Systematic Review and Meta-Analysis

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Add-on effect of Guizhi Fuling formula to mifepristone for endometriosis

A meta-analysis of randomized controlled trials

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Abstract

Background: Guizhi Fuling pill, a famous traditional Chinese herbal formula, has been widely used for treatment of gynecological diseases. This meta-analysis sought to evaluate the add-on effect of Guizhi Fuling capsule (GZFL) to mifepristone in women with endometriosis.

Methods: A comprehensively literature search was conducted using Pubed, Embase, Cochrane Library, Wanfang, CNKI, VIP databases from their inceptions to January 25, 2019. Randomized controlled trials that compared GZFL plus mifepristone to mifepristone alone for treatment of endometriosis were eligible. Main outcomes were pregnancy, reduction of the recurrence, and serum level of follicle-stimulating hormone, luteinizing hormone, estradiol or progesterone.

Results: A total of 1052 women with endometriosis from 10 trials were identified and analyzed. Meta-analyses showed that GZFL plus mifepristone was superior to mifepristone in reducing the recurrence of endometriosis (RR 0.40; 95% CI 0.27–0.59) and improving the pregnancy (risk ratio [RR] 1.74; 95% confidence intervals [CI] 1.40–2.17). Moreover, adjuvant treatment with GZFL also significantly reduced serum level of estradiol (mean difference [MD] −20.83 pmol/L; 95% CI −34.01 to −7.65) and progesterone (MD −0.18 mmol/L; 95% CI −0.23 to −0.12). However, there were no significant differences in serum level of follicle-stimulating hormone (MD −0.42 U/L; 95% CI −1.16 to 0.31) and luteinizing hormone (MD −0.04 U/L; 95% CI −0.43 to 0.34).

Conclusion: GZFL as adjuvant therapy to mifepristone appears to have additional benefits in preventing recurrence of endometriosis and improving pregnancy among women with endometriosis. However, these conclusions should be *interpreted* with caution due to the methodological flaws of the included trials.

Abbreviations: CI = confidence intervals, FSH = follicle-stimulating hormone, GZFL = Guizhi Fuling capsule, MD = mean difference, RCT = randomized controlled trials, RR = risk ratio, TCM = Traditional Chinese Medicine.

Keywords: endometriosis, guizhi fuling capsule, meta-analysis, mifepristone, randomized controlled trials

1. Introduction

Endometriosis is a gynecological condition characterized by the presence of endometrial tissue outside the uterus. Approximately 10% to 15% women during reproductive ages suffer from endometriosis across worldwide.[1,2] The common symptoms of endometriosis include pelvic pain, dysmenorrhea, fatigue, dyspareunia, and infertility. Women with endometriosis have an increased risk of ovarian cancer or endometriosis-associated adenocarcinoma.[3] Current therapeutic choices for endometriosis mainly include medication and surgical approach.[4] Unfortunately, higher recurrence rate post-surgical procedure remains a big challenge.[5,6] Therefore, it is warranted to seek new therapy for better management of endometriosis.

Traditional Chinese Medicine (TCM) has been widely applied to manage the gynecological diseases including endometriosis.[7] Guizhi Fuling Pill was firstly recorded in Jingui Yaolue of the Han dynasty. This formula consists of *Ramulus Cinnamomi*, *Semen Persicae*, *Radix Paeoniae Alba*, *Poria, and Cortex Moutan*. Based on TCM theory, Guizhi Fuling formula possesses the effects of activating blood and dissolving blood stasis. Guizhi Fuling Capsule (GZFL) is a compound Chinese medicine preparation refined by modern technology. Mifepristone, a progesterone antagonist, has been introduced for the treatment of endometriosis for decades.[8–11] GZFL alone or in combination with mifepristone have been widely used for management of endometriosis.[12,13] To date, no previous meta-analysis has been evaluated the add-on effect of GZFL in endometriosis. We therefore performed this meta-analysis of randomized controlled trials (RCT) to evaluate the effect of GZFL add-on therapy to mifepristone in patients with endometriosis.

2. Materials and methods

2.1. Literature search

This meta-analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[14]

Editor: Muhammad Shahzad Aslam.

The authors have no funding and conflicts of interest to disclose.

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Medicine (2019) 98:33(e16878)

Received: 18 February 2019 / Received in final form: 16 July 2019 / Accepted: 17 July 2019

http://dx.doi.org/10.1097/MD.0000000000016878

A comprehensively literature search was conducted using Pubmed, Embase, Cochrane Library, Wanfang, CNKI, VIP databases from their inceptions to January 25, 2019 without language restriction. Searched keywords included "Guizhi Fuling" OR "Gyejibokryeong-Hwan" AND mifepristone" OR "RU-486" AND "endometriosis" AND ("random" OR "randomized controlled trial". Furthermore, reference lists of all pertinent articles were manually reviewed to identify any additional studies. Ethical approval was not required because this study only analyzed the existing literature.

2.2. Study selection

Inclusion criteria were as follows:

1. RCT as study design;
2. participants were women with confirmed endometriosis;
3. GZFL formula (pill, capsule, decoction, or tablet) plus mifepristone versus mifepristone alone as intervention; and
4. outcome measures were pregnancy rate and recurrence of endometriosis.

Secondary outcomes were serum level of follicle-stimulating hormone (FSH), luteinizing hormone, estradiol or progesterone, and adverse events including irregular vaginal bleeding, gastrointestinal reaction, hot flashes or abnormal liver function. Exclusion criteria were:

1. non-randomized trials and suspected plagiarism;
2. modified Guizhi Fuling formula as intervention;
3. any different interventions except for GZFL; and
4. outcome measures were not of interests.

2.3. Data extraction and quality assessment

For each included trial, the following information was collected by two authors independently: first author's name, publication year, study design, duration of disease, sample sizes, mean age or range, dosage of GZFL and mifepristone, course of treatment, outcome measures, follow-up duration, and drug-related adverse events. The risk of bias tool of the Cochrane Handbook for Systematic Reviews of Interventions was used to evaluate the methodological quality of included trials, which assessing sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessors, incomplete outcome data, selective reporting, and other sources of bias. Disagreements in data extraction and quality assessment between two reviewers were resolved by consensus.

2.4. Statistical analysis

Pooled estimates were express by risk ratios (RR) with 95% confidence interval (CI) for binary variables. Estimates of

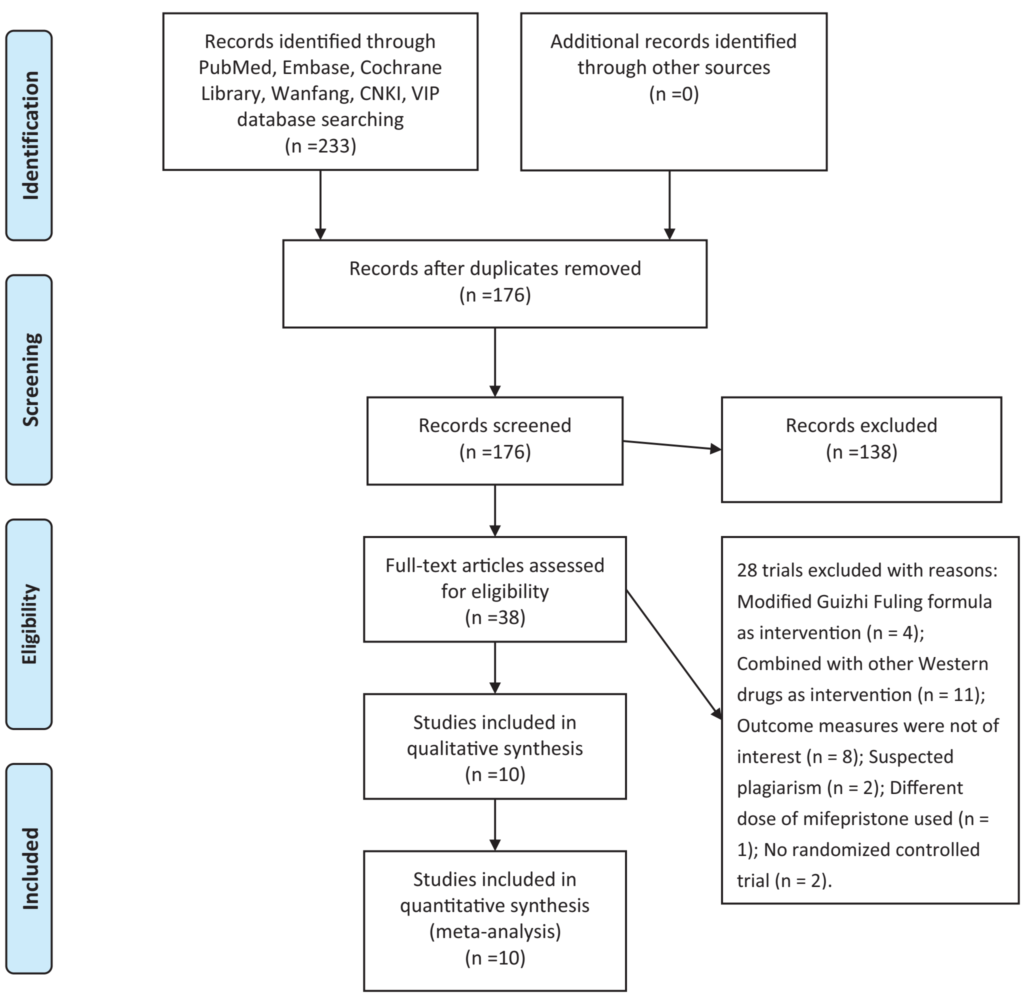

Figure 1. Flow chart of trials selection process.

continuous variables were pooled as the mean difference (MD) with 95% CI. The magnitude of heterogeneity across trials was examined using the Cochrane Q test and I^2 index. A fixed-effect model meta-analysis was applied in the absence of substantial heterogeneity (*P* value of Cochrane *Q* test >0.10 or I^2 index <50%). Otherwise, we selected a random effect model for pooling data. Sensitivity analysis was conducted by removing each study in turn from the meta-analysis to check the robustness of the pooling results. Subgroup analyses were performed by the length of treatment (3 months vs 6 months). Publication bias was scheduled using the Begg rank correlation test[15] and Egger regression test.[16] Meta-analysis was conducted using Review Manager 5.1 software (The Cochrane Collaboration, Copenhagen, Denmark) and STATA 12.0 (STATA Corp LP, College Station, TX).

3. Results

3.1. Search results and study characteristics

Our initial literature searches produced 233 records. A total of 176 records left after removal of duplicates. Of which, 138 were removed after scanning the titles and abstracts. Thirty-eight full-text articles were retrieved for detailed assessment. Twenty-eight articles were further excluded for various reasons (Fig. 1). Thus, 10 trials[17–26] were finally included in the current meta-analysis.

Table 1 summarizes the main characteristics of the included trials. All the included trials were conducted in China and published between 2007 and 2018. The included trials recruited a total of 1052 patients with endometriosis, with sample sizes ranging from 64 to 156. In most trials, GZFL was administrated orally 0.93 g at one time, 3 times per day. Clinically, 3 to 6 months duration of GZFL treatment is recommended. Table 2 shows the overview ingredients of GZFL. The methodological quality of included trials is summarized in Figure 2. Two trials[20,21] described the definition of recurrence of endometriosis, but others did not clearly define the recurrence. Based on the items of the methodological reporting, most of the trials were grouped as suboptimal methodological quality with unclear risk of bias. All the included trials did not consider TCM syndrome differentiation at the enrolment of patients.

3.2. Pregnancy rate and recurrence rate

Eight trials[17–23,25] reported pregnancy rate during up to 24-month of follow-up. As shown in Figure 3A, a fixed effect model was selected because no obvious heterogeneity was observed ($I^2=0\%$, $P=.86$). The pooled RR was 1.74 (95% CI 1.40 to 2.17) comparing GZFL plus mifepristone to mifepristone alone treatment. There was no evidence of publication bias according to the results of Begg test ($P=.536$) and Egger test ($P=.573$). Recurrence of endometriosis was assessed in 5 trials.[19–21,23,25] As shown in Figure 3B, we used a fixed-effect model due to no evidence of obvious heterogeneity ($I^2=0\%$, $P=.99$). Meta-analyses indicated that GZFL plus mifepristone was superior to mifepristone alone in reducing the recurrence (RR 0.40; 95% CI 0.27–0.59).

3.3. Serum level Of FSH, luteinizing hormone, estradiol, and progesterone

Four trials[18,22,24,26] provide serum level of hormone, including FSH, luteinizing hormone, estradiol, and progesterone. As shown in Figure 4, the pooled results showed that GZFL plus

Table 1

Characteristics of clinical trials included in the meta-analysis.

First author/year	Sample size	Age (years)	Duration of disease	Main interventions: GZFL group	Main interventions: Control group	Course of treatment	Follow-up duration	Outcome measures
Lu CH 2007[17]	GZFL:40 Con: 40	GZFL: 24–42 Con: 25–44	GZFL: 10 m–13y Con: 1–12 y	GZFL capsule + Mifepristone 8.3 mg/d	Mifepristone 8.3 mg/d	3 months	3 months	①+⑦
Lin TY 2010[18]	GZFL:32 Con:32	GZFL: 27–47 Con: 25–45	GZFL: 2.5–8 y Con: 3–9 y	GZFL capsule + Mifepristone 10 mg/d	Mifepristone 10 mg/d	3 months	6 months	①+③+④+⑤+⑥+⑦
Pan XR 2011[19]	GZFL:44 Con:41	24–43	3 m–12y	GZFL capsule + Mifepristone 12.5 mg/d	Mifepristone 12.5 mg/d	6 months	24 months	①+②+⑦
Gu ZY 2012[20]	GZFL:78 Con:78	GZFL: 24–44 Con: 25–42	GZFL: 5 m–10 y Con: 10 m–8 y	GZFL capsule + Mifepristone 12.5 mg/d	Mifepristone 12.5 mg/d	6 months	18 months	①+②+⑦
Gao Z 2012[21]	GZFL:74 Con:73	GZFL: 21–43 Con: 19–44	GZFL: 1–12 y Con: 11 m–13 y	GZFL capsule + Mifepristone 12.5 mg/d+ Laparoscopy	Mifepristone 12.5 mg/d+ Laparo-scopy	6 months	6-12 months	①+②
Shen WL 2013[22]	GZFL:50 Con: 50	GZFL: 32±7 Con: 33±5	GZFL: 2.6±1.8y Con: 2.7±2.0 y	GZFL capsule + Mifepristone 12.5 mg/d	Mifepristone 12.5 mg/d	3 months	24 months	①+⑤+⑥
Hao CR 2015[23]	GZFL:61 Con:61	33.0±5.8	1.5–13 y	GZFL capsule + Mifepristone 10 mg/d+ Laparoscopy	Mifepristone 10 mg/d + Laparo-scopy	3 months	24 months	①+②+⑦
Yang CQ 2015[24]	GZFL:55 Con: 55	32±5	5.3±2.7 y	GZFL capsule + Mifepristone 12.5 mg/d	Mifepristone 12.5 mg/d	3 months	6 months	③+④+⑤+⑥+⑦
Wang JY 2017[25]	GZFL:46 Con: 46	GZFL: 33.4±2.3 Con: 34.1±1.8	GZFL: 5.2±1.1 y Con: 5.4±0.8 y	GZFL capsule + Mifepristone 25 mg/d	Mifepristone 25 mg/d	3 months	12 months	①+②+⑦
Lv YL 2017[26]	GZFL:48 Con: 48	GZFL: 28.5±4.9 Con: 29.1±4.3	GZFL: 2.6±0.9 y Con: 2.9±0.8 y	GZFL capsule + Mifepristone 12.5 mg/d	Mifepristone 12.5 mg/d	3 months	6 months	③+④+⑤+⑥+⑦

Con = control, GZFL = Guizhi Fuling; ①pregnancy rate; ②recurrence rate; ③follicle-stimulating hormone; ④luteinizing hormone; ⑤estradiol; ⑥progesterone; ⑦adverse events.

Table 2

Overview ingredients of Guizhi Fuling capsule.

Chinese name	English name	Latin name	Genus	Family	Proportion
Guìzhī	Cassia Twig	Ramulus Cinnamomi	Cinnamomum	Lauraceae	1
Táo rén	Peach Seed	Semen Persicae	Prunus	Rosaceae	1
Bái Sháo	White Paeony Root	Radix Paeoniae Alba	Cynanchum	Apocynaceae	1
Báifúlíng	White Poria cocos	Poria Cocos	Smilax	Smilaceae	1
D⊠npí	Tree Peony Bark	Cortex Moutan	Paeonia	Paeoniaceae	1

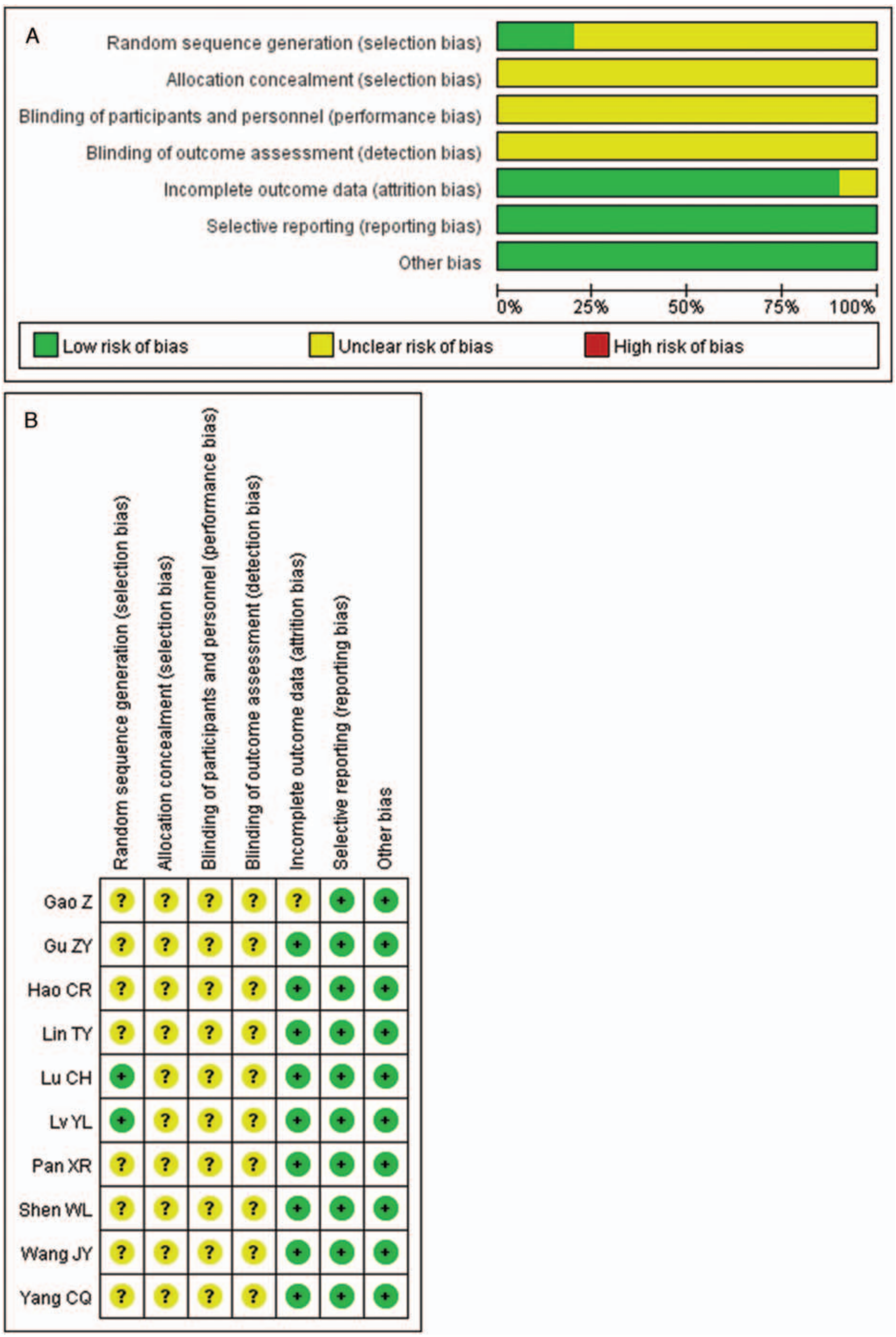

Figure 2. Risk of bias graph (A) and risk of bias summary (B).

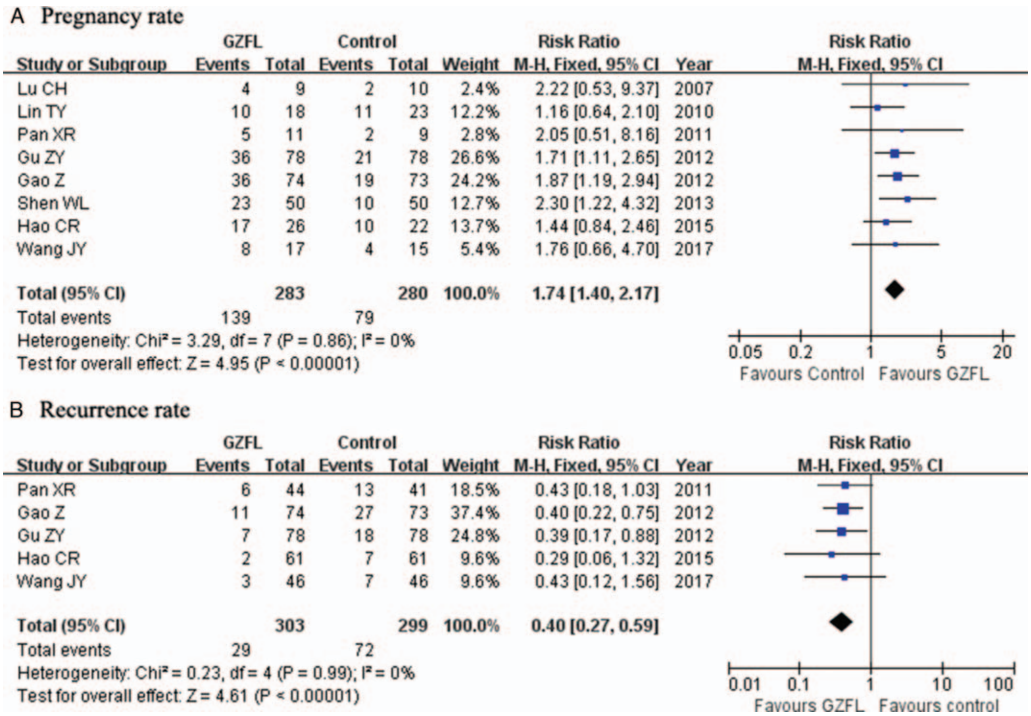

Figure 3. Forest plots showing comparison of pregnancy rate (A) and recurrence rate (B) comparing GZFL plus mifepristone to mifepristone alone treatment.

mifepristone significantly reduced serum level of estradiol (MD -20.83 pmol/L; 95% CI −34.01 to −7.65; $I^2=91\%$, $P<.001$) and progesterone (MD −0.18 mmol/L; 95% CI −0.23 to −0.12 $I^2=45\%$, $P=.14$) compared with mifepristone alone. However, there were no significant differences on serum level of FSH (MD -0.42 U/L; 95% CI −1.16 to 0.31; $I^2=67\%$, $P=.05$) and luteinizing hormone (MD −0.04 U/L; 95% CI −0.43 to 0.34; $I^2=0\%$, $P=.63$).

3.4. Adverse events

Nine trials[17–20,23–26] reported adverse events, including gastrointestinal reaction, irregular vaginal bleeding, hot flashes, and abnormal liver function. No trial reported any serious adverse events. As shown in Figure 5, a fixed effect model meta-analysis indicated that GZFL plus mifepristone was associated with less risk of irregular vaginal bleeding (RR 0.54; 95% CI 0.32–0.91; $I^2=0\%$, $P=.91$;5 trials [18–20,24,26]) and abnormal liver function (RR 0.45; 95% CI 0.22–0.90; $I^2=0\%$, $P=.88$; 5 trials [18,20,23,24]). However, there were no significant differences on the risk of gastrointestinal reaction (RR 0.45; 95% CI 0.19–1.04; $I^2=0\%$, $P=.42$; 4 trials [17,19,23,25]) and hot flashes events (RR 0.61; 95% CI 0.16–2.29; $I^2=45\%$, $P=.18$; 2 trials [17,19]).

3.5. Subgroup analyses and sensitivity analyses

We conducted the subgroup analysis on the pregnancy and recurrence rate according to the length of treatment. Results from the subgroup analysis revealed that the successful pregnancy rate was higher after 6-month treatment (RR 1.80; 95% CI 1.33–2.45) than 3-month treatment (RR 1.68; 95% CI 1.22–2.30). GZFL treatment was associated with greater reduction in recurrence of endometriosis after 6-month treatment (RR 0.40; 95% CI 0.26–0.62) than 3-month treatment subgroup (RR 0.36; 95% CI 0.13–0.95). Leave-out one trial sensitivity analyses indicated that exclusion of any individual studies each time did not alter the direction of the pooled effect sizes of pregnancy rate and recurrence rate (data not shown).

4. Discussion

The main findings of this meta-analysis indicated that GZFL plus mifepristone had additional benefits than mifepristone alone in terms of improving pregnancy rate and preventing disease recurrence among women with endometriosis. Adjuvant treatment with GZFL to mifepristone improved 74% clinical pregnancy rate and reduced 60% recurrence of endometriosis. Furthermore, GZFL as add-on therapy to mifepristone also significantly decreased serum level of estradiol and progesterone. These findings suggest that GZFL in combination with mifepristone can synergistically improve the clinical efficacy.

Suppression of sex hormone secretion may be possible therapeutic options for endometriosis. Mifepristone has been shown to inhibit the secretion of serum level of FSH, estradiol, and progesterone.[10] In the current meta-analysis, adjuvant treatment with GZFL significantly reduced the serum level of estradiol and progesterone, which indicating suppression of estradiol and progesterone production may be correlated with the better therapeutic action. CA125 and CA199 may represent a potential biomarker of endometriosis.[27] Mifepristone combined with GZFL significantly reduced the serum CA125 and CA199 level in women with endometriosis.[26] In addition, preclinical studies also demonstrated its anti-inflammatory activity,[28] anti-apoptosis,[29] and immunological regulation effect.[30] However, therapeutic mechanisms of GZFL remain largely unknown and should be further investigated in future studies.

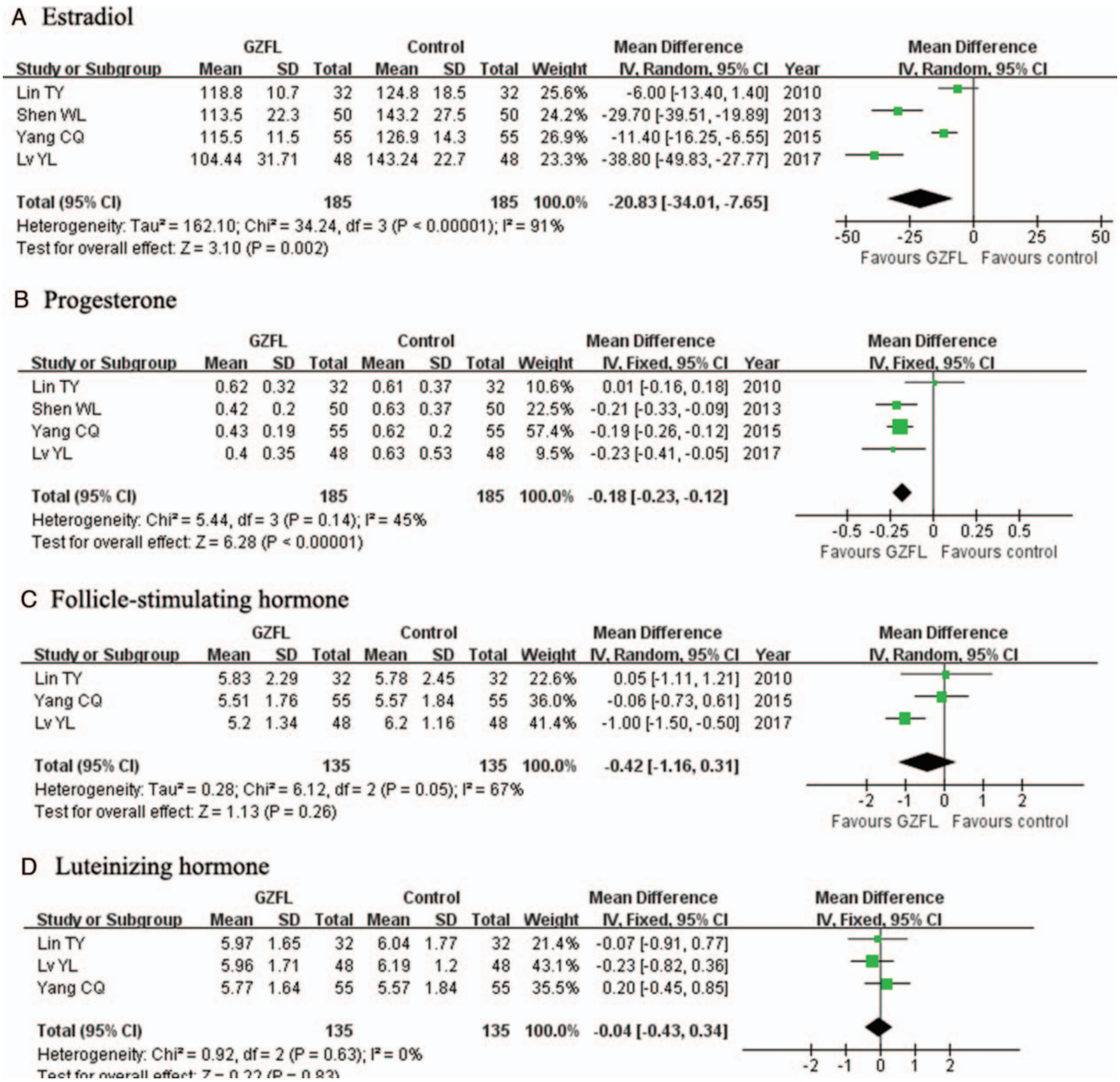

Figure 4. Forest plots showing comparison of serum level of estradiol (A), progesterone (B), follicle-stimulating hormone (C), and luteinizing hormone (D) comparing GZFL plus mifepristone to mifepristone alone treatment.

Another concern is whether add-on therapy using GZFL maybe increases the adverse events. Irregular vaginal bleeding, hot flushes, nausea, vomiting, and impaired liver function was the most common adverse effect of mifepristone.[31] In this meta-analysis, lower risk of irregular vaginal bleeding and abnormal liver function was observed in women with GZFL plus mifepristone therapy than mifepristone alone, suggesting GZFL could decrease mifepristone-related adverse effects. Moreover, GZFL as add-on therapy to mifepristone did not increase hot flushes and gastrointestinal discomfort. Post-marketing surveillance on GZFL based on literature showed that mild gastrointestinal system damage was its most common adverse effects and no serious adverse events were reported.[32]

When taken the length of GZFL treatment into account, long-term (6 months) treatment with GZFL could achieve greater reduction in recurrence rate and improvement in clinical pregnancy rate. Apart from mifepristone, GZFL also combined with leuprorelin, triptorelin, gestrinone, or danazol to treat endometriosis. The efficacy and safety of GZFL as an add-on therapy to these agents should be systematically evaluated.

This study had several weaknesses. First, methodological flaws of the included trials were a major concern. Most trials did not clearly report the method of randomization, allocation concealment, and sample sizes estimation. Second, TCM pattern differentiation was not taken into the diagnostic procedure, which could have resulted in potential selection bias of patients. Third, substantial heterogeneity was found in pooling serum hormone level (I^2 up to 91%). Different duration of treatment, patients' characteristics, and methodological quality may contribute to the significant heterogeneity. Fourth, lack of information on stage in most trials was another weakness. Variations of stages could have influenced the pooling result for

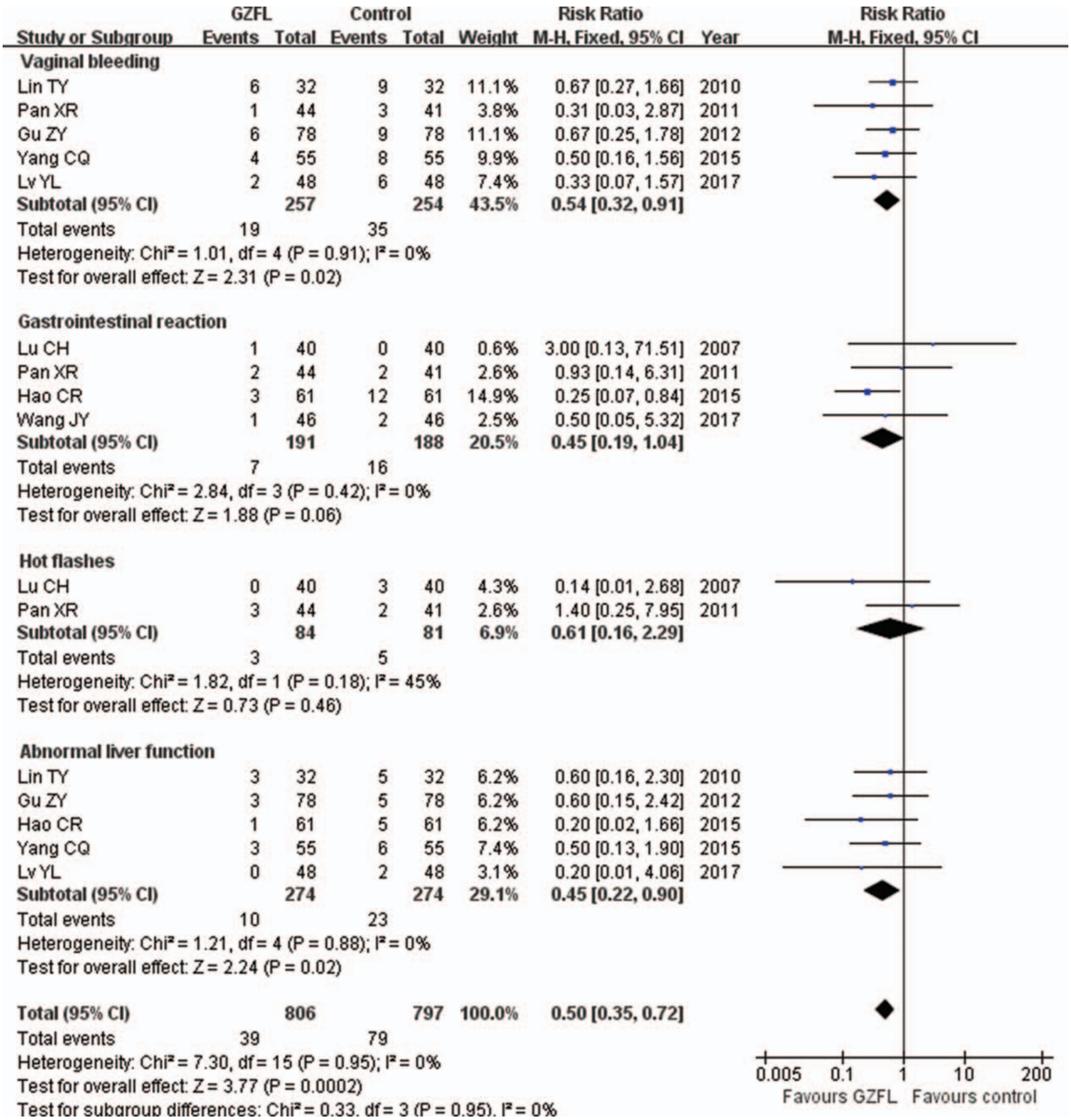

Figure 5. Forest plots showing comparison of adverse events comparing GZFL plus mifepristone to mifepristone alone treatment.

recurrence of endometriosis.[33] Fifth, a valid pain scale was not used to assess dysmenorrhea and pelvic pain. However, the pain scale was subjective, which could have led to measurement bias. Finally, the length of follow-up maybe not long enough to observe the recurrence of endometriosis and up to 5-year follow-up duration should be carried out.[34]

5. Conclusions

This meta-analysis indicates that GZFL as adjuvant therapy to mifepristone appears to have additional benefits in prevention of recurrence of endometriosis and improvement of pregnancy among women with endometriosis. Therefore, GZFL may be a candidate as an add-on therapy for management of endometriosis. However, future well-designed trials are required to confirm these findings because of methodological flaws in the analyzed trials.

Author contributions

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Supervision: Fei Wang.
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