drug (registered in France as Cyclo 3, containing extract of *Ruscus aculeatus* with ascorbic acid and hesperidin methyl chalcone) was used therapeutically in one trial (Monteil-Seurin 1985). In two trials (Subakir 2000 and d'Arcangues 2005), vitamin E was used therapeutically. Non-steroidal anti-inflammatory drugs (NSAIDs) were used therapeutically in five trials (Diaz 1990, Kaewrudee 1999, d'Arcangues 2005, Nathirojanakun 2006 and Tantiwattanakul 2004). The therapeutic effects of combined Vitamin E and NSAIDs were evaluated in a single trial (d'Arcangues 2005).

A selective estrogen receptor modulator (SERM) was used therapeutically in one trial (Abdel-Aleem 2005). An antifibrinolytic agent was used in one trial (Phupong 2006) and a matrix metalloproteinase inhibitor was used in one trial (Weisberg 2006).

All trials were placebo-controlled. Seventeen trials included a single intervention arm, while six trials were designed to test the effects of more than one intervention, singly or in combination. In two trials (El-Habashy 1970 and Parker 1980) the interventions tested, diethylstilbestrol and quinesterol, respectively, are no longer used in clinical practice, for any indication. In addition to the range of types of interventions, the treatments were used in different doses and according to different dosing schedules, and study participants were followed according to diverse schedules, for varying lengths of time.

Duration of Follow-Up:

The duration of follow-up varied among the trials, from less than three months to eighteen months. Most trials were designed to test the short-term effects of the interventions, with only seven trials treating or following participants for longer than six months (Parker 1980, Diaz 1990, Said 1996, Cheng 2000, Goldberg 2002, Massai 2004 and d'Arcangues 2005). The longest duration of follow-up, up to 18 months, was in a WHO trial (Said 1996); however, the long-term results were not reported.

Outcome measures:

Although nearly all trials were designed to evaluate the effects of treatment on bleeding episodes as a primary outcome, the authors reported the outcome in different ways, including cessation of bleeding, number of bleeding days during treatment, number of bleeding days after treatment, number of days of treatment required before bleeding stopped, percent of women with bleeding free intervals of more than a given number of days, percent of women with acceptable bleeding, and others. Moreover, the data were presented in different ways including means, medians, and percentages.

Due to the lack of consistency in study design, outcome measures, and statistical reporting, very few studies could be combined in the analyses.

METHODOLOGICAL QUALITY

This review included 23 trials. The methodological quality was assessed as mentioned above, in the methods section, with validity criteria scores based on allocation concealment, outcome assessment blinding and number/percent of study discontinuations. According to these criteria, seven of the trials were assigned "A" validity criteria scores with low risk of bias (Abdel-Aleem 2005, Cheng 2000, Kaewrudee 1999, Nathirojanakun 2006, Phupong 2006, Tantiwattanakul 2004, and Weisberg 2006). In these trials, allocation concealment was considered to be adequate, outcome assessment blinding was achieved and fewer than 10% of

the enrolled women discontinued prior to the end of the study. There were nine trials that were considered to be at moderate risk of bias and were therefore given validity criteria scores of "B". In many of these studies, the allocation concealment was unclear (Alvarez-Sanchez 1996, Boonkasemsanti 1996, Jain 2003, Johannisson 1982, Massai 2004, Subakir 2000). The outcome assessment blinding was unclear or inadequate in five of these trials (Alvarez-Sanchez 1996, El-Habashy 1970, Jain 2003, Johannisson 1982, Witjaksono 1996). Seven trials were given a validity criteria score of "C", meaning that the study may be subject to a high risk of bias (d'Arcangues 2005, Gemzell-Danielsson 2002, Diaz 1990, Goldberg 2002, Monteil-Seurin 1985, Parker 1980 and Said 1996). This score was based on a high discontinuation rate in four studies (d'Arcangues 2005, Gemzell-Danielsson 2002, Parker 1980 and Said 1996) and the other studies clearly failed to meet one or more of the criteria. For example, in the case of the Goldberg study, the rate of discontinuation (30-45%), combined with a very high rate of non-compliance with the study protocol meant that the study had a high risk of bias. Overall, more than one third of the trials were of moderate quality, with 30% being considered "poor." The seven trials (30% of all included studies) that were considered to be of good quality recruited 621 (23%) of 2,674 women enrolled in all included trials.

RESULTS

1. Estrogen versus placebo (therapeutic treatment for Norplant users)

In four of the included studies, women reporting bleeding irregularities while using Norplant were administered an estrogen formulation and followed for resolution of symptoms (Alvarez-Sanchez 1996, Boonkasemsanti 1996, Diaz 1990, and Witjaksono 1996). Together, these studies recruited 146 women in the respective estrogen treatment arms and 141 women in placebo groups; of these, data from 127 estrogen-treated women and 129 placebo-treated women were included in the analyses. Treatments included ethinyl estradiol (EE) tablets in three studies (Alvarez-Sanchez 1996, Diaz 1990 and Witjaksono 1996) and an estradiol patch in the fourth (Boonkasemsanti 1996).

The efficacy of the various treatments was reported in different manners in these studies. In Alvarez-Sanchez 1996, the primary outcomes included whether or not bleeding stopped within three days of the initiation of treatment and the number of bleeding days during the 20-day treatment interval. The Diaz 1990 study reported mean and total numbers of bleeding and spotting days during all treatment intervals throughout the entire year and did not separate individual treatment intervals. Women receiving estradiol reported shorter episodes of bleeding and spotting throughout the year and fewer days of bleeding and spotting. However, it is not clear how many treatment cycles were included in the analysis. But it is reported that the mean number of treatments per year per treated subject ranged from 2.2 to 3.1, with no differences between

groups. Witjaksono 1996 reported on the number of bleeding or spotting days and episodes in 90-day reference periods prior to and following the treatment, and the number of bleeding or spotting days per episode. The study results from the individual trials generally suggest that the estrogen treatment had a beneficial effect in stopping bleeding. Two of the included studies (Alvarez-Sanchez 1996 and Boonkasemsanti 1996) reported the number of women who experienced irregular bleeding during treatment; according to our combined analysis, the use of estrogen reduced irregular bleeding during the treatment interval [RR 0.43, 95% CI 0.30-0.61]. In addition, the Alvarez-Sanchez 1996 data support the conclusion that women receiving EE report a lower incidence of unacceptable bleeding patterns after treatment, as defined by the length of the post-treatment bleeding-free interval. Fewer women reported a bleeding-free interval of less than 11 days after receiving the oral EE regimen than after receiving placebo [RR 0.28, 95% CI 0.14-0.58].

Based on our analysis of data reported by Alvarez-Sanchez 1996, women receiving estrogen treatment appeared to be less likely to discontinue the use of Norplant for bleeding irregularities than were those receiving placebo, though the overall effect was not significant, as only one woman discontinued for this reason. Diaz 1990 did not report any method discontinuations for bleeding irregularities. Nausea or gastrointestinal discomfort was commonly reported in the former study: only two of 46 participants receiving placebo reported such side effects, whereas 17 of 43 receiving estrogen complained of gastric upset [RR 9.09, 95% CI 2.23, 37.06]. In the Diaz 1990 study, 5 of 13 study discontinuations in the estrogen group were associated with gastric intolerance, while none of the women in the placebo group discontinued from the study for this reason. Alvarez-Sanchez 1996 reported discontinuation of treatment due to gastralgia or nausea in 2 of 50 women receiving treatment and none of the women in the placebo group. When the data for these studies were combined, it was clear that women receiving estrogen tended to be more likely to discontinue their participation in the trial due to side effects of the treatment than were women receiving placebo [RR 8.1, 95% CI 1.04, 63.40].

2. Estrogen versus placebo (therapeutic treatment for DMPA users)

Only one of the included studies (Said 1996) was designed to evaluate the effects of an estrogen on bleeding irregularities in women using DMPA for family planning. This was one of the largest included studies, randomising 278 DMPA users with irregular bleeding to receive either EE 50 µg, oestrone sulfate 2.5 mg or placebo for 14 days. This study was also designed to report on both short- and long-term success, with follow-up at 14 days (the duration of the treatment) and 12-18 months; unfortunately, there was a high rate of discontinuation (over 40% in each group), giving the study a high risk of bias.

Ethinyl Estradiol was effective in stopping bleeding during treatment [RR 0.26, 95%CI 0.11, 0.60] and to a lesser extent after

three months [RR 0.06, 95%CI 0.00, 1.00]. While oestrone sulphate was ineffective in stopping bleeding during treatment [RR 1.03, 95%CI 0.41, 2.59] and after three months.

The authors reported discontinuations and their causes among the study participants who presented at the study centres. But due to the high numbers of study participants who were lost to follow-up and who dropped out of the study prematurely, without giving a reason, it was impossible to determine the true discontinuation rates, particularly as related to bleeding irregularities and side effects, respectively.

3. Estrogen versus placebo (prophylactic treatment for DMPA users)

Three studies were identified in which estrogen was administered to new acceptors of DMPA, with the goal of preventing or reducing bleeding irregularities. Two of these (El-Habashy 1970 and Parker 1980) examined the effects of orally administered estrogens, diethylstilbestrol (DES) and quinesterol, respectively, and the third (Goldberg 2002) evaluated the effects of a 17-beta estradiol-containing transdermal patch.

Only one of the studies reported efficacy of the treatment in terms that could be incorporated into the present analysis. El-Habashy 1970 reported that women administered DES 1 mg daily exhibited more acceptable bleeding patterns (defined as bleeding episodes of less than 8 days) than women receiving placebo [RR 0.45, 95% CI 0.21, 0.96]. Parker 1980 reported the percent of women with acceptable bleeding patterns in terms of numbers of bleeding episodes throughout 3-month intervals, following either one or three doses of quinesterol per DMPA injection segment (12 weeks). The primary outcome of the Goldberg 2002 study was DMPA continuation rates, but the estrogen treatment seemed to be ineffective as a means to improve DMPA continuation [RR 1.06, 95% CI 0.84, 1.33]; the authors reported that there was no association between the use of estrogen patches and regular bleeding patterns, over time. Two of the studies in this category suffered from very high discontinuation and non-compliance rates, in both treatment and placebo groups.

4. Estrogen versus placebo (therapeutic treatment for minipill users)

One small (n=12) study (Johannisson 1982) was designed to evaluate the effects of estrogen treatment on bleeding irregularities experienced by minipill (300 µg norethisterone) users. None of the bleeding data could be used in the current analysis, as confidence intervals, rather than standard deviations, were presented in the descriptions of bleeding during the treatment interval.

5. Combined estrogen and progestin versus placebo (therapeutic treatment for Norplant users)

There were two studies (Alvarez-Sanchez 1996; Witjaksono 1996) in which a combination of oral ethinyl estradiol and oral levonorgestrel was tested as a means to treat bleeding irregularities in Norplant users. The two studies together randomised 66 women

to receive the treatment regimen and 64 to receive placebo; of these 61 and 60, respectively, were included in the analyses. As above, Alvarez-Sanchez 1996 reported efficacy in terms of the percentage of women who experienced a cessation of bleeding within 3 days of treatment; the Witjaksono 1996 paper reported the number of bleeding days and episodes in 90-day reference periods. According to the reports of the author and to our analyses, in the former study, the combined approach significantly reduced continued irregular bleeding during treatment, when compared with placebo [RR 0.08, 95% CI 0.03, 0.24] and reduced unacceptable bleeding after treatment (as defined by the number of women experiencing bleed-free intervals of less than 11 days) [RR 0.02, 95% CI 0.00, 0.29].

Witjaksono 1996 did not report any discontinuations or side effects in the study results; Alvarez-Sanchez 1996 reported that the discontinuation of Norplant due to bleeding disturbances was not significantly different between women in the combined hormone treatment and placebo groups, which was supported by our analysis [RR 0.33, 95% CI 0.01, 7.99]. Discontinuation due to the side effects of the treatment did not differ between groups; however, our analysis of the Alvarez-Sanchez data revealed a higher incidence of reported side effects (nausea or gastralgia) in the treatment group than in the placebo group [RR 7.16, 95% CI 1.72, 29.71].

6. Combined estrogen and progestin versus placebo (therapeutic treatment for DMPA users)

One small trial (Sadeghi-Bazargani 2006) recruited DMPA users who had cessation of menstruation for two months. Twenty four women received low dose combined oral contraceptives (COCs) and 22 received placebo. Significantly fewer women in the treatment group than in the placebo group continued to experience amenorrhea [RR 0.38, 95% CI 0.19, 0.73]. The number of women who discontinued use of DMPA was less in the group assigned to receive low dose pills [RR 0.60, 95% CI 0.40, 0.88].

7. Progestin versus placebo (therapeutic treatment for Norplant users)

One study (Diaz 1990) evaluated the effect of administering an additional progestin to Norplant users experiencing bleeding episodes of eight or more days. These women received 0.03 mg levonorgestrel tablets, twice a day for 20 days, starting on the eighth consecutive day of bleeding. Women could treat extended bleeding up to five times in the year-long study. The authors described a significant decrease in the total number of bleeding days and bleeding and spotting days over the entire year in women who ever used the levonorgestrel, compared with those who ever used the placebo, even when the untreated bleeding cycles were included in the analysis; however, the numbers of women in the final analysis were small (21 per group).

Three of the 47 women enrolled in the levonorgestrel group elected to have their Norplant system removed, though none for reasons related to bleeding; only one woman in the placebo group asked

to discontinue the contraceptive method [RR 2.94, 95% CI 0.32, 27.21].

8. Antiprogestin versus placebo (therapeutic treatment for Norplant users)

One of the included studies (Cheng 2000) was designed to evaluate the effects of the anti-progestin mifepristone on bleeding irregularities experienced by users of levonorgestrel-containing subdermal contraceptive implants equivalent to Norplant. The study results stated that the women treated with mifepristone reported significantly shorter episodes of bleeding during the treatment than prior to the study; however, both the treatment and control groups demonstrated a decrease in the frequency of bleeding in the one year of follow up. In the current analysis, we found no significant difference between the groups with respect to the number of days of bleeding when reported 3 months after study initiation; at 6 months, however, women using the anti-progestin reported fewer days of bleeding than did those receiving placebo [WMD -8.00, 95% CI -12.41, -3.59]. No difference in the number of days of bleeding after the treatment was noted. No women in either group discontinued the use of the contraceptive method due to bleeding irregularities. There was a significant effect of mifepristone to decrease patient dissatisfaction with the treatment [RR 0.46; 95% CI 0.23, 0.91].

9. Antiprogestin versus placebo (prophylactic treatment for Norplant users)

A single study (Massai 2004) was designed to evaluate the effect of two subsequent daily oral doses of 100 mg mifepristone in preventing bleeding irregularities in new users of Norplant. Of the 120 women enrolled, 116 completed 6 months of treatment and 115 were included in the analysis. The mean number of bleeding or spotting days during the course of the 180 days of the treatment period of the trial was significantly lower in women who had taken the mifepristone for 2 days at 30 day intervals than in women given placebo [WMD -18.0; 95% CI -26.93, -9.07]. However, the improvement in bleeding patterns did not continue past the time of discontinuation of treatment and, by 6 months after treatment, there were no differences in reported acceptable bleeding patterns between the two groups. None of the women in the treatment group discontinued use of Norplant for continued irregular bleeding. Of importance, one woman who received the anti-progestin did become pregnant during the course of the study. Two women in the placebo group elected to have their implants removed due to continued irregular bleeding. This difference was not found to be significant, nor was the difference between groups with respect to discontinuation from the study due to side effects of the treatments, in the current analysis.

10. Antiprogestin versus placebo (therapeutic treatment for Implanon users)

One pilot RCT (Weisberg 2006) randomised women who used Implanon implant and had bleeding irregularities to receive mifepristone (25 mg twice/day for one day) then placebo for four

days or placebo only for five days. The authors reported that mifepristone alone was similar to placebo in stopping an episode of bleeding. Unfortunately, the results were presented in a way not suitable for our analysis. A similar proportion of women in both groups reported any side effect [0.93, 95% CI 0.61, 1.42] or, specifically, nausea and vomiting [0.64, 95% CI 0.23, 1.80].

11. Antiprogestin versus placebo (prophylactic treatment for DMPA users)

Results of one small study (Jain 2003) suggest that a single tablet of 50 mg mifepristone, taken orally every 14 days, can lessen bleeding irregularities in new users of DMPA, in terms of percent days with breakthrough bleeding and percent cycles with bleeding intervals of more than 8 days.

12. Antiprogestin versus placebo (prophylactic treatment for minipill users)

In one study (Gemzell-Danielsson 2002), 103 women were randomised to take either 150 mg of a novel antiprogestogen (Org 31710) or placebo tablets once every 28 days, for a maximum of seven treatment cycles. Although the study authors report an improvement in the bleeding patterns of women who received the antiprogestin, our analysis did not reveal any differences between groups in terms of efficacy, discontinuation of the contraceptive method due to bleeding irregularities or side effects, or the incidence of side effects or adverse events.

13. Combined antiprogestin and estrogen versus placebo (therapeutic treatment for Implanon users)

One pilot RCT (Weisberg 2006) randomised women using Implanon and experiencing bleeding irregularities to take either mifepristone 50 mg for one day, followed by EE 20 µg/day for four days, or placebo for five days. The efficacy results were presented in a way not suitable for our planned analysis but the authors reported that mifepristone followed by EE was significantly more effective than placebo in stopping an episode of bleeding. The present analysis demonstrated no significant differences between the two groups of women in reporting any side effects [RR 1.22, 95% CI 0.84, 1.75].

14. Venotonic versus placebo (therapeutic treatment for minipill users)

In one of the included studies (Monteil-Seurin 1985), women using a norethisterone acetate-containing minipill and complaining of bleeding irregularities were administered either a capillary protecting venotonic drug (registered in France as Cyclo 3, containing extract of *Ruscus aculeatus* with ascorbic acid and hesperidin methyl chalcone) or placebo. The treatment schedule was cyclic, with drug exposure for 20 continuous days, followed by a drug-free period during the expected time of menses. The mean number of bleeding days during treatment was lower in the group using the venotonic drug in comparison to the placebo group [WMD -2.0, CI -2.78, -1.22]. This was the only one of the included studies that attempted to quantify the amount of blood lost during treatment, as a listed endpoint, and the study authors indicated that women

who received the Cyclo 3 needed less menstrual protection than did women in the placebo group. There were no study drop outs reported and no data were presented on side effects due to the treatment. According to the study authors, treated women subjectively reported less discomfort due to bleeding after 3 treatment cycles than did women who received placebo.

15. Vitamin E versus placebo (therapeutic treatment for Norplant users)

Two of the included studies (Subakir 2000 and d'Arcangues 2005) were conducted to evaluate the effectiveness of vitamin E, 200 mg/day for 10 days, in the treatment of bleeding irregularities experienced by women using Norplant implants. In the first study, the mean number of bleeding days after the first treatment cycle was significantly less among the 38 women taking vitamin E than among the 34 women assigned to the placebo group [WMD -4.4, CI -5.02, -3.78]. However, in the second, larger study, with more than 100 women in each group, there were no statistically significant differences between the groups in terms of the length of bleeding/spotting episodes and the length of bleeding-free intervals that followed cessation of bleeding. d'Arcangues 2005 reported median numbers of days of bleeding, rather than means, given the non-normal distribution of the data. In this study, discontinuation rates were high but did not differ between groups, nor did the incidence of side effects.

16. Non-steroidal anti-inflammatory drug versus placebo (therapeutic treatment for Norplant users)

Three of the included studies (Diaz 1990, Kaewrudee 1999 and d'Arcangues 2005) were designed to evaluate the effects of non-steroidal anti-inflammatory drugs (NSAIDs) on bleeding irregularities experienced by women using Norplant. The regimens included oral ibuprofen 800 mg, three times/day for five days (Diaz 1990); oral mefenamic acid 500 mg, twice daily for 5 days (Kaewrudee 1999); and oral aspirin, 80 mg/day for 10 days (d'Arcangues 2005).

The earliest paper reported that women taking ibuprofen experienced a decrease in the mean number bleeding days after initiating treatment in all treated bleeding intervals over the course of a year and fewer bleeding and spotting days during the year (Diaz 1990).

Kaewrudee 1999 reported that eight of the 34 women taking mefenamic acid continued to experience irregular bleeding during the treatment, compared with 24 of 33 women in the placebo group; our analysis confirmed the significance of these results [RR 0.32; 95% CI 0.17, 0.61]. In addition, these women experienced fewer days of bleeding during the treatment [WMD -5.6; 95% CI -10.04, -1.16]. The percentage of women with unacceptable bleeding after treatment was significantly less in the treated group as reported by Kaewrudee 1999 and confirmed in the present analysis [RR 0.49; 95% CI 0.28, 0.83]. In the d'Arcangues 2005 trial, the median duration of bleeding/spotting episodes after treatment and the median lengths of the bleed-free intervals were not signif-

icantly different in the drug and placebo groups, as reported by the authors.

In the Diaz 1990 trial none of the women receiving ibuprofen requested removal of the Norplant system, while one woman in the placebo group requested removal, though not for bleeding-associated reasons. No differences in discontinuation rates or incidence of side effects (headache and gastrointestinal upset) were noted in the single studies or in the combined analyses (where combinations were feasible).

17. Combined non-steroidal anti-inflammatory drug and vitamin E versus placebo (therapeutic treatment for Norplant users)

In the large study reported in d'Arcangues 2005, over 120 women were randomly assigned to receive a combination of aspirin and vitamin E, while the same number received placebo. The efficacy data were reported as medians, and no benefit of the treatment was demonstrated in the original analysis. In addition, our analyses indicated that there were no differences between the groups with respect to study discontinuation or side effects related to the treatment (d'Arcangues 2005).

18. Non-steroidal anti-inflammatory drugs versus placebo (therapeutic treatment for DMPA users)

Two trials (Tantiwattanakul 2004 and Nathirojanakun 2006) evaluating the therapeutic effect of an NSAID on bleeding patterns in women using DMPA were included in the analysis. In the first, women were randomised to receive mefenamic acid (n=23) or placebo (n=25). In the second trial, 46 women were randomised to receive either valdecoxib or placebo. Both studies were determined to be of high quality. In a combined analysis, fewer women receiving NSAID treatment continued bleeding during or just after the treatment period, versus in the placebo group [RR 0.42; 95% CI 0.25, 0.72]. In the first trial gastrointestinal discomfort was reported by six women in the treatment group and by none in the control group; this difference was not found to be significant in our analysis. In the second trial no adverse effects were reported.

19. Selective estrogen receptor modulator versus placebo (therapeutic treatment for Norplant users)

One recently published trial (Abdel-Aleem 2005) was the only study to examine the efficacy of a selective estrogen receptor modulator (SERM), in this case tamoxifen, on bleeding irregularities experienced by women using progestin-only methods of fertility regulation. The study was limited to women using Norplant. Women randomised to the treatment arm were significantly less likely to experience irregular bleeding during treatment [RR 0.41; 95% CI 0.21, 0.80] or unacceptable bleeding after treatment [RR 0.38; 95% CI 0.18, 0.88] or to discontinue the use of Norplant for any reason [RR 0.20; 95% CI 0.05, 0.87]. The effect of the SERM in reducing Norplant discontinuation for bleeding-related reasons bordered on significance [RR 0.22; 95% CI 0.05, 0.98]. Women receiving tamoxifen were more likely to report satisfaction

with their treatment regimen [RR 0.22; 95% CI 0.11, 0.45] and were no more likely to report side effects.

20. Antifibrinolytic versus placebo (therapeutic treatment for Norplant users)

One randomised trial (Phupong 2006) evaluated the effects of an antifibrinolytic agent on bleeding patterns in women using Norplant and reporting irregular bleeding. Sixty-eight Norplant users were enrolled; half received tranexamic acid 500 mg twice/day for five days and the other half received similar placebo. The percentage of women whose irregular bleeding stopped at 7 days after the initiation of treatment was significantly higher in the tranexamic acid group than the placebo group [RR 0.55, 95% CI 0.32, 0.92]. The percentage of women with unacceptable bleeding by four weeks after the initiation of treatment was higher in the treatment group (41%) than in the control group (24%) [RR 1.75, 95% CI 0.85, 3.62].

21. Matrix metalloproteinase inhibitor versus placebo (therapeutic treatment for Implanon users)

In a single study (Weisberg 2006) Implanon users who experienced prolonged or frequent bleeding patterns were randomised to receive doxycycline 100 mg/twice daily or similar placebo, for five days. Doxycycline was used because it is a potent inhibitor of MMP-mediated matrix degradation, via mechanisms independent of its antimicrobial activity. Follow up was for a period of 90 days. The authors reported that doxycycline was more effective than placebo in stopping an episode of bleeding. There were no differences in the reporting of side effects between the two groups [RR 0.83, 95% CI 0.53, 1.29]. The authors reported that there was good compliance with treatment intake, with only 10% of study participants reporting having missed any tablet.

DISCUSSION

In performing the review it became clear that the original clinical trial authors reported efficacy outcomes in such divergent manners so as to make comparison of the outcomes across studies difficult or impossible. Due to the methodological differences among trials, very few could be combined in our analysis; therefore our findings primarily describe the results from analyses of individual studies. Data for some of the outcomes selected for the review were difficult to extract or interpret. In many studies discontinuation for bleeding reasons was not differentiated from discontinuation for other reasons. And, finally, the numbers of women in many of the trials were small, making the results difficult to interpret.

Several of the included studies were designed to evaluate the effects of **estrogen** administration on bleeding irregularities associated with Norplant or DMPA use. Estrogens may enhance those mechanisms that cause bleeding to cease, i.e. coagulation or tissue repair (Shaaban 1984 and Viegas 1988). Results were inconsistent, with ethinyl estradiol showing beneficial effects in stopping

a current bleeding episode as reported in several of the studies, and significant improvements in a combined analysis of two trials among Norplant users (Alvarez-Sanchez 1996 and Boonkasemsanti 1996). According to Said (Said 1996), among DMPA users, intake of ethinyl estradiol stopped bleeding better than placebo during the treatment period; however, part of the data was reported as medians and therefore could not be incorporated into our analyses. The higher rates of study discontinuation related to side effects of estrogenic compounds (Diaz 1990, Alvarez-Sanchez 1996) should encourage providers to exercise caution in recommending these regimens to their patients with bleeding irregularities, particularly those with known sensitivities to estrogens.

It is difficult to draw any firm conclusions from the data related to the prophylactic use of estrogens to prevent bleeding irregularities in DMPA users. While the first of the three studies (El-Habashy 1970) demonstrated a reduction in unacceptable bleeding during treatment with diethylstilbestrol, the study included only small numbers of women and was found to be of only moderate quality, due to possible inadequacies in allocation concealment and outcome assessment blinding. In fact, all of the trials in this category suffer from weaknesses in design or implementation, with high rates of discontinuations (23-38%) in two of the trials (Parker 1980 and Goldberg 2002, respectively). In two of the trials (El-Habashy 1970 and Parker 1980) therapies were tested that are no longer available for clinical use. The high rates of discontinuation and of non-compliance with the study protocol in the Goldberg study not only confuse the interpretation of the results so that they could not be incorporated into the present analysis, they also suggest that the tested therapy (transdermal estrogen delivered by means of a daily patch) would not be accepted by a large proportion of women.

Combined oral contraceptives (ethinyl estradiol and levonorgestrel) were used to treat bleeding irregularities among Norplant users in two trials, with the rationale being that most family planning service delivery facilities would have such a therapy readily available (Alvarez-Sanchez 1996 and Witjaksono 1996). The two studies reported a beneficial effect of treatment in stopping bleeding, though the endpoints and data in the latter study were reported in such a way as to make incorporation in our analysis impossible. We might presume to conclude that the addition of a progestin to the treatment regimen offered no benefit over and above the effects of an estrogen alone, but that it did not compromise the safety or effectiveness of an estrogen-only therapy. One study evaluated the role of combined oral contraceptives in treating amenorrhea associated with the use of DMPA (Sadeghi-Bazargani 2006). These investigators reported that more women resumed menstruation with the use of this therapy, and fewer women discontinued the use of DMPA in comparison to placebo; these positive results were confirmed in the present analysis. However, it is difficult to draw any conclusion about this regimen as the type, dose and duration of use of the combined oral contraceptive was

not reported; in addition, the sample size was small, with fewer than 25 women in each study group.

The use of an **additional progestin** to resolve bleeding irregularities in Norplant users met with limited success in a single study (Diaz 1990). While the study reported moderate improvements in bleeding in women using levonorgestrel compared with placebo, it suffered from high discontinuation rates, high rates of non-use of the treatment, even when required by the protocol, and other potential sources of bias. Because of the natural changes in bleeding patterns over the first year of Norplant use, the data describing the overall mean number of bleeding days in every treated bleeding interval (up to five in the year, but with a mean range of 2.2 to 3.1 treated cycles per woman per year) could not be included in our analyses. We could not compare these mean data with data on single intervals of treatment.

An **anti-progestin** (mifepristone) was used to treat bleeding among Norplant users in one trial (Cheng 2000). According to our analysis, users of mifepristone reported a significant decrease in bleeding during treatment at six months following initiation of treatment, but not before. This supports the authors' report that all women experienced a decrease in the frequency of bleeding over the course of the one-year study, but that the decrease was more gradual in the placebo group than for those women receiving mifepristone.

Anti-progestins have also been shown to be somewhat promising in the prevention of bleeding irregularities in DMPA (Jain 2003), minipill (Gemzell-Danielsson 2002) or Norplant (Massai 2004) users. In the first two studies, the authors reported that women taking antiprogestins reported fewer cycles with extended periods (more than 14 days) of breakthrough bleeding or better cycle control, respectively, than did placebo users; however, these outcomes were not identified for the present review, and therefore the data could not be included in this analysis. Massai et al (Massai 2004) demonstrated acute, but not long-term, improvements in bleeding patterns in new Norplant users taking mifepristone. In contrast, mifepristone was not effective in stopping an episode of bleeding in women using Implanon (Weisberg 2006). In this trial, the addition of an estrogen to mifepristone was more effective than placebo in stopping an episode of bleeding. The data were presented in terms of 90-day reference periods, before and after the treatment; our analysis was not able to capture the data presented in this manner.

Glasier et al (Glasier 2002) and Jain et al (Jain 2003) have suggested that mifepristone may functionally inhibit progesterone, leading to up-regulation of endometrial estrogen receptors and a positive effect on bleeding patterns similar to exogenous estrogen treatment. In contrast, Grow and co-workers (Grow 1998) have demonstrated, primarily in non-human primates, that even though estrogen receptors are increased following mifepristone exposure, the receptors may not be transcriptionally active.

While anti-progestins have been shown in some trials to improve bleeding. The results of these studies need to be substantiated in larger, well-controlled trials; an effective dose and regimen need to be defined. In addition, the safety of such a regimen needs to be established, as the approach to antagonize the effect of the progestin to achieve better bleeding patterns may potentially compromise the efficacy of the contraceptive method. In fact, one pregnancy was reported in the trial using the highest dose of mifepristone (Massai 2004).

The results of the single trial that was designed to evaluate the effects of a **SERM** (tamoxifen) on bleeding patterns in women using progestin-only contraceptive methods were quite promising in terms of effectiveness, safety, continuation of the contraceptive method and compliance with treatment. This was the only regimen that demonstrated an effect that lasted longer than the period of treatment. Again, this result needs to be substantiated in larger trials, with longer periods of follow-up, before any clinical recommendation can be made. Grow et al hypothesized that SERMs may improve bleeding patterns disrupted by the use of progestin-only contraceptives by antagonizing the angiogenic effect of estrogen (Grow 1998).

Several **other types of treatments** have been shown to be somewhat effective in small trials, but the results have not been reproduced in larger studies, possibly demonstrating an overestimation of the beneficial effects of drugs in small studies. Vitamin E, for example, was effective in reducing the number of bleeding days during treatment in a pilot study conducted in Indonesia (Subakir 2000); these results were not replicated in a large multi-centre study of the same regimen, even in the same Indonesian centre (d'Arcangues 2005). The d'Arcangues et al study (d'Arcangues 2005) also failed to replicate the positive results of NSAIDs on bleeding patterns found by Diaz et al (Diaz 1990), Kaewrudee et al (Kaewrudee 1999) and Nathirojanakun et al (Nathirojanakun 2006). These different results may be related to the use of different treatments - the studies that reported a positive effect of the treatment tested ibuprofen, as used by 21 women (Diaz 1990), mefenamic acid, in 34 women (Kaewrudee 1999) or the COX-2 inhibitor, valdecoxib, in 22 women (Nathirojanakun 2006); in the larger trial, in which an NSAID was not effective, over 100 women who received aspirin were included in the analysis. On the other hand, the rationale for testing both of these types of interventions is scientifically compelling. As the angiogenic response in the endometrium of Norplant users has been found to be lower than in women with normal menstrual cycles (Subakir 2000), the disturbance in the angiogenic process, as well as an imbalance of pro- and antioxidant processes in the endometrium, may contribute to irregular bleeding in Norplant users. Supplementation with vitamin E may serve as an effective method of preventing membrane damage caused by oxygen radicals (Halliwell 1992) or of increasing endometrial angiogenic activity (Subakir 2000).

Recently-published small studies have suggested that the antifibri-

lytic compound, tranexamic acid, can have a short-term therapeutic effect on bleeding disturbances in Norplant users (Phupong 2006) and that the matrix metalloproteinase inhibitor, doxycycline, can be effective in terminating an episode of prolonged bleeding in Implanon users (Weisberg 2006). These results remain to be confirmed in larger trials.

AUTHORS' CONCLUSIONS

Implications for practice

Based on the results of this review, women may benefit to a degree from the interventions described, particularly with regard to cessation of an ongoing bleeding episode. Several regimens offer promise in regulating bleeding in the short term, but positive results need to be reproduced in larger scale trials. However, the results of the review do not support the routine clinical use of any of the treatment or preventive regimens to exert anything other than a short-term effect on the current bleeding episode; no medium- or long-term beneficial effects were described in any of the studies. The review was focused on pharmacologic interventions; however, it is acknowledged that proper counseling at the time of method initiation can adequately prepare women for the bleeding irregularities that they may experience and improves method continuation rates.

Implications for research

Many women using progestin-only methods experience unacceptable bleeding disturbances, discontinue use, and are left without contraceptive protection. It is essential that the family planning research community develop standardized methodologies for research and reporting in this field of study. If a common set of outcomes could be developed and widely utilized, studies could be more easily and effectively interpreted and compared, and the findings would more readily make their way into evidence-based practice, as appropriate. It is recommended that future studies attempt to collect data on blood loss. Pictorial blood assessment scores can be used.

Through the process of performing the review, it became clear to the authors that additional research directed towards the possible underlying mechanisms of bleeding among users of these products is required. Results from such studies would not only help to further identify potential therapeutic interventions, but will help to ensure that clinical studies and, eventually, treatments can be based on etiological findings.

POTENTIAL CONFLICT OF INTEREST

CDA and HAA have conducted research in this area and have authored papers included in the review.

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REFERENCES

References to studies included in this review

Abdel-Aleem 2005 {published data only}

Abdel-Aleem H, Shaaban OM, Amin AE, Abdel-Aleem AM. Tamoxifen treatment of bleeding irregularities associated with Norplant use. *Contraception* 2005;**72**:432–437.

Alvarez-Sanchez 1996 {published data only}

Alvarez-Sanchez F, Brache V, Thevenin F, Cochon L, Faundes A. Hormonal treatment for bleeding irregularities in Norplant implant users. *American Journal of Obstetrics and Gynecology* 1996;**174**:919–922.

Boonkasemsanti 1996 {published data only}

Boonkasemsanti W, Reinprayoon D, Pruksananonda K, Niruttisard S, Triratanachai S, Leepipatpaiboon S, Wannakrairot P. The effect of transdermal oestradiol on bleeding pattern, hormonal profiles and sex steroid receptor distribution in the endometrium of Norplant users. *Human Reproduction* 1996;**11**:115–123.

Cheng 2000 {published data only}

Cheng L, Zhu H, Wang A, Ren F, Chen J, Glasier A. Once a month administration of mifepristone improves bleeding patterns in women using subdermal contraceptive implants releasing levonorgestrel. *Human Reproduction* 2000;**15**:1969–1972.

d'Arcangues 2005 {published and unpublished data}

d'Arcangues C, Piaggio G, Brache V, Aissa RB, Hazelden C, Massai R, Pinol A, Subakir SB, Su-juan G, Study Group on Progestogen-induced Vaginal Bleeding Disturbances. Effectiveness and acceptability of vitamin E and low-dose aspirin, alone or in combination, in Norplant-induced prolonged bleeding. *Contraception* 2004;**70**:451–462.

Diaz 1990 {published data only}

Diaz S, Croxatto HB, Pavez M, Belhadj H, Stern J, Sivin I. Clinical assessment of treatments for prolonged bleeding in users of Norplant implants. *Contraception* 1990;**42**:97–109.

El-Habashy 1970 {published data only}

El-Habashy MA, Mishell DR Jr, Moyer DL. Effect of supplementary oral estrogen on long-acting injectable progestogen contraception. *Obstetrics and Gynecology* 1970;**35**:51–54.

Gemzell-Danielsson 1996 {published data only}

Gemzell-Danielsson K, van Heusden AM, Killick SR, Croxatto HB, Bouchard P, Cameron S, Bygdeman M. Improving cycle control in progestogen-only contraceptive pill users by intermittent treatment with a new anti-progestogen. *Human Reproduction* 2002;**17**:2588–2593.

Goldberg 2002 {published data only}

Goldberg AB, Cardenas LH, Hubbard AE, Darney PD. Post-abortion depot medroxyprogesterone acetate continuation rates: a randomized trial of cyclic estradiol. *Contraception* 2002;**66**:215–220.

Jain 2003 {published data only}

Jain JK, Nicosia AF, Nucatola DL, Lu JJ, Felix JC. Mifepristone for the prevention of breakthrough bleeding in new starters of depot medroxyprogesterone acetate. *Steroids* 2003;**68**:1115–1119.

Johannisson 1982 {published data only}

Johannisson E, Landgren BM, Diczfalussy E. Endometrial morphology and peripheral steroid levels in women with and without intermenstrual bleeding during contraception with 300 mcg Norethisterone (NET) Minipill. *Contraception* 1982;**25**:13–30.

Kaewrudee 1999 *[published data only]*

Kaewrudee S, Taneepanichskul S, Jaisamraun U, Reinprayoon D. The effect of mefenamic acid on controlling irregular uterine bleeding secondary to Norplant use. *Contraception* 1999;**60**:25–30.

Massai 2004 *[published data only]*

Massai MR, Pavez MR, Fuentealba B, Croxatto H, d'Arcangues C. Effect of intermittent treatment with mifepristone on bleeding patterns in Norplant implant users. *Contraception* 2004;**70**:442–450.

Monteil-Seurin 1985 *[published data only]*

Monteil-Seurin J, Bernard-Fernier MF, Martinaggi P, Demarez JP, Cauquil J, Lafont A. Evaluation of the efficacy of a ventonic capillary protector in the treatment of metrorrhagia due to IUD or micropill contraception [Appreciation de l'efficacité d'une association veino-tonique protecteur capillaire comme traitement des metrorragies de la contraception par D.I.U. ou par micropilule]. *Contraception-fertilité-sexualité* 1985;**13**:721–725.

Nathirojanakun 2006 *[published data only]*

Nathirojanakun P, Taneepanichskul S, Sappakitumjorn N. Efficacy of a selective COX-2 inhibitor for controlling irregular uterine bleeding in DMPA users. *Contraception* 2006;**73**:584–587.

Parker 1980 *[published data only]*

Parker RA. The use of Quinesterol for the control of vaginal bleeding irregularities caused by DMPA. *Contraception* 1980;**22**:1–7.

Phupong 2006 *[published data only]*

Phupong V, Sophonsritsuk A, Taneepanichskul S. The effect of tranexamic acid for treatment of irregular uterine bleeding secondary to Norplant use. *Contraception* 2006;**73**:253–256.

Sadeghi-Bazargani *[published data only]*

Sadeghi-Bazargani H, Ehdadivand F, Arshi S, Eftekhari H, Sezavar H, Amanati L. Low-dose oral contraceptive to re-induce menstrual bleeding in amenorrheic women on DMPA treatment: A randomized clinical trial. *Medical Science Monitor* 2006;**12**:CR420–CR425.

Said 1996 *[published data only]*

Said S, Sadek W, Rocca M, Koetsawang S, Kirwat O, Piya-Anant M, Dusitsin N, Sethavanich S, Affandi B, Hadisaputra W, Kazi A, Ramos RM, d'Arcangues C, Belsey EM, Noonan E, Olayinka I, Pinol A, World Health Organization, Special Programme of Research, Development and Research Training in Human Reproduction, Task Force on Long-acting Systemic Agents For Fertility Regulation. Clinical evaluation of the therapeutic effectiveness of ethinyl oestradiol and oestrone sulphate on prolonged bleeding in women using depot medroxyprogesterone acetate for contraception. *Human Reproduction* 1996;**11**:1–13.

Subakir 2000 *[published data only]*

Subakir SB, Setiadi E, Affandi B, Pringgoutomo, Freisleben HJ. Benefits of vitamin E supplementation to Norplant users - in vitro and in vivo studies. *Toxicology* 2000;**148**:173–8.

Tantiwattanakul 2004 *[published data only]*

Tantiwattanakul P, Taneepanichskul S. Effect of mefenamic acid on controlling irregular uterine bleeding in DMPA users. *Contraception* 2004;**70**:277–279.

Weisberg 2006 *[published data only]*

Weisberg E, Hickey M, Palmer D, O'Connor V, Salamonsen L, Findlay JK, Fraser IS. A pilot study to assess the effect of three short-

term treatments on frequent and/or prolonged bleeding compared to placebo in women using Implanon. *Human Reproduction* 2006;**21**:295–302.

Witjaksono 1996 *[published data only]*

Witjaksono J, Lau TM, Affandi B, Rogers PA. Oestrogen treatment for increased bleeding in Norplant users: preliminary results. *Human Reproduction* 1996;**11**:109–114.

References to studies excluded from this review

Archer 1996

Archer DF, Philput CA, Weber ME. Management of irregular uterine bleeding and spotting associated with Norplant. *Human Reproduction* 1996;**11**:24–30.

Cseffalvay 1965

Cseffalvay T, Klose S. (Estrogen-gestagen therapy with hormonally induced uterine bleeding. 11. Therapeutic use of Klimovan). *Deutsche Gesundheitswesen* 1965;**20**:1334–1339.

d'Arcangues 2000

d'Arcangues C. Management of vaginal bleeding irregularities induced by progestin-only contraceptives. *Human Reproduction* 2000;**15**:24–29.

Glazier 2002

Glazier AF, Wang H, Davie JE, Kelly RW, Critchley HO. Administration of antiprogesterone up-regulates estrogen receptors in the endometrium of women using norplant: a pilot study. *Fertility and Sterility* 2002;**77**:366–372.

Piya-Anant 1998

Piya-Anant M, Koetsawang S, Patrasupapong N, Dinchuen P, d'Arcangues C, Piaggio G, Pinol A. Effectiveness of cyclofem in the treatment of depot medroxyprogesterone acetate induced amenorrhea. *Contraception* 1998;**57**(1):23–28.

Additional references

Affandi 1998

Affandi B. An integrated analysis of vaginal bleeding patterns in clinical trials of Implanon. *Contraception* 1998;**58**:99s–107s.

d'Arcangues 1992

d'Arcangues C, Odland V, Fraser IS. Dysfunctional uterine bleeding induced by exogenous hormones. In: Alexander NJ, d'Arcangues C editor(s). *Steroid hormones and uterine bleeding*. Washington: AAAS Press, 1992:81–105.

Datey 1995

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**:155–165. [MedLine: PMID 7621684 UI 95347181].

Fan 1996

Fan M, Sujuan G. Menstrual bleeding patterns in Chinese women using the Norplant subdermal implant. *Human Reproduction* 1996;**11**:14–19.

Fraser 1983

Fraser IS. A survey of different approaches to management of menstrual disturbances in women using injectable contraceptives. *Contraception* 1983;**28**:385–397.

Fraser 1998

Fraser IS, Tiitinen A, Affandi B, Brache V, Croxatto H, Diaz S, Ginsburg J, Gu S, Holma P, Johansson E, Meirik O, Mishell DR Jr, Nash HA, von Schoultz B, Sivin I. Norplant consensus statement and background review. *Contraception* 1998;**57**:1–9.

Grow 1998

Grow DR, Reece MT, Hsiu JG, Adams L, Newcomb PM, Williams RF, Hodgen GD. Chronic antiprogesterin therapy produces a stable atrophic endometrium with decreased fibroblast growth factor: a 1-year primate study in contraception and amenorrhea. *Fertility and Sterility* 1998;**69**(5):936–943.

Halliwell 1992

Halliwell B, Gutteridge JM, Cross CE. Free radical, antioxidants and human disease: where are we now?. *Journal of Laboratory and Clinical Medicine* 1992;**119**:598–620.

Newton 1994

Newton JR, d'Arcangues C, Hall PE. A review of “once-a-month” combined injectable contraceptives. *Journal of Obstetrics and Gynaecology* 1994;**4**:S1–S34.

Nutley 1997

Nutley T, Dunson TR. Treatment of bleeding problems associated with progestin-only contraceptives: survey results. *Advances in Contraception* 1997;**13**:419–428.

Said 1987

Said S, Omar K, Koetsawang S, Kiriwat O, Srisatayapan Y, Kazi A, Ajmal F, Wynter HH, Pretnar-Darovec A, Benitez IB, World Health Organization, Task Force on Long-Acting Systemic Agents for Fertility Regulation, Special Programme of Research, Development and Research Training in Human Reproduction. A multicentered phase III comparative clinical trial of depot-medroxyprogesterone acetate given three-monthly at doses of 100 mg or 150 mg: II. The comparison of bleeding patterns. *Contraception* 1987;**35**:591–610.

Shaaban 1984

Shaaban MM, Elwan SI, el-Kabsh MY, Farghaly SA, Thabet N. Effect of levonorgestrel contraceptive implants, Norplant, on blood coagulation. *Contraception* 1984;**30**:421–430.

Suvisaari 1996

Suvisaari J, Lahteenmaki P. Detailed analysis of menstrual bleeding patterns after postmenstrual and postabortion insertion of a copper IUD or a levonorgestrel-releasing intrauterine system. *Contraception* 1996;**54**:201–208.

Viegas 1988

Viegas OA, Singh K, Koh S, Singh P, Ratnam SS. The effects of Norplant on clinical chemistry in Singaporean acceptors after 1 year of use: I. Haemostatic changes. *Contraception* 1988;**38**:313–323.

TABLES

Characteristics of included studies

Study	Abdel-Aleem 2005
Methods	Randomized trial Study duration: 3 months Type of trial: parallel Outcome assessment blinding: yes Drop outs: 7 (7%) Validity criteria: A
Participants	100 women in the first year of Norplant use, complaining of increased bleeding Age: Tamoxifen: 32.48 ± 5.6 Pl: 32.28 ± 6.1 Education level: Tamoxifen: 26/50 illiterate; 24/50 some education Pl: 24/50 illiterate; 26/50 some education Setting: Family planning clinic, university hospital Diagnostic criteria: Abnormal/increased bleeding defined as current episode of bleeding/spotting longer than 8 days OR bleeding-free interval less than 15 days.
Interventions	Agents: Tamoxifen: 10 mg twice a day, for 10 days, oral; Placebo: twice a day, for 10 days, oral. Treatment length: 10 days

Characteristics of included studies (Continued)

	Follow up: 3 months
Outcomes	<p>Percent of women who stopped bleeding during the treatment: Overall, within 3 days, within 7 days, within 10 days.</p> <p>Bleeding, spotting or bleeding/spotting days during follow up: First month, second month, third month</p> <p>Bleed-free interval post-treatment (days)</p> <p>B/S episodes in 90 day reference period</p> <p>Discontinuation of contraceptive method due to bleeding</p> <p>Discontinuation of treatment due to lack of improvement</p> <p>Side effects related to treatment: Headache, GI disturbance, dizziness, fatigue, hot flush, other</p> <p>Patient satisfaction with treatment, over time: First month, second month, Third month - data not given (no difference between groups)</p>
Notes	
Allocation concealment	A – Adequate
Study	Alvarez-Sanchez 1996
Methods	<p>Randomized trial</p> <p>Study duration: 8 weeks</p> <p>Type of trial: parallel</p> <p>Outcome assessment blinding: inadequate</p> <p>Drop outs: 16 (10.66%)</p> <p>Validity criteria: B (moderate risk of bias)</p>
Participants	<p>150 Norplant users in the first year of use enrolled; 134 included in analysis</p> <p>Age (years): EE (n=43) 23±4.2 LNG+EE (n=45): 24.6±3.8 PI (n=46): 25.0±4.5</p> <p>Setting: Family planning clinic</p> <p>Diagnostic criteria: Prolonged bleeding: (bleeding or spotting 8 days or more) Irregular bleeding (bleeding-free interval <15 days)</p>
Interventions	<p>EE: 50 mcg/day x 20 days, orally;</p> <p>LNG: 250 mcg/day + EE 50 mcg/day x 20 days orally;</p> <p>PI: 1/day x 20 days, orally</p> <p>Treatment length: 20 days</p> <p>Follow-up 8 weeks</p>
Outcomes	<p>Effectiveness of treatment, as measured by a cessation of B/S in 3 days of treatment or less</p> <p>Mean number of bleeding days during treatment interval</p> <p>Percentage of women with bleeding-free interval of 20 days or more</p> <p>Percentage of women with bleeding-free interval of less than 11 days</p> <p>Discontinuation of contraceptive method because of bleeding</p> <p>Side-effects related to treatment (stomach pain, nausea)</p> <p>Discontinuation rate because of side-effects</p>

Characteristics of included studies (Continued)

Notes

Allocation concealment B – Unclear

Study	Boonkasemsanti 1996
Methods	Randomized trial Study duration: 10 weeks Type of trial: parallel Outcome assessment blinding: yes Drop-outs: 0 Validity criteria: B (moderate risk of bias)
Participants	64 Norplant users in the first year of use. Age (years): Estradiol patch (E) 27±3; PI 25±4. Setting: University Ob/Gyn Dept Diagnostic criteria: Bleeding problems as defined by bleeding more than 8 days, and/or bleeding-free interval less than 10 days.
Interventions	Agents: Estradiol patch (n=33) releasing 100 mcg/24 hours x 6 weeks; PI patch (n=31) x 6 weeks. Follow-up: 6 weeks
Outcomes	“Clinical improvement” refers to women with an initially abnormal pattern, who develop a normal pattern (bleeding less than 8 days and/or bleeding free interval more than 20 days). Continued irregular bleeding

Notes

Allocation concealment B – Unclear

Study	Cheng 2000
Methods	Randomized trial Study duration: 360 days Type of trial: parallel Outcome assessment blinding: yes Drop-outs: 0 Validity criteria: A (low risk of bias)
Participants	100 women using Norplant for 3-43 months. Age (years): Mifepristone 29.5; Placebo 30 Setting: Family planning clinic Diagnostic criteria: Frequent vaginal bleeding, defined as bleeding episode occurring more often than once every 24 days.
Interventions	Agents: Mifepristone (n=50) 50 mg (2x25 mg tablets) once, orally. PI (n=50) 2 tablets once, orally. Treatment started on the third day after the start of a B/S episode.

Characteristics of included studies (Continued)

	<p>After the first treatment, women were given a date to return to the clinic once/28 days for 5 months (a total of 6 treatments in all).</p> <p>Follow-up: 12 months</p> <p>Reference period 1: 90 days before the first treatment;</p> <p>Reference periods 2 and 3 cover 180 days from the first treatment, and together include 6 treatment months and the first 12 days of the seventh month.</p> <p>Reference period 4 started 39 days after the last treatment and ended 90 days later.</p>
Outcomes	<p>Number of bleeding days over time:</p> <p>Reference period 1, reference period 2, reference period 3, reference period 4</p> <p>Average duration of bleeding episodes (days):</p> <p>Reference period 1, after treatment</p> <p>Women rating their treatment as satisfactory</p> <p>Discontinuation rate because of bleeding</p> <p>Side effects related to treatment</p>
Notes	
Allocation concealment	A – Adequate

Study	Diaz 1990
Methods	<p>Quasi-randomized trial</p> <p>Study duration:</p> <p>one year</p> <p>Type of trial:</p> <p>Parallel</p> <p>Outcome assessment blinding: Yes</p> <p>Drop outs:</p> <p>Total: 43/183 (24%)</p> <p>LNG 13/47 (28%)</p> <p>EE 12/45 (27%)</p> <p>Ibuprofen 10/45 (22%)</p> <p>PI 8/46 (17%).</p> <p>Validity criteria: C (High risk of bias)</p>
Participants	<p>183 women using Norplant for 3-43 months.</p> <p>Age (years; mean \pm SD):</p> <p>LNG 26 \pm 4;</p> <p>EE 27 \pm 4;</p> <p>Ibuprofen 27 \pm 4;</p> <p>PI 27 \pm 4.</p> <p>Setting: Family planning clinic</p> <p>Diagnostic criteria:</p> <p>Frequent vaginal bleeding, defined as bleeding episode occurring more often than once every 24 days.</p>
Interventions	<p>Agents:</p> <p>LNG 0.03 mg tablets, twice daily x 20 days, orally;</p> <p>EE 0.05 mg tablets once daily x 20 days, orally;</p> <p>Ibuprofen 800 mg, three times daily x 5 days, orally;</p> <p>PI once daily, x 20 days, orally.</p> <p>Schedule:</p>

Characteristics of included studies (Continued)

	Treatment began on the 8th consecutive day of each B/S episode, as needed throughout the year, but no more than five treatments in the year.
	Follow-up: Each time a B/S episode lasted more than 7 days, and at three month intervals.
Outcomes	Mean number of bleeding days per woman in intervals of days 1-20, 1-5, and 6-20 of treatment. Mean number of B/S days per woman in intervals of days 1-20, 1-5, and 6-20 of treatment Mean number of B/S days per treated woman in the year: Discontinuation of contraceptive method because of lack of improvement at the end of the year Discontinuation of treatment due to side effects (gastric intolerance)

Notes

Allocation concealment B – Unclear

Study El-Habashy 1970

Methods	Randomized trial Type of trial: parallel Study duration: 3 months Outcome assessment blinding: unclear Drop-outs: 2/63 (3.2%) validity criteria: B (moderate risk of bias)
Participants	63 post-partum women who chose DMPA as their method of contraception Age: data not given Setting: Hospital Diagnostic criteria: Prophylactic prevention of bleeding problems. No definition of normal or abnormal bleeding patterns provided.
Interventions	Diethylstilbestrol (DES; n=32): 1mg tablet/daily x 90 days, orally; PI (n=31) 1 vitamin tablet/daily x 90 days. Follow-up: monthly
Outcomes	Number of women experiencing bleeding episodes of less than 8 days (including 0 days): First month, second month, third month Compliance, as defined as taking the agent 25 days/month or more:

Notes

Allocation concealment B – Unclear

Study Gemzell-Danielsson

Methods	Randomized trial Study duration: 16-28 weeks Type of trial: parallel Outcome assessment blinding: yes Drop-outs: 12/103 (12%) Anti-progesterone: 3/52 (5.8%) Placebo: 9/51(17.6%) Validity criteria: C (high risk of bias)
Participants	103 women using 75 mcg desogestrel pill daily Age (mean): Antiprogesterone 31.6; Placebo 32.8

Characteristics of included studies (Continued)

	Setting: Research institutes Diagnostic criteria, within a 90-day reference period: Amenorrhea: no B/S Infrequent bleeding: fewer than three B/S episodes, excluding amenorrhea Frequent bleeding: more than five B/S episodes Prolonged bleeding: one or more B/S episode lasting more than 14 days Irregular bleeding: range of the length of bleeding-free intervals less than 17 days
Interventions	Agents: Org 31710 (antiprogesterone) 150 mg (three tablets x 50 mg), once/28 days, orally Placebo three similar tablets, once/28 days, orally Schedule: One dose every 28 days for a maximum of seven treatments. Follow-up: 16-28 weeks.
Outcomes	Effectiveness of treatment: Number (percentage) of days with recorded B/S, cycle day 8-28: Cycle 1, cycle 3, cycle 6 Number (percent) of subjects with B/S episodes starting day 8-28: Cycle 1, cycle 3, cycle 6 Discontinuation rate because of bleeding Side effects related to treatment (headache, emotional lability, acne, breast pain) Discontinuation of the study because of side effects
Notes	
Allocation concealment	A – Adequate

Study	Goldberg 2002
Methods	Randomized trial Type of trial: parallel Study duration: 12 months Outcome assessment blinding: adequate Drop-outs: 50/132 (38%) Estradiol 30/66 (45%); Pl: 20/66 (30%) Validity criteria: C (high risk of bias)
Participants	132 post-abortion DMPA users in the first year of use Age (years): Estradiol patch 24±5.2; Pl 23±5.9. Education: No significant difference between groups Setting: Hospital-based research unit.
Interventions	Agents and schedule: 17-beta Estradiol patch (0.1 mg/day, brand name Climara)/weekly x 3 patches per month (3 weeks on + 1 week off/month), transdermal. Pl patch 1 patch/weekly x 3 patches per month (3 weeks on + 1 week off/month), transdermal. Duration of treatment: 3 months. Follow-up: at months 4, 8 and 12.
Outcomes	Effectiveness of treatment as defined by association between use of estrogen patches and regular bleeding patterns, over time: Discontinuation of the contraceptive method over time:

Characteristics of included studies (Continued)

	At 4 months, 8 months, 12 months
	Discontinuation of the contraceptive method due to bleeding:
	Non-compliance with treatment due to side effects (inconvenience and skin irritation): (Compliance defined as using 6 out of 9 treatment patches)
	Reasons for non-compliance
	Side effects related to treatment (skin irritation, inconvenience)
Notes	High rate of DMPA discontinuation. High rate of non-compliance with the study protocol.
Allocation concealment	A – Adequate

Study	Jain 2003
Methods	Randomized trial Study duration: 6 treatment cycles of 28 days each Type of trial: parallel Outcome assessment blinding: not clear Drop-outs: 0 Validity criteria: B (moderate risk of bias)
Participants	20 new users of DMPA Age: not described Setting: University Ob/Gyn department Diagnostic criteria: not described
Interventions	Agents: Mifepristone: 50 mg, every 14 days, orally Pl: similar tablet every 14 days, orally Treatment length: six cycles (6 x 28 days) Follow-up: six cycles
Outcomes	Percent days with breakthrough bleeding (median) Cycles 1-3, cycles 4-6, total cycles 1-6 Number (percent) cycles with bleeding intervals 8 or more days Cycles 1-3, cycles 4-6, total cycles 1-6 Number (percent) cycles with bleeding intervals 14 or more days Cycles 1-3, cycles 4-6, total cycles 1-6 Ovulation
Notes	
Allocation concealment	B – Unclear

Study	Johannisson 1982
Methods	Randomized trial Type of trial: parallel Study duration: 4 months (1 month control + 3 months treatment) Outcome assessment blinding: unclear Drop-outs: 0 Validity criteria: B (moderate risk of bias)
Participants	12 minipill users (300 µg norethisterone (Net)) Age: 25-30 years Setting: clinical research settings

Characteristics of included studies (Continued)

	Diagnostic criteria: Intermenstrual bleeding in second month of Net use.
Interventions	Agents and schedule: EE (n=6) 50 µg/daily x 7 days, orally. PI (n=6) once/daily x 7 days, orally. Treatment started in case of intermenstrual bleeding, after endometrial biopsy. Follow-up: 7 days.
Outcomes	Number of days with bleeding during 7 days treatment
Notes	
Allocation concealment	B – Unclear

Study	Kaewrudee 1999
Methods	Randomized trial Type of trial: parallel Study duration: 4 weeks Outcome assessment blinding: yes Drop-outs: 2/69 (2.9%) Validity criteria: A (low risk of bias)
Participants	69 women using Norplant for 3-36 months recruited; 67 included in analysis.. Age (years): Mefenamic acid (MEF n=34) 27.2±9.4; PI (n=33) 25.0±5.9. Setting: Family planning clinic in hospital Ob/Gyn Department Diagnostic criteria: Prolonged bleeding defined as 8 or more continuous days of bleeding or spotting; Irregular bleeding defined as a current bleeding episode following a bleeding-free interval of less than 15 days.
Interventions	Agents and schedule: MEF 500 mg/twice daily x 5 days, orally; PI 2 capsules/twice daily x 5 days, orally. Follow-up: One and four weeks after treatment.
Outcomes	Percentage of women who stopped bleeding within 7 days after initiation of treatment Bleeding free interval more than 20 days at 28 days follow-up Number of B/S days within the 28 day follow up period (Mean±SD) Side effects related to treatment (headache, dysmenorrhea, breast tenderness and leukorrhea) Discontinuation rate due to side effects
Notes	
Allocation concealment	A – Adequate

Study	Massai 2004
Methods	Randomized trial Study duration: 13 months Type of trial: parallel Outcome assessment blinding: yes Drop-outs: 5/120 (4%) Validity criteria: B (moderate risk of bias)

Characteristics of included studies (Continued)

Participants	<p>120 new Norplant users enrolled 116 completed 6 months of treatment 115 included in analysis</p> <p>Age (Mean \pm SD): Mifepristone (n=58): 30.1 \pm 4.1; PI (n=57): 28.3 \pm 4.8.</p> <p>Setting: Research institute</p> <p>Diagnostic criteria: Prolonged bleeding episode: more than 8 consecutive days of B/S.</p>
Interventions	<p>Agents: Mifepristone 100 mg/day x 2 days at 30 day intervals, orally Placebo: pill/day x 2 days at 30 day intervals, orally.</p> <p>Treatment duration: 2 days, repeated at 30 day intervals for 6 months (months 2-7 of implant use) Start 30 days after implant insertion.</p> <p>Follow-up: monthly during treatment and for 6 additional months. Additional follow up after treatment, for 6 months (total 13 months).</p>
Outcomes	<p>The number of B/S days per woman during the 180-day treatment (Mean+SD), over time; At end of treatment, 6 months after end of treatment</p> <p>Number of bleeding episodes in treatment period: Number (%) of women with 5-8 bleeding episodes during 6 months treatment, number (%) of women with more than 8 bleeding episodes during treatment</p> <p>Mean length of B/S episodes (days)</p> <p>Women with 1 or more episode of prolonged bleeding, number (%), over time At the end of treatment, 6 months after end of treatment</p> <p>Total number B/S episodes</p> <p>Number of prolonged bleeding episodes</p> <p>Total number of B/S days at 6 months and post-treatment</p> <p>Proportion of bleeding episodes that were prolonged</p> <p>Mean length (days) of B/S episodes longer than 8 days</p> <p>Discontinuation of the contraceptive method</p> <p>Discontinuation of the contraceptive method due to bleeding</p> <p>Discontinuation of treatment due to lack of improvement</p> <p>Side effects (headache, weight loss, acne, nervousness, abdominal pain, lichen sclerosis)</p>
Notes	
Allocation concealment	B – Unclear

Study **Monteil-Seurin 1985**

Methods	<p>Randomized trial Type of trial: parallel Study duration: 3 months Outcome assessment blinding: no</p>
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Characteristics of included studies (Continued)

	Drop-outs: 0 Validity criteria: C (high risk of bias)
Participants	40 Minipill (Norethisterone acetate - NET) users for at least one month. Age: average 25 years. Setting: Clinical practice
Interventions	Agents and schedule: Cyclo 3 (Capillary protecting venotonic drug containing <i>Ruscus aculeatus</i>) 4 capsules daily x 20 days PI 4 capsules daily x 20 days Duration: 20 days, stopped during menses, repeated for 3 months. Follow-up: 3 months.
Outcomes	Duration of bleeding in intermenstrual bleeding episodes (days), over time: Pre-treatment, at 1-month, at 3 cycles Number of days pads or tampons used Pre-treatment, at 1-month, at 3 cycles Subjective assessment of discomfort caused by bleeding: Pre-treatment, during treatment (after 1 cycle), after 3 cycles Tolerance to drug
Notes	
Allocation concealment	B – Unclear

Study	Nathirojanakun 2006
Methods	Randomized trial Type of trial: parallel Study duration: 28 days Outcome assessment blinding: yes Drop outs: 5/51 (9.8%) Validity criteria: A (low risk of bias)
Participants	51 DMPA users (3-12 months) reporting abnormal bleeding Age (years): Valdecobix (n=25) 24.1 ± 6.6; PI (n=26) 25.1 ± 7.3. Setting: Family planning clinic in hospital Ob/Gyn department Diagnostic criteria: 8 or more days of bleeding or spotting prior to bleeding on the day of admission
Interventions	Agents and schedule: Valdecobix (Cox-2 inhibitor): two tablets (20 mg /tablet) daily x 5 days, orally; PI 2 tablets daily x 5 days, orally. Follow-up: 4 weeks.
Outcomes	Number of treatment days required to stop bleeding Percentage of women who stopped bleeding within 7 days following initiation of treatment Total number of bleeding-free days in 28 day follow-up period Length of the bleeding-free interval in the 28 day follow up period
Notes	
Allocation concealment	A – Adequate

Study	Parker 1980
Methods	Randomized trial

Characteristics of included studies (Continued)

	Type of trial: parallel Study duration: 12 months Outcome assessment blinding: yes Drop-outs: 55/236 (23%). Validity criteria: C (high risk of bias)
Participants	236 women who used DMPA for 90 days; 214 women included in analysis. Age: Varying from 24.0±3.84 to 26.0±5.43, with no differences between groups. Setting: Clinic Diagnostic criteria: Acceptable bleeding pattern: 2-4 bleeding episodes in a 12 week injection segment, with no episode longer than 8 days; Prolonged bleeding pattern: a bleeding episode longer than 8 days; Amenorrhea: no bleeding; Irregular bleeding: one bleeding episode or more than 4 bleeding episodes in a 12 week injection segment.
Interventions	Agents. Quinestrol (Quin) 400 ug, orally. Placebo, orally Doses: One capsule Quin or Pl/injection segment; Three capsules Quin or Pl/injection segment. Regimens: One capsule Quin or Pl with DMPA injection; One capsule Quin or Pl two weeks after DMPA injection; One capsule Quin or Pl at 0, 4, and 8 weeks after DMPA injection (total 3 capsules); One capsule Quin or Pl at 2, 6, and 10 weeks after DMPA injection (total 3 capsules).
Outcomes	Acceptable bleeding, over time First injection segment, all segments combined: Discontinuation because of bleeding Discontinuation because of amenorrhea Discontinuation due to side effects (headache, weight change, palpitations, sickness)
Notes	
Allocation concealment	B – Unclear

Study	Phupong 2006
Methods	Randomized trial Type of trial: parallel Study duration: 4 weeks Outcome assessment blinding: yes Drop outs: 0 Validity criteria: A (low risk of bias)
Participants	68 women using Norplant for 3-36 months and reporting irregular bleeding. Age (years): Tranexamic acid (n=34) 27.0 ± 5.7; Pl (n=34) 29.1 ± 6.1 Setting: Family planning clinic in hospital Ob/Gyn Department Diagnostic criteria: Diagnostic criteria:

Characteristics of included studies (Continued)

	Bleeding or spotting for eight or more continuous days, or a current bleeding episode initiated after a bleeding-free interval of 14 days or less
Interventions	Agents and schedule: Tranexamic acid: two capsules (250 mg /capsule) 4 times daily x 5 days, orally; Pl: two capsules 4 times daily x 5 days, orally Follow up: one and four weeks
Outcomes	Percentage of women who stopped bleeding after one week Percentage of women who stopped bleeding after four weeks Mean duration of b/s days during 28 days of follow up.
Notes	
Allocation concealment	A – Adequate

Study	Sadeghi-Bazargani
Methods	Randomized trial Type of trial: parallel Study duration: undefined Outcome assessment blinding: yes Drop outs: unclear Validity criteria: B (moderate risk of bias)
Participants	46 DMPA users with amenorrhea Combined oral contraceptive: n = 24 Pl: n = 22 Age: not given for trial population. Setting: District Health centres. Education: not given for trial population. Diagnostic criteria: Amenorrhea as defined as two months without menstrual bleeding following DMPA injection
Interventions	Agents: Low dose combined oral contraceptives (components not reported), daily, orally. Pl daily, orally. Treatment duration: not reported Follow up duration: not reported.
Outcomes	Effectiveness of combined oral contraceptive in comparison to Pl in resolving amenorrhea. Discontinuation of the contraceptive.
Notes	
Allocation concealment	A – Adequate

Study	Said 1996
Methods	Randomized trial Type of trial: parallel Study duration: 18 months Outcome assessment blinding: yes Drop-outs: Total: 117/278 (44%) EE: 40/90 (44.4%); Oestrone sulfate (OS): 37/91 (40.7%); Pl: 40/97 (41.2%).

Characteristics of included studies (Continued)

	Validity criteria: C (high risk of bias)
Participants	<p>278 women using DMPA for <6 months EE n=90, OS n=91, PI n=97</p> <p>Age: EE 27.0±4.7; OS 27.6±4.7; PI 27.0±4.9.</p> <p>Settings: Hospitals, University Ob/Gyn Department, Research Institute, Family Planning Centre.</p> <p>Diagnostic criteria: Vaginal bleeding episode >7 days, during first or second injection interval; Prolonged bleeding: a bleeding episode lasting 10 days or more; Amenorrhea: no bleeding within a 90 day reference period; Frequent bleeding: more than 4 bleeding episodes in a 90 day reference period; Infrequent bleeding: fewer than 2 B/S episodes in a 90 day reference period; Irregular bleeding: bleeding-free intervals greater than 17 days in a 90 day reference period.</p>
Interventions	<p>Agents: EE (n=90) 50 µg/day x 14 days, orally. OS (n=91) 2.5 mg/day x 14days, orally. PI (n=97) 1/day x 14 days, orally.</p> <p>Follow-up At the end of 14 days treatment (short-term success). 12 months follow-up (long-term success).</p>
Outcomes	<p>Bleeding stopped during the 14 day treatment course, with at least 2 days bleed-free interval</p> <p>Continued irregular bleeding</p> <p>Median time to cessation of bleeding and spotting (days)</p> <p>The median number of B/S days during treatment</p> <p>Number of B/S days in 90 day reference period after treatment (mean ± SD)</p> <p>Number of B/S episodes in 90 day reference period following treatment</p> <p>Discontinuation due to bleeding, at one year</p> <p>Discontinuation due to amenorrhea, at one year</p> <p>Discontinuation due to Oestrogen treatment failure, at one year</p>
Notes	
Allocation concealment	B – Unclear

Study	Subakir 2000
Methods	<p>Randomized trial</p> <p>Type of trial: parallel</p> <p>Study duration: 2 months</p> <p>Outcome assessment blinding: yes</p> <p>Drop-outs: zero</p> <p>Validity criteria: B (moderate risk of bias)</p>
Participants	<p>72 women using Norplant for 3-12 months.</p> <p>Age: 18-40 years.</p> <p>Setting: University</p> <p>Diagnostic criteria:</p>

Characteristics of included studies (Continued)

	"Bleeding problems" presumably as reported by the study participants
Interventions	<p>Agents:</p> <p>Vitamin E (Vit) (n=38) 200 mg /day x 10 days, oral;</p> <p>PI (n=34) 1/day x 10 days, oral.</p> <p>Treatment repeated 30 days from Day 1 of first treatment.</p> <p>Follow-up: 2 months.</p>
Outcomes	<p>Number of bleeding days before first treatment cycle</p> <p>Number of bleeding days after first treatment cycle</p>
Notes	<p>Diagnostic criteria are not reported.</p> <p>No data given for second treatment cycle.</p>
Allocation concealment	B – Unclear

Study	Tantiwattanakul 2004
Methods	<p>Randomized trial</p> <p>Type of trial: parallel</p> <p>Study duration: 28 days</p> <p>Outcome assessment blinding: yes</p> <p>Dropouts: 6/54 (11%)</p> <p>Validity criteria: A (low risk of bias)</p>
Participants	<p>54 women using DMPA for 3-12 months enrolled</p> <p>48 women in analysis</p> <p>Age (Mean \pm SD):</p> <p>Mefenamic acid (MEF; n=23): 30 \pm 6.8;</p> <p>PI (n=25): 27 \pm 5.8.</p> <p>Setting: Family planning clinic at hospital Ob/GYN department</p> <p>Diagnostic criteria:</p> <p>Bleeding on day of admission, following 8 or more days of continuous B/S (Abnormal bleeding)</p>
Interventions	<p>Mefenamic acid (MEF) 500 mg twice daily x 5 days, orally;</p> <p>PI: capsules 2X/day x 5 days, orally.</p> <p>Treatment duration: 5 days</p> <p>Follow-up duration 1 and 4 weeks.</p>
Outcomes	<p>Women who stopped bleeding within 7 days of initiation of treatment (number, percent)</p> <p>Women who did not stop bleeding within 7 days of initiation of treatment</p> <p>Mean bleed-free interval during 28 days following initiation of treatment (days)</p> <p>Other outcomes listed, but no data reported:</p> <p>Total number of days B/S</p> <p>Number of days of treatment required to stop bleeding.</p>
Notes	No data reported for some of the listed outcomes.
Allocation concealment	A – Adequate

Study	Weisberg 2006
Methods	<p>Randomized trial</p> <p>Type of trial: parallel</p>

Characteristics of included studies (Continued)

	<p>Study duration: 180 days (90 days before and 90 days after treatment)</p> <p>Outcome assessment blinding: yes</p> <p>Drop outs: 17/179 (9.5%)</p> <p>Validity criteria: A (low risk of bias)</p>
Participants	<p>179 Implanon users</p> <p>Age (years):</p> <p>Mifepristone 29.9 ± 1.0;</p> <p>Mifepristone+EE 27.6 ± 1.0;</p> <p>Doxycycline 28.8 ± 1.0;</p> <p>Pl 28.9 ± 1.0.</p> <p>Setting: University women's health research centres</p> <p>Diagnostic criteria:</p> <p>Prolonged bleeding: B/S episode longer than 10 days in 90 day reference period (as per WHO);</p> <p>Frequent bleeding: more than 4 B/S episodes in 90 day reference period (as per WHO).</p>
Interventions	<p>Agents and schedule:</p> <p>Mifepristone 25 mg twice daily x 1 day + Pl twice daily x 4 days, orally.</p> <p>Mifepristone 25 mg twice daily x 1 day +EE 20 ug x 4 days, orally.</p> <p>Doxycycline 100 mg twice daily x 5 days.</p> <p>Placebo twice daily x 5 days.</p> <p>Follow up: 90 days.</p>
Outcomes	<p>Number of days of B/S following start of treatment.</p> <p>Duration of the first B/S interval after treatment.</p> <p>Mean number of B/S episodes in the 90 day reference period.</p> <p>Mean duration of first B/S episode in the 90 day reference period post-treatment.</p> <p>Total number of B/S days during the pre- and post-treatment 90 day reference periods.</p> <p>Number of bleed-free days post-treatment.</p> <p>Side effects.</p>
Notes	
Allocation concealment	A – Adequate

Study	Witjaksono 1996
Methods	<p>Randomized trial</p> <p>Type of trial: parallel</p> <p>Study duration: 3 months</p> <p>Outcome assessment blinding: unclear</p> <p>Drop-outs: not given</p> <p>Validity criteria: B (moderate risk of bias)</p>
Participants	<p>91 women using Norplant for 3-12 months were recruited; 48 women included in analysis</p> <p>Age (mean \pm SE):</p> <p>EE: (n=18) 30.2 ± 2.6;</p> <p>EE + LNG: (n=16) 29.5 ± 2.8;</p> <p>Pl: (n=38) 29.3 ± 3.2.</p> <p>Setting: University Obstetric and Gynecology departments</p> <p>Diagnostic criteria:</p> <p>Prolonged bleeding, frequent bleeding, irregular bleeding as defined by WHO (1990)</p>
Interventions	<p>Agents:</p> <p>EE 50 ug/day x 21 days, orally;</p> <p>EE 30 ug/day + LNG 150 ug/day x 21 days, orally;</p> <p>Pl daily/21 days, orally</p>

Characteristics of included studies (Continued)

	Follow-up: 90 days.
Outcomes	<p>Number of B/S days in 90 day reference period pre-treatment (mean \pm SD)</p> <p>Number of B/S days in 90 day reference period post-treatment (mean \pm SD)</p> <p>Number of B/S episodes in 90 day reference period pre-treatment (mean \pm SD)</p> <p>Number of B/S episodes in 90 day reference period post-treatment (mean \pm SD)</p> <p>Number of B/S days per episode, pre-treatment (mean \pm SD)</p> <p>Number of B/S days per episode, post-treatment (mean \pm SD)</p>
Notes	
Allocation concealment	C – Inadequate
Study	d'Arcangues 2005
Methods	<p>Randomized trial</p> <p>Study duration: 1 year, with follow up at end of treatment, 3 months and 6 months</p> <p>Type of trial: parallel</p> <p>Outcome assessment blinding: yes</p> <p>Drop outs:</p> <p>Total: 139/486 (28.6%)</p> <p>Aspirin: 30/122 (25%);</p> <p>Vitamin E: 38/120 (32%);</p> <p>Combined aspirin and vitamin E: 40/121 (33%);</p> <p>Pl: 31/123 (25%).</p> <p>Validity criteria: C (high risk of bias)</p>
Participants	<p>486 women in the first 6 months of Norplant use</p> <p>347 women completed the study</p> <p>Age: all groups: 29.0 \pm 5.0</p> <p>Setting: Developing country research institutes, University Ob/Gyn department; family planning clinic</p> <p>Diagnostic criteria:</p> <p>Prolonged bleeding: 8 or more days;</p> <p>Clinically important bleeding patterns in 90-day reference period:</p> <p>Amenorrhea: no bleeding</p> <p>Infrequent: fewer than 2 B/S episodes in ref. pd</p> <p>Frequent: more than 4 B/S episodes in ref pd</p> <p>Irregular: a range of lengths of bleeding-free intervals greater than 17 days</p> <p>Prolonged: at least one B/S episode lasting more than 10 days</p>
Interventions	<p>Agents:</p> <p>Aspirin 80 mg/day x 10 days, orally</p> <p>Vitamin E 200 mg/day x 10 days, orally</p> <p>Combined aspirin + vitamin E x 10 days, orally</p> <p>Pl x 10 days, orally</p> <p>Treatment length: 10 days; repeated up to 5 times in year, if 20 days have passed between treatment cycles</p> <p>Follow up: 1 year, with visits after each treatment period and at 3 and 6 months</p>
Outcomes	<p>Efficacy in management of 1-5 episodes of prolonged bleeding:</p> <p>Number of B/S days in episode;</p> <p>Number of B/S days from the first day of treatment;</p> <p>Number of B/S days following the treatment episode.</p> <p>Discontinuation of treatment due to lack of improvement</p> <p>Discontinuation of treatment due to side effects</p>

Side effects related to treatment:

Headache, GI discomfort

Patient dissatisfaction with treatment at 3 months:

Improved pattern, unchanged pattern, worse pattern, no answer/unknown

Notes

Allocation concealment A – Adequate

EE - Ethinyl Estradiol

LNG - Levonorgestrel

NSAID - Nonsteroidal antiinflammatory drug

PI - Placebo

B/S - Bleeding/Spotting

Characteristics of excluded studies

Study	Reason for exclusion
Archer 1996	Interim data
Cseffalvay 1965	Non-randomized trial
Glasier 2002	Non-randomized trial.
Piya-Anant 1998	Treatment involved switching contraceptive methods.
d'Arcangues 2000	Review article

ANALYSES

Comparison 01. Estrogen vs placebo (Norplant/Therapeutic)

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Continued irregular bleeding during treatment	2	153	Relative Risk (Fixed) 95% CI	0.43 [0.30, 0.61]
02 Bleeding during treatment (days)	1	89	Weighted Mean Difference (Fixed) 95% CI	-6.90 [-9.08, -4.72]
03 Unacceptable bleeding after treatment	1	84	Relative Risk (Fixed) 95% CI	0.28 [0.14, 0.58]
04 Discontinuation of contraceptive method			Relative Risk (Fixed) 95% CI	Subtotals only
05 Discontinuation of treatment due to lack of improvement	1	100	Relative Risk (Fixed) 95% CI	0.33 [0.01, 7.99]
06 Discontinuation of treatment due to side-effects	2	191	Relative Risk (Fixed) 95% CI	8.10 [1.04, 63.40]
07 Side-effects related to treatment	1	89	Relative Risk (Fixed) 95% CI	9.09 [2.23, 37.06]
08 Patient dissatisfaction with treatment	0	0	Relative Risk (Fixed) 95% CI	Not estimable
09 Blood loss during treatment	0	0	Weighted Mean Difference (Fixed) 95% CI	Not estimable
10 Non-compliance with treatment	0	0	Relative Risk (Fixed) 95% CI	Not estimable

Comparison 02. Estrogen vs placebo (DMPA/Therapeutic)

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Continued irregular bleeding during treatment			Relative Risk (Fixed) 95% CI	Subtotals only
02 Bleeding during treatment (days)	0	0	Weighted Mean Difference (Fixed) 95% CI	Not estimable
03 Continued irregular bleeding after treatment(3 months).	2	290	Relative Risk (Fixed) 95% CI	0.53 [0.24, 1.16]
04 Discontinuation of contraceptive method because of bleeding	0	0	Relative Risk (Fixed) 95% CI	Not estimable
05 Discontinuation of treatment due to lack of improvement	0	0	Relative Risk (Fixed) 95% CI	Not estimable
06 Discontinuation of treatment due to side-effects	0	0	Relative Risk (Fixed) 95% CI	Not estimable
07 Side-effects related to treatment	0	0	Relative Risk (Fixed) 95% CI	Not estimable
08 Patient dissatisfaction with treatment	0	0	Relative Risk (Fixed) 95% CI	Not estimable
09 Blood loss during treatment (mls)	0	0	Weighted Mean Difference (Fixed) 95% CI	Not estimable
10 Non-compliance with treatment	0	0	Relative Risk (Fixed) 95% CI	Not estimable

Comparison 03. Estrogen vs placebo (DMPA/Prophylactic)

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Unacceptable bleeding during treatment	1	61	Relative Risk (Fixed) 95% CI	0.45 [0.21, 0.96]
02 Bleeding during treatment (days)	0	0	Weighted Mean Difference (Fixed) 95% CI	Not estimable
03 Bleeding after treatment (days)	0	0	Weighted Mean Difference (Fixed) 95% CI	Not estimable
05 Discontinuation of contraceptive method			Relative Risk (Fixed) 95% CI	Subtotals only
06 Discontinuation of treatment due to side-effects	0	0	Relative Risk (Fixed) 95% CI	Not estimable
07 Side-effects related to treatment	0	0	Relative Risk (Fixed) 95% CI	Not estimable
08 Patient dissatisfaction with treatment	0	0	Relative Risk (Fixed) 95% CI	Not estimable
09 Blood loss during treatment (mls)	0	0	Weighted Mean Difference (Fixed) 95% CI	Not estimable
10 Non-compliance with treatment	1	132	Relative Risk (Fixed) 95% CI	1.16 [0.93, 1.45]

Comparison 04. Estrogen vs placebo (Minipill/Therapeutic)

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Continued irregular bleeding during treatment	0	0	Relative Risk (Fixed) 95% CI	Not estimable
02 Bleeding during treatment (days)	0	0	Weighted Mean Difference (Fixed) 95% CI	Not estimable
04 Bleeding after treatment (at 3 months)	0	0	Weighted Mean Difference (Fixed) 95% CI	Not estimable
05 Discontinuation of contraceptive method because of bleeding	0	0	Relative Risk (Fixed) 95% CI	Not estimable
06 Discontinuation of treatment due to lack of improvement	0	0	Relative Risk (Fixed) 95% CI	Not estimable
07 Discontinuation of treatment due to side-effects	0	0	Relative Risk (Fixed) 95% CI	Not estimable
08 Side-effects related to treatment	0	0	Relative Risk (Fixed) 95% CI	Not estimable
09 Patient dissatisfaction with treatment	0	0	Relative Risk (Fixed) 95% CI	Not estimable
10 Blood loss during treatment (mls)	0	0	Weighted Mean Difference (Fixed) 95% CI	Not estimable
11 Non-compliance with treatment	0	0	Relative Risk (Fixed) 95% CI	Not estimable

Comparison 05. Estrogen and progestin vs placebo (Norplant/Therapeutic)

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Continued irregular bleeding during treatment	1	91	Relative Risk (Fixed) 95% CI	0.08 [0.03, 0.24]
02 Bleeding during treatment (days)	1	91	Weighted Mean Difference (Fixed) 95% CI	-9.70 [-11.31, -8.09]
03 Unacceptable bleeding after treatment	1	87	Relative Risk (Fixed) 95% CI	0.02 [0.00, 0.29]
04 Discontinuation of contraceptive method because of bleeding	1	100	Relative Risk (Fixed) 95% CI	0.33 [0.01, 7.99]
05 Discontinuation of treatment due to lack of improvement	1	2	Relative Risk (Fixed) 95% CI	Not estimable
06 Discontinuation of treatment due to side-effects	1	100	Relative Risk (Fixed) 95% CI	3.00 [0.13, 71.92]
07 Side-effects related to treatment	1	91	Relative Risk (Fixed) 95% CI	7.16 [1.72, 29.71]
08 Patient dissatisfaction with treatment	0	0	Relative Risk (Fixed) 95% CI	Not estimable
09 Blood loss during treatment (mls)	0	0	Relative Risk (Fixed) 95% CI	Not estimable
10 Non-compliance with treatment	0	0	Relative Risk (Fixed) 95% CI	Not estimable

Comparison 06. Estrogen and progestin vs placebo (DMPA /Therapeutic for amenorrhea)

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Continued amenorrhea during treatment	1	46	Relative Risk (Fixed) 95% CI	0.38 [0.19, 0.73]
02 Discontinuation of the contraceptive method	1	46	Relative Risk (Fixed) 95% CI	0.60 [0.40, 0.88]
03 Discontinuation of treatment due to lack of improvement	0	0	Relative Risk (Fixed) 95% CI	Not estimable
04 Discontinuation of treatment due to side effects	0	0	Relative Risk (Fixed) 95% CI	Not estimable
05 Side effects related to treatment	0	0	Relative Risk (Fixed) 95% CI	Not estimable
06 Patient dissatisfaction with treatment	0	0	Odds Ratio (Fixed) 95% CI	Not estimable
07 Blood loss during treatment (mls)	0	0	Weighted Mean Difference (Fixed) 95% CI	Not estimable
08 Non compliance with treatment	0	0	Relative Risk (Fixed) 95% CI	Not estimable

Comparison 07. Progestin vs placebo (Norplant/Therapeutic)

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Continued irregular bleeding during treatment	0	0	Relative Risk (Fixed) 95% CI	Not estimable
02 Bleeding during treatment (days)	0	0	Weighted Mean Difference (Fixed) 95% CI	Not estimable
03 Unacceptable bleeding after treatment	0	0	Relative Risk (Fixed) 95% CI	Not estimable
04 Discontinuation of contraceptive method	1	93	Relative Risk (Fixed) 95% CI	2.94 [0.32, 27.21]
05 Discontinuation of treatment due to lack of improvement	0	0	Relative Risk (Fixed) 95% CI	Not estimable
06 Discontinuation of treatment due to side-effects	0	0	Relative Risk (Fixed) 95% CI	Not estimable
07 Side-effects related to treatment	0	0	Relative Risk (Fixed) 95% CI	Not estimable
08 Patient dissatisfaction with treatment	0	0	Relative Risk (Fixed) 95% CI	Not estimable
09 Blood loss during treatment (mls)	0	0	Relative Risk (Fixed) 95% CI	Not estimable
10 Non-compliance with treatment	0	0	Relative Risk (Fixed) 95% CI	Not estimable

Comparison 08. Antiprogestin vs placebo (Norplant/Therapeutic)

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Continuous irregular bleeding during treatment	0	0	Relative Risk (Fixed) 95% CI	Not estimable
02 Bleeding during treatment (days)	2	198	Weighted Mean Difference (Fixed) 95% CI	-6.56 [-10.09, -3.03]

03 Bleeding after treatment (days)	1	91	Weighted Mean Difference (Fixed) 95% CI	-3.00 [-7.75, 1.75]
04 Discontinuation of contraceptive method because of bleeding	1	100	Relative Risk (Fixed) 95% CI	Not estimable
05 Discontinuation of treatment due to lack of improvement	0	0	Relative Risk (Fixed) 95% CI	Not estimable
06 Discontinuation of treatment due to side-effects	0	0	Relative Risk (Fixed) 95% CI	Not estimable
07 Side-effects related to treatment	0	0	Relative Risk (Fixed) 95% CI	Not estimable
08 Patient dissatisfaction with treatment	1	97	Relative Risk (Fixed) 95% CI	0.46 [0.23, 0.91]
09 Blood loss during treatment (mls)	0	0	Weighted Mean Difference (Fixed) 95% CI	Not estimable
10 Non-compliance with treatment	0	0	Relative Risk (Fixed) 95% CI	Not estimable

Comparison 09. Antiprogesterin vs placebo (Norplant/Prophylactic)

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Unacceptable bleeding during treatment	0	0	Relative Risk (Fixed) 95% CI	Not estimable
02 Bleeding during treatment (days)	1	115	Weighted Mean Difference (Fixed) 95% CI	-18.00 [-26.93, -9.07]
03 Unacceptable bleeding after treatment	1	111	Relative Risk (Fixed) 95% CI	1.09 [0.65, 1.83]
04 Discontinuation of contraceptive method because of bleeding	1	115	Relative Risk (Fixed) 95% CI	0.20 [0.01, 4.01]
05 Non-compliance with treatment	0	0	Relative Risk (Fixed) 95% CI	Not estimable
06 Side-effects related to treatment	1	2	Relative Risk (Fixed) 95% CI	Not estimable
07 Patient dissatisfaction with treatment	0	0	Relative Risk (Fixed) 95% CI	Not estimable
08 Blood loss during treatment (mls)	0	0	Weighted Mean Difference (Fixed) 95% CI	Not estimable

Comparison 10. Antiprogesterin vs placebo (Implanon/Therapeutic)

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Continuous irregular bleeding during treatment	0	0	Relative Risk (Fixed) 95% CI	Not estimable
02 Bleeding during treatment (days).	0	0	Weighted Mean Difference (Fixed) 95% CI	Not estimable
03 Bleeding after treatment (days)	0	0	Weighted Mean Difference (Fixed) 95% CI	Not estimable
04 Discontinuation of contraceptive method because of bleeding	0	0	Relative Risk (Fixed) 95% CI	Not estimable
05 Discontinuation of treatment due to lack of improvement	0	0	Relative Risk (Fixed) 95% CI	Not estimable

06 Discontinuation of treatment due to side effects	0	0	Relative Risk (Fixed) 95% CI	Not estimable
07 Side effects related to treatment	2	178	Relative Risk (Fixed) 95% CI	0.86 [0.58, 1.28]
08 Patient dissatisfaction with treatment	0	0	Relative Risk (Fixed) 95% CI	Not estimable
09 Blood loss during treatment	0	0	Weighted Mean Difference (Fixed) 95% CI	Not estimable
10 Non-compliance with treatment	0	0	Relative Risk (Fixed) 95% CI	Not estimable

Comparison 11. Antiprogesterin vs placebo (DMPA/Prophylactic)

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Unacceptable bleeding during treatment	0	0	Relative Risk (Fixed) 95% CI	Not estimable
02 Bleeding during treatment (days)	0	0	Weighted Mean Difference (Fixed) 95% CI	Not estimable
03 Unacceptable bleeding after treatment	0	0	Relative Risk (Fixed) 95% CI	Not estimable
04 Discontinuation of contraceptive method because of bleeding	0	0	Relative Risk (Fixed) 95% CI	Not estimable
05 Side-effects related to treatment	0	0	Relative Risk (Fixed) 95% CI	Not estimable
06 Patient dissatisfaction with treatment	0	0	Relative Risk (Fixed) 95% CI	Not estimable
07 Blood loss during treatment (mls)	0	0	Weighted Mean Difference (Fixed) 95% CI	Not estimable
08 Non-compliance with treatment	0	0	Relative Risk (Fixed) 95% CI	Not estimable

Comparison 12. Antiprogesterin vs placebo (Minipill/Prophylactic)

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Percentage of women with B/S episodes starting day 8-28	3	260	Relative Risk (Random) 95% CI	0.95 [0.71, 1.27]
02 Discontinuation of the contraceptive method because of bleeding	1	103	Relative Risk (Random) 95% CI	0.98 [0.14, 6.70]
03 Percentage of women having side effects related to treatment (headache, emotional lability, acne, breast pain).	1	103	Relative Risk (Random) 95% CI	1.08 [0.79, 1.47]
04 Discontinuation of the contraceptive because of side effects.	1	103	Relative Risk (Random) 95% CI	0.74 [0.17, 3.12]
05 Non-compliance with treatment	0	0	Relative Risk (Fixed) 95% CI	Not estimable

Comparison 13. Antiprogesterin and estrogen vs placebo (Implanon/Therapeutic)

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Continued irregular bleeding during treatment	0	0	Relative Risk (Fixed) 95% CI	Not estimable
02 Bleeding during treatment (days)	0	0	Weighted Mean Difference (Fixed) 95% CI	Not estimable
03 Bleeding after treatment (days)	0	0	Weighted Mean Difference (Fixed) 95% CI	Not estimable
04 Discontinuation of the contraceptive method because of bleeding	0	0	Relative Risk (Fixed) 95% CI	Not estimable
05 Discontinuation of treatment due to lack of improvement	0	0	Relative Risk (Fixed) 95% CI	Not estimable
06 Discontinuation of treatment due to side effects.	0	0	Relative Risk (Fixed) 95% CI	Not estimable
07 Side effects related to treatment	2	180	Relative Risk (Fixed) 95% CI	1.03 [0.72, 1.48]
08 Patient dissatisfaction with treatment	0	0	Relative Risk (Fixed) 95% CI	Not estimable
09 Blood loss during treatment	0	0	Weighted Mean Difference (Fixed) 95% CI	Not estimable
10 Non-compliance with treatment	0	0	Relative Risk (Fixed) 95% CI	Not estimable

Comparison 14. Venotonic vs placebo (Minipill/Therapeutic)

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Continued irregular bleeding during treatment	0	0	Relative Risk (Fixed) 95% CI	Not estimable
02 Bleeding during treatment (days)	1	40	Weighted Mean Difference (Fixed) 95% CI	-2.00 [-2.78, -1.22]
03 Unacceptable bleeding during treatment	0	0	Relative Risk (Fixed) 95% CI	Not estimable
04 Unacceptable bleeding after treatment	0	0	Relative Risk (Fixed) 95% CI	Not estimable
05 Discontinuation of contraceptive method because of bleeding	0	0	Relative Risk (Fixed) 95% CI	Not estimable
06 Side-effects related to treatment	0	0	Relative Risk (Fixed) 95% CI	Not estimable
07 Patient dissatisfaction with treatment	0	0	Relative Risk (Fixed) 95% CI	Not estimable
08 Blood loss during treatment (mls)	0	0	Weighted Mean Difference (Fixed) 95% CI	Not estimable
11 Non-compliance with treatment	0	0	Relative Risk (Fixed) 95% CI	Not estimable

Comparison 15. Vitamin E vs placebo (Norplant/Therapeutic)

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Continued irregular bleeding during treatment	0	0	Relative Risk (Fixed) 95% CI	Not estimable
02 Bleeding during treatment (days)	1	72	Weighted Mean Difference (Fixed) 95% CI	-4.40 [-5.02, -3.78]
03 Unacceptable bleeding after treatment	0	0	Relative Risk (Fixed) 95% CI	Not estimable
04 Discontinuation rate of contraceptive method because of bleeding	0	0	Relative Risk (Fixed) 95% CI	Not estimable
05 Discontinuation of treatment due to lack of improvement	1	218	Relative Risk (Fixed) 95% CI	1.73 [0.83, 3.61]
06 Discontinuation of treatment because of side-effects	1	218	Relative Risk (Fixed) 95% CI	1.02 [0.06, 16.08]
07 Side-effects related to treatment			Relative Risk (Fixed) 95% CI	Subtotals only
08 Patient dissatisfaction with treatment	0	0	Relative Risk (Fixed) 95% CI	Not estimable
09 Blood loss during treatment	0	0	Weighted Mean Difference (Fixed) 95% CI	Not estimable
10 Non-compliance with treatment	0	0	Relative Risk (Fixed) 95% CI	Not estimable

Comparison 16. NSAIDs vs placebo (Norplant/Therapeutic)

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Continued irregular bleeding during treatment	1	67	Relative Risk (Fixed) 95% CI	0.32 [0.17, 0.61]
02 Bleeding during treatment (days)	1	67	Weighted Mean Difference (Fixed) 95% CI	-5.60 [-10.04, -1.16]
03 Unacceptable bleeding after treatment	1	67	Relative Risk (Fixed) 95% CI	0.49 [0.28, 0.83]
04 Discontinuation of contraceptive method	1	91	Relative Risk (Fixed) 95% CI	0.34 [0.01, 8.15]
05 Discontinuation of treatment due to lack of improvement	1	221	Relative Risk (Fixed) 95% CI	1.39 [0.64, 2.99]
06 Discontinuation of treatment due to side-effects	3	379	Relative Risk (Fixed) 95% CI	2.35 [0.35, 15.61]
07 Side-effects related to treatment	3	557	Relative Risk (Fixed) 95% CI	0.87 [0.55, 1.35]
08 Patient dissatisfaction with treatment	0	0	Relative Risk (Fixed) 95% CI	Not estimable
09 Blood loss during treatment (mls)	0	0	Weighted Mean Difference (Fixed) 95% CI	Not estimable
10 Non-compliance with treatment	0	0	Relative Risk (Fixed) 95% CI	Not estimable

Comparison 17. Vitamin E + NSAID vs placebo (Norplant/Therapeutic)

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Continued irregular bleeding during treatment	0	0	Relative Risk (Fixed) 95% CI	Not estimable
02 Bleeding during treatment (days)	0	0	Weighted Mean Difference (Fixed) 95% CI	Not estimable
03 Unacceptable bleeding after treatment	0	0	Relative Risk (Fixed) 95% CI	Not estimable
04 Discontinuation of contraceptive method because of bleeding	0	0	Relative Risk (Fixed) 95% CI	Not estimable
05 Discontinuation of treatment due to lack of improvement	1	220	Relative Risk (Fixed) 95% CI	2.00 [0.98, 4.07]
06 Discontinuation of treatment due to side-effects	1	220	Relative Risk (Fixed) 95% CI	2.00 [0.18, 21.74]
07 Side-effects related to treatment	2	488	Relative Risk (Fixed) 95% CI	1.33 [0.88, 2.03]
08 Patient dissatisfaction with treatment	0	0	Relative Risk (Fixed) 95% CI	Not estimable
09 Blood loss during treatment	0	0	Weighted Mean Difference (Fixed) 95% CI	Not estimable
10 Non-compliance with treatment	0	0	Relative Risk (Fixed) 95% CI	Not estimable

Comparison 18. NSAID vs placebo (DMPA/Therapeutic)

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Continued irregular bleeding during treatment	2	94	Relative Risk (Fixed) 95% CI	0.42 [0.25, 0.72]
02 Bleeding during treatment (days)	0	0	Weighted Mean Difference (Fixed) 95% CI	Not estimable
03 Unacceptable bleeding after treatment	0	0	Relative Risk (Fixed) 95% CI	Not estimable
04 Discontinuation of contraceptive method because of bleeding	0	0	Relative Risk (Fixed) 95% CI	Not estimable
05 Discontinuation of treatment due to lack of improvement	0	0	Relative Risk (Fixed) 95% CI	Not estimable
06 Discontinuation of treatment due to side-effects	0	0	Relative Risk (Fixed) 95% CI	Not estimable
07 Side-effects related to treatment	1	48	Relative Risk (Fixed) 95% CI	14.08 [0.84, 236.85]
08 Patient dissatisfaction with treatment	0	0	Relative Risk (Fixed) 95% CI	Not estimable
09 Blood loss during treatment (mls)	0	0	Weighted Mean Difference (Fixed) 95% CI	Not estimable
10 Non-compliance with treatment	0	0	Relative Risk (Fixed) 95% CI	Not estimable

Comparison 19. Selective estrogen receptor modulator vs placebo (Norplant/Therapeutic)

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Continued irregular bleeding during treatment	1	100	Relative Risk (Fixed) 95% CI	0.41 [0.21, 0.80]
02 Bleeding during treatment (days)	0	0	Weighted Mean Difference (Fixed) 95% CI	Not estimable
03 Unacceptable bleeding after treatment	1	100	Relative Risk (Fixed) 95% CI	0.38 [0.16, 0.88]
04 Discontinuation of contraceptive method			Relative Risk (Fixed) 95% CI	Subtotals only
05 Discontinuation of treatment due to lack of improvement	0	0	Relative Risk (Fixed) 95% CI	Not estimable
06 Discontinuation of treatment due to side-effects	0	0	Relative Risk (Fixed) 95% CI	Not estimable
07 Side-effects related to treatment	2	200	Relative Risk (Fixed) 95% CI	1.08 [0.52, 2.26]
08 Patient dissatisfaction with treatment	1	100	Relative Risk (Fixed) 95% CI	0.22 [0.11, 0.45]
09 Blood loss during treatment	0	0	Weighted Mean Difference (Fixed) 95% CI	Not estimable
10 Non-compliance with treatment	0	0	Relative Risk (Fixed) 95% CI	Not estimable

Comparison 20. Antifibrinolytic vs placebo (Norplant/Therapeutic)

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Continued irregular bleeding during treatment	1	68	Relative Risk (Fixed) 95% CI	0.55 [0.32, 0.92]
02 Bleeding during treatment (days)	0	0	Weighted Mean Difference (Fixed) 95% CI	Not estimable
03 Unacceptable bleeding after treatment	1	68	Relative Risk (Fixed) 95% CI	1.75 [0.85, 3.62]
04 Discontinuation of the contraceptive method	0	0	Relative Risk (Fixed) 95% CI	Not estimable
05 Discontinuation of treatment due to lack of improvement	0	0	Relative Risk (Fixed) 95% CI	Not estimable
06 Discontinuation of treatment due to side effects	0	0	Relative Risk (Fixed) 95% CI	Not estimable
07 Side effects related to treatment	0	0	Relative Risk (Fixed) 95% CI	Not estimable
08 Patient dissatisfaction with treatment	0	0	Relative Risk (Fixed) 95% CI	Not estimable
09 Blood loss during treatment	0	0	Weighted Mean Difference (Fixed) 95% CI	Not estimable
10 Non-compliance with treatment	0	0	Relative Risk (Fixed) 95% CI	Not estimable

Comparison 21. Matrix metalloproteinase inhibitor vs placebo (Implanon/Therapeutic).

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Continued irregular bleeding during treatment	0	0	Relative Risk (Fixed) 95% CI	Not estimable
02 Bleeding during treatment (days)	0	0	Weighted Mean Difference (Fixed) 95% CI	Not estimable
03 Bleeding after treatment (days)	0	0	Weighted Mean Difference (Fixed) 95% CI	Not estimable
04 Discontinuation of the contraceptive method because of bleeding	0	0	Relative Risk (Fixed) 95% CI	Not estimable
05 Discontinuation of treatment due to lack of improvement.	0	0	Relative Risk (Fixed) 95% CI	Not estimable
06 Discontinuation of treatment due to side effects	0	0	Relative Risk (Fixed) 95% CI	Not estimable
07 Side effects related to treatment	2	180	Relative Risk (Fixed) 95% CI	0.68 [0.44, 1.05]
08 Patient dissatisfaction with treatment	0	0	Relative Risk (Fixed) 95% CI	Not estimable
09 Blood loss during treatment	0	0	Weighted Mean Difference (Fixed) 95% CI	Not estimable
10 Non-compliance with treatment	0	0	Relative Risk (Fixed) 95% CI	Not estimable

INDEX TERMS

Medical Subject Headings (MeSH)

Contraceptive Agents, Female [*therapeutic use]; Contraceptives, Oral, Synthetic [therapeutic use]; Delayed-Action Preparations [therapeutic use]; Levonorgestrel [therapeutic use]; Medroxyprogesterone 17-Acetate [therapeutic use]; Menstruation Disturbances [*drug therapy]; Progestins [*therapeutic use]; Randomized Controlled Trials

MeSH check words

Female; Humans

COVER SHEET

Title	Treatment of vaginal bleeding irregularities induced by progestin only contraceptives
Authors	Abdel-Aleem H, d'Arcangues C, Vogelsong KM, Gülmezoglu AM
Contribution of author(s)	HAA, CDA, AMG had the idea. HAA prepared the protocol with comments from CDA, KV and AMG. KV and HAA extracted the data. HAA and KV prepared and updated the review.
Issue protocol first published	2002/1
Review first published	2007/2
Date of most recent amendment	20 August 2007
Date of most recent SUBSTANTIVE amendment	28 May 2007
What's New	This update includes new four trials including 339 participants (Nathirojanakun 2006; Phupong 2006; Sadeghi-Bazargani 2006 and Weisberg 2006). One of the trials enrolled women using Implanon implants. This is the first trial in the review that enrolled women

using Implanon. The same trial is the first to report on the effects of a matrix metalloproteinase inhibitor in the treatment of bleeding due to use of progestin only contraceptives. The update includes one trial addressing treatment of amenorrhea associated with use of DMPA.

Date new studies sought but none found	Information not supplied by author
Date new studies found but not yet included/excluded	Information not supplied by author
Date new studies found and included/excluded	15 April 2007
Date authors' conclusions section amended	20 May 2007
Contact address	Prof Hany Abdel-Aleem Department of Obstetrics and Gynaecology Faculty of Medicine, Assiut University, Assiut, Egypt Assiut EGYPT E-mail: aleemh@yahoo.com
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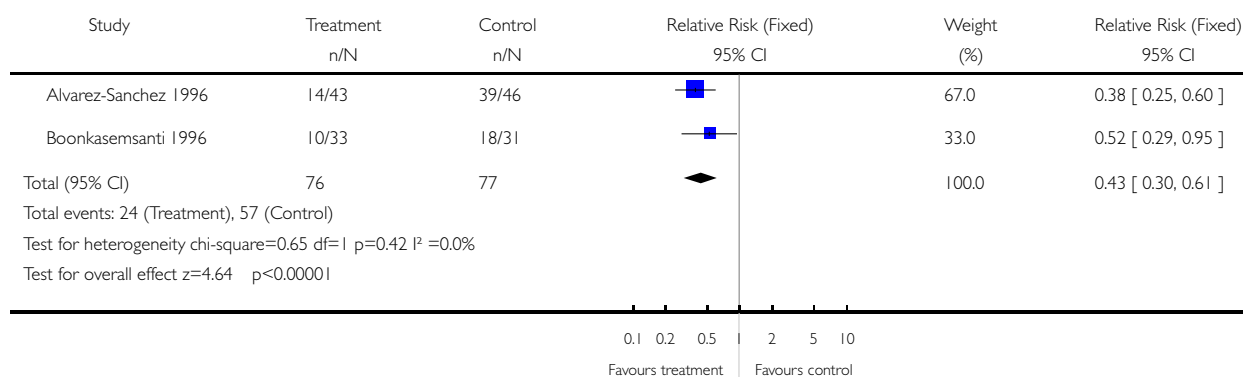
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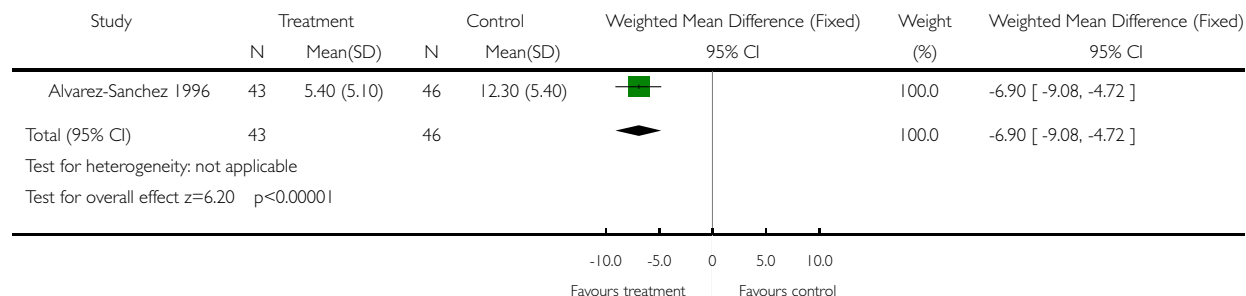


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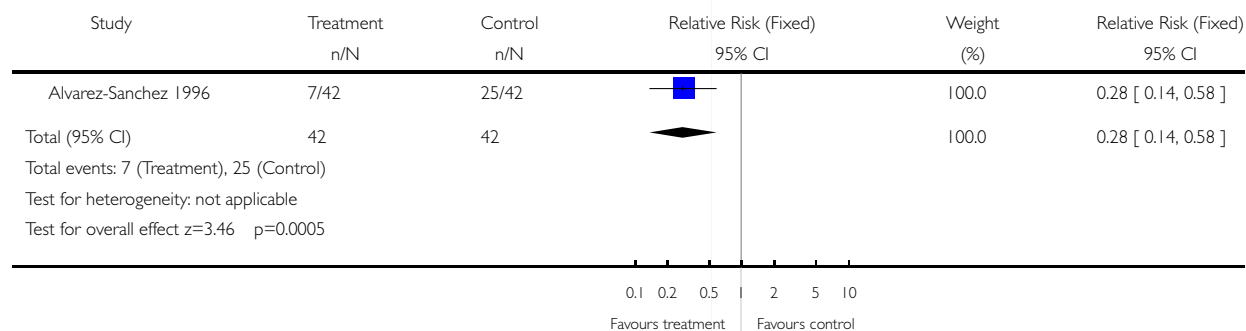


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Outcome: 03 Unacceptable bleeding after treatment

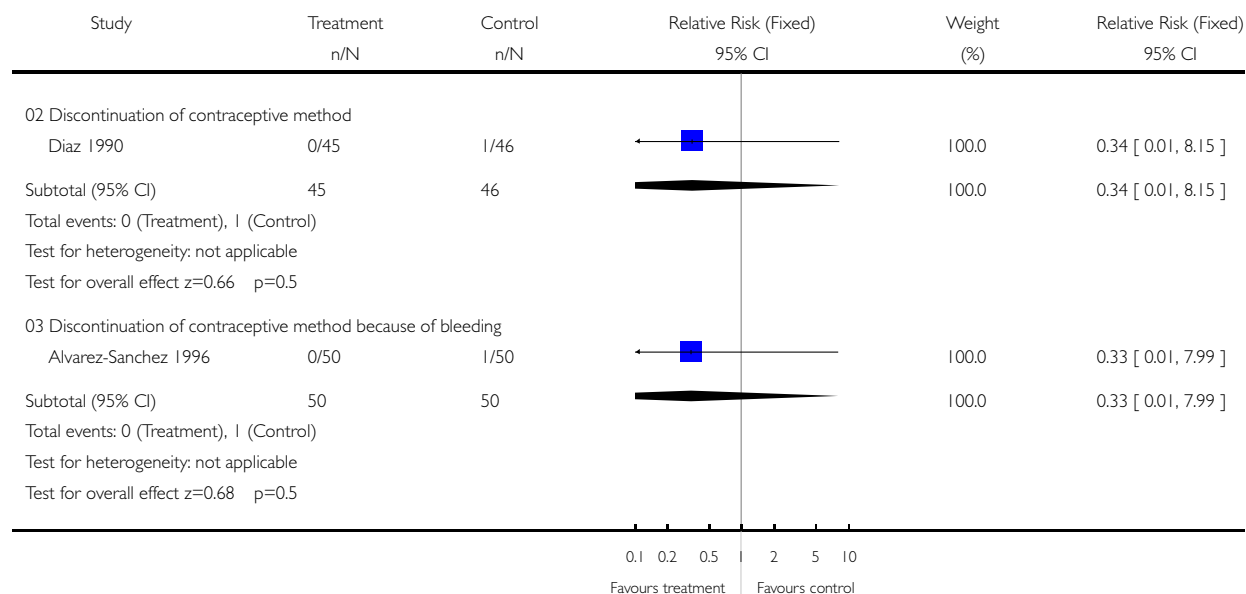


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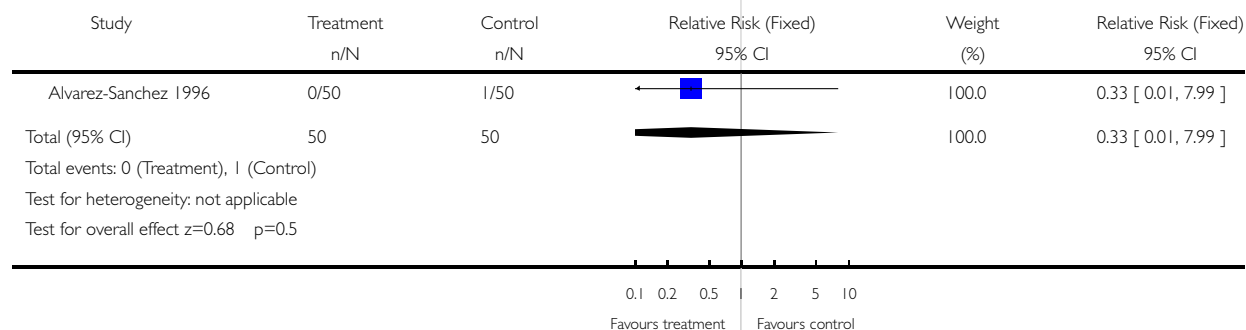


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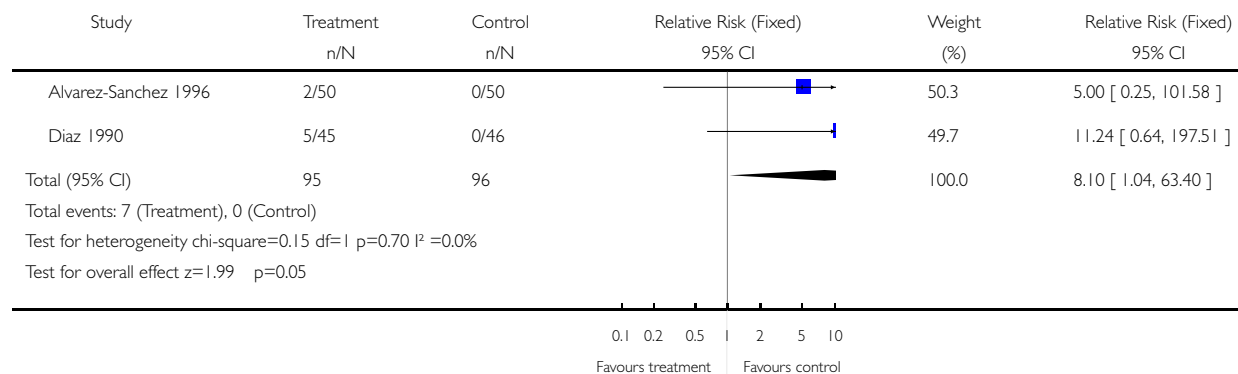


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Review: Treatment of vaginal bleeding irregularities induced by progestin only contraceptives

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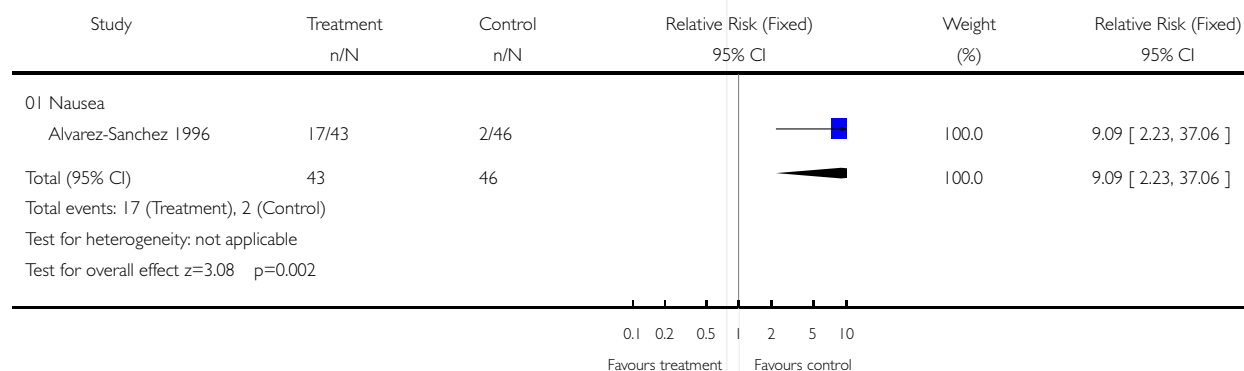


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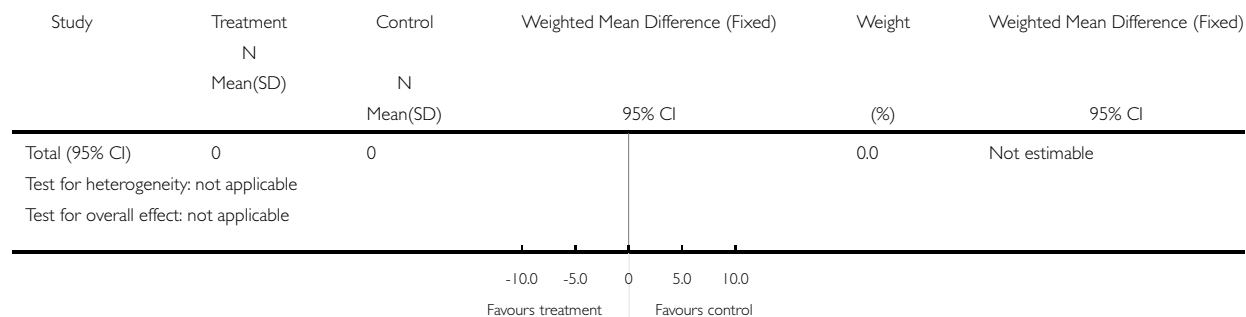


Analysis 01.09. Comparison 01 Estrogen vs placebo (Norplant/Therapeutic), Outcome 09 Blood loss during treatment

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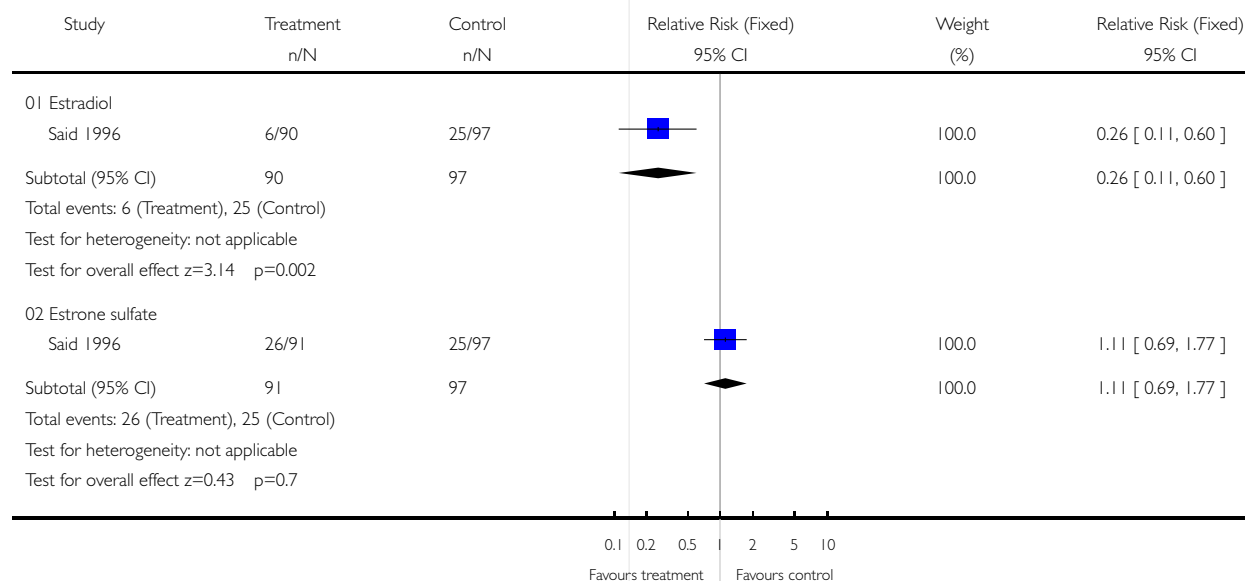


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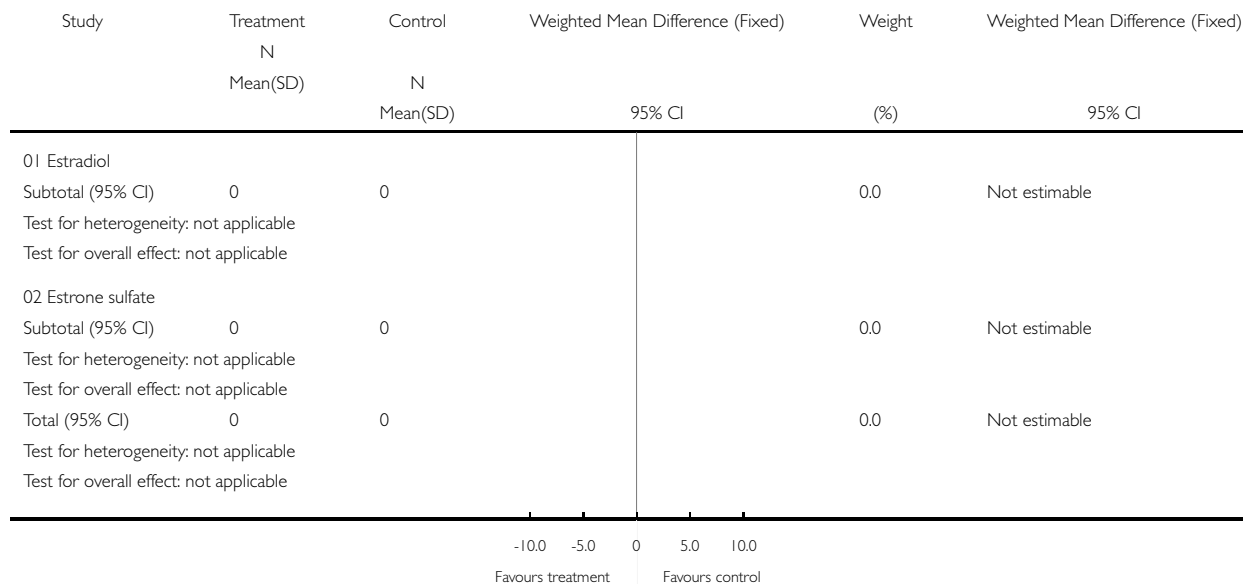


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Comparison: 02 Estrogen vs placebo (DMPA/Therapeutic)

Outcome: 02 Bleeding during treatment (days)

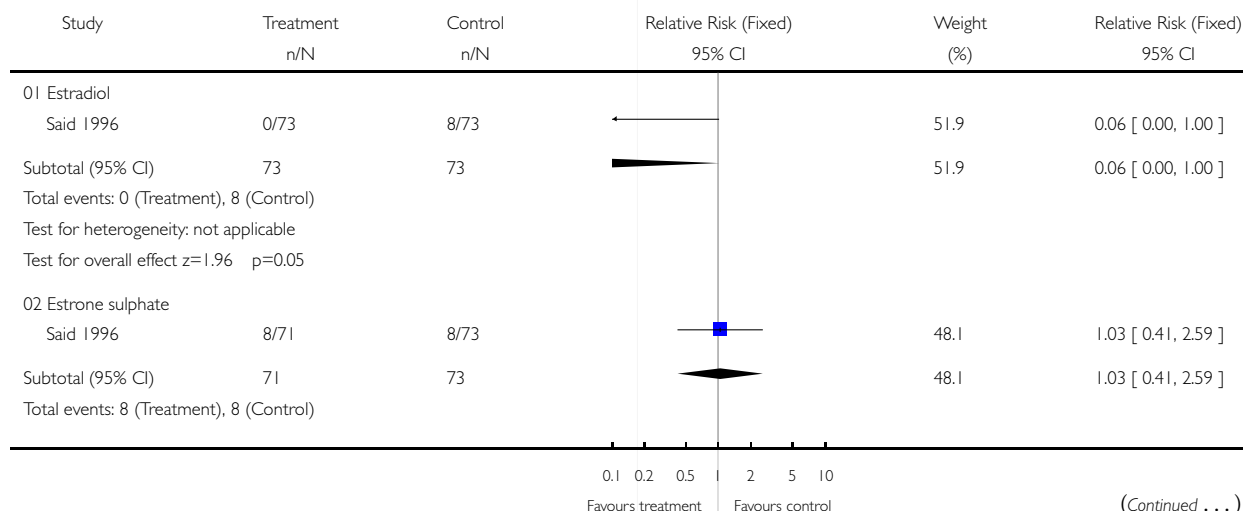


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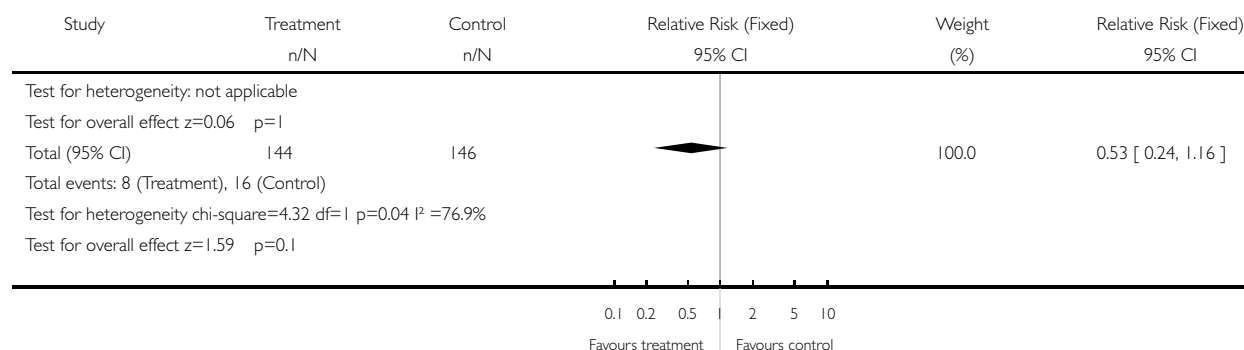
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Outcome: 03 Continued irregular bleeding after treatment(3 months).



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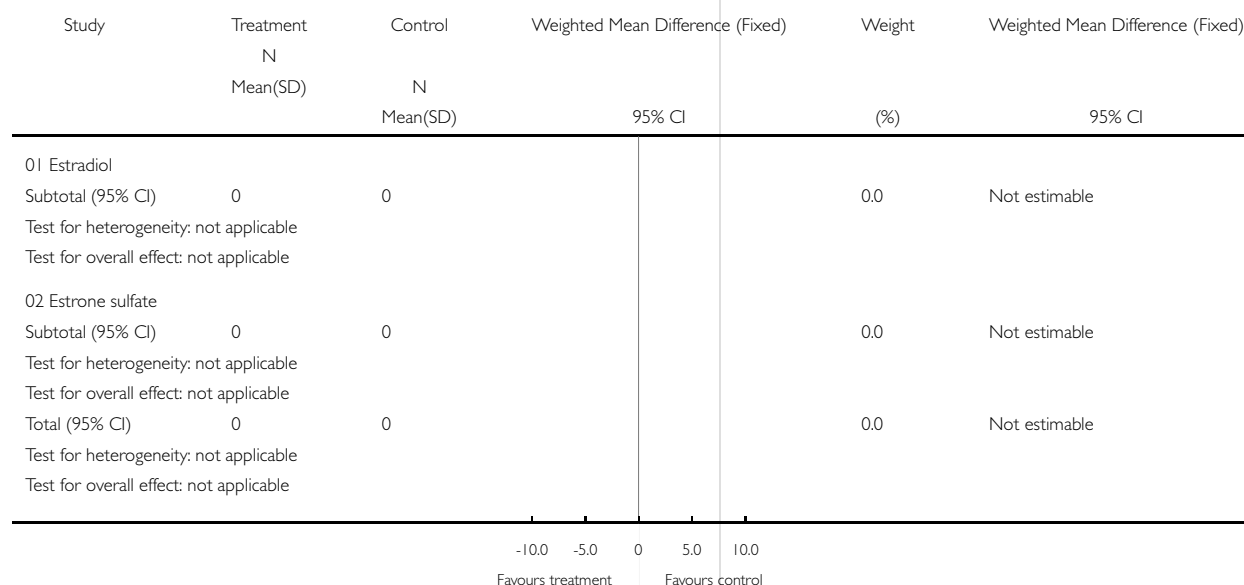


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Comparison: 02 Estrogen vs placebo (DMPA/Therapeutic)

Outcome: 09 Blood loss during treatment (mls)

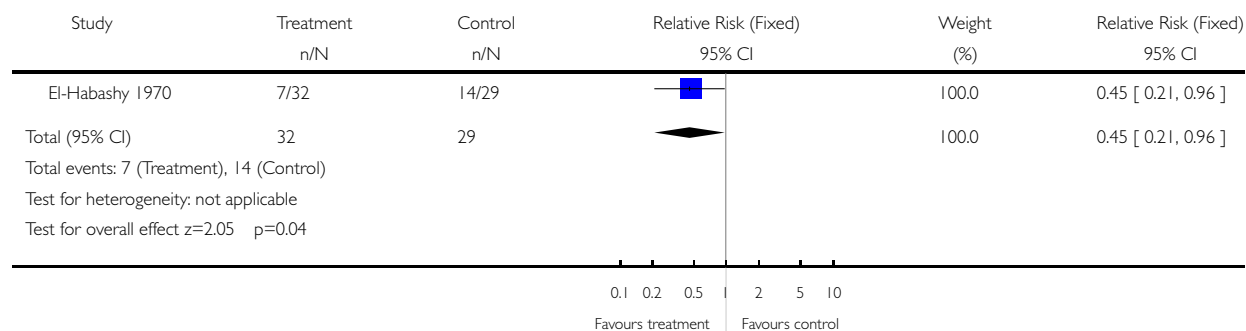


Analysis 03.01. Comparison 03 Estrogen vs placebo (DMPA/Prophylactic), Outcome 01 Unacceptable bleeding during treatment

Review: Treatment of vaginal bleeding irregularities induced by progestin only contraceptives

Comparison: 03 Estrogen vs placebo (DMPA/Prophylactic)

Outcome: 01 Unacceptable bleeding during treatment

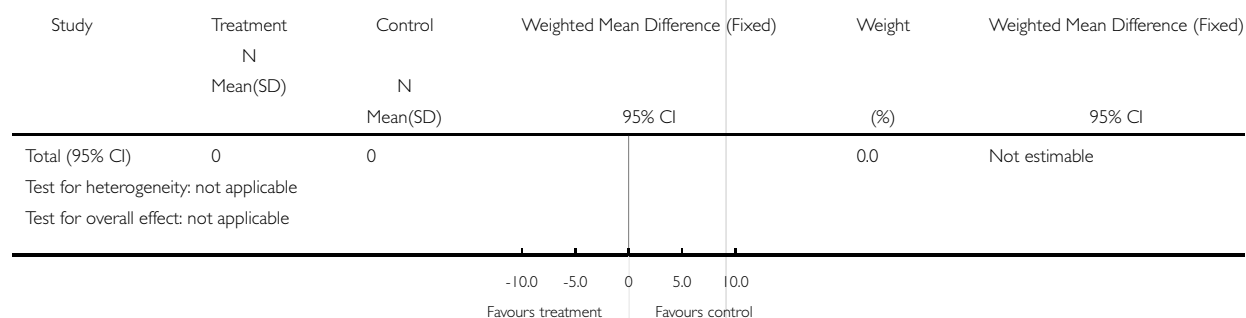


Analysis 03.02. Comparison 03 Estrogen vs placebo (DMPA/Prophylactic), Outcome 02 Bleeding during treatment (days)

Review: Treatment of vaginal bleeding irregularities induced by progestin only contraceptives

Comparison: 03 Estrogen vs placebo (DMPA/Prophylactic)

Outcome: 02 Bleeding during treatment (days)

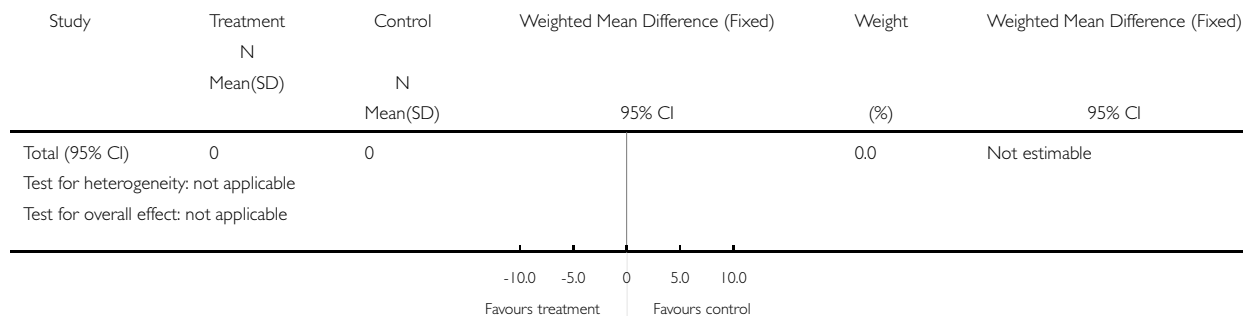


Analysis 03.03. Comparison 03 Estrogen vs placebo (DMPA/Prophylactic), Outcome 03 Bleeding after treatment (days)

Review: Treatment of vaginal bleeding irregularities induced by progestin only contraceptives

Comparison: 03 Estrogen vs placebo (DMPA/Prophylactic)

Outcome: 03 Bleeding after treatment (days)

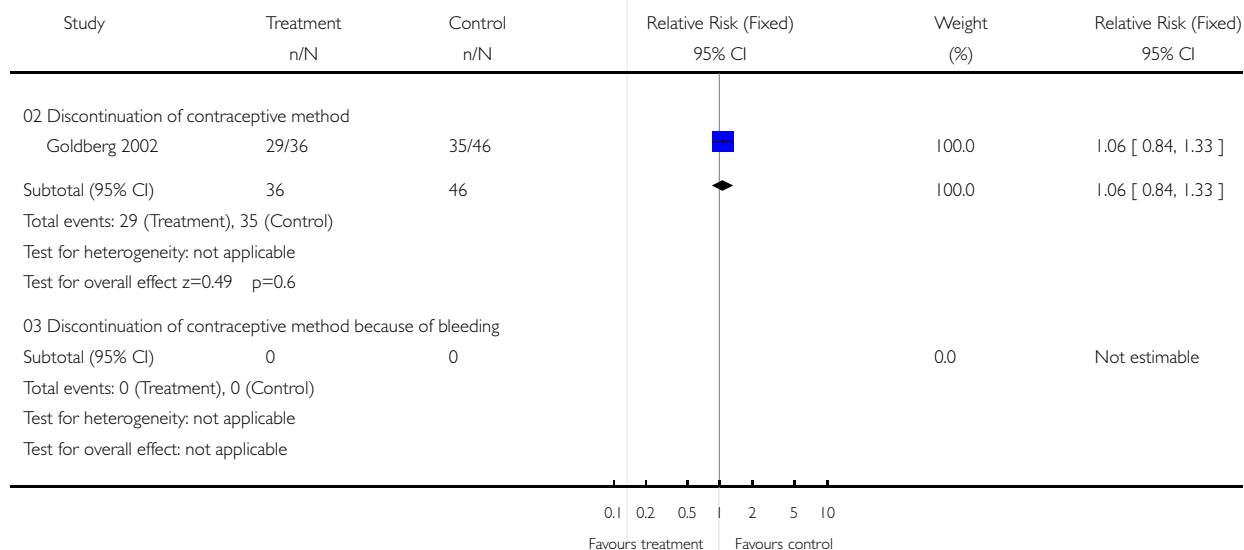


Analysis 03.05. Comparison 03 Estrogen vs placebo (DMPA/Prophylactic), Outcome 05 Discontinuation of contraceptive method

Review: Treatment of vaginal bleeding irregularities induced by progestin only contraceptives

Comparison: 03 Estrogen vs placebo (DMPA/Prophylactic)

Outcome: 05 Discontinuation of contraceptive method

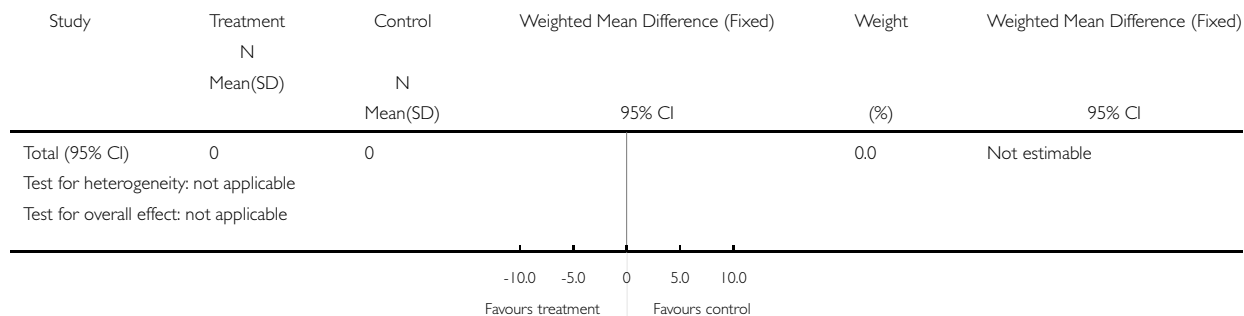


Analysis 03.09. Comparison 03 Estrogen vs placebo (DMPA/Prophylactic), Outcome 09 Blood loss during treatment (mls)

Review: Treatment of vaginal bleeding irregularities induced by progestin only contraceptives

Comparison: 03 Estrogen vs placebo (DMPA/Prophylactic)

Outcome: 09 Blood loss during treatment (mls)

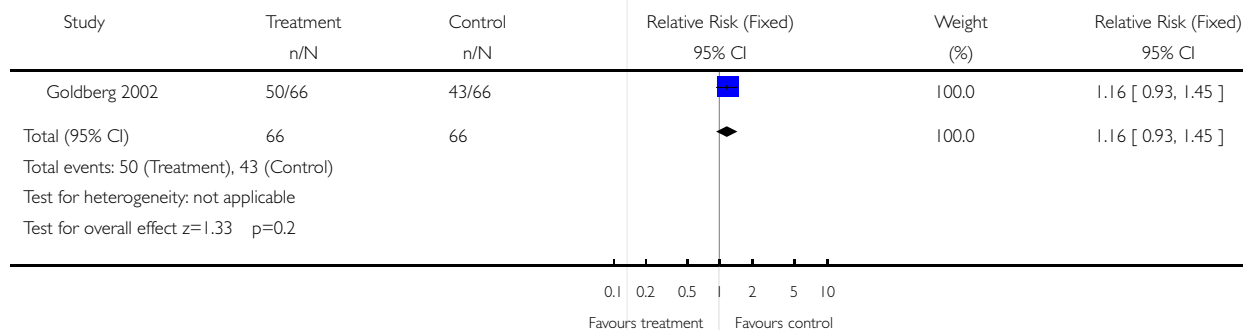


Analysis 03.10. Comparison 03 Estrogen vs placebo (DMPA/Prophylactic), Outcome 10 Non-compliance with treatment

Review: Treatment of vaginal bleeding irregularities induced by progestin only contraceptives

Comparison: 03 Estrogen vs placebo (DMPA/Prophylactic)

Outcome: 10 Non-compliance with treatment

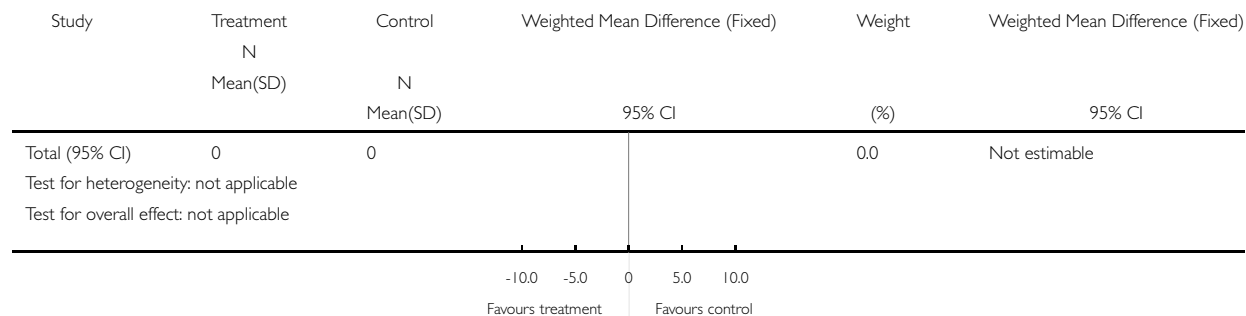


Analysis 04.02. Comparison 04 Estrogen vs placebo (Minipill/Therapeutic), Outcome 02 Bleeding during treatment (days)

Review: Treatment of vaginal bleeding irregularities induced by progestin only contraceptives

Comparison: 04 Estrogen vs placebo (Minipill/Therapeutic)

Outcome: 02 Bleeding during treatment (days)

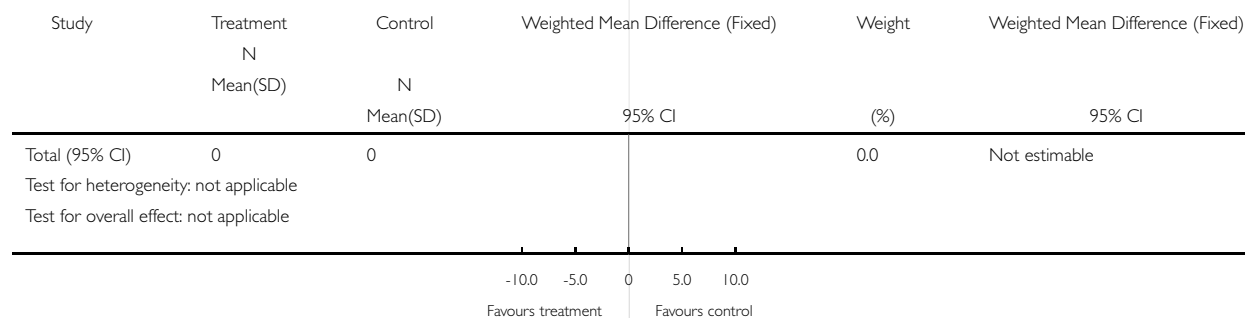


Analysis 04.04. Comparison 04 Estrogen vs placebo (Minipill/Therapeutic), Outcome 04 Bleeding after treatment (at 3 months)

Review: Treatment of vaginal bleeding irregularities induced by progestin only contraceptives

Comparison: 04 Estrogen vs placebo (Minipill/Therapeutic)

Outcome: 04 Bleeding after treatment (at 3 months)

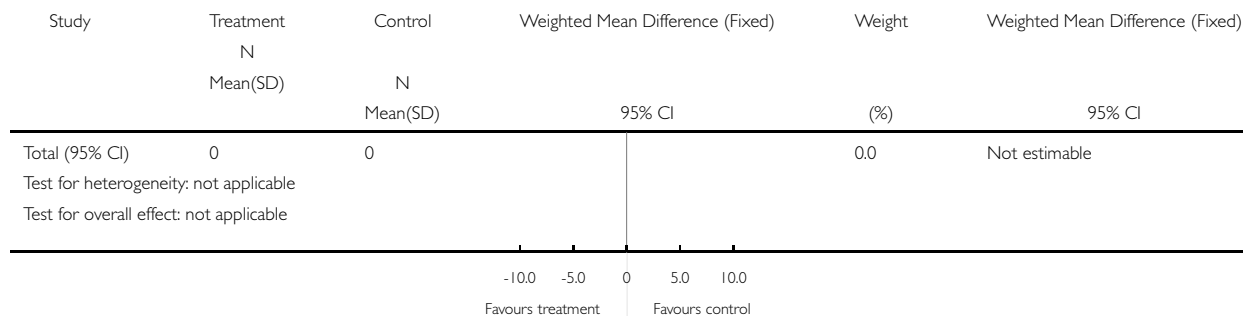


Analysis 04.10. Comparison 04 Estrogen vs placebo (Minipill/Therapeutic), Outcome 10 Blood loss during treatment (mls)

Review: Treatment of vaginal bleeding irregularities induced by progestin only contraceptives

Comparison: 04 Estrogen vs placebo (Minipill/Therapeutic)

Outcome: 10 Blood loss during treatment (mls)

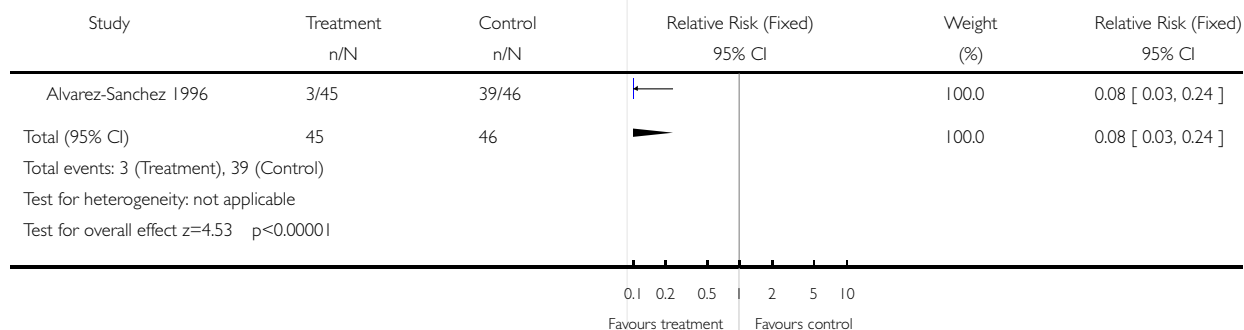


Analysis 05.01. Comparison 05 Estrogen and progestin vs placebo (Norplant/Therapeutic), Outcome 01 Continued irregular bleeding during treatment

Review: Treatment of vaginal bleeding irregularities induced by progestin only contraceptives

Comparison: 05 Estrogen and progestin vs placebo (Norplant/Therapeutic)

Outcome: 01 Continued irregular bleeding during treatment

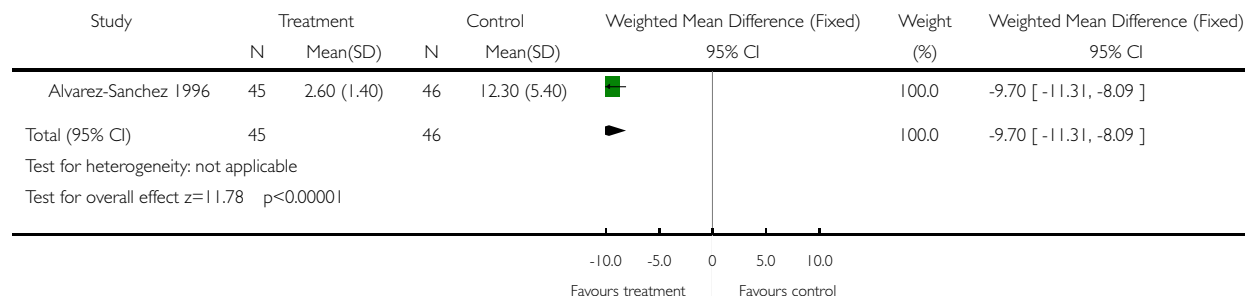


Analysis 05.02. Comparison 05 Estrogen and progestin vs placebo (Norplant/Therapeutic), Outcome 02 Bleeding during treatment (days)

Review: Treatment of vaginal bleeding irregularities induced by progestin only contraceptives

Comparison: 05 Estrogen and progestin vs placebo (Norplant/Therapeutic)

Outcome: 02 Bleeding during treatment (days)

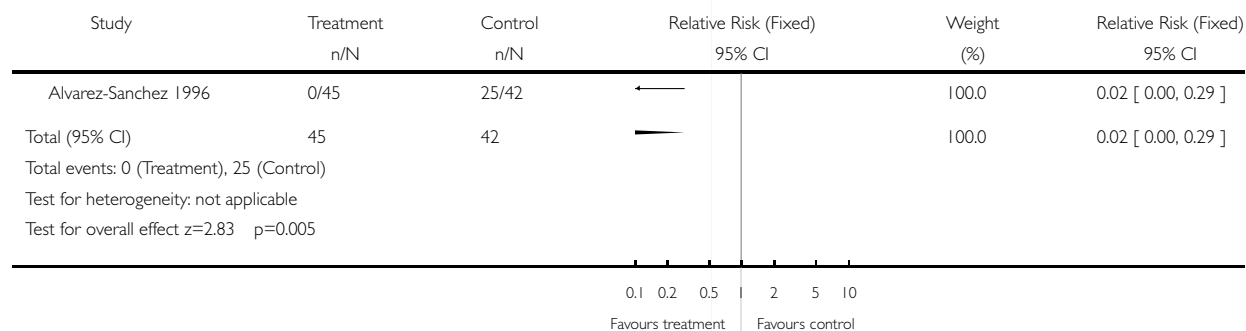


Analysis 05.03. Comparison 05 Estrogen and progestin vs placebo (Norplant/Therapeutic), Outcome 03 Unacceptable bleeding after treatment

Review: Treatment of vaginal bleeding irregularities induced by progestin only contraceptives

Comparison: 05 Estrogen and progestin vs placebo (Norplant/Therapeutic)

Outcome: 03 Unacceptable bleeding after treatment

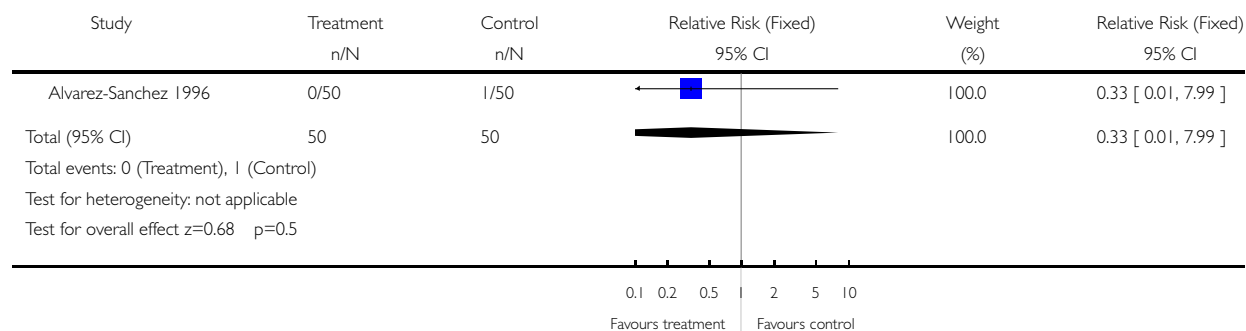


Analysis 05.04. Comparison 05 Estrogen and progestin vs placebo (Norplant/Therapeutic), Outcome 04 Discontinuation of contraceptive method because of bleeding

Review: Treatment of vaginal bleeding irregularities induced by progestin only contraceptives

Comparison: 05 Estrogen and progestin vs placebo (Norplant/Therapeutic)

Outcome: 04 Discontinuation of contraceptive method because of bleeding

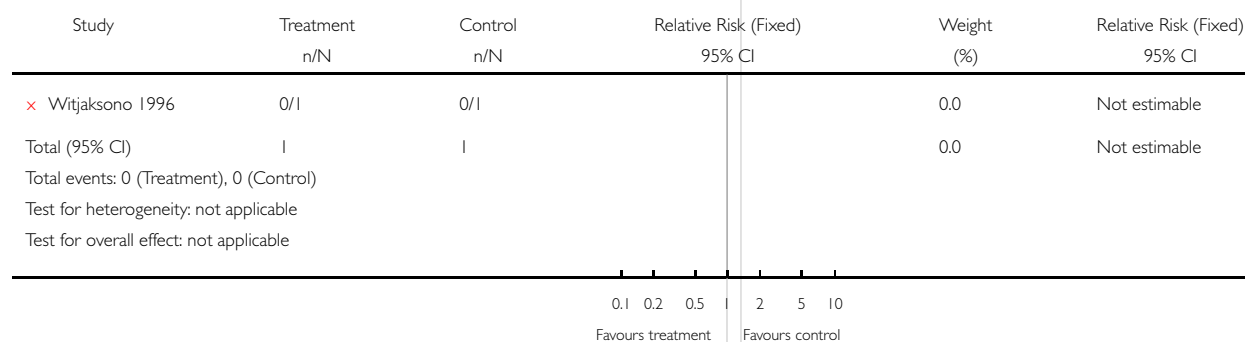


Analysis 05.05. Comparison 05 Estrogen and progestin vs placebo (Norplant/Therapeutic), Outcome 05 Discontinuation of treatment due to lack of improvement

Review: Treatment of vaginal bleeding irregularities induced by progestin only contraceptives

Comparison: 05 Estrogen and progestin vs placebo (Norplant/Therapeutic)

Outcome: 05 Discontinuation of treatment due to lack of improvement

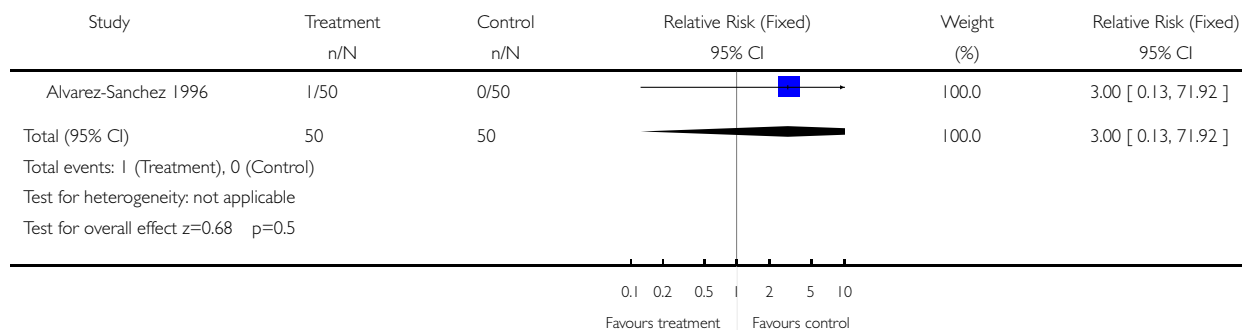


Analysis 05.06. Comparison 05 Estrogen and progestin vs placebo (Norplant/Therapeutic), Outcome 06 Discontinuation of treatment due to side-effects

Review: Treatment of vaginal bleeding irregularities induced by progestin only contraceptives

Comparison: 05 Estrogen and progestin vs placebo (Norplant/Therapeutic)

Outcome: 06 Discontinuation of treatment due to side-effects

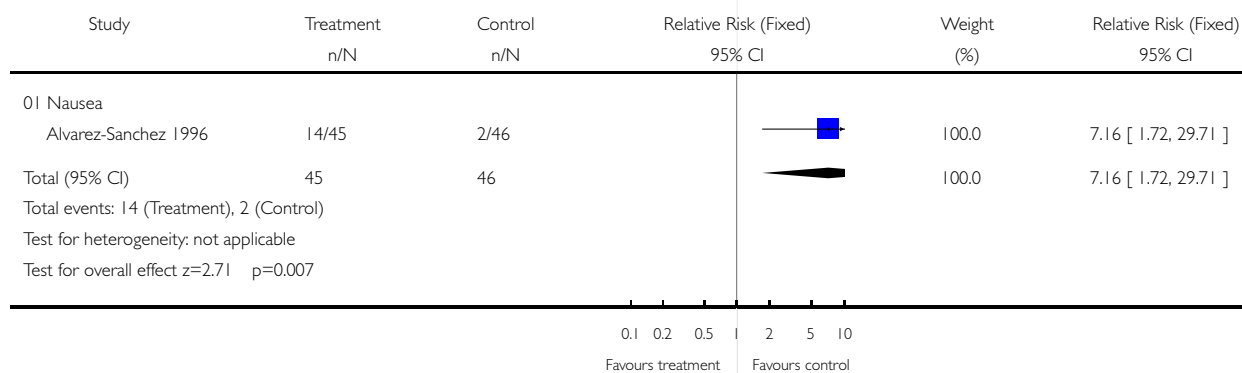


Analysis 05.07. Comparison 05 Estrogen and progestin vs placebo (Norplant/Therapeutic), Outcome 07 Side-effects related to treatment

Review: Treatment of vaginal bleeding irregularities induced by progestin only contraceptives

Comparison: 05 Estrogen and progestin vs placebo (Norplant/Therapeutic)

Outcome: 07 Side-effects related to treatment

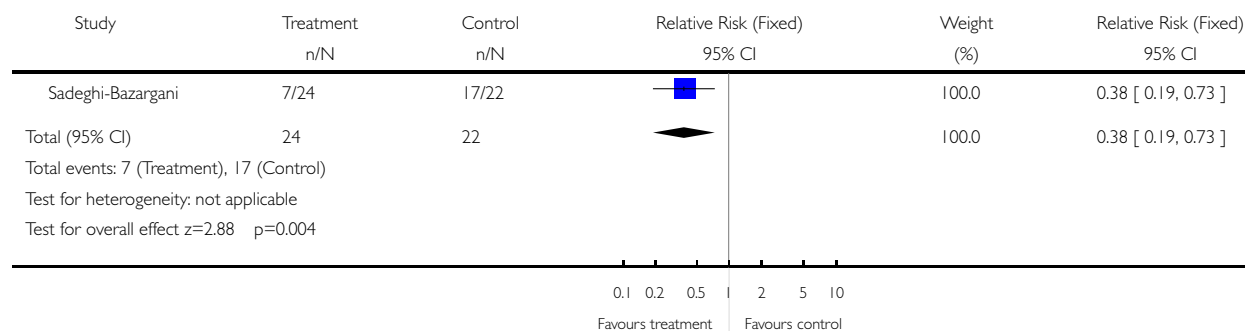


Analysis 06.01. Comparison 06 Estrogen and progestin vs placebo (DMPA /Therapeutic for amenorrhea), Outcome 01 Continued amenorrhea during treatment

Review: Treatment of vaginal bleeding irregularities induced by progestin only contraceptives

Comparison: 06 Estrogen and progestin vs placebo (DMPA /Therapeutic for amenorrhea)

Outcome: 01 Continued amenorrhea during treatment

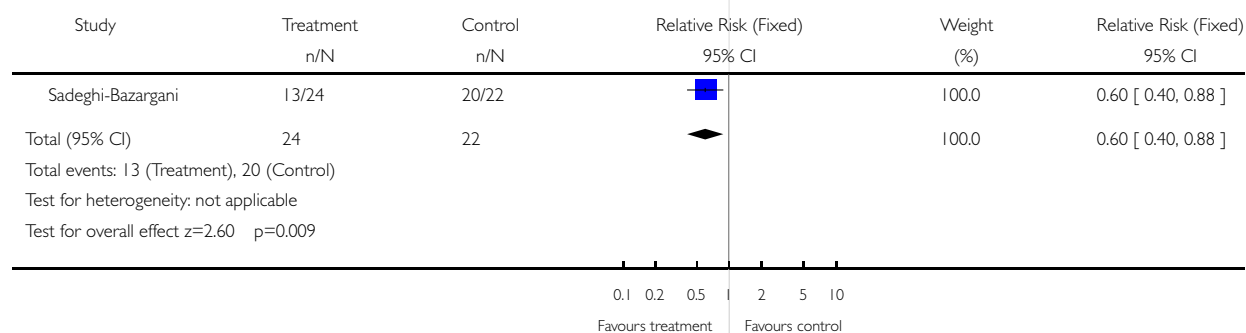


Analysis 06.02. Comparison 06 Estrogen and progestin vs placebo (DMPA /Therapeutic for amenorrhea), Outcome 02 Discontinuation of the contraceptive method

Review: Treatment of vaginal bleeding irregularities induced by progestin only contraceptives

Comparison: 06 Estrogen and progestin vs placebo (DMPA /Therapeutic for amenorrhea)

Outcome: 02 Discontinuation of the contraceptive method

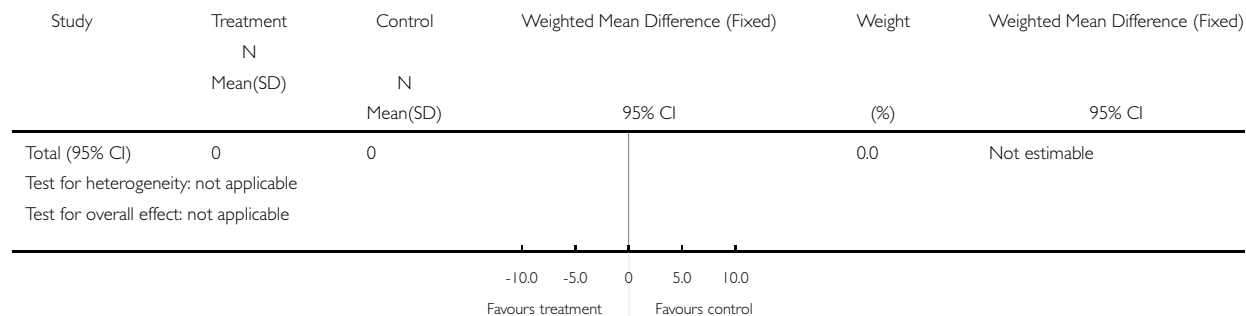


Analysis 06.07. Comparison 06 Estrogen and progestin vs placebo (DMPA /Therapeutic for amenorrhea), Outcome 07 Blood loss during treatment (mls)

Review: Treatment of vaginal bleeding irregularities induced by progestin only contraceptives

Comparison: 06 Estrogen and progestin vs placebo (DMPA /Therapeutic for amenorrhea)

Outcome: 07 Blood loss during treatment (mls)

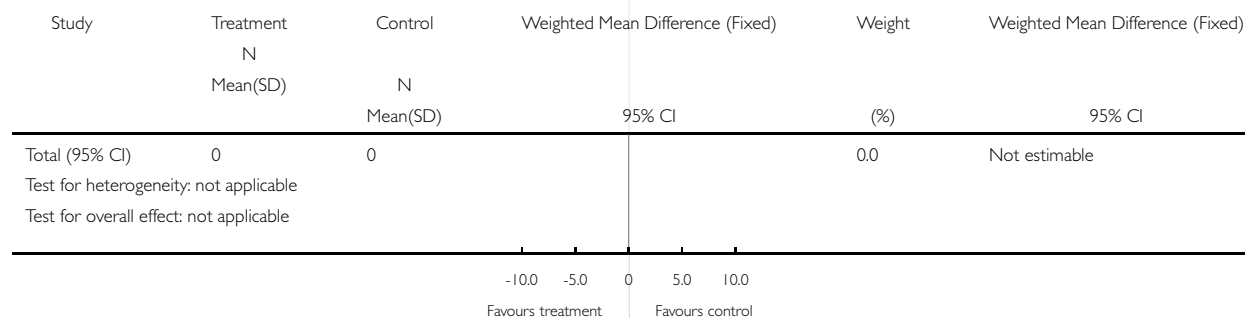


Analysis 07.02. Comparison 07 Progestin vs placebo (Norplant/Therapeutic), Outcome 02 Bleeding during treatment (days)

Review: Treatment of vaginal bleeding irregularities induced by progestin only contraceptives

Comparison: 07 Progestin vs placebo (Norplant/Therapeutic)

Outcome: 02 Bleeding during treatment (days)

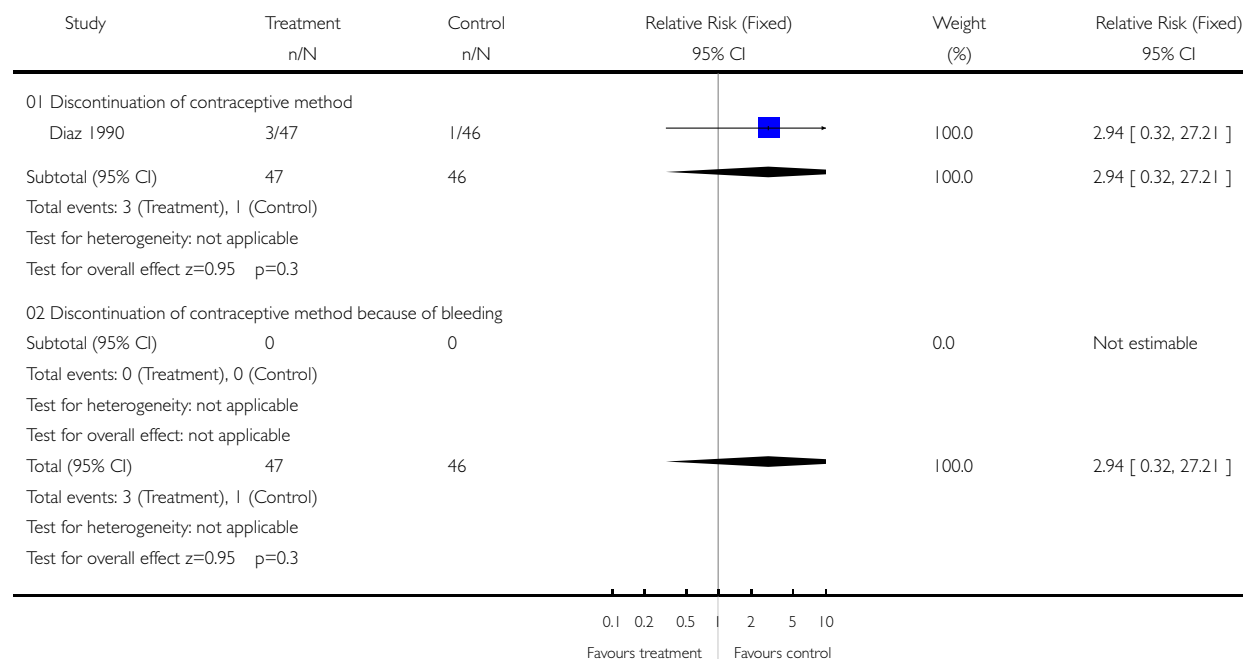


Analysis 07.04. Comparison 07 Progestin vs placebo (Norplant/Therapeutic), Outcome 04 Discontinuation of contraceptive method

Review: Treatment of vaginal bleeding irregularities induced by progestin only contraceptives

Comparison: 07 Progestin vs placebo (Norplant/Therapeutic)

Outcome: 04 Discontinuation of contraceptive method

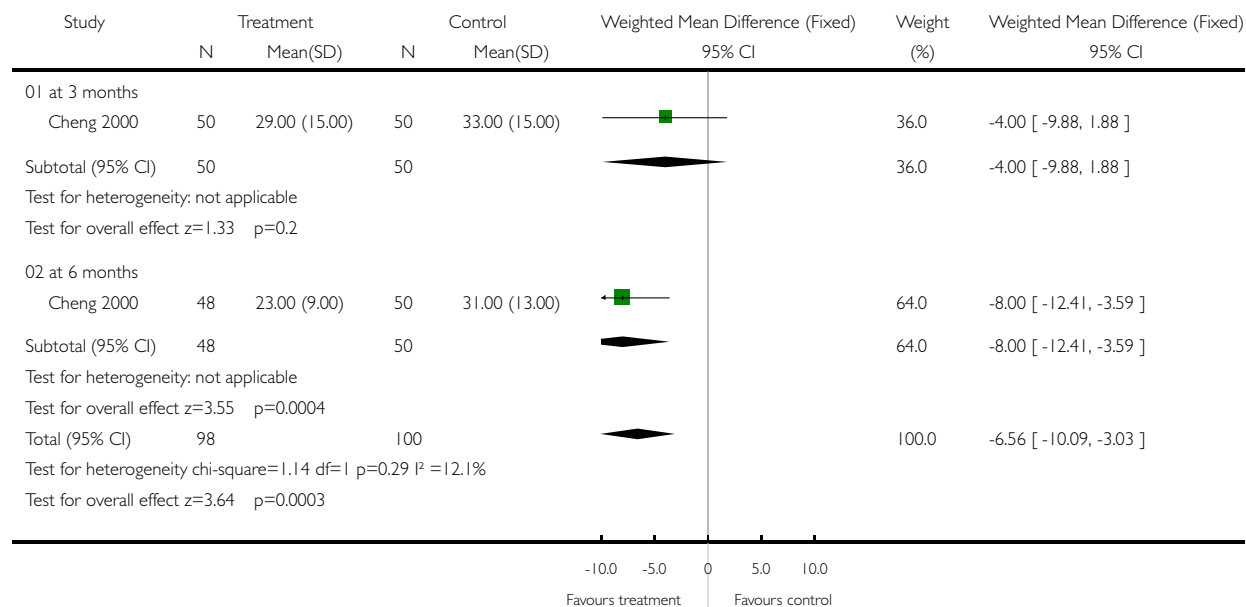


Analysis 08.02. Comparison 08 Antiprogesterin vs placebo (Norplant/Therapeutic), Outcome 02 Bleeding during treatment (days)

Review: Treatment of vaginal bleeding irregularities induced by progestin only contraceptives

Comparison: 08 Antiprogesterin vs placebo (Norplant/Therapeutic)

Outcome: 02 Bleeding during treatment (days)

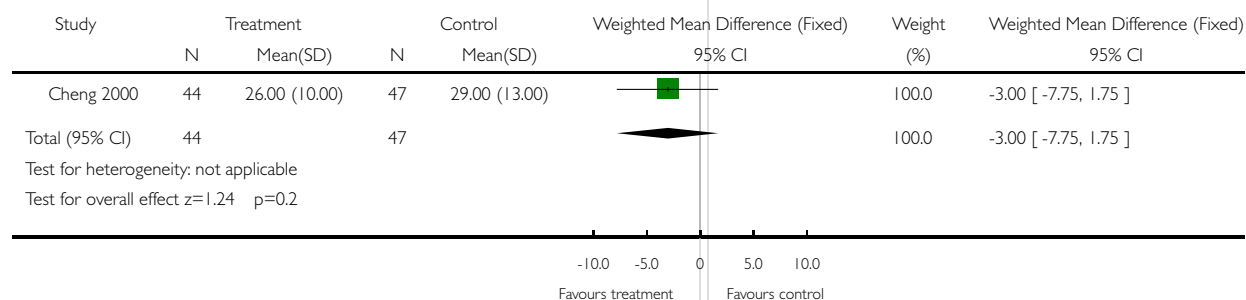


Analysis 08.03. Comparison 08 Antiprogesterin vs placebo (Norplant/Therapeutic), Outcome 03 Bleeding after treatment (days)

Review: Treatment of vaginal bleeding irregularities induced by progestin only contraceptives

Comparison: 08 Antiprogesterin vs placebo (Norplant/Therapeutic)

Outcome: 03 Bleeding after treatment (days)

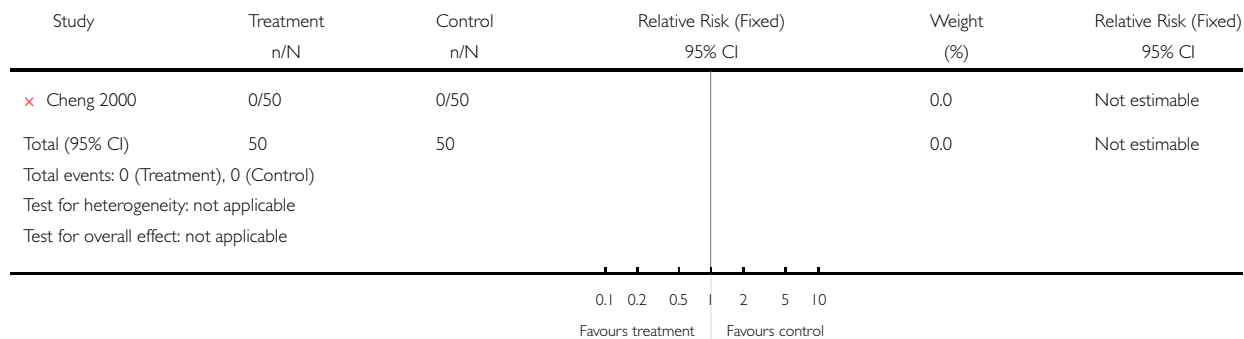


Analysis 08.04. Comparison 08 Antiprogesterin vs placebo (Norplant/Therapeutic), Outcome 04 Discontinuation of contraceptive method because of bleeding

Review: Treatment of vaginal bleeding irregularities induced by progestin only contraceptives

Comparison: 08 Antiprogesterin vs placebo (Norplant/Therapeutic)

Outcome: 04 Discontinuation of contraceptive method because of bleeding

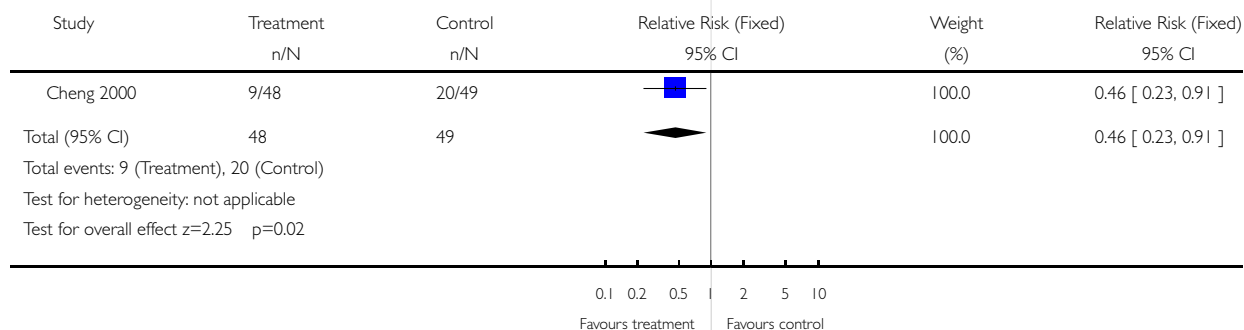


Analysis 08.08. Comparison 08 Antiprogesterin vs placebo (Norplant/Therapeutic), Outcome 08 Patient dissatisfaction with treatment

Review: Treatment of vaginal bleeding irregularities induced by progestin only contraceptives

Comparison: 08 Antiprogesterin vs placebo (Norplant/Therapeutic)

Outcome: 08 Patient dissatisfaction with treatment

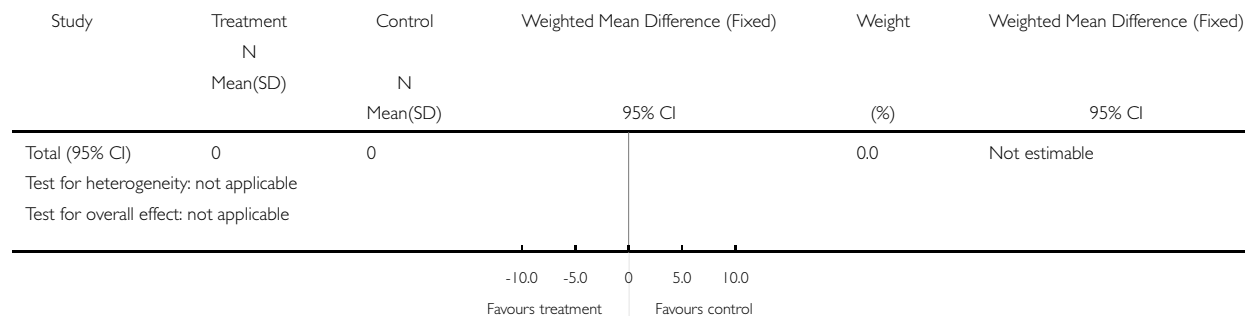


Analysis 08.09. Comparison 08 Antiprogesterin vs placebo (Norplant/Therapeutic), Outcome 09 Blood loss during treatment (mls)

Review: Treatment of vaginal bleeding irregularities induced by progestin only contraceptives

Comparison: 08 Antiprogesterin vs placebo (Norplant/Therapeutic)

Outcome: 09 Blood loss during treatment (mls)

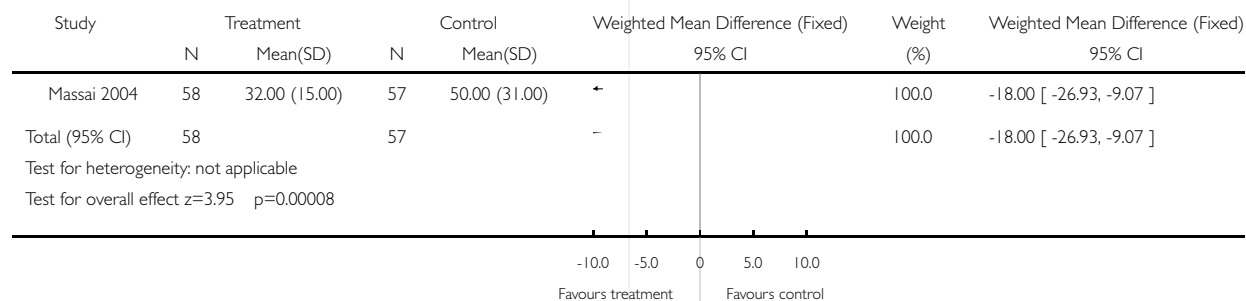


Analysis 09.02. Comparison 09 Antiprogesterin vs placebo (Norplant/Prophylactic), Outcome 02 Bleeding during treatment (days)

Review: Treatment of vaginal bleeding irregularities induced by progestin only contraceptives

Comparison: 09 Antiprogesterin vs placebo (Norplant/Prophylactic)

Outcome: 02 Bleeding during treatment (days)

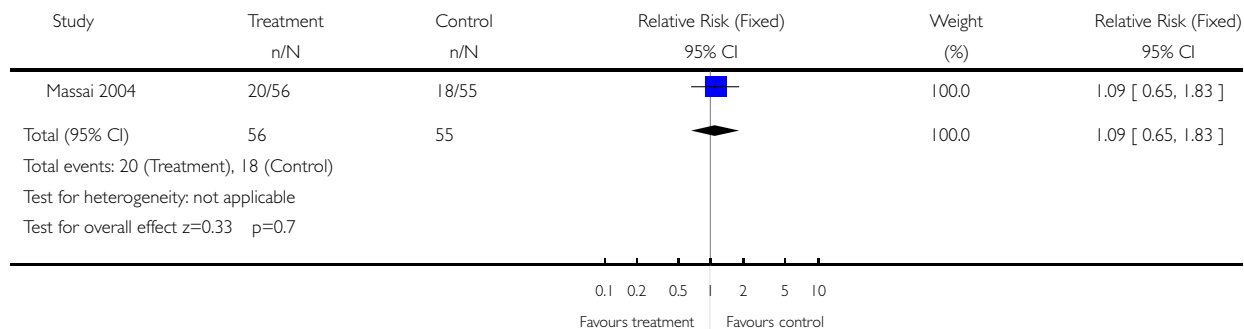


Analysis 09.03. Comparison 09 Antiprogesterin vs placebo (Norplant/Prophylactic), Outcome 03 Unacceptable bleeding after treatment

Review: Treatment of vaginal bleeding irregularities induced by progestin only contraceptives

Comparison: 09 Antiprogesterin vs placebo (Norplant/Prophylactic)

Outcome: 03 Unacceptable bleeding after treatment

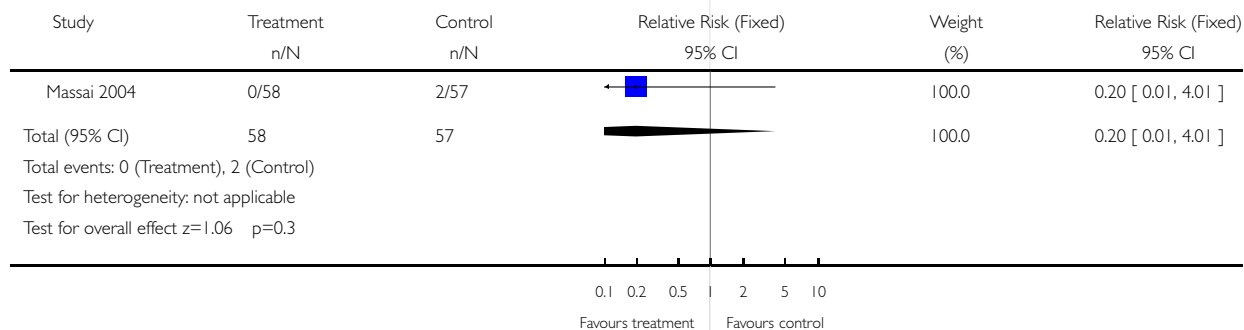


Analysis 09.04. Comparison 09 Antiprogesterin vs placebo (Norplant/Prophylactic), Outcome 04 Discontinuation of contraceptive method because of bleeding

Review: Treatment of vaginal bleeding irregularities induced by progestin only contraceptives

Comparison: 09 Antiprogesterin vs placebo (Norplant/Prophylactic)

Outcome: 04 Discontinuation of contraceptive method because of bleeding

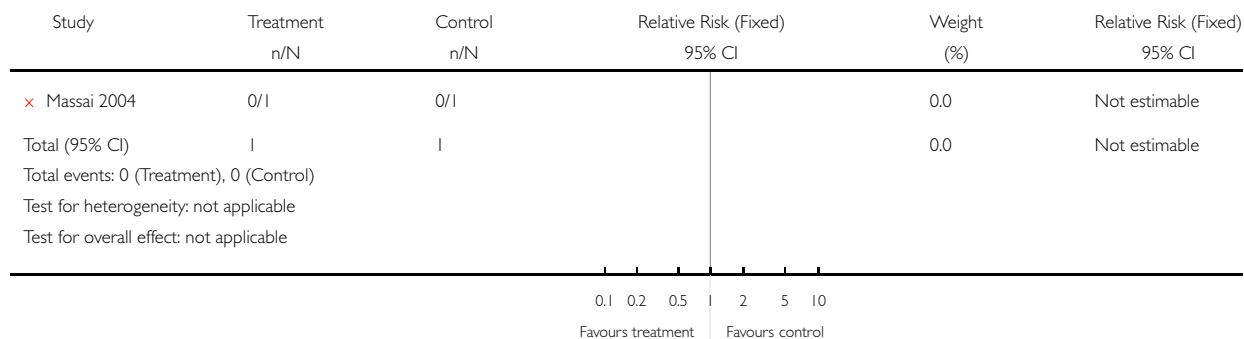


Analysis 09.06. Comparison 09 Antiprogesterin vs placebo (Norplant/Prophylactic), Outcome 06 Side-effects related to treatment

Review: Treatment of vaginal bleeding irregularities induced by progestin only contraceptives

Comparison: 09 Antiprogesterin vs placebo (Norplant/Prophylactic)

Outcome: 06 Side-effects related to treatment

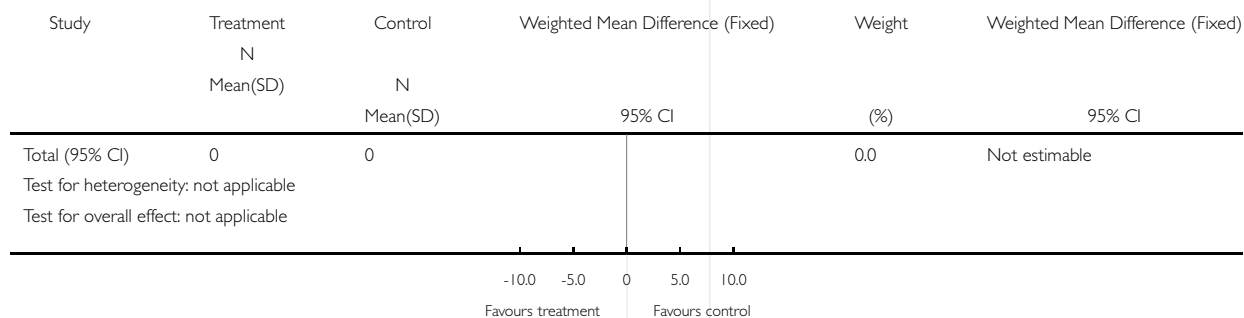


Analysis 09.08. Comparison 09 Antiprogesterin vs placebo (Norplant/Prophylactic), Outcome 08 Blood loss during treatment (mls)

Review: Treatment of vaginal bleeding irregularities induced by progestin only contraceptives

Comparison: 09 Antiprogesterin vs placebo (Norplant/Prophylactic)

Outcome: 08 Blood loss during treatment (mls)

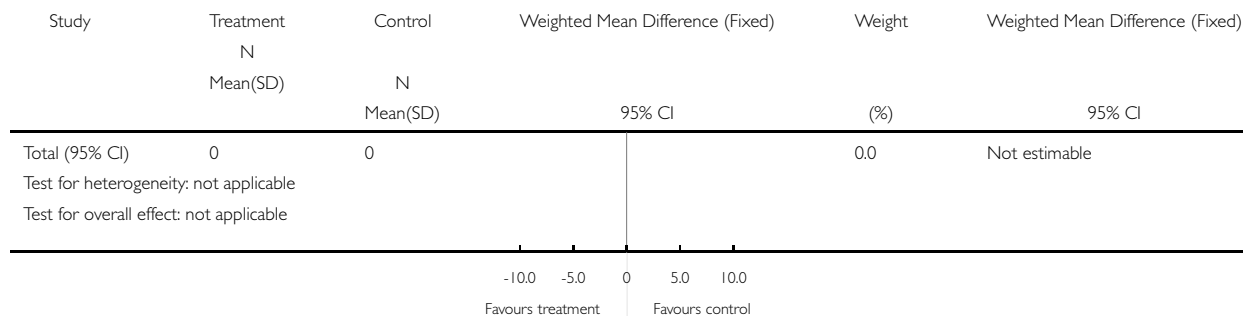


Analysis 10.02. Comparison 10 Antiprogesterin vs placebo (Implanon/Therapeutic), Outcome 02 Bleeding during treatment (days).

Review: Treatment of vaginal bleeding irregularities induced by progestin only contraceptives

Comparison: 10 Antiprogesterin vs placebo (Implanon/Therapeutic)

Outcome: 02 Bleeding during treatment (days).

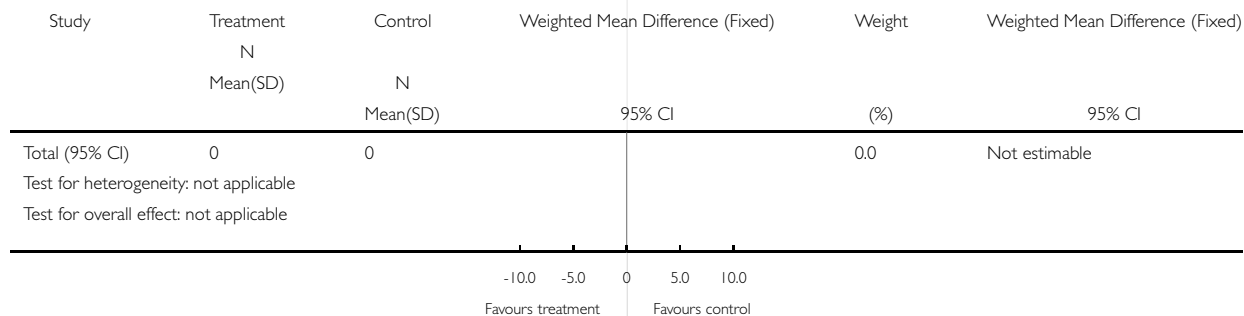


Analysis 10.03. Comparison 10 Antiprogesterin vs placebo (Implanon/Therapeutic), Outcome 03 Bleeding after treatment (days)

Review: Treatment of vaginal bleeding irregularities induced by progestin only contraceptives

Comparison: 10 Antiprogesterin vs placebo (Implanon/Therapeutic)

Outcome: 03 Bleeding after treatment (days)

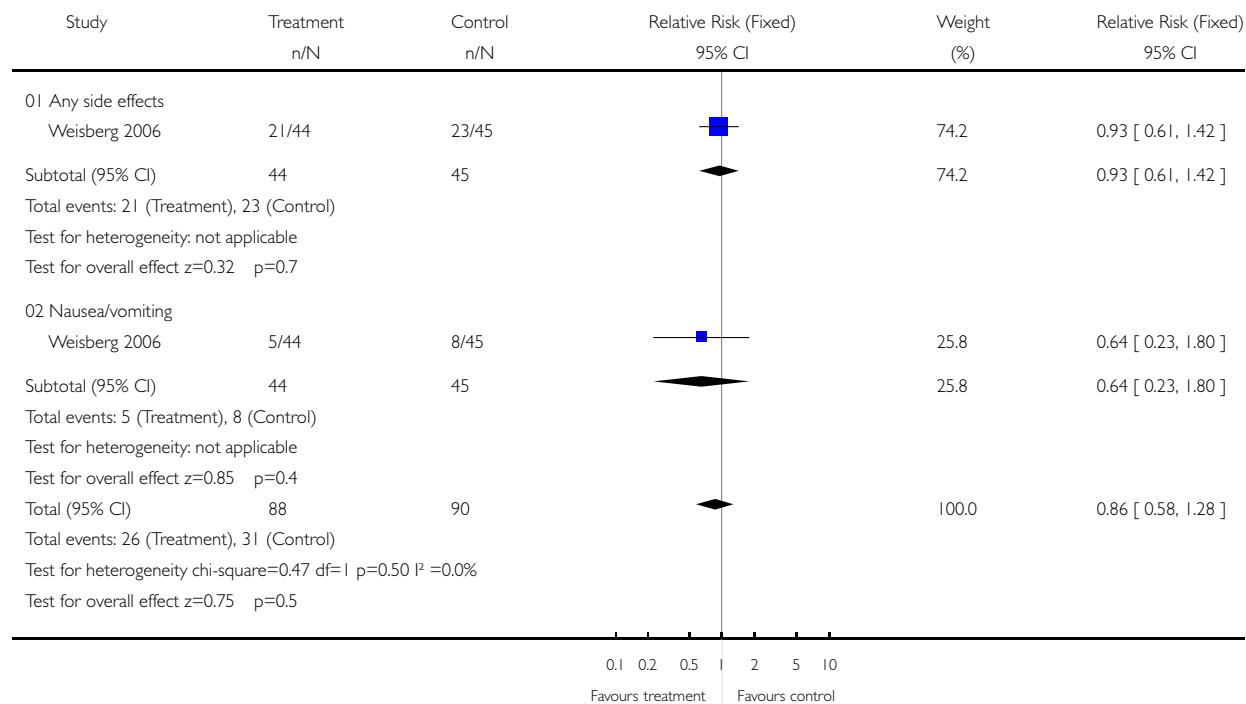


Analysis 10.07. Comparison 10 Antiprogesterin vs placebo (Implanon/Therapeutic), Outcome 07 Side effects related to treatment

Review: Treatment of vaginal bleeding irregularities induced by progestin only contraceptives

Comparison: 10 Antiprogesterin vs placebo (Implanon/Therapeutic)

Outcome: 07 Side effects related to treatment

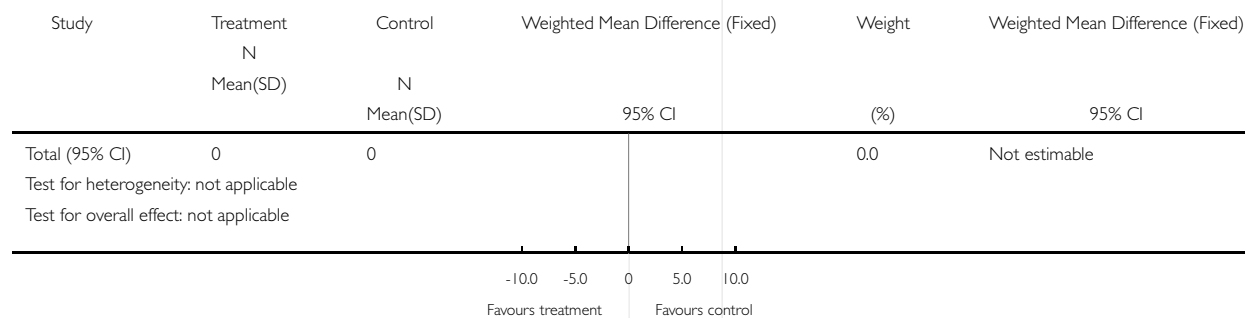


Analysis 10.09. Comparison 10 Antiprogesterin vs placebo (Implanon/Therapeutic), Outcome 09 Blood loss during treatment

Review: Treatment of vaginal bleeding irregularities induced by progestin only contraceptives

Comparison: 10 Antiprogesterin vs placebo (Implanon/Therapeutic)

Outcome: 09 Blood loss during treatment

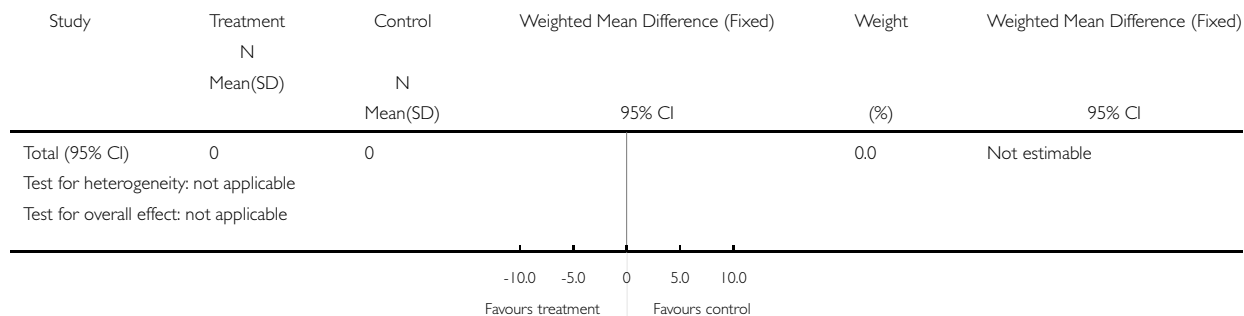


Analysis 11.02. Comparison 11 Antiprogesterin vs placebo (DMPA/Prophylactic), Outcome 02 Bleeding during treatment (days)

Review: Treatment of vaginal bleeding irregularities induced by progestin only contraceptives

Comparison: 11 Antiprogesterin vs placebo (DMPA/Prophylactic)

Outcome: 02 Bleeding during treatment (days)

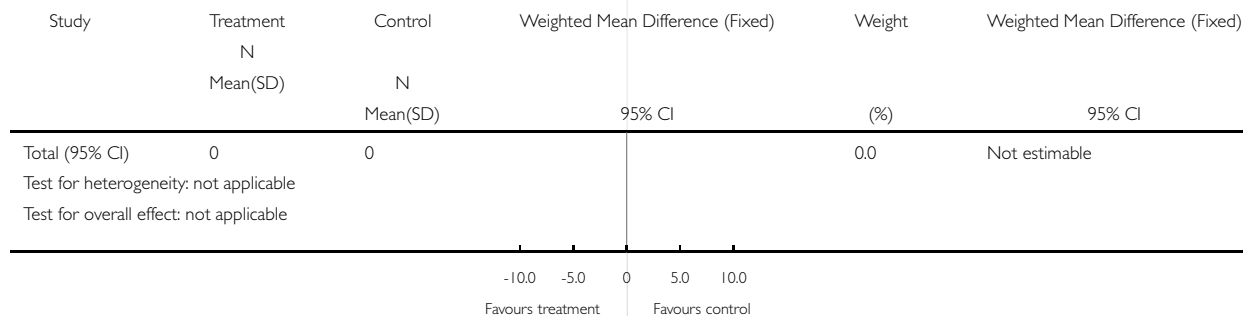


Analysis 11.07. Comparison 11 Antiprogesterin vs placebo (DMPA/Prophylactic), Outcome 07 Blood loss during treatment (mls)

Review: Treatment of vaginal bleeding irregularities induced by progestin only contraceptives

Comparison: 11 Antiprogesterin vs placebo (DMPA/Prophylactic)

Outcome: 07 Blood loss during treatment (mls)

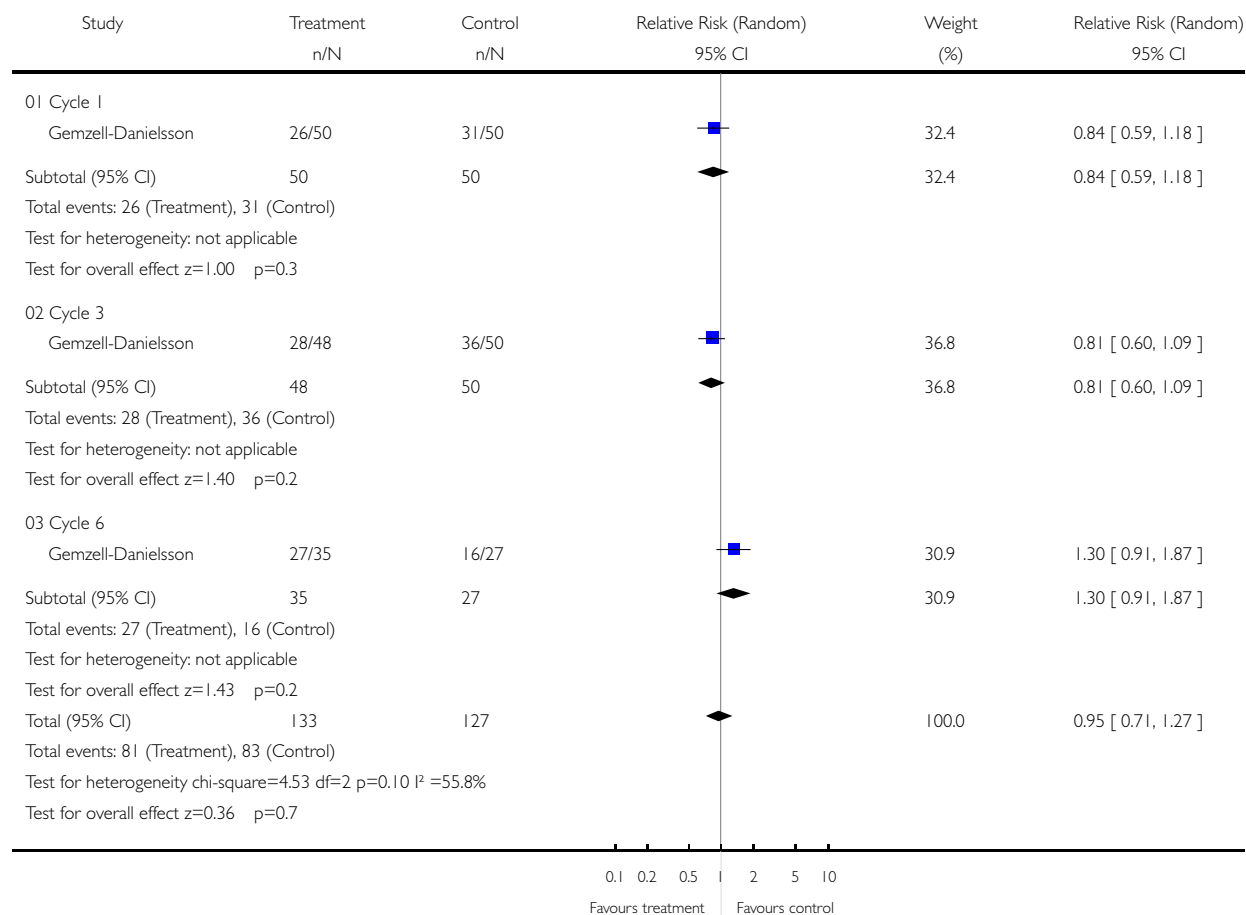


Analysis 12.01. Comparison 12 Antiprogesterin vs placebo (Minipill/Prophylactic), Outcome 01 Percentage of women with B/S episodes starting day 8-28

Review: Treatment of vaginal bleeding irregularities induced by progestin only contraceptives

Comparison: 12 Antiprogesterin vs placebo (Minipill/Prophylactic)

Outcome: 01 Percentage of women with B/S episodes starting day 8-28

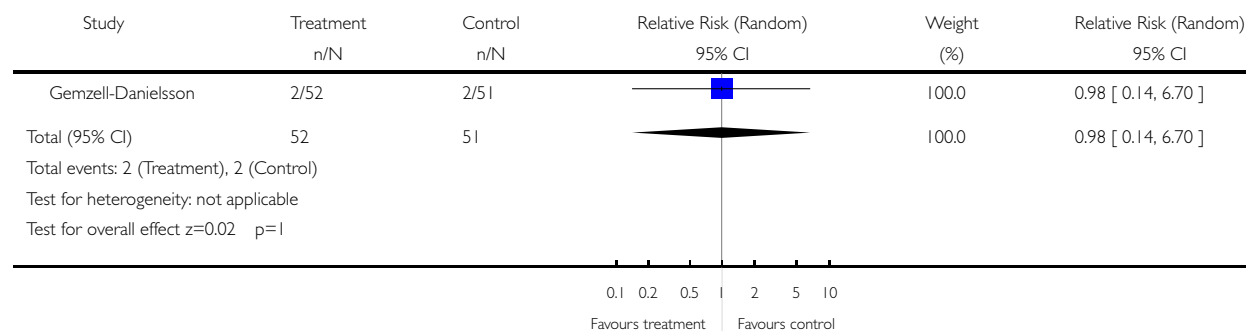


Analysis 12.02. Comparison 12 Antiprogesterin vs placebo (Minipill/Prophylactic), Outcome 02 Discontinuation of the contraceptive method because of bleeding

Review: Treatment of vaginal bleeding irregularities induced by progestin only contraceptives

Comparison: 12 Antiprogesterin vs placebo (Minipill/Prophylactic)

Outcome: 02 Discontinuation of the contraceptive method because of bleeding

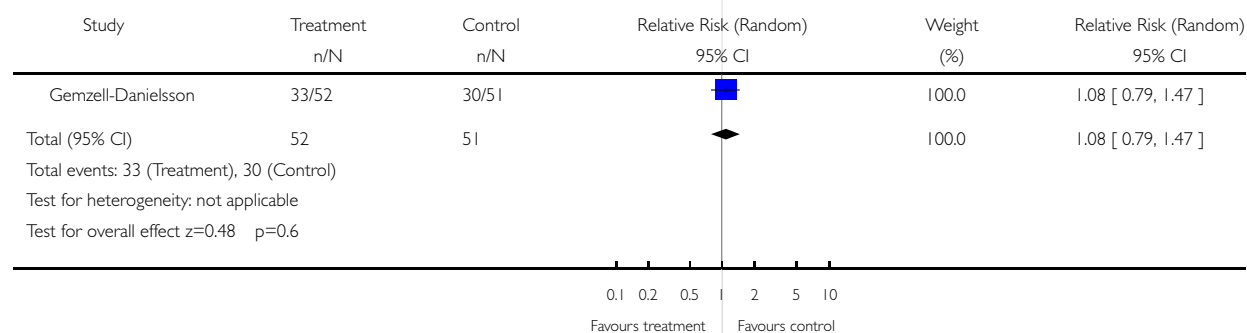


Analysis 12.03. Comparison 12 Antiprogesterin vs placebo (Minipill/Prophylactic), Outcome 03 Percentage of women having side effects related to treatment (headache, emotional lability, acne, breast pain).

Review: Treatment of vaginal bleeding irregularities induced by progestin only contraceptives

Comparison: 12 Antiprogesterin vs placebo (Minipill/Prophylactic)

Outcome: 03 Percentage of women having side effects related to treatment (headache, emotional lability, acne, breast pain).

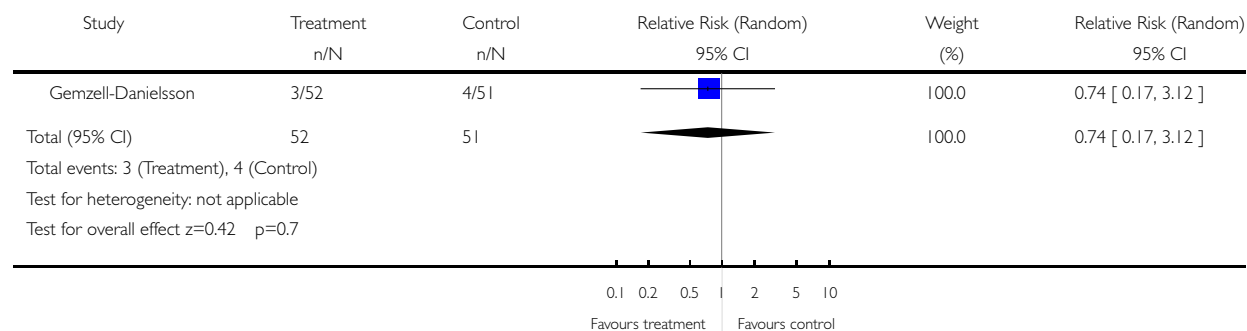


Analysis 12.04. Comparison 12 Antiprogesterin vs placebo (Minipill/Prophylactic), Outcome 04 Discontinuation of the contraceptive because of side effects.

Review: Treatment of vaginal bleeding irregularities induced by progestin only contraceptives

Comparison: 12 Antiprogesterin vs placebo (Minipill/Prophylactic)

Outcome: 04 Discontinuation of the contraceptive because of side effects.

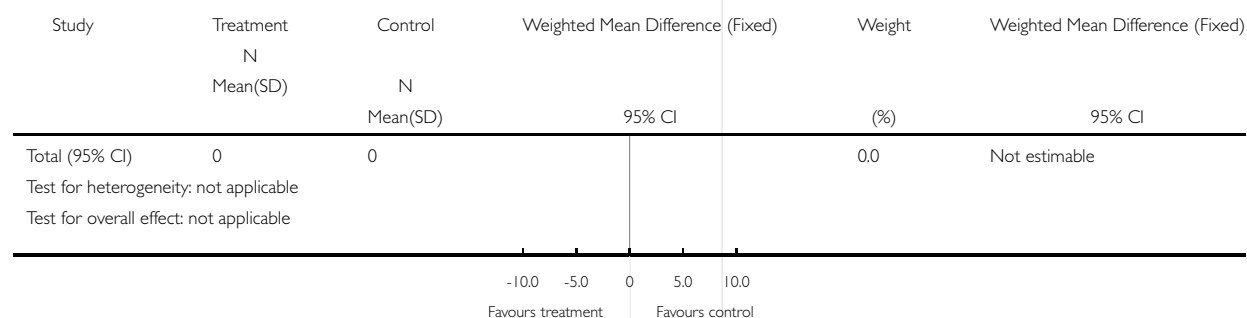


Analysis 13.02. Comparison 13 Antiprogesterin and estrogen vs placebo (Implanon/Therapeutic), Outcome 02 Bleeding during treatment (days)

Review: Treatment of vaginal bleeding irregularities induced by progestin only contraceptives

Comparison: 13 Antiprogesterin and estrogen vs placebo (Implanon/Therapeutic)

Outcome: 02 Bleeding during treatment (days)

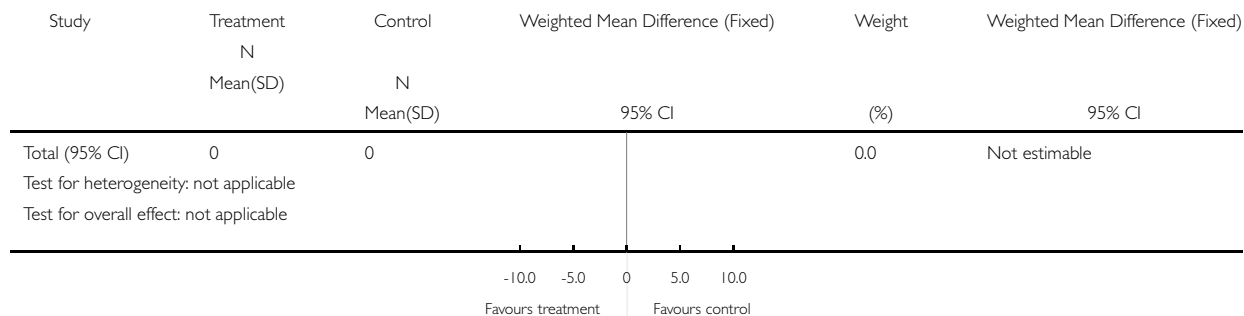


Analysis 13.03. Comparison 13 Antiprogesterin and estrogen vs placebo (Implanon/Therapeutic), Outcome 03 Bleeding after treatment (days)

Review: Treatment of vaginal bleeding irregularities induced by progestin only contraceptives

Comparison: 13 Antiprogesterin and estrogen vs placebo (Implanon/Therapeutic)

Outcome: 03 Bleeding after treatment (days)

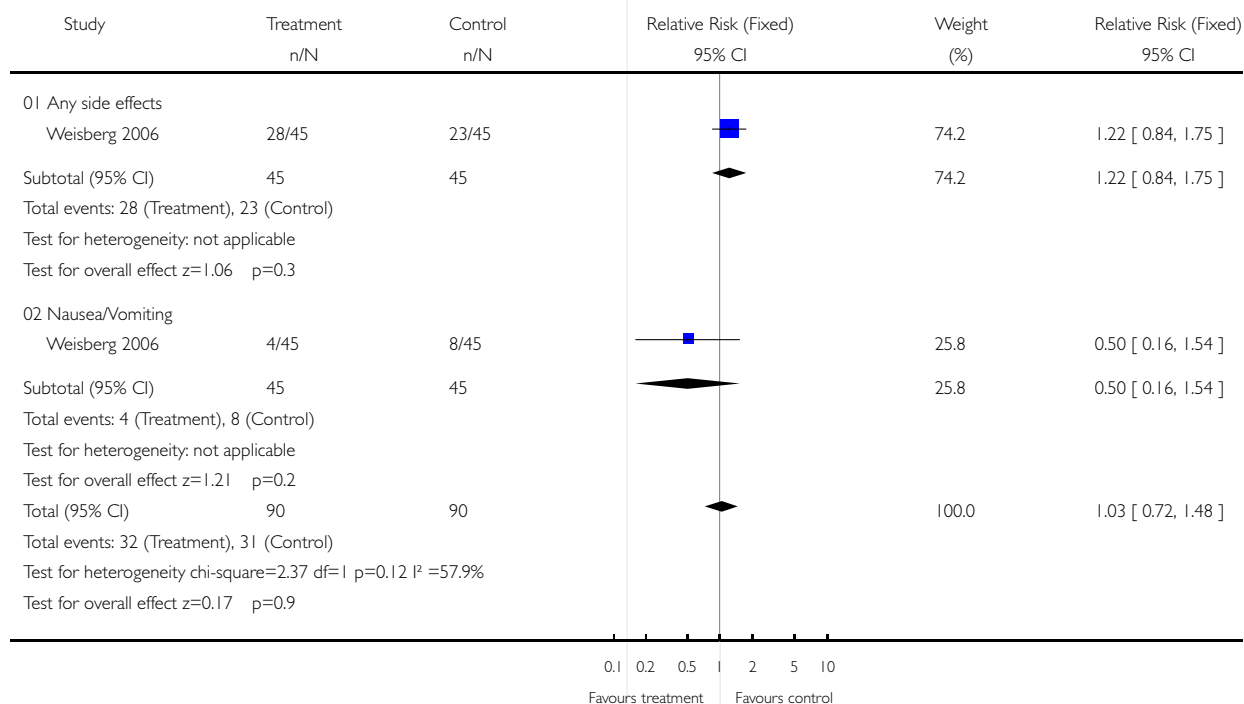


Analysis 13.07. Comparison 13 Antiprogesterin and estrogen vs placebo (Implanon/Therapeutic), Outcome 07 Side effects related to treatment

Review: Treatment of vaginal bleeding irregularities induced by progestin only contraceptives

Comparison: 13 Antiprogesterin and estrogen vs placebo (Implanon/Therapeutic)

Outcome: 07 Side effects related to treatment

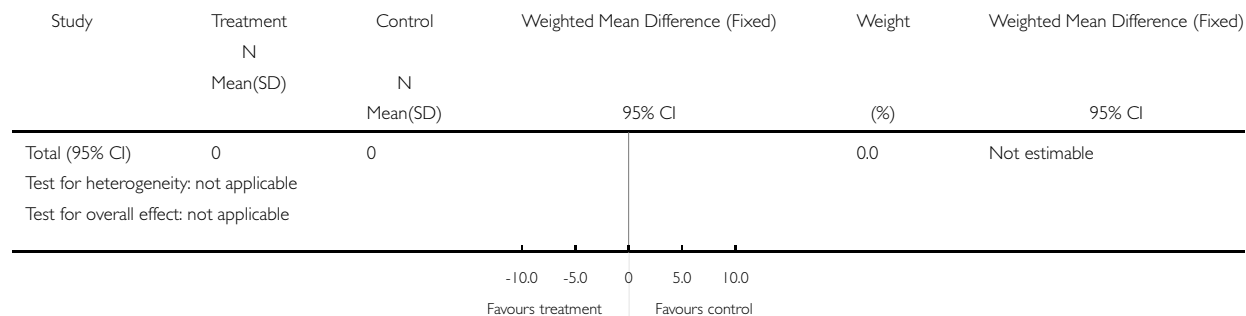


Analysis 13.09. Comparison 13 Antiprogesterin and estrogen vs placebo (Implanon/Therapeutic), Outcome 09 Blood loss during treatment

Review: Treatment of vaginal bleeding irregularities induced by progestin only contraceptives

Comparison: 13 Antiprogesterin and estrogen vs placebo (Implanon/Therapeutic)

Outcome: 09 Blood loss during treatment

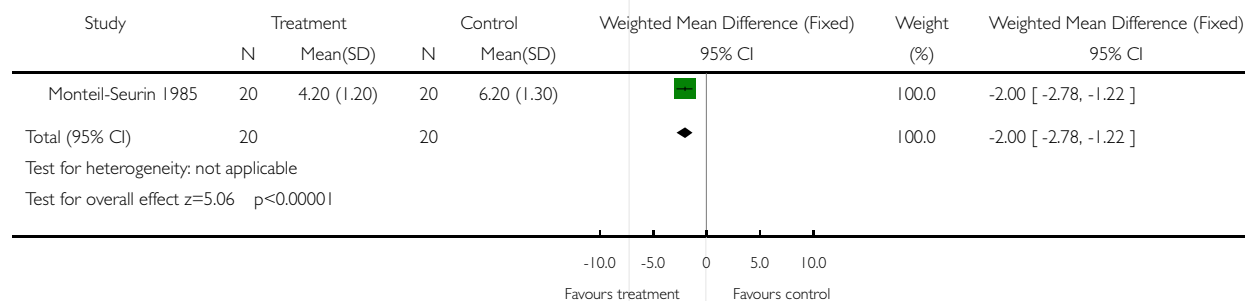


Analysis 14.02. Comparison 14 Venotonic vs placebo (Minipill/Therapeutic), Outcome 02 Bleeding during treatment (days)

Review: Treatment of vaginal bleeding irregularities induced by progestin only contraceptives

Comparison: 14 Venotonic vs placebo (Minipill/Therapeutic)

Outcome: 02 Bleeding during treatment (days)

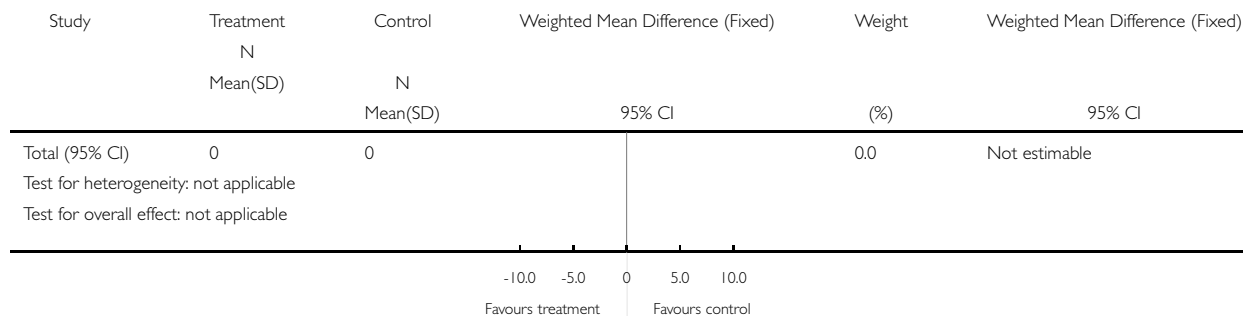


Analysis 14.08. Comparison 14 Venotonic vs placebo (Minipill/Therapeutic), Outcome 08 Blood loss during treatment (mls)

Review: Treatment of vaginal bleeding irregularities induced by progestin only contraceptives

Comparison: 14 Venotonic vs placebo (Minipill/Therapeutic)

Outcome: 08 Blood loss during treatment (mls)

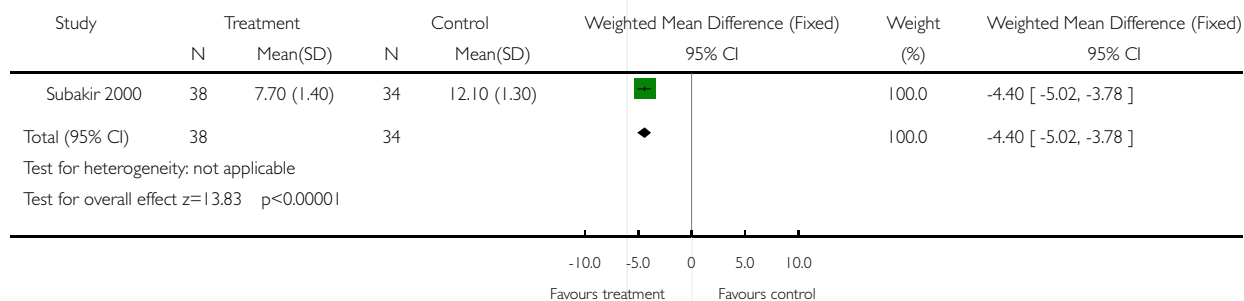


Analysis 15.02. Comparison 15 Vitamin E vs placebo (Norplant/Therapeutic), Outcome 02 Bleeding during treatment (days)

Review: Treatment of vaginal bleeding irregularities induced by progestin only contraceptives

Comparison: 15 Vitamin E vs placebo (Norplant/Therapeutic)

Outcome: 02 Bleeding during treatment (days)

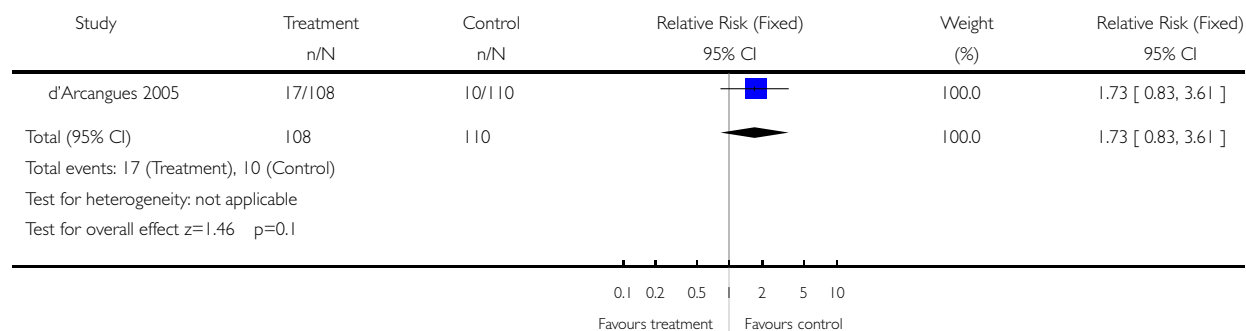


Analysis 15.05. Comparison 15 Vitamin E vs placebo (Norplant/Therapeutic), Outcome 05 Discontinuation of treatment due to lack of improvement

Review: Treatment of vaginal bleeding irregularities induced by progestin only contraceptives

Comparison: 15 Vitamin E vs placebo (Norplant/Therapeutic)

Outcome: 05 Discontinuation of treatment due to lack of improvement

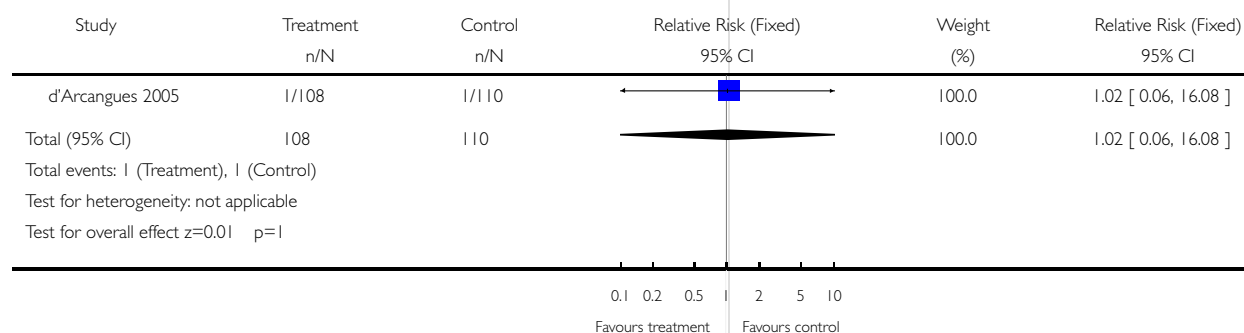


Analysis 15.06. Comparison 15 Vitamin E vs placebo (Norplant/Therapeutic), Outcome 06 Discontinuation of treatment because of side-effects

Review: Treatment of vaginal bleeding irregularities induced by progestin only contraceptives

Comparison: 15 Vitamin E vs placebo (Norplant/Therapeutic)

Outcome: 06 Discontinuation of treatment because of side-effects

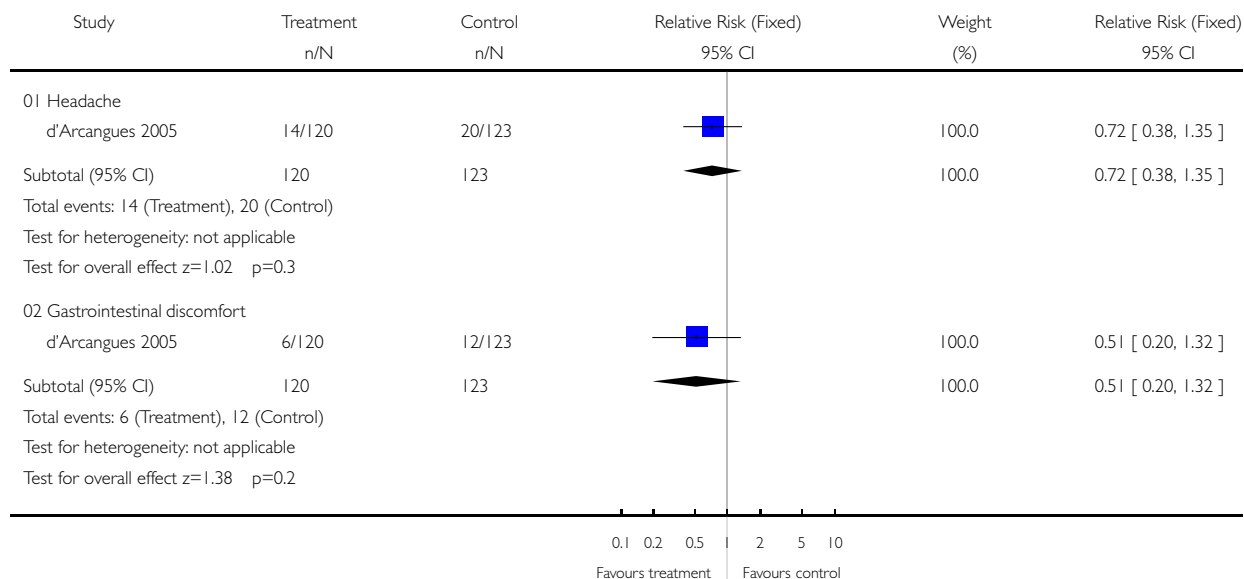


Analysis 15.07. Comparison 15 Vitamin E vs placebo (Norplant/Therapeutic), Outcome 07 Side-effects related to treatment

Review: Treatment of vaginal bleeding irregularities induced by progestin only contraceptives

Comparison: 15 Vitamin E vs placebo (Norplant/Therapeutic)

Outcome: 07 Side-effects related to treatment

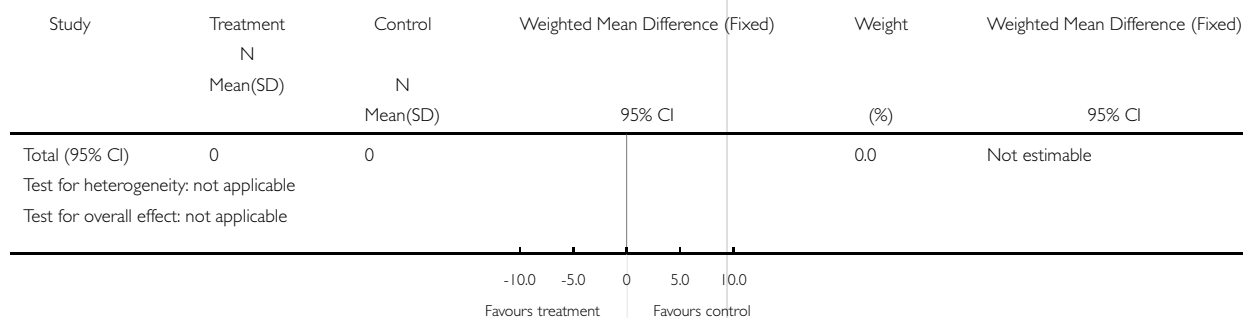


Analysis 15.09. Comparison 15 Vitamin E vs placebo (Norplant/Therapeutic), Outcome 09 Blood loss during treatment

Review: Treatment of vaginal bleeding irregularities induced by progestin only contraceptives

Comparison: 15 Vitamin E vs placebo (Norplant/Therapeutic)

Outcome: 09 Blood loss during treatment

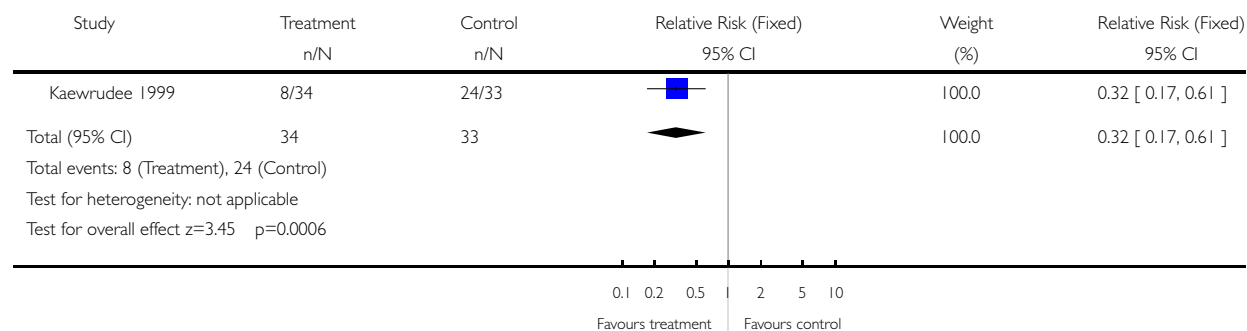


Analysis 16.01. Comparison 16 NSAIDs vs placebo (Norplant/Therapeutic), Outcome 01 Continued irregular bleeding during treatment

Review: Treatment of vaginal bleeding irregularities induced by progestin only contraceptives

Comparison: 16 NSAIDs vs placebo (Norplant/Therapeutic)

Outcome: 01 Continued irregular bleeding during treatment

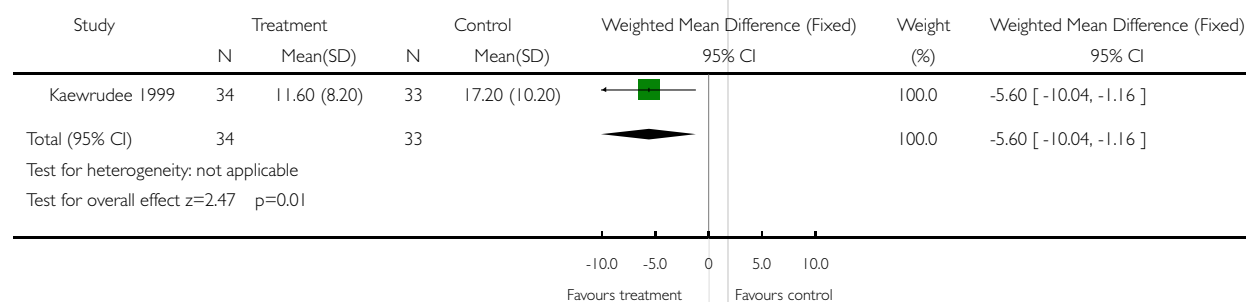


Analysis 16.02. Comparison 16 NSAIDs vs placebo (Norplant/Therapeutic), Outcome 02 Bleeding during treatment (days)

Review: Treatment of vaginal bleeding irregularities induced by progestin only contraceptives

Comparison: 16 NSAIDs vs placebo (Norplant/Therapeutic)

Outcome: 02 Bleeding during treatment (days)

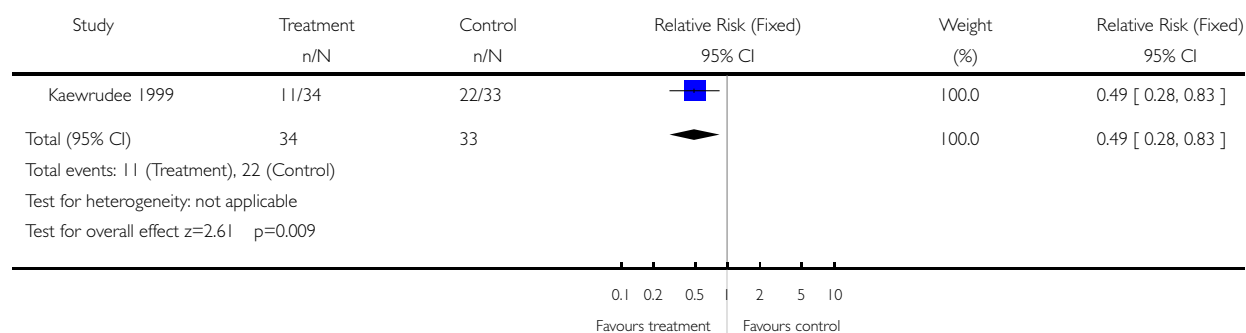


Analysis 16.03. Comparison 16 NSAIDs vs placebo (Norplant/Therapeutic), Outcome 03 Unacceptable bleeding after treatment

Review: Treatment of vaginal bleeding irregularities induced by progestin only contraceptives

Comparison: 16 NSAIDs vs placebo (Norplant/Therapeutic)

Outcome: 03 Unacceptable bleeding after treatment

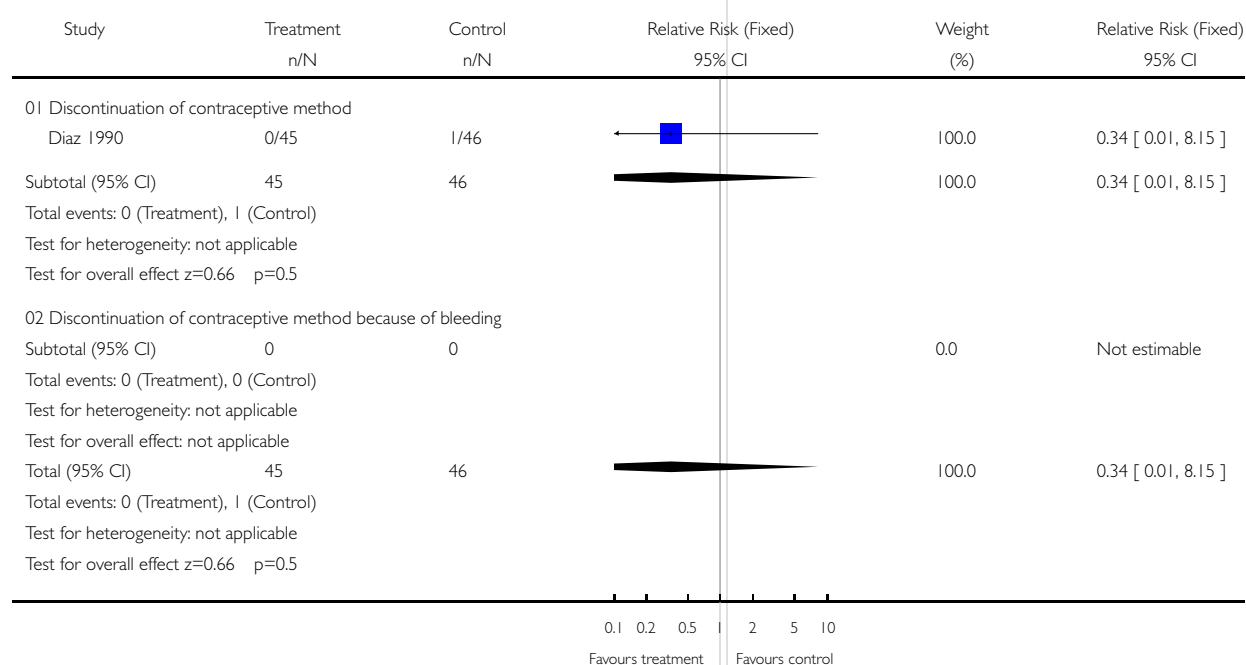


Analysis 16.04. Comparison 16 NSAIDs vs placebo (Norplant/Therapeutic), Outcome 04 Discontinuation of contraceptive method

Review: Treatment of vaginal bleeding irregularities induced by progestin only contraceptives

Comparison: 16 NSAIDs vs placebo (Norplant/Therapeutic)

Outcome: 04 Discontinuation of contraceptive method

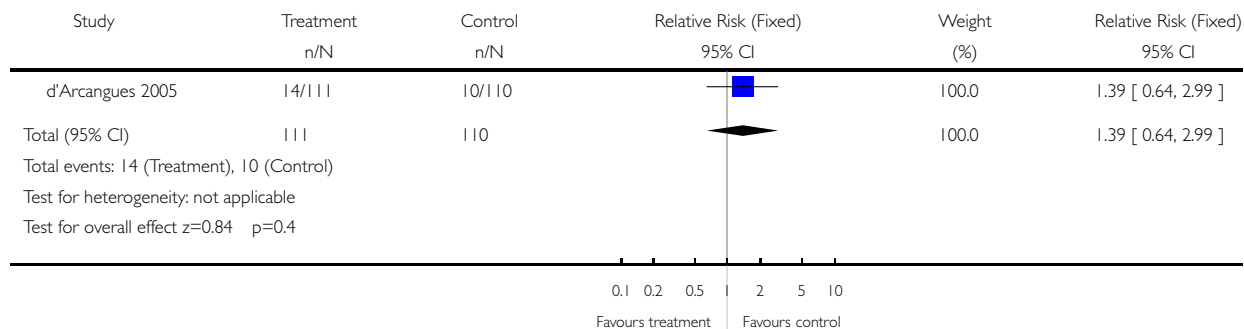


Analysis 16.05. Comparison 16 NSAIDs vs placebo (Norplant/Therapeutic), Outcome 05 Discontinuation of treatment due to lack of improvement

Review: Treatment of vaginal bleeding irregularities induced by progestin only contraceptives

Comparison: 16 NSAIDs vs placebo (Norplant/Therapeutic)

Outcome: 05 Discontinuation of treatment due to lack of improvement

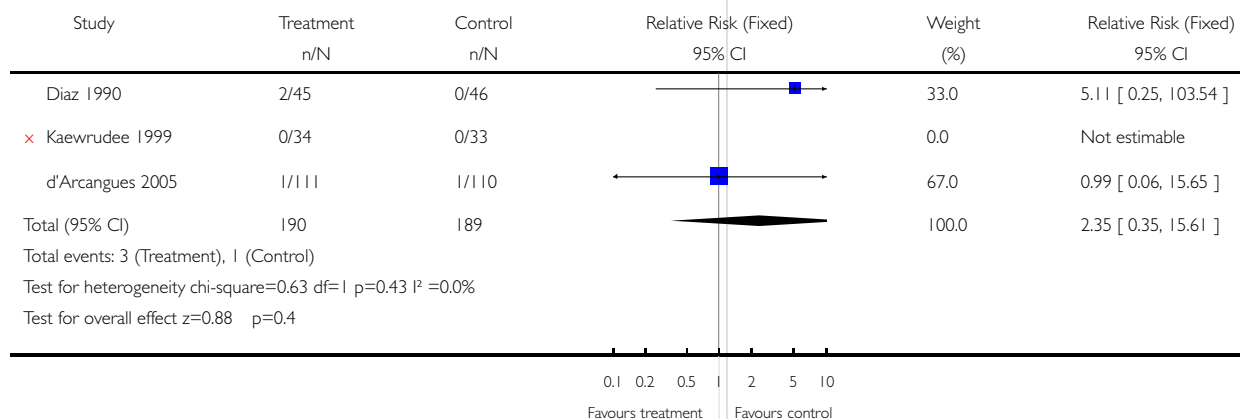


Analysis 16.06. Comparison 16 NSAIDs vs placebo (Norplant/Therapeutic), Outcome 06 Discontinuation of treatment due to side-effects

Review: Treatment of vaginal bleeding irregularities induced by progestin only contraceptives

Comparison: 16 NSAIDs vs placebo (Norplant/Therapeutic)

Outcome: 06 Discontinuation of treatment due to side-effects

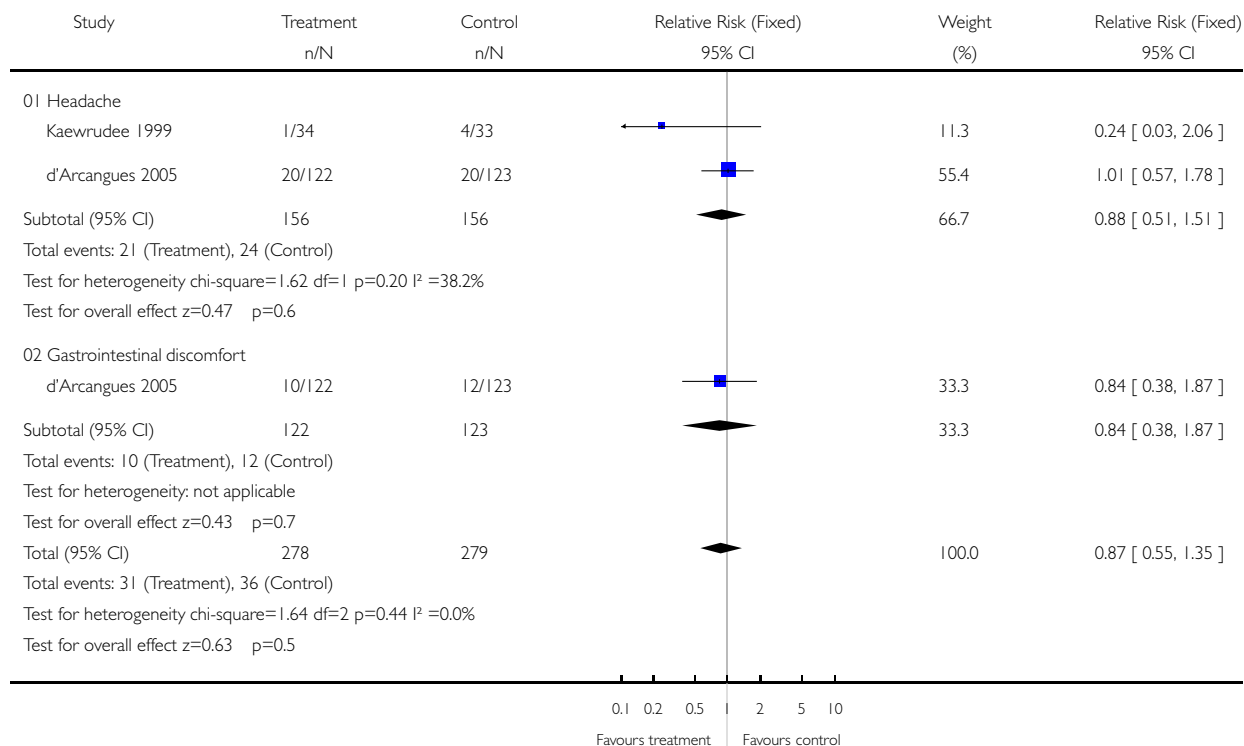


Analysis 16.07. Comparison 16 NSAIDs vs placebo (Norplant/Therapeutic), Outcome 07 Side-effects related to treatment

Review: Treatment of vaginal bleeding irregularities induced by progestin only contraceptives

Comparison: 16 NSAIDs vs placebo (Norplant/Therapeutic)

Outcome: 07 Side-effects related to treatment

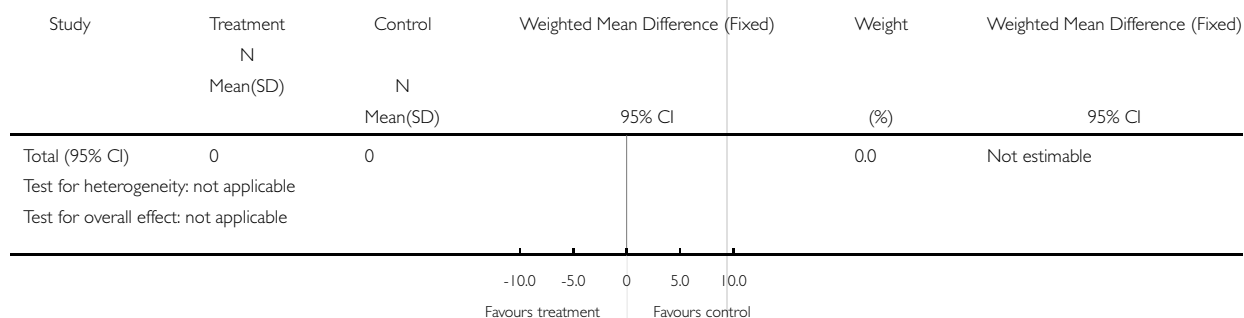


Analysis 16.09. Comparison 16 NSAIDs vs placebo (Norplant/Therapeutic), Outcome 09 Blood loss during treatment (mls)

Review: Treatment of vaginal bleeding irregularities induced by progestin only contraceptives

Comparison: 16 NSAIDs vs placebo (Norplant/Therapeutic)

Outcome: 09 Blood loss during treatment (mls)

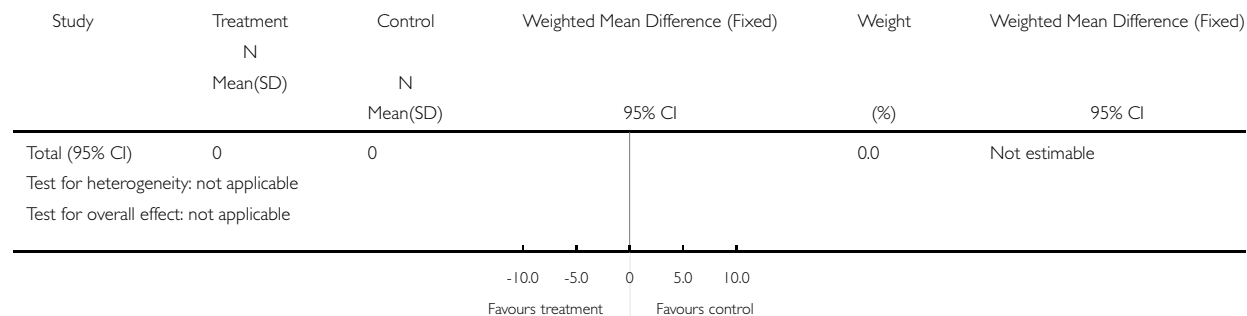


Analysis 17.02. Comparison 17 Vitamin E + NSAID vs placebo (Norplant/Therapeutic), Outcome 02 Bleeding during treatment (days)

Review: Treatment of vaginal bleeding irregularities induced by progestin only contraceptives

Comparison: 17 Vitamin E + NSAID vs placebo (Norplant/Therapeutic)

Outcome: 02 Bleeding during treatment (days)

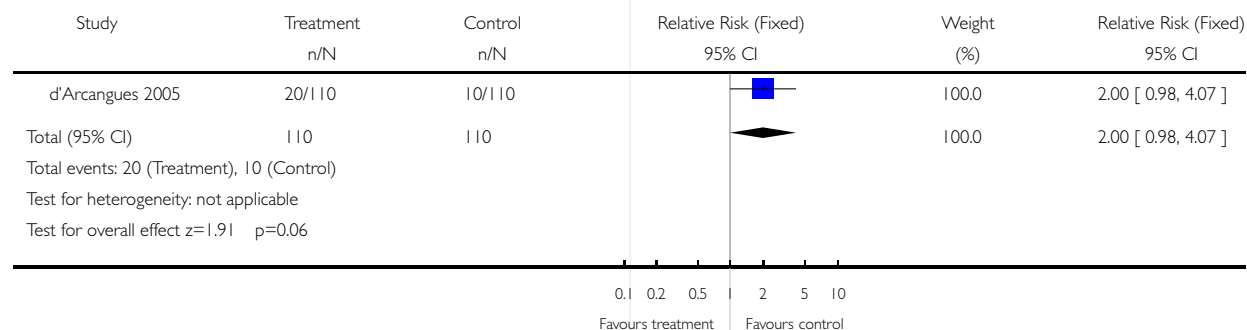


Analysis 17.05. Comparison 17 Vitamin E + NSAID vs placebo (Norplant/Therapeutic), Outcome 05 Discontinuation of treatment due to lack of improvement

Review: Treatment of vaginal bleeding irregularities induced by progestin only contraceptives

Comparison: 17 Vitamin E + NSAID vs placebo (Norplant/Therapeutic)

Outcome: 05 Discontinuation of treatment due to lack of improvement

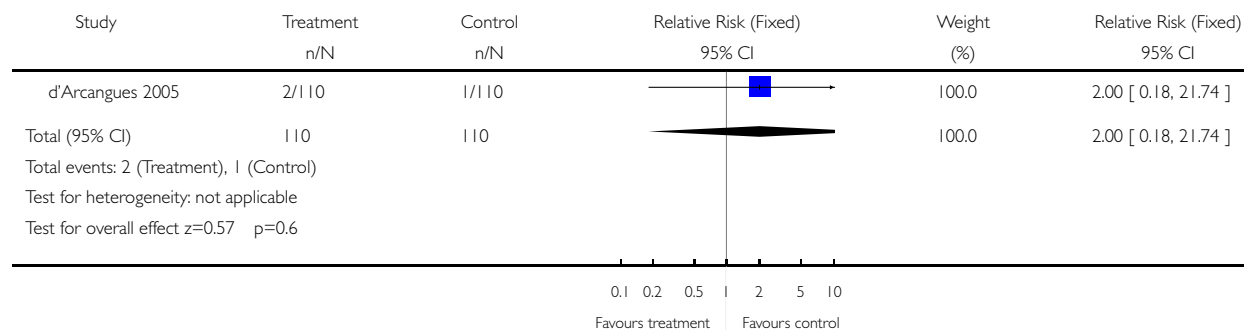


Analysis 17.06. Comparison 17 Vitamin E + NSAID vs placebo (Norplant/Therapeutic), Outcome 06 Discontinuation of treatment due to side-effects

Review: Treatment of vaginal bleeding irregularities induced by progestin only contraceptives

Comparison: 17 Vitamin E + NSAID vs placebo (Norplant/Therapeutic)

Outcome: 06 Discontinuation of treatment due to side-effects

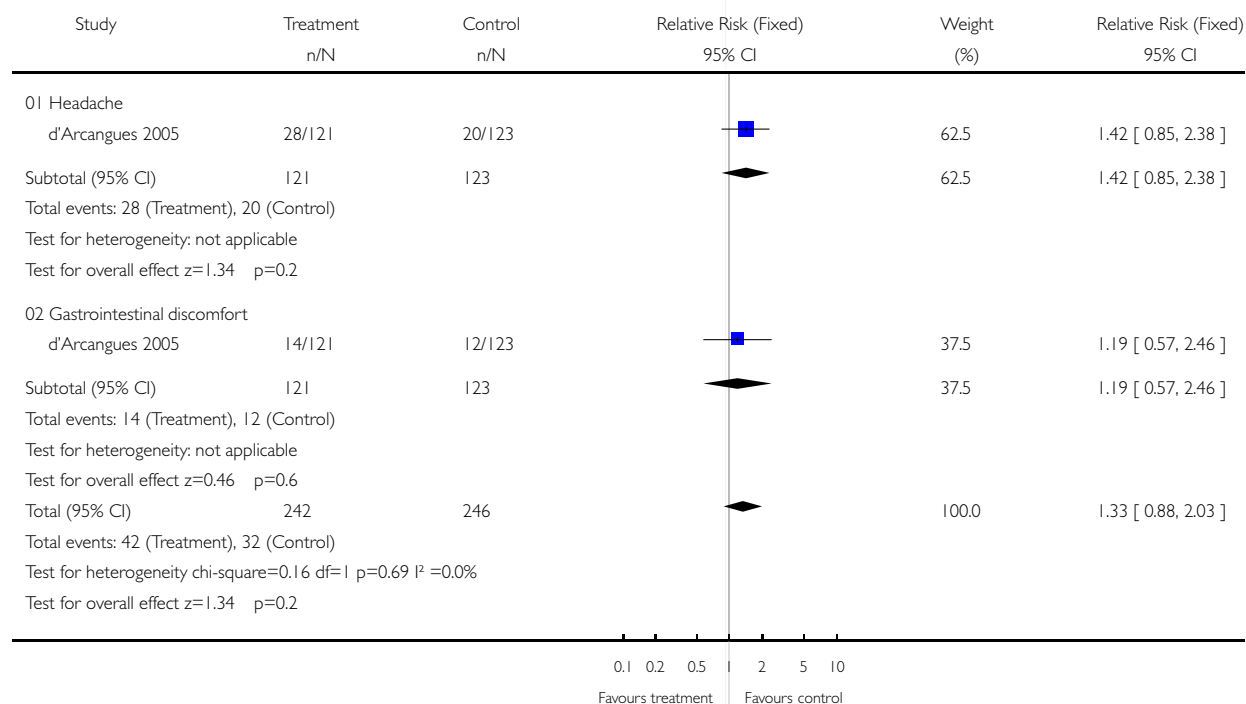


Analysis 17.07. Comparison 17 Vitamin E + NSAID vs placebo (Norplant/Therapeutic), Outcome 07 Side-effects related to treatment

Review: Treatment of vaginal bleeding irregularities induced by progestin only contraceptives

Comparison: 17 Vitamin E + NSAID vs placebo (Norplant/Therapeutic)

Outcome: 07 Side-effects related to treatment

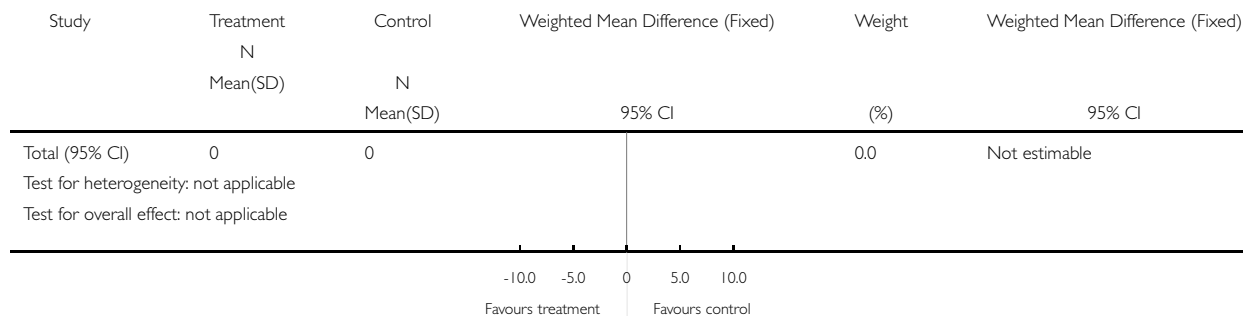


Analysis 17.09. Comparison 17 Vitamin E + NSAID vs placebo (Norplant/Therapeutic), Outcome 09 Blood loss during treatment

Review: Treatment of vaginal bleeding irregularities induced by progestin only contraceptives

Comparison: 17 Vitamin E + NSAID vs placebo (Norplant/Therapeutic)

Outcome: 09 Blood loss during treatment

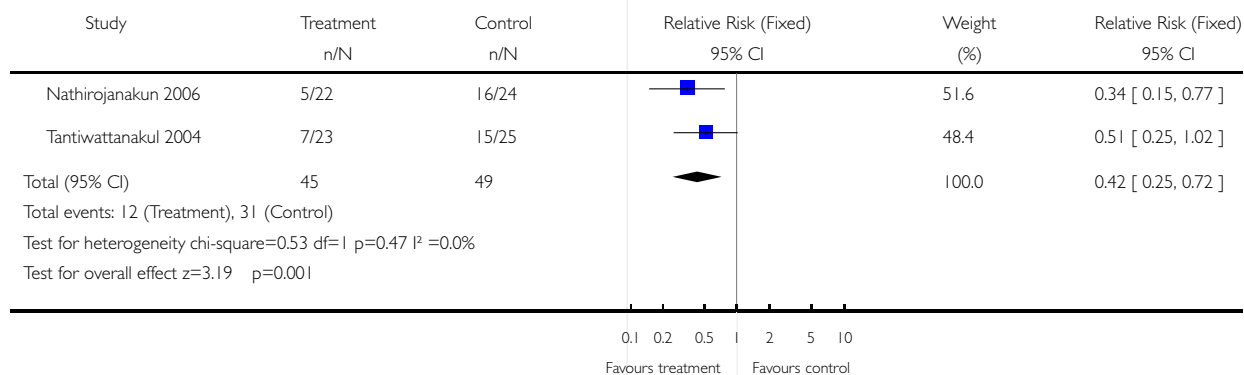


Analysis 18.01. Comparison 18 NSAID vs placebo (DMPA/Therapeutic), Outcome 01 Continued irregular bleeding during treatment

Review: Treatment of vaginal bleeding irregularities induced by progestin only contraceptives

Comparison: 18 NSAID vs placebo (DMPA/Therapeutic)

Outcome: 01 Continued irregular bleeding during treatment

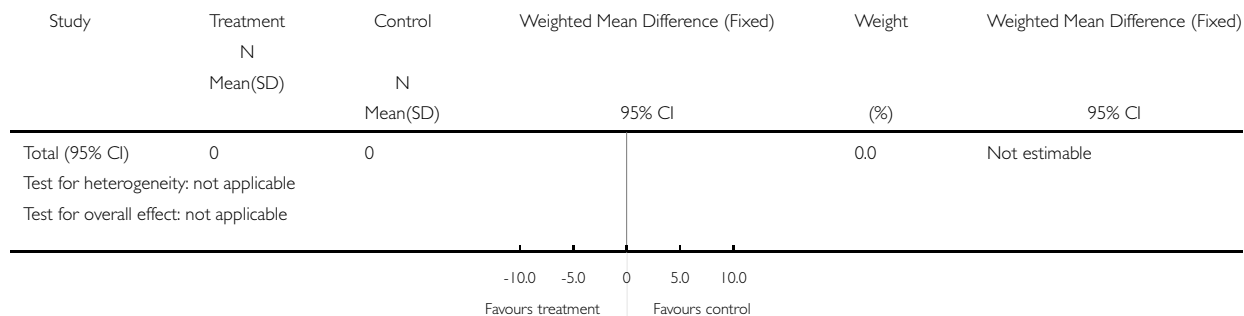


Analysis 18.02. Comparison 18 NSAID vs placebo (DMPA/Therapeutic), Outcome 02 Bleeding during treatment (days)

Review: Treatment of vaginal bleeding irregularities induced by progestin only contraceptives

Comparison: 18 NSAID vs placebo (DMPA/Therapeutic)

Outcome: 02 Bleeding during treatment (days)

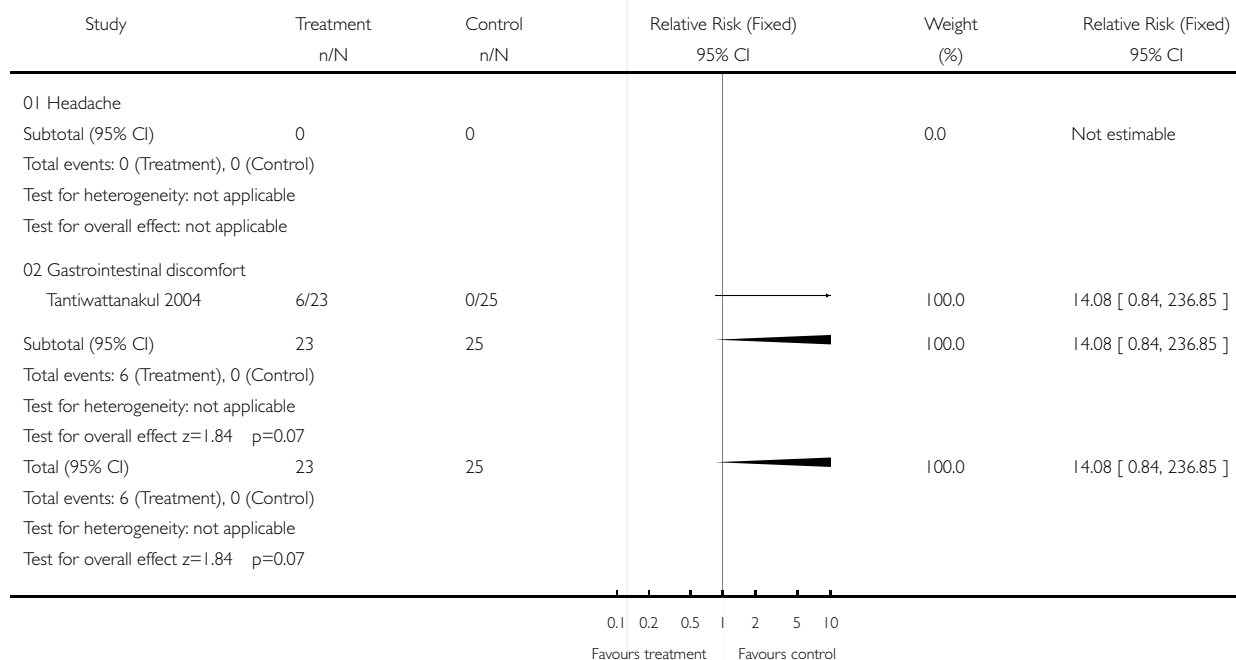


Analysis 18.07. Comparison 18 NSAID vs placebo (DMPA/Therapeutic), Outcome 07 Side-effects related to treatment

Review: Treatment of vaginal bleeding irregularities induced by progestin only contraceptives

Comparison: 18 NSAID vs placebo (DMPA/Therapeutic)

Outcome: 07 Side-effects related to treatment

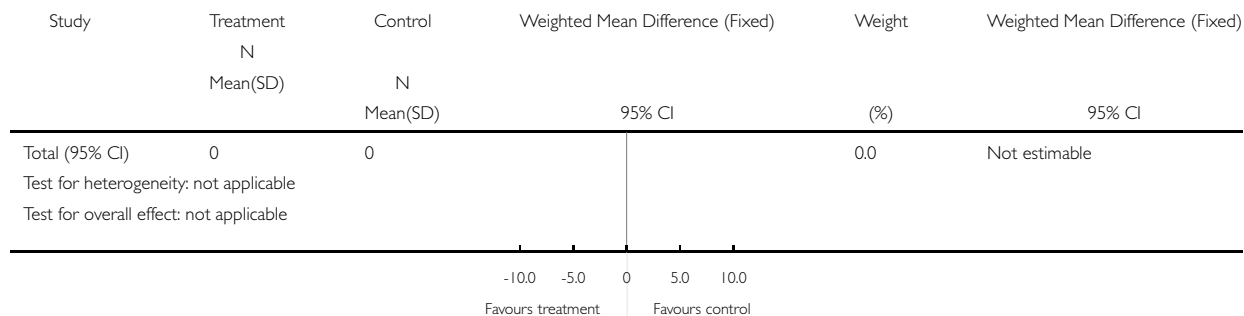


Analysis 18.09. Comparison 18 NSAID vs placebo (DMPA/Therapeutic), Outcome 09 Blood loss during treatment (mls)

Review: Treatment of vaginal bleeding irregularities induced by progestin only contraceptives

Comparison: 18 NSAID vs placebo (DMPA/Therapeutic)

Outcome: 09 Blood loss during treatment (mls)

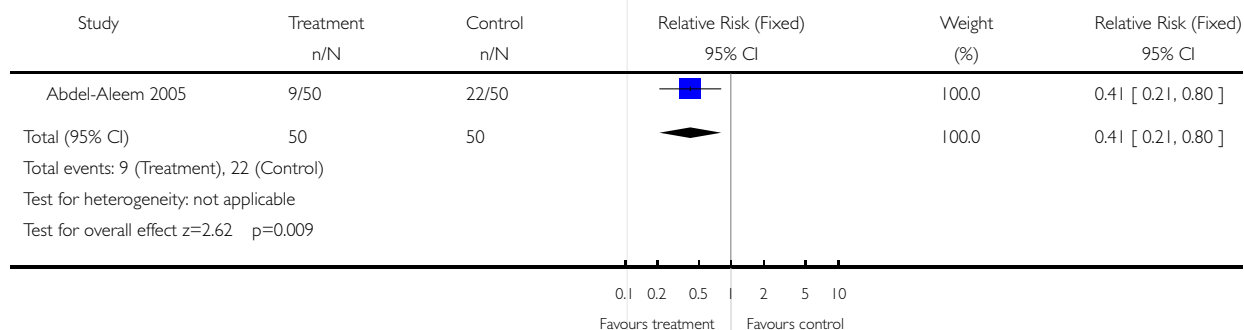


Analysis 19.01. Comparison 19 Selective estrogen receptor modulator vs placebo (Norplant/Therapeutic), Outcome 01 Continued irregular bleeding during treatment

Review: Treatment of vaginal bleeding irregularities induced by progestin only contraceptives

Comparison: 19 Selective estrogen receptor modulator vs placebo (Norplant/Therapeutic)

Outcome: 01 Continued irregular bleeding during treatment

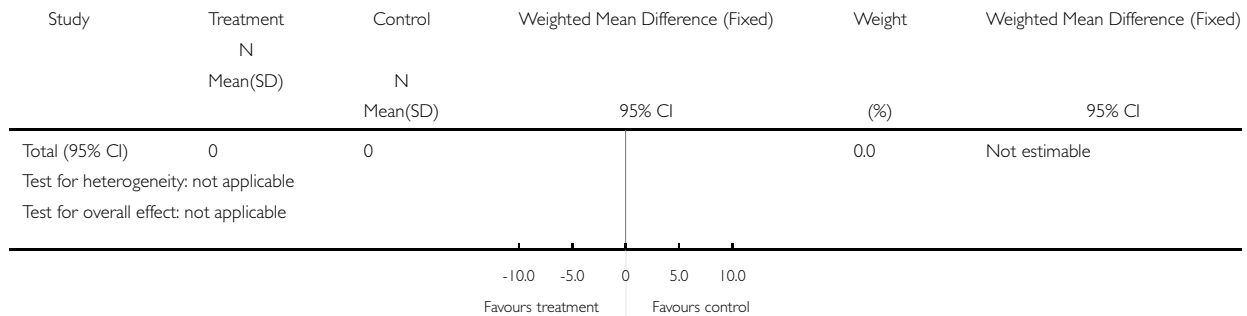


Analysis 19.02. Comparison 19 Selective estrogen receptor modulator vs placebo (Norplant/Therapeutic), Outcome 02 Bleeding during treatment (days)

Review: Treatment of vaginal bleeding irregularities induced by progestin only contraceptives

Comparison: 19 Selective estrogen receptor modulator vs placebo (Norplant/Therapeutic)

Outcome: 02 Bleeding during treatment (days)

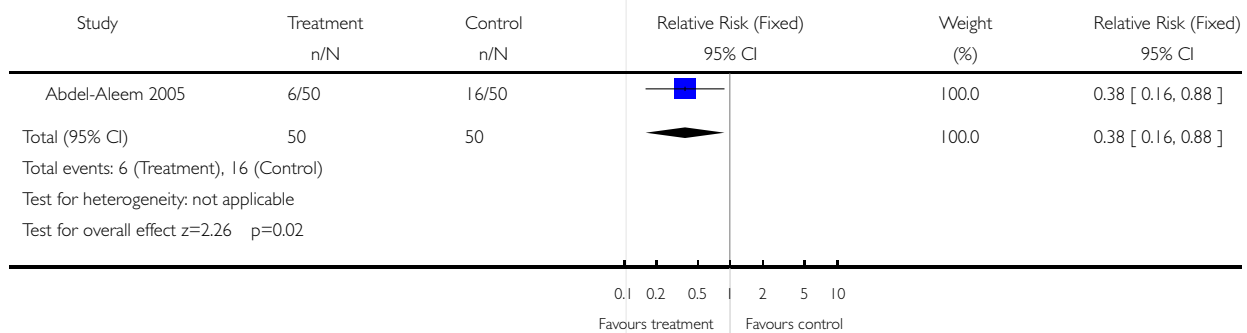


Analysis 19.03. Comparison 19 Selective estrogen receptor modulator vs placebo (Norplant/Therapeutic), Outcome 03 Unacceptable bleeding after treatment

Review: Treatment of vaginal bleeding irregularities induced by progestin only contraceptives

Comparison: 19 Selective estrogen receptor modulator vs placebo (Norplant/Therapeutic)

Outcome: 03 Unacceptable bleeding after treatment

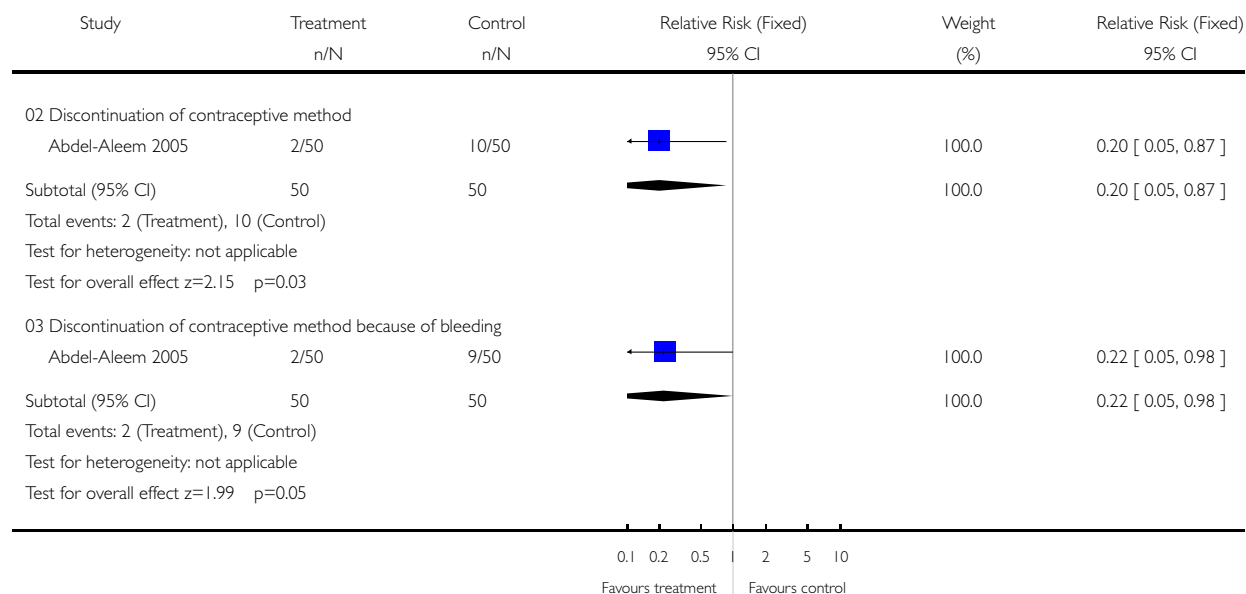


Analysis 19.04. Comparison 19 Selective estrogen receptor modulator vs placebo (Norplant/Therapeutic), Outcome 04 Discontinuation of contraceptive method

Review: Treatment of vaginal bleeding irregularities induced by progestin only contraceptives

Comparison: 19 Selective estrogen receptor modulator vs placebo (Norplant/Therapeutic)

Outcome: 04 Discontinuation of contraceptive method

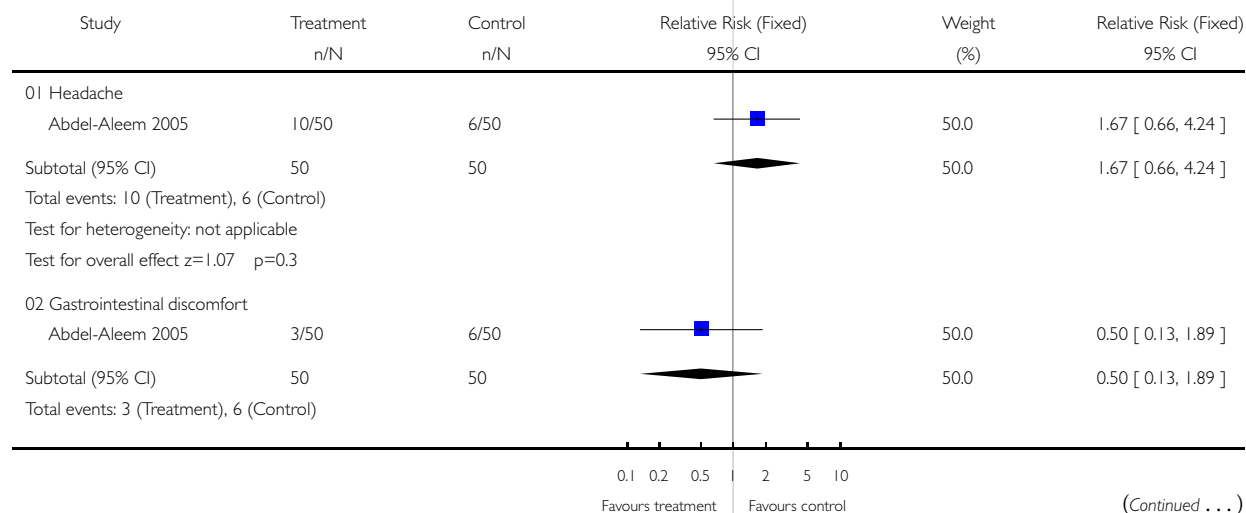


Analysis 19.07. Comparison 19 Selective estrogen receptor modulator vs placebo (Norplant/Therapeutic), Outcome 07 Side-effects related to treatment

Review: Treatment of vaginal bleeding irregularities induced by progestin only contraceptives

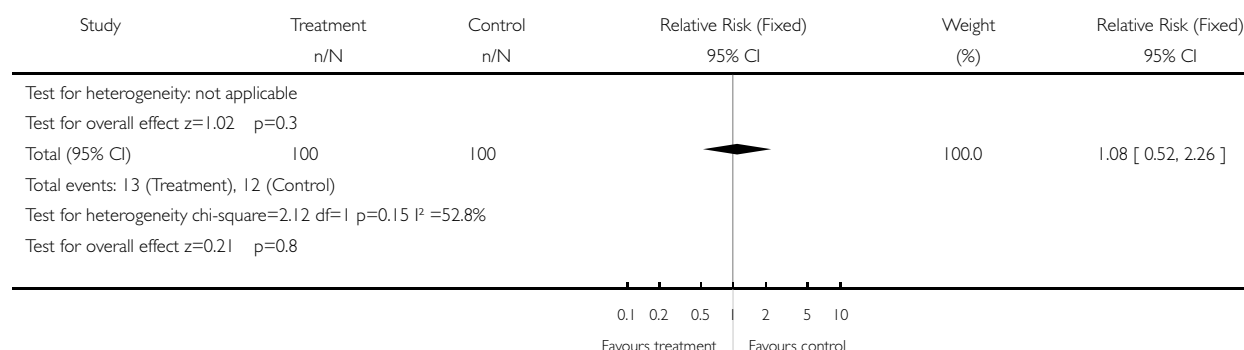
Comparison: 19 Selective estrogen receptor modulator vs placebo (Norplant/Therapeutic)

Outcome: 07 Side-effects related to treatment



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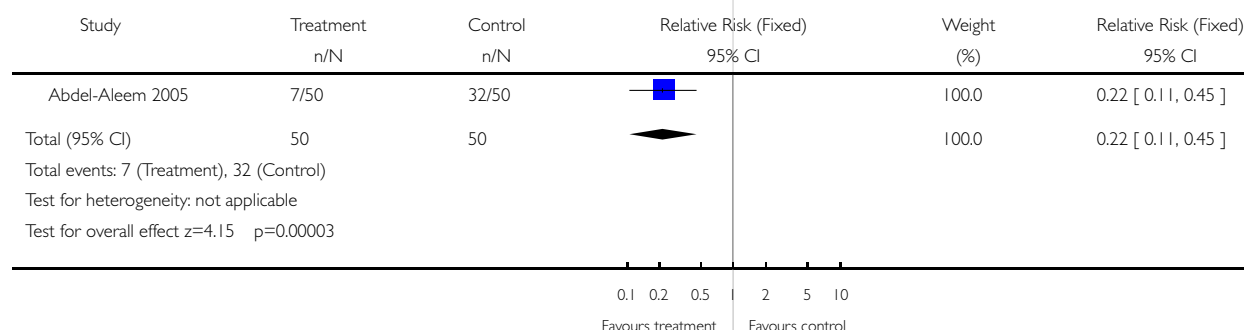


Analysis 19.08. Comparison 19 Selective estrogen receptor modulator vs placebo (Norplant/Therapeutic), Outcome 08 Patient dissatisfaction with treatment

Review: Treatment of vaginal bleeding irregularities induced by progestin only contraceptives

Comparison: 19 Selective estrogen receptor modulator vs placebo (Norplant/Therapeutic)

Outcome: 08 Patient dissatisfaction with treatment

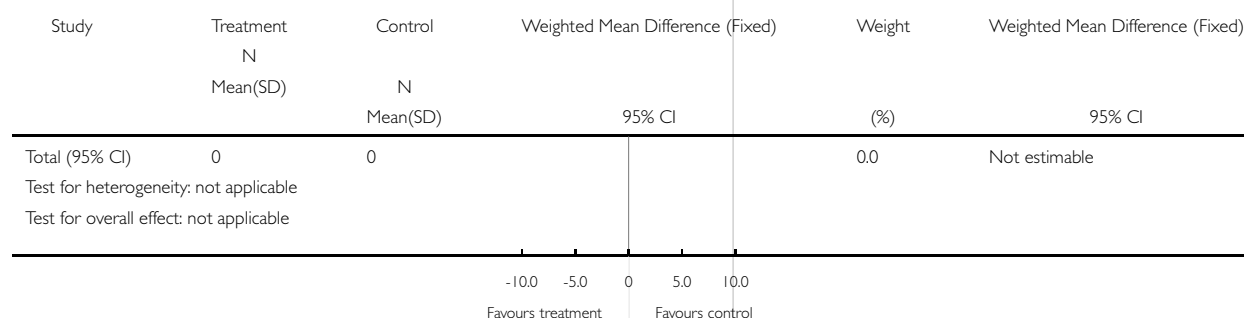


Analysis 19.09. Comparison 19 Selective estrogen receptor modulator vs placebo (Norplant/Therapeutic), Outcome 09 Blood loss during treatment

Review: Treatment of vaginal bleeding irregularities induced by progestin only contraceptives

Comparison: 19 Selective estrogen receptor modulator vs placebo (Norplant/Therapeutic)

Outcome: 09 Blood loss during treatment

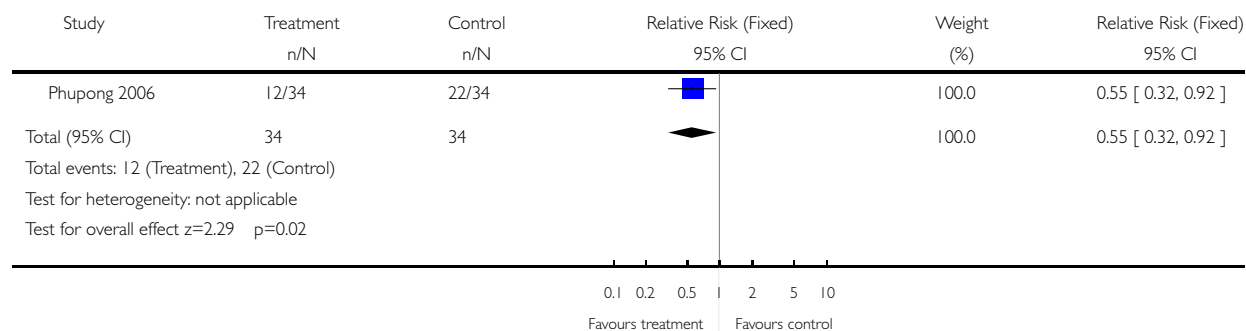


Analysis 20.01. Comparison 20 Antifibrinolytic vs placebo (Norplant/Therapeutic), Outcome 01 Continued irregular bleeding during treatment

Review: Treatment of vaginal bleeding irregularities induced by progestin only contraceptives

Comparison: 20 Antifibrinolytic vs placebo (Norplant/Therapeutic)

Outcome: 01 Continued irregular bleeding during treatment

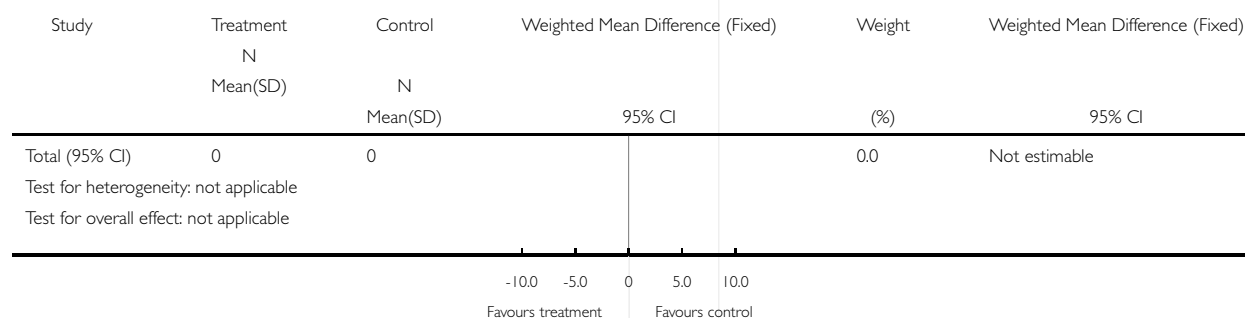


Analysis 20.02. Comparison 20 Antifibrinolytic vs placebo (Norplant/Therapeutic), Outcome 02 Bleeding during treatment (days)

Review: Treatment of vaginal bleeding irregularities induced by progestin only contraceptives

Comparison: 20 Antifibrinolytic vs placebo (Norplant/Therapeutic)

Outcome: 02 Bleeding during treatment (days)

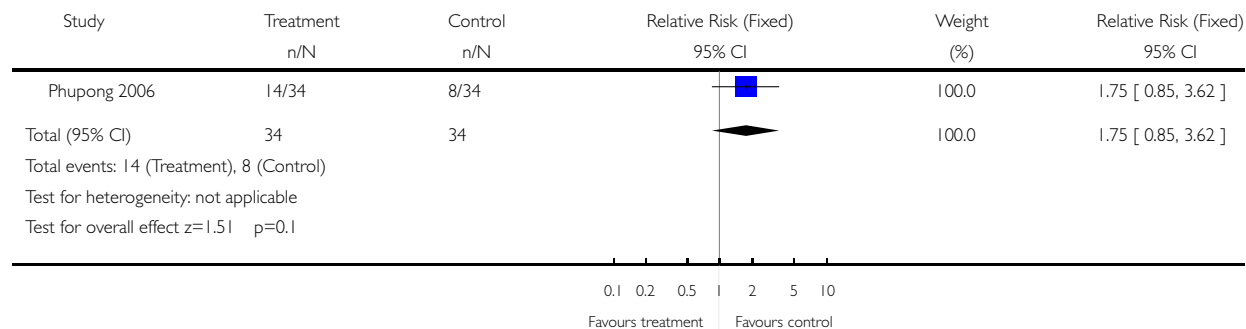


Analysis 20.03. Comparison 20 Antifibrinolytic vs placebo (Norplant/Therapeutic), Outcome 03 Unacceptable bleeding after treatment

Review: Treatment of vaginal bleeding irregularities induced by progestin only contraceptives

Comparison: 20 Antifibrinolytic vs placebo (Norplant/Therapeutic)

Outcome: 03 Unacceptable bleeding after treatment

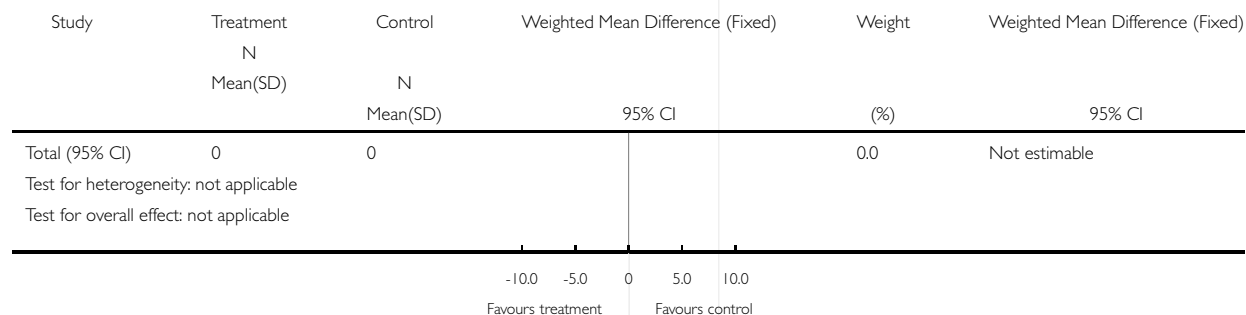


Analysis 20.09. Comparison 20 Antifibrinolytic vs placebo (Norplant/Therapeutic), Outcome 09 Blood loss during treatment

Review: Treatment of vaginal bleeding irregularities induced by progestin only contraceptives

Comparison: 20 Antifibrinolytic vs placebo (Norplant/Therapeutic)

Outcome: 09 Blood loss during treatment

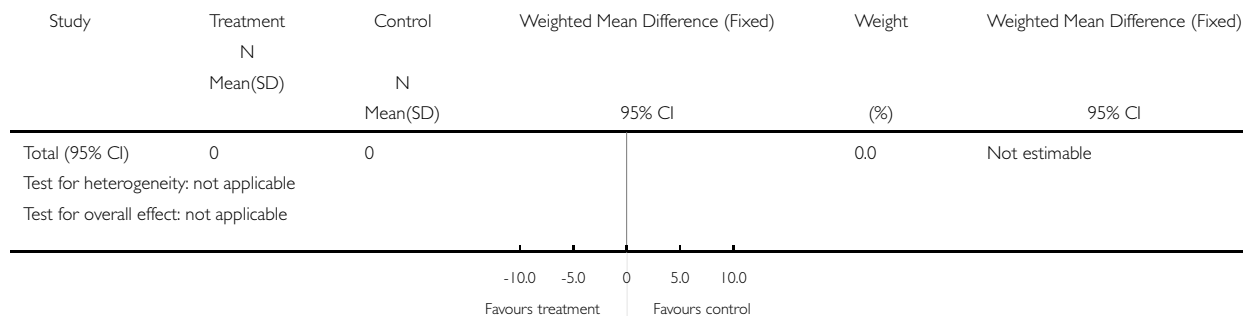


Analysis 21.02. Comparison 21 Matrix metalloproteinase inhibitor vs placebo (Implanon/Therapeutic), Outcome 02 Bleeding during treatment (days)

Review: Treatment of vaginal bleeding irregularities induced by progestin only contraceptives

Comparison: 21 Matrix metalloproteinase inhibitor vs placebo (Implanon/Therapeutic).

Outcome: 02 Bleeding during treatment (days)

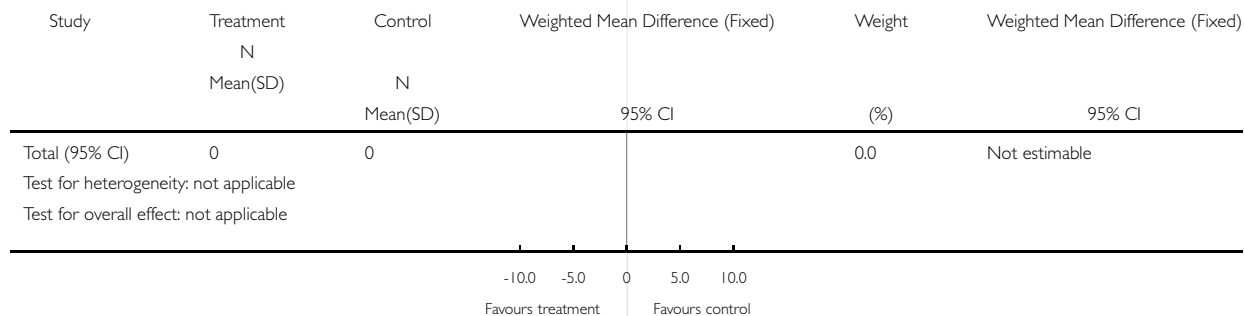


Analysis 21.03. Comparison 21 Matrix metalloproteinase inhibitor vs placebo (Implanon/Therapeutic), Outcome 03 Bleeding after treatment (days)

Review: Treatment of vaginal bleeding irregularities induced by progestin only contraceptives

Comparison: 21 Matrix metalloproteinase inhibitor vs placebo (Implanon/Therapeutic).

Outcome: 03 Bleeding after treatment (days)

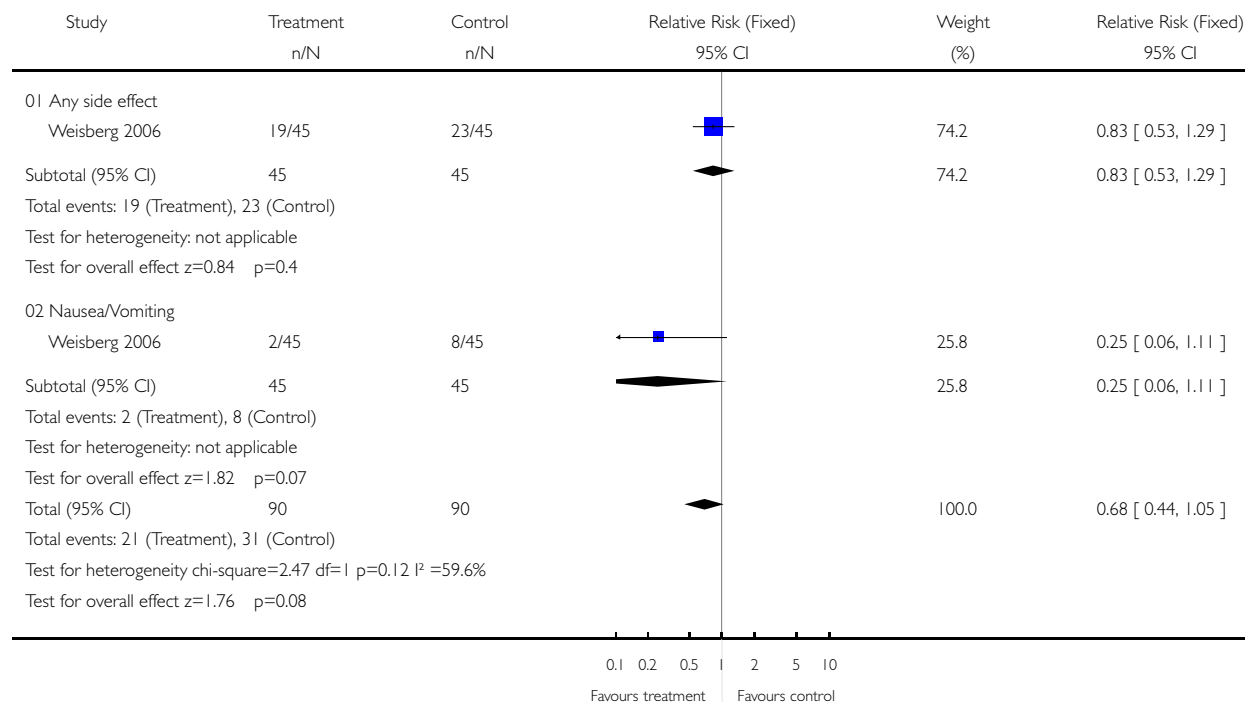


Analysis 21.07. Comparison 21 Matrix metalloproteinase inhibitor vs placebo (Implanon/Therapeutic), Outcome 07 Side effects related to treatment

Review: Treatment of vaginal bleeding irregularities induced by progestin only contraceptives

Comparison: 21 Matrix metalloproteinase inhibitor vs placebo (Implanon/Therapeutic).

Outcome: 07 Side effects related to treatment



Analysis 21.09. Comparison 21 Matrix metalloproteinase inhibitor vs placebo (Implanon/Therapeutic), Outcome 09 Blood loss during treatment

Review: Treatment of vaginal bleeding irregularities induced by progestin only contraceptives

Comparison: 21 Matrix metalloproteinase inhibitor vs placebo (Implanon/Therapeutic).

Outcome: 09 Blood loss during treatment

