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[Intervention Protocol]

Progesterone receptor antagonists and progesterone receptor modulators for endometriosis

Jing Fu[1], Lina Hu[2], Wei Huang[1], Huili Zhu[1], Qiushi Wang[1], Fan He[3], Lingxia Xie[1], Xiaoling Gan[2]

[1]Department of Obstetrics and Gynecology, West China Second University Hospital, West China Women's and Children's Hospital, Chengdu, China. [2]The Obstetrics and Gynecology Department, The Second Affiliated Hospital of Chongqing Medical University, Chongqing, China. [3]West China Hospital, Sichuan University, Chengdu, China

Contact address: Wei Huang, Department of Obstetrics and Gynecology, West China Second University Hospital, West China Women's and Children's Hospital, No. 17, Section Three, Ren Min Nan Lu Avenue, Chengdu, Sichuan, 610041, China. weihuang64@163.com.

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ABSTRACT

This is the protocol for a review and there is no abstract. The objectives are as follows:

To assess the effectiveness and safety of PAs and PRMs primarily in terms of pain relief in comparison to other treatments in women of reproductive age with endometriosis.

BACKGROUND

Description of the condition

The uterine cavity is lined by endometrial cells, which are under the influence of female hormones. Endometriosis is defined as the presence of endometrial tissue (glands and stroma) outside the uterine cavity. It is a condition that is oestrogen-dependent and thus seen primarily during the reproductive years. Progesterone counteracts oestrogen and inhibits the growth of the endometrium. These endometrial-like cells in areas outside the uterus are influenced by hormones and respond in a way that is similar to the cells found inside the uterus (Hooghe 2007; Giudice 2010). The prevalence of endometriosis ranges from 6% to 10% in women of reproductive-age, 50% to 60% of women and teenage girls with pelvic pain, and up to 50% of women with infertility (Goldstein 1980; Eskenazi 1997; Cramer 2002). Endometriosis can also be found in asymptomatic women during surgical procedures such as laparoscopic approach or sterilisation.

Rokitansky reported this disease for the first time in 1860. Although considerable progress has been made, the pathogenesis remains unclear. The 'Retrograde menstruation theory' proposed in the 1920s (Sampson 1927) speculated that during menstruation, a certain amount of menstrual fluid flowed backward from the uterus to 'shower the pelvic organs and pelvis lining' with endometrium cells. However, studies have shown that many women experience retrograde menstruation but do not go on to develop endometriosis. Another theory is 'Coelomic Metaplasia', which holds that certain cells, when stimulated, can transform themselves into different kinds of cells, thus endometriosis has been found in abdominal incisional scars after surgery for endometriosis. On rare occasions endometriosis may be transplanted by blood or by

the lymphatic system into peripheral organs such as the lungs and brain.

Description of the intervention

In women with endometriosis who wish to conceive in the future, minimally invasive surgical treatment may play an important role in the diagnosis and removal of endometriosis and also preservation of the ovaries without damaging normal tissue. Unfortunately, this approach is limited by recurrences of endometriosis. The goal of management is to provide pain relief, to limit recurrences, and to restore or preserve fertility where needed. As endometriosis is an oestrogen-dependent condition (see above), current medical treatment has focused at blocking ovarian oestrogen secretion (with gonadotropin releasing hormone analogues or antagonists, GnRH-a or GnRH-antagonists) or halting oestrogen-induced growth of ectopic endometrium (with oral contraceptives and androgens). The downside of this approach includes hot flushes and bone mineral loss (secondary to GnRHa), and acne and hirsutism (secondary to androgen therapy), all of which limit the long-term use of these drugs. Furthermore, the mean length of time before recurrence of pain after drug therapy is completed is between six and 18 months (Mahutte 2003). For this reason, there is an urgent need for a new approach to medical and surgical therapy for endometriosis.
Mifepristone (RU 486), a progesterone and glucocorticoid receptor antagonist, was first synthesized in 1980. Since then, numerous related compounds of progesterone receptor ligands have been synthesised exhibiting a spectrum of activity ranging from pure progesterone receptor antagonists (PA), to mixed agonists/antagonists. These latter compounds are also known as progesterone receptor modulators (PRM). PA and partial agonist antagonists - selective progesterone receptor modulators (SPRM) belong to the large progesterone receptor ligand family, and have many potential clinical applications in female reproduction. Due to the antiproliferative effect in the endometrium, PAs and PRMs have been advocated in the treatment of endometriosis. Unlike long acting GnRH-a, PA and PRM treatment is not associated with a decrease in bone mineral density, and is accompanied by an increase in oestradiol and progesterone receptors (Neulen 1996), suggesting that the endometrial antiproliferative effect is due to progesterone antagonism. This offers a new alternative: suppression of endometrial proliferation in the midst of an oestrogenic environment. To date, a few studies of PAs and PRMs for endometriosis have been published and some show significant clinical benefits (Kettel 1996; Chwalisz 2004). In an uncontrolled study, mifepristone (the most commonly administered PA) relieved pelvic pain without significant side effects (Koide 1998). However, it is reported that mifepristone caused down-regulation of progesterone receptors (PR) and oestrogen receptors(ER) and up-regulation of androgen receptors (AR) (Narvekar 2004), and in low daily doses inhibited ovulation and induced amenorrhoea in the majority of women (Brown 2002). The clinical effectiveness of PAs and PRMs still needs further evaluation.

How the intervention might work

The primary action of progesterone is to maintain pregnancy. PAs block the action of progesterone. It is therefore not surprising that they have clinical application in the medical termination of pregnancy (Brenner 2002; Brenner 2005). PAs work as antiprogestins, a substance that prevents cells from making or using progesterone. PRMs or SPRMs represent a new class of progesterone receptor ligands that exert clinically relevant tissue-selective progesterone agonist, antagonist, or partial (mixed) agonist/antagonist effects on various progesterone target tissues in an in vivo situation depending on the biological action studied. The endometriosis could be a consequence of direct effects on endometrial vasculature (Spitz 2003). Other potential explanations include the PR: an isoform that inhibits ER gene transcription induced by progestins and antiprogestins, but the exact mechanism has yet to established. As PAs and PRMs have a relatively minor effect on serum oestradiol and androgen levels, the application of PAs and PRMs could result in fewer side effects than current therapies.

Why it is important to do this review

Up to now, there has been no systematic review in this field. In this review, we hope to evaluate the clinical effectiveness of PAs and PRMs primarily in terms of pain relief and to collate the best evidence for their use as single agents in women with endometriosis.

OBJECTIVES

To assess the effectiveness and safety of PAs and PRMs primarily in terms of pain relief in comparison to other treatments in women of reproductive age with endometriosis.

METHODS

Criteria for considering studies for this review

Types of studies

We will include randomised controlled trials (RCTs) in all languages that examine the effect of PAs or PRMs in the treatment of symptomatic endometriosis. We will not include quasi-RCTs in

this review. Cross-over trials will be excluded as the design is not valid in this context.

Types of participants

Women of reproductive age who have symptoms ascribed to the diagnosis of endometriosis. The diagnosis must have been established during a surgical procedure performed prior to the start of treatment. Trials where women have asymptomatic disease or infertility alone will not be considered.

Types of interventions

We will consider the following comparisons.
1. PAs or PRMs versus placebo.
2. PAs or PRMs versus no treatment.
3. PAs or PRMs versus other medical therapies (danazol, gonadotrophin releasing hormone analogues, Combined oral contraceptive pill (OCP), levonorgestrel releasing intrauterine systems).
4. PAs or PRMs versus surgical treatment.
5. PAs Versus PRMs.
Studies involving surgical removal of pelvic organs will not be considered. Studies exploring the use of hormonal treatment as an adjunct to surgery or other medical treatment for endometriosis will not be considered.

Types of outcome measures

Primary outcomes

1. Relief in endometriosis-related pain at the end of therapy (decrease of pain scores).
2. Side effects occurring during therapy (Including numbers of women with fatigue, nausea, anorexia, vomiting, weight loss, skin rashes, amenorrhoea, endometrial hyperplasia or hypoadrenalism).

Secondary outcomes

3. Quality of life (QOL). If studies report more than one scale, preference will be given to the SF-36, then other validated generic scales, and finally condition-specific scales.
4. Changes of size and extent of endometrial cysts.
5. Change of cancer antigen 125 (CA125).
6. Re-occurrence rates (percentage of women with recurrence).
7. Side effects persisting after treatment.

Search methods for identification of studies

Electronic searches

We will develop a comprehensive literature search strategy in consultation with the Trials Search Coordinator of the Cochrane Menstrual Disorders and Subfertility Group. The two review authors JF and HZ will independently conduct a systematic search of the published and unpublished literature. There will be no restrictions on language or publication status.
We will search the following databases.

- Menstrual Disorders and Subfertility Group Specialised Register (MDSG) (Appendix 1).
- Ovid The Cochrane Central Register of Controlled Trials (CENTRAL) (Appendix 2).
- Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) (Appendix 3).
- Ovid EMBASE (Appendix 4).
- Ovid PsycINFO (Appendix 5).

Searching other resources

We will scan the references of all included studies and relevant reviews to identify further relevant articles, and handsearch relevant journals and articles which may not be included in the electronic databases. We will scan the following databases.

- CINAHL database (Appendix 6).
- *The Cochrane Library* - http://www.cochrane.org/index.htm for DARE - Database of Abstracts of Reviews of Effects (reference lists from non Cochrane reviews on similar topics).
- Trial registers for ongoing and registered trials - 'The World Health Organization International Trials Registry Platform search portal' http://www.who.int/trialsearch/Default.aspx.
- Conference abstracts on the ISI Web of Knowledge http://isiwebofknowledge.com/.
- Herbal or complimentary therapy protocols/reviews need to search at least one Chinese database as described in the MDSG Module.
- OpenSigle for Grey literature from Europe- http://opensigle.inist.fr/.
- LILACS database provides a source of trials from the Portuguese and Spanish speaking world - http://regional.bvsalud.org/php/index.php?lang=en.
- ClinicalStudyResults provides clinical trial results of marketed pharmaceuticals http://www.clinicalstudyresults.org/.

Data collection and analysis

Selection of studies

All titles and abstracts retrieved by electronic searching will be downloaded to a reference management database (e.g. Reference Manager or Endnote), duplicates will be removed and the remaining references will be examined by two review authors (JF, FH) independently. Those studies which clearly do not meet the inclusion criteria will be excluded and copies of the full text of potentially relevant references will be obtained.The eligibility of retrieved papers will be assessed independently by two review authors (JF, FH). Reasons for exclusion will be documented. The selection process will be documented with a "PRISMA" flow chart.

Data extraction and management

Two review authors will independently extract data from eligible studies using a data extraction form designed and pilot-tested by the authors.

Data extraction will include:

- participants' characteristics;
- number of participants in each arm of the trial;
- number excluded from analysis;
- type of intervention;
- proportion of participants who received all/part/none of the intended treatment;
- methods of randomisation, blinding and allocation concealment;
- length of follow-up;
- data on outcome;

Differences between review authors will be resolved by discussion or by appeal to a third author (LH or WH) if necessary. No blinding of review authors to article author or journal title will occur. Where appropriate, we will contact trial authors for further information and updated data.

Assessment of risk of bias in included studies

Two review authors will independently assess the methodological risk of bias of each trial according to the guidelines of *Cochrane Handbook of Systematic Reviews of Interventions* (Higgins 2011). According to the Cochrane 'Risk of bias' assessment tool, the assessment for risk of bias of included studies will consist of six domains: random sequence generation and allocation concealment (selection bias); blinding of participants and personnel performance bias); blinding of outcome assessment (detection bias); incomplete outcome data (attrition bias); selective reporting (reporting bias); and other sources of bias (other bias), with a judgement of low risk, high risk or unclear risk. We will resolve differences by discussion among the review authors or by consulting the Cochrane Menstrual Disorders and Subfertility Group.

Measures of treatment effect

For dichotomous data (e.g. recurrence rates), we will use the numbers of events in the control and intervention groups of each study to calculate Peto odds ratios. For continuous data (e.g. change of size and extent of endometrial cysts), we will calculate mean differences between treatment groups if all studies report exactly the same outcomes. If similar outcomes are reported on different scales, we will calculate the standardised mean difference. Ordinal data (e.g. quality of life scores) will be treated as continuous data. We will present 95% confidence intervals for all outcomes.

Unit of analysis issues

The primary analysis will be per woman randomised. Reported data that do not allow valid analysis (e.g. "per cycle" rather than "per woman" where women contribute more than one cycle) will be briefly summarised in an additional table and will not be meta-analysed.

Multiple live births (e.g. twins or triplets) will be counted as one live birth event. Only first-phase data from cross-over trials will be included.

Dealing with missing data

The data will be analysed on an intention-to-treat basis as far as possible and attempts will be made to obtain missing data from the original investigators. Where these are unobtainable, imputation of individual values will be undertaken for the primary outcomes only. If studies report sufficient detail to calculate mean differences but no information on associated standard deviation (SD), the outcome will be assumed to have a standard deviation equal to the highest SD from other studies within the same analysis. For other outcomes, only the available data will be analysed. Any imputation undertaken will be subjected to sensitivity analysis (see below).

Assessment of heterogeneity

We will assess heterogeneity between studies by visual inspection of forest plots, by estimation of the I^2 test which summarises the percentage of heterogeneity between trials which cannot be ascribed to sampling variation. An $I^2 < 25\%$ will be considered as low level, 25% to 50% as moderate level, and higher than 50% as high level heterogeneity. If there is evidence of substantial heterogeneity, we will investigate and report the possible reasons for this. We do not intend to combine results of trials with different comparator drugs.

Assessment of reporting biases

In view of the difficulty in detecting and correcting for publication bias and other reporting biases, the review authors will aim to minimise their potential impact by ensuring a comprehensive search for eligible studies and by being alert for duplication of data.

If there are 10 or more studies in an analysis, a funnel plot will be used to explore the possibility of small study effects (a tendency for estimates of the intervention effect to be more beneficial in smaller studies).

Data synthesis

We will combine the data from primary studies using fixed-effect models in the following comparisons.

1. PAs or PRMs versus placebo, stratified by mode of administration and dose:
   i) Low dose oral
   ii) High dose oral
2. PAs or PRMs versus no treatment, stratified by mode of administration and dose:
   i) Low dose oral
   ii) High dose oral
3. PAs or PRMs versus other medical therapies, stratified by alternative: danazol, gonadotrophin releasing hormone analogues, Combined OCP, levonorgestrel releasing intrauterine systems
4. PAs or PRMs versus surgical treatment
5. PAs versus PRMs

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

Subgroup analysis and investigation of heterogeneity

We intend to explore the following potential sources of heterogeneity using subgroup analyses. Subgroup analyses may be based on:

1. different drug;
2. different course or dosage.

Sensitivity analysis

Sensitivity analyses will be conducted for the primary outcomes to determine whether the conclusions are robust to arbitrary decisions made regarding the eligibility and analysis. These analyses will include consideration of whether conclusions would have differed if:

1. eligibility were restricted to studies without high risk of bias;
2. studies with outlying results had been excluded;
3. alternative imputation strategies had been adopted;
4. a random-effects model had been adopted.

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

A 'Summary of findings' table will be generated using GRADEPRO software. This table will evaluate the overall quality of the body of evidence for main review outcomes, using GRADE criteria (study limitations (i.e. risk of bias), consistency of effect, imprecision, indirectness and publication bias). Judgements about evidence quality (high, moderate or low) will be justified, documented, and incorporated into the reporting of results for each outcome.

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* *Indicates the major publication for the study*

APPENDICES

Appendix 1. keyword search

Menstrual Disorders and Subfertility Specialised Register search for LH993 11.04.11
Keywords CONTAINS "endometriosis"or"Endometriosis-Symptoms"or"pelvic pain"or "dyspareunia" or Title CONTAINS"endometriosis"or"Endometriosis-Symptoms"or"pelvic pain"or "dyspareunia"
AND
Keywords CONTAINS "progestagen antagonists"or "mifepristone"or"RU486"or"gestrinone"or"Onapristone" or Title CONTAINS "progestagen antagonists"or "mifepristone"or"RU486"or"gestrinone"or"Onapristone"

Appendix 2. CENTRAL

1 exp Endometriosis/
2 Endometriosis.tw.
3 exp Dyspareunia/
4 Dyspareunia.tw.
5 pelvi$ pain.tw.
6 or/1-5
7 exp Mifepristone/
8 mifepristone.tw.
9 RU486.tw.

10 (progest$ adj1 antagonist$).tw.
11 (progest$ adj1 modulator$).tw.
12 ru 486.tw.
13 mifegyne.tw.
14 ru38486.tw.
15 ru-38486.tw.
16 mifeprex.tw.
17 zk98296.tw.
18 zk 98296.tw.
19 r-38486.tw.
20 r38486.tw.
21 exp Gestrinone/
22 Gestrinone.tw.
23 Lilopristone.tw.
24 Onapristone.tw.
25 Aglepristone.tw.
26 Toripristone.tw.
27 (dimetriose or dimetrose).tw.
28 Nemestran.tw.
29 anti-progestin$.tw.
30 antiprogestin$.tw.
31 or/7-30
32 6 and 31

Appendix 3. MEDLINE

1 exp Endometriosis/
2 Endometriosis.tw.
3 exp Dyspareunia/
4 Dyspareunia.tw.
5 pelvi$ pain.tw.
6 or/1-5
7 exp Mifepristone/
8 mifepristone.tw.
9 RU486.tw.
10 (progest$ adj1 antagonist$).tw.
11 (progest$ adj1 modulator$).tw.
12 ru 486.tw.
13 mifegyne.tw.
14 ru38486.tw.
15 ru-38486.tw.
16 mifeprex.tw.
17 zk98296.tw.
18 zk 98296.tw.
19 r-38486.tw.
20 r38486.tw.
21 exp Gestrinone/
22 Gestrinone.tw.
23 Lilopristone.tw.
24 Onapristone.tw.
25 Aglepristone.tw.
26 Toripristone.tw.

27 (dimetriose or dimetrose).tw.
28 Nemestran.tw.
29 anti-progestin$.tw.
30 antiprogestin$.tw.
31 or/7-30
32 6 and 31
33 randomized controlled trial.pt.
34 controlled clinical trial.pt.
35 randomized.ab.
36 placebo.tw.
37 clinical trials as topic.sh.
38 randomly.ab.
39 trial.ti.
40 (crossover or cross-over or cross over).tw.
41 or/33-40
42 exp animals/ not humans.sh.
43 41 not 42
44 32 and 43

Appendix 4. EMBASE

1 exp endometriosis/
2 Endometriosis.tw.
3 Dyspareunia.tw.
4 pelvi$ pain.tw.
5 or/1-4
6 exp mifepristone/
7 mifepristone.tw.
8 RU486.tw.
9 (progest$ adj1 antagonist$).tw.
10 exp antigestagen/
11 (progest$ adj1 modulator$).tw.
12 exp progesterone receptor modulator/
13 ru 486.tw.
14 mifegyne.tw.
15 ru38486.tw.
16 ru-38486.tw.
17 mifeprex.tw.
18 zk98296.tw.
19 zk 98296.tw.
20 r-38486.tw.
21 r38486.tw.
22 exp GESTRINONE/
23 Gestrinone.tw.
24 Lilopristone.tw.
25 Onapristone.tw.
26 Aglepristone.tw.
27 Toripristone.tw.
28 (dimetriose or dimetrose).tw.
29 Nemestran.tw.
30 anti-progestin$.tw.
31 antiprogestin$.tw.

32 or/6-31
33 5 and 32
34 Clinical Trial/
35 Randomized Controlled Trial/
36 exp randomization/
37 Single Blind Procedure/
38 Double Blind Procedure/
39 Crossover Procedure/
40 Placebo/
41 Randomi?ed controlled trial$.tw.
42 Rct.tw.
43 random allocation.tw.
44 randomly allocated.tw.
45 allocated randomly.tw.
46 (allocated adj2 random).tw.
47 Single blind$.tw.
48 Double blind$.tw.
49 ((treble or triple) adj blind$).tw.
50 placebo$.tw.
51 prospective study/
52 or/34-51
53 case study/
54 case report.tw.
55 abstract report/ or letter/
56 or/53-55
57 52 not 56
58 33 and 57
59 (2010$ or 2011$).em.
60 58 and 59

Appendix 5. PsycINFO

1 exp Dyspareunia/
2 Dyspareunia.tw.
3 Endometriosis.tw.
4 pelvi$ pain.tw.
5 or/1-4
6 mifepristone.tw.
7 RU486.tw.
8 ru 486.tw.
9 Gestrinone.tw.
10 anti-progestin$.tw.
11 antiprogestin$.tw.
12 (progest$ adj1 antagonist$).tw.
13 (progest$ adj1 modulator$).tw.
14 or/6-13
15 5 and 14

Appendix 6. CINAHL

1 exp Dyspareunia/
2 Dyspareunia.tw.
3 Endometriosis.tw.
4 pelvi$ pain.tw.
5 or/1-4
6 mifepristone.tw.
7 RU486.tw.
8 ru 486.tw.
9 ru38486.tw.
10 zk98296.tw.
11 r38486.tw.
12 Gestrinone.tw.
13 Lilopristone.tw.
14 Onapristone.tw.
15 Aglepristone.tw.
16 Toripristone.tw.
17 Nemestran.tw.
18 or/6-17
19 5 and 14

CONTRIBUTIONS OF AUTHORS

All authors contributed to protocol development.

DECLARATIONS OF INTEREST

None known.