https://doi.org/10.31925/farmacia.2026.3.3 **REVIEW**

META-ANALYSIS OF THE EFFECTIVENESS OF BUSHEN DECOCTION IN INFERTILITY CAUSED BY OVARIAN DYSFUNCTION

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Abstract

Ovarian dysfunction, including diminished ovarian reserve and premature ovarian insufficiency, significantly reduces female fertility. This study aimed to evaluate the clinical efficacy of Bushen decoction formula (BSF) in treating infertility associated with ovarian dysfunction through a meta-analysis. Chinese and English databases were systematically searched for relevant clinical studies, and the methodological quality of the included studies was assessed. Studies were categorized into a BSF treatment group and a control group. Meta-analysis was performed using RevMan 5.3 software. A total of 11 studies involving 1,163 patients were included. Compared with the control group, the BSF group showed significantly higher clinical effectiveness and pregnancy rates. Additionally, levels of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) were reduced, while estradiol (E2), anti-Müllerian hormone (AMH), antral follicle count (AFC), and endometrial thickness were increased. No significant difference was observed in abortion rates between groups. In conclusion, BSF may improve ovarian reserve and enhance pregnancy outcomes in infertile women with ovarian dysfunction, likely through modulation of sex hormone levels.

Rezumat

Disfuncția ovariană, caracterizată printr-o rezervă ovariană diminuată și insuficiența ovariană prematură, reprezintă o cauză importantă a infertilității feminine. Acest studiu a avut ca obiectiv evaluarea eficacității clinice a formulei Bushen Decoction (BSF) în tratamentul infertilității asociate disfuncției ovariene, prin intermediul unei meta-analize. Au fost căutate studii clinice relevante în baze de date în limbile chineză și engleză. Studiile au fost împărțite în două grupuri: tratat cu BSF și de control, iar meta-analiza a fost realizată utilizând software-ul RevMan 5.3. Au fost incluse 11 studii, însumând 1.163 de paciente. Comparativ cu grupul de control, grupul tratat cu BSF a prezentat rate semnificativ mai mari de succes terapeutic și de obținere a sarcinii. De asemenea, s-au observat scăderi ale nivelurilor hormonului foliculostimulant (FSH) și ale hormonului luteinizant (LH), concomitent cu creșteri ale nivelurilor de estradiol (E2), ale hormonului anti-Müllerian (AMH), ale numărului de foliculi antrali (AFC) și ale grosimii endometriale. Nu au fost identificate diferențe semnificative între grupuri în ceea ce privește rata avorturilor spontane. În concluzie, BSF poate îmbunătăți rezerva ovariană la femeile infertile cu disfuncție ovariană, probabil prin modularea nivelurilor hormonilor sexuali.

Keywords: Bushen decoction formula, infertility, ovarian reserve, pregnancy rate, meta-analysis

Introduction

Ovarian reserve refers to the ability of ovarian cortical region to carry out follicle growth, development, and formation of fertilized eggs, which reflects the fertility of women (1). When the number of oocytes in the ovarian cortical area is reduced or the quality is poor, it is considered that the ovarian reserve is decreased or the ovarian function is decreased. Patients with ovarian hypofunction often show ovulation disorder, sex hormone deficiency, functional uterine bleeding, decreased libido, and infertility, and will progress to premature ovarian failure in severe cases (2). Usually, ovarian dysfunction is irreversible. In clinical practice, hormone replacement therapy and other methods are often used to treat ovarian dysfunction, which can improve the ovarian function of patients to a certain extent, but there will be serious adverse reactions during the treatment process, even increasing the risk of endometrial cancer, breast cancer, stroke, and other diseases (3, 4).

Traditional Chinese medicine (TCM) in ovarian dysfunction has gradually received people's attention. According to TCM, ovarian dysfunction belongs to the categories of "hypomenorrhea", "amenorrhea", "infertility", and the main pathogenesis is kidney deficiency, blood stasis, and spleen qi deficiency (5). The kidney dominates women's reproductive function and also plays a decisive role in ovarian function. Kidney deficiency will lead to the occurrence of "blood stasis", and blood stasis is a pathological

product, a pathogenic factor (6). Blood stasis is not conducive to follicular development and expulsion, implantation of fertilized eggs. Tonifying the kidney can fill the kidney essence and refine Yang qi. Wu *et al*. (7) pointed out that the decoction tonifying the kidney and promoting blood circulation used in infertility due to polycystic ovary syndrome can improve the pregnancy outcome of patients by improving the inflammatory state, regulating endometrial epithelial mesenchymal transition, and restoring endometrial pathological changes. Pan *et al*. (8) pointed out that Bushen Jieyu decoction can markedly improve the abnormal cystic expansion of ovaries in rats with polycystic ovary syndrome and reduce serum luteinizing hormone (LH) and LH/follicle stimulating hormone (FSH) levels. Huang *et al*. (9) prepared the premature ovarian insulin model and found that the decoction tonifying the kidney and promoting blood circulation could markedly improve the estrous cycle and hormone disorder of the model after 28 days of continuous gavage and could also regulate ovarian microvascular formation and improve its ovarian reserve. Jiang *et al*. (10) suggested that Bushen Quyu decoction may play a protective role by regulating the gonadal hormone level of hypothalamus-pituitary-ovary axis and protecting ovarian granulosa cells from pyroptosis. Therefore, tonifying the kidney is the basic principle in infertility caused by ovarian dysfunction.

This article is intended to conduct evidence-based analysis on the clinical effect of Bushen decoction formula (BSF) in infertility due to ovarian dysfunction through a literature search and analysis, and a meta-analysis was carried out to explore its therapeutic effectiveness. Finally, it provides a reference for the formulation of a clinical treatment plan for infertility caused by ovarian dysfunction.

Materials and Methods

Data source

The relevant articles in Chinese and English databases such as CNKI, WanFang, Embase, Medline and Pubmed were thoroughly searched electronically, starting from its creation and extending up to May 1, 2024, to identify relevant records. NoteExpress software was used to screen duplicate literature. The search terms include poor ovarian response, decline in ovarian reserve, ovarian reserve, ovarian insufficiency, infertility, recurrent miscarriage, Bushen, traditional Chinese medicine, etc.

Selection criteria

Inclusion: (1) clinical randomized controlled trials (RCTs); (2) The subjects of the study were women with infertility caused by ovarian dysfunction or disorders, and there were no restrictions on age, gender, and nationality; (3) The BSF group (BSFG) received therapy with BSF alone or in conjunction with conventional treatments or other TCM, whereas the control group (CG) was administered conventional medicine solely or a sham treatment; (4) Bushen decoction formula (BSF) focus on replenishing the kidney essence as the core therapeutic principle; although specific formula names may vary, their core components consistently include herbs that tonify the kidney and replenish essence, such as *Rehmannia glutinosa*, *Dioscorea opposita*, *Epimedium brevicornum*, *Cuscuta chinensis* and *Lycium barbarum*, with no significant incompatibility among the medicinal constituents; (5)The outcome measures included clinical total effective rate, pregnancy rate, FSH, LH, estradiol (E2), anti-Müllerian hormone (AMH), antral follicle count (AFC), endometrial thickness, and abortion rate; (6) There is no language restriction.

Exclusion: (1) duplicate published articles; (2) Literature review, meta-analysis, case, or experience reports; (3) Basic experiments; (4) Non-RCTs studies; (5) Study on therapeutic intervention of non-kidney tonifying decoction; (6) Outcome measures were not clear; (7) The outcome index data could not be extracted; (8) Articles unable to get full text.

Information extraction

Information was extracted by two researchers independently from the articles, followed by a cross-verification. When faced with inconsistencies, it is imperative to engage in a discussion to find a resolution. If the situation calls for it, the third researcher could be enlisted to help arrive at a consensus. The extracted data included: (1) the basic content of the article (the number of research subjects, the intervention measures). (2) Outcome index data, clinical total effective rate, pregnancy rate, FSH, LH, E2, AMH, AFC, endometrial thickness, and abortion rate. For this meta-analysis, data extraction prioritized intention-to-treat (ITT) analysis data. For studies that did not report ITT data, the analysis was performed using data from completers.

Quality evaluation

The tool recommended by the Cochrane Collaboration was used to evaluate the literatures in the meta-analysis. The evaluation included: (1) selection bias (random sequence generation and allocation concealment); (2) Implementation bias (whether the blinded method was adopted for subjects and experimenters); (3) Measurement bias (whether the blinded method was adopted for outcome assessors); (4) Follow up bias (the integrity of the outcome data, whether to report the reasons for loss to follow-up and exclusion); (5) Reporting bias (whether to selectively report research results); (6) Other bias (whether there are pre-set questions or entries to explain other sources of bias). The evaluation results included low, high, or unclear risk.

Statistical methods

RevMan5.3 software provided by Cochrane Collaboration was used for meta-analysis. I^2 test was used to analyze the heterogeneity (Het) of outcome indicators. If $I^2 < 50\%$ and $p > 0.10$, there is no obvious Het among the studies, and the fixed effect model (FEM) can be adopted; If $I^2 \geq 50\%$ and $p \leq 0.10$, there is obvious Het among studies, which can be analyzed by random effect model (REM). The extent of impact for continuous data was indicated by mean difference (MD), and that of dichotomous data was expressed by odds ratio (OR). 95% confidence interval (CI) was utilized to evaluate the reliability of the results derived from both data. Subgroup analysis or sensitivity analysis were used for analyzing the reasons for Het. If the data source could not be found, only descriptive analysis was performed. An inverted funnel plot (FUP) was drawn for publication bias (PB) analysis. A P-value that is less than 0.05 was deemed to signify statistical meaning.

Results and Discussion

Documents inclusion process

In accordance with the systematic approach to literature searching, 381 potentially relevant pieces of literature were preliminarily identified and extracted from a variety of digital databases, 105 duplicate literatures were excluded, and 276 literatures were included for subsequent evaluation. Following an examination of the titles and abstracts, 225 literatures including literature review or meta-analysis, case or experience reports, and basic research literatures were excluded, and 51 literatures were included for further screening. After downloading and reading the full text, a total of 40 non-RCTs studies and literatures with unclear outcome indicators, unclear intervention methods, unable to extract data, and unable to obtain the full text were excluded. Finally, 11 literatures (11-21) were included in this meta-analysis. The procedure for identifying relevant literature is depicted in Figure 1.

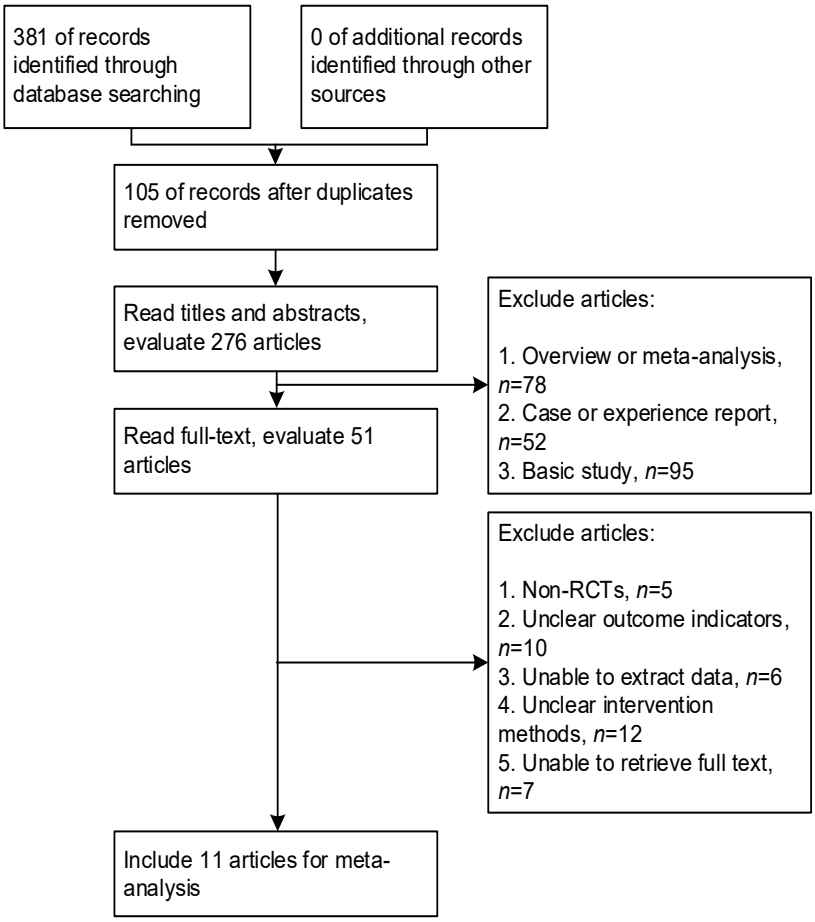

Figure 1.

Viscosity curves and the statistical mean of differences expressed by the regression lines

Literatures assessment

Eleven literatures (11-21) were included for quality evaluation, and it was found that each item in the article was evaluated as low or unclear risk, and there was no high risk, indicating that the overall quality of the literature met the requirements of meta-analysis. The findings from the appraisal are depicted in Figure 2.

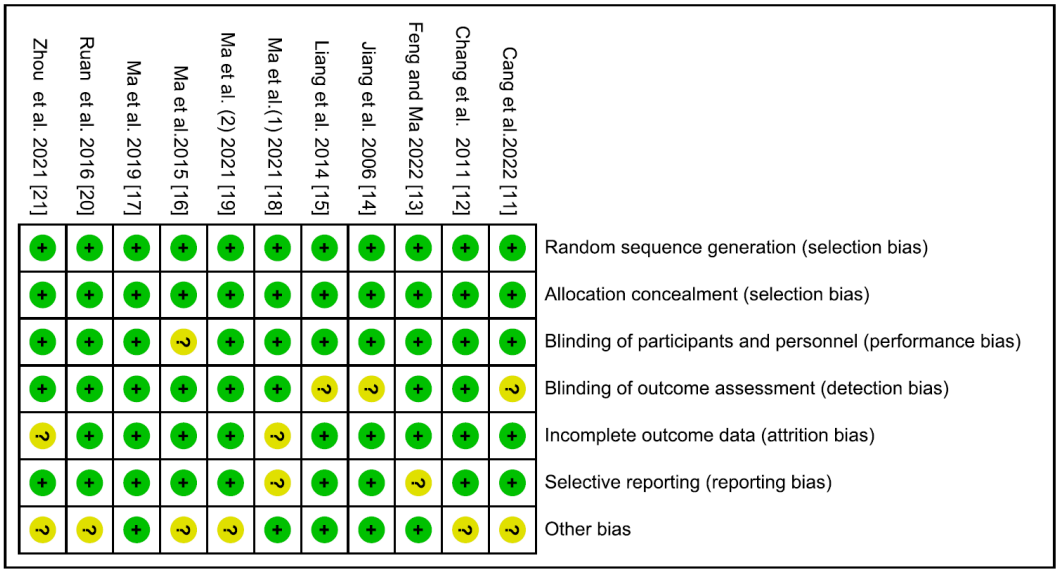

Figure 2.
Evaluation of literature methodology

Analysis of fundamental features

Eleven literatures (11-21) including 1,163 patients were included. 582 patients in BSFG were treated with BSF. In the CG, 581 patients were treated with western medicine or placebo except BSF. The treatment cycle of all patients was at least 3 months. Analysis of the primary components in BSF prescriptions across 11 studies (11-21) identified *Cuscuta chinensis* (10 studies) (11-20), *Ligustrum lucidum* (8 studies) (12,13, 15-19, 21) and *Angelica sinensis* (8 studies) (12-16, 18, 19, 21) as the most frequent core constituents. Cuscuta chinensis, as a representative herb for tonifying the kidney and replenishing essence, was employed in most studies. Classical kidney-tonifying and essence-replenishing herbs such as *Rehmannia glutinosa*, *Lycium barbarum* and *Cornus officinalis* were also widely utilized (*Rehmannia glutinosa*: 6 studies (12-15,18,21); *Cornus officinalis*: 4 studies (12,15,18,20); *Dioscorea opposita*: 4 studies (11, 12, 15, 18)), further confirming the consistency of replenishing kidney essence as the core therapeutic principle. The essential features of the incorporated articles are displayed in Table I.

Table I
Essential details of the incorporated articles

Authors	Year	Sample size		Intervention methods		Main components of BSF formula	Course of treatment
		BSF	Control	BSF	Control		
Cang *et al.* [11]	2022	50	50	Bushen Shugan decoction	Dihydroprogesterone + low molecular weight heparin sodium + hydroxychloroquine	*Cuscuta chinensis, Eucommia ulmoides, Cistanche deserticola, Cervus Cornu Degelatinatum, Poria cocos, Stir-baked Atractylodes macrocephala, Pogostemon cablin, Scutellaria baicalensis, Citrus reticulata, Bupleurum chinense, Raw Astragalus membranaceus, Dioscorea opposita, Paeonia lactiflora*	To 14 weeks after pregnancy
Chang *et al.* [12]	2011	30	28	Adding Bushen Tiaojing prescription	Pituitary down-regulation by gonadotropin-releasing hormone agonist	*Rehmannia glutinosa (steamed), Angelica sinensis, Dioscorea opposita, Cornus officinalis, Lycium barbarum, Ligustrum lucidum, Epimedium brevicornum,* Human Placenta, *Rubus chingii, Cuscuta chinensis, Cyperus rotundus, Carthamus tinctorius, Paeonia lactiflora, Cistanche deserticola, Salvia miltiorrhiza*	At least three follicles in bilateral ovaries with a diameter ≥ 18mm

Authors	Year	Sample size		Intervention methods		Main components of BSF formula	Course of treatment
		BSF	Control	BSF	Control		
Feng and Ma [13]	2022	50	50	Bushen Culuan prescription	Sequential estrogen therapy	*Astragalus membranaceus, Rehmannia glutinosa* (steamed), *Cuscuta chinensis, Epimedium brevicornum, Ligustrum lucidum, Eclipta prostrata, Angelica sinensis, Ligusticum chuanxiong, Paeonia lactiflora, Cyperus rotundus* (processed), *Glycyrrhiza uralensis* (honey-fried)	Three menstrual cycles are one course, one course
Jiang *et al*. [14]	2006	30	20	Adding Bushen Huoxue prescription	Fallopian tube intervention	*Cuscuta chinensis, Dipsacus asper, Taxillus chinensis, Eucommia ulmoides, Rehmannia glutinosa* (steamed), *Paeonia lactiflora, Ligusticum chuanxiong, Angelica sinensis, Prunus persica, Salvia miltiorrhiza*	Three months are a course, four courses
Liang *et al*. [15]	2014	20	40	Adding Bushen Tiaojing prescription	Gonadotropin releasing hormone agonist for ovulation induction	*Rehmannia glutinosa* (steamed), *Angelica sinensis, Paeonia lactiflora, Dioscorea opposita, Cornus officinalis, Lycium barbarum, Ligustrum lucidum, Epimedium brevicornum, Human Placenta, Rubus chingii, Cuscuta chinensis, Cyperus rotundus*	At least three follicles in bilateral ovaries with a diameter ≥ 18mm
Ma *et al*. [16]	2015	133	130	Bushen Culuan granule + clomiphene simulated drugs	Clomiphene + Bushen Culuan granule simulated drugs	*Cuscuta chinensis, Taxillus chinensis, Dipsacus asper, Lycium barbarum, Ligustrum lucidum, Spatholobus suberectus, Lycopus lucidus, Typha angustifolia pollen, Angelica sinensis, Cyathula officinalis, Leonurus japonicus, Paeonia lactiflora* (red peony), *Salvia miltiorrhiza*	Three menstrual cycles are one course, one to two courses
Ma *et al*. [17]	2019	43	43	Bushen Culuan prescription	Progesterone + clomiphene + progesterone	*Cuscuta chinensis, Epimedium brevicornum, Curculigo orchioides, Dipsacus asper, Lycium barbarum, Ligustrum lucidum, Lycopus lucidus, Raw Typha angustifolia pollen, Cyperus rotundus, Dioscorea nipponica*	Three menstrual cycles are one course, one to two courses
Ma *et al*. (1) [18]	2021	33	29	Bushen Tiaojing prescription	Placebo	*Rehmannia glutinosa* (steamed), *Cornus officinalis, Dioscorea opposita, Lycium barbarum, Cuscuta chinensis, Rubus chingii, Cistanche deserticola, Human Placenta, Ligustrum lucidum, Angelica sinensis, Paeonia lactiflora*	Three months
Ma *et al*. (2) [19]	2021	50	50	Progesterone capsules + Bushen Huoxue Culuan prescription	Climen + Clomiphene	*Ligustrum lucidum, Cuscuta chinensis, Epimedium brevicornum, Morinda officinalis, Salvia miltiorrhiza, Angelica sinensis, Ligusticum chuanxiong, Paeonia rubra, Lycopus lucidus, Typha pollen*	Three menstrual cycles are one course, one course

Authors	Year	Sample size		Intervention methods		Main components of BSF formula	Course of treatment
		BSF	Control	BSF	Control		
Ruan *et al.* [20]	2016	85	85	Adding acupuncture + Bushen Quyu prescription	Cold needle drainage	*Astragalus membranaceus, Cuscuta chinensis, Poria cocos, Atractylodes macrocephala, Gleditsia sinensis, Cornus officinalis, Epimedium brevicornum, Paeonia suffruticosa, Acorus tatarinowii, Bupleurum chinense, Panax notoginseng*	Three menstrual cycles are one course, two courses
Zhou *et al.* [21]	2021	58	56	Bushen Yiqi Huoxue decoction	Norethisterone + Dupaston	*Anemarrhena asphodeloides, Phellodendron chinense, Rehmannia glutinosa* (raw), *Testudinis Carapax et Plastrum, Lycium barbarum, Ligustrum lucidum, Epimedium brevicornum, Psoralea corylifolia, Paeonia rubra, Paeonia alba, Astragalus membranaceus, Angelica sinensis, Prunus persica, Ligusticum chuanxiong*	12 months

Meta-analysis results

Effect of BSF on total effective rate

Six articles (11, 13, 14, 16, 17, 19) reported the effect of BSF on the total clinical effective rate. There was no obvious Het between the groups (I^2 = 0%, p = 0.54), and the FEM was utilized for analyzing. It revealed that the clinical effectiveness rate of the BSFG was considerably superior to that observed in the CG (OR = 3.91, 95% CI = 2.44~6.27, p < 0.00001) (Figure 3A).

Ten articles (11-20) reported the effect of BSF on pregnancy rate. There was no visible Het (35%, 0.13), and the FEM was adopted. The pregnancy rate in the BSFG was markedly higher as against the CG (OR = 2.17, 1.66 ~ 2.84, p < 0.00001) (Figure 3B).

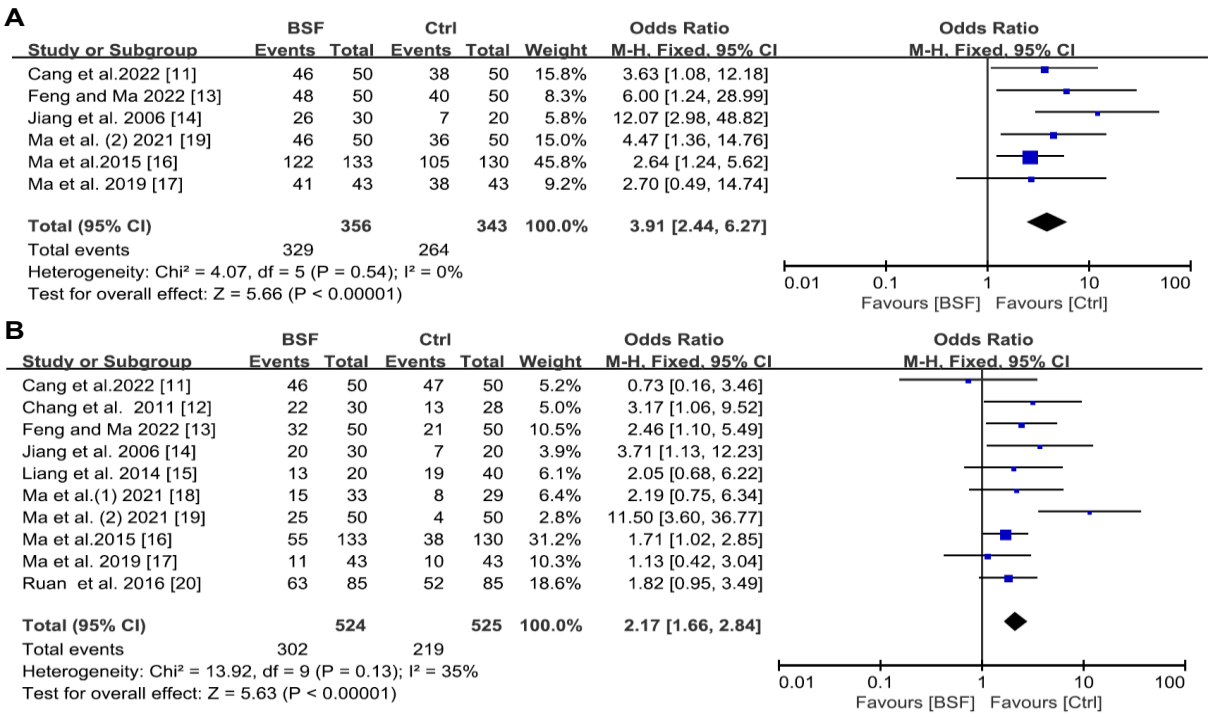

Figure 3.

Meta-analysis of clinical total effective rate and pregnancy rate after different methods of intervention. A: clinical total effective rate, B: pregnancy rate

Effect of BSF on FSH, LH, and E2 hormone levels

Seven articles (13, 15-17, 19-21) reported the effect of BSF on FSH level. Het was clearly observable (99%, p < 0.00001), and the REM was adopted; FSH was markedly lower in the BSFG as against the CG (MD = -3.78 mIU/mL, 95% CI = -7.00 ~ -0.55, p = 0.02) (Figure 4A).

Seven articles (13, 15-17, 19-21) reported the effect of BSF on LH level. Het was clearly observable (95%, p < 0.00001), and REM was adopted; LH was markedly lower in the BSFG as against the CG (MD = -1.12 mIU/mL, -2.16 ~ -0.09, 0.03) (Figure 4B).

Nine articles (11, 13-17, 19-21) reported the impact of BSF on E2 level. Het was clearly observable (100%, p < 0.00001), and the REM was adopted; E2 was markedly higher in the BSFG as against the CG (MD = 134.11 pmol/L, 85.93 ~ 182.29, p < 0.00001) (Figure 4C).

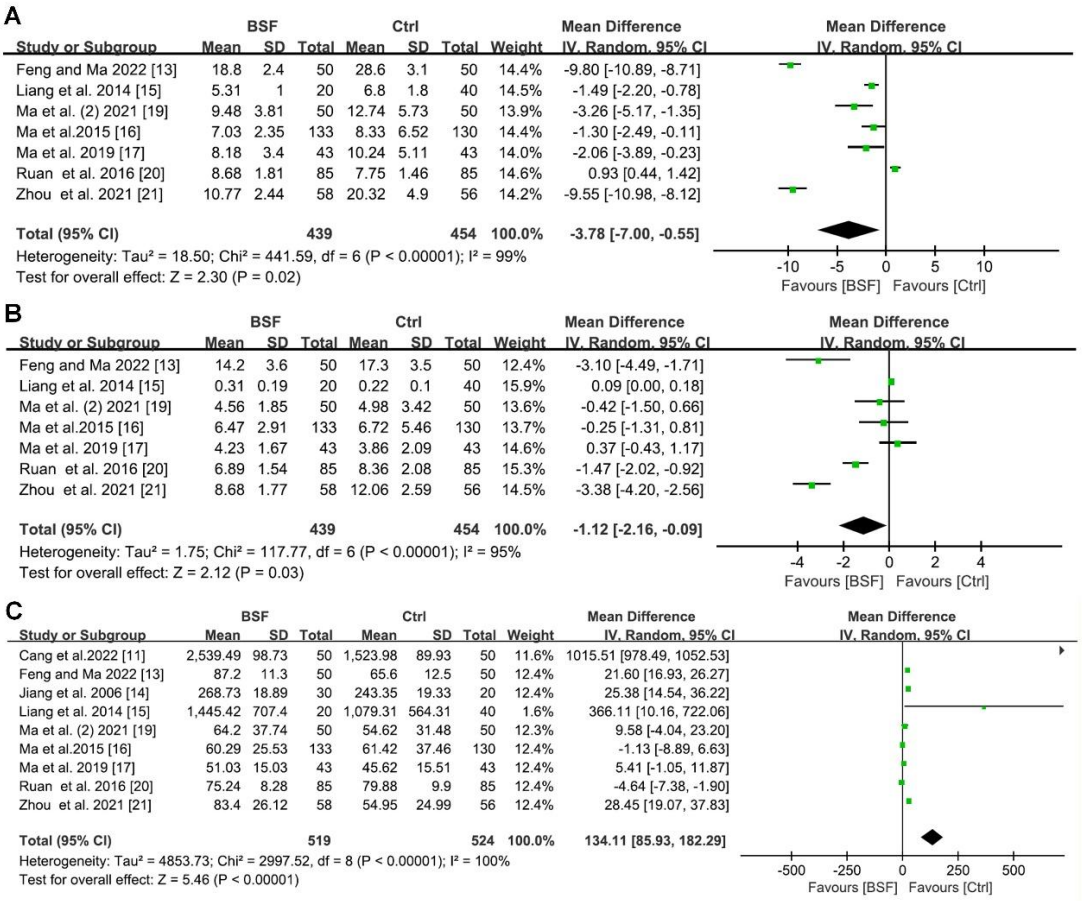

Figure 4.

Meta-analysis of FSH, LH, and E2 levels after different methods of intervention. A: FSH, B: LH, and C: E2

Impact of BSF on ovarian reserve

Four articles (17-19, 21) reported the impact of BSF on AMH level. Het was clearly observable (93%, p < 0.00001), and the REM was adopted. AMH was markedly higher in the BSFG as against the CG (MD = 0.96 μg/L, 0.19 ~ 1.72, 0.01) (Figure 5A).

Six articles (12, 13, 17-19, 21) reported the impact of BSF on AFC. Het was clearly observable (95%, p < 0.00001), and the REM was adopted. The results suggested that AFC was markedly more in the BSFG as against the CG (MD = 2.06, 0.68 ~ 3.44, p = 0.004) (Figure 5B).

Impact of BSF on endometrial thickness

Five of the articles (13, 14, 16, 18, 21) reported the impact of BSF on endometrial thickness. Het was clearly observable (85%, p < 0.0001), and the REM was adopted. The endometrial thickness was markedly greater in the BSFG as against the CG (MD = 0.63, 0.04 ~ 1.22, p = 0.04) (Figure 6).

Impact of BSF on abortion rate

Four articles (11, 17, 19, 20) reported the impact of BSF on the abortion rate. Het was clearly observable (60%, p = 0.06), and the REM was adopted. There was not obviously different in the abortion rate between BSFG and CG (OR = 0.81, 0.18 - 3.58, p = 0.78) (Figure 7).

Analysis of PB

In this meta-analysis, the FUP of pregnancy rate and LH index was selected for PB analysis. It was found that the FUP was basically symmetrical, without obvious PB (Figure 8).

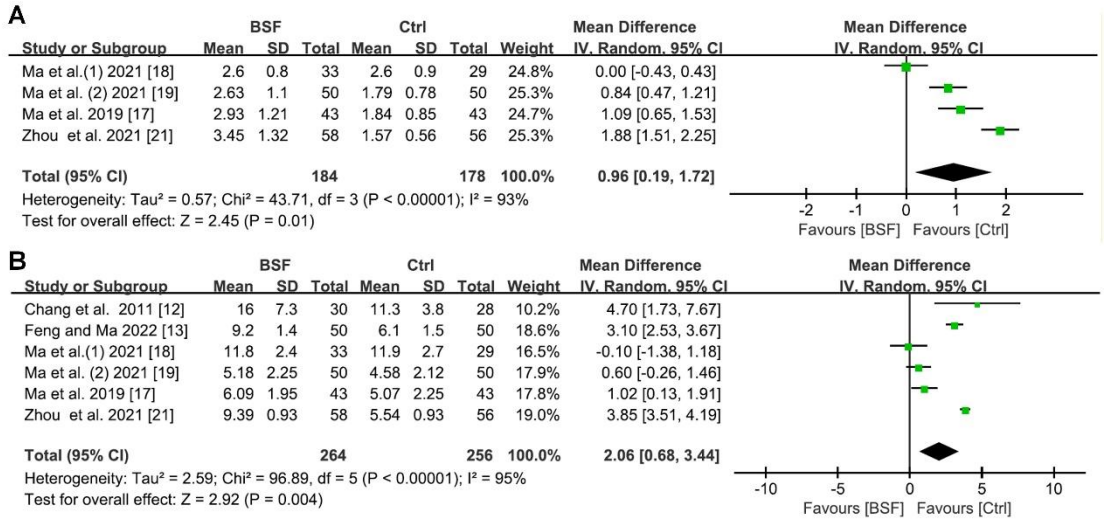

Figure 5.

Meta-analysis of ovarian reserve indicators after different methods of intervention. A: AMH, B: AFC

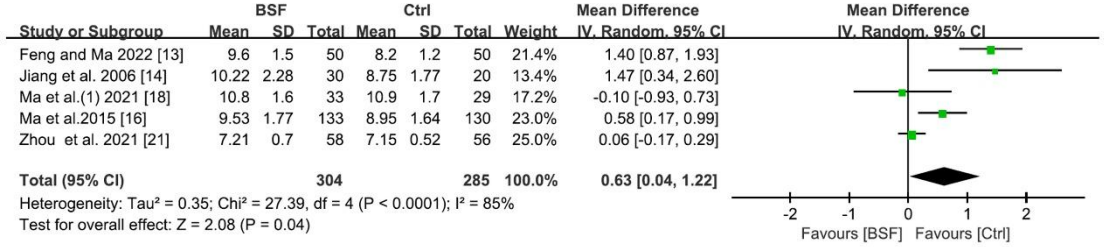

Figure 6.

Meta-analysis of endometrial thickness after different methods of intervention

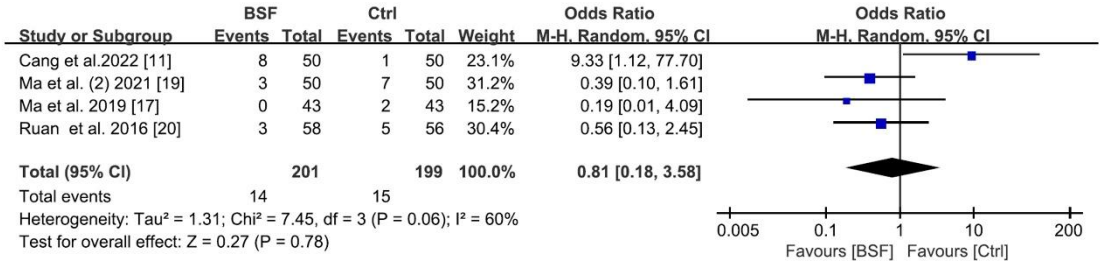

Figure 7.

Meta-analysis of abortion rate after different methods of intervention

Sensitivity analysis

Since the 11 included articles could not determine the specific influencing results analysis after subgroup analysis, sensitivity analysis was not conducted.

Eleven clinical studies of BSF in infertility caused by ovarian dysfunction were included through meta-analysis. The analysis found that BSF could improve the total effective rate of clinical treatment of the disease, improve the ovarian function of patients, and increase the pregnancy rate. The ovary is a female gonad, and when ovarian dysfunction occurs, the secretion of estrogen and other hormones decreases, resulting in reduced menstrual volume, shortened menstrual period, and even amenorrhea (22). Moreover, after ovarian dysfunction, poor quality, reduced number, or no ovulation of eggs will directly affect women's fertility, and cause infertility in severe cases (23, 24). Therefore, the treatment of ovarian hypofunction is of great significance to improve various health problems caused by hormone level disorders, improve the QoL of patients, improve the pregnancy rate and achieve fertility wishes, and prevent and treat some serious complications.According to the actual situation of patients with ovarian dysfunction, estrogen or progesterone supplement therapy, immunotherapy, life psychological regulation, and other methods are often used in clinical treatment of the disease (25). Western medicine mostly uses hormone drugs in ovarian dysfunction,

but long-term application will produce gastrointestinal discomfort, liver and kidney function injury, endocrine disorders, osteoporosis, etc., and will increase the risk of endometrial cancer (26, 27). TCM believes that kidney essence is the material basis to promote the maturation of reproductive organs and maintain normal reproductive capacity. Kidney deficiency can lead to reproductive system dysfunction, and tonifying the kidney can improve the function of the kidney, which is conducive to regulating the endocrine system, especially the hormone secretion related to the ovary (28). Therefore, articles with Bushen Shugan, Bushen Tiaojing, Bushen Quyu decoctions were selected in this meta-analysis. Bushen Shugan decoction is commonly used to treat liver blood deficiency, epigastric pain, and fecal dryness (29). Bushen Tiaojing decoction has the effects of tonifying kidney and nourishing blood, warming meridians, and dispersing cold. Bushen Culuan decoction is mainly used to regulate liver and remove stasis, benefit kidney, promote ovulation, and help pregnancy, which can markedly improve the symptoms of anovulation or luteal function defect, hypomenorrhea, etc. (30). The decoction tonifying the kidney and promoting blood circulation has the effects of activating blood circulation, removing blood stasis, tonifying kidney, and is often used to treat qi stagnation and blood stasis diseases (31). Bushen Quyu decoction has the effects of deficiency of Qi and blood, deficiency of liver and kidney, and blockage of meridians.

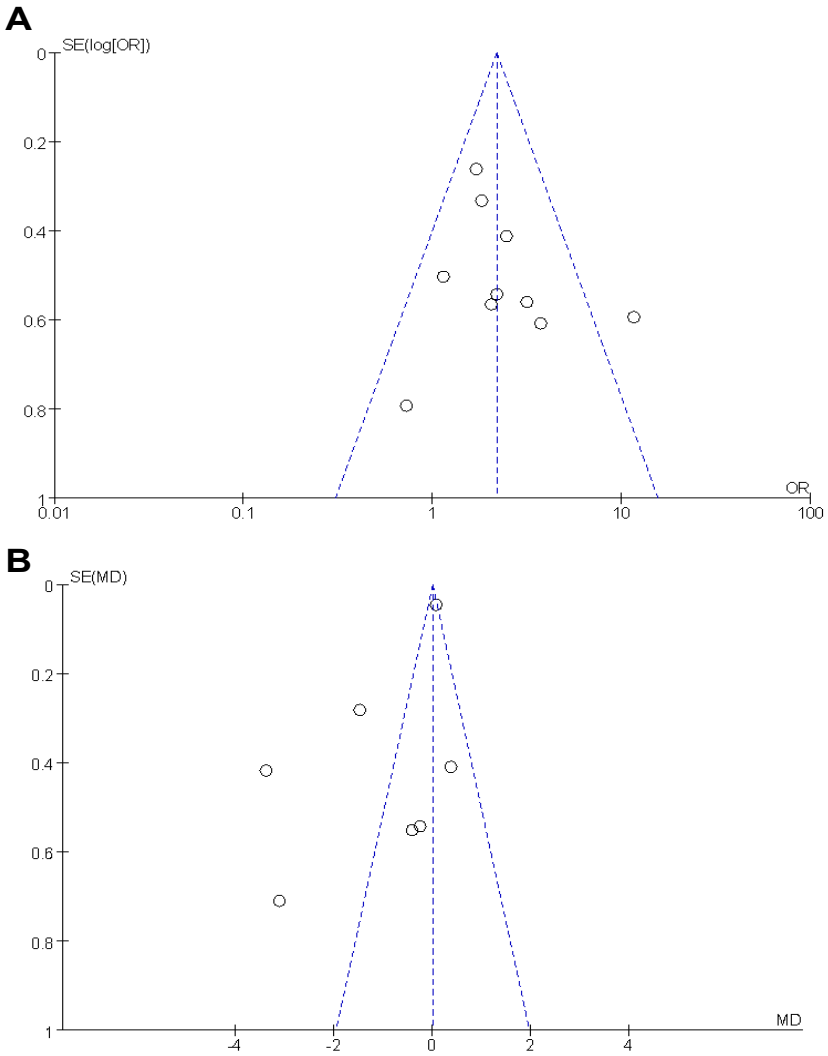

Figure 8.
Inverted FUP analysis of PB

At present, the clinical diagnostic criteria for ovarian dysfunction have not been unified. In clinical practice, ovarian function is comprehensively evaluated by FSH, LH, E2, AMH, AFC, and other indicators. The ovarian secretion function will also be impaired after ovarian hypofunction, and the poor ovarian response will stimulate the pituitary to secrete a large amount of gonadotropin FSH to act on the ovary, so

it shows an increase in FSH level (32, 33). As the ovarian reserve diminishes, there is a progressive reduction in the quantity of follicles, accompanied by a corresponding decline in E2 secretion, showing a persistent low estrogen state (34). This meta-analysis found that after treatment with BSF, FSH and LH were markedly decreased, while E2 was markedly increased. According to the *American Society for Reproductive Medicine* (ASRM) guidelines (35), FSH > 10 IU/L indicates diminished ovarian reserve, while FSH > 40 IU/L suggests primary ovarian insufficiency. In this study, patients receiving kidney-tonifying formula intervention showed a reduction of 3.78 IU/L in FSH, lowering baseline FSH levels to a range of 12 - 16 IU/L. Multiple clinical studies have confirmed (36, 37) that a reduction of 2 - 5 IU/L in FSH levels improves ovarian sensitivity to ovulation-inducing drugs and is associated with a 12 - 18% increase in clinical pregnancy rates, indicating the clear clinical significance of this reduction. Kidney-tonifying formulas may exert their effects through multi-level regulation of the hypothalamic–pituitary–ovarian (HPO) axis. The reduction in FSH and LH suggests alleviation of pituitary overstimulation, which aligns with findings from animal studies demonstrating that kidney-tonifying Chinese herbs downregulate gonadotropin-releasing hormone receptor sensitivity and reduce gonadotropin secretion (38). Meanwhile, the increase in E2 levels may further suppress excessive FSH secretion via negative feedback, a process highly consistent with the reversal pathway of HPO axis dysregulation in patients with ovarian insufficiency. It shows that BSF can improve the sensitivity of pituitary gland to hypothalamic response and thus improve the low estrogen level. This meta-analysis found that AMH in patients after treatment with BSF was markedly increased, and the number of AFC increased. AMH level will increase with the number of follicles in the ovary, so this level can indirectly reflect the reserve of follicles in the ovary (39, 40). The European Society of Human Reproduction and Embryology (ESHRE) defines AMH < 1.1 ng/mL as the diagnostic criterion for DOR (41), while the domestic Guidelines for the Integrated Diagnosis and Treatment of Diminished Ovarian Reserve (2023) indicate (42) that AMH levels of 1.1 - 3.0 ng/mL represent the lower limit of normal ovarian reserve. In this study, the baseline AMH of enrolled patients mostly ranged from 0.5 to 1.0 ng/mL. After intervention, AMH increased by 0.96 ng/mL, raising the baseline AMH to 1.5 - 1.96 ng/mL. Furthermore, study results show that every 0.5 ng/mL increase in AMH is associated with a 9% improvement in clinical pregnancy rate. The 0.96 ng/mL increase in AMH observed in this study was accompanied by a significant rise in pregnancy rates, further supporting its clinical relevance. Active components in kidney-tonifying formulas have been demonstrated to scavenge local reactive oxygen species (ROS) in ovary and inhibit granulosa cell apoptosis (43, 44). As a marker of preantral follicles, the elevated AMH levels may reflect that kidney-tonifying formulas enhance the functional follicle pool reserve by promoting primordial follicle activation and suppressing follicle atresia. Additionally, animal studies have found that kidney-tonifying Chinese herbs can upregulate the SDF-1/CXCR4 pathway, facilitating the homing of bone marrow mesenchymal stem cells to the ovary and participating in follicle repair and regeneration (45), providing a cytological basis for the improvements in AMH and AFC. Counting the antral follicles is a key step in tracking the journey from immature to mature follicles, providing a valuable measure of their developmental stages and a reliable indicator of ovarian potential (46). BSF can promote the growth, development, and maturation of follicles by regulating the hormone level and the function of hypothalamus-pituitary-ovarian axis in patients and ultimately improve and restore ovarian function. In summary, the observed changes in hormone levels and improvements in ovarian reserve and pregnancy outcomes in this study result from the synergistic multi-mechanistic actions of kidney-tonifying formulas, including regulation of HPO axis function, optimization of the follicular microenvironment, and enhancement of endometrial receptivity. The clinical significance is reflected not only in numerical changes but also in the overall reversal of the pathophysiological state of ovarian dysfunction.

The results of this study indicate that the I^2 values for the outcome measures (FSH, LH, E2, AMH, AFC) all exceeded 90%, suggesting substantial statistical heterogeneity. Potential sources may be related to the following factors: (1) Diversity of interventions. Among the 11 included studies, the composition of Chinese herbal medicines varied significantly. Herbs with different therapeutic effects may regulate ovarian function through distinct mechanisms, leading to inconsistent magnitudes of change in outcomes. (2) Variation in treatment duration. The treatment courses in the 11 included studies can be categorized into three types: i) Fixed duration (3 menstrual cycles/3 months, 4 courses/12 months); ii) Event-driven duration (until 14 weeks after pregnancy, or bilateral ovaries with ≥ 3 follicles of diameter ≥ 18 mm); iii) Unspecified duration with discontinuation based on clinical symptom improvement. Differences in treatment duration may influence outcomes through the following pathways: short-term courses may more readily observe rapid modulation of sex hormone levels, while long-term courses may show more pronounced improvements in ovarian reserve markers (AMH, AFC) and pregnancy rates; event-driven courses may result in varying actual intervention durations due to individual ovarian

responsiveness, and individual differences in menstrual cycle length and follicular development speed may affect cumulative drug efficacy. (3) Heterogeneity in control group (CG) interventions. CGs included Western medicine ovulation induction, hormone replacement therapy (Climen), placebo, and combined acupuncture, among others. The mechanisms of these different control interventions may exert complex interactive effects with the BSF group by inversely influencing sex hormone levels or ovarian reserve indicators. (4) Lack of stratified analysis based on baseline characteristics of the study population. Patients with lower baseline AMH or AFC levels may exhibit greater sensitivity to treatment; detection methods for outcome measures were not standardized across studies, and measurement errors may also contribute to data variability. (5) Variation in sample size. Differences in sample size may introduce random error, with smaller studies being more susceptible to extreme values, thereby increasing heterogeneity. These factors collectively contribute to the substantial heterogeneity observed in this study, indicating that conclusions should be interpreted cautiously in clinical context. Future research should standardize prescription composition, unify treatment duration and dosage, refine baseline stratification, and adopt standardized detection methods to reduce heterogeneity.

There is a certain relationship between infertility and endometrial thickness. Under normal conditions, endometrial thickness will change with the change of menstrual cycle. Endometrial thickness in early, severe, and late menstruation ranges from 3 to 5mm, 5 to 10mm, and 10mm. The endometrium is too thin and may not provide sufficient nutrition and support for the fertilized egg, which leads to the implantation failure of the fertilized egg and causes abortion (47). This meta-analysis found that the pregnancy rate of patients after BSF treatment was markedly increased, and the endometrial thickness was also markedly increased. The results suggested that BSF could affect the endometrial thickness of infertile patients with ovarian dysfunction to a certain extent, thereby increasing the pregnancy rate. This may be through the regulation of endocrine environment, hormone secretion, and other effects on the endometrium.

Regarding safety, among the 11 included studies, only the study of Cang *et al*. (11) reported adverse events in the CG (3 cases of rash, 4 cases of subcutaneous hematoma, and 1 case of gingival bleeding), while no adverse events occurred in the BSF group. The remaining 10 studies did not record or report adverse events such as liver and kidney function indicators, gastrointestinal reactions, allergic reactions, or drug interactions; no serious adverse events were mentioned in any of the studies. As the primary endpoints of the included studies focused on efficacy indicators, most did not designate safety indicators as core outcomes, resulting in insufficient data for meta-analysis. Therefore, the safety assessment in this study can currently only be evaluated based on the single indicator of miscarriage rate.

Conclusions

This meta-analysis confirmed that BSF used in infertility caused by ovarian dysfunction can improve the ovarian reserve of patients and increase the pregnancy rate. However, there are still some limitations in this meta-analysis: (1) the literature included in the analysis is mostly small sample research, and the research area is China, so the source is relatively single and not comprehensive; (2) There are many types of BSF. Given the limited number of articles, a subgroup analysis to assess the efficacy of different types of decoctions could not be conducted; (3) The CGs in the included studies consisted of diverse Western medical regimens with varying mechanisms of action, such as ovulation induction, luteal phase support, and immunomodulation. Some involved combination therapies or regimen with unclear mechanisms, resulting in substantial heterogeneity among CGs. This may affect the robustness of the meta-analysis results, particularly limiting precise assessment of the specific efficacy differences between Bushen decoction and different Western drug regimens; (4) Only the adverse event of miscarriage rate was compared; (5) Due to the lack of systematic reporting of adverse events such as liver/kidney function and gastrointestinal reactions in the included literature, the safety assessment in this study is limited. Therefore, a future requirement for medical research is a high-quality, multicenter, and large-scale RCT. In conclusion, the results of this meta-analysis can provide a help for selecting options for remedy of infertility caused by ovarian dysfunction.

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Conflict of interest

The authors declare no conflict of interest.

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