Use of mifepristone to treat endometriosis: a review of clinical trials and trial-like studies conducted in China

Sun-Wei Guo†1, Maohua Liu1, Fanghua Shen1 & Xishi Liu1

Endometriosis, characterized by the ectopic presence of an endometrial gland and stroma, is a common and debilitating gynecological disorder with an enigmatic pathogenesis [1]. Its presenting symptomology includes dysmenorrhea, dyspareunia, chronic pelvic pain and subfertility. Although the treatment of choice is currently surgery, medical treatment is often needed, either as a first-line therapy or owing to the high recurrence risk after surgery [1].

The use of progestins to treat endometriosis resulted from a somewhat serendipitous clinical finding in the 1950s that endometriosis-related symptoms were apparently resolved during pregnancy [2]. With the advent of oral and intrauterine contraceptives in the 1960s, their use in treating endometriosis was also proposed [3]. In 1973, danazol, an isoxazole derivative of 17α-ethinyl testosterone, began to be used in treating endometriosis [4]. The role of danazol was recognized as an anti-gonadotropin or a gonadotropin inhibitor [5,6]. With the recognition of estrogen dependency in endometriosis and the elucidation of the negative feedback mechanism in the hypothalamic–pituitary–gonadal axis at approximately the same time and, in particular, the availability of a gonadotrophin releasing hormone agonist (GnRHa), Buserelin, in the early 1980s, GnRHa was introduced as an alternative treatment for endometriosis [7].

While the three treatment modalities – progestins, androgenic agents and GnRHas – are somewhat effective in relieving endometriosis-associated pains, the relief of pain appears to be relatively short-term [8]. In addition, they have many undesirable, and sometimes severe, side effects [9–11]. Consequently, one strong impetus for endometriosis research is to search for more efficacious medical treatment, preferably with more tolerable side effects and cost profiles.

Mifepristone & its potential in treating endometriosis

In 1980, a synthetic steroid compound, known as RU-486, was discovered by scientists at Roussel-Uclaf Company in France during the development of novel glucocorticoid receptor antagonists. Its antiprogesterin activity was soon realized and it was later used as an abortifacient under the name mifepristone [12]. The WHO and the Royal College of Obstetricians

Keywords

- clinical trials
- efficacy
- endometriosis
- mifepristone
- quality
- review

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China was the first country in the world that approved mifepristone (RU-486) for abortion. A total of 6 years after the report published in the Western world indicated that mifepristone may also be effective in treating endometriosis, the first paper on the same topic was published in China in 1997. Since then, over 160 studies on this topic have been published in China. We retrieved 104 papers on clinical trials and trial-like studies conducted in China evaluating the use of mifepristone to treat endometriosis that were published in the last 11 years. We found that the quality of these studies is well below an acceptable level, making it difficult to judge whether mifepristone is truly efficacious. There are intriguing signs that these studies, as a whole, have serious anomalies. The areas that are glaringly deficient are informed consent, choice of outcome measures, the evaluation of outcome measures, data analysis and randomization. The uniformly low quality is disquieting, given the large quantity of studies, the enormous amount of resource and energy put into these studies and, above all, the weighty issue of treatment efficacy that concerns each and every patient with endometriosis. Equally disquieting are the low-quality repetition, the absence of a critical, systematic review on the subject, the lack of suggestions for multicenter clinical trials and the seemingly unnecessary duplication of clinical trials without due informed consent. In view of this, it may be time to institute changes in attitude and practice, and to change education and training programs in the methodology of clinical trials in obstetrics and gynecology research in China.

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and Gynaecologists have demonstrated that a combination of mifepristone followed by misoprostol is the most effective and safe medical method for inducing abortion in the first and second trimester of pregnancy [13].

Mifepristone was the first drug known to compete with progesterone at its receptor and the first member of the selective progesterone receptor modulators or SPRMs, agents that act on the progesterone receptor with tissue-specific agonist/agonist profiles of action. In 1991, Kettel et al. reported that in six women with endometriosis, the administration of RU-486 100 mg/d for 3 months resulted in an improvement in pelvic pain in all subjects without a significant change in the extent of disease as evaluated by follow-up laparoscopy [14]. Based on a case series, the same group also reported that the lower doses of RU-486 were also effective in relieving endometriosis-associated pelvic pain and causing regression of endometriosis in the absence of significant side effects [15–17]. The effect of suppression of ectopic implants was also confirmed in cynomolgus monkeys with induced endometriosis [18].

Despite these earlier promising reports, no clinical trials on the use of mifepristone to treat endometriosis seem to have been conducted since then in the USA or other parts of the world, except China. It is likely that the lack of availability of mifepristone in the USA may have contributed to this situation. Indeed, Roussel-Uclaf did not seek US approval, probably bowing to pressure from prolife groups and the importation of mifepristone, often labeled as the abortion pill in the media, was banned by the US FDA during the first Bush administration in 1989. It was approved for abortion by the FDA in 2000, yet it is not available to the public through pharmacies as other prescription drugs are – its distribution is restricted to specially qualified licensed physicians under the tradename Mifeprex [12].

In China, clinical trials examining mifepristone for induced abortion began as early as 1985, at the time when there was a great demand for abortifacient in order to rigorously enforce the ‘one family, one child’ policy. Since the homemade abortifacient, Trichosanthin, which was derived from the herb Trichosanthes kirilowii, did not work very well and was not easy to use, mifepristone, with its excellent abortion-inducing efficacy and ease of use, was a fortuitous and timely development. In 1986, mifepristone was quickly approved for termination of pregnancy for up to 49 days gestation in China [19], making China the first country in the world to approve mifepristone.

A total of 6 years after the first report on the use of mifepristone to treat endometriosis was published by Kettel et al. [14], the first clinical study conducted in China on the same topic was published in 1997 [20] following a brief review paper on the topic [21] and an animal study [22], both published in 1995. Since then, over 160 clinical studies have been published in Chinese medical journals; many of them appear to be clinical trials or trial-like studies. These papers are almost always published in Chinese in journals usually confined to China that are not easily accessible to western medical professionals. Such a copious research publication on the efficacy of a single drug is not very common in clinical studies.

Motivations for this review

After over 160 published papers over a period of 15 years, it is perhaps reasonable to expect that certain conclusive findings regarding the efficacy of mifepristone may have arisen from these studies, given the enormous economic burden that endometriosis has and the debilitating nature of the disease. Has any verdict been reached from these studies? What is the verdict, if any? Do the benefits of mifepristone outweigh the risks for treating endometriosis?

Before examining these questions in greater detail, it should be noted that clinical studies designed to evaluate the efficacy of potential therapeutics are prone to biases of various kinds. For this reason, there are universally accepted principles and guidelines for the design, execution and analysis of clinical trials. In fact, harmonization of clinical trial protocols was shown to be feasible across countries of the EU approximately 30 years ago. Coordination between Europe, Japan and the USA led to a joint regulatory-industry initiative on international harmonization named after 1990 as the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use [201]. Currently, most, if not all, clinical trial programs worldwide follow the ICH guidelines, aimed at “ensuring that good quality, safe and effective medicines are developed and registered in the most efficient and cost-effective manner”. These activities are pursued in the interest of the consumer and public health, to prevent unnecessary duplication of clinical trials in humans and to minimize the use of animal testing without
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compromising the regulatory obligations of safety and effectiveness’ [201].

With these guidelines, it seems logical to assess the quality of those published clinical studies on mifepristone to treat endometriosis. In other words, how trustworthy are these published studies?

**Objective**

The objective was to assess the quality of published clinical trials or trial-like clinical studies, all conducted and published in China, which evaluated the efficacy of mifepristone in relieving symptoms of endometriosis and in improving the fertility of women with endometriosis. Herein, trial-like studies refer to those clinical studies that have the ‘look and feel’ of a clinical trial aimed at the evaluation of a drug of interest, yet in many cases lack the methodological vigor and reporting quality normally required for a clinical trial. As previously stated, this is not a meta-analysis of these published studies.

**Methods of the review**

We followed the Quality of Reporting of Meta-analyses (QUOROM) guidelines [23] in the report of this review.

**Search strategy**

We searched the Cochrane Central Register of Controlled Trials, PubMed and the following Chinese language electronic databases: Chinese Biomedical Literature Database (CBM), Chinese Science & Technology Journals (VIP account), and China National Knowledge Infrastructure (CNKI) for all publications starting from 1979 to 1 April, 2010. We identified relevant studies using the terms ‘RU-486’, ‘mifepristone’, ‘clinical trial’, ‘endometriosis’, ‘endometrial ovarian cyst’, ‘chocolate cyst’ and a combination of them. Manual searches of bibliographies of all relevant trials or trial-like studies were also conducted independently by Maohua Liu and Fanghua Shen. Review articles and commentaries were excluded. There was no language restriction, but there were restrictions on the population and regions in which the study was conducted, namely, all studies had to be conducted within mainland China.

**Study selection & validity assessment**

We included studies if they met at least one of the following criteria:

- They were clinical trials or trial-like clinical studies of mifepristone compared with controls (i.e., placebo, nonmifepristone or conventional medicine [CM]);
- The diagnostic criteria of endometriosis included ultrasonography or other imaging techniques (if ovarian endometrial cyst), laparoscopic diagnosis or criteria established by the Integrated Chinese and Western Medicine Diagnostic Criteria for Endometriosis [24].

![Figure 1. The identification, selection and assessment of included clinical studies.](image)

FHS: Fanghua Shen; MHL: Maohua Liu; RCT: Randomized controlled trial.
No restriction on the formulation, dosage or route of administration was made. The contents of 165 retrieved citations were reviewed independently by two investigators (Maohua Liu and Fanghua Shen) to determine if they met eligibility criteria for inclusion. Discrepancies were resolved by consensus.

Of the 165 studies retrieved for detailed assessment, 104 fulfilled our inclusion criteria [25–128]. Figure 1 summarizes the search results.

**Data extraction**

All data from eligible studies were independently extracted by Maohua Liu and Fanghua Shen with a standard protocol (Figure 1). Discrepancies were resolved by consensus. Recorded variables were as follows: the first author's name, the year of publication, the type of hospital (i.e., primary, secondary, tertiary or unknown) in which the study was conducted, impact factor (IF) of the journal in which the study was published, whether surgery was performed or not, the number of authors on the paper, the sample size of each arm (group), whether or not combined with surgery, the mean duration of follow-up, the mean age in mifepristone and the control groups, the dosage of mifepristone used in the study, the overall effective rate (OER), the recurrence rate (RR) and the pregnancy rate (PR) in each arm/group. It should be noted that in most, if not all, studies, the duration of follow-up for calculating RR and the exact time interval between the termination of mifepristone treatment and the conception or pregnancy were not explicitly defined.

**Quality assessment of included studies**

Well designed and executed, properly powered randomized clinical trials (RCTs) can provide unequivocal evidence for or against the efficacy of a drug. Based on the basic principles of design, execution of RCTs and the characteristics of endometriosis, we developed a list of criteria for evaluating the quality of an included study (Table 1). This list had 10 categories: randomization, control, informed consent, diagnosis, outcome measurement, follow-up, bias (blindness in evaluating outcome measures), data analysis, report of adverse events and conclusion. Each category would give a maximum score of 5–15 for highest quality in that category, with a maximum total score of 100. In addition, we also used Jadad scale, which had the following questions [129]:

- Was the study described as randomized?
- Was the study described as double blind?
- Was there a description of withdrawals and dropouts?

An affirmative answer to each of the above questions would give 1 point while a negative one would yield none. Additional points were given if:

- The method of randomization was described in the paper, and that method was appropriate
- The method of blinding was described, and it was appropriate

Points would however be deducted if:

- The method of randomization was described, but was inappropriate
- The method of blinding was described, but was inappropriate [129]

Thus, the Jadad scale score of a study would range from 0 to 5.

For reference purpose, we also chose three recently published clinical trials on endometriosis [130–132]. Their quality and Jadad scores were also evaluated independently by Maohua Liu and Fanghua Shen.

**Measures of the therapeutic efficacy**

The primary outcome measure used in almost all included studies was the OER. Following the guidelines set by the Ministry of Health of China [133] and the Integrated Chinese and Western Medicine Diagnostic Criteria for Endometriosis [24], OER was defined to be the proportion of patients who underwent the treatment and who were later found to be cured, or significantly improved, or improved. Here, cured was also defined to be the complete disappearance of all symptoms, disappearance of pelvic mass or palpable tenderness; for women with infertility, cured was defined to be successfully getting pregnant or giving birth to a child within 3 years after the treatment. The significant improvement was defined to be at least two events of the following:

- Near or complete resolution of dysmenorrhea or dyspareunia
- Near or complete resolution of lumbosacral pain or lower abdominal pain
- Near or complete disappearance of nodules, along with significantly reduced or disappearance of palpable tenderness
Table 1. Criteria for assessing the quality of a clinical study.

| Category                  | Explanation                                                                 | Scoring                                                                                   | Max. score |
|---------------------------|-----------------------------------------------------------------------------|--------------------------------------------------------------------------------------------|------------|
| Randomization             | Randomization procedure should be used and adequately described to prevent biased selection | Was the randomization procedure used? 5 if yes, 0 if no  
Was the procedure adequately described? 5 if yes, 0 if no or incorrectly | 10         |
| Control                   | There should be a control group and its choice should be appropriate for comparison purpose | Was the control employed? 5 if yes, 0 if no  
Was the choice of controls reasonable? 3 if yes, 0 if no  
Was the control group comparable? 2 if yes, 0 if no | 10         |
| Consent                   | Informed consent should be obtained from participants                       | Did the study seek informed consent from participating patients? 5 if yes, 0 if no       | 5          |
| Diagnosis                 | Diagnosis of patients recruited to the study                                | Diagnostic criteria: 6 if laparoscopically confirmed, or 5 if based on ultrasonographic diagnosis (for ovarian endometriomas), 4 if based on criteria made by the National Miferpristone Specialty Group 4 if adequately spelled out inclusion and exclusion criteria, 0 if no | 10         |
| Outcome measures          | There should be a clear definition of primary outcome measures, and their evaluation should be made in an unbiased fashion | Dysmenorrhea severity: 4 if based on objective measurement (e.g., VAS) or 2 if based on subjective feel  
Size of pelvic mass or nodules: 4 if measured by imaging techniques or 2 if measured by gynecologic examination  
Pregnancy: 4 if adequately described the number of cycles since treatment or 0 if otherwise.  
Recurrence: 3 if defined recurrence and specified the duration or 0 otherwise | 15         |
| Follow-up                 | The duration of follow-up should be clearly stated and adequately described | Duration of follow-up: 3 if specified or 0 if otherwise  
Soundness of follow-up: (e.g., for pregnancy, 6 months minimum) 0–4  
Reported loss of follow-up? 3 if yes, 0 if no | 10         |
| Bias                      | Appropriate measures should be taken to minimize possible biases when evaluating outcome measures and these measures should be clearly described | Any measures taken to minimize potential biases when evaluating outcome measures: 10 if the evaluator was blinded; 2 if the evaluator was not blinded; If aware of and also took steps to minimize the bias; If aware of but did not take any steps; 0 if otherwise | 10         |
| Statistical analysis      | The analytical methodology should be adequately described and the methods should be appropriate | Were the statistical methods used sound? 5 if sound and adequately described; 0 if incorrect or no description at all.  
Was intention-to-treat method used? 5 if yes, 0 if no | 10         |
| Adverse events            | Adverse events should be described and reported. Even if there is no such event, this should be stated | Were any possible adverse events adequately described? 5 if yes, 0 if no  
Was adverse event mentioned in the paper? 5 if yes, 0 if no | 10         |
| Conclusion                | The conclusion of the study should be based on the data                     | If all conclusions were supported by the presented data: 10  
If x% of the author(s)' conclusions were supported by the presented data: x/10  
If none of the author(s)' conclusions were supported by the presented data: 0 | 10         |
| Total                     | Summation of all categories                                                 | Summation of all categories                                                                | 100        |
Improvement was defined to be at least two events of the following:
- Reduced dysmenorrhea or dyspareunia
- Reduced lumbosacral pain or lower abdominal pain
- Slightly deflated nodules, along with reduced or disappearance of palpable tenderness

Ineffective treatment was defined to be at least one of the following:
- Unabated dysmenorrhea or dyspareunia
- Unabated lumbosacral pain or lower abdominal pain
- No change in nodular lesions

Other outcome measures included dysmenorrhea remission rate, cyst shrinkage rate, PR and RR. However, more often than not, these rates were not explicitly defined; for example, the recurrence rate was often defined as the recurrence of some symptoms without specifying the length of follow-up after the start of the treatment. For this review, we only considered OER, RR and PR.

Statistical analysis
For descriptive statistics, we used boxplot [134] to graphically depict the distribution of data, in which the bottom and top of the box represent the lower and upper quartiles, respectively, the band near the middle of the box represents the median, and the ends of the whiskers represent the smallest and the largest nonoutlier observations. The comparison of distributions of continuous variables between two or among three or more groups was made using the Wilcoxon test and Kruskal-Wallis test, respectively. Pearson’s correlation coefficient was used when evaluating correlations between two variables when both variables are continuous. When at least one variable is ordinal, Spearman’s rank correlation coefficient was used instead.

To evaluate which factors were associated with the difference in OER, RR or PR between the mifepristone and the control groups, a multiple linear regression model was used in conjunction with a stepwise regression.

In order to observe whether publication bias exists in reporting the efficacy of mifepristone, funnel plots were employed [135]. In funnel plots, risk (for being effective, recurrent or pregnant) estimates, such as odds ratios (ORs) or log ORs, are placed on the horizontal axis against some measure of study size or precision, such as the standard errors (SEs), on the vertical axis. In the absence of selection biases (such as publication bias and bias in inclusion criteria), true heterogeneity (i.e., size of effect differs according to study size) and data irregularities (such as poor methodological design of small studies, inadequate analysis, and fraud), studies of large or small sample sizes should be symmetrically scattered around the true log OR in the funnel plot. Hence the plot should have the shape of a funnel with a wide opening on the top (due to
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Table 3. Characteristics of the 104 retrieved studies.

| Variable          | Distribution, n                                                                 |
|-------------------|----------------------------------------------------------------------------------|
| Sample size       | Mean (SD) of 96.2 (44.4)                                                         |
|                   | Median: 88.5; range: 16–350                                                      |
| Number of authors |                                                                                 |
| Number of authors | Median: 2; range: 1–6; 25% lower and upper quantiles:                            |
|                   | 1 and 3, respectively                                                           |
| Single author     | 41 (39.4%)                                                                      |
| 2 authors         | 35 (33.7%)                                                                      |
| 3 authors         | 11 (10.6%)                                                                      |
| 4 or more authors | 17 (16.3%)                                                                      |
| Number of arms    |                                                                                 |
| 2 arms            | 66 (63.5%)                                                                       |
| 3 arms            | 36 (34.6%)                                                                       |
| 4 arms            | 2 (1.9%)                                                                         |
| Surgical removal of lesions |                                                     |
| No                | 5 (4.8%)                                                                         |
| Yes               | 99 (95.2%)                                                                       |
| Type of controls† |                                                                                 |
| Unmedicated       | 65                                                                               |
| GnRH agonists     | 9                                                                                |
| Danazol           | 24                                                                               |
| Progestins        | 38                                                                               |
| Other             | 8                                                                                |
| Overall effective rate |                                                                                           |
| Treatment group   | Mean: 74.9%; median: 75.0% (range 23.0–100%) (n = 101)                             |
| Unmedicated group | Mean: 46.6%; median: 48.0% (range 14.0–86.0%) (n = 61)                            |
| GnRH agonists group | Mean: 85.4%; median: 90.0% (range 67.0–97.0%) (n = 8)                            |
| Danazol group     | Mean: 77.2%; median: 80.0% (range 40.0–100.0%) (n = 22)                          |
| Progestin group   | Mean: 74.5%; median: 76.0% (range 17.0–100.0%) (n = 36)                          |
| Other control group | Mean: 69.4%; median: 72.9% (range 16.0–100.0%) (n = 8)                          |
| Recurrence rate   |                                                                                 |
| Treatment group   | Mean: 11.3%; median: 10.0% (0.0–46.0%) (n = 91)                                  |
| Unmedicated group | Mean: 29.3%; median: 33.0% (9.0–86.0%) (n = 64)                                  |
| GnRHAs group      | Mean: 6.3%; median: 6.0% (3.0–13.0%) (n = 9)                                     |
| Danazol group     | Mean: 19.6%; median: 15.0% (3.0–48.0%) (n = 15)                                  |
| Progestin group   | Mean: 9.6%; median: 9.0% (0.0–33.0%) (n = 36)                                    |
| Other control group | Mean: 15.5%; median: 10.0% (8.0–33.0%) (n = 5)                                  |
| Pregnancy rate    |                                                                                 |
| Treatment group   | Mean: 31.8%; median: 31.0% (6.0–67.0%) (n = 28)                                  |
| Unmedicated group | Mean: 19.6%; median: 17.0% (4.0–44.0%) (n = 19)                                  |
| GnRH agonists group | Mean: NA median: NA (NA–NA) (n = 0)                                             |
| Danazol group     | Mean: 51.7%; median: 40.0% (40.0–75.0%) (n = 3)                                  |
| Progestin group   | Mean: 39.8%; median: 42.0% (19.0–67.0%) (n = 15)                                 |
| Other control group | Mean: 64.0%; median: 64.0% (64.0–64.0%) (n = 1)                                  |

†These numbers, when added up, exceeded 104 because 38 studies had more than two arms.

GnRHa: Gonadotrophin releasing hormone agonist; SD: Standard deviation.

sampling variability), with the tip of the funnel pointing to the bottom and centering on the true log ORs [135]. The choice of log OR instead of OR is a result of the fact that the SE of OR is somehow related with the OR, while the SE of log OR is purely a function of sample sizes in different exposure-disease status combinations.

The use of log ORs also renders ORs that are greater or less than 1 symmetric at 1. When SEs are used, funnel plots are considered to be an excellent tool to detect publication bias [136]. p-values of less than 0.05 were considered to be statistically significant. All computations were made with R 2.10.1 [137,202].
Role of the funding source
The sponsors of this study had no role in study design, data collection, data analysis, data interpretation or writing of this report.

Results
There were five different control groups in the 104 studies: unmedicated (i.e., surgery alone); GnRHa; danazol; progestins; and other medications (including traditional Chinese medicine and norethisterone). No study used a placebo as a control. There were a total of five studies that evaluated the efficacy of mifepristone without performing surgery, one used danazol control and the other four used other medications. In the remaining 99 studies, surgery was performed to remove endometriotic lesions, followed by treatment with mifepristone, no medication (unmedicated), GnRHa, danazol, progestins or other medications. The number of studies and their year of publication can be seen in Figure 2. From the figure it can be observed that the number of studies increased rapidly since 2004, peaked in 2007, and declined precipitously ever since.

The 104 studies had recruited a total of 10,003 patients. The sample size of these studies ranged from 16 to 350, with a median of 88.5. A substantial proportion of studies did not report basic information on their studies or recruited patients, such as age, the revised American Fertility Society classification stage and length of follow-up. Some important outcome measures, such as recurrence rate and/or pregnancy rate, were also not reported (Table 2). Some characteristics of a portion of the 104 studies are listed in Table 3.

Quality of the retrieved mifepristone studies
The quality scores by the two evaluators correlated very closely ($r = 0.97$, $p = 2.2 \times 10^{-16}$; Figure 3), with a maximum absolute difference of 5 points. The Jadad scores by the two evaluators also correlated very closely ($r = 0.94$, $p = 2.2 \times 10^{-16}$), with a maximum absolute difference of 1 point. The quality score and the Jadad score were also correlated, with the Spearman’s correlation coefficient being 0.53 ($p = 4.9 \times 10^{-9}$) and 0.53 ($p = 4.6 \times 10^{-9}$), respectively, for the two evaluators. Thus, we used their average scores in the following analyses.

For the 104 studies, their quality scores ranged from 34 to 78, with a median of 59.3 and a mean standard deviation of 7.8, which were significantly lower than that of the reference study group ($p = 0.003$; Figure 4). Only four (3.8%) of them had a score of 70 or higher, and 49 (47.1%) of them had a score of 60 or higher. That is, slightly over half of these studies had a ‘fail’ if a score of 60 was used as a passing cutoff, as commonly used in China. By contrast, the reference studies scored 84, 90 and 95, respectively – all above 80.

The Jadad score demonstrated the same results. The 104 studies had an average Jadad score of 1.2 (0.80). In fact, only four (3.8%) studies had a Jadad score of 3. No study had a Jadad score higher than 3, which is the minimum standard for the study’s results to be included in any systematic review or meta-analysis [138]. Approximately 73 or 70.2% of the studies had a score of lower than 2. By contrast, the three reference studies all had a full Jadad score of 5, which, as a group, were significantly higher than the mifepristone studies ($p = 0.002$).

When broken down into 10 composition categories, we can see from Figure 5 that in five out of 10 categories the average quality scores in the study group, now standardized from 0 to 10, were lower than 6. The score in the ‘consent’ category was the lowest in all studies – only

Figure 3. Scatter plot of quality scores assessed independently by Maohua Liu and Fanghua Shen. The dashed straight line designates a perfect match. The blue dots represent the 104 studies and the three red dots represent the reference studies.

FHS: Fanghua Shen, MHL: Maohua Liu.
nine (8.7%) studies reported informed consent, but the remaining studies did not mention it at all. The second lowest average score was in the ‘bias’ category, indicating serious deficiencies in assessing outcome measures. The average scores in analysis, randomization and outcome categories were also low, indicating various deficiencies in these aspects in the mifepristone studies. In particular, only one (1.0%) study had a full score and only two (1.9%) studies had a score of six or higher in the ‘bias’ category; only five (4.8%) studies had a full score in the ‘randomization’ category. All studies had a score of 5 or lower in the ‘analysis’ category, and no study had a full score in the ‘outcome’ category.

**The trend of quality scores**

In addition, we examined the time trend of the average quality score among all mifepristone studies. From Figure 6, we can see that the average quality score stayed around 60 in the last 11 years.

To identify which categories the increase in quality, or lack of it, is the most notable, we plotted the time trend for the standardized quality scores in nine categories – except for the consent category. It can be seen from Figure 7 that the quality scores in the control and conclusion categories, and, to a lesser extent, adverse event and analysis categories, were consistently high but those in the randomization, bias, and outcome categories were consistently low, especially in the bias category (Figure 7). While the quality in the diagnosis category gradually increased in the last 3–4 years, the quality in the follow-up category went downhill in a progressive manner (Figure 7).

**Factors associated with the quality score**

We examined potential factors that may have influenced the quality of the published mifepristone studies. We examined the IF score of the journal in which the study was published, the number of authors, the sample size of the study, whether surgery was used, whether the control was unmedicated, or used GnRHAs, danazol, progestins, or other treatment, as well as the year of publication. Univariate analysis indicated that the journal IF score \( (r = 0.20, p = 0.038) \) and the surgery \( (p = 0.01) \) were both positively associated with the quality score. The multiple linear regression analysis only identified whether surgery was used \( (p = 0.007) \) as the only variable positively associated with the quality score.

**Outcome measures**

In view of low quality and the Jadad scores in these studies, we next examined the outcome measures used in these studies to see whether there is any anomaly or idiosyncrasy. First we produced a scatter plot of the OER and RR in the control and mifepristone groups. For the five types of controls, the correlation coefficient in OER between the mifepristone and unmedicated, GnRHAs, danazol, progestins, and other treatment groups was 0.17 \( (p = 0.19) \), 0.81 \( (p = 0.01) \), 0.85 \( (p = 6.4 \times 10^{-5}) \), 0.88 \( (p = 1.4 \times 10^{-12}) \) and 0.88 \( (p = 0.0001) \), respectively. While the correlation coefficient between mifepristone and the unmedicated groups was not significant, the trend appeared to be linear. Further examination revealed that the two studies with the smallest sample sizes (mifepristone and unmedicated groups combined) – one 27, and the other, 35 – were apparently outliers (the two both had 100% OER in the mifepristone group). Removing the two studies yielded a correlation coefficient of 0.30, which was significant \( (p = 0.02; \text{Figure 8A}) \).

The situation for recurrence rate was similar, but in the following we only focus on the mifepristone and the unmedicated groups since the other control groups did not have sufficient sample size. The correlation coefficient
in recurrence rate between the mifepristone and the unmedicated groups was 0.23 ($p = 0.07$). Yet one study had only 27 patients and appeared to be an outlier (Figure 8B), as discussed previously. Removing this study gave a correlation coefficient of 0.49 ($p = 5.4 \times 10^{-5}$).

Normally, the efficacy of an experimental drug should not depend on that of the standard treatment used in the control group. Thus, the positive correlation between the experiment and the control groups, consistently seen in OER and RR, signaled something peculiar and was worth investigating further. Therefore, we attempted to determine which factors were associated with the rate in the mifepristone group.

We performed multiple linear regression analyses of the OER, recurrence rate and pregnancy rate in the mifepristone group using the respective rate in the control group, quality score of the study, year of publication, proportion of revised American Fertility Society classification III/IV patients, number of authors, dose of mifepristone, IF score of the journal in which the study was published, length of follow-up, the square root of the sample size of the mifepristone and the unmedicated groups. Interestingly, we determined that for OER, the difference in rate was associated with the OER in the control group ($p = 2.9 \times 10^{-9}$), dose of mifepristone ($p = 0.03$), and the number of patients in the control group ($p = 0.002$).

Using the same method, we found that the recurrence rate in the control group is the only variable that is associated with the difference in recurrence rate between the mifepristone and the unmedicated group ($p = 2.0 \times 10^{-16}$). Each 1% increase in the recurrence rate in the control group would decrease the difference by 0.92%. Strangely, the length of follow-up was not associated with the recurrence rate.

For pregnancy rate, while the correlation coefficient between the mifepristone and unmedicated groups was 0.37, it did not reach statistical significance ($p = 0.12; n = 19$). The pregnancy rate in the mifepristone group did correlate positively with the length of the follow-up period ($r = 0.76$, $p = 0.01; n = 10$; Figure 8D). The multiple linear regression analysis demonstrated that the length of follow-up period was positively associated with the difference ($p = 0.03$). In other words, the longer the follow-up period is, the larger difference in pregnancy rate between the mifepristone and unmedicated groups – each additional month in follow-up would increase the difference by 1.7%. However, caution should be exercised here since the result was based on only seven observations.

**Relationship among outcome measures**

For mifepristone and unmedicated groups, we plotted the recurrence rate against OER (Figure 9).
Since the definition of 'effectiveness' and that of recurrence both involve pain symptoms, especially when the former was not always defined within a specific timeframe, one would expect that these two rates would be somehow negatively correlated. We found that while in the unmedicated group recurrence rate (RR) correlated negatively with OER ($r = -0.35, p = 0.006$), it did not correlate with the OER in the mifepristone group ($r = -0.08, p = 0.48$). In addition, for the GnRHα and progestin groups, no such correlation was found (all $p > 0.2$).

**Indications for publication bias**

In a funnel plot, all calculated ORs would be approximatley 1 (or 0 if the log scale is used) if there is no difference in OER, RR, or PR between the mifepristone and the control group. However, the funnel plot for OER (Figure 10A) very closely resembled an asymmetric funnel. Barrering the existence of a systematic heterogeneity in which study effects correlate with sample sizes, the plot strongly suggests publication bias. In addition, as OR estimates became more precise, they gravitated to the null (Figure 10A).
For the unmedicated group, the publication bias did not seem to be evident (Figure 10b). However, for the pregnancy rate, the publication bias also appeared to be present (Figure 10c). It is interesting to note that studies with small sample sizes (thus less accurate, as measured by larger standard errors) tended to give estimates of larger effect size, yet larger studies (thus more accurate, as measured by smaller standard errors) tended to give estimates of smaller or even negative effect size.

Discussion
This study provides a systematic evaluation of the design, execution, and reporting of clinical trials and trial-like studies on the use of mifepristone to treat endometriosis published in China during 1999–2010. We found that:

- The majority of included studies had a low quality score, effectively in the fail category
- Less than 4% of studies had acceptable quality scores yet none of the included studies had an acceptable Jadad score of 4 or above
- Overall, there was a significant difference in both quality and Jadad scores between mifepristone and the reference studies
- In general, the outcome measures used in most, if not all, studies are questionable and are open to debate
- Consistent with the quality assessment, there is indication that the overall effective rates reported in many studies are problematic, as revealed by the positive correlation in OERs between the mifepristone and the control groups
• There is indication that publication bias is present in these studies.

**Much ado about nothing?**

Aside from the low quality and the Jadad scores, the lack of some basic information on the recruited patients found in the majority of these studies (Table 2), and the use of rather unconventional or idiosyncratic outcome measures, such as the overall effective rate, strongly suggest that the quality of design, execution and reporting of clinical trials and trial-like studies on the use of mifepristone to treat endometriosis in China is well below an acceptable level. Because of this low quality, it is difficult to make any inference on the efficacy of mifepristone in treating endometriosis, either based on individual studies or collectively. This suggests that most clinical studies on the use of mifepristone published in China in the last 11 years are low-quality repetitions. It seems as though no one cared as to why such studies should be repeated, or as to whether their own study can bring anything new or meaningful to the knowledge base. In addition, no one voiced the need for a multicenter study or ventured any meta-analysis or systemic review. For a country with a gross domestic product (GDP) per capita ranks the 98th in the world [203] this, in our opinion, is truly a waste of resources and energy – on an incredible scale.

**Signs of problems**

There are suggestive signs that these studies, as a whole, have serious problems. The areas with glaring deficiency are, of course, informed consent, bias in evaluating outcome measures, data analysis and randomization. However, there are other less conspicuous signs: correlation in OER and RR between the mifepristone and the control groups, the dependence of the magnitude of the

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**Figure 9.** Scatter plot of (A) recurrence rate (RR) versus OER for the mifepristone group; (B) RR versus OER for the unmedicated group; (C) RR versus OER for the GnRHa group; and (D) RR versus OER for the progestin group.

GnRHa: Gonadotrophin releasing hormone agonist; OER: Overall effective rate.
It is possible that the OER in both mifepristone and unmedicated groups may depend on the experience and skills of the practicing physicians in the hospital where the study was conducted, resulting in the correlation of OER in both groups. However, there has been no formal documentation that the different hospitals may have different OERs and RRs even though their patient populations are similar. The difference in the presence of negative correlation between the OER and RR in the unmedicated group but not in the mifepristone group suggests that there could be other explanations; for example, systematic biases, perhaps unknown to authors of the study, in the outcome evaluation may exist. The signs for publication bias (Figure 10A & C), as we found here, may also suggest that researchers, as well as journal editors and reviewers, may prefer impressive results.

The lack of dependence of RR on the length of follow-up is certainly problematic, since one quintessential measurement in quantifying recurrence is the time to recurrence after surgery [139]. This lack of dependence, coupled with the correlation in RR between the mifepristone and the unmedicated groups, casts serious doubts as to how useful these reported RRs are, especially in view of the fact that many studies did not even report the length of follow-up period.

**Informed consent**

Very few of the 104 studies mentioned informed consent, thus resulting in no point in the ‘consent’ category of the quality score. The requirement for consent to participate in a human experimentation such as a clinical trial is the first principle of the Nuremberg Code and a major component of the
A number of steps needs to be dramatically improved. On the one hand, the peer review in Chinese journals also attempts to carry out randomization. On the other hand, the essence of randomization, or simply made no attempt, that many investigators did not fully understand could be deemed authentic RCTs accepted methodology of randomization and appears to be more glaring for RCTs conducted in China. A recent study reported that among 3137 purported RCTs only 6.8% of them adhered to accepted methodology of randomization and could be deemed authentic RCTs. This signals that many investigators did not fully understand the essence of randomization, or simply made no attempt to carry out randomization. On the other hand, the peer review in Chinese journals also needs to be dramatically improved.

Bias

Next to consent, the quality score in the bias category was low (Figure 6). A number of steps could be taken to minimize any bias when evaluating outcome measures, for example, two persons could evaluate the outcome independently or without asking patients as which drugs they have taken. Without any assurance that the bias is minimized, the data could be laden with errors, rendering the results useless.

Randomization

Nearly 95% of the included studies did not adequately describe the randomization procedure, hence the low quality score in the randomization category. Inadequate reporting of research methods and processes and providing a misleading explanation of randomization by referring to a nonrandomized study as an RCT are parallel and are a worldwide problem. The problem appears to be more glaring for RCTs conducted in China. A recent study reported that among 3137 purported RCTs only 6.8% of them adhered to accepted methodology of randomization and could be deemed authentic RCTs. This signals that many investigators did not fully understand the essence of randomization, or simply made no attempt to carry out randomization. On the other hand, the peer review in Chinese journals also needs to be dramatically improved.

Causes for concern?

The overall low quality in the 104 studies spanning over a decade is certainly somewhat troubling. There are other issues that are equally disquieting. First, while we did find several review papers on the status of research on mifepristone as therapeutics for endometriosis, there has been no attempt, at least in published form, to systematically review the status and progress in this area. Most review papers are uncritical and certainly uninspiring, merely cataloging and rehashing published results. Second, we did not observe any clinical trials or trial-like studies reporting findings from two different institutions. Worse, no one has ever suggested pooling resources to carry out a multicenter RCT to unequivocally address the question of efficacy. Everyone just repeats, more or less, what others have published.

Third, for a single drug, over 100 trials and trial-like clinical studies over a span of 11 years seem to be somewhat excessive, especially when many of these studies were conducted without any informed consent. One of several impetuses that prompted the International Committee of Medical Journal Editors (ICMJE) to announce, in 2004, that its journals would not publish the results of any clinical trial that had not been appropriately registered at ClinicalTrials.gov or another qualified public registry by 13 September, 2005, is to avoid unnecessary duplication of clinical trials. By repeating over and over again clinical studies involving a potential drug with known side effects, the investigators effectively put patients at risk unnecessarily. This is not fair to the unsuspecting patients.

Finally, we note that the quality and the Jadad scores used in this review did not reflect some recent changes in raising the standard of quality in design, execution and reporting of clinical trials. The mandatory requirement for the registration of clinical trials as a prerequisite for publication has now been instituted by major international biomedical journals, and the Consolidated Standards of Reporting Trials (CONSORT) has also been recently updated. Besides the 10 categories that we used, a quality study is now also expected to report allocation concealment mechanism, sample size justification, registration and funding sources. Hence, while the quality score of all 104 studies remained more or less the same in the last 11 years, the actual gap in quality of clinical trials between China and the West may be widening.

Limitations of study

Our study has several limitations. First, since the data extraction and quality scoring were by two junior investigators (Maohua Liu and Fanghua Shen), it is possible that they may have missed some studies and the scoring may be erroneous. However, before data extraction the two investigators were given detailed instructions as to how the search should be done. The search was carried out with utmost care. It is unlikely that they would miss any relevant studies, especially those with higher quality (which tend to be published in journals with higher IF and thus higher impact factor).

Declaration of Helsinki. It provides an instrument for the protection of the patient’s rights and an important safeguard against unethical behaviors for personal and professional gains.

While the concept of informed consent is only approximately 20 years old in China, and while ordinary people in China may not feel quite comfortable participating in a clinical trial and may thus be apprehensive reading a consent form, the informed consent is absolutely necessary for any clinical trial and should and can be implemented with more education.
visibility (and thus less likely to be missed). The scoring was also performed independently and with great care. When in doubt, they always turned to the senior authors for clarification and guidance. The close correlation in quality scores between them strongly indicate the scoring was properly carried out.

Second, we used a quality score that we developed on our own. While we did not purposefully validate the scoring, the scoring list was developed based on the core principles of clinical trials and was not biased particularly against any studies. Consistent with this notion, the scoring system correlated with the Jadad score, indicating that our scoring system is valid for our purpose. The informed consent category is merely one component of it, comprising only 5 points of the quality score. The list actually did not include more recent requirements of CONSORT, such as allocation concealment mechanism, trial registration and disclosure of funding source. The correlation of the quality score and the Jadad score indicates that the quality score captures the essence of quality and should be appropriate.

Conclusion & future perspective

The quality of design, execution and reporting of clinical trials and trial-like studies conducted in China on the use of mifepristone to treat endometriosis that were published in the last 11 years is well below an acceptable level, making it difficult to judge whether mifepristone is truly efficacious. There are intriguing signs that these studies, as a whole, have serious problems. The areas that are glaringly deficient are informed consent, choice of outcome measures, evaluation of outcome measures, data analysis and randomization.

The uniformly low quality of mifepristone studies is alarming, given the large quantity of these studies the enormous resources and energy put into these studies, and, above all, the weighty issue of treatment efficacy that concerns each and every patient with endometriosis. While the peer review system should share part of the responsibility, the education and research systems also share the responsibility. Unless dramatic measures are taken to change this, clinical studies of this kind are not going to be sustainable and may backfire. Given the weighty issues of drug efficacy and safety that concern each and every patient with endometriosis, the time is ripe for a full evaluation of the problem.

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Executive summary

• A total of 104 clinical trials and trial-like studies have been conducted in China on the use of mifepristone to treat endometriosis, all of them published in the last 11 years in Chinese journals and all are not easily accessible to medical professionals outside of China.

• The majority of the 104 studies had a low quality score, effectively in the ‘fail’ category.

• Less than 4% of studies had acceptable quality scores, yet none of the included studies had an acceptable Jadad score of 4 or above. Overall, there was a significant difference in both quality and Jadad scores between mifepristone studies and similar clinical trials conducted in the West.

• In general, the outcome measures used in most, if not all, studies are questionable and open to debate.

• Consistent with the quality assessment, there is indication that the overall effective rates reported in many studies are problematic, as revealed by the positive correlation in overall effective rates between the mifepristone and the control groups.

• There is an indication that publication bias is present within these studies.

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