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Progesterone receptor modulators for endometriosis (Review)

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[Intervention Review]

Progesterone receptor modulators for endometriosis

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ABSTRACT

Background

Endometriosis is defined as the presence of endometrial tissue (glands and stroma) outside the uterine cavity. This condition is oestrogen-dependent and thus is seen primarily during the reproductive years. Owing to their antiproliferative effects in the endometrium, progesterone receptor modulators (PRMs) have been advocated for treatment of endometriosis.

Objectives

To assess the effectiveness and safety of PRMs primarily in terms of pain relief as compared with other treatments or placebo or no treatment in women of reproductive age with endometriosis.

Search methods

We searched the following electronic databases, trial registers, and websites: the Cochrane Gynaecology and Fertility Group (CGFG) Specialised Register of Controlled Trials, the Central Register of Studies Online (CRSO), MEDLINE, Embase, PsycINFO, clinicaltrials.gov, and the World Health Organization (WHO) platform, from inception to 28 November 2016. We handsearched reference lists of articles retrieved by the search.

Selection criteria

We included randomised controlled trials (RCTs) published in all languages that examined effects of PRMs for treatment of symptomatic endometriosis.

Data collection and analysis

We used standard methodological procedures as expected by the Cochrane Collaboration. Primary outcomes included measures of pain and side effects.

Main results

We included 10 randomised controlled trials (RCTs) with 960 women. Two RCTs compared mifepristone versus placebo or versus a different dose of mifepristone, one RCT compared asoprisnil versus placebo, one compared ulipristal versus leuprolide acetate, and four compared gestrinone versus danazol, gonadotropin-releasing hormone (GnRH) analogues, or a different dose of gestrinone. The quality of evidence ranged from high to very low. The main limitations were serious risk of bias (associated with poor reporting of methods and high or unclear rates of attrition in most studies), very serious imprecision (associated with low event rates and wide confidence intervals), and indirectness (outcome assessed in a select subgroup of participants).

Mifepristone versus placebo

One study made this comparison and reported rates of painful symptoms among women who reported symptoms at baseline.

At three months, the mifepristone group had lower rates of dysmenorrhoea (odds ratio (OR) 0.08, 95% confidence interval (CI) 0.04 to 0.17; one RCT, n =352; moderate-quality evidence), suggesting that if 40% of women taking placebo experience dysmenorrhoea, then between 3% and 10% of women taking mifepristone will do so. The mifepristone group also had lower rates of dyspareunia (OR 0.23, 95% CI 0.11 to 0.51; one RCT, n = 223; low-quality evidence). However, the mifepristone group had higher rates of side effects: Nearly 90% had amenorrhoea and 24% had hot flushes, although the placebo group reported only one event of each (1%) (high-quality evidence). Evidence was insufficient to show differences in rates of nausea, vomiting, or fatigue, if present.

Mifepristone dose comparisons

Two studies compared doses of mifepristone and found insufficient evidence to show differences between different doses in terms of effectiveness or safety, if present. However, subgroup analysis of comparisons between mifepristone and placebo suggest that the 2.5 mg dose may be less effective than 5 mg or 10 mg for treating dysmenorrhoea or dyspareunia.

Gestrinone comparisons

Ons study compared gestrinone with danazol, and another study compared gestrinone with leuprolin.

Evidence was insufficient to show differences, if present, between gestrinone and danazol in rate of pain relief (those reporting no or mild pelvic pain) (OR 0.71, 95% CI 0.33 to 1.56; two RCTs, n = 230; very low-quality evidence), dysmenorrhoea (OR 0.72, 95% CI 0.39 to 1.33; two RCTs, n = 214; very low-quality evidence), or dyspareunia (OR 0.83, 95% CI 0.37 to 1.86; two RCTs, n = 222; very low-quality evidence). The gestrinone group had a higher rate of hirsutism (OR 2.63, 95% CI 1.60 to 4.32; two RCTs, n = 302; very low-quality evidence) and a lower rate of decreased breast size (OR 0.62, 95% CI 0.38 to 0.98; two RCTs, n = 302; low-quality evidence). Evidence was insufficient to show differences between groups, if present, in rate of hot flushes (OR 0.79, 95% CI 0.50 to 1.26; two RCTs, n = 302; very low-quality evidence) or acne (OR 1.45, 95% CI 0.90 to 2.33; two RCTs, n = 302; low-quality evidence).

When researchers compared gestrinone versus leuprolin through measurements on the 1 to 3 verbal rating scale (lower score denotes benefit), the mean dysmenorrhoea score was higher in the gestrinone group (MD 0.35 points, 95% CI 0.12 to 0.58; one RCT, n = 55; low-quality evidence), but the mean dyspareunia score was lower in this group (MD 0.33 points, 95% CI 0.62 to 0.04; low-quality evidence). The gestrinone group had lower rates of amenorrhoea (OR 0.04, 95% CI 0.01 to 0.38; one RCT, n = 49; low-quality evidence) and hot flushes (OR 0.20, 95% CI 0.06 to 0.63; one study, n = 55; low quality evidence) but higher rates of spotting or bleeding (OR 22.92, 95% CI 2.64 to 198.66; one RCT, n = 49; low-quality evidence).

Evidence was insufficient to show differences in effectiveness or safety between different doses of gestrinone, if present.

Asoprisnil versus placebo

One study (n = 130) made this comparison but did not report data suitable for analysis.

Ulipristal versus leuprolide acetate

One study (n = 38) made this comparison but did not report data suitable for analysis.

Authors' conclusions

Among women with endometriosis, moderate-quality evidence shows that mifepristone relieves dysmenorrhoea, and low-quality evidence suggests that this agent relieves dyspareunia, although amenorrhoea and hot flushes are common side effects. Data on dosage were inconclusive, although they suggest that the 2.5 mg dose of mifepristone may be less effective than higher doses. We found insufficient evidence to permit firm conclusions about the safety and effectiveness of other progesterone receptor modulators.

PLAIN LANGUAGE SUMMARY

Progesterone receptor modulators for endometriosis

Review question

Researchers in the Cochrane Collaboration reviewed evidence on the effectiveness and safety of progesterone receptor modulators for women with endometriosis.

Background

Endometriosis is a disease of endometrial tissue (glands and stroma) outside the uterine cavity. It is oestrogen-dependent and thus is seen primarily during the reproductive years. It can cause pain in the abdomen, generally during periods (menstruation) or associated with sexual intercourse. Progesterone receptor modulators have been advocated as one of the hormonal treatments for endometriosis.

Study characteristics

We found 10 randomised controlled trials including 960 women; the evidence is current to November 2016.

Key results

Three studies assessed mifepristone. Moderate-quality evidence shows that mifepristone relieves dysmenorrhoea (painful periods) in women with endometriosis. Evidence suggests that if 40% of women taking placebo experience dysmenorrhoea, then between 3% and 10% of women taking mifepristone will do so. Low-quality evidence suggests that mifepristone also relieves dyspareunia (pain during sexual intercourse). However, amenorrhoea (absence of menstrual periods) and hot flushes were common side effects of mifepristone. Nearly 90% of the mifepristone group had amenorrhoea, and 24% had hot flushes, although researchers reported only one event of each (1%) among women taking placebo. Evidence was insufficient to show differences in rates of nausea, vomiting, or fatigue, if present.

Comparisons of different doses of mifepristone were inconclusive, although evidence suggests that the 2.5 mg dose may be less effective than higher doses.

Other studies assessed other progesterone receptor modulators. Researchers compared gestrinone versus other treatments (danazol or leuprolin), ulipristal versus leuprolide acetate, and asoprisnil verus placebo. However, evidence was insufficient to allow firm conclusions regarding the safety and effectiveness of these interventions.

Quality of the evidence

The quality of the evidence ranged from moderate to low. The main limitations were serious risk of bias (associated with poor reporting of methods and high or unclear rates of attrition in most studies), very serious imprecision (associated with low event rates and wide confidence intervals), and indirectness (outcome assessed in a select subgroup of participants).

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Mifepristone versus placebo for endometriosis

Mifepristone versus placebo for endometriosis

Patient or population: women with symptomatic endometriosis

Settings: gynaecology clinic

Intervention: progesterone receptor modulator (mifepristone)

Comparison: placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo	Mifepristone				
Prevalence of dysmenorrhoea Follow-up: 3 months	402 per 1000	51 per 1000 (26 to 103)	OR 0.08 (0.04 to 0.17)	352 (1)	⊕⊕⊕⊖ Moderate[a,b]	
Prevalence of dyspareunia Follow-up: 3 months	288 per 1000	85 per 1000 (43 to 171)	OR 0.23 (0.10 to 0.51)	223 (1)	⊕⊕⊖⊖ Low[a,c]	
Side effects: amenorrhoea Follow-up: 3 months	11 per 1000	884 per 1000 (507 to 983)	OR 686.16 (92.29 to 5101.33)	360 (1)	⊕⊕⊕⊖ High	239/270 events in the mifepristone group vs 1/90 in the placebo group
Side effects: hot flushes Follow-up: 3 months	11 per 1000	243 per 1000 (42 to 701)	OR 28.79 (3.93 to 210.73)	360 (1)	⊕⊕⊕⊖ High	66/270 events in the mifepristone group vs 1/90 in the placebo group

*The basis for the **assumed risk** is the mean control group risk across studies. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI)
CI: confidence interval; OR: odds ratio

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate
Very low quality: We are very uncertain about the estimate

[a]Downgraded one level for serious imprecision (wide confidence intervals and/or very few events)
[b]Outcome applied only to women with dysmenorrhoea at baseline, but this was 352/360 women randomised, so not downgraded for indirectness
[c]Outcome applied only to women with dyspareunia at baseline, which was 223/360 women randomised. Downgraded one level for serious indirectness

Summary of findings 2. Gestrinone versus danazol for endometriosis

Gestrinone versus danazol for endometriosis

Patient or population: women with symptomatic endometriosis

Settings: gynaecology clinic

Intervention: progesterone receptor modulator (gestrinone)

Comparison: danazol

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Danazol	Gestrinone				
Pelvic pain: none or mild	890 per 1000	852 per 1000 (727 to 927)	OR 0.71 (0.33 to 1.56)	230 (2)	⊕⊕⊖⊖ Very low[a,b,c]	
Dysmenorrhoea: none or mild Follow-up: 6 months	721 per 1000	650 per 1000 (502 to 775)	OR 0.72 (0.39 to 1.33)	214 (2)	⊕⊖⊖⊖ Very low[a,b,c]	
Dyspareunia: none or mild Follow-up: 6 months	889 per 1000	869 per 1000 (748 to 937)	**OR** 0.83 (0.37 to 1.86)	222 (2)	⊕⊖⊖⊖ Very low[a,b,c]	
Side effects: hirsutism Follow-up: 6 months	248 per 1000	464 per 1000 (345 to 587)	**OR** 2.63 (1.60 to 4.32)	302 (2)	⊕⊖⊖⊖ Very low[b,c,d]	I^2 = 68%
Decreased breast size Follow-up: 6 months	477 per 1000	360 per 1000 (257 to 472)	**OR** 0.62 (0.38 to 0.98)	302 (2)	⊕⊕⊖⊖ Low[b,c]	

Side effects: hot flushes Follow-up: 6 months	425 per 1000	368 per 1000 (270 to 482)	OR 0.79 (0.50 to 1.26)	302 (2 studies)	⊕⊖⊖⊖ Very low[b,c,d]	I^2 = 72%
Side effects: acne Follow-up: 6 months	556 per 1000	644 per 1000 (529 to 744)	OR 1.45 (0.90 to 2.33)	302 (2 studies)	⊕⊕⊖⊖ Low[b,c]	

*The basis for the **assumed risk** is the mean control group risk across studies. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI)
CI: confidence interval; OR: odds ratio

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate
Very low quality: We are very uncertain about the estimate

[a]Assessed in all randomised participants. Not all were symptomatic at baseline (although results show no significant differences in baseline symptoms between groups). Outcome therefore applies only to a select subgroup of participants: downgraded one level for serious indirectness
[b]Downgraded one level for serious risk of bias associated with poor reporting of study methods, high attrition in one study, and high risk of other bias in both studies
[c]Imprecision of results (wide confidence intervals and/or few events), downgraded one level for serious imprecision
[d]Downgraded one level for serious inconsistency

Summary of findings 3. Gestrinone versus leuprolin for endometriosis

Gestrinone versus leuprolin for endometriosis

Patient or population: women with symptomatic endometriosis

Settings: gynaecology clinic

Intervention: progesterone receptor modulator (gestrinone)

Comparison: leuprolin

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Leuprolin	Gestrinone				
Dysmenorrhoea, verbal rating scale	In control group, mean score for dysmenor-	Mean score in gestrinone group was 0.35 points		55 (1)	⊕⊕⊖⊖ Low[a]	Verbal rating scale defines dysmenorrhoea according to limita-

Follow-up: 6 months	rhoea on verbal rating scale was 0.04 points	higher (0.12 to 0.58 higher)				tion of ability to work (mild = 1, moderate = 2, incapacitated = 3)
Dyspareunia, verbal rating scale Follow-up: 6 months	In control group, mean score for dyspareunia on verbal rating scale was 0.43 points	Mean score in gestrinone group was 0.33 points lower (0.62 to 0.04 lower)		52 (1)	⊕⊕⊖⊖ Low[a]	Verbal rating scale defines dyspareunia according to limitation of sexual activity (discomfort tolerated = 1; pain interrupts intercourse = 2, intercourse avoided owing to pain = 3)
Amenorrhoea Follow-up: 6 months	962 per 1000	500 per 1000 (26 to 908)	**OR** 0.04 (0.01 to 0.38)	49 (1)	⊕⊕⊖⊖ Low[b]	Only 55 events overall
Spotting or bleeding Follow-up: 6 months	38 per 1000	475 per 1000 (94 to 887)	**OR** 22.92 (2.64 to 198.66)	49 (1)	⊕⊕⊖⊖ Low[b]	Only 12 events overall
Side effects: hot flushes Follow-up: 6 months	679 per 1000	297 per 1000 (112 to 571)	**OR 0.20** (0.06 to 0.63)	55 (1)	⊕⊕⊖⊖ Low[b]	Only 27 events overall

*The basis for the **assumed risk** is the mean control group risk across studies. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; OR: odds ratio

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate
Very low quality: We are very uncertain about the estimate

[a]Downgraded two levels for very serious imprecision: confidence intervals were compatible with no clinically meaningful difference between groups, or with small benefit in one group
[b]Downgraded two levels for very serious imprecision: small overall sample size (n = 55) and low event rates

BACKGROUND

Description of the condition

Endometriosis is defined as the presence of endometrial tissue (glands and stroma) outside the uterine cavity. It is a condition that is oestrogen-dependent and thus is seen primarily during the reproductive period (Berek 2007; Giudice 2010). The prevalence of endometriosis ranges from 6% to 10% in women of reproductive age, from 50% to 60% in women and teenage girls with pelvic pain, and has been reported as up to 50% among women with infertility (Cramer 2002; Eskenazi 1997; Goldstein 1980); endometriosis can also be found in asymptomatic women during surgical procedures such as laparoscopy or sterilisation. Endometriosis constitutes a substantial burden on the health-related quality of life of women and on the finite healthcare resources of national health systems worldwide (Vercellini 2014).

Rokitansky reported this disease for the first time in 1860. Although considerable progress has been made, the pathogenesis remains unclear. The 'retrograde menstruation theory' proposed in the 1920s (Sampson 1927) speculated that endometriosis derives from reflux of endometrial fragments regurgitated through the fallopian tubes during menstruation, with subsequent implantation on the peritoneum and the ovary. Hormonal imbalance involved in development of endometriosis includes increased oestrogen synthesis and metabolism and progesterone resistance (Tosti 2016).

Minimally invasive surgical treatments play an important role in the diagnosis and removal of endometriosis. Unfortunately, this approach is limited by recurrences of endometriosis. Goals of management are to provide pain relief, to limit recurrences, and to restore or preserve fertility when needed. Current medical treatment (Brown 2014) has focused on blocking ovarian oestrogen secretion (with gonadotropin-releasing hormone analogues or antagonists (GnRH-a or GnRH antagonists)) or halting oestrogen-induced growth of ectopic endometrium (with oral contraceptives and androgens). The downside of these approaches includes a significant decrease in bone mass, along with hot flushes, vaginal dryness, acne, and hirsutism, which impair quality of life for many women. Furthermore, the mean length of time before recurrence of pain after completion of medical therapy is between 6 and 18 months (Mahutte 2003). The ideal medical therapy for endometriosis should relieve pain and inhibit endometrial proliferation while avoiding a hypo-oestrogenic state.

Description of the intervention

Progesterone, acting via its cognate receptors, plays a central role in regulation of uterine function, making progesterone receptor an attractive therapeutic target. Progesterone receptor modulators (PRMs) represent a class of synthetic ligands that can exert agonist, antagonist, or mixed effects on various progesterone target tissues. Mifepristone (MFP, RU486) is a progesterone and glucocorticoid receptor antagonist that was first synthesised in 1980. Since that time, numerous related compounds of progesterone receptor ligands have been synthesised, exhibiting a spectrum of activity ranging from pure progesterone receptor antagonists (PRAs) to mixed agonists/antagonists. PRAs and partial agonist antagonists - selective progesterone receptor modulators (SPRMs) - belong to the large progesterone receptor ligand family.

Owing to their antiproliferative effects in the endometrium, PRMs have been advocated for treatment of symptomatic endometriosis but may not provide appropriate treatment for asymptomatic endometriosis-associated infertility. Unlike long-acting GnRH-a, PRMs are not associated with a decrease in bone mineral density, and their use is accompanied by an increase in oestradiol and progesterone receptors (Neulen 1996), suggesting that the endometrial antiproliferative effect is due to progesterone antagonism. This offers a new alternative: suppression of endometrial proliferation in the midst of an oestrogenic environment. To date, compared with the widely used steroidal progesterone receptor agonists, only three PRMs have been approved by the FDA as emergency contraceptives: RU486, ulipristal acetate (UPA or CDB 2914), and asoprisnil (J867) (Li 2016). Few studies of PRMs for endometriosis have been published, and some show clinical benefit (Chwalisz 2004; Kettel 1996; Kettel 1998). In an uncontrolled study, mifepristone relieved pelvic pain without producing significant side effects (Koide 1998). However, it is reported that mifepristone caused downregulation of progesterone receptors (PRs) and oestrogen receptors (ERs) and upregulation of androgen receptors (ARs) (Narvekar 2004), and in low daily doses, it inhibited ovulation and induced amenorrhoea in most women (Brown 2002). Administration of PRMs also has been found to be accompanied by morphological changes within the endometrium, described as PRM-associated endometrial changes (PAECs) (Williams 2007). These histological changes are recognised as a distinct histological entity, and the mechanisms by which they develop are poorly understood. The clinical effectiveness of PRMs remains to be evaluated.

How the intervention might work

Progesterone receptor antagonists block the action of progesterone. Therefore, it is not surprising that they have clinical application in the medical termination of pregnancy (Brenner 2002; Brenner 2005). PRAs work as antiprogestins - substances that prevent cells from making or using progesterone. SPRMs represent a new class of progesterone receptor ligands that exert clinically relevant tissue-selective progesterone agonist, antagonist, or partial (mixed) agonist/antagonist effects on various progesterone target tissues in an in vivo situation, depending on the biological action studied (Spitz 2003). In human cell lines, mifepristone, asoprisnil, ulipristal acetate, lonaprisan, and telapristone acetate suppress endometrial proliferation, resulting in endometrial atrophy. Additional studies on animal models show that mifepristone, onapristone, and ZK136799 suppressed endometrial growth and reduced the production of prostaglandins with possible benefits for pain (Bouchard 2011). As PRMs have a relatively minor effect on serum oestradiol and androgen levels, application of PRMs may have greater efficacy and flexibility than traditional treatments for endometriosis as the result of selective inhibition of endometrial proliferation without systemic effects of oestrogen deprivation. PRMs also have the potential to suppress endometrial prostaglandin and decrease menstruation; this mechanism is proposed to reduce endometriosis-related pain (Tosti 2016).

Why it is important to do this review

Until now, no systematic review has examined this topic. Doctors considering the use of PRMs in clinical practice are uncertain about the balance between benefit in terms of pain relief and unacceptable side effects. In this review, we evaluated the clinical

effectiveness and safety of PRMs, primarily in terms of pain relief, and collated the best evidence for their use as single agents in women with endometriosis.

OBJECTIVES

To assess the effectiveness and safety of PRMs primarily in terms of pain relief as compared with other treatments or placebo or no treatment in women of reproductive age with endometriosis.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomised controlled trials (RCTs) published in all languages that examined effects of PRMs for treatment of symptomatic endometriosis. We excluded quasi-RCTs from this review. We also excluded cross-over trials, as the design is not valid in this context.

Types of participants

Women of reproductive age who have symptoms ascribed to the diagnosis of endometriosis. The diagnosis must have been established during a surgical procedure performed before the start of treatment. We did not consider trials that included women with asymptomatic disease or infertility alone.

Types of interventions

We included trials comparing PRMs versus any other drug therapy or placebo or no treatment. We also included studies that compared doses or regimens of PRMs.

We did not consider studies involving surgical removal of pelvic organs, nor studies exploring the use of hormonal treatment as an adjunct to therapeutic surgery or other medical treatment for endometriosis.

Types of outcome measures

Primary outcomes

- Pain measures: relief of endometriosis-related pain at completion of therapy (decrease in pain scores, dysmenorrhoea, and dyspareunia) or other pain-related outcomes, as reported by included studies
- Side effects that occur during therapy (Including fatigue, nausea, anorexia, vomiting, weight loss, skin rash, amenorrhoea, endometrial hyperplasia, or hypoadrenalism)

Secondary outcomes

- Quality of life (QOL). If studies report use of more than one scale, preference is given to the Short Form (SF)-36, then to other validated generic scales, and finally to condition-specific scales
- Change in size and extent of endometrial cysts
- Change in cancer antigen 125 (CA125)
- Recurrence rates (percentage of women with recurrence)
- Side effects that persist after treatment

Search methods for identification of studies

Electronic searches

We developed a comprehensive literature search strategy in consultation with the Information Specialist of the Cochrane Gynaecology and Fertility Group (CGFG). Two review authors (JF and HS) independently conducted a systematic search of the published and unpublished literature from inception of the databases to 28 November 2016 with no restrictions on language or publication status.

We searched the following databases.

- CGFG Specialised Register (Appendix 1).
- Central Register of Studies (CRS Online) (Appendix 2).
- Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily, and Ovid MEDLINE(R) (Appendix 3).
- Ovid Embase (Appendix 4).
- Ovid PsycINFO (Appendix 5).

Searching other resources

We scanned the references of all included studies and relevant reviews to identify additional relevant trials, and we handsearched relevant journals and articles that may not be included in the electronic databases. We also scanned the following databases from inception to 28 November 2016.

- Trial registers for ongoing and registered trials.
  - http://www.clinicaltrials.gov (a service of the US National Institutes of Health).
  - http://www.who.int/trialsearch/Default.aspx (World Health Organization International Trials Registry Platform search portal).
- DARE (Database of Abstracts of Reviews of Effects) in the Cochrane Library (http://onlinelibrary.wiley.com/o/cochrane/cochrane_cldare_articles_fs.html) for reference lists from relevant non-Cochrane reviews.
- Web of Knowledge (http://wokinfo.com/) (another source of trials and conference abstracts).
- OpenGrey (http://www.opengrey.eu/) for unpublished literature from Europe.
- LILACS (Latin American Caribbean Health Sciences Literature) (http://regional.bvsalud.org/php/index.php?lang=en).
- PubMed and Google for recent trials not yet indexed on MEDLINE.

Data collection and analysis

Selection of studies

We downloaded to a reference management database (Endnote) all titles and abstracts retrieved by electronic searching and removed duplicates; two review authors (JF and YW) independently examined the remaining references. We excluded studies that clearly do not meet the inclusion criteria and obtained copies of the full text of potentially relevant references. Two review authors (MZ and HZ) independently assessed the eligibility of retrieved papers. Review authors resolved differences by discussion or by appeal to a third review author (WH), if required. We documented reasons for exclusion and presented the selection process in a PRISMA flow chart.

Data extraction and management

Two review authors (JFand HZ) independently extracted data from eligible studies using a data extraction form that they designed and pilot-tested.

Data extracted include:

- participant characteristics;
- number of participants in each arm of the trial;
- number excluded from analysis;
- type of intervention;
- proportion of participants who received all/part/none of the intended treatment;
- methods of randomization, blinding, and allocation concealment applied;
- length of follow-up; and
- outcome measurements.

We resolved differences between review authors by discussion or by appeal to a third review author (WH), if necessary. Review authors were not blinded to article, author, or journal title, and tried to contact trial authors for further information and updated data.

Assessment of risk of bias in included studies

Two review authors (JF and HS) independently assessed the methodological risk of bias of each trial according to the guidelines provided in the *Cochrane Handbook for Systematic Reviews of Interventions,* Section 8.5 (Higgins 2011). According to the Cochrane 'Risk of bias' assessment tool, assessment for risk of bias in included studies consists of six domains - random sequence generation and allocation concealment (selection bias); blinding of participants and personnel (performance bias); blinding of outcome assessment (detection bias); incomplete outcome data (attrition bias); selective reporting (reporting bias); and other sources of bias (other bias) - and yields a judgement of low risk, high risk, or unclear risk. We resolved differences by discussion among review authors or by consultation with the CGFG.

Measures of treatment effect

For dichotomous data (e.g. recurrence rates), we used numbers of events in control and intervention groups of each study to calculate Mantel-Haenszel odds ratios. If similar outcomes were reported on different scales, we calculated standardized mean differences. We treated ordinal data (e.g. pain scores) as continuous data and presented 95% confidence intervals for all outcomes.

Unit of analysis issues

We conducted the primary analysis per woman randomised.

Dealing with missing data

We analyzed data on an intention-to-treat basis as far as possible and attempted to obtain missing data from the original investigators. If studies reported sufficient detail for calculation of mean differences but no information on associated standard deviation (SD), we planned to assume that outcomes had a standard deviation equal to the highest standard deviation used for other studies within the same analysis. Otherwise, we analyzed only available data. We found that no imputation was necessary.

Assessment of heterogeneity

We assessed heterogeneity between studies by visually inspecting forest plots and by estimating the I^2 value, which summarises the percentage of heterogeneity between trials that cannot be ascribed to sampling variation. We will consider an $I^2 < 25\%$ to show heterogeneity of low level, 25% to 50% moderate level, and > 50% high level. If we found evidence of substantial heterogeneity in later updates, we considered possible reasons for it. We did not combine results of trials using different comparator drugs.

Assessment of reporting biases

In view of the difficulty involved in detecting and correcting for publication bias and other reporting biases, we aimed to minimise their potential impact by ensuring a comprehensive search for eligible studies and by staying alert for duplication of data. If we included 10 or more studies in an analysis, we planned to use a funnel plot to explore the possibility of a small-study effect (tendency for estimates of the intervention effect to be more beneficial in smaller studies).

Data synthesis

We considered the following comparisons.

We combined data from primary studies using a fixed-effect model for the following.

- PRMs versus placebo, stratified by dose.
- PRMs versus no treatment, stratified by dose.
- PRMs versus other medical therapies, stratified by dose (danazol, GnRH analogue, combined oral contraceptive pill (OCP), levonorgestrel-releasing intrauterine system, each in a separate analysis, not stratified).
- Dose or regimen comparison of PRMs.

In the meta-analyses, we will display graphically to the right of the centre line an increase in the odds of a particular outcome that may be beneficial (e.g. pain relief) or detrimental (e.g. adverse effects), and we will display to the left of the centre line a decrease in the odds of a particular outcome.

For Comparison 1 (PRMs vs placebo), two analyses showed that the event rate was too low in control groups to allow review authors to split the group for the purpose of stratification. Therefore, we pooled all data in a single analysis and reported a separate analysis stratified by dose but not pooled (this applied to the outcomes 'amenorrhoea at 3 months' and 'hot flushes at 3 months').

Subgroup analysis and investigation of heterogeneity

We planned to explore the following potential sources of heterogeneity by conducting subgroup analyses: different mode of administration and different course.

Sensitivity analysis

We planned to conduct sensitivity analyses for the primary outcomes to determine whether conclusions were robust to arbitrary decisions made regarding trial eligibility and analysis of results. Through these analyses, we planned to consider whether conclusions would have differed if:

- eligibility were restricted to studies without high risk of bias;

- studies with outlying results had been excluded; or
- a random-effects model had been adopted.

Overall quality of the body of evidence: 'Summary of findings' table

We prepared a 'Summary of findings' table using GRADEpro and Cochrane methods. This table presents our evaluation of the overall quality of the body of evidence for the main review outcomes ('Relief in endometriosis-related pain', 'Side effects occurring during therapy') for the main review comparison ('Mifeprostone vs placebo'). We assessed the quality of the evidence using GRADE criteria: risk of bias, consistency of effect, imprecision, indirectness, and publication bias. Two review authors independently judged evidence quality (as high, moderate, low, or very low) and resolved disagreements by discussion. We justified judgements and documented and incorporated them into reporting of results for each outcome.

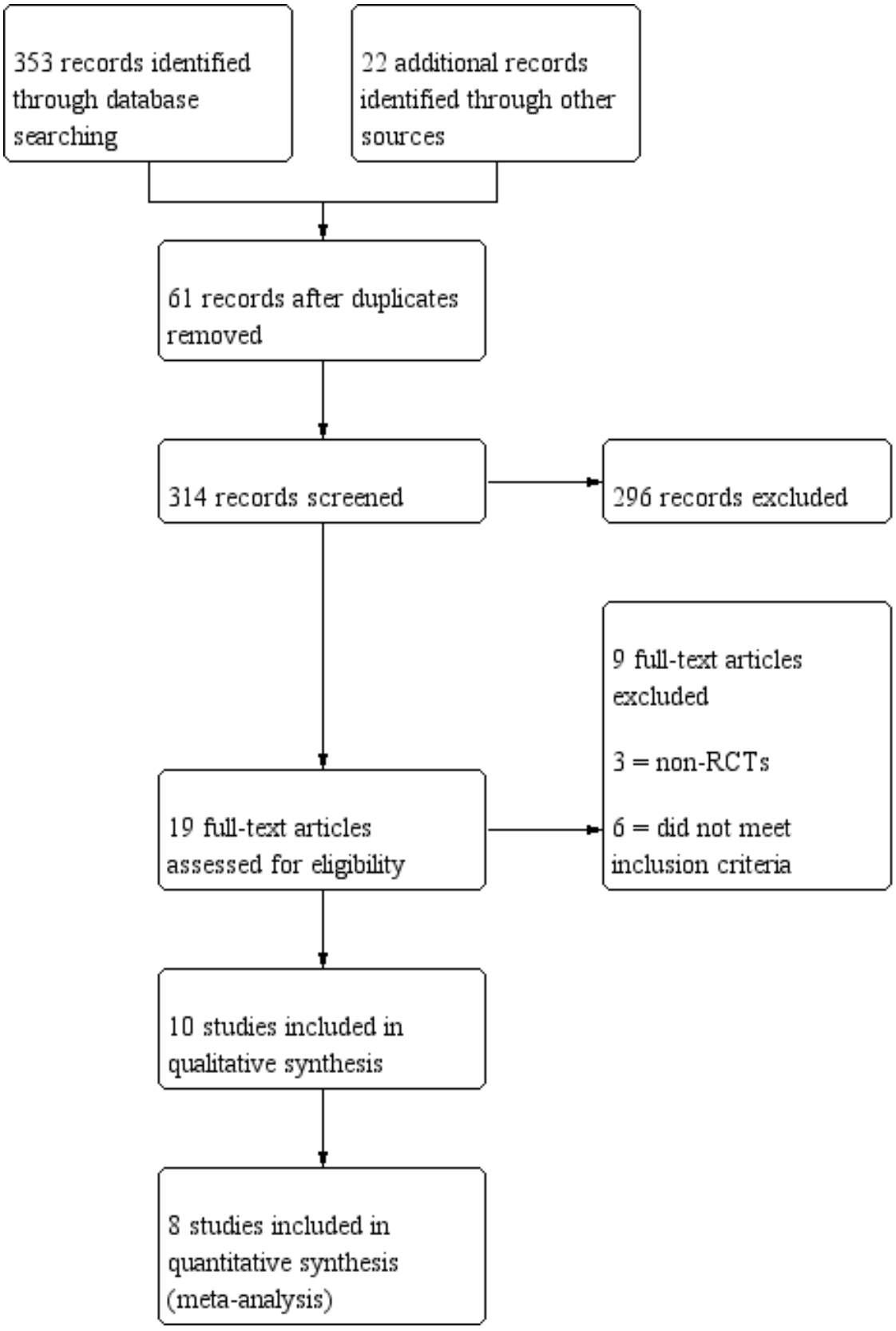
RESULTS

Description of studies

Results of the search

Through the search, we retrieved 353 articles. We retrieved in full text 19 that were potentially eligible. Ten articles met our inclusion criteria. We excluded nine studies. (See Characteristics of included studies, Characteristics of excluded studies, and the PRISMA flow chart – Figure 1.) We tried to contact trial authors to request information including missing data. We reported in Table 1 data that were unsuitable for analysis.

Figure 1. Study flow diagram.



Included studies

Study design and setting

We included in the review eight RCTs (Bromham 1995; Carbonell 2012; Carbonell 2016; Chwalisz 2004; Fedele 1989; GISG 1996; Hornstein 1990; Spitz 2009). We included two other RCTs (Dawood 1997; Worthington 1993) that did not report the primary and secondary outcomes of our review.

Participants

We included 960 women with endometriosis confirmed by laparoscopy.

Interventions

Carbonell 2016 and Carbonell 2012 compared different dosages of mifepristone for laparoscopically confirmed endometriosis, Chwalisz 2004 compared three doses of asoprisnil with placebo, and Spitz 2009 compared three doses of ulipristal with leuprolide acetate. Bromham 1995 and Fedele 1989 compared gestrinone with danazol, GISG 1996 compared gestrinone with leuprolin depot, and Hornstein 1990 compared different dosages of gestrinone.

Outcomes

Eight studies reported one or more of our primary outcomes. Investigators reported some specific outcomes only in women who were symptomatic at baseline.

Excluded studies

We excluded nine studies from the review. Bulun 2016, Kettel 1996, and Kettel 1998 are not RCTs; Mettler 1987, Nieto 1996, Yang 2006, and Zhang 2016 provided interventions that were a mixture of surgical and medical therapy; Nobel 1980 compared danazol with an OCP; and Thomas 1987 concentrated on asymptomatic endometriosis and its effects on fertility.

Risk of bias in included studies

Refer to the 'Risk of bias' tables and Figure 2 and Figure 3.

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

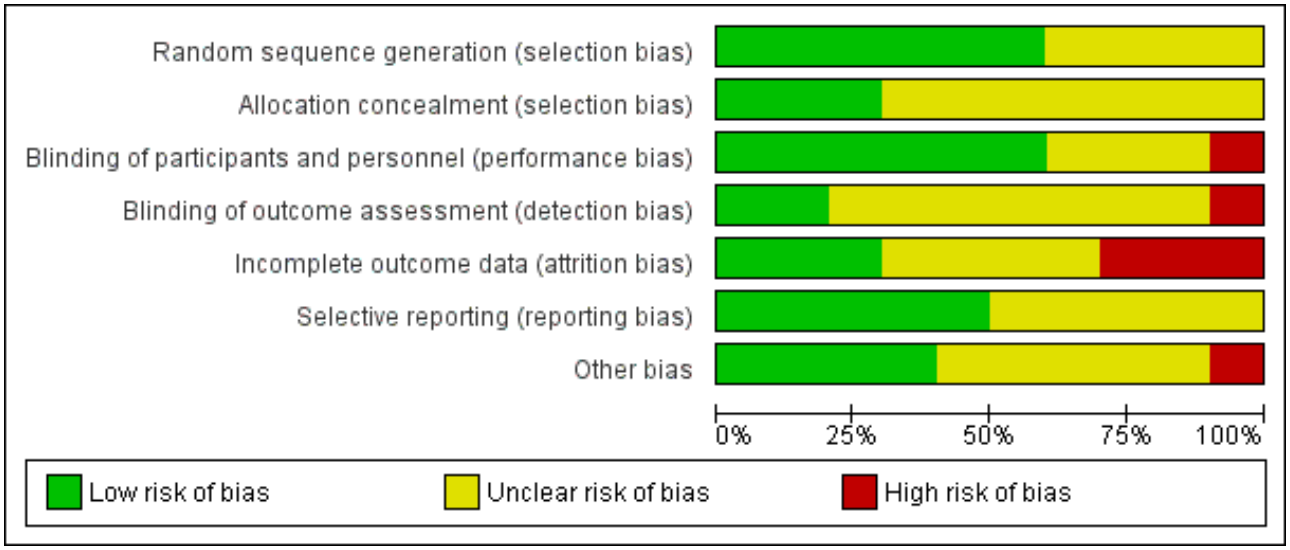
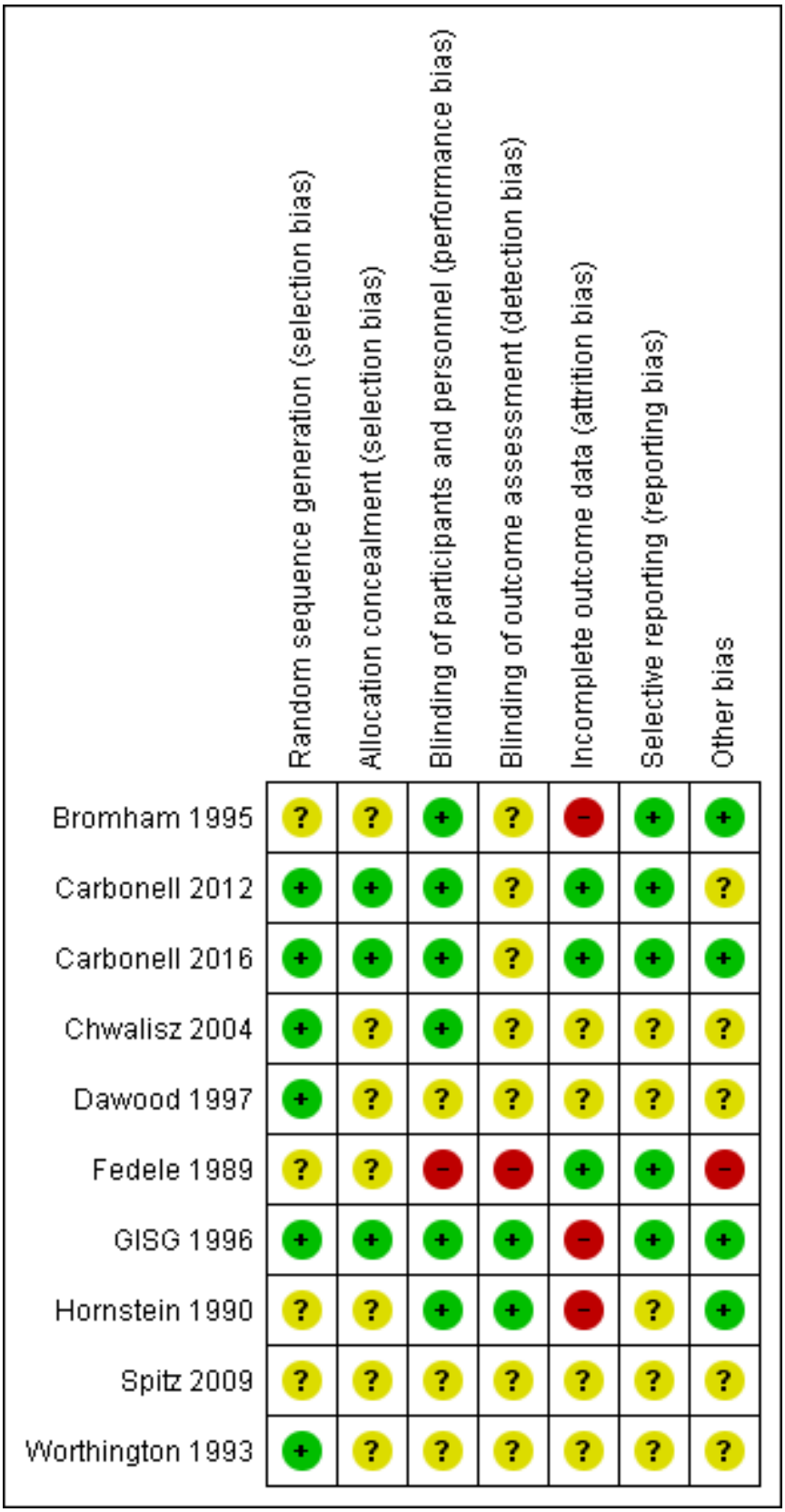


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Allocation

Sequence generation

Carbonell 2016 used a random list obtained from the MEDSTAT 2.1 programme (low risk of bias). Carbonell 2012 used a computer-generated randomization process (low risk of bias); Chwalisz 2004 and GISG 1996 included details of their randomization process and were at low risk of this bias. Bromham 1995, Fedele 1989, Hornstein 1990, and Spitz 2009 did not describe the method used and were at unclear risk of bias for this domain.

Allocation concealment

Carbonell 2016 applied opaque sealed envelopes that contained a card indicating the treatment group to which the participant was assigned (low risk of bias). Carbonell 2012 applied opaque sealed envelopes that contained a card indicating the treatment group to which the participant was assigned (low risk of bias). GISG 1996 also included allocation concealment in the study design and was at low risk of selection bias. The other seven studies did not describe the method used and were at unclear risk of bias for this domain.

Blinding

We rated six studies as having low risk of performance bias (Bromham 1995; Carbonell 2012; Carbonell 2016; Chwalisz 2004; GISG 1996; Hornstein 1990) and two as having low risk of detection bias (GISG 1996; Hornstein 1990). Fedele 1989 was unblinded, and we rated it as having high risk of performance bias and detection bias. Other studies did not clearly describe blinding procedures, and we rated them as having unclear risk of bias in one or both of these domains.

Incomplete outcome data

Carbonell 2016 and Carbonell 2012 analyzed all women randomised, and we judged them to be at low risk of attrition bias. Three studies reported large losses to follow-up (> 10%), and we rated them as having high risk of attrition bias (Bromham 1995; GISG 1996; Hornstein 1990). Other studies did not clearly state attrition rates, and we rated them as having unclear risk.

Selective reporting

Five studies reported our main review outcomes, and we rated them as having low risk of selective reporting (Bromham 1995; Carbonell 2012, Carbonell 2016; Fedele 1989; GISG 1996). We rated other studies as having unclear risk of selective reporting, as they reported insufficient data for review authors to make a judgement.

Other potential sources of bias

We rated four studies as having low risk of other bias (Bromham 1995; Carbonell 2016; GISG 1996; Hornstein 1990). We rated one study (Fedele 1989) as having high risk because researchers amended drug doses during the trial, and only seven participants given gestrinone and nine taking danazol had repeat laparoscopy. We rated the other studies as having unclear risk of bias in this domain because information was insufficient for review authors to make a judgement as to other potential sources of bias.

Effects of interventions

See: **Summary of findings for the main comparison** Mifepristone versus placebo for endometriosis; **Summary of findings 2** Gestrinone versus danazol for endometriosis; **Summary of findings 3** Gestrinone versus leuprolin for endometriosis

1. Mifepristone

Carbonell 2016 compared three doses of mifepristone (2.5 mg, 5 mg, 10 mg) versus placebo for three months and as a dose comparison (without placebo) for six months. Carbonell 2012 compared 5 mg versus 25 mg of mifepristone for six months.

1.1 Mifepristone versus placebo

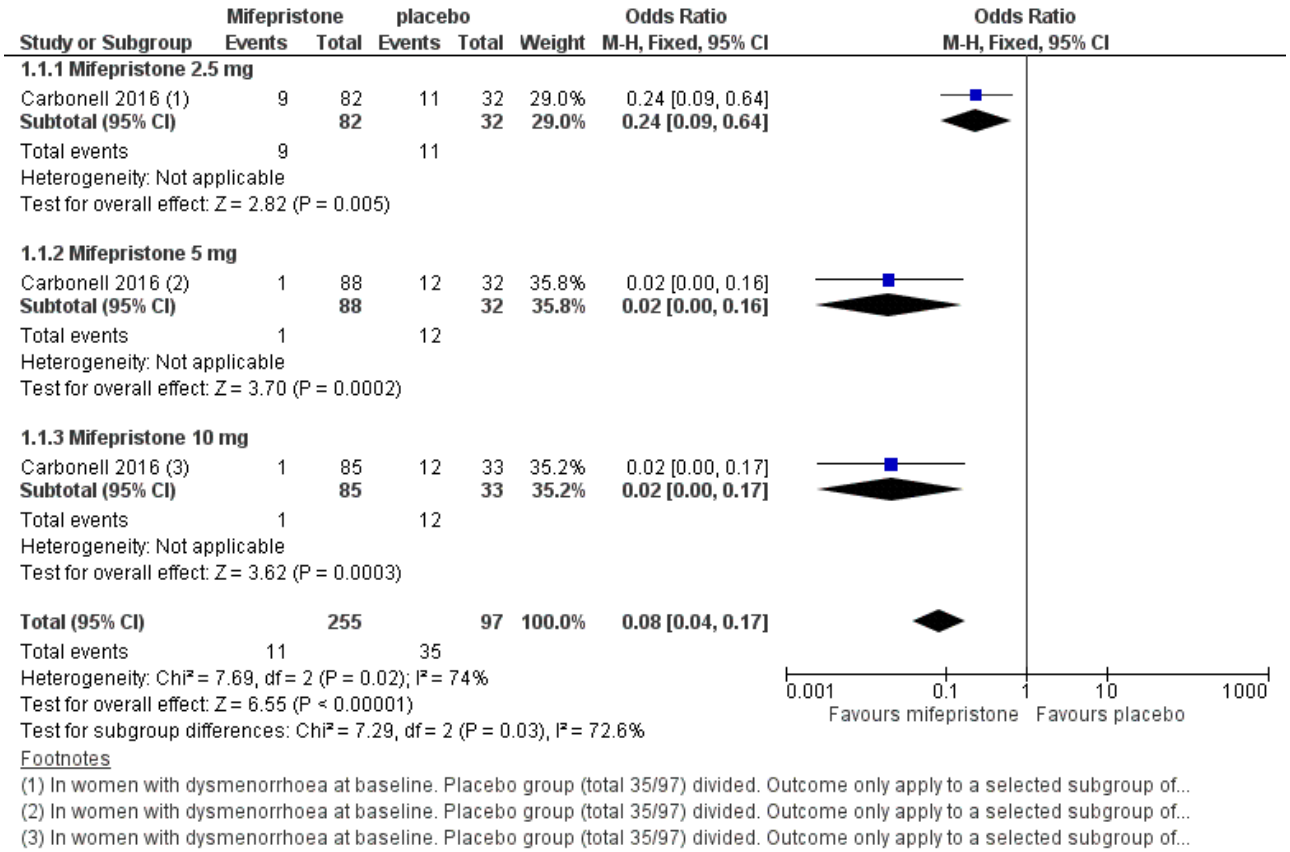
Primary outcomes

1.1.1 Pain measures

One study (Carbonell 2016) reported rates of patient-assessed dysmenorrhoea or dyspareunia (respectively) at three months among women who reported these symptoms at baseline.

Symptoms were less common in the mifepristone group for both dysmenorrhoea (OR 0.08, 95% CI 0.04 to 0.17; one RCT, n = 352; moderate-quality evidence; Figure 4) and dyspareunia (OR 0.23, 95% CI 0.10 to 0.51; one RCT, n = 223; low-quality evidence).

Figure 4. Forest plot of comparison: 1 Effectiveness of mifepristone versus placebo, patient-assessed outcomes, outcome: 1.1 Dysmenorrhoea at three months.



Subgroup analysis

We stratified the data by dose of mifepristone (2.5 mg, 5 mg, 10 mg).

With respect to dysmenorrhoea, all three doses were more effective than placebo, but the test for subgroup differences indicated a significant difference in effectiveness between doses (Chi^2 = 7.29, df = 2 (P = 0.03), I^2 = 72.6%). When we excluded the 2.5 mg dose from the analysis, the effect estimate showed increased benefit for mifepristone (OR 0.02, 95% CI 0.00 to 0.09), and the test for subgroup differences showed no evidence of a difference between groups (Chi^2 = 0.00, df = 1 (P = 0.96), I^2 = 0%). This suggests that 5 mg and 10 mg doses are more effective than the 2.5 mg dose, and that results show no clear difference in effectiveness between 5 mg and 10 mg doses.

With respect to dyspareunia, all three doses were more effective than placebo, but the test for subgroup differences indicated a significant difference in effectiveness between doses (Chi^2 = 3.68, df = 2 (P = 0.16), I^2 = 45.6%). When we exclude the 2.5 mg dose from the analysis, the effect estimate shows increased benefit for mifepristone (OR 0.09, 95% CI 0.03 to 0.30), and the test for subgroup differences shows no evidence of a difference between groups (Chi^2 = 0.63, df = 1 (P = 0.43), I^2 = 0%). This suggests that 5 mg and 10 mg doses are more effective than the 2.5 mg dose, and that results show no clear difference in effectiveness between 5 mg and 10 mg doses.

1.1.2 Side effects at three months

The mifepristone group had higher rates of amenorrhoea (OR 686.16, 95% CI 92.29 to 5101.33; one RCT, n = 360; high-quality evidence) and hot flushes (OR 28.79, 95% CI 3.93 to 210.73; one RCT, n = 360; high-quality evidence) at three months of treatment. These CIs are extremely wide because nearly 90% of the mifepristone group had amenorrhoea and 24% had hot flushes, and investigators reported only one event of each (1%) in the placebo group.

Evidence was insufficient to show differences between groups in rates of nausea (OR 1.72 , 95% CI 0.20 to 15.03; one RCT, n = 360), vomiting (OR 1.02, 95% CI 0.10 to 10.01), or fatigue/tiredness (OR 5.48, 95% CI 0.71 to 42.27; one RCT, n = 360; very low-quality evidence) at three months, if present. No studies reported endometrial hyperplasia or hypoadrenalism. See Figure 5 and Figure 6.

Figure 5. Forest plot of comparison. 2 Mifepristone versus placebo, patient-assessed outcomes, outcome: 2.1 Amenorrhoea at three months.

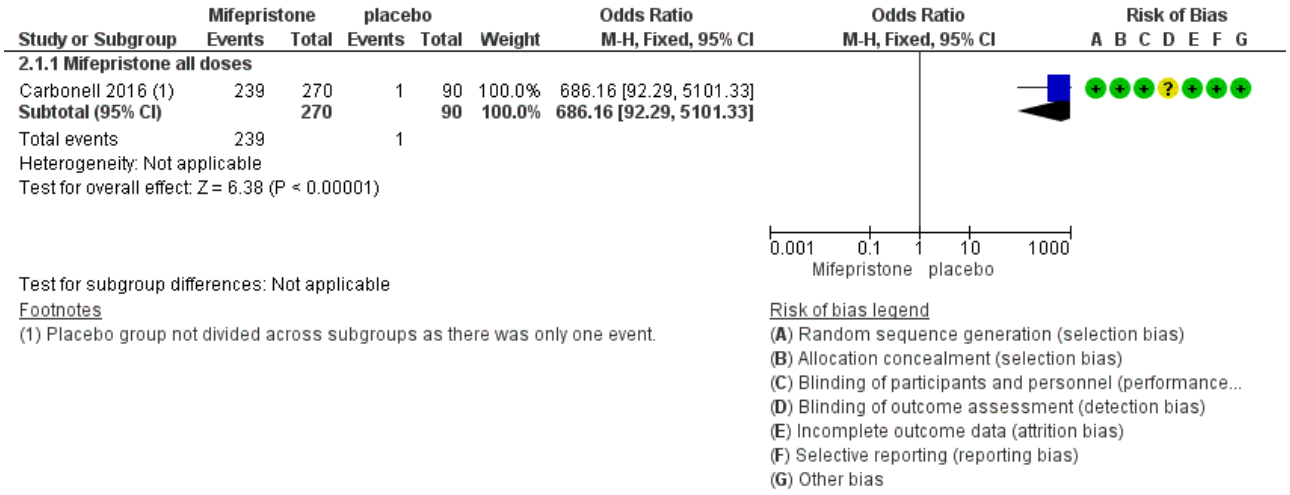
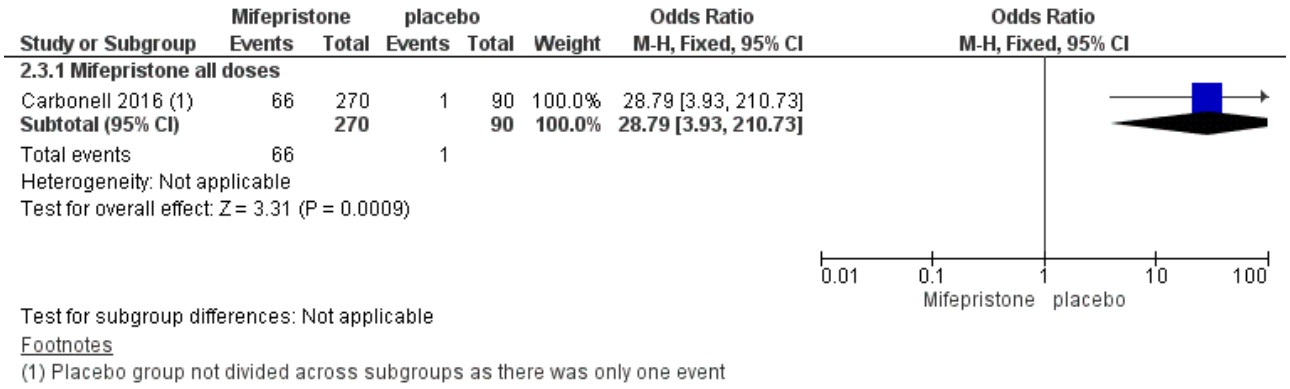


Figure 6. Forest plot of comparison: side effects at three months, mifepristone versus placebo, patient-assessed outcomes, outcome: 2.2 Hot flushes at three months.



Subgroup analysis

We subgrouped data by dose of mifepristone (2.5 mg, 5 mg, 10 mg).

All three doses were associated with higher rates of amenorrhoea than occurred with placebo, but the test for subgroup differences indicated a significant difference in effectiveness between doses (test for subgroup differences: $Chi^2 = 4.73$, df = 2 (P = 0.09), $I^2 = 57.7\%$). When we excluded the 2.5 mg dose from the analysis, the test for subgroup differences showed no evidence of a difference between groups (test for subgroup differences: $Chi^2 = 0.00$, df = 1 (P = 1.00), $I^2 = 0\%$). This suggests that 5 mg and 10 mg doses are more likely than the 2.5 mg dose to be associated with amenorrhoea.

For other reported side effects (nausea, vomiting, and fatigue or tiredness), results show no indication of a difference between subgroups (test for subgroup differences, $I^2 = 0\%$).

Secondary outcomes

No studies reported on our secondary outcomes.

1.2 Mifepristone dose comparison

Two studies compared different doses of mifepristone at six months of follow-up. One trial (Carbonell 2016) compared 2.5 mg versus 5 mg and 10 mg, and the other (Carbonell 2012) compared 5 mg versus 25 mg. Carbonell 2016 reported data on effectiveness as well as side effects. Carbonell 2012 provided a graph showing pain scores on a 0 to 10 visual analogue scale (VAS). As investigators reported the standard deviation for only one group, we assumed equal variances in the two groups. Carbonell 2012 also reported data on selected side effects.

Primary outcomes

1.2.1 Pain measures at six months

When we compared lower doses versus higher doses of mifepristone, the data were too imprecise to reveal differences between groups in rates of dysmenorrhoea, dyspareunia, or pelvic pain, as follows.

Dysmenorrhoea (Analysis 3.1; Analysis 3.2).

- 2.5 mg vs 5 mg: OR 0.85, 95% CI 0.22 to 3.29; one RCT, n = 170; very low-quality evidence.
- 5 mg vs 10 mg: OR 1.22, 95% CI 0.32 to 4.71; one RCT, n = 173; very low-quality evidence.
- 5 mg vs 25 mg: MD on VAS 0 to 10 scale -0.50 points, 96% CI -2.04 to 1.04; one RCT, n = 26; very low-quality evidence).

Dyspareunia (Analysis 3.3; Analysis 3.4).

- 2.5 mg vs 5 mg: OR 6.37, 95% CI 0.74 to 54.81; one RCT, n = 108; very low-quality evidence.
- 5 mg vs 10 mg: OR 0.52, 95% CI 0.05 to 5.90; one RCT, n = 109; very low-quality evidence.
- 5 mg vs 25 mg: MD on VAS 0 to 10 scale 0.00 points, 95% CI -1.23 to 1.23; n = 26; very low-quality evidence.

Pelvic pain (Analysis 3.5).

- 2.5 mg vs 5 mg: OR 1.81, 95% CI 0.63 to 5.17; one RCT, n = 110; very low-quality evidence.
- 5 mg vs 10 mg: OR 3.97, 95% CI 0.79 to 19.97; one RCT, n = 120; very low-quality evidence.

1.2.2 Side effects at six months

When we compared lower doses versus higher doses of mifepristone, amenorrhoea was less common among women taking 2.5 mg than in those taking 5 mg, and fatigue or tiredness was less common among women taking 5 mg than in those taking 10 mg. For other outcomes, the data were too imprecise to show whether differences between groups occurred. Effect estimates were as follows.

Amenorrhoea (Analysis 3.6).

- 2.5 mg vs 5 mg: OR 0.45, 95% CI 0.21 to 0.97; n = 180; very low-quality evidence.
- 5 mg vs 10 mg: OR 1.10, 95% CI 0.47 to 2.56; n = 180; very low-quality evidence.
- 5 mg vs 25 mg: OR 0.61, 95% CI 0.08 to 4.41; n = 52; very low-quality evidence.

Hot flushes (Analysis 3.7).

- 2.5 mg vs 5 mg: OR 0.84, 95% CI 0.38 to 1.89; n = 180; very low-quality evidence.
- 5 mg vs 10 mg: OR 0.75, 95% CI 0.35 to 1.58; n = 180; very low-quality evidence.
- 5 mg vs 25 mg: OR 3.24, 95% CI 0.12 to 87.13; n = 52; very low-quality evidence.

Nausea (Analysis 3.8).

- 2.5 mg vs 5 mg: OR 2.02, 95% CI 0.18 to 22.71; n = 180; very low-quality evidence.
- 5 mg vs 10 mg: OR 1.00, 95% CI 0.06 to 16.24; n = 180; very low-quality evidence.

Vomiting (Analysis 3.9).

- 2.5 mg vs 5 mg: OR 3.03, 95% CI 0.12 to 75.46; n = 180; very low-quality evidence.
- 5 mg vs 10 mg: OR 0.33, 95% CI 0.01 to 8.20; n = 180; very low-quality evidence.

Fatigue/tiredness (Analysis 3.10).

- 2.5 mg vs 5 mg: OR 13.92, 95% CI 0.77 to 250.94; n = 180; very low-quality evidence.
- 5 mg vs 10 mg: OR 0.03, 95% CI 0.00 to 0.54; n = 180; very low-quality evidence.

Endometrial thickness > 20 mm (Analysis 3.11).

- 2.5 mg vs 25 mg: OR 1.41, 95% CI 0.28 to 1.86; n = 52; very low-quality evidence.

Secondary outcomes

No studies reported on secondary outcomes.

2. Gestrinone

Gestrinone was another PRM assessed in the included trials. No RCTs compared gestrinone versus no treatment or placebo.

2.1 Gestrinone versus danazol

Primary outcomes

2.1.1 Pain measures

Two studies reported this outcome (Bromham 1995; Fedele 1989).

Data were insufficient to show differences between groups, if present, in the rate of pain relief (those reporting no or mild symptoms), with respect to pelvic pain (OR 0.71, 95% CI 0.33 to 1.56; two RCTs, n = 214; I^2 = 0%; very low-quality evidence), dysmenorrhoea (OR 0.72, 95% CI 0.39 to 1.33; two RCTs, n = 214; I^2 = N/A; very low-quality evidence), and dyspareunia (OR 0.83, 95% CI 0.37 to 1.86; two RCTs, n = 222; I^2 = 0%; very low-quality evidence).

2.1.2 Side effects

The gestrinone group had lower rates of decreased breast size (OR 0.62, 95% CI 0.38 to 0.98; two RCTs, n = 302; I^2 = 0%; low-quality evidence), muscle cramps (OR 0.49, 95% CI 0.30 to 0.78; two RCTs, n = 302; I^2 = 0%; low-quality evidence), and hunger (OR 0.59, 95% CI 0.36 to 0.97; one RCT, n = 264; very low-quality evidence), but higher rates of hirsutism (OR 2.73, 95% CI 1.67 to 4.46; two RCTs, n = 302; I^2 = 68%; very low-quality evidence) and seborrhoea (greasy skin) (OR 2.74, 95% CI 1.69 to 4.46; two RCTs, n = 302; I^2 = 65%; low-quality evidence, respectively).

Evidence was insufficient to show differences between groups, if present, in rates of acne, voice problems, swelling of hands or feet, hot flushes, headache, nausea, vomiting, loss of appetite, dizziness, tiredness, faintness, skin rash, weight gain, vaginal dryness, and raised liver transaminase.

Evidence shows substantial statistical heterogeneity for the outcomes of hirsutism, seborrhoea, and hot flushes (I^2= 68%, 65%, 72%). We considered that this was likely due to clinical heterogeneity related to variations in study location and patient population.

No studies reported endometrial hyperplasia or hypoadrenalism.

Secondary outcomes

No studies reported on our secondary outcomes.

2.2 Gestrinone versus leuprolin

Primary outcomes

2.2.1 Pain measures

One study compared gestrinone versus the GnRH analogue leuprolin (GISG 1996). This study reported symptom scores at six months.

When researchers compared gestrinone versus leuprolin, measurements on the 1 to 3 verbal rating scale (lower score denotes benefit) show that the mean dysmenorrhoea score was higher in the gestrinone group (MD 0.35 points, 95% CI 0.12 to 0.58; one RCT, n = 55; low-quality evidence), but the mean dyspareunia score was lower in the gestrinone group (MD 0.33 points, 95% CI 0.62 to 0.04; low-quality evidence).

Outcomes measured on a 0 to 10 VAS scale showed a lower mean dysmenorrhoea score in the leuprolin group (MD 0.82 points, 95% CI 0.15 to 1.49) and a higher mean dyspareunia score in the leuprolin group (MD 1.16 points, 95% CI 2.08 to 0.24). (See Figure 7 and Figure 8.)

Figure 7. Forest plot of comparison: 7 Gestrinone versus leuprolin for six months: efficacy and side effects, outcome: 7.1 Painful periods, visual analogue scale.

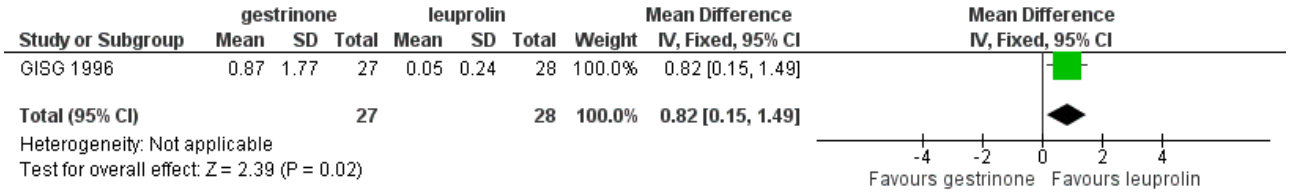
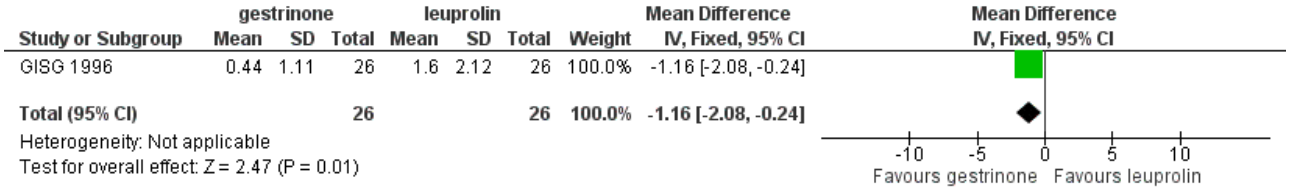


Figure 8. Forest plot of comparison: 7 Gestrinone versus leuprolin for six months: efficacy and side effects, outcome: 7.3 Pain on intercourse, visual analogue scale.



2.2.2 Side effects

The gestrinone group had lower rates of hot flushes (OR 0.20, 95% CI 0.06 to 0.63; one RCT, n = 55; very low-quality evidence), amenorrhoea (OR 0.04, 95% CI 0.01 to 0.38; one RCT, n = 49; very low-quality evidence), and headache (OR 0.20, 95% CI 0.06 to 0.63; one RCT, n = 55; very low-quality evidence), but higher rates of spotting or bleeding (OR 22.92, 95% CI 2.64 to 198.66; one RCT, n = 55; very low-quality evidence). Evidence was insufficient to show differences between groups, if present, in rates of seborrhoea, swelling hands/feet, leg or muscle cramps, nausea, dizziness, skin rash, vaginal dryness, mood changes, joint pain, drowsiness, and tachycardia. Investigators reported no data on endometrial hyperplasia or hypoadrenalism.

Secondary outcomes

No studies reported on secondary outcomes.

2.3 Gestrinone dose comparison

Primary outcomes

2.2.1 Pain measures

Hornstein 1990 compared two doses of gestrinone (1.25 mg vs 2.5 mg). Evidence was insufficient to show differences between groups, if present, in rates of pain relief (OR 0.27, 95% CI 0.01 to 8.46; one RCT, n = 10; very low-quality evidence). .

2.2.2 Side effects

Evidence was insufficient to show differences between groups, if present, in rates of any adverse effect (OR 0.04, 95% CI 0.00 to 1.12; one RCT, n = 12; very low-quality evidence), discontinuation due to headaches (OR 0.28, 95% CI 0.01 to 8.42; one RCT, n = 12), or irregular bleeding (OR 2.5, 95% CI 0.16 to 38.60; one RCT, n = 12). Reported adverse effects included weight gain, headache, palpitations, peripheral oedema, and hirsutism. No studies reported on endometrial hyperplasia or hypoadrenalism.

Secondary outcomes

No studies reported on our secondary outcomes.

3. SPRMs

Two studies compared SPRMs versus placebo (Chwalisz 2004) or leuprolide acetate (Spitz 2009). These studies were presented as abstracts and did not report data suitable for analysis.

3.1 Asoprisnil versus placebo

Chwalisz 2004 (n = 130) compared three different doses of asoprisnil versus placebo.

Primary outcome

3.1.1 Pain measures

Study authors reported that asoprisnil reduced average daily combined non-menstrual pelvic pain/dysmenorrhoea scores during all treatment months compared with placebo, and that this treatment induced amenorrhoea during the entire treatment period in a dose-dependent manner (placebo: 0%; 5 mg: 50%; 10 mg: 71%; and 25 mg: 93%).

3.1.2 Side effects

The included study did not report these effects.

Secondary outcomes

The included study did not report these outcomes.

3.2 Uliprisnil versus leuprolide acetate

Spitz 2009 compared six months of treatment with three doses of ulipristal (12.5 mg, 25 mg, and 50 mg) versus leuprolide acetate depot in 38 women.

Primary outcome

3.2.1 Pain measures

Study authors reported that the 50 mg dose of ulipristal was associated with fewer days of pain, less severe pain, and accompanying distress when compared with lower doses, and that it was as effective as leuprolide acetate.

3.1.2 Side effects

The included study did not report these effects.

Secondary outcomes

The included study did not report these outcomes.

Other analyses

Data were too few for review authors to conduct planned subgroup and sensitivity analyses, or to construct a funnel plot to assess reporting bias.

DISCUSSION

Summary of main results

Mifepristone represents relief of dysmenorrhoea and dyspareunia with side effects of amenorrhoea and hot flushes. We found no evidence of benefit of gestrinone compared with other treatments. Data on asoprisnil and ulipristal are limited. Results were based on very limited evidence and thus should be interpreted with caution.

Overall completeness and applicability of evidence

The included studies partially answered the review question. Studies investigated relevant participants and interventions, but future studies must be more unified and specific about study outcomes. Methods of outcome evaluation differed among studies. Progesterone receptor modulators (PRMs) showed effects of relieving pain, but more evidence is needed. Evidence is limited by the small number of comparisons reported and by the small sample size included for each comparison.

Quality of the evidence

Five of eight trials adequately described randomization and allocation concealment, and seven trials reported blinding. Five studies reported on a priori outcomes; two were at unclear risk and one at high risk of reporting bias. The quality of the body of evidence ranged from very low to high.

The main limitations were serious risk of bias (associated with poor reporting of methods and high or unclear rates of attrition in most studies), very serious imprecision with low event rates, small sample sizes, and very wide confidence intervals for most comparisons, as well as indirectness (outcomes assessed in a selected subgroup of participants). Only two studies were at low risk of attrition bias, which is a matter of concern because attrition may well have been related to participant response. The main limitation remains the issue of multiple comparisons with a small number of trials. Results show lack of consistency in outcome measures used, which leads to difficulties in combining data in a suitable meta-analysis, thus making it difficult for review authors to draw clinically relevant conclusions.

Potential biases in the review process

We aimed to identify all relevant studies by performing comprehensive database searches. Rare side effects of voice problems found in randomised controlled trials (RCTs) examining gestrinone versus danazol may introduce bias. Our choice of multiple measures for primary outcomes (e.g. dysmenorrhoea, dyspareunia, amenorrhoea, hot flushes) could be another potential source of bias, especially as selective reporting is apparent in at least one of the included studies.

Agreements and disagreements with other studies or reviews

The conclusions of other non-Cochrane reviews (Bouchard 2011; Giudice 2010; Tosti 2016) and of studies that were excluded from this review were substantially the same as the conclusions of this review, and more studies are needed to evaluate the effectiveness and safety of PRMs.

AUTHORS' CONCLUSIONS

Implications for practice

Among women with endometriosis, moderate-quality evidence shows that mifepristone relieves dysmenorrhoea, and low-quality evidence suggests that this agent also relieves dyspareunia; however, amenorrhoea and hot flushes are common side effects. Data on dosage, although inconclusive, suggest that the 2.5 mg dose may be less effective than higher doses. We found insufficient evidence to permit firm conclusions about the safety and effectiveness of other progesterone receptor modulators.

Implications for research

Effects of PRM-associated endometrial change on endometriotic lesions are unclear, and long-term effects remain to be determined. This systematic review has identified the need for well-designed, larger RCTs with minimal attrition, to confirm and extend the findings of the trials reviewed here. Studies comparing the relative efficacy and safety of different PRMs including mifepristone, gestrinone, ulipristal, and asoprisnil would provide important clinical evidence. Future studies should report quality of life

and pain relief scores (dysmenorrhoea and dyspareunia scores measured on a 0 to 10 visual analogue scale (VAS)).

ACKNOWLEDGEMENTS

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CHARACTERISTICS OF STUDIES

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

Bromham 1995

Methods	Randomised double-blind multi-centre study Method of randomization not described Pharmaceutical company stated
Participants	269 British women aged 18 to 45 years Inclusion criteria: endometriosis confirmed by laparoscopy or laparotomy. Exclusion criteria: requiring surgical excision, serious systemic disease, requiring long-term treatment, previous failure of danazol treatment, other hormonal treatment within 2 months, unwillingness to use mechanical contraception
Interventions	Gestrinone 2.5 mg twice weekly plus 'dummy' danazol for 6 months (132 women) Danazol 200 mg bd plus 'dummy' gestrinone for 6 months (137 women) Duration of treatment: 6 months
Outcomes	AFS scores at laparoscopy after 6 months of treatment Pain scores during treatment and at 1 year follow-up Side effects Fertility
Notes	Repeat laparoscopy 23 days (median) after cessation of treatment Follow-up: 12 months

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Allocated at random, no other details
Allocation concealment (selection bias)	Unclear risk	Unclear, no details
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind', 'double-dummy'. Participants received 2 identical tablets Study authors state that participants were blinded but do not reveal who else was blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Unclear, no details
Incomplete outcome data (attrition bias) All outcomes	High risk	A total of 15 participants from the gestrinone group, including 4 with hirsutism, and 17 participants from the danazol group, including 6 with headache, withdrew because of adverse symptoms. An additional 22 participants, including 10 from the gestrinone group and 12 from the danazol group, withdrew because of lack of efficacy, pregnancy, elevated hepatic function tests, or reasons unrelated to the trial (19% attrition rate for efficacy outcomes)

Bromham 1995 *(Continued)*

Selective reporting (reporting bias)	Low risk	Includes main outcomes and side effects
Other bias	Low risk	No other specific source of bias detected

Carbonell 2012

Methods	Randomised double-blind study Method of randomization described Pharmaceutical company stated
Participants	26 women Inclusion criteria: endometriosis confirmed by laparoscopy
Interventions	Group I received 1 tablet of 25 mg mifepristone daily Group II received 1 tablet of 5 mg mifepristone daily Duration of treatment: 6 months
Outcomes	AFS scores at laparoscopy after 6 months of treatment Pain scores during treatment Side effects
Notes	Laparoscopy and endometrial biopsy were performed before and after treatment

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Used a random list
Allocation concealment (selection bias)	Low risk	Applied opaque sealed envelopes that contained a card indicating the treatment group to which the participant was assigned
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Unclear, no details
Incomplete outcome data (attrition bias) All outcomes	Low risk	All women completed 6 months of treatment
Selective reporting (reporting bias)	Low risk	Reports main review outcomes
Other bias	Unclear risk	No other specific source of bias detected

Carbonell 2016

Methods	Randomised double-blind study Method of randomization described Pharmaceutical company stated
Participants	360 women Inclusion criteria: endometriosis confirmed by laparoscopy
Interventions	Group I received 1 tablet of 2.5 mg mifepristone daily for 6 months (90 women) Group II received 1 tablet of 5 mg mifepristone daily for 6 months (90 women) Group III received 1 tablet of 10 mg mifepristone daily for 6 months (90 women) Group IV received 1 tablet of placebo daily for 3 months (90 women)
Outcomes	AFS scores at laparoscopy after 6 months of treatment Pain scores during treatment Side effects
Notes	Laparoscopy and endometrial biopsy were performed before and after treatment

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Used a random list obtained from the MEDSTAT 2.1 programme
Allocation concealment (selection bias)	Low risk	Applied opaque sealed envelopes that contained a card indicating the treatment group to which the participant was assigned
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Unclear, no details
Incomplete outcome data (attrition bias) All outcomes	Low risk	All women in treatment group completed 6 months of treatment, and placebo group finished 3 months of treatment
Selective reporting (reporting bias)	Low risk	Includes main outcomes
Other bias	Low risk	No other specific source of bias detected

Chwalisz 2004

Methods	Multi-centre double-blind placebo-controlled parallel-group study
Participants	130 women

Chwalisz 2004 *(Continued)*

Interventions	Asoprisnil 5 mg (n = 31), 10 mg (n = 33), 25 mg (n = 32), or placebo (n = 34) was administered orally once daily for 12 weeks
Outcomes	Pain scores during treatment and at 1 year follow-up Side effects, serum E_2
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomised double-blind study Pharmaceutical company stated
Allocation concealment (selection bias)	Unclear risk	Unclear, no details
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Unclear, no details
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unclear, no details
Selective reporting (reporting bias)	Unclear risk	Unclear, no details
Other bias	Unclear risk	Unclear, insufficient details to permit a judgement

Dawood 1997

Methods	Phase II prospective randomised double-blind study
Participants	11 patients
Interventions	Gestrinone 1.25 mg (5 participants) or 2.5 mg (6 participants) orally twice a week for 24 weeks
Outcomes	Revised AFS scores before and at the end of treatment Serum hormone, sex hormone binding globulin, and lipid concentrations were measured Quantitated computerised tomography of thoracic 12 through lumbar 4 vertebral bodies
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement

Dawood 1997 *(Continued)*

Random sequence generation (selection bias)	Low risk	Participants were randomised to 1 of 2 treatment groups according to a computer-generated order
Allocation concealment (selection bias)	Unclear risk	Unclear, no details
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Unclear, no details
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Unclear, no details
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unclear, no details
Selective reporting (reporting bias)	Unclear risk	Unclear, insufficient details to allow a judgement
Other bias	Unclear risk	Unclear, insufficient details to allow a judgement

Fedele 1989

Methods	Open randomised trial No source of funding stated
Participants	39 Italian women aged 23 to 35 years Inclusion criteria: infertility, laparoscopic diagnosis of endometriosis in preceding 3 months Exclusion criteria: bilateral tubal occlusion, severe dyspermia in partner, use of danazol or other sex steroids in preceding 6 months, severe systemic or endocrine disease
Interventions	Gestrinone 2.5 mg twice weekly (20 women) increasing to 3 times a week if no amenorrhoea by 1 month (7 of the 20) Danazol 600 mg per day (19 women) increasing to 800 mg per day if no amenorrhoea by 1 month (2 of the 19) Duration of treatment: 6 months
Outcomes	rAFS scores at laparoscopy 1 month after cessation of treatment Pain scores during treatment and at 18 month follow-up Plasma hormone levels before and during treatment Pregnancy rates post treatment Side effects
Notes	Follow-up: 12 months Losses to follow-up: 1

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	'patients were randomly assigned'

Fedele 1989 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	No details provided
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding
Blinding of outcome assessment (detection bias) All outcomes	High risk	No blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	All women accounted for
Selective reporting (reporting bias)	Low risk	Includes main outcomes
Other bias	High risk	Only 7 participants given gestrinone and 9 participants taking danazol had repeat laparoscopy. If amenorrhoea was not obtained after 1 month of treatment, the gestrinone dose was increased to 2.5 mg 3 times a week (7 participants) and the danazol dose to 800 mg a day (2 participants)

GISG 1996

Methods	Randomised double-blind double-dummy multi-centre trial Method of randomization described Pharmaceutical company stated
Participants	55 Italian women aged 18 to 40 years Inclusion criteria: chronic pelvic pain, laparoscopic diagnosis of endometriosis with no attempts at endometriosis reduction other than biopsy up to 3 months before study entry, no medical or surgical treatment for endometriosis between laparoscopy and study entry, not wanting pregnancy in the immediate future Exclusion criteria: treatment for endometriosis other than non-steroidal anti-inflammatory drugs in the previous 6 months, concomitant pelvic pain causing disorder, contraindications to the use of gestrinone or GnRH analogues, abnormal baseline bone density values, unwillingness to use barrier contraception
Interventions	Gestrinone 2.5 mg twice weekly plus placebo injections (27 women) Intramuscular (IM) leuprolide acetate 3.75 mg once a month plus placebo tablets (28 women) Duration of treatment: 6 months
Outcomes	Pain symptoms Bone mineral density Lipid profile
Notes	Follow-up: 6 months 6 withdrawals during treatment period 7 lost to follow-up 8 pregnancies

Risk of bias

Bias	Authors' judgement	Support for judgement

GISG 1996 *(Continued)*

Random sequence generation (selection bias)	Low risk	'randomized', 'allocating consecutively numbered anonymous packages'
Allocation concealment (selection bias)	Low risk	Sealed envelopes containing randomization codes
Blinding of participants and personnel (performance bias) All outcomes	Low risk	'double blind, double dummy'. Each participant received an active drug and a dummy placebo. Participants and clinicians were blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	'double blind, double dummy'. Each participant received an active drug and a dummy placebo. Participants and clinicians were blinded
Incomplete outcome data (attrition bias) All outcomes	High risk	Losses to follow-up detailed, 6 withdrawals during treatment period, 7 lost to follow-up (11%)
Selective reporting (reporting bias)	Low risk	Includes main outcomes
Other bias	Low risk	No other specific source of bias detected

Hornstein 1990

Methods	Randomised double-blind trial Pharmaceutical company stated
Participants	12 American women Inclusion criteria: endometriosis (stage 2 to 3 disease according to rAFS classification) diagnosed on videotaped laparoscopy within previous 6 weeks Exclusion criteria: none specified
Interventions	Gestrinone 1.25 mg twice weekly (6 women) Gestrinone 2.5 mg twice weekly (6 women) Duration of treatment: 6 months
Outcomes	rAFS scores for endometriosis at laparoscopy following treatment Symptom scores during treatment and follow-up Side effects Bone densitometry Hormonal, lipoprotein, haematological, and biochemical measurements
Notes	Second laparoscopy within 4 weeks of treatment completion Follow-up: 6 months Losses to follow-up: 2

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Randomised trial, method not mentioned

Hornstein 1990 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Not mentioned
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind
Incomplete outcome data (attrition bias) All outcomes	High risk	Losses to follow-up: 2 (17%)
Selective reporting (reporting bias)	Unclear risk	Reports main outcomes. No details on pelvic pain scores after treatment
Other bias	Low risk	No other specific source of bias detected

Spitz 2009

Methods	Randomised, double-blind
Participants	38 women
Interventions	6 months of treatment with 3 doses of ulipristal, CDB-4124 (12.5 mg, 25 mg, and 50 mg) compared with leuprolide acetate depot
Outcomes	Pain scores during treatment
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Allocated at random, no other details
Allocation concealment (selection bias)	Unclear risk	Unclear, no details
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Unclear, no details
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Unclear, no details
Incomplete outcome data (attrition bias)	Unclear risk	Unclear, no details

Spitz 2009 *(Continued)*

All outcomes		
Selective reporting (reporting bias)	Unclear risk	Unclear, insufficient details to allow a judgement
Other bias	Unclear risk	Unclear, insufficient details to allow a judgement

Worthington 1993

Methods	Randomised double-blind	
Participants	20 premenopausal women with mild to moderate endometriosis	
Interventions	1.25 mg or 2.5 mg gestrinone 2 times per week for 6 months	
Outcomes	Metabolic effects of oral gestrinone on plasma lipoprotein risk markers for cardiovascular disease and on bone density Median total endometriosis scores	
Notes		
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomised
Allocation concealment (selection bias)	Unclear risk	Unclear, no details
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Unclear, no details
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Unclear, no details
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unclear, no details
Selective reporting (reporting bias)	Unclear risk	Unclear, insufficient details to allow a judgement
Other bias	Unclear risk	Unclear, insufficient details to allow a judgement

AFS: American Fertility Society
GnRH: gonadotropin-releasing hormone
rAFS: retrospective American Fertility Society score

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

Study	Reason for exclusion
Bulun 2016	Not an RCT; single-arm study
Kettel 1996	Not an RCT
Kettel 1998	Not an RCT
Mettler 1987	The "three step" therapy discussed in this study is a mixture of surgical and medical therapy
Nieto 1996	23/25 participants taking gestrinone and 18/18 participants given danazol had surgery before receiving medical treatment
Nobel 1980	Comparison of danazol vs oral contraceptive pill
Thomas 1987	This study concentrates on effects on asymptomatic endometriosis and fertility
Yang 2006	Conservative or half-conservative surgery combined with drug therapy
Zhang 2016	Using laparoscopic minimally invasive combined drug therapy

RCT: randomised controlled trial

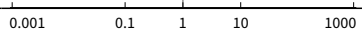
DATA AND ANALYSES

Comparison 1. Effectiveness of mifepristone versus placebo, patient-assessed outcomes

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Dysmenorrhoea at 3 months	1	352	Odds Ratio (M-H, Fixed, 95% CI)	0.08 [0.04, 0.17]
1.1 Mifepristone 2.5 mg	1	114	Odds Ratio (M-H, Fixed, 95% CI)	0.24 [0.09, 0.64]
1.2 Mifepristone 5 mg	1	120	Odds Ratio (M-H, Fixed, 95% CI)	0.02 [0.00, 0.16]
1.3 Mifepristone 10 mg	1	118	Odds Ratio (M-H, Fixed, 95% CI)	0.02 [0.00, 0.17]
2 Dyspareunia at 3 months	1	223	Odds Ratio (M-H, Fixed, 95% CI)	0.23 [0.10, 0.51]
2.1 Mifepristone 2.5 mg	1	74	Odds Ratio (M-H, Fixed, 95% CI)	0.62 [0.18, 2.13]
2.2 Mifepristone 5 mg	1	73	Odds Ratio (M-H, Fixed, 95% CI)	0.04 [0.00, 0.40]
2.3 Mifepristone 10 mg	1	76	Odds Ratio (M-H, Fixed, 95% CI)	0.13 [0.03, 0.60]

Analysis 1.1. Comparison 1 Effectiveness of mifepristone versus placebo, patient-assessed outcomes, Outcome 1 Dysmenorrhoea at 3 months.

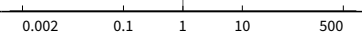
Study or subgroup	Mifepristone n/N	placebo n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
1.1.1 Mifepristone 2.5 mg					
Carbonell 2016	9/82	11/32		29%	0.24[0.09,0.64]
Subtotal (95% CI)	**82**	**32**		**29%**	**0.24[0.09,0.64]**
Total events: 9 (Mifepristone), 11 (placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=2.82(P=0)					
1.1.2 Mifepristone 5 mg					
Carbonell 2016	1/88	12/32		35.82%	0.02[0,0.16]
Subtotal (95% CI)	**88**	**32**		**35.82%**	**0.02[0,0.16]**
Total events: 1 (Mifepristone), 12 (placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=3.7(P=0)					
1.1.3 Mifepristone 10 mg					
Carbonell 2016	1/85	12/33		35.17%	0.02[0,0.17]
Subtotal (95% CI)	**85**	**33**		**35.17%**	**0.02[0,0.17]**
Total events: 1 (Mifepristone), 12 (placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=3.62(P=0)					
Total (95% CI)	**255**	**97**		**100%**	**0.08[0.04,0.17]**
Total events: 11 (Mifepristone), 35 (placebo)					
Heterogeneity: Tau^2=0; Chi^2=7.69, df=2(P=0.02); I^2=74.01%					
Test for overall effect: Z=6.55(P<0.0001)					
Test for subgroup differences: Chi^2=7.29, df=1 (P=0.03), I^2=72.55%					



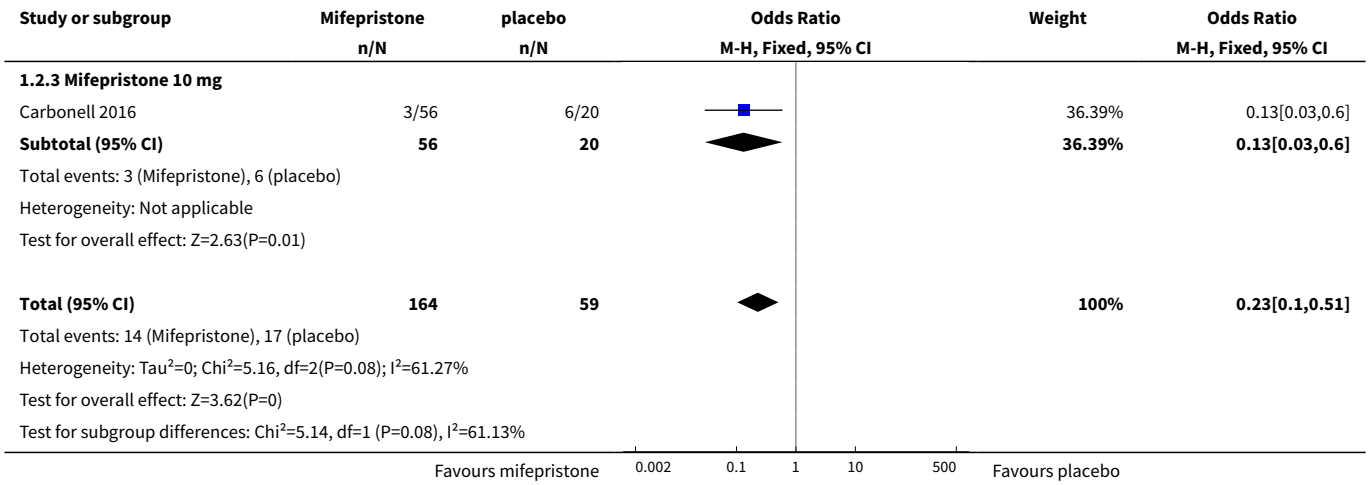
Favours mifepristone | Favours placebo

Analysis 1.2. Comparison 1 Effectiveness of mifepristone versus placebo, patient-assessed outcomes, Outcome 2 Dyspareunia at 3 months.

Study or subgroup	Mifepristone n/N	placebo n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
1.2.1 Mifepristone 2.5 mg					
Carbonell 2016	10/55	5/19		26.44%	0.62[0.18,2.13]
Subtotal (95% CI)	**55**	**19**		**26.44%**	**0.62[0.18,2.13]**
Total events: 10 (Mifepristone), 5 (placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.76(P=0.45)					
1.2.2 Mifepristone 5 mg					
Carbonell 2016	1/53	6/20		37.17%	0.04[0,0.4]
Subtotal (95% CI)	**53**	**20**		**37.17%**	**0.04[0,0.4]**
Total events: 1 (Mifepristone), 6 (placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=2.77(P=0.01)					



Favours mifepristone | Favours placebo



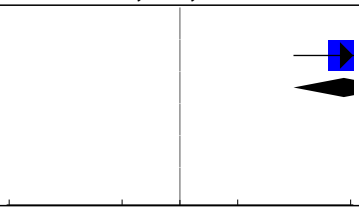
Comparison 2. Side effects at three months, mifepristone versus placebo, patient-assessed outcomes

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Amenorrhoea at 3 months	1		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Mifepristone all doses	1	360	Odds Ratio (M-H, Fixed, 95% CI)	686.16 [92.29, 5101.33]
2 Amenorrhoea at 3 months: subgroup analysis	1		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 Mifepristone 2.5 mg	1	180	Odds Ratio (M-H, Fixed, 95% CI)	207.67 [27.50, 1568.36]
2.2 Mifepristone 5 mg	1	180	Odds Ratio (M-H, Fixed, 95% CI)	3916.0 [348.75, 43971.52]
2.3 Mifepristone 10 mg	1	180	Odds Ratio (M-H, Fixed, 95% CI)	3916.0 [348.75, 43971.52]
3 Hot flushes at 3 months	1		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 Mifepristone all doses	1	360	Odds Ratio (M-H, Fixed, 95% CI)	28.79 [3.93, 210.73]
4 Hot flushes at 3 months: subgroup analysis	1		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
4.1 Mifepristone 2.5 mg	1	180	Odds Ratio (M-H, Fixed, 95% CI)	19.24 [2.49, 148.54]
4.2 Mifepristone 5 mg	1	180	Odds Ratio (M-H, Fixed, 95% CI)	23.82 [3.11, 182.24]
4.3 Mifepristone 10 mg	1	180	Odds Ratio (M-H, Fixed, 95% CI)	46.76 [6.21, 351.92]
5 Nausea at 3 months	1	360	Odds Ratio (M-H, Fixed, 95% CI)	1.72 [0.20, 15.03]
5.1 Mifepristone 2.5 mg	1	120	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
5.2 Mifepristone 5 mg	1	120	Odds Ratio (M-H, Fixed, 95% CI)	1.02 [0.04, 25.76]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.3 Mifepristone 10 mg	1	120	Odds Ratio (M-H, Fixed, 95% CI)	2.44 [0.12, 48.60]
6 Vomiting at 3 months	1	360	Odds Ratio (M-H, Fixed, 95% CI)	1.02 [0.10, 10.01]
6.1 Mifepristone 2.5 mg	1	120	Odds Ratio (M-H, Fixed, 95% CI)	1.02 [0.04, 25.76]
6.2 Mifepristone 5 mg	1	120	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
6.3 Mifepristone 10 mg	1	120	Odds Ratio (M-H, Fixed, 95% CI)	1.02 [0.04, 25.76]
7 Fatigue/Tiredness at 3 months	1	360	Odds Ratio (M-H, Fixed, 95% CI)	5.48 [0.71, 42.27]
7.1 Mifepristone 2.5 mg	1	120	Odds Ratio (M-H, Fixed, 95% CI)	3.92 [0.21, 73.08]
7.2 Mifepristone 5 mg	1	120	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
7.3 Mifepristone 10 mg	1	120	Odds Ratio (M-H, Fixed, 95% CI)	7.11 [0.40, 125.92]

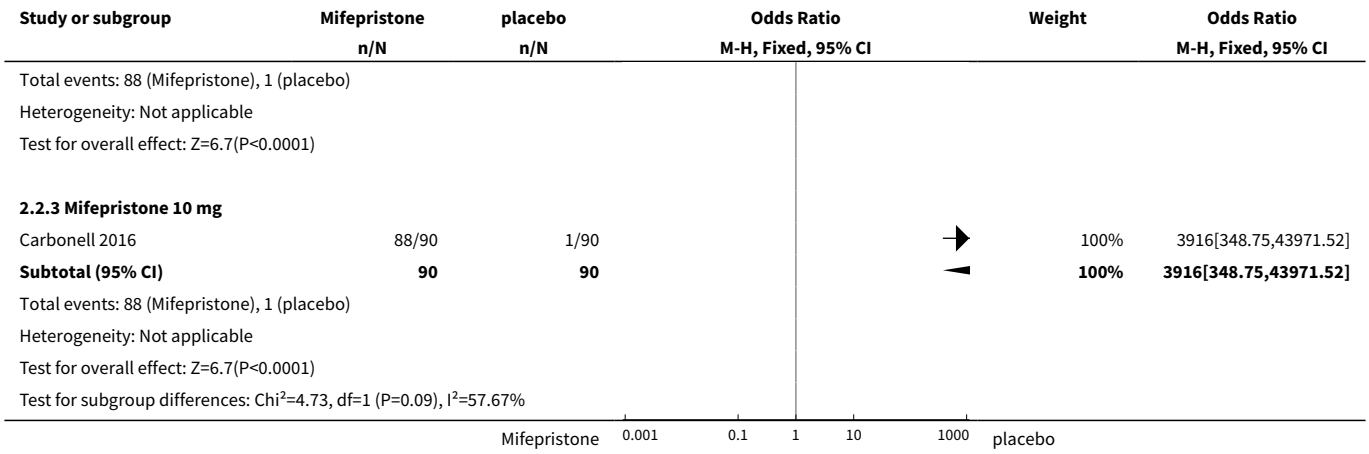
Analysis 2.1. Comparison 2 Side effects at three months, mifepristone versus placebo, patient-assessed outcomes, Outcome 1 Amenorrhoea at 3 months.

Study or subgroup	Mifepristone n/N	placebo n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
2.1.1 Mifepristone all doses					
Carbonell 2016	239/270	1/90		100%	686.16[92.29,5101.33]
Subtotal (95% CI)	**270**	**90**		**100%**	**686.16[92.29,5101.33]**
Total events: 239 (Mifepristone), 1 (placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=6.38(P<0.0001)					

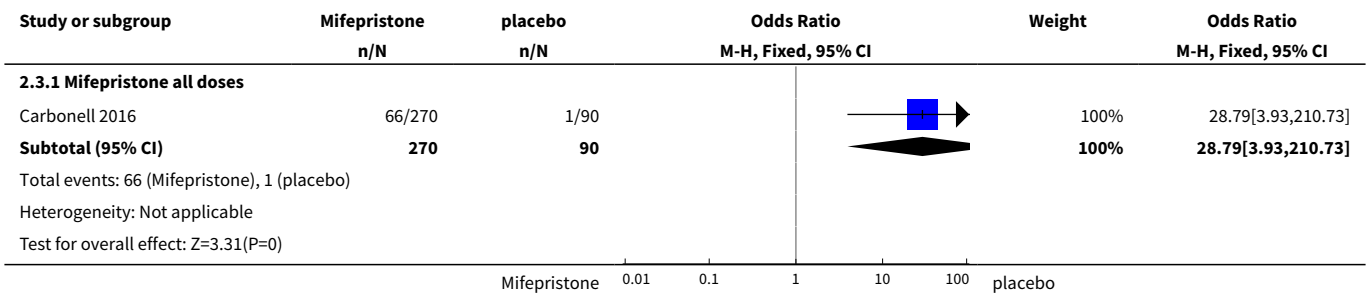


Analysis 2.2. Comparison 2 Side effects at three months, mifepristone versus placebo, patient-assessed outcomes, Outcome 2 Amenorrhoea at 3 months: subgroup analysis.

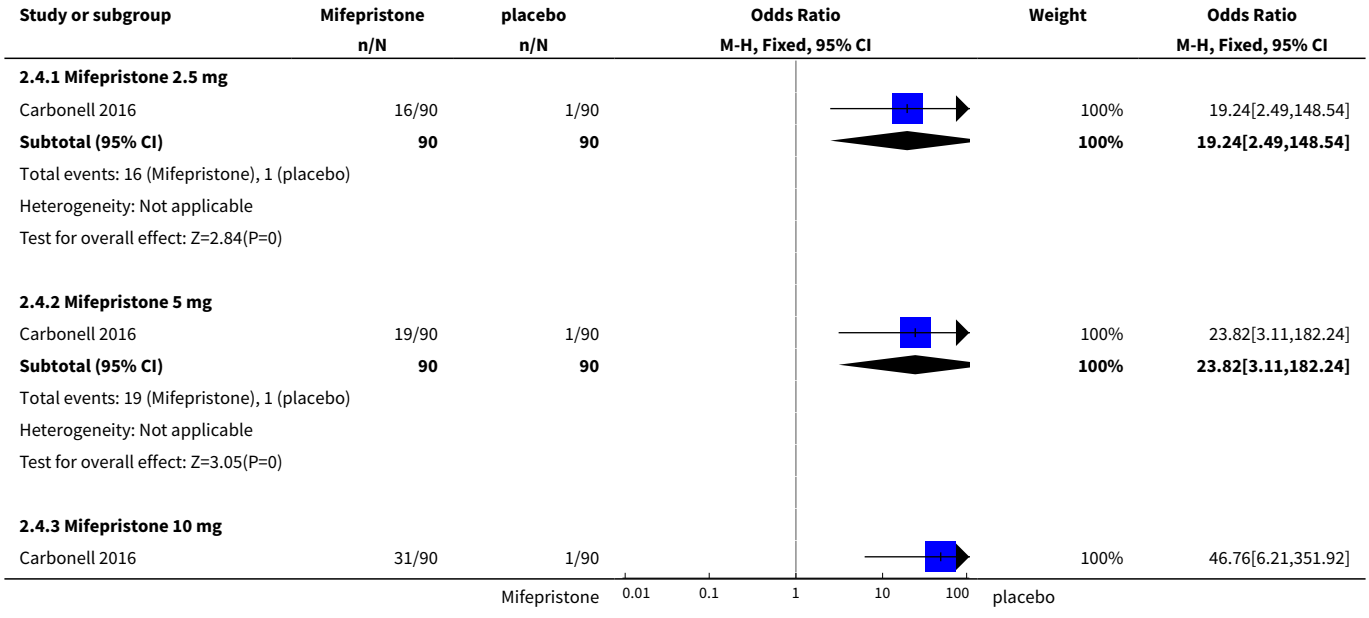
Study or subgroup	Mifepristone n/N	placebo n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
2.2.1 Mifepristone 2.5 mg					
Carbonell 2016	63/90	1/90		100%	207.67[27.5,1568.36]
Subtotal (95% CI)	**90**	**90**		**100%**	**207.67[27.5,1568.36]**
Total events: 63 (Mifepristone), 1 (placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=5.17(P<0.0001)					
2.2.2 Mifepristone 5 mg					
Carbonell 2016	88/90	1/90		100%	3916[348.75,43971.52]
Subtotal (95% CI)	**90**	**90**		**100%**	**3916[348.75,43971.52]**

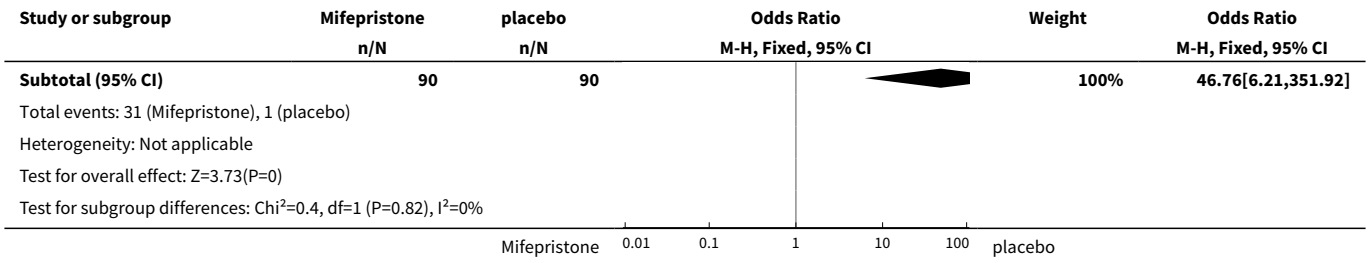


Analysis 2.3. Comparison 2 Side effects at three months, mifepristone versus placebo, patient-assessed outcomes, Outcome 3 Hot flushes at 3 months.

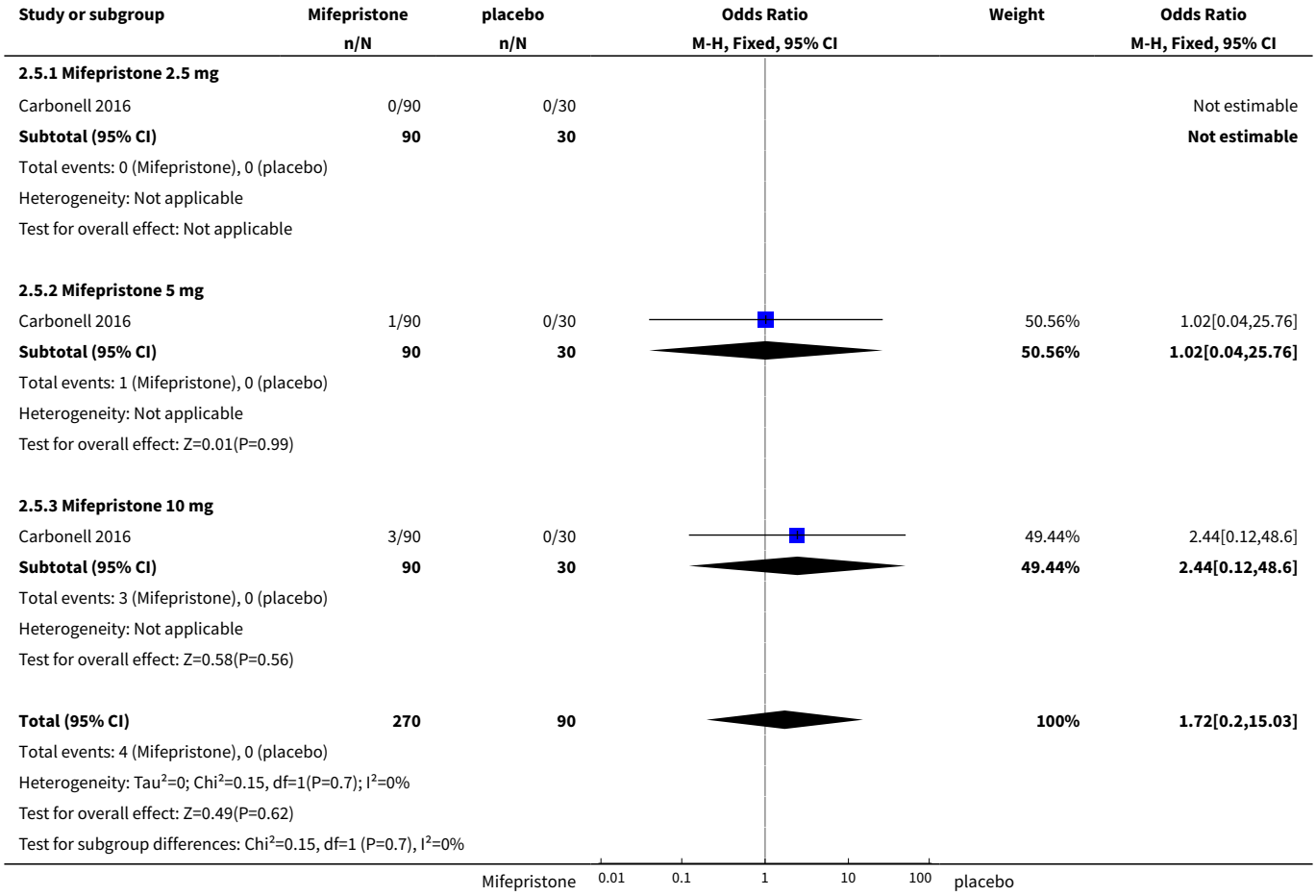


Analysis 2.4. Comparison 2 Side effects at three months, mifepristone versus placebo, patient-assessed outcomes, Outcome 4 Hot flushes at 3 months: subgroup analysis.

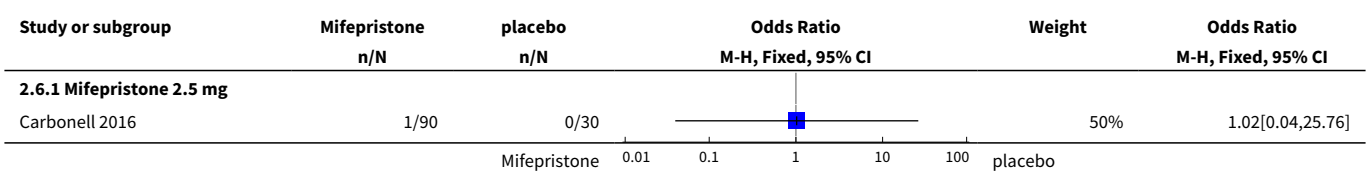


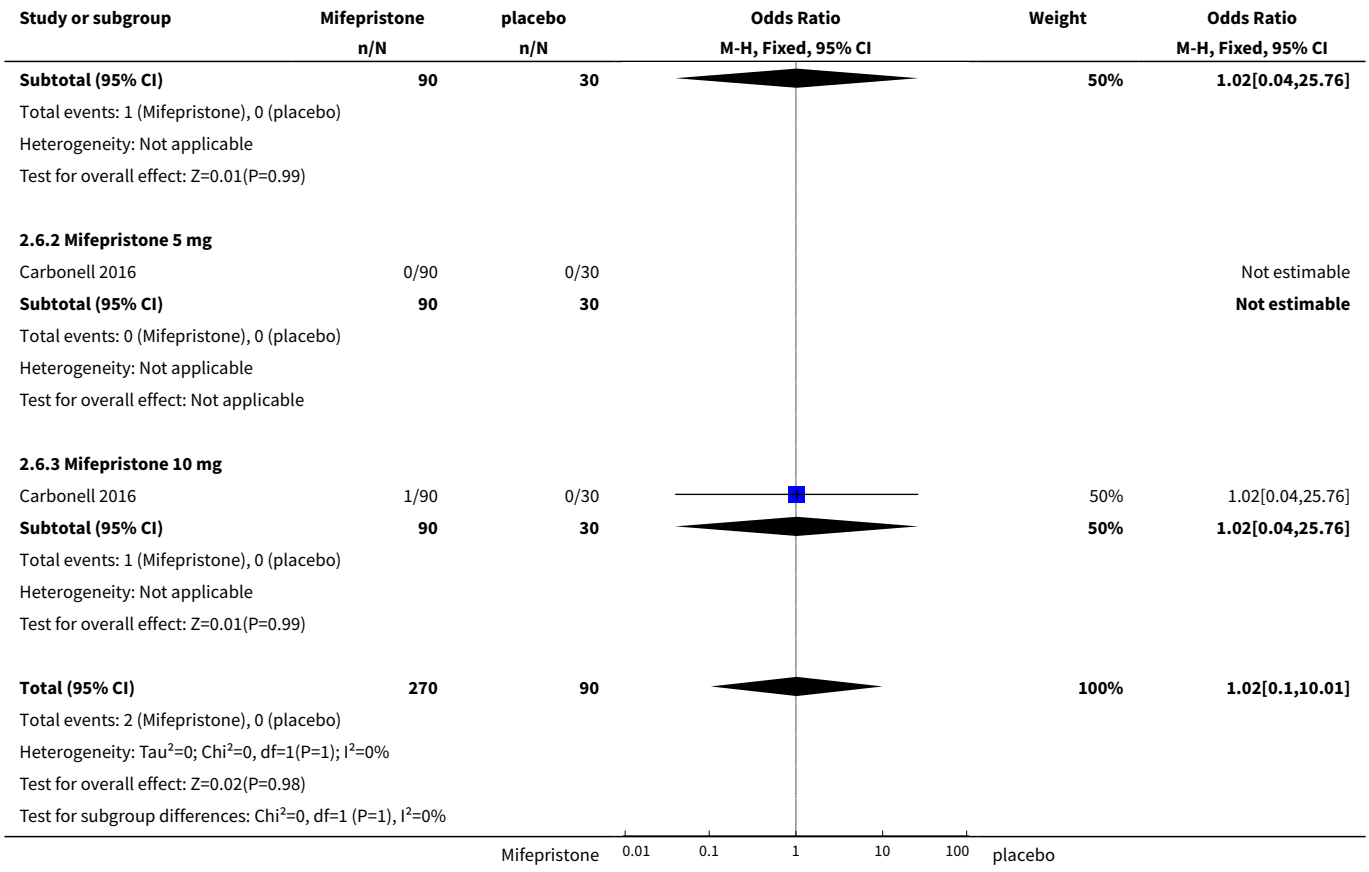


Analysis 2.5. Comparison 2 Side effects at three months, mifepristone versus placebo, patient-assessed outcomes, Outcome 5 Nausea at 3 months.

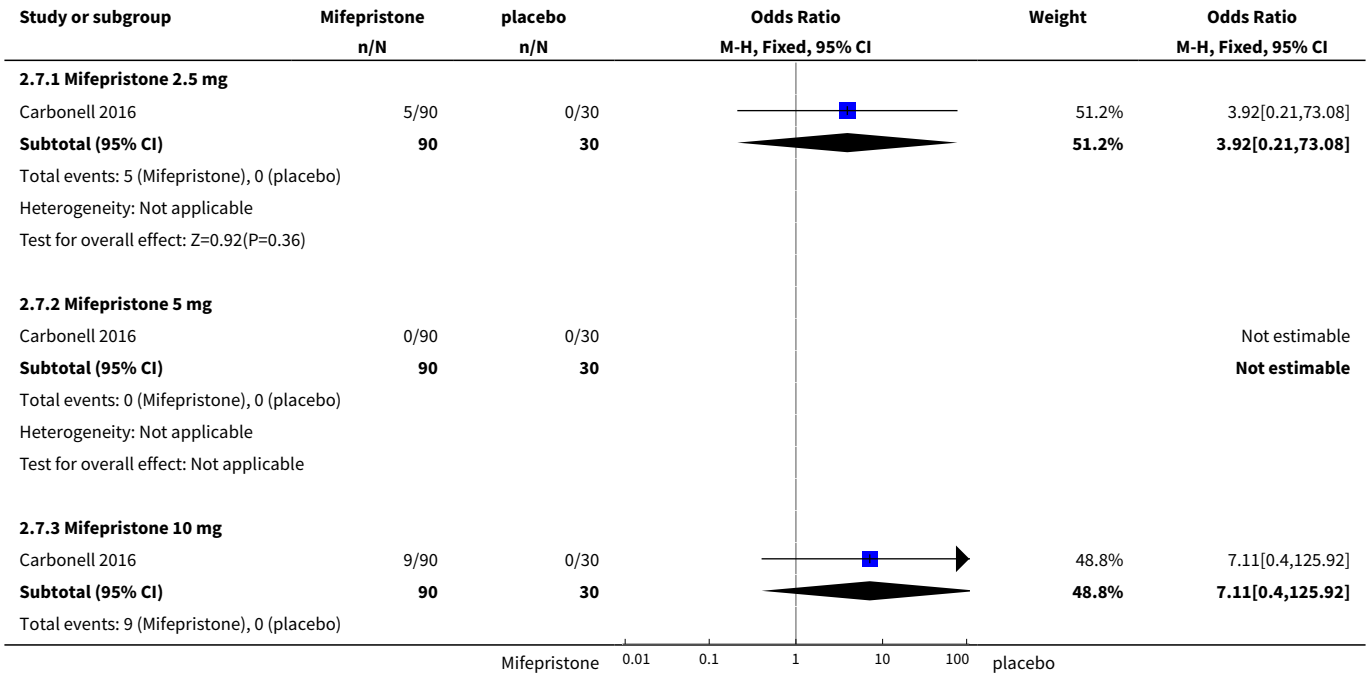


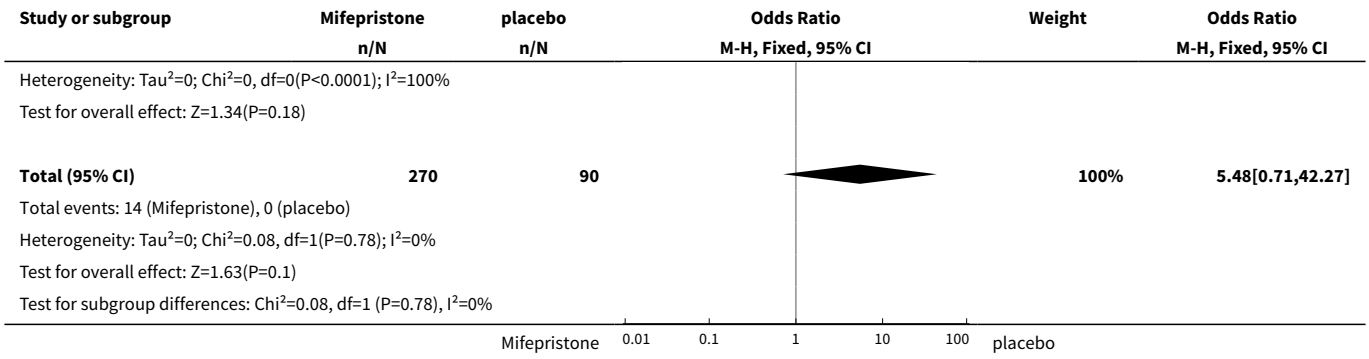
Analysis 2.6. Comparison 2 Side effects at three months, mifepristone versus placebo, patient-assessed outcomes, Outcome 6 Vomiting at 3 months.





Analysis 2.7. Comparison 2 Side effects at three months, mifepristone versus placebo, patient-assessed outcomes, Outcome 7 Fatigue/Tiredness at 3 months.



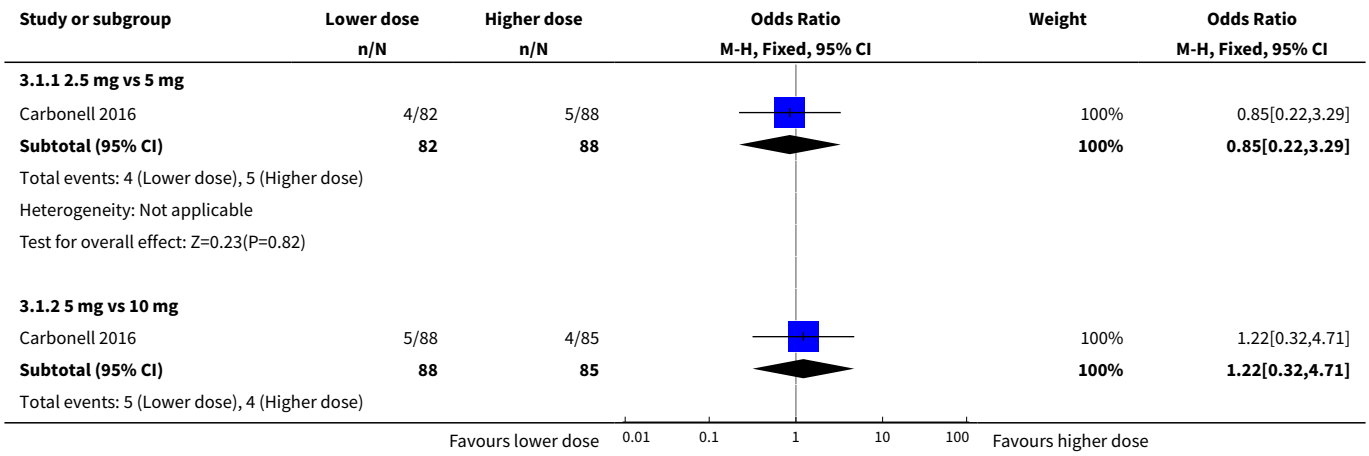


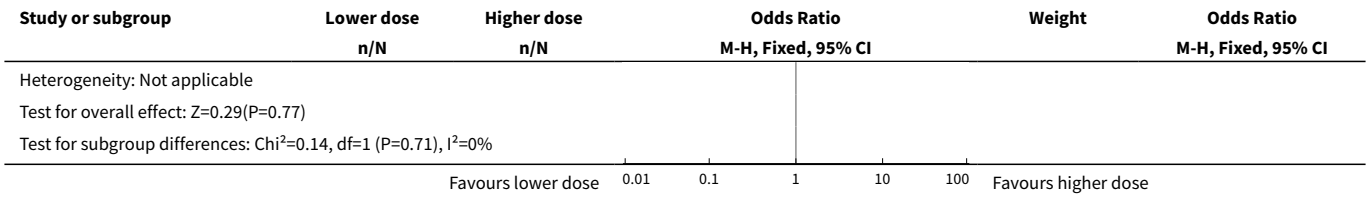
Comparison 3. Mifepristone lower dose versus higher dose: efficacy and side effects at six months

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Prevalence of dysmenorrhoea	1		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 2.5 mg vs 5 mg	1	170	Odds Ratio (M-H, Fixed, 95% CI)	0.85 [0.22, 3.29]
1.2 5 mg vs 10 mg	1	173	Odds Ratio (M-H, Fixed, 95% CI)	1.22 [0.32, 4.71]
2 Dysmenorrhoea score 0-10 VAS scale	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
2.1 5 mg vs 25 mg	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
3 Prevalence of dyspareunia	1		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 2.5 mg vs 5 mg	1	108	Odds Ratio (M-H, Fixed, 95% CI)	6.37 [0.74, 54.81]
3.2 5 mg vs 10 mg	1	109	Odds Ratio (M-H, Fixed, 95% CI)	0.52 [0.05, 5.90]
4 Dyspareunia score 0-10 VAS scale	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
4.1 5 mg vs 25 mg	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
5 Prevalence of pelvic pain	1		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
5.1 2.5 mg vs 5 mg	1	110	Odds Ratio (M-H, Fixed, 95% CI)	1.81 [0.63, 5.17]
5.2 5 mg vs 10 mg	1	120	Odds Ratio (M-H, Fixed, 95% CI)	3.97 [0.79, 19.97]
6 Prevalence of amenorrhoea	2		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
6.1 2.5 mg vs 5 mg	1	180	Odds Ratio (M-H, Fixed, 95% CI)	0.45 [0.21, 0.97]
6.2 5 mg vs 10 mg	1	180	Odds Ratio (M-H, Fixed, 95% CI)	1.10 [0.47, 2.56]

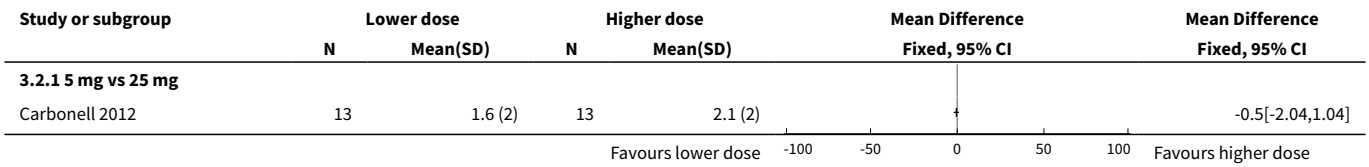
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6.3 5 mg vs 25 mg	1	26	Odds Ratio (M-H, Fixed, 95% CI)	0.61 [0.08, 4.41]
7 Prevalence of hot flushes	2		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
7.1 2.5 mg vs 5 mg	1	180	Odds Ratio (M-H, Fixed, 95% CI)	0.84 [0.38, 1.89]
7.2 5 mg vs 10 mg	1	180	Odds Ratio (M-H, Fixed, 95% CI)	0.75 [0.35, 1.58]
7.3 5 mg vs 25 mg	1	26	Odds Ratio (M-H, Fixed, 95% CI)	3.24 [0.12, 87.13]
8 Prevalence of nausea	1		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
8.1 2.5 mg vs 5 mg	1	180	Odds Ratio (M-H, Fixed, 95% CI)	2.02 [0.18, 22.71]
8.2 5 mg vs 10 mg	1	180	Odds Ratio (M-H, Fixed, 95% CI)	1.0 [0.06, 16.24]
9 Prevalence of vomiting	1		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
9.1 2.5 mg vs 5 mg	1	180	Odds Ratio (M-H, Fixed, 95% CI)	3.03 [0.12, 75.46]
9.2 5 mg vs 10 mg	1	180	Odds Ratio (M-H, Fixed, 95% CI)	0.33 [0.01, 8.20]
10 Prevalence of fatigue/tiredness	1		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
10.1 2.5 mg vs 5 mg	1	180	Odds Ratio (M-H, Fixed, 95% CI)	13.92 [0.77, 250.94]
10.2 5 mg vs 10 mg	1	180	Odds Ratio (M-H, Fixed, 95% CI)	0.03 [0.00, 0.54]
11 Prevalence of endometrial thickness > 20 mm	1		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
11.1 5 mg vs 25 mg	1	26	Odds Ratio (M-H, Fixed, 95% CI)	1.41 [0.28, 7.13]

Analysis 3.1. Comparison 3 Mifepristone lower dose versus higher dose: efficacy and side effects at six months, Outcome 1 Prevalence of dysmenorrhoea.

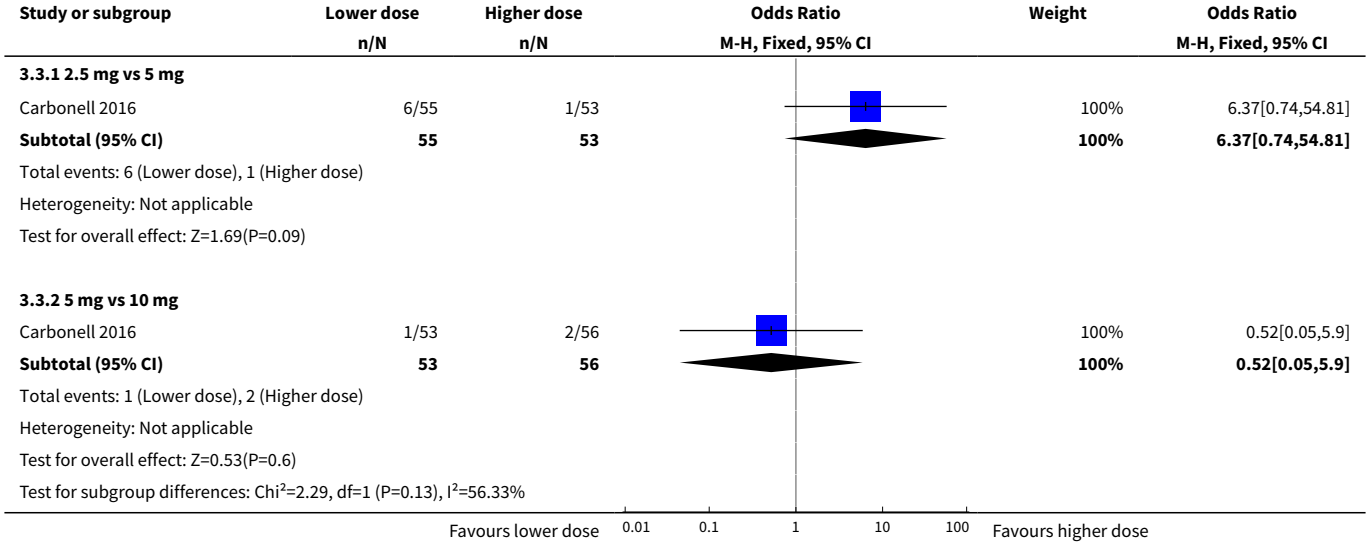




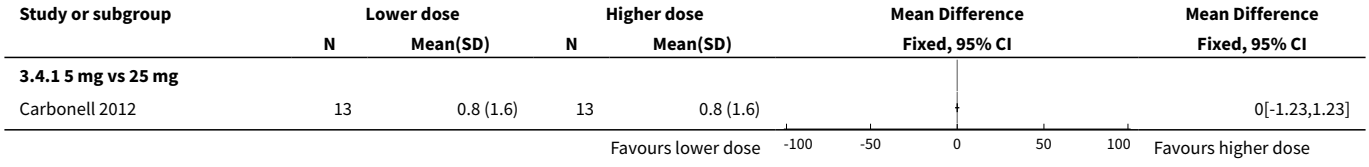
Analysis 3.2. Comparison 3 Mifepristone lower dose versus higher dose: efficacy and side effects at six months, Outcome 2 Dysmenorrhoea score 0-10 VAS scale.



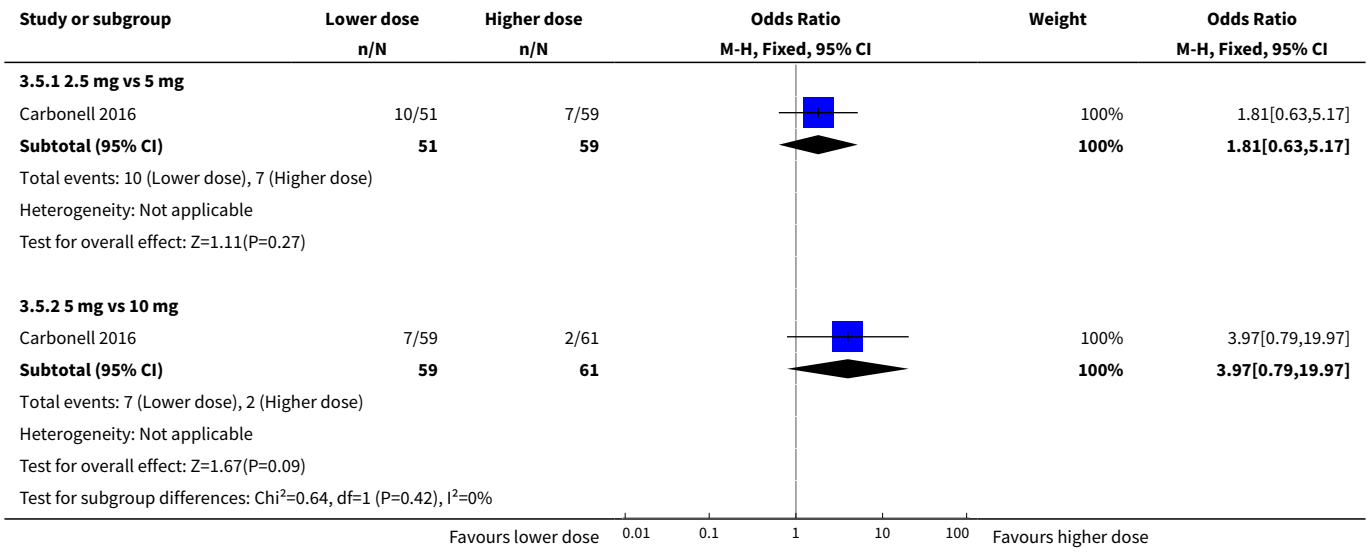
Analysis 3.3. Comparison 3 Mifepristone lower dose versus higher dose: efficacy and side effects at six months, Outcome 3 Prevalence of dyspareunia.



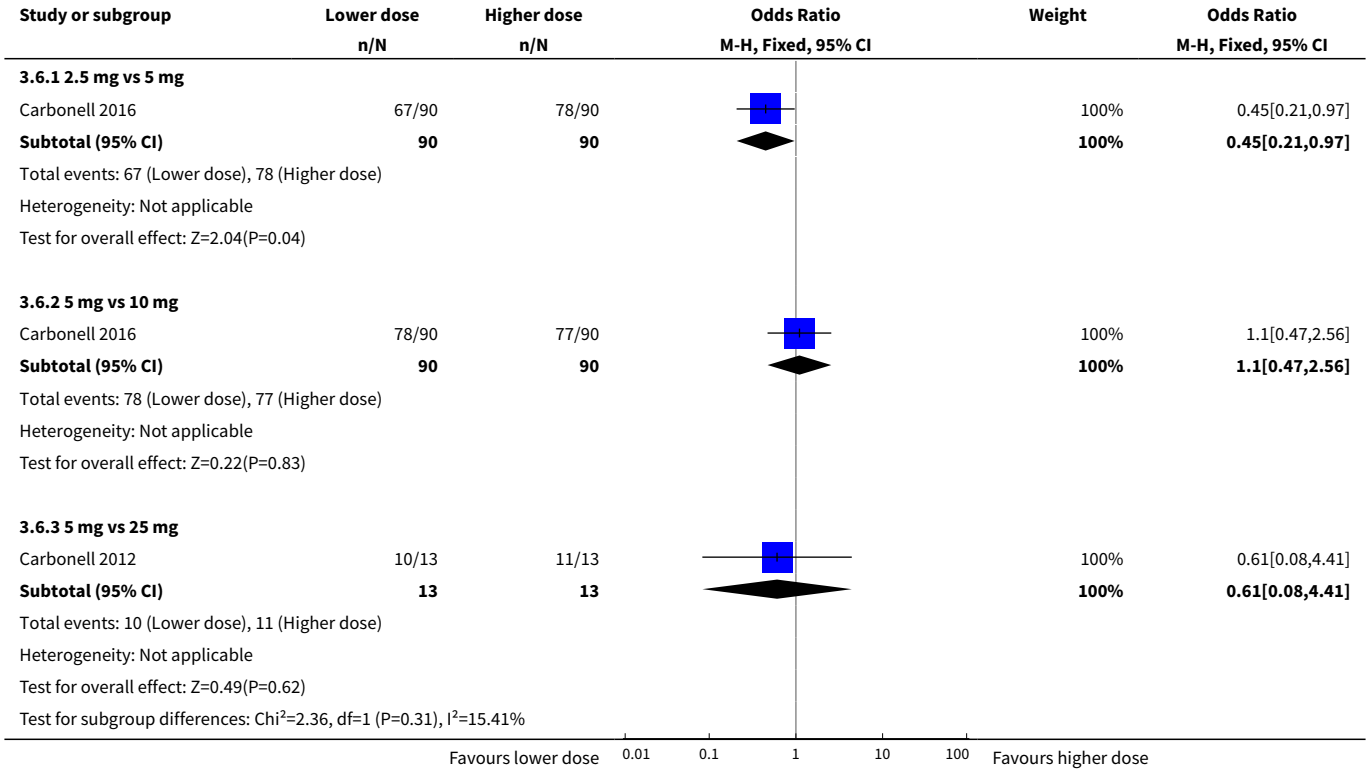
Analysis 3.4. Comparison 3 Mifepristone lower dose versus higher dose: efficacy and side effects at six months, Outcome 4 Dyspareunia score 0-10 VAS scale.



Analysis 3.5. Comparison 3 Mifepristone lower dose versus higher dose: efficacy and side effects at six months, Outcome 5 Prevalence of pelvic pain.



Analysis 3.6. Comparison 3 Mifepristone lower dose versus higher dose: efficacy and side effects at six months, Outcome 6 Prevalence of amenorrhoea.



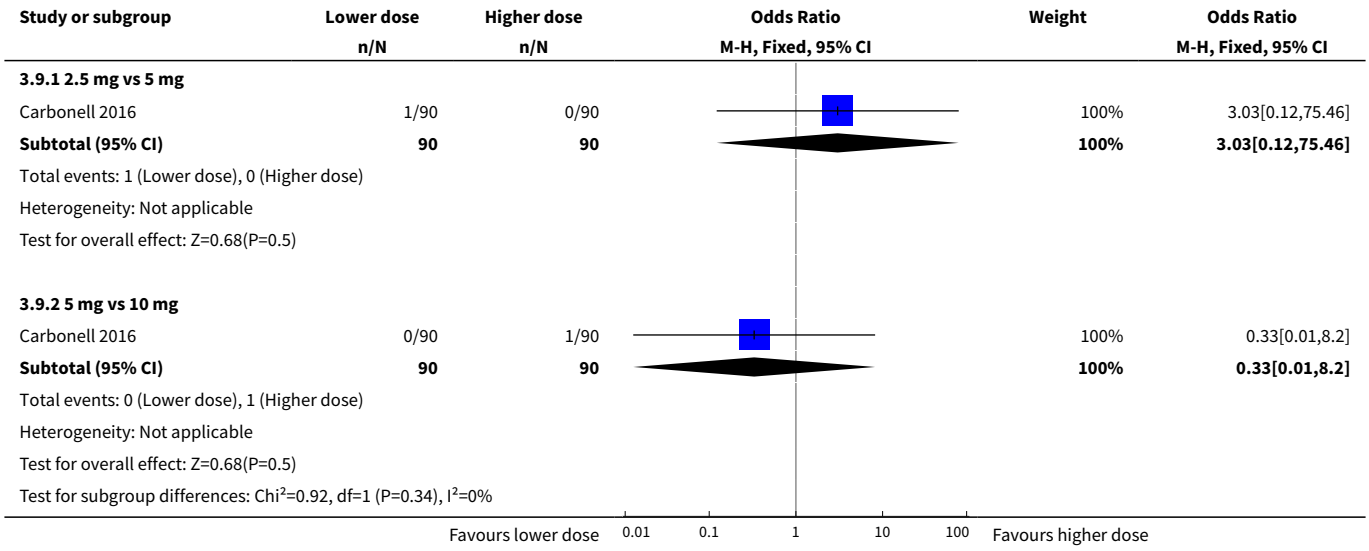
Analysis 3.7. Comparison 3 Mifepristone lower dose versus higher dose: efficacy and side effects at six months, Outcome 7 Prevalence of hot flushes.

Study or subgroup	Lower dose n/N	Higher dose n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
3.7.1 2.5 mg vs 5 mg					
Carbonell 2016	13/90	15/90		100%	0.84[0.38,1.89]
Subtotal (95% CI)	**90**	**90**		**100%**	**0.84[0.38,1.89]**
Total events: 13 (Lower dose), 15 (Higher dose)					
Heterogeneity: Tau^2=0; Chi^2=0, df=0(P<0.0001); I^2=100%					
Test for overall effect: Z=0.41(P=0.68)					
3.7.2 5 mg vs 10 mg					
Carbonell 2016	15/90	19/90		100%	0.75[0.35,1.58]
Subtotal (95% CI)	**90**	**90**		**100%**	**0.75[0.35,1.58]**
Total events: 15 (Lower dose), 19 (Higher dose)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.76(P=0.45)					
3.7.3 5 mg vs 25 mg					
Carbonell 2012	1/13	0/13		100%	3.24[0.12,87.13]
Subtotal (95% CI)	**13**	**13**		**100%**	**3.24[0.12,87.13]**
Total events: 1 (Lower dose), 0 (Higher dose)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.7(P=0.48)					
Test for subgroup differences: Chi^2=0.73, df=1 (P=0.69), I^2=0%					

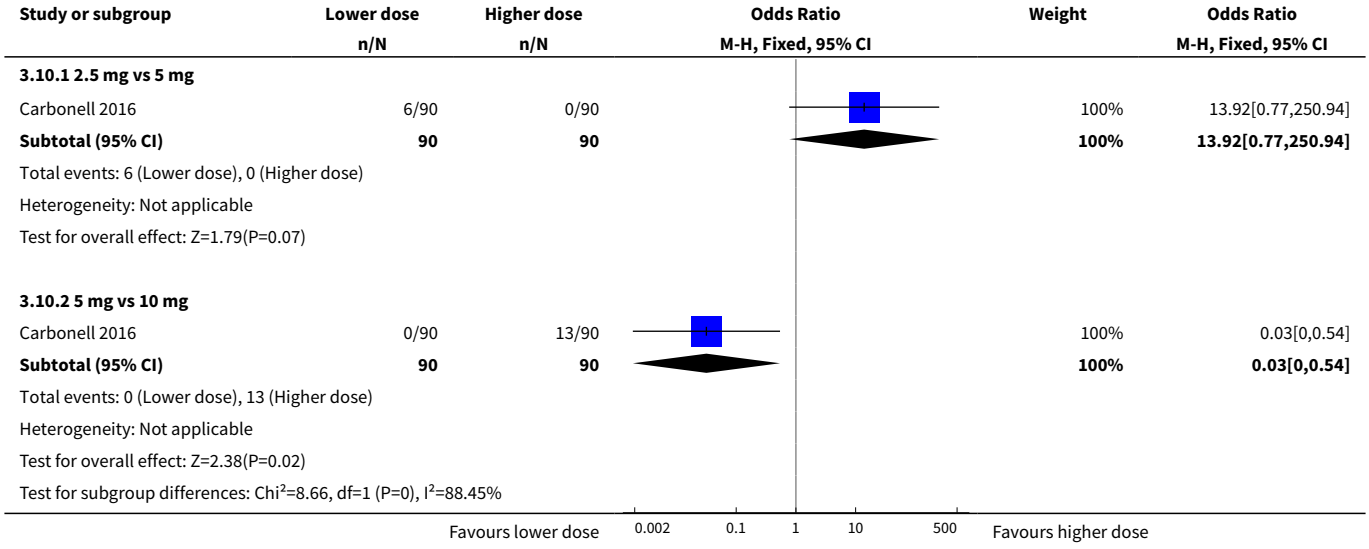
Analysis 3.8. Comparison 3 Mifepristone lower dose versus higher dose: efficacy and side effects at six months, Outcome 8 Prevalence of nausea.

Study or subgroup	Lower dose n/N	Higher dose n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
3.8.1 2.5 mg vs 5 mg					
Carbonell 2016	2/90	1/90		100%	2.02[0.18,22.71]
Subtotal (95% CI)	**90**	**90**		**100%**	**2.02[0.18,22.71]**
Total events: 2 (Lower dose), 1 (Higher dose)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.57(P=0.57)					
3.8.2 5 mg vs 10 mg					
Carbonell 2016	1/90	1/90		100%	1[0.06,16.24]
Subtotal (95% CI)	**90**	**90**		**100%**	**1[0.06,16.24]**
Total events: 1 (Lower dose), 1 (Higher dose)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
Test for subgroup differences: Chi^2=0.14, df=1 (P=0.71), I^2=0%					

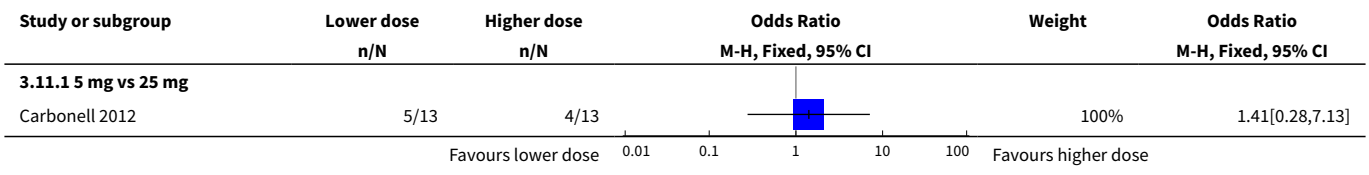
Analysis 3.9. Comparison 3 Mifepristone lower dose versus higher dose: efficacy and side effects at six months, Outcome 9 Prevalence of vomiting.

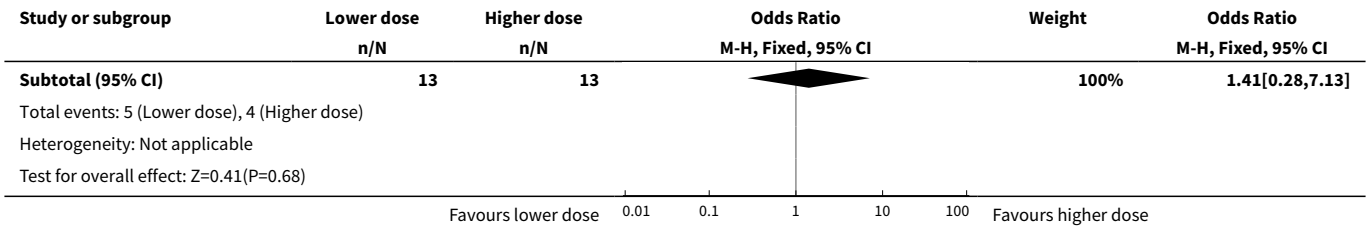


Analysis 3.10. Comparison 3 Mifepristone lower dose versus higher dose: efficacy and side effects at six months, Outcome 10 Prevalence of fatigue/tiredness.



Analysis 3.11. Comparison 3 Mifepristone lower dose versus higher dose: efficacy and side effects at six months, Outcome 11 Prevalence of endometrial thickness > 20 mm.





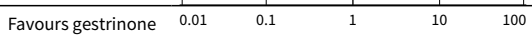
Comparison 4. Gestrinone versus danazol for six months: efficacy and side effects

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 None or mild pelvic pain	2	230	Odds Ratio (M-H, Fixed, 95% CI)	0.71 [0.33, 1.56]
2 None or mild dysmenorrhoea	2	214	Odds Ratio (M-H, Fixed, 95% CI)	0.72 [0.39, 1.33]
3 None or mild dyspareunia	2	222	Odds Ratio (M-H, Fixed, 95% CI)	0.83 [0.37, 1.86]
4 Adverse effects	2		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
4.1 Acne	2	302	Odds Ratio (M-H, Fixed, 95% CI)	1.45 [0.90, 2.33]
4.2 Seborrhoea	2	302	Odds Ratio (M-H, Fixed, 95% CI)	2.73 [1.67, 4.46]
4.3 Hirsutism	2	302	Odds Ratio (M-H, Fixed, 95% CI)	2.63 [1.60, 4.32]
4.4 Voice problems	2	302	Odds Ratio (M-H, Fixed, 95% CI)	0.70 [0.34, 1.43]
4.5 Swelling hands/feet	1	264	Odds Ratio (M-H, Fixed, 95% CI)	1.40 [0.82, 2.38]
4.6 Hot flushes	2	302	Odds Ratio (M-H, Fixed, 95% CI)	0.79 [0.50, 1.26]
4.7 Decreased breast size	2	302	Odds Ratio (M-H, Fixed, 95% CI)	0.62 [0.38, 0.98]
4.8 Leg or muscle cramps	2	302	Odds Ratio (M-H, Fixed, 95% CI)	0.49 [0.30, 0.78]
4.9 Headache	1	264	Odds Ratio (M-H, Fixed, 95% CI)	1.36 [0.84, 2.21]
4.10 Nausea	2	302	Odds Ratio (M-H, Fixed, 95% CI)	1.36 [0.84, 2.19]
4.11 Vomiting	1	264	Odds Ratio (M-H, Fixed, 95% CI)	0.67 [0.32, 1.43]
4.12 Loss of appetite	1	264	Odds Ratio (M-H, Fixed, 95% CI)	1.31 [0.72, 2.37]
4.13 Hunger	1	264	Odds Ratio (M-H, Fixed, 95% CI)	0.59 [0.36, 0.97]
4.14 Dizziness	1	264	Odds Ratio (M-H, Fixed, 95% CI)	1.24 [0.75, 2.05]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.15 Tiredness	1	264	Odds Ratio (M-H, Fixed, 95% CI)	1.44 [0.84, 2.45]
4.16 Faintness	1	264	Odds Ratio (M-H, Fixed, 95% CI)	1.23 [0.54, 2.76]
4.17 Skin rash	1	264	Odds Ratio (M-H, Fixed, 95% CI)	1.71 [0.91, 3.20]
4.18 Weight gain	1	38	Odds Ratio (M-H, Fixed, 95% CI)	0.34 [0.09, 1.27]
4.19 Vaginal dryness	1	38	Odds Ratio (M-H, Fixed, 95% CI)	0.18 [0.01, 4.00]
4.20 Raised liver transaminases	1	38	Odds Ratio (M-H, Fixed, 95% CI)	0.18 [0.01, 4.00]

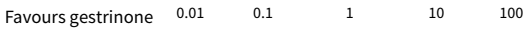
Analysis 4.1. Comparison 4 Gestrinone versus danazol for six months: efficacy and side effects, Outcome 1 None or mild pelvic pain.

Study or subgroup	gestrinone n/N	danazol n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
Bromham 1995	86/102	79/90		87.42%	0.75[0.33,1.71]
Fedele 1989	17/19	18/19		12.58%	0.47[0.04,5.7]
Total (95% CI)	**121**	**109**		**100%**	**0.71[0.33,1.56]**
Total events: 103 (gestrinone), 97 (danazol)					
Heterogeneity: Tau^2=0; Chi^2=0.12, df=1(P=0.73); I^2=0%					
Test for overall effect: Z=0.84(P=0.4)					



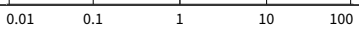
Analysis 4.2. Comparison 4 Gestrinone versus danazol for six months: efficacy and side effects, Outcome 2 None or mild dysmenorrhoea.

Study or subgroup	gestrinone n/N	danazol n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
Bromham 1995	53/91	56/85		100%	0.72[0.39,1.33]
Fedele 1989	19/19	19/19			Not estimable
Total (95% CI)	**110**	**104**		**100%**	**0.72[0.39,1.33]**
Total events: 72 (gestrinone), 75 (danazol)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.04(P=0.3)					



Analysis 4.3. Comparison 4 Gestrinone versus danazol for six months: efficacy and side effects, Outcome 3 None or mild dyspareunia.

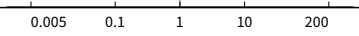
Study or subgroup	gestrinone n/N	danazol n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
Bromham 1995	82/95	79/89		86.18%	0.8[0.33,1.93]
Fedele 1989	17/19	17/19		13.82%	1[0.13,7.94]
Total (95% CI)	**114**	**108**		**100%**	**0.83[0.37,1.86]**
Total events: 99 (gestrinone), 96 (danazol)					
Heterogeneity: Tau^2=0; Chi^2=0.04, df=1(P=0.84); I^2=0%					
Test for overall effect: Z=0.46(P=0.64)					



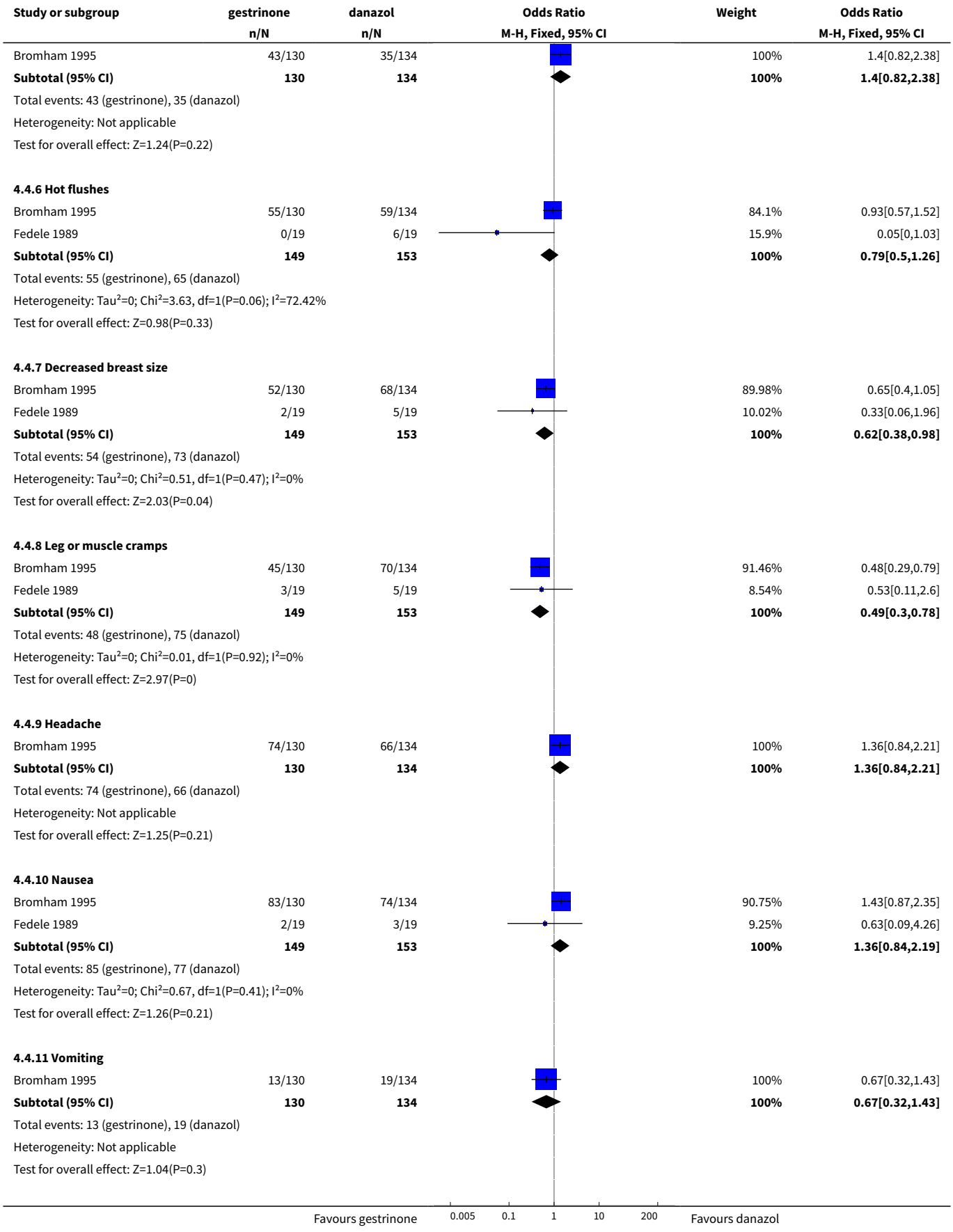
Favours gestrinone | Favours danazol

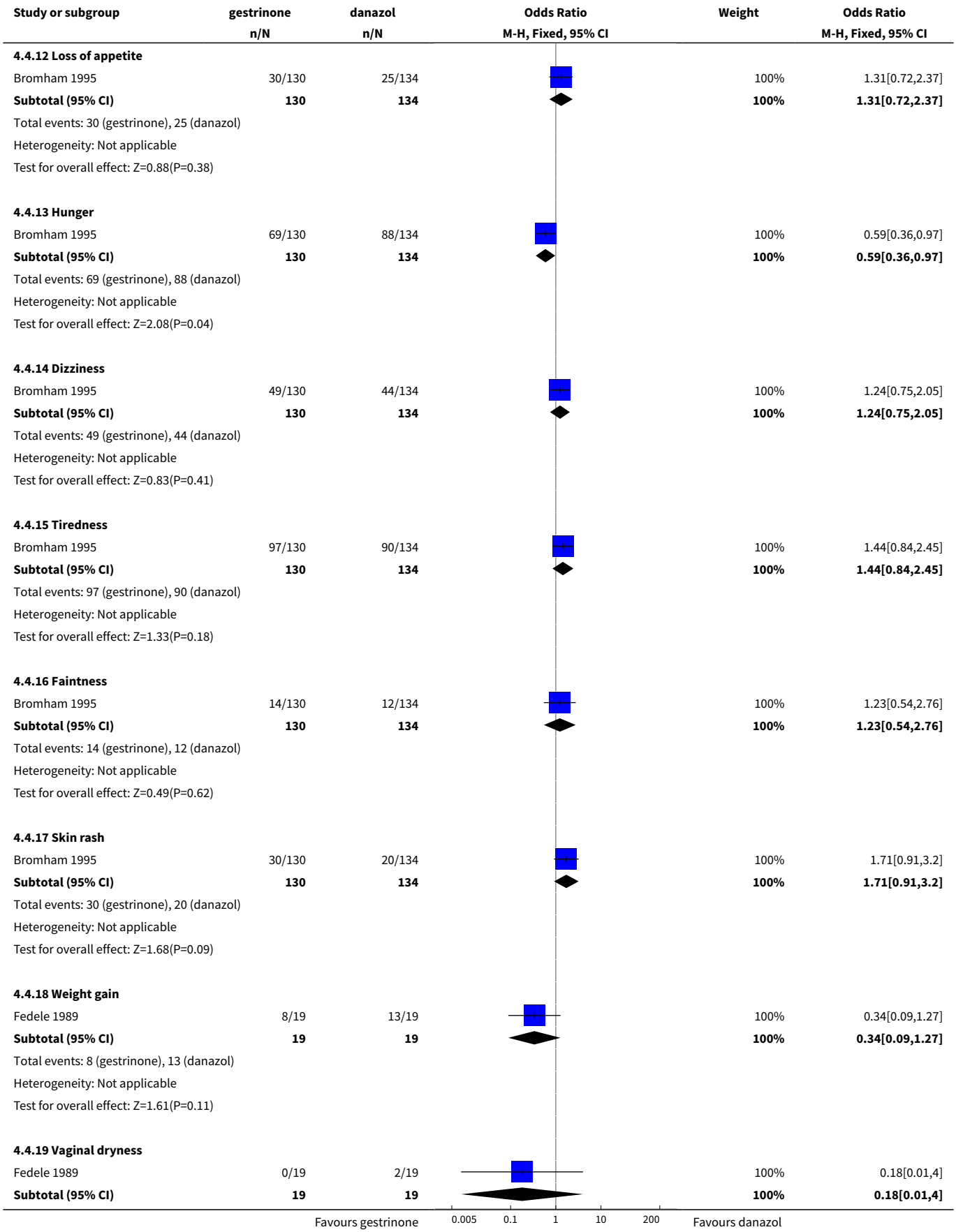
Analysis 4.4. Comparison 4 Gestrinone versus danazol for six months: efficacy and side effects, Outcome 4 Adverse effects.

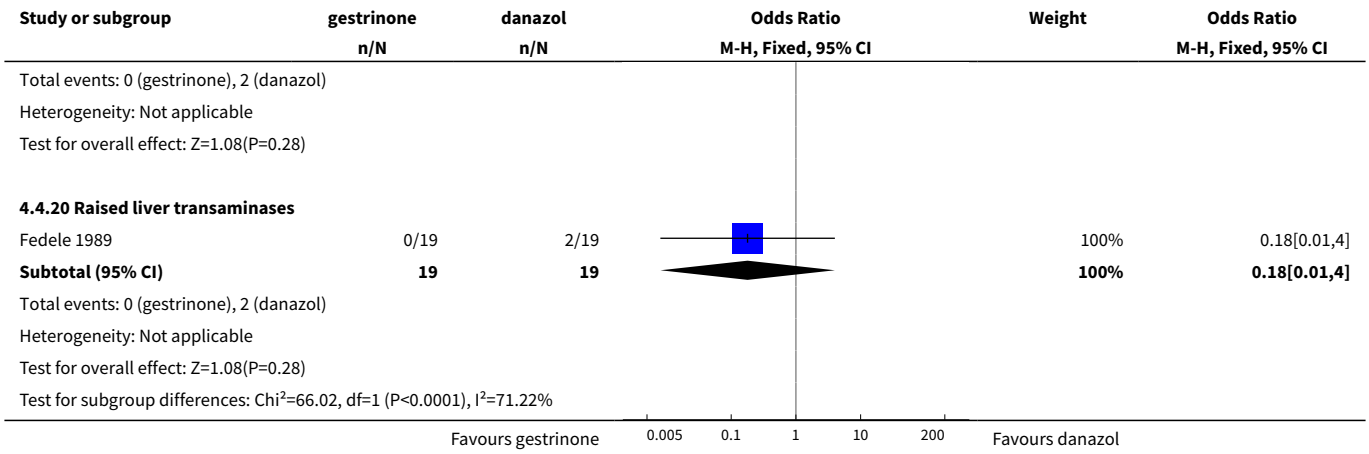
Study or subgroup	gestrinone n/N	danazol n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
4.4.1 Acne					
Bromham 1995	91/130	79/134		83.13%	1.62[0.98,2.7]
Fedele 1989	4/19	6/19		16.87%	0.58[0.13,2.51]
Subtotal (95% CI)	**149**	**153**		**100%**	**1.45[0.9,2.33]**
Total events: 95 (gestrinone), 85 (danazol)					
Heterogeneity: Tau^2=0; Chi^2=1.7, df=1(P=0.19); I^2=41.27%					
Test for overall effect: Z=1.52(P=0.13)					
4.4.2 Seborrhoea					
Bromham 1995	66/130	33/134		82.61%	3.16[1.87,5.32]
Fedele 1989	3/19	4/19		17.39%	0.7[0.13,3.68]
Subtotal (95% CI)	**149**	**153**		**100%**	**2.73[1.67,4.46]**
Total events: 69 (gestrinone), 37 (danazol)					
Heterogeneity: Tau^2=0; Chi^2=2.88, df=1(P=0.09); I^2=65.27%					
Test for overall effect: Z=4(P<0.0001)					
4.4.3 Hirsutism					
Bromham 1995	68/130	36/134		87.4%	2.99[1.79,4.99]
Fedele 1989	0/19	2/19		12.6%	0.18[0.01,4]
Subtotal (95% CI)	**149**	**153**		**100%**	**2.63[1.6,4.32]**
Total events: 68 (gestrinone), 38 (danazol)					
Heterogeneity: Tau^2=0; Chi^2=3.11, df=1(P=0.08); I^2=67.8%					
Test for overall effect: Z=3.83(P=0)					
4.4.4 Voice problems					
Bromham 1995	14/130	19/134		91.95%	0.73[0.35,1.53]
Fedele 1989	0/19	1/19		8.05%	0.32[0.01,8.26]
Subtotal (95% CI)	**149**	**153**		**100%**	**0.7[0.34,1.43]**
Total events: 14 (gestrinone), 20 (danazol)					
Heterogeneity: Tau^2=0; Chi^2=0.24, df=1(P=0.62); I^2=0%					
Test for overall effect: Z=0.99(P=0.32)					
4.4.5 Swelling hands/feet					



Favours gestrinone | Favours danazol







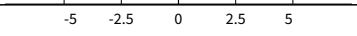
Comparison 5. Gestrinone versus leuprolin for six months: efficacy and side effects

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Painful periods, visual analogue scale	1	55	Mean Difference (IV, Fixed, 95% CI)	0.82 [0.15, 1.49]
2 Painful periods, verbal rating scale	1	55	Mean Difference (IV, Fixed, 95% CI)	0.35 [0.12, 0.58]
3 Pain on intercourse, visual analogue scale	1	52	Mean Difference (IV, Fixed, 95% CI)	-1.16 [-2.08, -0.24]
4 Pain on intercourse, verbal rating scale	1	52	Mean Difference (IV, Fixed, 95% CI)	-0.33 [-0.62, -0.04]
5 Non-menstrual pain, visual analogue scale	1	55	Mean Difference (IV, Fixed, 95% CI)	-0.41 [-1.76, 0.94]
6 Side effects	1	813	Odds Ratio (M-H, Fixed, 95% CI)	0.65 [0.42, 1.01]
6.1 Seborrhoea	1	55	Odds Ratio (M-H, Fixed, 95% CI)	3.23 [0.13, 82.71]
6.2 Swelling hands/feet	1	55	Odds Ratio (M-H, Fixed, 95% CI)	5.59 [0.26, 121.96]
6.3 Hot flushes	1	55	Odds Ratio (M-H, Fixed, 95% CI)	0.20 [0.06, 0.63]
6.4 Leg or muscle cramps	1	55	Odds Ratio (M-H, Fixed, 95% CI)	0.33 [0.01, 8.55]
6.5 Headache	1	55	Odds Ratio (M-H, Fixed, 95% CI)	0.20 [0.06, 0.63]
6.6 Nausea	1	55	Odds Ratio (M-H, Fixed, 95% CI)	1.04 [0.06, 17.49]
6.7 Dizziness	1	55	Odds Ratio (M-H, Fixed, 95% CI)	2.16 [0.18, 25.32]
6.8 Skin rash	1	55	Odds Ratio (M-H, Fixed, 95% CI)	3.23 [0.13, 82.71]
6.9 Vaginal dryness	1	55	Odds Ratio (M-H, Fixed, 95% CI)	0.19 [0.01, 4.21]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6.10 Mood changes	1	55	Odds Ratio (M-H, Fixed, 95% CI)	0.67 [0.10, 4.34]
6.11 Joint pain	1	55	Odds Ratio (M-H, Fixed, 95% CI)	2.16 [0.18, 25.32]
6.12 Drowsiness	1	55	Odds Ratio (M-H, Fixed, 95% CI)	2.16 [0.18, 25.32]
6.13 Tachycardia	1	55	Odds Ratio (M-H, Fixed, 95% CI)	1.04 [0.06, 17.49]
6.14 Amenorrhoea	1	49	Odds Ratio (M-H, Fixed, 95% CI)	0.04 [0.01, 0.38]
6.15 Spotting or bleeding	1	49	Odds Ratio (M-H, Fixed, 95% CI)	22.92 [2.64, 198.66]

Analysis 5.1. Comparison 5 Gestrinone versus leuprolin for six months: efficacy and side effects, Outcome 1 Painful periods, visual analogue scale.

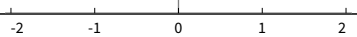
Study or subgroup	gestrinone N	gestrinone Mean(SD)	leuprolin N	leuprolin Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
GISG 1996	27	0.9 (1.8)	28	0.1 (0.2)		100%	0.82[0.15,1.49]
Total ***	**27**		**28**			**100%**	**0.82[0.15,1.49]**
Heterogeneity: Not applicable							
Test for overall effect: Z=2.39(P=0.02)							



Favours gestrinone — Favours leuprolin

Analysis 5.2. Comparison 5 Gestrinone versus leuprolin for six months: efficacy and side effects, Outcome 2 Painful periods, verbal rating scale.

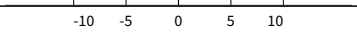
Study or subgroup	gestrinone N	gestrinone Mean(SD)	leuprolin N	leuprolin Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
GISG 1996	27	0.4 (0.6)	28	0 (0.2)		100%	0.35[0.12,0.58]
Total ***	**27**		**28**			**100%**	**0.35[0.12,0.58]**
Heterogeneity: Not applicable							
Test for overall effect: Z=2.97(P=0)							



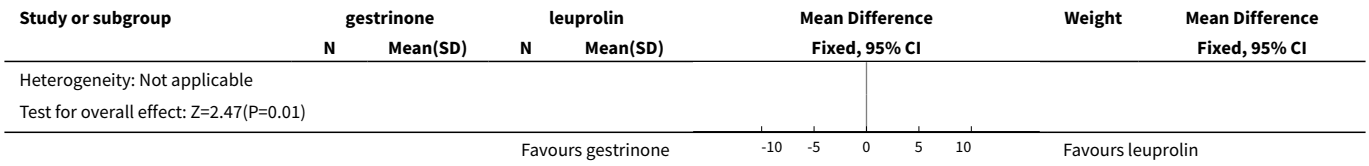
Favours gestrinone — Favours leuprolin

Analysis 5.3. Comparison 5 Gestrinone versus leuprolin for six months: efficacy and side effects, Outcome 3 Pain on intercourse, visual analogue scale.

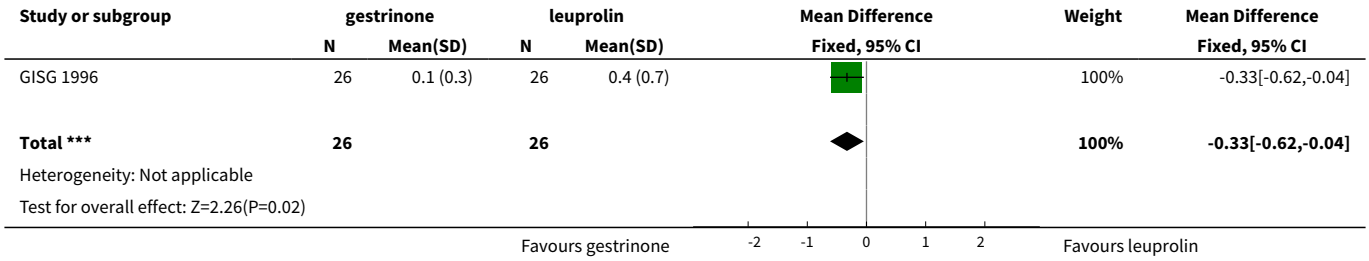
Study or subgroup	gestrinone N	gestrinone Mean(SD)	leuprolin N	leuprolin Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
GISG 1996	26	0.4 (1.1)	26	1.6 (2.1)		100%	-1.16[-2.08,-0.24]
Total ***	**26**		**26**			**100%**	**-1.16[-2.08,-0.24]**



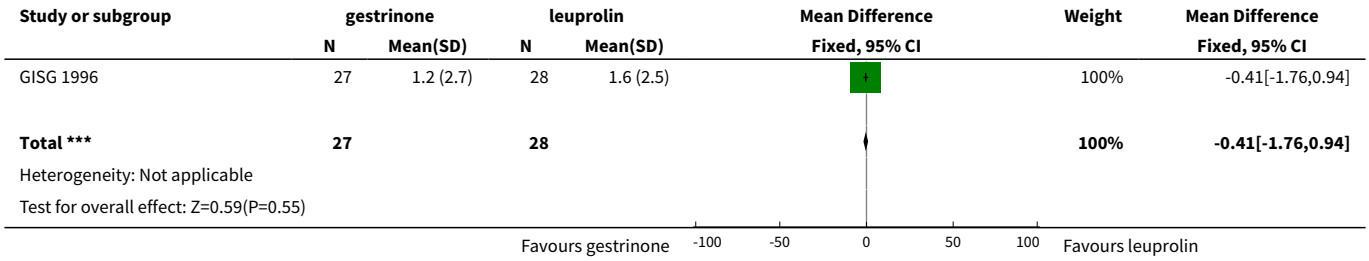
Favours gestrinone — Favours leuprolin



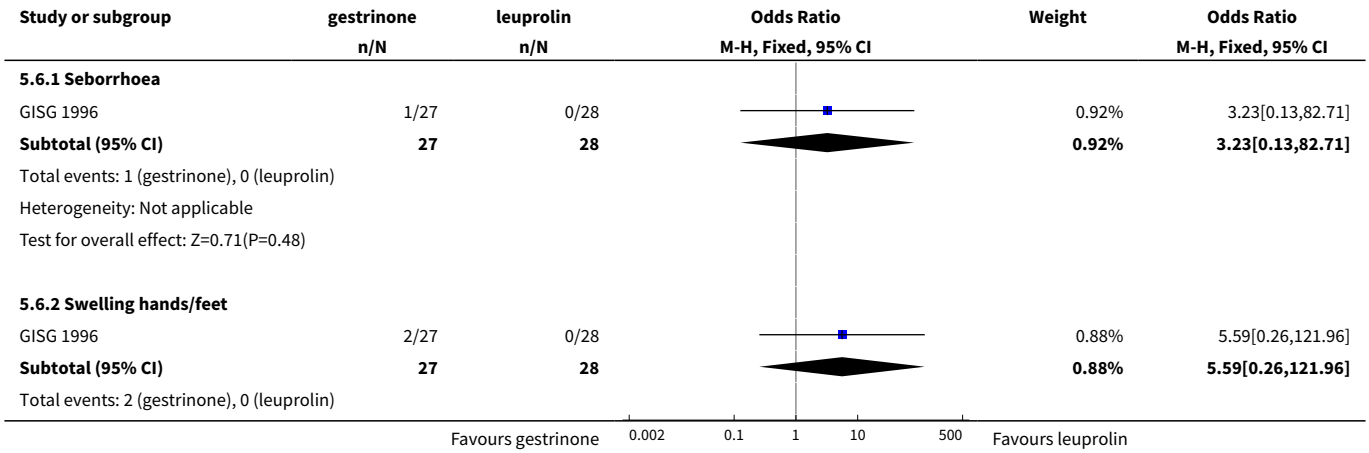
Analysis 5.4. Comparison 5 Gestrinone versus leuprolin for six months: efficacy and side effects, Outcome 4 Pain on intercourse, verbal rating scale.



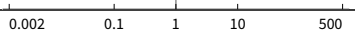
Analysis 5.5. Comparison 5 Gestrinone versus leuprolin for six months: efficacy and side effects, Outcome 5 Non-menstrual pain, visual analogue scale.

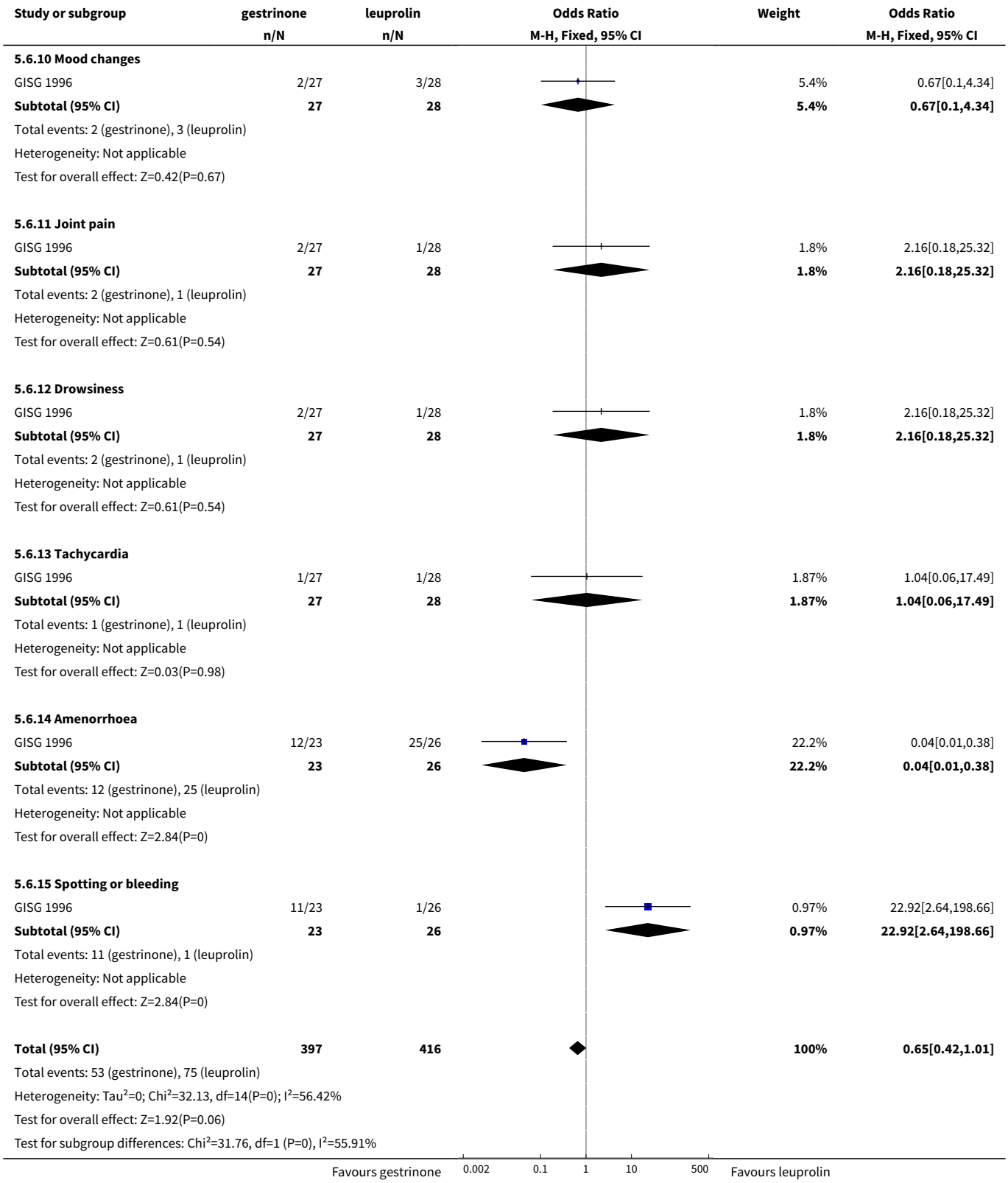


Analysis 5.6. Comparison 5 Gestrinone versus leuprolin for six months: efficacy and side effects, Outcome 6 Side effects.



Study or subgroup	gestrinone n/N	leuprolin n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
Heterogeneity: Not applicable					
Test for overall effect: Z=1.09(P=0.27)					
5.6.3 Hot flushes					
GISG 1996	8/27	19/28		25.97%	0.2[0.06,0.63]
Subtotal (95% CI)	**27**	**28**		**25.97%**	**0.2[0.06,0.63]**
Total events: 8 (gestrinone), 19 (leuprolin)					
Heterogeneity: Not applicable					
Test for overall effect: Z=2.76(P=0.01)					
5.6.4 Leg or muscle cramps					
GISG 1996	0/27	1/28		2.86%	0.33[0.01,8.55]
Subtotal (95% CI)	**27**	**28**		**2.86%**	**0.33[0.01,8.55]**
Total events: 0 (gestrinone), 1 (leuprolin)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.66(P=0.51)					
5.6.5 Headache					
GISG 1996	8/27	19/28		25.97%	0.2[0.06,0.63]
Subtotal (95% CI)	**27**	**28**		**25.97%**	**0.2[0.06,0.63]**
Total events: 8 (gestrinone), 19 (leuprolin)					
Heterogeneity: Not applicable					
Test for overall effect: Z=2.76(P=0.01)					
5.6.6 Nausea					
GISG 1996	1/27	1/28		1.87%	1.04[0.06,17.49]
Subtotal (95% CI)	**27**	**28**		**1.87%**	**1.04[0.06,17.49]**
Total events: 1 (gestrinone), 1 (leuprolin)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.03(P=0.98)					
5.6.7 Dizziness					
GISG 1996	2/27	1/28		1.8%	2.16[0.18,25.32]
Subtotal (95% CI)	**27**	**28**		**1.8%**	**2.16[0.18,25.32]**
Total events: 2 (gestrinone), 1 (leuprolin)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.61(P=0.54)					
5.6.8 Skin rash					
GISG 1996	1/27	0/28		0.92%	3.23[0.13,82.71]
Subtotal (95% CI)	**27**	**28**		**0.92%**	**3.23[0.13,82.71]**
Total events: 1 (gestrinone), 0 (leuprolin)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.71(P=0.48)					
5.6.9 Vaginal dryness					
GISG 1996	0/27	2/28		4.77%	0.19[0.01,4.21]
Subtotal (95% CI)	**27**	**28**		**4.77%**	**0.19[0.01,4.21]**
Total events: 0 (gestrinone), 2 (leuprolin)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.05(P=0.3)					

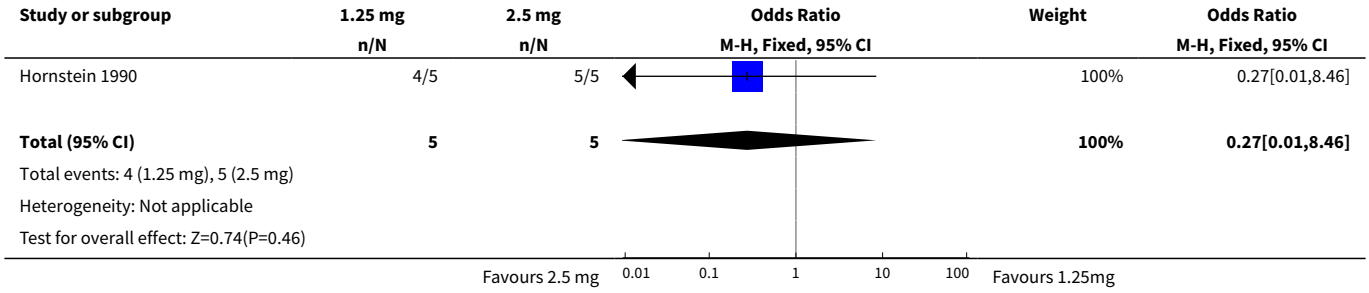




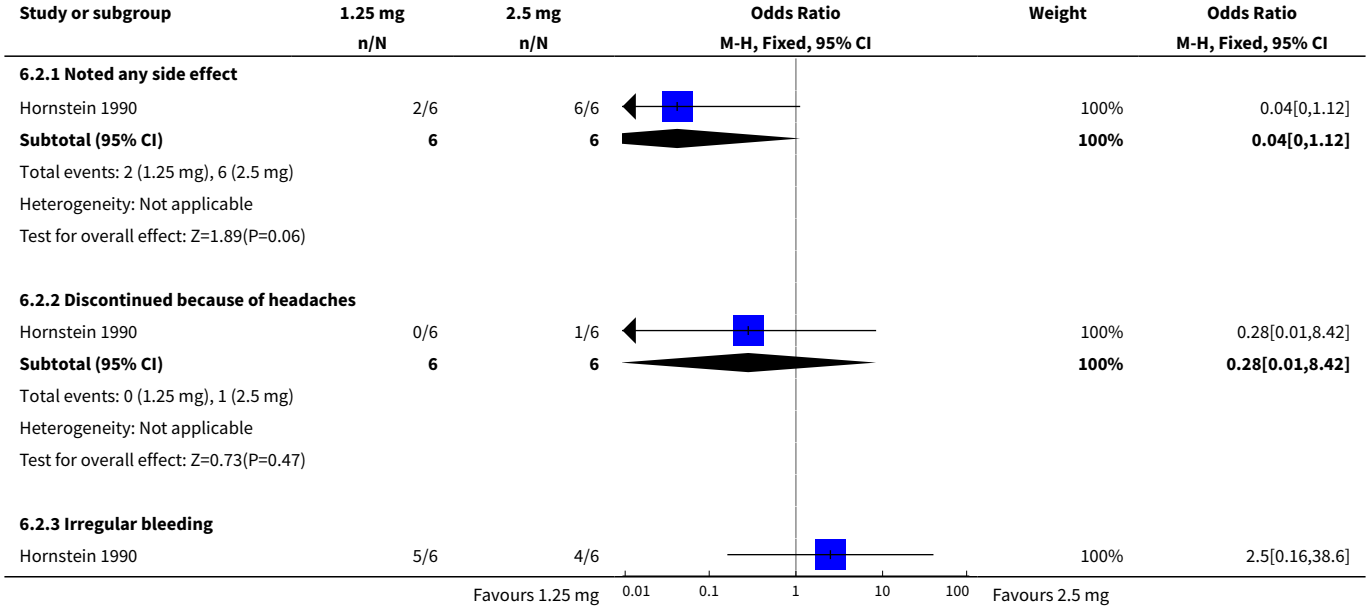
Comparison 6. Gestrinone 1.25 mg versus gestrinone 2.5 mg: efficacy and side effects

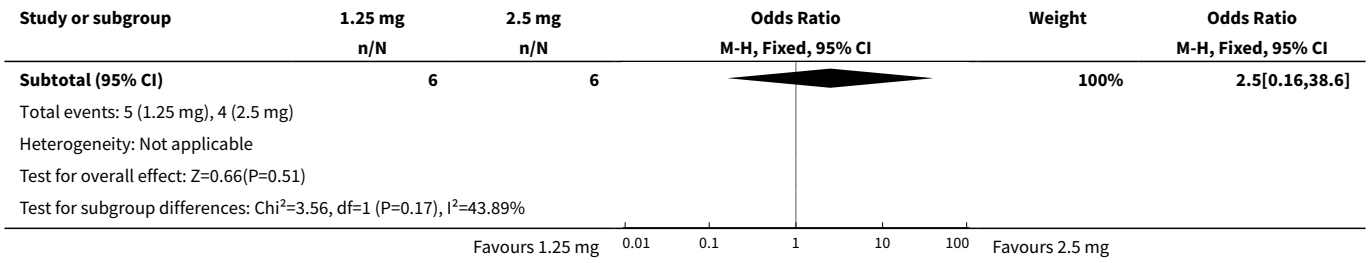
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 improvement in pain	1	10	Odds Ratio (M-H, Fixed, 95% CI)	0.27 [0.01, 8.46]
2 Side effect	1		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 Noted any side effect	1	12	Odds Ratio (M-H, Fixed, 95% CI)	0.04 [0.00, 1.12]
2.2 Discontinued because of headaches	1	12	Odds Ratio (M-H, Fixed, 95% CI)	0.28 [0.01, 8.42]
2.3 Irregular bleeding	1	12	Odds Ratio (M-H, Fixed, 95% CI)	2.5 [0.16, 38.60]

Analysis 6.1. Comparison 6 Gestrinone 1.25 mg versus gestrinone 2.5 mg: efficacy and side effects, Outcome 1 improvement in pain.



Analysis 6.2. Comparison 6 Gestrinone 1.25 mg versus gestrinone 2.5 mg: efficacy and side effects, Outcome 2 Side effect.





ADDITIONAL TABLES

Table 1. Data unsuitable for analysis

Outcome	Study	Comparison	Measure	Int group	Control group	P value
Combined non-pelvic pain, dysmenorrhoea, and dyspareunia	Chwalisz 2004	Asoprisnil: 5 mg (n = 31), 10 mg (n = 33), 25 mg (n = 32) Placebo (n = 34)	Mean reduction at 3 months on 0-4 pain scale	0.5 points for each dose	< 0.1 points	< 0.05

APPENDICES

Appendix 1. Cochrane Gynaecology and Fertility Group specialised register search strategy

From inception to 28 November 2016

Procite platform

Keywords CONTAINS "endometriosis" or "Endometriosis-Symptoms" or "pelvic pain" or "dyspareunia" or Title CONTAINS "endometriosis" or "Endometriosis-Symptoms" or "pelvic pain" or "dyspareunia"

AND

Keywords CONTAINS "mifepristone"or"RU486"or"gestrinone"or"Onapristone" or "asoprisnil" or "CBD 2914" or "CDB-2914" or "CDB-4124" or "Ulipristal" or "ulipristal acetate" or "progestagen receptor levels" or" progesterone receptor agonist" or "Progesterone Receptor Modulator" or "selective progesterone receptor modulator" or Title CONTAINS "mifepristone"or"RU486"or"gestrinone"or"Onapristone" or "asoprisnil" or "CBD 2914" or "CDB-2914" or "CDB-4124" or "Ulipristal" or "ulipristal acetate" or "progestagen receptor levels" or" progesterone receptor agonist" or "Progesterone Receptor Modulator" or "selective progesterone receptor modulator" (44 hits)

Appendix 2. CENTRAL CRSO search strategy

Searched 28 November 2016

Web platform

#1 MESH DESCRIPTOR Endometriosis EXPLODE ALL TREES 513

#2 Endometrio*:TI,AB,KY 1289

#3 (pelvi* pain):TI,AB,KY 878

#4 #1 OR #2 OR #3 1934

#5 MESH DESCRIPTOR Mifepristone EXPLODE ALL TREES 376

#6 mifepristone:TI,AB,KY 714

#7 RU486:TI,AB,KY 47

#8 (progest* adj1 antagonist*):TI,AB,KY 68

#9 (progest* adj1 modulator*):TI,AB,KY 33

#10 (ru 486 or ru486):TI,AB,KY 143

#11 ru38486:TI,AB,KY 5

#12 ru-38486:TI,AB,KY 1

#13 MESH DESCRIPTOR Gestrinone EXPLODE ALL TREES 29

#14 Gestrinone:TI,AB,KY 58

#15 Onapristone:TI,AB,KY 9

#16 Aglepristone:TI,AB,KY 2

#17 anti-progestin*:TI,AB,KY 2

#18 antiprogestin*:TI,AB,KY 47

#19 Asoprisnil:TI,AB,KY 10

#20 J867:TI,AB,KY 1

#21 Telapristone:TI,AB,KY 1

#22 CDB-2914:TI,AB,KY 9

#23 Ulipristal:TI,AB,KY 37

#24 (SPRM* or PRAs or PRA):TI,AB,KY 788

#25 MESH DESCRIPTOR Receptors, Progesterone EXPLODE ALL TREES WITH QUALIFIERS AD,AG,AI,ME,TU 159

#26 #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 1782

#27 #4 AND #26 65

Appendix 3. MEDLINE search strategy

From 1946 to 28 November 2016

Ovid platform

1 exp Endometriosis/ (19876)
2 Endometri$.tw. (84071)
3 exp Dyspareunia/ (1809)
4 Dyspareunia.tw. (3194)
5 pelvi$ pain.tw. (7650)
6 or/1-5 (95322)
7 exp Mifepristone/ (5981)
8 mifepristone.tw. (3252)
9 RU486.tw. (2312)
10 (progest$ adj1 antagonist$).tw. (512)
11 (progest$ adj1 modulator$).tw. (11)
12 ru 486.tw. (1780)
13 mifegyne.tw. (13)
14 ru38486.tw. (409)
15 ru-38486.tw. (465)
16 mifeprex.tw. (12)
17 r38486.tw. (1)
18 exp Gestrinone/ (198)
19 Gestrinone.tw. (192)
20 Lilopristone.tw. (20)
21 Onapristone.tw. (187)
22 Aglepristone.tw. (82)
23 (dimetriose or dimetrose).tw. (1)
24 Nemestran.tw. (4)
25 anti-progestin$.tw. (151)
26 antiprogestin$.tw. (935)
27 Asoprisnil.tw. (47)
28 J867.tw. (13)
29 Telapristone.tw. (9)
30 CDB-2914.tw. (48)
31 CDB-4124.tw. (19)
32 Proellex.tw. (8)
33 Ulipristal.tw. (254)
34 (SPRM$ or PRAs).tw. (340)
35 exp Receptors, Progesterone/me, tu [Metabolism, Therapeutic Use] (9329)
36 or/7-35 (18327)
37 6 and 36 (2106)
38 randomized controlled trial.pt. (469810)
39 controlled clinical trial.pt. (95074)
40 randomized.ab. (404455)
41 randomised.ab. (81254)
42 placebo.tw. (197050)
43 clinical trials as topic.sh. (189502)
44 randomly.ab. (285441)
45 trial.ti. (178951)

46 (crossover or cross-over or cross over).tw. (76010)
47 or/38-46 (1208254)
48 exp animals/ not humans.sh. (4669479)
49 47 not 48 (1114154)
50 37 and 49 (212)

Appendix 4. Embase search strategy

From 1980 to 28 November 2016

Ovid platform

1 exp endometriosis/ (30876)
2 Endometri$.tw. (104349)
3 Dyspareunia.tw. (5475)
4 pelvi$ pain.tw. (11229)
5 or/1-4 (120810)
6 exp mifepristone/ (11579)
7 mifepristone.tw. (3888)
8 RU486.tw. (2483)
9 (progest$ adj1 antagonist$).tw. (521)
10 exp antigestagen/ (12402)
11 (progest$ adj1 modulator$).tw. (18)
12 exp progesterone receptor modulator/ (586)
13 ru 486.tw. (4148)
14 mifegyne.tw. (181)
15 ru38486.tw. (406)
16 ru-38486.tw. (913)
17 mifeprex.tw. (111)
18 zk 98296.tw. (3)
19 r38486.tw. (1)
20 exp GESTRINONE/ (621)
21 Gestrinone.tw. (204)
22 Lilopristone.tw. (22)
23 Onapristone.tw. (216)
24 Aglepristone.tw. (80)
25 (dimetriose or dimetrose).tw. (14)
26 Nemestran.tw. (11)
27 anti-progestin$.tw. (178)
28 antiprogestin$.tw. (968)
29 Asoprisnil.tw. (63)
30 J867.tw. (15)
31 Telapristone.tw. (16)
32 CDB-2914.tw. (106)
33 CDB-4124.tw. (47)
34 Proellex.tw. (22)
35 Ulipristal.tw. (466)
36 (SPRM$ or PRAs).tw. (596)
37 exp progesterone receptor/dt, pd [Drug Therapy, Pharmacology] (65)
38 or/6-37 (14686)
39 5 and 38 (1698)
40 Clinical Trial/ (995452)
41 Randomized Controlled Trial/ (461742)
42 exp randomization/ (83639)
43 Single Blind Procedure/ (27251)
44 Double Blind Procedure/ (136941)
45 Crossover Procedure/ (53825)
46 Placebo/ (321968)
47 Randomi?ed controlled trial$.tw. (149359)
48 Rct.tw. (22353)
49 random allocation.tw. (1629)
50 randomly.tw. (338581)
51 randomly allocated.tw. (26583)

52 allocated randomly.tw. (2208)
53 (allocated adj2 random).tw. (843)
54 Single blind$.tw. (18663)
55 Double blind$.tw. (172862)
56 ((treble or triple) adj blind$).tw. (647)
57 placebo$.tw. (247461)
58 prospective study/ (386445)
59 or/40-58 (1967839)
60 case study/ (92866)
61 case report.tw. (323319)
62 abstract report/ or letter/ (986309)
63 or/60-62 (1393358)
64 59 not 63 (1916879)
65 (exp animal/ or animal.hw. or nonhuman/) not (exp human/ or human cell/ or (human or humans).ti.) (5725014)
66 64 not 65 (1793800)
67 39 and 66 (434)

Appendix 5. PsycINFO search strategy

From 1806 to 28 November 2016

Ovid platform

1 exp Dyspareunia/ (240)
2 Dyspareunia.tw. (528)
3 Endometriosis.tw. (209)
4 pelvi$ pain.tw. (489)
5 or/1-4 (1140)
6 mifepristone.tw. (226)
7 RU486.tw. (159)
8 ru 486.tw. (88)
9 Gestrinone.tw. (0)
10 anti-progestin$.tw. (4)
11 antiprogestin$.tw. (18)
12 (progest$ adj1 antagonist$).tw. (19)
13 Ulipristal.tw. (3)
14 SPRM$.tw. (3)
15 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 (434)
16 5 and 15 (3)
17 random.tw. (48413)
18 control.tw. (375365)
19 double-blind.tw. (20296)
20 clinical trials/ (10020)
21 placebo/ (4732)
22 exp Treatment/ (669135)
23 or/17-22 (1033445)
24 16 and 23 (1)

CONTRIBUTIONS OF AUTHORS

Selection of studies: JF, YW, MZ, HZ.

Data extraction and management: JF, HZ.

Assessment of risk of bias in included studies: JF, HS.

Consultation: WH.

Review writing: JF, HC.

DECLARATIONS OF INTEREST

JF, HS, MZ, HZ, YW, HC and WH have no interests to declare.

SOURCES OF SUPPORT

Internal sources

- None, Other.

External sources

- None, Other.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Change to title

Upon consultation with the Cochrane Gynaecology and Fertility Group, we changed the title of this review from "Progesterone receptor antagonists and progesterone receptor modulators for endometriosis" to "Progesterone receptor modulators for endometriosis" as PRMs include PRA and SPRM. We added "asoprisnil" or "CBD 2914" or "CDB-2914" or "CDB-4124" or "Ulipristal" or "ulipristal acetate" to the search strategies.

Change to objectives

We edited the objectives to make it clear that comparisons with no treatment or with placebo were eligible for the review, as this was unclear from objectives stated in the protocol.

Change to types of interventions in the methods

We edited the types of interventions section to make it clear that surgical interventions were not eligible.

We added decreases in dysmenorrhoea and dyspareunia to the primary outcomes, as these are the types of endometriosis pain reported in most reports.

We added dose or regimen comparisons of PRMs. This was previously a subgroup analysis, but we wished to allow inclusion of studies in which this was the main comparison.

Change to data synthesis

We removed progesterone receptor antagonists because they are a type of progesterone receptor modulator. We added dose or regimen comparisons of PRMs as a main comparison.

We edited the data synthesis section to make it clear that surgical interventions were not eligible.

Change to subgroup analysis and investigation of heterogeneity

As the data synthesis section states that different comparisons will be made for different drugs, we kept 'different course or dosage' in the subgroup and deleted 'different drug'.

Change to types of outcome measures

The protocol stated that pain scores would be used to measure the primary outcome, and this was our preferred measure. However, we also included other pain-related data if reported by the included studies because we determined that this type of measure would be informative.

Change to measures of treatment effect

The protocol stated that Peto odds ratios would be calculated. Instead, we used Mantel-Haenszel odds ratios, as Peto odds ratios are not recommended as a default approach for meta-analysis (Higgins 2011).

INDEX TERMS

Medical Subject Headings (MeSH)

Danazol [therapeutic use]; Dysmenorrhea [drug therapy] [epidemiology]; Dyspareunia [drug therapy] [epidemiology]; Endometriosis [*drug therapy]; Estrenes [therapeutic use]; Gestrinone [adverse effects] [therapeutic use]; Gonadotropin-Releasing Hormone [analogs & derivatives]; Hormone Antagonists [administration & dosage] [adverse effects] [*therapeutic use]; Leuprolide [adverse effects] [therapeutic use]; Mifepristone [administration & dosage] [adverse effects] [*therapeutic use]; Norpregnadienes [therapeutic use]; Oximes [therapeutic use]; Prevalence; Randomized Controlled Trials as Topic; Receptors, Progesterone [*antagonists & inhibitors]

MeSH check words

Female; Humans