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[Intervention Review]

Danazol for uterine fibroids

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ABSTRACT

Background

Uterine fibroids (myomas, fibromyomas, leiomyomas) are the most common benign tumours of the female genital tract. Danazol, a synthetic isoxazole derivative chemically related to 17-ethinyl testosterone, has been used for many years for the treatment of women with uterine fibroids. This is an update of the review published in 2009.

Objectives

To evaluate the effectiveness and safety of danazol in women with uterine fibroids.

Search methods

We searched the Cochrane Menstrual Disorders and Subfertility Review Group Specialised Register; Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2010, Issue 4); MEDLINE; EMBASE; Chinese Biomedical Disc; and the China National Knowledge Infrastructure for relevant trials (to December 2010). Attempts were made to identify trials from references in published studies. We also searched for ongoing trials in the five major clinical trials registries.

Selection criteria

Randomised controlled trials of danazol versus placebo or any other medical therapy in women with uterine fibroids confirmed by medical procedures, regardless of the women's symptoms or age. Studies of women with malignancies were excluded.

Data collection and analysis

Data extraction and risk of bias assessment were not performed because there were no identified studies.

Main results

We did not identify any studies which met our full inclusion criteria.

Authors' conclusions

There is no reliable evidence available from randomised controlled trials regarding the benefits or harms of the use of danazol for treating uterine fibroids.

PLAIN LANGUAGE SUMMARY

Danazol for treatment of women with symptoms caused by uterine fibroids

There is no evidence from randomised controlled trials demonstrating that the benefits of danazol outweigh its risks in treating uterine fibroids. Danazol is a synthetic isoxazole derivative chemically related to 17-ethinyl testosterone which creates a high androgen and low estrogen environment, resulting in the wasting of endometrium and shrinkage of fibroids. Despite its benefits, various undesirable side effects have also been reported. These include acne, hirsutism (excess hair in females, with an adult male pattern of distribution), weight gain, irritability, musculoskeletal pain, hot flushes, and breast atrophy, which many women may not tolerate. The review found no evidence demonstrating that the benefits of danazol outweigh the risks in treating uterine fibroids.

BACKGROUND

Description of the condition

The most common benign tumours of the female genital tract are uterine fibroids (myomas, fibromyomas, leiomyomas), which cause abnormal vaginal bleeding, abdominal pain, and pressure symptoms such as frequent and urgent urination or constipation. Fibroids are a common disorder, occurring in at least half of women in the USA of reproductive age, and account for 200,000 to 300,000 hysterectomies each year in the United States (Schwartz 2001; Payson 2006). Diagnosed uterine fibroids increase the need for medical resources and result in increased healthcare costs as well as loss of employment for the women themselves. Average annual excess costs for each woman with uterine fibroids were estimated at USD 4624 (with USD 771 in work-loss costs). Total costs for women with uterine fibroids were 2.6 times higher than for the controls (Hartmann 2006). The aetiology of uterine fibroids still remains obscure although much progress has been made in the understanding of hormonal, genetic, and growth factors, and the molecular biology of these benign tumours (Parker 2007).

Treatment of uterine fibroids depends on women's age, parity, symptoms, and desire for continuing fertility. Women with fibroids but no symptoms are usually managed expectantly (that is, by observation) since no effective medical alternatives have been identified and clinically relevant growth of the lesions is rare and unpredictable (Stewart 2001). In symptomatic cases, surgical approaches, including hysteroscopy for intracavitary fibroids and laparotomy or laparoscopy for intramural and subserosal lesions, are generally thought to be effective but they are invasive and expensive (Donnez 2002; Manyonda 2004; Mauskopf 2005). Treatments such as bilateral uterine artery embolisation (fibroid embolisation); laparoscopic myolysis; and magnetic resonance imaging (MRI) guided, focused ultrasound are other options in the management of fibroids, although they are currently not supported by randomised controlled trials (Donnez 2000; Pron 2003; Olive 2004; Wallach 2004; Worthington-Kirsch 2005; Goldberg 2006; Smart 2006; Stewart 2006; Somigliana 2007).

Medical treatment involving gonadotropin-releasing hormone agonists (GnRHa), androgen, antiprogesterone, oral contraceptives, selective estrogen receptor modulators (SERMs), and the levonorgestrel intrauterine system (levonorgestrel IUS) is primarily aimed at alleviating or eliminating symptoms related to fibroids, by decreasing the size of fibroids and the amount of bleeding. Complementary treatments such as acupuncture and herbs are other medical options although they are not currently supported by randomised controlled trials. Medical treatment is also used as a preoperative measure or combined with surgical therapies (Chavez 2001; Wu 2007).

Description of the intervention

Danazol, a synthetic isoxazole derivative chemically related to 17-ethinyl testosterone, is administered orally to women for the treatment of uterine fibroids.

How the intervention might work

Danazol has a complex mechanism of action, acting at different levels of the hypothalamic-pituitary-ovarian axis. It competes with the natural steroidal androgens, progesterone, and glucocorticoids in binding with high affinity to intracellular steroid receptors

(Donaldson 1989; Chavez 2001; Selak 2007). Its main action is an androgenic effect, increasing serum free testosterone by decreasing serum sex hormone-binding globulin production and by displacing testosterone from sex hormone-binding globulin. Danazol also lowers estrogen levels by suppressing gonadotropin secretion at the hypothalamic level and directly in the ovaries and uterus (Kogo 1992; Panidis 1994; Chavez 2001). Therefore, it creates a high androgen and low estrogen environment, resulting in the atrophy of the endometrium and shrinkage of fibroids. Despite its benefits, various undesirable side effects have also been reported. These include acne, hirsutism (excess hair in females, with an adult male pattern of distribution), weight gain, irritability, musculoskeletal pain, hot flushes, liver damage, and breast atrophy, which many women may not tolerate (Spooner 1977; Seifer 1990; Zawar 2004; Beaumont 2007).

Why it is important to do this review

Danazol has been used in the treatment of uterine fibroids for many years. Nevertheless, so far no systematic review has evaluated its benefits and risks when used for uterine fibroids.

OBJECTIVES

To evaluate the effectiveness and safety of danazol in women with uterine fibroids.

METHODS

Criteria for considering studies for this review

Types of studies

We intended to include randomised controlled trials (RCTs) in which women with uterine fibroids were treated with danazol. We would have included crossover studies if they reported pre-crossover data; they would have been subjected to a systematic assessment because of the persisting treatment effect of danazol. Abstracts or unpublished data were to be included and quasi-randomised and non-randomised studies were excluded.

Types of participants

We planned to include women with uterine fibroids that were confirmed by ultrasound scanning, computed tomography (CT), magnetic resonance imaging (MRI), laparoscopy, hysteroscopy, colposcopy, or combinations of these procedures, regardless of the women's symptoms or age. We excluded women with malignancy.

Types of interventions

1. Danazol versus no treatment or placebo
2. Danazol versus surgery
3. Danazol versus uterine artery embolism
4. Danazol versus other hormone treatments, such as GnRH agonists, antagonists, and receptor blockers (mifepristone); SERMs; oral contraceptives; the levonorgestrel IUS; and combinations of these treatments
5. Danazol versus complementary therapies, such as acupuncture or herbs
6. Danazol versus a combination of the comparisons above
7. Danazol prior to surgery versus other treatment or placebo prior to surgery
8. Danazol versus other kinds of treatment, as reported

Types of outcome measures

All the outcome measures listed below, both at the end of treatment and after a drug-free period.

Primary outcomes

Improvements in uterine fibroid-related symptoms both at the end of treatment and after a drug-free period:

- abnormal vaginal bleeding, measured by haemoglobin, haematocrit, or ferritin level;
- pain, measured by women on a visual analogue scale (VAS), or by pain improvement;
- pressure symptoms such as frequent and urgent urination, or constipation; reported by women with qualitative measures such as symptom free, better, the same, or worse.

Secondary outcomes

1. Adverse effects, measured both subjectively by occurrence and severity of any symptom or sign (listed below) as reported by participants and objectively by laboratory variables, both during and at the end of treatment as well as after a drug-free period.

(a) Major adverse effects

- Hypo-estrogenic (low estrogen levels): including decreased breast size, atrophic vaginitis, hot flushes, emotional lability, vaginal dryness, changes in libido
- Androgenic (excess male hormone): including acne, weight gain, hirsutism (excess hair in females, with an adult male pattern of distribution), oedema, muscle cramps, oily skin
- Laboratory variables to evaluate liver and renal function: measured by alanine aminotransferase (ALT), aspartate aminotransferase (AST), serum total bilirubin (STB), connect bilirubin (CB), unconnected bilirubin (UCB), blood urea nitrogen (BUN), blood creatinine (Cr) levels

(b) Other adverse effects

- Nausea
- Headaches
- Dizziness
- Fatigue
- Depression
- Nervousness
- Insomnia
- Skin rash

2. Reduction of uterine fibroid size: measured by ultrasound scanning, computed tomography (CT), nuclear magnetic resonance (MRI), laparoscopy, hysteroscopy, colposcopy, or a combination of these procedures.

3. Quality of life: measured by a validated instrument.

Search methods for identification of studies

Electronic searches

We drew on the search strategy developed for the Cochrane Menstrual Disorders and Subfertility Group. We identified relevant trials from the Cochrane Menstrual Disorders and Subfertility

Review Group Specialised Register; Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2010, Issue 4); MEDLINE; EMBASE; Chinese Biomedical Disc; and China National Knowledge Infrastructure (to December 2010). The following search strategy was carried out by Marian Showell (Trials Search Coordinator) and adapted for use in other databases and in other languages (see [Appendix 1](#); [Appendix 2](#); [Appendix 3](#); [Appendix 4](#); [Appendix 5](#)).

Keywords CONTAINS "fibroid" or "Leiomyoma*" or Title CONTAINS "fibroid" or "Leiomyoma*" or "myoma" or "myomas" or "uterine leiomyomas" or "uterine myoma" or "uterine myomas" or "uterine fibroids" or "fibroids" or Title CONTAINS "fibroid" or "Leiomyoma*" or Title CONTAINS "fibroid" or "Leiomyoma*" or "myoma" or "myomas" or "uterine leiomyomas" or "uterine myoma" or "uterine myomas" or "uterine fibroids" or "fibroids"

AND

Keywords CONTAINS Danazol or Title CONTAINS Danazol

We also searched for ongoing trials on the following websites:

- WHO International Clinical Trials Registry Platform (www.who.int/ictrp/);
- Australian and New Zealand Clinical Trials Registry (www.anzctr.org.au/);
- ClinicalTrials.gov (www.clinicaltrials.gov/);
- Chinese Clinical Trial Register (www.chictr.org/);
- Clinical Trial Registry - India (www.ctri.in).

Searching other resources

1. References from published studies

We checked these for further trials. We tried to identify additional studies by searching the reference lists of relevant trials and reviews that had been identified; and reference lists of theses, conference proceedings, and journals, in particular those journals that are not indexed in the electronic databases.

2. Unpublished literature

We contacted authors and pharmaceutical companies to identify unpublished and ongoing trials.

Data collection and analysis

Two authors (Lin-qiu Ke and Kun Yang) independently scanned the title, abstract section, and keywords of every record retrieved and assessed full articles if the information given suggested that the study might conform to our inclusion criteria. Since no trials were found that met the full inclusion criteria, all the methods below will be used when we update the review and identify trials for inclusion.

Selection of studies

In order to select studies for further assessment, two authors (Lin-qiu Ke, Kun Yang) will independently scan the title, abstract, and keywords of every record retrieved. Full articles will be assessed if the information given suggests that the study may conform to our criteria, described above. We then plan to contact all the authors of these articles by e-mail to ensure that all the self-described RCTs are authentic RCTs. We will record the study identity number (ID), name and contact details of the authors, date of the query to the

authors, method of the query (for example the e-mail address), and responses of the authors. All the information on included studies will be recorded in a table 'Characteristics of included studies'; excluded studies, with reasons for exclusion, will be recorded in the table 'Characteristics of excluded studies'. Decisions on inclusion will be made independently by two authors (Lin-qiu Ke, Kun Yang) according to the criteria stated above. Disagreements will be discussed and another person (Chun-Mei Li) will be consulted if these can not be resolved. If no clarification is provided, the Review Group editorial base will be consulted.

Data extraction and management

Data extraction was to be performed independently by two authors (Lin-qiu Ke, Kun Yang) using a data extraction form which will include at least the items listed in [Appendix 6 \(Higgins 2011\)](#). Differences in data extraction were to be resolved by discussion; another person (Chun-Mei Li) was to be consulted if disagreement continued.

Assessment of risk of bias in included studies

Lin-qiu Ke and Kun Yang would have independently assessed the risk of bias of the eligible studies, and any disagreements were to be resolved by Chun-Mei Li. We created a risk of bias table with six domains (listed below), judgements, and descriptions for each domain. We were to assess the following six domains using the Cochrane criteria for judgement of bias (listed in [Appendix 7](#)) for each eligible study ([Higgins 2011](#)):

1. sequence generation;
2. allocation concealment;
3. blinding of participants, personnel, and outcome assessors;
4. incomplete outcome data;
5. selective outcome reporting;
6. other potential threats to validity.

Measures of treatment effect

The treatment effect was to be expressed as Peto odds ratio (OR) with 95% confidence interval (CI) for dichotomous outcomes; and mean difference (MD) with 95% CI for continuous outcomes, or the standardised mean difference (SMD) for those data where different scales were used.

Unit of analysis issues

The unit of analysis was to be individual women.

Dealing with missing data

We were proposing to contact the corresponding authors by e-mail for missing data needed for the review. We would have performed intention-to-treat (ITT) and sensitivity analyses.

Assessment of heterogeneity

Assessment of heterogeneity would have been carried out using the Chi² test with significance set at $P < 0.1$. The I^2 statistic would have been used to assess the total variation across studies, with a value from 0% to 40% considered as low level heterogeneity, 30% to 60% as moderate heterogeneity, 50% to 90% as substantial heterogeneity, and 90% to 100% as considerable heterogeneity ([Higgins 2011](#)).

Assessment of reporting biases

A funnel plot was to be drawn to assess reporting biases.

Data synthesis

The meta-analysis was to be carried out using Review Manager 5.1. The fixed-effect model was to be used for the combined analysis of Peto ORs for dichotomous outcomes, and MDs or SMDs for continuous outcomes.

Subgroup analysis and investigation of heterogeneity

No randomised trials were identified so no subgroup analysis was performed to consider the different types of fibroids (submucosal, intramural, or subserosal fibroids). If heterogeneity was present, then we intended to explore it by considering the clinical settings and statistical issues.

Sensitivity analysis

Sensitivity analysis would have been performed to test the robustness of the evidence by excluding studies based on the extent of risk of bias seen, regardless of the source of the bias.

RESULTS

Description of studies

We found no studies meeting all the inclusion criteria. Five trials ([DeCherney 1983](#) ; [Ueki 1995](#) ; [Jie Zhang 1998](#); [Peng Xue-feng 2002](#) ; [Triolo O 2006](#)) which seemed to conform to our inclusion criteria were excluded after two authors (Lin-qiu Ke, Kun Yang) independently assessed the full articles.

Results of the search

Five trials were retrieved by the electronic searches.

Included studies

No studies were included.

Excluded studies

Five studies were excluded ([DeCherney 1983](#) ; [Ueki 1995](#) ; [Jie Zhang 1998](#); [Peng Xue-feng 2002](#) ; [Triolo O 2006](#)). Please refer to the [Characteristics of excluded studies](#) table for details of the studies that were excluded.

Risk of bias in included studies

No studies were included.

Allocation

No studies were included.

Blinding

No studies were included.

Incomplete outcome data

No studies were included.

Selective reporting

No studies were included.

Other potential sources of bias

No studies were included.

Effects of interventions

Since no studies were included, we could not evaluate the effects of the intervention.

DISCUSSION

([Ueki 1995](#) ; [Jie Zhang 1998](#); [Peng Xue-feng 2002](#) ; [Triolo O 2006](#)).

Summary of main results

Two studies reported a regression of fibroids with danazol therapy over two months and three months, respectively ([DeCherney 1983](#) ; [Jie Zhang 1998](#)). The third study, which studied the response of uterine fibroids to danazol compared to mifepristone, reported that there were no significant differences between the two treatment groups for improvement of uterine fibroid-related symptoms, such as abnormal vaginal bleeding and lower abdominal pain. With regard to the size of uterine fibroids, although danazol was more effective than mifepristone in shrinking the fibroids at three months there was no difference between the two treatment groups at six months ([Peng Xue-feng 2002](#)). In the fourth study danazol was less effective than buserelin, a GnRH analogue, in shrinking fibroids ([Ueki 1995](#)). The fifth study compared danazol and gestrinone treatment as a preoperative endometrial preparation for operative hysteroscopy. It included women with endo-uterine pathologies (endometrial polyps, submucosal myoma, septate uterus) and only nine women with submucosal myoma, diameter no greater than 3 cm, were included. The study reported that gestrinone was preferable to danazol in preparing the endometrium for operative hysteroscopy without separately analysing the results of the submucosal myoma subgroup ([Triolo O 2006](#)).

Side effects were reported in all five studies. Nausea and weight gain were the most common side effects; others were acne, hot flushes, and elevated hepatic enzymes. According to these five studies, danazol might be effective in the short term (less than three months) but no evidence was found for long-term effectiveness (use for more than six months). Danazol effects might be less favourable compared to new medicines such as GnRH agonists, which seem to be more powerful and with fewer side effects. Overall, the use of danazol for uterine fibroids is mainly limited by its side effects and duration of effectiveness.

Overall completeness and applicability of evidence

No studies were included.

Quality of the evidence

No studies were included.

Potential biases in the review process

No studies were included.

Agreements and disagreements with other studies or reviews

Although no RCTs were found to test the effects and potential risks of danazol for uterine fibroids the five excluded studies may give us some indication of why its usefulness is limited in clinical practice. The five excluded studies included comparisons with alternative therapies and none claimed a statistically significant lasting benefit of danazol. All five reported adverse events including nausea and weight gain which were the most common side effects.

AUTHORS' CONCLUSIONS

Implications for practice

Since there is no evidence from randomised controlled trials (RCTs) to demonstrate that the benefits of danazol outweigh its risks when used in the treatment of uterine fibroids we can make no recommendation about its use in clinical practice.

Implications for research

Well-designed RCTs with sufficient power are needed to test the benefits and risks of danazol compared to other medical therapies when used for uterine fibroids. It is suggested that these studies would need to consider and compare medical and surgical options for the relief of uterine fibroid-related symptoms.

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Peng Xue-feng 2002 {published data only}

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CHARACTERISTICS OF STUDIES

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
DeCherney 1983	Non-randomised clinical trial. An observational study to evaluate the effectiveness of danazol for uterine fibroids after three months of therapy.
Jie Zhang 1998	Non-randomised clinical trial. A retrospective study of 32 cases of uterine fibroids without any randomisation, control or blinding.
Peng Xue-feng 2002	Non-randomised clinical trial.
Triolo O 2006	Does not conform to the inclusion criteria for this study did not consider the primary outcome of this review. The main outcomes of this article are the endometrial response to the medical pre-treatment, side effects, procedure time, intraoperative bleeding, infusion volume, patient satisfaction. The study did not evaluate the improvements in uterine fibroid-related symptoms, both at the end of treatment and after a drug-free period.
Ueki 1995	The study was described as a non-randomised trial. In addition, the main outcomes of this study were the shrinkage of the fibroids, serum hormone change and histological changes in those with hysterectomised uterus.

APPENDICES

Appendix 1. CENTRAL

- 1 exp Leiomyoma/ (329)
- 2 Leiomyom\$.tw. (181)
- 3 fibroid\$.tw. (196)
- 4 fibromyoma\$.tw. (11)
- 5 fibroma\$.tw. (21)
- 6 myoma\$.tw. (190)
- 7 or/1-6 (554)
- 8 exp Danazol/ (182)
- 9 (danazol or norgestrel).tw. (284)
- 10 (danazone or azo).tw. (0)
- 11 dzol.tw. (0)
- 12 (danatrol or danova).tw. (2)
- 13 (danol or danova).tw. (1)
- 14 or/8-13 (297)
- 15 7 and 14 (6)

Appendix 2. CINAHL

- 1 exp Uterus Myoma/
- 2 leiomyoma\$.tw.
- 3 fibroid\$.tw.
- 4 (fibromyoma\$ or fibroma).tw.
- 5 (myoma or hysteromyoma\$).tw.
- 6 or/1-5
- 7 exp Danazol/
- 8 (danazol or danol).tw.
- 9 (danatrol or azo).tw.
- 10 or/7-9
- 11 6 and 10

Appendix 3. EMBASE

- 1 exp Uterus Myoma/ (7005)
- 2 leiomyoma\$.tw. (10074)
- 3 fibroid\$.tw. (3985)
- 4 (fibromyoma\$ or fibroma).tw. (5143)
- 5 (myoma or hysteromyoma\$).tw. (2921)
- 6 or/1-5 (22760)
- 7 exp Danazol/ (6424)
- 8 (danazol or danol).tw. (2494)
- 9 (danatrol or azo).tw. (244)
- 10 or/7-9 (6743)
- 11 6 and 10 (201)
- 12 Clinical Trial/ (823718)
- 13 Randomized Controlled Trial/ (286803)
- 14 exp randomization/ (53394)
- 15 Single Blind Procedure/ (13793)
- 16 Double Blind Procedure/ (99940)
- 17 Crossover Procedure/ (30214)
- 18 Placebo/ (177547)
- 19 Randomized controlled trial\$.tw. (60975)
- 20 Rct.tw. (6896)
- 21 random allocation.tw. (1022)
- 22 randomly allocated.tw. (15063)
- 23 allocated randomly.tw. (1675)
- 24 (allocated adj2 random).tw. (684)
- 25 Single blind\$.tw. (10778)
- 26 Double blind\$.tw. (116013)
- 27 ((treble or triple) adj blind\$).tw. (231)

28 placebo\$.tw. (155989)
29 prospective study/ (168039)
30 or/12-29 (1129628)
31 case study/ (11859)
32 case report.tw. (201863)
33 abstract report/ or letter/ (780126)
34 or/31-33 (989992)
35 30 not 34 (1096815)
36 11 and 35 (72)

Appendix 4. MEDLINE

1 exp Leiomyoma/ (15117)
2 Leiomyom\$.tw. (9070)
3 fibroid\$.tw. (3253)
4 fibromyoma\$.tw. (620)
5 fibroma\$.tw. (8382)
6 myoma\$.tw. (3981)
7 or/1-6 (27940)
8 exp Danazol/ (2089)
9 (danazol or norgestrel).tw. (2074)
10 (danazone or norgestrel).tw. (42)
11 dzol.tw. (0)
12 (danatrol or danova).tw. (14)
13 (danol or danova).tw. (10)
14 or/8-13 (2698)
15 7 and 14 (66)
16 randomized controlled trial.pt. (306071)
17 controlled clinical trial.pt. (82323)
18 randomized.ab. (221911)
19 placebo.tw. (131491)
20 clinical trials as topic.sh. (153882)
21 randomly.ab. (163652)
22 trial.ti. (94892)
23 (crossover or cross-over or cross over).tw. (50435)
24 or/16-23 (748627)
25 exp animals/ not humans.sh. (3581102)
26 24 not 25 (691363)
27 15 and 26 (9)

Appendix 5. PsycINFO

1 exp Gynecological Disorders/ (1260)
2 Leiomyom\$.tw. (9)
3 fibroid\$.tw. (32)
4 fibromyoma\$.tw. (1)
5 fibroma\$.tw. (17)
6 myoma\$.tw. (18)
7 or/1-6 (1317)
8 (danazol or norgestrel).tw. (12)
9 (danazone or norgestrel).tw. (1)
10 dzol.tw. (0)
11 (danatrol or danova).tw. (0)
12 (danol or danova).tw. (0)
13 or/8-12 (13)
14 7 and 13 (2)

Appendix 6. Data extraction form items

1. General information on the data: title, authors, source, contact address, country, published/unpublished, language, and year of publication.
2. Eligibility: confirm eligibility for review and reason for exclusion.

3. Methods: study design, total study duration, sequence generation, allocation sequence, blinding, concealment, other concerns about bias.
4. Participants: total number, setting, diagnostic criteria, age, country, ethnicity.
5. Interventions: total number of intervention groups, specific intervention and intervention details (dose and duration) for each intervention and comparison group of interest.
6. Outcomes: outcomes and time points, outcome definition and details (only for the outcomes listed in the protocol), upper and lower limits, and whether high or low score is good for scales used.
7. Results: number of participants allocated to each intervention group, and for each outcome listed in the protocol sample size, missing participants, and summary data for each intervention group.
8. Other information: funding source, key conclusions of the study authors, references to other relevant studies, correspondence required, miscellaneous comments by the review authors.

Appendix 7. Criteria for judging risk of bias in the risk of bias assessment tool

1. Sequence generation

Was the allocation sequence adequately generated?

Criteria for a judgement of 'YES' (low risk of bias)

The investigators describe a random component in the sequence generation process such as:

- referring to a random number table;
- using a computer random number generator;
- coin tossing;
- shuffling cards or envelopes;
- throwing dice;
- drawing of lots;
- minimisation*.

*Minimisation may be implemented without a random element, and this is considered to be equivalent to being random.

Criteria for the judgement of 'NO' (high risk of bias)

The investigators describe a non-random component in the sequence generation process. Usually the description would involve some systematic, non-random approach, for example sequence generated by:

- odd or even date of birth;
- some rule based on date (or day) of admission;
- some rule based on hospital or clinic record number.

Other non-random approaches are used much less frequently than the systematic approaches mentioned above and tend to be obvious. They usually involve judgement or some method of non-random categorisation of participants, for example allocation:

- by judgement of the clinician;
- by preference of the participant;
- based on the results of a laboratory test or a series of tests;
- by availability of the intervention.

Criteria for the judgement of 'UNCLEAR' (uncertain risk of bias)

Insufficient information about the sequence generation process to permit judgement of 'YES' or 'NO'.

2. Allocation concealment

Was allocation adequately concealed?

Criteria for a judgement of 'YES' (low risk of bias)

Participants and investigators enrolling participants could not foresee assignment because one of the following, or an equivalent method, was used to conceal allocation:

- central allocation (including telephone, web-based, and pharmacy-controlled randomisation);

- sequentially numbered drug containers of identical appearance;
- sequentially numbered, opaque, sealed envelopes.

Criteria for the judgement of 'NO' (high risk of bias)

Participants or investigators enrolling participants could possibly foresee assignments and thus introduce selection bias, such as allocation based on:

- using an open random allocation schedule (e.g. a list of random numbers);
- assignment envelopes were used without appropriate safeguards (e.g. if envelopes were unsealed or non-opaque or not sequentially numbered);
- alternation or rotation;
- date of birth;
- case record number;
- any other explicitly unconcealed procedure.

Criteria for the judgement of 'UNCLEAR' (uncertain risk of bias)

Insufficient information to permit judgement of 'YES' or 'NO'. This is usually the case if the method of concealment is not described or not described in sufficient detail to allow a definite judgement, for example if the use of assignment envelopes is described but it remains unclear whether envelopes were sequentially numbered, opaque, and sealed.

3. Blinding of participants, personnel, and outcome assessors

Was knowledge of the allocated interventions adequately prevented during the study?

Criteria for a judgement of 'YES' (low risk of bias)

Any one of the following.

- No blinding, but the review authors judge that the outcome and the outcome measurement are not likely to be influenced by lack of blinding.
- Blinding of participants and key study personnel ensured, and unlikely that the blinding could have been broken.
- Either participants or some key study personnel were not blinded, but outcome assessment was blinded and the non-blinding of others unlikely to introduce bias.

Criteria for the judgement of 'NO' (high risk of bias)

Any one of the following.

- No blinding or incomplete blinding, and the outcome or outcome measurement is likely to be influenced by lack of blinding.
- Blinding of key study participants and personnel attempted, but likely that the blinding could have been broken.
- Either participants or some key study personnel were not blinded, and the non-blinding of others likely to introduce bias.

Criteria for the judgement of 'UNCLEAR' (uncertain risk of bias)

Any one of the following.

- Insufficient information to permit judgement of 'YES' or 'NO'.
- The study did not address blinding to allocated intervention.

4. Incomplete outcome data

Were incomplete outcome data adequately addressed?

Criteria for a judgement of 'YES' (low risk of bias)

Any one of the following.

- No missing outcome data.
- Reasons for missing outcome data unlikely to be related to true outcome (for survival data, censoring unlikely to be introducing bias).
- Missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups.
- For dichotomous outcome data, the proportion of missing outcomes compared with observed event risk not enough to have a clinically relevant impact on the intervention effect estimate.

- For continuous outcome data, plausible effect size (difference in means or standardised difference in means) among missing outcomes not enough to have a clinically relevant impact on observed effect size.
- Missing data have been imputed using appropriate methods.

Criteria for the judgement of 'NO' (high risk of bias)

Any one of the following.

- Reason for missing outcome data likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across intervention groups.
- For dichotomous outcome data, the proportion of missing outcomes compared with observed event risk enough to introduce clinically relevant bias in intervention effect estimate.
- For continuous outcome data, plausible effect size (difference in means or standardised difference in means) among missing outcomes enough to introduce clinically relevant bias in observed effect size.
- 'As-treated' analysis done with substantial departure of the intervention received from that assigned at randomisation.
- Potentially inappropriate application of simple imputation.

Criteria for the judgement of 'UNCLEAR' (uncertain risk of bias)

Any one of the following.

- Insufficient reporting of attrition or exclusions to permit judgement of 'YES' or 'NO' (e.g. number randomised not stated, no reasons provided for missing data).
- The study did not address this outcome.

5. Selective outcome reporting

Are reports of the study free of suggestion of selective outcome reporting? (Short form: Free of selective reporting?)

Criteria for a judgement of 'YES' (low risk of bias)

Any of the following.

- The study protocol is available and all of the study's pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way.
- The study protocol is not available but it is clear that the published reports include all expected outcomes, including those that were pre-specified (convincing text of this nature may be uncommon).

Criteria for the judgement of 'NO' (high risk of bias)

Any one of the following.

- Not all of the study's pre-specified primary outcomes have been reported.
- One or more primary outcome is reported using measurements, analysis methods, or subsets of the data (e.g. sub-scales) that were not pre-specified.
- One or more reported primary outcome is not pre-specified (unless clear justification for reporting is provided, such as an unexpected adverse effect).
- One or more outcomes of interest in the review are reported incompletely so that they cannot be entered in a meta-analysis.
- The study report fails to include results for a key outcome that would be expected to have been reported for such a study.

Criteria for the judgement of 'UNCLEAR' (uncertain risk of bias)

Insufficient information to permit judgement of 'YES' or 'NO'. It is likely that the majority of studies will fall into this category.

6. Other potential threats to validity

Was the study apparently free of other problems that could put it at risk of bias?

Criteria for a judgement of 'YES' (low risk of bias)

The study appears to be free of other sources of bias.

Criteria for the judgement of 'NO' (high risk of bias)

There is at least one important risk of bias. For example, the study:

- had a potential source of bias related to the specific study design used; or
- stopped early due to some data-dependent process (including a formal stopping rule); or
- had extreme baseline imbalance; or
- has been claimed to have been fraudulent; or
- had some other problem.

Criteria for the judgement of 'UNCLEAR' (uncertain risk of bias)

There may be a risk of bias, but there is either:

- insufficient information to assess whether an important risk of bias exists; or
- insufficient rationale or evidence that an identified problem will introduce bias.

WHAT'S NEW

Date	Event	Description
13 July 2011	Review declared as stable	No relevant studies have been found and it appears unlikely that any will be undertaken.

HISTORY

Protocol first published: Issue 2, 2009

Review first published: Issue 3, 2009

Date	Event	Description
20 September 2010	Amended	Contact details amended

CONTRIBUTIONS OF AUTHORS

Chun-Mei Li: developed a search strategy and was to carry out and interpret the analysis, drafted the final review, and will update the review.

Lin-qiu Ke: was to extract data from trials and carry out and interpret the analysis, drafted the final review, and will update the review.

Kun Yang: was to extract data from trials, and drafted the protocol.

Li Jing: was to obtain copies of trials and contact corresponding authors of trials.

DECLARATIONS OF INTEREST

None known

INDEX TERMS

Medical Subject Headings (MeSH)

Danazol [*therapeutic use]; Estrogen Antagonists [*therapeutic use]; Leiomyoma [*drug therapy]; Uterine Neoplasms [*drug therapy]

MeSH check words

Female; Humans