Danazol for pelvic pain associated with endometriosis (Review)

Farquhar C, Prentice A, Singla AA, Selak V

This is a reprint of a Cochrane review, prepared and maintained by The Cochrane Collaboration and published in *The Cochrane Library* 2007, Issue 4

http://www.thecochranelibrary.com

WILEY

TABLE OF CONTENTS

[Intervention Review]

Danazol for pelvic pain associated with endometriosis

Cindy Farquhar[1], Andrew Prentice[2], Amita A Singla[3], Vanessa Selak[4]

[1]Obstetrics and Gynaecology, University of Auckland, Auckland, New Zealand. [2]Department of Obstetrics and Gynaecology, Rosie Maternity Hospital, Cambridge, UK. [3]Department of Obstetrics & Gynaecology, The Queen Elizabeth Hospital, Adelaide, Australia. [4]Waitemata District Health Board, Level 1, 15 Shea Terrace, Auckland, New Zealand

Contact address: Cindy Farquhar, Obstetrics and Gynaecology, University of Auckland, FMHS Park Road, Grafton, Auckland, 1003, New Zealand. c.farquhar@auckland.ac.nz.

Editorial group: Cochrane Gynaecology and Fertility Group.
Publication status and date: Stable (no update expected for reasons given in 'What's new'), published in Issue 11, 2010.
Review content assessed as up-to-date: 14 June 2007.

Citation: Farquhar C, Prentice A, Singla AA, Selak V. Danazol for pelvic pain associated with endometriosis. *Cochrane Database of Systematic Reviews* 2007, Issue 4. Art. No.: CD000068. DOI: 10.1002/14651858.CD000068.pub2.

ABSTRACT

Background

Endometriosis is defined as the presence of endometrial tissue (stromal and glandular) outside the normal uterine cavity. Conventional medical and surgical treatments for endometriosis aim to remove or decrease the deposits of ectopic endometrium. The observation that hyper androgenic states (an excess of male hormone) induce atrophy of the endometrium has led to the use of androgens in the treatment of endometriosis. Danazol is one of these treatments. The efficacy of danazol is based on its ability to produce a high androgen and low oestrogen environment (a pseudo menopause) which results in atrophy of the endometriotic implants and thus an improvement in painful symptoms.

Objectives

To determine the effectiveness of danazol compared to placebo or no treatment in the treatment of the symptoms and signs, other than infertility, of endometriosis in women of reproductive age.

Search methods

We searched the Cochrane Menstrual Disorders and Subfertility Group Specialised Register of trials (searched April 2007), the Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library Issue 2, 2007), and MEDLINE (1966 to April 2007). In addition, all reference lists of included trials were searched, and relevant drug companies were contacted for details of unpublished trials.

Selection criteria

Randomised controlled trials in which danazol (alone or as adjunctive therapy) was compared to placebo or no therapy. Trials which only reported infertility outcomes were excluded.

Data collection and analysis

Only five trials met the inclusion criteria and two authors independently extracted data from these trials. All trials compared danazol to placebo. Three trials used danazol as sole therapy and three trials used danazol as an adjunct to surgery. Although the main outcome was pain improvement other data relating to laparoscopic scores and hormonal parameters were also collected.

Main results

Treatment with danazol (including adjunctive to surgical therapy) was effective in relieving painful symptoms related to endometriosis when compared to placebo. Laparoscopic scores were improved with danazol treatment (including as adjunctive therapy) when compared with either placebo or no treatment. Side effects were more commonly reported in those patients receiving danazol than for placebo.

Authors' conclusions

Danazol is effective in treating the symptoms and signs of endometriosis. However, its use is limited by the occurrence of androgenic side effects.

PLAIN LANGUAGE SUMMARY

Danazol for pelvic pain associated with endometriosis

Danazol reduces the painful symptoms of endometriosis but has androgenic effects. Endometriosis is a painful condition where endometrial tissue grows outside the uterus. It can cause cysts and infertility. Danazol is a hormone that produces male characteristics as well as weight gain and acne. It does, however, relieve the painful symptoms of endometriosis, although the side effects can be unacceptable. The improvement was still present six months after treatment was stopped. There was some evidence that women who took danazol were satisfied with the treatment compared with women who had inactive treatment.

BACKGROUND

Endometriosis is a common gynaecological condition affecting women in their reproductive years. Endometriosis is defined as the presence of endometrial tissue (stromal and glandular) outside the normal uterine cavity. The condition presents most commonly with symptoms of pelvic pain or infertility, or both, or the presence of an endometriotic cyst (Barbieri 1990).

The development of endometriosis remains unclear. It is probable that endometriosis arises by the dissemination of endometrium to other sites, either by retrograde menstruation or by lymphatic and haemato genous routes, where they are subsequently established as deposits of ectopic endometrium (McLaren 1996). It is assumed that the presence of these ectopic deposits gives rise to the symptoms associated with the condition (Rock 1992).

Conventional medical and surgical treatments for endometriosis aim to remove or decrease deposits of ectopic endometrium. They achieve this either by inducing atrophy within the hormonally dependent ectopic endometrium or by destroying the endometriotic implant. Surgery is also used to alleviate painful symptoms by dividing adhesions and interrupting neural pathways.

The observation that hyper androgenic states (an excess of male hormone) induce atrophy of the endometrium has led to the use of androgens in the treatment of endometriosis (Barbieri 1990). Androgens are steroid hormones that promote male characteristics. One such androgen is danazol, a synthetic isoxazole derivative chemically related to 17-ethinyl testosterone. Danazol has a complex mechanism of action. The effects of danazol are due to its inherent androgenic properties and its ability to increase the concentration of free testosterone by binding to sex hormone-binding globulin (the concentration of which is decreased by danazol) to displace testosterone. Furthermore, danazol inhibits steroid production in the ovary, resulting in a decrease in ovarian oestrogen production (Barbieri 1977). In addition, danazol interferes with follicle stimulating hormone (FSH) and luteinizing hormone (LH) secretion by the pituitary. Danazol also has a specific inhibitory effect upon endometrial growth. Thus, the efficacy of danazol is based on its ability to produce a high androgen and low oestrogen environment (a pseudo menopause) which results in the atrophy of endometriotic implants and thus an improvement in painful symptoms (Barbieri 1990).

The cost of endometriosis is high in both economic and human terms. Treatment that is available is dependent not only upon available resources but also upon the preference and skills of the individual gynaecologist. This review aims to evaluate the role of danazol in the treatment of endometriosis.

OBJECTIVES

To determine the effectiveness of danazol compared to placebo or

no treatment the treatment of painful symptoms associated with endometriosis in women of reproductive age.

The effect of danazol on fertility in women with endometriosis is dealt with in another review (Hughes 2007).

METHODS

Criteria for considering studies for this review

Types of studies

All randomised controlled trials (RCT's) of the use of danazol in the treatment of endometriosis in women of reproductive age.

Types of participants

This review considered studies that included women of reproductive age with the diagnosis of endometriosis made by direct visualisation (laparoscopy or laparotomy). This included patients who were asymptomatic and where endometriosis was an incidental finding. In such patients, symptoms were obviously not one of the studied outcomes but American Fertility Society (AFS) scores and side effects were studied. Studies of women who had undergone surgery and were given postoperative medical therapy were also included (see also the review on postoperative medical therapy by Yap 2004). Quasi-randomised trials were not included in this review.

Studies in any appropriate care setting (secondary or tertiary) were considered.

Types of interventions

Studies were included that compared danazol, as sole or adjunctive therapy, with placebo or no treatment. Any dosage or duration of treatment was included. Studies in which surgery may have been performed at the time of initial diagnosis were analysed separately. The review did not consider comparison of danazol with the following:

- gonadotrophin releasing hormone (GnRH) agonists;
- progestogen;
- progestogens and oestrogen;
- the surgical treatments of ablation or excision of endometriotic deposits;
- surgical treatments involving removal of pelvic organs (e.g. hysterectomy);
- treatments that attempt to interrupt neural pathways (e.g. LUNA or presacral neurectomy);
- alternative or complementary therapies.

Types of outcome measures

Both subjective and objective outcome measures were considered. Outcome measures were considered both during and at the end of treatment as well as after a drug-free period.

Subjective relief of any or all of the symptoms or signs listed below were considered using both quantitative measures such as visual analogue scales; or qualitative measures such as symptom free, better, the same or worse.

Objective evaluation of improvement of endometriotic implants was assessed by the American Fertility Society (AFS) classification of endometriosis (AFS 1979). A distinction was made between those studies where repeat laparoscopy occurred during treatment and studies that repeated the laparoscopy after treatment.

Other outcome measures that were considered included side effects (listed below) both in the short term during therapy and long term extending beyond the treatment period.

Compliance with therapy and withdrawal from studies due to side effects were also considered, as was recurrence of the disease (symptoms, signs and laparoscopic evidence of disease).

The symptoms and signs considered were as follows.

(1) Symptoms

(a) Major - pain

(i) general or a total pain score
(ii) dysmenorrhoea
(iii) pelvic
(iv) dyspareunia
(v) defecation or dysuria
(vi) low back

(b) Minor

Any other symptom ascribed to endometriosis and studied in any relevant trial were to be considered

(2) Signs

(a) Major

(i) pelvic tenderness
(ii) induration

(b) Minor

(i) beading nodularity and tenderness of uterosacral ligaments on vaginal examination
(ii) palpable adnexal masses
(iii) uterus - position and fixity

(3) Adverse effects

(a) Major

(i) hypo estrogenic (low oestrogen levels) including decreased breast size, atrophic vaginitis, hot flushes, emotional lability, vaginal dryness, changes in libido
(ii) androgenic (excess male hormone) including weight gain, oedema, muscle cramps, acne, oily skin, sweating, deepening of voice, hirsutism

(b) Other

(i) nausea

(ii) headaches
(iii) dizziness
(iv) fatigue
(v) depression
(vi) nervousness
(vii) insomnia
(viii) skin rash
(ix) abnormal bleeding pattern

Search methods for identification of studies

(1) We searched the Menstrual Disorders and Subfertility Group Specialised Register for any trials (searched April 2007). See Review Group for more details on the make up of this Specialised Register.
(2) The Cochrane Central Register of Controlled Trials (CENTRAL) on The Cochrane Library 2007, Issue 3 was searched in all fields.
(3) The following databases were searched see Appendix 1.
(4) The citation lists of relevant publications, review articles, and included studies were also searched.
(5) All UK distributors of danazol were approached for details of unpublished trials of danazol as known to or undertaken by them or their parent companies.

Data collection and analysis

The assessment of the quality of trials identified by the search strategy was undertaken by two of the review authors who were unblinded to the source of the studies. Where uncertainty existed regarding suitability for inclusion, or where discrepancy existed between the two review authors, a third review author made a further assessment. Authors were contacted to determine pre-publishing data manipulation (such as exclusion of patients from the final analysis), method of allocation concealment and to provide additional data, if required. The quality of trials for inclusion was assessed using a standard checklist developed by the Review Group. The quality of allocation concealment was graded as either A (adequate), B (unclear) or C (inadequate). For all trials included, the following information was collected: the method of randomisation, allocation concealment, blinding, the possibility of performing an intention-to-treat analysis, the intended interventions and the outcomes measured.
Data was extracted by two assessors who were unblinded. One of the assessors was an expert in the content matter. For data extraction, forms developed according to Cochrane guidelines were utilised. Attempts were made to contact the appropriate author(s) to obtain data if these were presented in a graphical form only in the trial reports. If these attempts failed, data were extracted directly from the graphs by two assessors.
Statistical analysis was performed in accordance with the guidelines for statistical analysis developed by the Cochrane Collaboration and in the Cochrane Handbook for Systematic Reviews of Interventions. Heterogeneity between the results of different studies was examined by inspecting the scatter in the data points, the overlap in their confidence intervals and, more formally, by checking the results of the chi-squared tests and the I-squared value. A priori, it was planned to look at the postoperative studies separately.
Where possible, the outcomes were pooled statistically. For dichotomous data (for example, proportion of patients with a specific adverse side effect) results for each study were expressed as a relative risk (RR) with 95% confidence intervals (CI) and combined for meta-analysis with RevMan software using the Peto-modified Mantel-Haenszel method.
Continuous differences between groups in the meta-analysis (for example, multidimensional pain scores) were shown as weighted mean difference (WMD) and 95% confidence interval (CI). A fixed-effect approach was used unless there was significant heterogeneity as determined by Chi-squared test or the I-squared value, in which case results were investigated using a random-effects statistical model. Sources of heterogeneity were investigated as stated above.
It is unlikely that further RCTs of danazol will be undertaken and further updates are not planned unless new studies are reported.

RESULTS

Description of studies

Five trials were identified which met the inclusion criteria, but three of these were subsequently excluded because the outcomes that were published related to infertility only. The possibility of patient overlap between two studies (Telimaa 1987a; Telimaa 1990) cannot be excluded as this was not clear in the reports and we have received no reply from the author.
Additional information was sought from every author in each of the included studies; no replies were received regarding either method of randomisation or additional data. Additional data would have been particularly useful as each of the included trials presented some, if not all, data in a graphical form only. Also, in one study only absolute values for AFS scores were provided, without standard deviations. These data had to be excluded as the authors did not respond to our requests for those standard deviations.
Participants were women of reproductive age. All trials specified confirmed endometriosis as an inclusion criterion (either at laparoscopy or laparotomy). In three studies the majority of women (Kauppila 1988; Telimaa 1987a; Telimaa 1990) had AFS stage one or two disease. In the one study (Telimaa 1987b) only one

third of women had AFS stage one and in another study (Bianchi 1999) the participants had Stage III and IV disease and were being treated postoperatively.

The interventions used were the same in all trials. These were danazol (200 mg three times/day), oral medroxyprogesterone acetate (100 mg once/day + placebo twice/day) and placebo (three times/day). Duration of treatment varied from three months in one trial (Bianchi 1999) to six months in the other trials. In three of the trials medical therapy was used as an adjunct to surgery (Bianchi 1999; Kauppila 1988; Telimaa 1987b). The extent of the surgery was not mentioned except to state that it was conservative.

In Telimaa 1987a, four danazol patients and five placebo patients had electrocautery at the time of diagnosis, in addition to medical therapy.

Three studies reported on pain Bianchi 1999; Telimaa 1987a; Telimaa 1987b and one study reported on improvement in laparoscopic appearance(Kauppila 1988) . Two studies (Bianchi 1999; Kauppila 1988) did not report on adverse events. Bianchi 1999 did not repeat the laparoscopy. The follow up was six to 36 months in the studies.

Risk of bias in included studies

The methods used in the included trials are described in detail in the 'Characteristics of included studies' and in the 'Table 1T'. One study was open (danazol versus no treatment (Bianchi 1999) and one of the included trials did not mention blinding (Telimaa 1990). Concealment of allocation was not described in any of the trials and the trials were rated as B for their attempts to control selection bias. Bianchi 1999 described using a computer generated randomisation list. There were no reported losses to follow up in any of the trials. Also, withdrawals were few, overall, with none in three of the studies (Bianchi 1999; Kauppila 1988; Telimaa 1990) and nine in each of the other two studies (Telimaa 1987a (n = 59 participants) and Telimaa 1987b (n = 60) due mainly to adverse effects or conception.

Effects of interventions

(1) Symptoms

At each visit (one, three, six and 12 months), patients recorded the occurrence and severity of pelvic pain, lower back pain, defecation pain, dysuria and dyspareunia on a four-point scale (0 = symptoms absent, 1 = slight symptoms, 2 = moderate symptoms, 3 = severe symptoms).

Without surgery

Only one study recorded symptoms as an outcome (Telimaa 1987a). This study found a significant decrease in the levels of pelvic pain, lower back pain, defecation pain and total pain (total score for all pain symptoms) in patients treated with danazol compared to those treated with placebo, at three and six months of therapy and six months after medication. Total pain scores were reduced at six months in those patients on danazol when compared to placebo (weighted mean difference (WMD) -5.7; 95% confidence interval (CI) -7.5 to -3.8). This improvement in pain scores was still present after six months without danazol therapy. However, no significant difference was found between the two groups in terms of the levels of dysuria and dyspareunia.

With surgery

Two studies reported on improvement in pain symptoms (Bianchi 1999; Telimaa 1987b). One study (Telimaa 1987a) found a significant decrease in the levels of total pain in patients treated with danazol compared to those treated with placebo, at six months of therapy (WMD -3.4; 95% CI -4.8 to -1.8). This improvement in pain scores was still present after six months off therapy with danazol. Pelvic pain was also improved in those patients receiving six months therapy with danazol (WMD -1.1; 95% CI -1.3 to -0.8). However, no significant difference was found between the two groups in terms of the levels of lower back pain, defecation pain, dysuria and dyspareunia.

(2) American Fertility Society (AFS) scores

Without surgery

Two studies examined the change in AFS scores at repeat laparoscopy six months after end of medication (Kauppila 1988 ; Telimaa 1987a). However, Telimaa 1987a reported only the peritoneal deposits and not the total AFS scores while Kauppila 1988 reported only the total AFS score, therefore, the data could not be combined. There was no significant difference in total AFS score (WMD -0.4; 95% CI -1.5 to 0.7) (Kauppila 1988). Telimaa 1987a found that danazol caused a decrease in peritoneal AFS scores (WMD -1.4; 95% CI -2.2 to -0.6).

With surgery

Two studies examined the change in AFS scores at laparoscopy six months after the end of medication (Kauppila 1988;Telimaa 1987b). However, Telimaa 1987b only reported the peritoneal deposits and not the total AFS scores while Kauppila 1988 reported only the total AFS score; data, therefore, could not be combined. There was a significant difference in the total AFS score at 12 months (six months after the end of therapy) in those patients who received danazol (WMD -3.5; 95% CI -5.2 to -1.7). A difference was reported in peritoneal AFS scores for patients treated with danazol (WMD -2.1; CI -3.9 to -0.2). There was no difference in complete resolution of deposits between danazol therapy and placebo (WMD 1.72; 95% CI 0.44 to 6.74).

With surgery

There were no studies that included hormonal data.

(5) Patient satisfaction with treatment

With surgery

Only one study looked at patient satisfaction with treatment (Telimaa 1987b). This study found that satisfaction at six months was significantly higher in those patients receiving danazol (OR 9.9; 95% CI 2.6 to 37.8).

(6) Adverse effects

Without surgery

Only one study looked at adverse effects (Telimaa 1987a). This study found a significant increase in the following symptoms at six months: acne (OR 10.8; 95% CI 2.7 to 42.8), muscle cramps (OR 9.7; 95% CI 1.7 to 55.3) and oedema (OR 7.11; 95% CI 1.5 to 31.6). Vaginal spotting occurred more often in patients treated with danazol, at one and three months (OR 14.0; 95% CI 3.3 to 59.7) but did not persist at six months. There was a 5% increase in weight at six months in patients treated with danazol compared to those treated with placebo. However, no significant difference was found between the two groups in terms of the occurrence of greasy hair, hot flushes, sweating, decreased breast size, dizziness, decreased libido, nausea, nervousness, hirsutism, headache, insomnia, skin rash and depression.

With surgery

Only one study looked at adverse effects (Telimaa 1987b). This study found a significant increase in the following symptoms at six months: acne (OR 8.9; 95% CI 2.16 to 36.7), weight gain (WMD 3.0; 95% CI 1.3 to 4.6) and spotting (OR 8.9; 95% CI 2.6 to 36.7). However, no significant difference was found between the two groups in terms of the occurrence of muscle cramps, oedema, greasy hair, hot flushes, sweating, decreased breast size, dizziness, decreased libido, nausea, nervousness, hirsutism, headache, insomnia, skin rash and depression.

DISCUSSION

The included trials have shown that six months therapy with danazol was significantly better than placebo at relieving painful symptoms. The improvement was still present six months after treatment was stopped. Danazol also had a significant effect on AFS scores, CA-125 levels and free androgen index (FAI). Patient satisfaction was significantly greater with six months of danazol than with placebo. However, this positive effect may be offset by the fact that danazol also caused a significant occurrence of side effects not experienced by those taking placebo.

There were several inadequacies in the available trials. The method of randomisation was only specified in one trial; therefore, the results may not be valid as the method of randomisation may not have been adequate. None of the trials that used blinding were truly double blind as women who received placebo tablets continued menstruating while women who received danazol became amenorrhoeic, making identification of therapy possible. In addition, most of the trials looked at different outcomes thus making statistical pooling of results between trials impossible. Furthermore, the measurement of pain was inadequate as none of the trials used visual analogue scales or other recognised methods for measuring pain. Finally, there was insufficient power in the study design (even when data are combined) to detect, with significance at the 5% level, a difference between danazol and placebo in improvement of pain of 30%. A total of at least 70 participants in each treatment group would be required to show such a difference. It is noted that there is uncertainty about duplication of patients within the included trials and, therefore, the results should be interpreted with caution.

AUTHORS' CONCLUSIONS

Implications for practice

Danazol is an effective therapy for the symptoms and signs of endometriosis but also causes unpleasant side effects such as weight gain and acne. Since its introduction in the 1970s it has become the gold standard for comparing both the medical and surgical treatment of endometriosis in spite of paucity of evidence of its efficacy (in the form of randomised controlled trials). Other treatments are now available which have different side-effect profiles and should also be considered (See a Cochrane review on progestogens: Prentice 2000).

Implications for research

The included trials were mostly conducted in the late eighties. All of the early literature on which the use of danazol was recommended used data from non-controlled non-randomised clinical trials. The limited number of randomised controlled trials of danazol versus placebo or no treatment highlights the need for more well-designed studies to investigate the overall effects of the drug on women. The lack of data on patient satisfaction, compliance and need for future therapy highlights the need for new research to incorporate these outcomes. The side-effect profile and the availability of other treatments such as gonadotrophin releasing hormone agonist and progestogens makes danazol an unpopular choice for the management of the endometriosis and it is unlikely that further studies will be undertaken in the future.

ACKNOWLEDGEMENTS

The authors wish to thank the following people:

Dr Antti Kauppila for providing additional information about randomisation for all of the included studies (Kauppila 1988; Telimaa 1987a; Telimaa 1987b; Telimaa 1990):

Dr Tahir Mahmood for providing additional information for two trials (Mahmood 1990; Mahmood 1991).

REFERENCES

References to studies included in this review

Bianchi 1999 *{published data only}*

Bianchi S, Agnoli B, Sgherzi MR, Candiani M, Busacca M. Effect of three-month treatment with danazol after laparoscopic surgery for stage III-IV endometriosis: a randomized clinical trial. Fertility and Sterility 1999. Bianchi S, Busacca M, Agnoli B, Candiani M, Calia C, Vignali M. Effect of three-month treatment with danazol after laparoscopic surgery for stage III-IV endometriosis: a randomized clinical trial. *Fertility and Sterility* 1999;**Suppl**: 22–3.

Kauppila 1988 *{published data only}*

Kauppila A, Telimaa S, Ronnberg L, Vuori J. Placebo-controlled study on serum concentrations of CA-125 before and after treatment of endometriosis with danazol or high-dose medroxyprogesterone acetate alone or after surgery. *Fertility & Sterility* 1988;**49**:37–41.

Telimaa 1987a *{published data only}*

Telimaa S, Puolakka J, Ronnberg L, Kauppila A. Placebo-controlled comparison of danazol and medroxyprogesterone acetate in the treatment of endometriosis. *Gynecological Endocrinology* 1987;**1**:13–23.

Telimaa 1987b *{published data only}*

Telimaa S, Ronnberg L, Kauppila A. Placebo-controlled comparison of danazol and high-dose medroxyprogesterone acetate in the treatment of endometriosis after conservative surgery. *Gynecological Endocrinology* 1987;**1**:363–71.

Telimaa 1990 *{published data only}*

Telimaa S, Apter D, Reinila M, Ronnberg L, Kauppila A. Placebo-controlled comparison of hormonal and biochemical effects of danazol and high-dose medroxyprogesterone acetate. *European Journal of Obstetrics Gynecology and Reproductive Biology* 1990;**36**:97–105.

References to studies excluded from this review

Bayer 1988 *{published data only}*

Bayer S, Seibel M, Saffan D, Berger M, Taymor M. Efficacy of danazol treatment for minimal endometriosis in infertile women. A prospective, randomized study. *Journal of Reproductive Medicine* 1988;**33**:179–83.

Mahmood 1990 *{published data only}*

Mamood TA. The impact of treatment on the natural history of endometriosis. *Human Reproduction* 1990;**5**: 965–70.

Mahmood 1991 *{published data only}*

Mamood TA. Peritoneal fluid volume and sex steroids in the preovulatory period in mild endometriosis. *British Journal of Obstetrics and Gynaecology* 1991;**98**:179–83.

Morgante 1999 *{published data only}*

Morgante G, Ditto A, La Marca A, De Leo V. Low dose danazol after combined surgical and medical therapy reduces the incidence of pelvic pain in women with moderate and severe endometriosis. *Human Reproduction* 1999;**14(9)**: 2371–4.

Nezhat 1996 *{published data only}*

* Nezhat CH, Nezhat F, Borhan S, Seidman DS, Nezhat CR. Is hormonal treatment efficacious in the management of ovarian cysts in women with histories of endometriosis?. *Human Reproduction* 1996;**11**:874–7..

Seibel 1982 *{published data only}*

Seibel M, Berger M, Weinstein F, Taymor M. The effectiveness of danazol on subsequent fertility in minimal endometriosis. *Fertility and Sterility* 1982;**38**:534–7.

Telimaa 1988 *{published data only}*

Telimaa S. Danazol and medroxyprogesterone acetate inefficacious in the treatment of infertility in endometriosis. *Fertility and Sterility* 1988;**50**:872–5.

Additional references

Barbieri 1990

Barbieri RL. Endometriosis 1990 - current treatment approaches. *Drugs* 1990;**39**(4):502–10.

Hughes 2007

Hughes E, Fedorkow D, Collins J, Vandekerckhove P. Ovulation suppression for endometriosis (Cochrane Review). *Cochrane Database of Systematic Reviews* 2007, Issue 3.

McLaren 1996

McLaren J, Prentice A. New aspects of pathogenesis of endometriosis. *Current Opinion in Obstetrics & Gynecology* 1996;**6**:85–91.

Prentice 2000

Prentice A, Deary AJ, Bland E. Progestagens and anti-progestagens for pain associated with endometriosis. *Cochrane Database of Systematic Reviews* 2000, Issue 2.

Rock 1992

Rock JA, Markham SM. Pathogenesis of endometriosis. *Lancet* 1992;**340**:1264–7.

Yap 2004

C Yap, S Furness, C Farquhar. Pre and post operative medical therapy for endometriosis surgery. Cochrane Database of Systematic Reviews 2004, Issue 3. Art. No.: CD003678. DOI: 10.1002/14651858.CD003678.pub2. Pre and post operative medical therapy for endometriosis surgery. *Cochrane Database of Systematic Reviews* 2004, Issue 3.

* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Bianchi 1999

Methods	Randomised, placebo-controlled open trial Method of randomisation: not specified Exclusions post randomisation: none
Participants	Country: Italy 77 women <41 yrs old with moderate or severe endometriosis who had undergone laparoscopic surgery
Interventions	Danazol 600 mg/day for 3 months versus no treatment
Outcomes	Pelvic pain recurrence, pregnancy
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Kauppila 1988

Methods	Randomised, placebo-controlled double blind trial Method of randomisation: not specified Exclusions postrandomisation: none Unusual study design: factorial
Participants	Country: Finland 87 patients divided into two groups of 47 and 40 to undergo laparoscopy or laparotomy respectively. Patients in each group were then randomised to one of 3 intervention groups (medroxyprogesterone acetate (MPA), danazol or placebo) post laparoscopy group: MPA group: n = 16, age = 32.5 +/- 5.9 SD years danazol group: n = 17, age = 31.1 +/- 5.6 SD years placebo group: n = 14, age= 31.9 +/- 6.0 SD years Post laparotomy group: MPA group: n = 13, age = 29.5 +/- 5.8 SD years danazol group: n = 15, age = 32.1 +/- 6.7 SD years placebo group: n = 12, age= 28.2 +/- 5.6 SD years Inclusion criteria: endometriosis confirmed at laparoscopy or laparotomy AFS scores: 72 of 87 women had stage I and II Exclusion criteria: none

Kauppila 1988 (*Continued*)

Interventions	Treatments: MPA 100 mg x 1/day + placebo x 2/day; danazol 200 mg x 3/day Control: placebo x 3/day Duration: 6 months	
Outcomes	AFS scores Levels of CA-125	
Notes		
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment?	Unclear risk	B - Unclear

Telimaa 1987a

Methods	Randomised, placebo-controlled double blind trial Method of randomisation: not specified Exclusions post randomisation: x 4 MPA (x 1 hot flushes, x 1 nervousness, x 1 psychological, x 1 conception) ; x 2 danazol (x 1 skin rash, x 1 conception); x 3 placebo (x 3 conceptions) Losses to follow up: none	
Participants	Country: Finland 59 patients randomised to one of 3 intervention groups (MPA, danazol or placebo) MPA group: n = 20, age = 32.2 +/- 5.4 SD years danazol group: n = 20, age = 31.4+/- 5.2 SD years placebo group: n = 19, age = 32.4 +/- 5.7 SD years Inclusion criteria: laparoscopically confirmed endometriosis, no previous surgical and/or medical treatment for endometriosis AFS scores: all women had stage I or II disease Exclusion criteria: none stated	
Interventions	Treatments: MPA 100 mg/day; danazol 200 mg 3 x/day Control: placebo Duration: 6 months	
Outcomes	AFS scores (peritoneal implants component) Symptoms Adverse effects	
Notes		
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment?	Unclear risk	B - Unclear

Telimaa 1987b

Methods	Randomised, placebo-controlled double blind trial Method of randomisation: not specified Exclusions post randomisation: x 3 MPA (x 3 conceptions), x 2 danazol (x 2 conceptions), x 4 placebo (x 3 conceptions, x 1 insomnia/nervousness/depression) Losses to follow up: none
Participants	Country: Finland 60 patients randomised to one of 3 intervention groups (MPA, danazol or placebo) MPA group: n = 20, age = 29.4 +/- 5.4 SD years danazol group: n = 20, age = 31.5 +/- 6.0 SD years placebo group: n = 20 age = 29.1 +/- 5.9 SD years Inclusion criteria: recent conservative surgery for endometriosis, no previous surgical and/or medical treatment for endometriosis AFS scores: 11 of 33 women had stage I or II disease Exclusion criteria: not stated
Interventions	Treatments: MPA 100 mg/day; danazol 200 mg 3 x/day Control: placebo Duration: 6 months
Outcomes	AFS scores (peritoneal implants component) Symptoms Adverse effects
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Telimaa 1990

Methods	Randomised, placebo-controlled trial Blinding: unclear Method of randomisation: not specified Exclusions post randomisation: none Losses to follow-up: none
Participants	Country: Finland 87 patients divided into two groups of 33 and 54 evaluated for hormonal parameters and biochemical parameters respectively. Each group of patients was randomised to one of 3 intervention groups (MPA, danazol or placebo) Hormonal group: MPA: n = 11, age = 31.1 +/- 6.3 SD years danazol: n = 11, age = 30.7 +/- 4.6 SD years placebo: n = 11, age = 32.8 +/- 5.7 SD years Biochemical group:

Telimaa 1990 (*Continued*)

	MPA: n = 18, age = 29.8 +/- 5.7 SD years danazol: n = 18, age = 31.5 +/- 6.0 SD years placebo: n = 18, age = 29.6 +/- 6.0 SD years Inclusion criteria: endometriosis confirmed by laparoscopy or laparotomy AFS scores: all women had stage I or II disease Exclusion criteria: none
Interventions	Treatments: MPA 100 mg/day; danazol 200 mg 3 x/day Control: placebo Duration: 6 months
Outcomes	Levels of hormonal parameters -LH -FSH -prolactin -progesterone -oestradiol -testosterone/free androgen index -sex-hormone binding globulin Levels of biochemical parameters -albumin -ALT -AST -ALP -GGT -bilirubin (total and conjugated) -creatinine -sodium -potassium -white cell count -platelets Haemoglobin
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment?	Unclear risk	B - Unclear

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

Study	Reason for exclusion
Bayer 1988	Outcomes published relate to infertility only
Mahmood 1990	No outcomes of interest, unclear randomisation process.
Mahmood 1991	Did not include outcomes of interest to this review
Morgante 1999	Treatment period was post opertative and included surgery
Nezhat 1996	Women had oviarian cysts and endometriosis was not confirmed
Seibel 1982	Outcomes published relate to infertility only
Telimaa 1988	Outcomes published relate to infertility only

DATA AND ANALYSES

Comparison 1. Danazol versus placebo - no surgery

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Total pain	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.1 Three months of treatment	1	35	Mean Difference (IV, Fixed, 95% CI)	-4.95 [-6.61, -3.29]
1.2 Six months of treatment	1	35	Mean Difference (IV, Fixed, 95% CI)	-5.7 [-7.51, -3.89]
1.3 Six months after stopping treatment	1	35	Mean Difference (IV, Fixed, 95% CI)	-7.50 [-9.38, -5.62]
2 Pelvic pain	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
2.1 Three months of treatment	1	35	Mean Difference (IV, Fixed, 95% CI)	-0.65 [-0.90, -0.40]
2.2 Six months of treatment	1	35	Mean Difference (IV, Fixed, 95% CI)	-1.40 [-1.68, -1.12]
2.3 Six months after stopping treatment	1	35	Mean Difference (IV, Fixed, 95% CI)	-1.05 [-1.33, -0.77]
3 Low back pain	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
3.1 Six months of treatment	1	35	Mean Difference (IV, Fixed, 95% CI)	-0.90 [-1.25, -0.55]
3.2 Six months after stopping treatment	1	35	Mean Difference (IV, Fixed, 95% CI)	-1.2 [-1.55, -0.85]
4 Defaecation pain	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
4.1 6 months of treatment	1	35	Mean Difference (IV, Fixed, 95% CI)	-0.77 [-1.10, -0.44]
4.2 6 months after stopping treatment	1	35	Mean Difference (IV, Fixed, 95% CI)	-0.68 [-0.99, -0.37]
5 Adverse events	1		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
5.1 Oedema at six months	1	35	Odds Ratio (M-H, Fixed, 95% CI)	12.8 [1.38, 118.32]
5.2 Acne at six months	1	35	Odds Ratio (M-H, Fixed, 95% CI)	25.14 [2.70, 234.17]
5.3 Vaginal spotting at six months	1	35	Odds Ratio (M-H, Fixed, 95% CI)	1.79 [0.36, 9.05]
5.4 Muscle cramps at six months	1	35	Odds Ratio (M-H, Fixed, 95% CI)	18.2 [0.94, 353.55]
6 AFS scores, total - 12 months (six months after stopping treatment)	1	31	Mean Difference (IV, Fixed, 95% CI)	-0.40 [-1.58, 0.78]
7 AFS scores, total - change in	1	31	Mean Difference (IV, Fixed, 95% CI)	-1.9 [-4.16, 0.36]
8 Total or partial resoultion of peritoneal endometriotic implants	1	32	Odds Ratio (M-H, Fixed, 95% CI)	5.0 [0.83, 30.28]

Comparison 2. Danazol versus placebo - post surgery

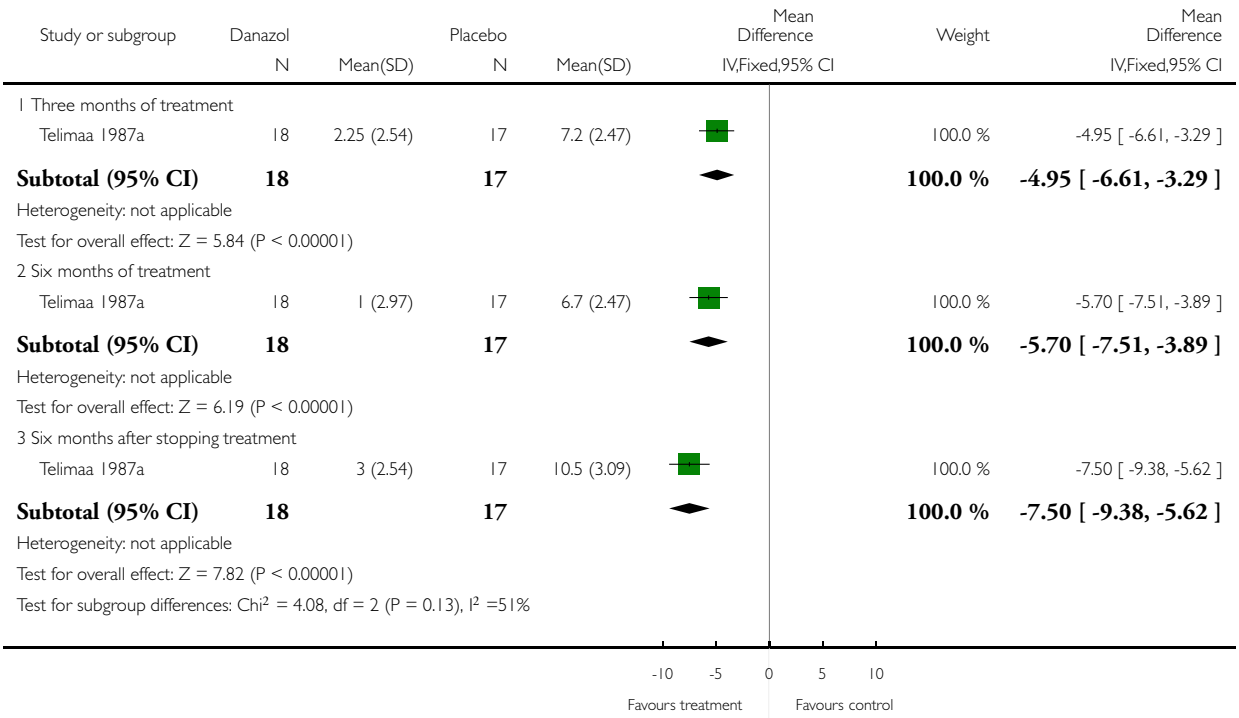
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Total pain	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.1 3 months of treatment	1	34	Mean Difference (IV, Fixed, 95% CI)	-2.2 [-3.59, -0.81]
1.2 6 months of treatment	1	34	Mean Difference (IV, Fixed, 95% CI)	-4.2 [-5.71, -2.69]
1.3 6 months or more after treatment	1	34	Mean Difference (IV, Fixed, 95% CI)	-1.80 [-3.18, -0.42]
2 Pelvic pain	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
2.1 3 months of treatment	1	34	Mean Difference (IV, Fixed, 95% CI)	-0.52 [-0.80, -0.24]
2.2 6 months of treatment	1	34	Mean Difference (IV, Fixed, 95% CI)	-1.1 [-1.38, -0.82]
2.3 6 months after treatment	1	34	Mean Difference (IV, Fixed, 95% CI)	-0.47 [-0.75, -0.19]
3 Moderate or severe pain 6 months or more after followup	1	60	Odds Ratio (M-H, Fixed, 95% CI)	0.65 [0.20, 2.05]
4 Adverse events	1		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
4.1 vaginal spotting	1	34	Odds Ratio (M-H, Fixed, 95% CI)	18.75 [2.02, 173.94]
4.2 acne	1	34	Odds Ratio (M-H, Fixed, 95% CI)	18.75 [2.02, 173.94]
5 Satisfaction with treatment	1	34	Peto Odds Ratio (Peto, Fixed, 95% CI)	9.94 [2.61, 37.81]
6 Weight gain	1	34	Mean Difference (IV, Fixed, 95% CI)	3.0 [1.34, 4.66]
7 AFS scores, total - 12 months (six months after stopping treatment)	1	27	Mean Difference (IV, Fixed, 95% CI)	-3.50 [-5.27, -1.73]
8 AFS scores, total - change in	1	27	Mean Difference (IV, Fixed, 95% CI)	-0.90 [-3.02, 1.22]
9 AFS scores, peritoneal and ovarian - 12 months (six months after stopping treatment)	1	34	Mean Difference (IV, Fixed, 95% CI)	-2.1 [-3.90, -0.30]
10 Resolution of endometriotic implants at laparoscopy	1	34	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.72 [0.44, 6.74]

Analysis 1.1. Comparison 1 Danazol versus placebo - no surgery, Outcome 1 Total pain.

Review: Danazol for pelvic pain associated with endometriosis

Comparison: 1 Danazol versus placebo - no surgery

Outcome: 1 Total pain



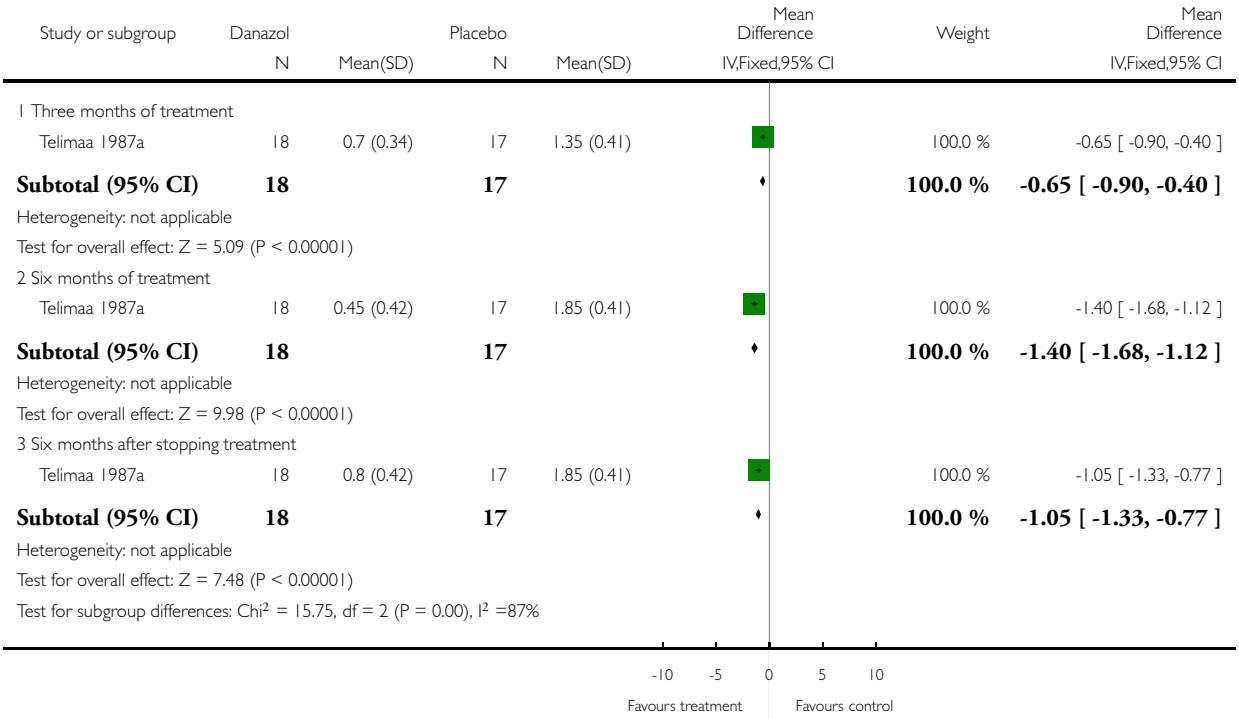
Analysis 1.2. Comparison 1 Danazol versus placebo - no surgery, Outcome 2 Pelvic pain.

Review: Danazol for pelvic pain associated with endometriosis

Comparison: 1 Danazol versus placebo - no surgery

Outcome: 2 Pelvic pain

Study or subgroup	Danazol N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 Three months of treatment							
Telimaa 1987a	18	0.7 (0.34)	17	1.35 (0.41)		100.0 %	-0.65 [-0.90, -0.40]
Subtotal (95% CI)	**18**		**17**			**100.0 %**	**-0.65 [-0.90, -0.40]**
Heterogeneity: not applicable							
Test for overall effect: Z = 5.09 (P < 0.00001)							
2 Six months of treatment							
Telimaa 1987a	18	0.45 (0.42)	17	1.85 (0.41)		100.0 %	-1.40 [-1.68, -1.12]
Subtotal (95% CI)	**18**		**17**			**100.0 %**	**-1.40 [-1.68, -1.12]**
Heterogeneity: not applicable							
Test for overall effect: Z = 9.98 (P < 0.00001)							
3 Six months after stopping treatment							
Telimaa 1987a	18	0.8 (0.42)	17	1.85 (0.41)		100.0 %	-1.05 [-1.33, -0.77]
Subtotal (95% CI)	**18**		**17**			**100.0 %**	**-1.05 [-1.33, -0.77]**
Heterogeneity: not applicable							
Test for overall effect: Z = 7.48 (P < 0.00001)							
Test for subgroup differences: Chi^2 = 15.75, df = 2 (P = 0.00), I^2 =87%							



Analysis 1.3. Comparison 1 Danazol versus placebo - no surgery, Outcome 3 Low back pain.

Review: Danazol for pelvic pain associated with endometriosis

Comparison: 1 Danazol versus placebo - no surgery

Outcome: 3 Low back pain

Study or subgroup	Danazol N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 Six months of treatment							
Telimaa 1987a	18	0.45 (0.64)	17	1.35 (0.41)		100.0 %	-0.90 [-1.25, -0.55]
Subtotal (95% CI)	**18**		**17**			**100.0 %**	**-0.90 [-1.25, -0.55]**
Heterogeneity: not applicable							
Test for overall effect: Z = 4.98 (P < 0.00001)							
2 Six months after stopping treatment							
Telimaa 1987a	18	0.5 (0.42)	17	1.7 (0.62)		100.0 %	-1.20 [-1.55, -0.85]
Subtotal (95% CI)	**18**		**17**			**100.0 %**	**-1.20 [-1.55, -0.85]**
Heterogeneity: not applicable							
Test for overall effect: Z = 6.67 (P < 0.00001)							
Test for subgroup differences: Chi^2 = 1.38, df = 1 (P = 0.24), I^2 =28%							

Analysis 1.4. Comparison 1 Danazol versus placebo - no surgery, Outcome 4 Defaecation pain.

Review: Danazol for pelvic pain associated with endometriosis

Comparison: 1 Danazol versus placebo - no surgery

Outcome: 4 Defaecation pain

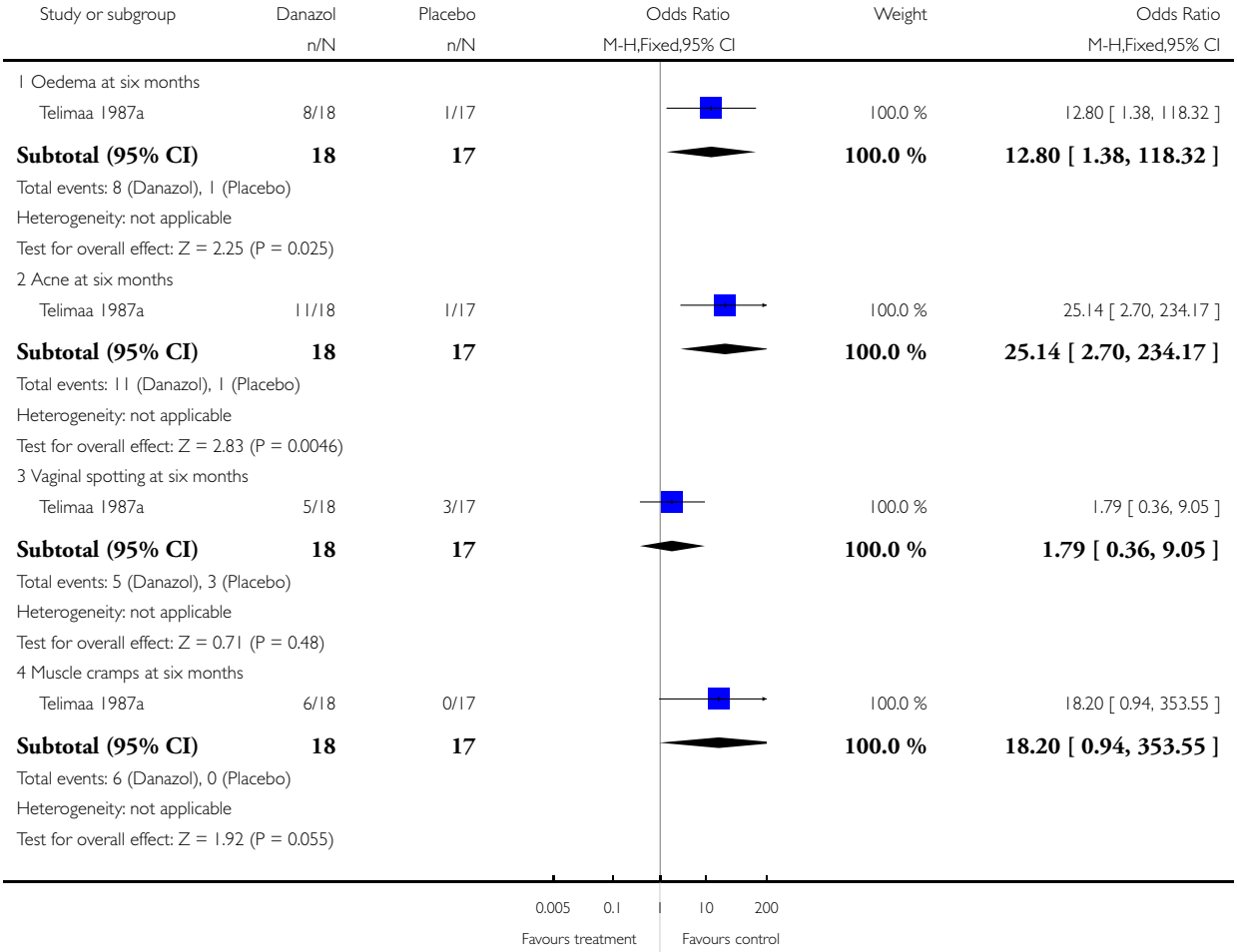
Study or subgroup	Danazol N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 6 months of treatment							
Telimaa 1987a	18	0.02 (0.64)	17	0.79 (0.31)		100.0 %	-0.77 [-1.10, -0.44]
Subtotal (95% CI)	**18**		**17**			**100.0 %**	**-0.77 [-1.10, -0.44]**
Heterogeneity: not applicable							
Test for overall effect: Z = 4.57 (P < 0.00001)							
2 6 months after stopping treatment							
Telimaa 1987a	18	0.2 (0.59)	17	0.88 (0.33)		100.0 %	-0.68 [-0.99, -0.37]
Subtotal (95% CI)	**18**		**17**			**100.0 %**	**-0.68 [-0.99, -0.37]**
Heterogeneity: not applicable							
Test for overall effect: Z = 4.24 (P = 0.000023)							
Test for subgroup differences: Chi^2 = 0.15, df = 1 (P = 0.70), I^2 =0.0%							

Analysis 1.5. Comparison 1 Danazol versus placebo - no surgery, Outcome 5 Adverse events.

Review: Danazol for pelvic pain associated with endometriosis

Comparison: 1 Danazol versus placebo - no surgery

Outcome: 5 Adverse events



Analysis 1.6. Comparison 1 Danazol versus placebo - no surgery, Outcome 6 AFS scores, total - 12 months (six months after stopping treatment).

Review: Danazol for pelvic pain associated with endometriosis

Comparison: 1 Danazol versus placebo - no surgery

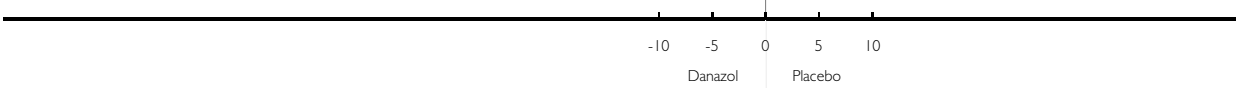
Outcome: 6 AFS scores, total - 12 months (six months after stopping treatment)

Study or subgroup	Danazol N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Kauppila 1988	17	1.6 (1.5)	14	2 (1.8)		100.0 %	-0.40 [-1.58, 0.78]
Total (95% CI)	**17**		**14**			**100.0 %**	**-0.40 [-1.58, 0.78]**

Heterogeneity: not applicable

Test for overall effect: Z = 0.66 (P = 0.51)

Test for subgroup differences: Not applicable



Analysis 1.7. Comparison 1 Danazol versus placebo - no surgery, Outcome 7 AFS scores, total - change in.

Review: Danazol for pelvic pain associated with endometriosis

Comparison: 1 Danazol versus placebo - no surgery

Outcome: 7 AFS scores, total - change in

Study or subgroup	Danazol N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Kauppila 1988	17	-1.7 (3.7)	14	0.2 (2.7)		100.0 %	-1.90 [-4.16, 0.36]
Total (95% CI)	**17**		**14**			**100.0 %**	**-1.90 [-4.16, 0.36]**

Heterogeneity: not applicable

Test for overall effect: Z = 1.65 (P = 0.099)

Test for subgroup differences: Not applicable

Analysis 1.8. Comparison 1 Danazol versus placebo - no surgery, Outcome 8 Total or partial resoultion of peritoneal endometriotic implants.

Review: Danazol for pelvic pain associated with endometriosis

Comparison: 1 Danazol versus placebo - no surgery

Outcome: 8 Total or partial resoultion of peritoneal endometriotic implants

Study or subgroup	Danazol n/N	Placebo n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Telimaa 1987a	6/15	2/17		100.0 %	5.00 [0.83, 30.28]
Total (95% CI)	**15**	**17**		**100.0 %**	**5.00 [0.83, 30.28]**
Total events: 6 (Danazol), 2 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.75 (P = 0.080)					

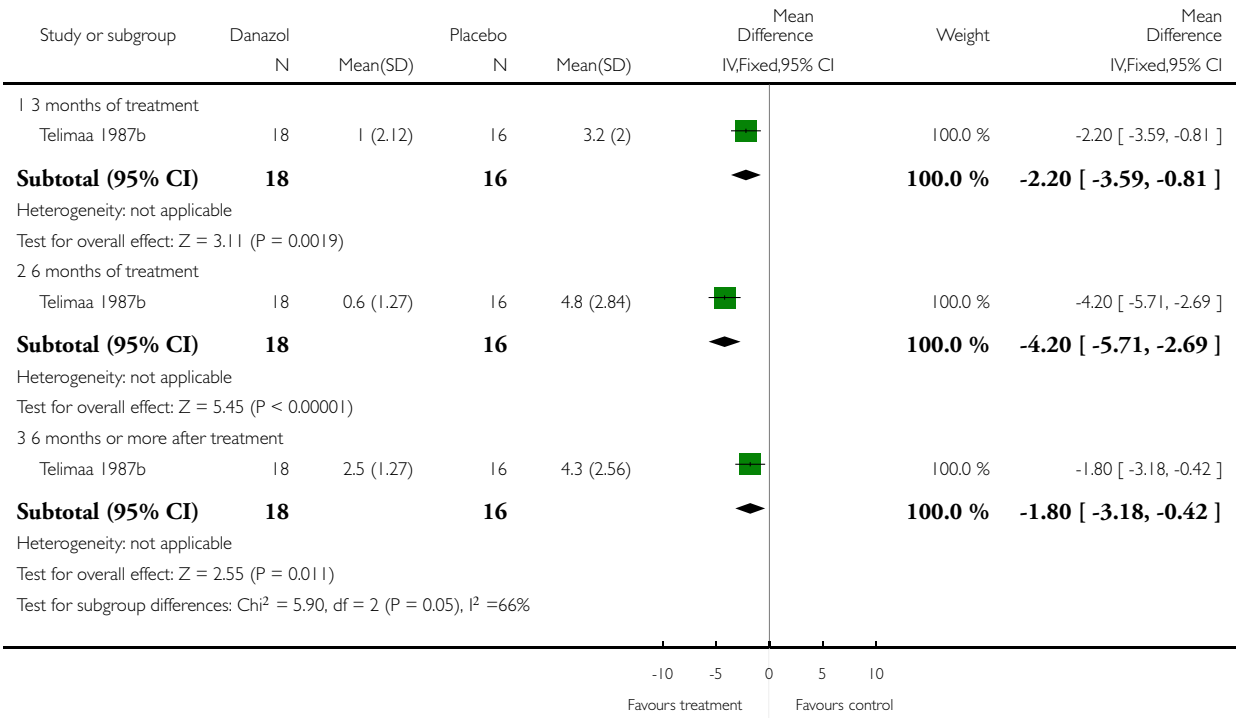
Analysis 2.1. Comparison 2 Danazol versus placebo - post surgery, Outcome 1 Total pain.

Review: Danazol for pelvic pain associated with endometriosis

Comparison: 2 Danazol versus placebo - post surgery

Outcome: 1 Total pain

Study or subgroup	Danazol N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 3 months of treatment							
Telimaa 1987b	18	1 (2.12)	16	3.2 (2)		100.0 %	-2.20 [-3.59, -0.81]
Subtotal (95% CI)	**18**		**16**			**100.0 %**	**-2.20 [-3.59, -0.81]**
Heterogeneity: not applicable							
Test for overall effect: Z = 3.11 (P = 0.0019)							
2 6 months of treatment							
Telimaa 1987b	18	0.6 (1.27)	16	4.8 (2.84)		100.0 %	-4.20 [-5.71, -2.69]
Subtotal (95% CI)	**18**		**16**			**100.0 %**	**-4.20 [-5.71, -2.69]**
Heterogeneity: not applicable							
Test for overall effect: Z = 5.45 (P < 0.00001)							
3 6 months or more after treatment							
Telimaa 1987b	18	2.5 (1.27)	16	4.3 (2.56)		100.0 %	-1.80 [-3.18, -0.42]
Subtotal (95% CI)	**18**		**16**			**100.0 %**	**-1.80 [-3.18, -0.42]**
Heterogeneity: not applicable							
Test for overall effect: Z = 2.55 (P = 0.011)							
Test for subgroup differences: Chi^2 = 5.90, df = 2 (P = 0.05), I^2 =66%							



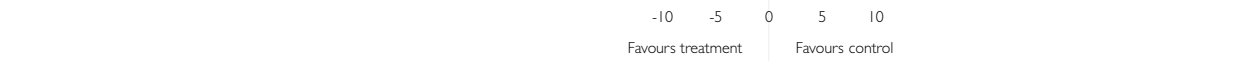
Analysis 2.2. Comparison 2 Danazol versus placebo - post surgery, Outcome 2 Pelvic pain.

Review: Danazol for pelvic pain associated with endometriosis

Comparison: 2 Danazol versus placebo - post surgery

Outcome: 2 Pelvic pain

Study or subgroup	Danazol N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 3 months of treatment							
Telimaa 1987b	18	0.7 (0.42)	16	1.22 (0.4)		100.0 %	-0.52 [-0.80, -0.24]
Subtotal (95% CI)	**18**		**16**			**100.0 %**	**-0.52 [-0.80, -0.24]**
Heterogeneity: not applicable							
Test for overall effect: Z = 3.70 (P = 0.00022)							
2 6 months of treatment							
Telimaa 1987b	18	0.45 (0.42)	16	1.55 (0.4)		100.0 %	-1.10 [-1.38, -0.82]
Subtotal (95% CI)	**18**		**16**			**100.0 %**	**-1.10 [-1.38, -0.82]**
Heterogeneity: not applicable							
Test for overall effect: Z = 7.82 (P < 0.00001)							
3 6 months after treatment							
Telimaa 1987b	18	1.15 (0.42)	16	1.62 (0.4)		100.0 %	-0.47 [-0.75, -0.19]
Subtotal (95% CI)	**18**		**16**			**100.0 %**	**-0.47 [-0.75, -0.19]**
Heterogeneity: not applicable							
Test for overall effect: Z = 3.34 (P = 0.00084)							
Test for subgroup differences: Chi^2 = 12.39, df = 2 (P = 0.00), I^2 =84%							



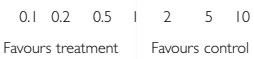
Analysis 2.3. Comparison 2 Danazol versus placebo - post surgery, Outcome 3 Moderate or severe pain 6 months or more after followup.

Review: Danazol for pelvic pain associated with endometriosis

Comparison: 2 Danazol versus placebo - post surgery

Outcome: 3 Moderate or severe pain 6 months or more after followup

Study or subgroup	Danazol n/N	Placebo n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Bianchi 1999	7/31	9/29		100.0 %	0.65 [0.20, 2.05]
Total (95% CI)	**31**	**29**		**100.0 %**	**0.65 [0.20, 2.05]**
Total events: 7 (Danazol), 9 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.74 (P = 0.46)					



Analysis 2.4. Comparison 2 Danazol versus placebo - post surgery, Outcome 4 Adverse events.

Review: Danazol for pelvic pain associated with endometriosis

Comparison: 2 Danazol versus placebo - post surgery

Outcome: 4 Adverse events

Study or subgroup	Danazol n/N	Placebo n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
1 vaginal spotting					
Telimaa 1987b	10/18	1/16		100.0 %	18.75 [2.02, 173.94]
Subtotal (95% CI)	**18**	**16**		**100.0 %**	**18.75 [2.02, 173.94]**
Total events: 10 (Danazol), 1 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.58 (P = 0.0099)					
2 acne					
Telimaa 1987b	10/18	1/16		100.0 %	18.75 [2.02, 173.94]
Subtotal (95% CI)	**18**	**16**		**100.0 %**	**18.75 [2.02, 173.94]**
Total events: 10 (Danazol), 1 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.58 (P = 0.0099)					

Analysis 2.5. Comparison 2 Danazol versus placebo - post surgery, Outcome 5 Satisfaction with treatment.

Review: Danazol for pelvic pain associated with endometriosis

Comparison: 2 Danazol versus placebo - post surgery

Outcome: 5 Satisfaction with treatment

Study or subgroup	Danazol n/N	Placebo n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
Telimaa 1987b	15/18	4/16		100.0 %	9.94 [2.61, 37.81]
Total (95% CI)	**18**	**16**		**100.0 %**	**9.94 [2.61, 37.81]**

Total events: 15 (Danazol), 4 (Placebo)

Heterogeneity: not applicable

Test for overall effect: Z = 3.37 (P = 0.00076)

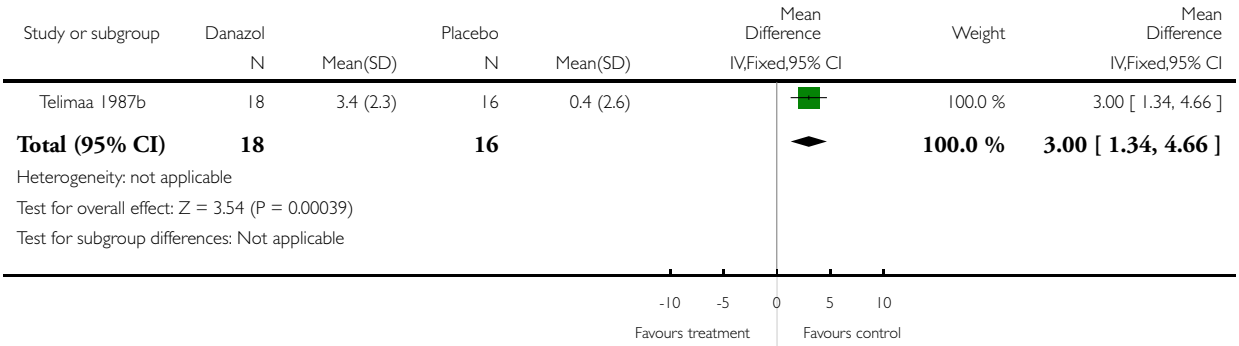
Test for subgroup differences: Not applicable

Analysis 2.6. Comparison 2 Danazol versus placebo - post surgery, Outcome 6 Weight gain.

Review: Danazol for pelvic pain associated with endometriosis

Comparison: 2 Danazol versus placebo - post surgery

Outcome: 6 Weight gain

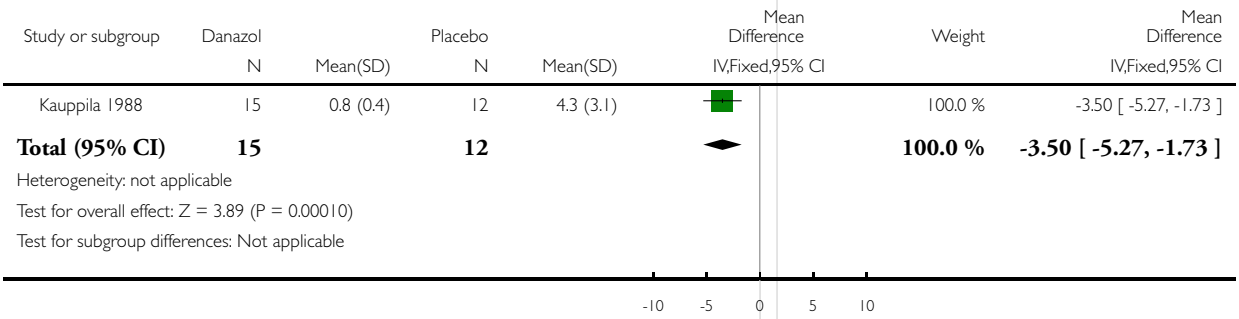


Analysis 2.7. Comparison 2 Danazol versus placebo - post surgery, Outcome 7 AFS scores, total - 12 months (six months after stopping treatment).

Review: Danazol for pelvic pain associated with endometriosis

Comparison: 2 Danazol versus placebo - post surgery

Outcome: 7 AFS scores, total - 12 months (six months after stopping treatment)

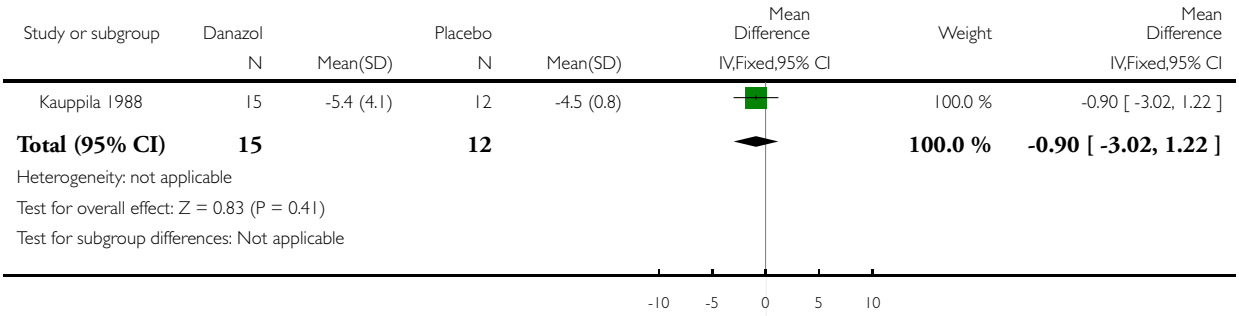


Analysis 2.8. Comparison 2 Danazol versus placebo - post surgery, Outcome 8 AFS scores, total - change in.

Review: Danazol for pelvic pain associated with endometriosis

Comparison: 2 Danazol versus placebo - post surgery

Outcome: 8 AFS scores, total - change in

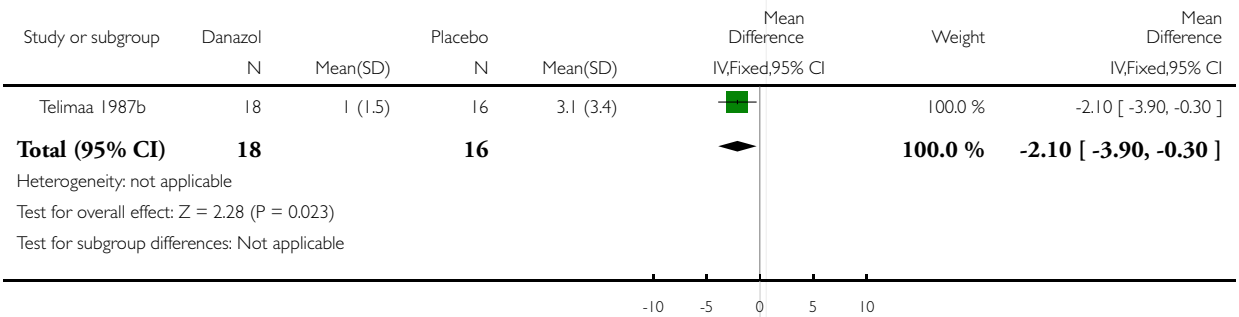


Analysis 2.9. Comparison 2 Danazol versus placebo - post surgery, Outcome 9 AFS scores, peritoneal and ovarian - 12 months (six months after stopping treatment).

Review: Danazol for pelvic pain associated with endometriosis

Comparison: 2 Danazol versus placebo - post surgery

Outcome: 9 AFS scores, peritoneal and ovarian - 12 months (six months after stopping treatment)

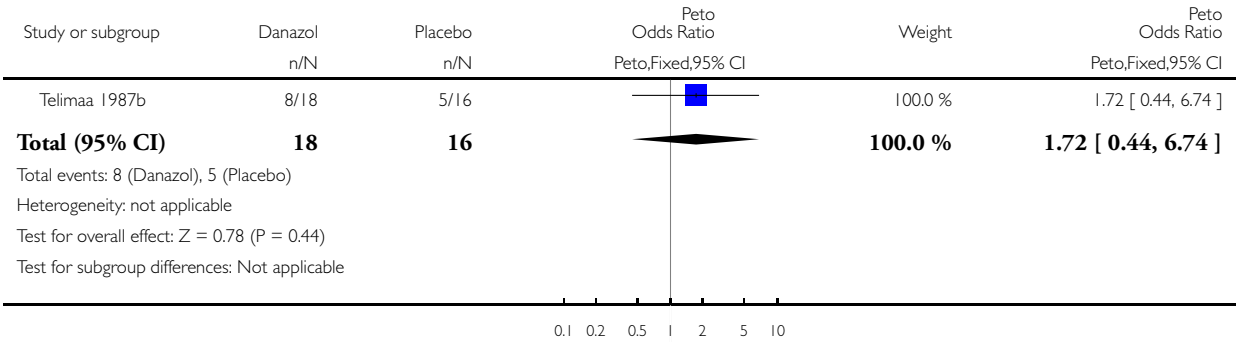


Analysis 2.10. Comparison 2 Danazol versus placebo - post surgery, Outcome 10 Resolution of endometriotic implants at laparoscopy.

Review: Danazol for pelvic pain associated with endometriosis

Comparison: 2 Danazol versus placebo - post surgery

Outcome: 10 Resolution of endometriotic implants at laparoscopy



ADDITIONAL TABLES

Table 1. Table of included studies risk of bias

Study ID	Concealed allocation	Method of randomisat	Losses to followup	Post random exclus	Intention to treat	Blinding
Bianci 1999	Not stated	Computer generated list	None	None	yes	Open study
Kaupilla 1988	Not stated	Not stated	None	None	yes	Double blind
Telimaa 1987a	Not stated	Not stated	None	9 - 4 in the MPA group and 2 in the danazol group and 3 in the placebo group (5 for pregnancies)	no	Double blind
Telimaa 1987b	Not stated	Not stated	None	9 - 3 in the MPA group, 2 in the danazol group and 4 in the placebo group, 8 for preg-	no	Double blind

Table 1. Table of included studies risk of bias (*Continued*)

				nancies		
Telimaa 1990	Not stated	Not stated	None	None	yes	Unclear

APPENDICES

Appendix 1. Search string

MEDLINE (1950 to April Week 3 2007)
1 endometriosis/ (11531)
2 adenomyosis.tw. (996)
3 endometrio$.tw. (12163)
4 or/1-3 (15147)
5 Danazol/ (1950)
6 danazol.tw. (1838)
7 (azol or cyclomen or danatrol or danazant or danocrine or danol or danoval).tw. (76)
8 (ladogal or norciden or panacrine).tw. (3)
9 or/5-8 (2404)
10 4 and 9 (848)
11 randomised controlled trial.pt. (233672)
12 controlled clinical trial.pt. (74707)
13 Randomized Controlled Trials/ (48151)
14 Random allocation/ (57661)
15 Double-blind method/ (90848)
16 Single-blind method/ (10848)
17 or/11-16 (396309)
18 clinical trial.pt. (434900)
19 exp clinical trials/ (190060)
20 (clin$ adj25 trial$).ti,ab,sh. (128953)
21 ((singl$ or doubl$ or tripl$ or trebl$) adj25 (blind$ or mask$)).ti,ab,sh. (90139)
22 Placebos/ (26065)
23 placebo$.ti,ab,sh. (114213)
24 random$.ti,ab,sh. (488137)
25 Research design/ (47102)
26 or/18-25 (863717)
27 animal/ not (human/ and animal/) (3077794)
28 17 or 26 (870958)
29 28 not 27 (798160)
30 10 and 29 (156)
31 (200412$ or 2005$ or 2006$ or 2007$).ed. (1527294)
32 30 and 31 (7)
33 from 32 keep 1-7 (7)
EBM Reviews - Cochrane Central Register of Controlled Trials (2nd quarter 2007)
1 endometriosis/ (338)
2 adenomyosis.tw. (19)

3 endometrio$.tw. (577)
4 or/1-3 (621)
5 Danazol/ (177)
6 danazol.tw. (271)
7 (azol or cyclomen or danatrol or danazant or danocrine or danol or danoval).tw. (7)
8 (ladogal or norciden or panacrine).tw. (0)
9 or/5-8 (284)
10 4 and 9 (142)
11 from 10 keep 1-142 (142)
CINAHL - Cumulative Index to Nursing & Allied Health Literature (1982 to April Week 3 2007)
1 endometriosis/ (446)
2 adenomyosis.tw. (21)
3 endometrio$.tw. (397)
4 or/1-3 (541)
5 Danazol/ (47)
6 danazol.tw. (39)
7 (azol or cyclomen or danatrol or danazant or danocrine or danol or danoval).tw. (1)
8 (ladogal or norciden or panacrine).tw. (1)
9 or/5-8 (68)
10 4 and 9 (20)
11 exp clinical trials/ (43534)
12 Clinical trial.pt. (20632)
13 (clinic$ adj trial$1).tw. (10183)
14 ((singl$ or doubl$ or trebl$ or tripl$) adj (blind$3 or mask$3)).tw. (6101)
15 Randomi?ed control$ trial$.tw. (8914)
16 Random assignment/ (15102)
17 Random$ allocat$.tw. (1021)
18 Placebo$.tw. (8530)
19 Placebos/ (3470)
20 Quantitative studies/ (3182)
21 Allocat$ random$.tw. (60)
22 or/11-21 (61045)
23 10 and 22 (6)
24 from 23 keep 1-6 (6)
EMBASE (1980 to 2007 Week 16)
1 endometriosis/ (9383)
2 adenomyosis.tw. (886)
3 endometrio$.tw. (10448)
4 or/1-3 (12980)
5 DANAZOL/ (4834)
6 danazol.tw. (1813)
7 (azol or cyclomen or danatrol or danazant or danocrine or danol or danoval).tw. (481)
8 (Chronogyn or Danokrin or ladogal or norciden or panacrine).tw. (12)
9 or/5-8 (4989)
10 4 and 9 (1326)
11 Controlled study/ or randomised controlled trial/ (2394072)
12 double blind procedure/ (63565)
13 single blind procedure/ (6516)
14 crossover procedure/ (18516)
15 drug comparison/ (81250)
16 placebo/ (97296)
17 random$.ti,ab,hw,tn,mf. (365334)
18 latin square.ti,ab,hw,tn,mf. (1063)

19 crossover.ti,ab,hw,tn,mf. (32445)
20 cross-over.ti,ab,hw,tn,mf. (11244)
21 placebo$.ti,ab,hw,tn,mf. (145658)
22 ((doubl$ or singl$ or tripl$ or trebl$) adj5 (blind$ or mask$)).ti,ab,hw,tn,mf. (105970)
23 (comparative adj5 trial$).ti,ab,hw,tn,mf. (5721)
24 (clinical adj5 trial$).ti,ab,hw,tn,mf. (480555)
25 or/11-24 (2873461)
26 nonhuman/ (2870879)
27 animal/ not (human/ and animal/) (12846)
28 or/26-27 (2874481)
29 25 not 28 (1687251)
30 10 and 29 (351)
31 (200412$ or 2005$ or 2006$ or 2007$).em. (1388022)
32 30 and 31 (43)
33 from 32 keep 1-43 (43)

WHAT'S NEW

Last assessed as up-to-date: 14 June 2007.

Date	Event	Description
20 September 2010	Amended	Contact details updated.
10 November 2008	Review declared as stable	The findings of this review are regarded as being stable

HISTORY

Protocol first published: Issue 2, 1997

Review first published: Issue 2, 1997

Date	Event	Description
7 November 2008	Amended	Converted to new review format.
14 June 2007	New citation required and conclusions have changed	Substantive amendment

DECLARATIONS OF INTEREST

None

SOURCES OF SUPPORT

Internal sources

- Department of Obstetrics and Gynaecology, University of Auckland, New Zealand.
- Wellington Medical Research Foundation, New Zealand.
- Department of Obstetrics and Gynaecology, University of Cambridge, UK.

External sources

- Wellington School of Medicine, New Zealand.

NOTES

A new search for further randomised controlled trials in July 2001 did not identify any further trials. The outcomes were revised and only outcomes that were considered clinically relevant were included.

INDEX TERMS

Medical Subject Headings (MeSH)

Danazol [*therapeutic use]; Endometriosis [*drug therapy]; Estrogen Antagonists [*therapeutic use]; Pelvic Pain [*drug therapy]; Randomized Controlled Trials as Topic

MeSH check words

Female; Humans