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Review article

Zishen yutai pill as an adjuvant therapy in threatened Miscarriage: A meta-analysis of 23 randomized controlled trials

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ABSTRACT

Objective: The purpose of this study was to evaluate the efficacy and safety of Zishen Yutai Pill combined with western medicine for the treatment of women with threatened miscarriage during the first trimester of pregnancy.

Methods: Randomized controlled trials published before the end of Apr 1, 2023 on Zishen Yutai Pill and threatened miscarriage were systematically retrieved from China National Knowledge Infrastructure, Wanfang, Sinomed, VIP, PubMed, EMBASE, Web of Science and the Cochrane Library. The international clinical trial registration platform and the Chinese clinical trial registration platform of clinical trials was searched from their inception until Apr 1, 2023. Meta analysis of random effect model was used to combine the research data. Chi-squared test and I^2 statistics were used for heterogeneity test.

Results: Twenty-three trials (enrolling 2411 participants) were included in the review. Zishen Yutai pill combined with western medicine therapy showed significant improvement on human chorionic gonadotropin [MD 19.33 IU/ml, 95% CI (15.84, 22.81)], the total effective rate [RR 1.19, 95% CI (1.15–1.23)], progesterone [MD 7.14 ng/ml, 95% CI (6.14, 8.13)], estradiol [MD 33.69 pg/ml, 95% CI (27.42, 39.96)], duration of abdominal pain [MD -2.36 d, 95% CI (- 3.54, - 1.18)], duration of vaginal bleeding [MD -1.94 d, 95% CI (- 2.93, - 0.94)], and fibrinogen [MD -0.34 g/L, 95% CI (- 0.57, - 0.11)]. There was no significant difference in hematocrit [MD 0.68%, 95% CI (- 0.08, 1.44)] between the experimental and the control group. Zishen Yutai Pill may improve the clinical symptoms in women with threatened miscarriage, such as human chorionic gonadotropin the total effective rate, progesterone, estradiol, duration of abdominal pain, duration of vaginal bleeding, and fibrinogen. Especially for progesterone, the effect of treatment $\leqq$2 weeks is significantly better than treatment of >2 weeks. For estradiol, the effect of treatment >2 weeks is significantly better than treatment of $\leqq$ 2 weeks.

Conclusion: Zishen Yutai Pill, as a complementary therapy, significantly improved human chorionic gonadotropin, the total effective rate, progesterone, estradiol, abdominal pain, vaginal bleeding, and fibrinogen in patients with threatened miscarriage in first-trimester pregnancy. However, the systematic review has some limitations, such as degraded information quality, no blinding of patients or doctors, etc. Due to the small sample size and low quality of research, it needs to be further confirmed by large sample and high-quality randomized controlled trials, such

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as blinding of patients, doctors and outcome assessment should be complemented, clinical follow-up, live birth rate, fetal growth should be supplemented.
Systematic review registration: INPLASY202320039.

1. Introduction

Threatened miscarriage (TM) is a common complication in the first trimester pregnancy, with an incidence of 15%–25% [1]. The early symptoms are mild, manifested as a small amount of vaginal bleeding and slight lower abdominal pain or low back pain [2]. If not treated in time, the amount of vaginal bleeding will increase, and the gestational sac will discharge [3]. Among them, 3%–16% of pregnant women will experience inevitable TM [2]. Western medicine believes that the common cause of TM is luteal insufficiency [4, 4]. Therefore, hormone therapy is used to treat patients wih TM in order to improve the luteal function of patients and maintain pregnancy [5]. In western medicine, drugs including natural progesterone, represented by progesterone, synthetic progesterone and didroxyprogesterone are most commonly used to treat patients with TM [6,7]. Mode of administration include vaginal administration, oral administration and intramuscular administration, which can effectively reduce the incidence of TM in first trimester pregnancy [7]. In addition, doctors advise pregnant women to stay in bed and avoid sexual intercourse [2].

TM belongs to the category of "fetal restlessness" or "fetal leakage" in the field of traditional Chinese medicine (TCM) [8]. Zishen Yutai Pill (ZYP) has long been used in the treatment of TM [9]. Moreover, clinical studies confirmed that TCM can maintain pregnancy through various ways, and significantly improve the fetal live birth rate [10]. ZYP is mainly composed of 15 kinds of Chinese herbal medicines (Table 1), which is mainly used to treat TM, habitual abortion and infertility caused by abortion [11]. There are few studies on the mechanism of ZYP in the treatment of TM in first-trimester pregnancy. Yi et al. [9] established a rat model of threatened abortion with mifepristone, and found from the perspective of cytokines that the ZYP group, the ZYP combined with progesterone group can increase serum E2 and P levels, promote the transition of IL-4/IL-2, IL-10/IL-2 balance to Th2 type, regulate the Th1/TH2 balance, and increase the number of live offspring of threatened abortion rats. Research on network pharmacology has showed that ZYP can intervene in threatened abortion through multiple targets and pathways, including interfering with the excessive activation of PI3K/Akt and MAPK signaling pathways, improving the disorder of VEGF signaling pathways, reducing the occurrence of inflammation and apoptosis, antioxidant, immune regulation, hematopoietic activity, etc. [12]. Atractylodes macrocephala can prevent and treat threatened abortion by inhibiting uterine contraction, as well as multiple pharmacological actions such as anti-inflammatory and analgesic, antiplatelet anticoagulation, bacteriostasis, and enhancing immune function of the body [13]. Artemisia argyi has pharmacological effects such as antibacterial, antiviral, hemostatic, anticoagulant, antioxidant, and immune regulation [14]. Ass hide glue has multiple pharmacological effects such as regulating hormone level, enhancing immunity, anti-inflammatory, anti fatigue, improving ovarian function, improving luteal function, improving uterine and ovarian blood supply, enriching blood, and stopping bleeding [15].

Our systematic review was performed to evaluate the efficacy and safety of ZYP used for the treatment of TM in first trimester pregnancy.

2. Materials and methods

2.1. Search strategy

Mesh terms and related synonyms were found in databases. Keywords and searching strategies were as follows: ("threatened miscarriage" [mh] OR "threatened abortion" [mh] OR "fetal loss" [mh] OR "pregnancy loss" [mh]) AND ("Zishen Yutai Pill" [tiab]).

Table 1
Basic information of Zishen Yutai Pill.

Chinese botanical drugs	Latin name	Part of botanical drugs
Tu si zi	*Cuscuta australis R.Br.*	seed
Sha ren	*Amomum villosum Lour.*	fruit
Shu di huang	Rehmannia glutinosa (Gaertn.) DC.	rhizome
Ren shen	*Panax ginseng C. A. Mey.*	Rhizome and root
Sang jisheng	*Taxillus chinensis (DC.) Danser*	stalk
e'jiao	*Equus asinus* L.	skin
Shou wu	*Polygonum multiflorum Thunb.*	cane
Ai ye	*Artemisia argyi Levl.et Vant.*	foliage
Ba ji tian	*Morinda officinalis How*	root
Bai zhu	*Atractylodes macrocephala Koidz.*	rhizome
Dang shen	*Codonopsis pilosula (Franch.)Nannf.*	root
Lu jiao shuang	-	degummed antler
Gou qi zi	*Lycium barbarum* L.	fruit
Xu duan	*Dipsacus asper Wall. Ex Henry*	root
Du zhong (tan)	*Eucommia ulmoides Oliv.*	bark

The studies were extracted from the following seven databases to Apr 1, 2023: PubMed, EMBASE, Web of Science, Cochrane Library, China National Knowledge Infrastructure (CNKI), Wan Fang Database (WanFang), Sinomed and Weipu Database for Chinese Technical Periodicals (VIP). A search of the international and Chinese clinical trial registration platforms was conducted to Apr 1, 2023. The search included all articles published up to Apr 1, 2023. In this study, only English and Chinese publications were included. All the individual search strategies for each database were included in Appendix S1.

2.2. Inclusion and exclusion criteria

2.2.1. Type of study

We included all randomized controlled trials (RCTs) comparing ZYP plus Western medicine with TM in women. Western medicine included progesterone, allylestrenol, serumβ-Human Chorionic Gonadotropin, vitamin E, folic acid and glucose.

2.2.2. Type of participants

The eligible patients with TM: 1) 20–45 years old; 2) have a gestational age between 1 and 12 weeks. The diagnosis of TM is based on documented fetal cardiac activity on ultrasound and vaginal bleeding. However, three or more consecutive spontaneous abortions were excluded. Race/ethnicity, socioeconomic status, or geography will not be restricted.

2.2.3. Type of intervention

Eligible interventions wereZYP combined with Western medicine. Western medicine (e.g., progesterone, allylestrenol, serumβ-Human Chorionic Gonadotropin, vitamin E, folic acid and glucose) was used as a control.

2.2.4. The exclusion criteria

Studies were excluded in case of: 1) Repeated studies, 2) non randomized controlled trials, self-controlled trials, medical records reports, reviews, animal experiments, 3) no control group in the study, 4) comparator arm used Zishen Yutai Pill in the study design, 5) the intervention group used Zishen Yutai Pill combined with other TCMs.

2.2.5. The outcome

Primary outcome was human chorionic gonadotropin ((IU/ml)). Secondary outcomes included: (1)The total effective rate (%), (2) progesterone ((ng/ml)), (3) estradiol ((pg/mL)), (4) the treatment length of time of abdominal pain (d), (5) the treatment length of time of vaginal bleeding(d), (6) fibrinogen (g/L), (7) hematocrit (%), (8)adverse reactions.

2.3. Reference screening and data extraction

Two investigators extracted and crossed check data independently, any disagreements were resolved through three investigators. The items are as follows: 1) the first author, 2) year of publication, 3) sample size, 4) characteristics of patients included age and gender, 5) duration of the intervention (days), 6) intervention of experimental group, 7) intervention of control group, 8) dose of drugs, 9) drug type, 10) outcome and adverse reactions.

2.4. Risk of assessment of bias of the included studies

Two investigators assessed the risk of bias, any disagreements were resolved through three investigators. The risk of bias was assessed using the Cochrane Handbook for Systematic Reviews of Interventions (Version 6.3, 2022), which includes six items. We measured trial quality using six domains: randomization process; deviations from intended interventions; missing outcome data; measurement of the outcome; selection of the reported result; overall result.

2.5. Statistical analyses

Data from individual RCTs were combined in the meta-analysis using the random effects model. Odds ratio (OR) or relative risk (RR), 95% Confidence interval (CI) and *P* values were used to estimate dichotomous variables included. The continuous data will be analyzed by Mean difference (MD) or Std Mean difference (SMD), 95% Confidence interval (CI) and *P* values. The chi-squared test and I^2 values were used to assess statistical heterogeneity, with significance levels of $P > 0.1$ and $I^2 > 50\%$, respectively. In addition, subgroup analyses stratified by treatment time ($\leq$2 week versus >2 week) to explore the source of heterogeneity. A funnel plot and Egger's test were used to detect publication bias when the number of studies exceeded ten.

3. Results

3.1. Screening results

At the initial stage of our search for ZYP and TM, 900 abstracts were searched from 8 databases. After the title, abstract and full-text rescreening, 23 RCTs [8,10,11,16–35] were ultimately included in the systematic review (Fig. 1).

3.2. Characteristics of the included studies

A total of 2411 patients were enrolled in the 23 studies, ranging in size from 40 to 240. The duration of ZYP was between 1 and 4 weeks. In 16 studies, ZYP lasted for two weeks, and in seven studies, it lasted for more than one week. All RCTs were compared between ZYP plus Western medicine and Western medicine alone. Western medicine included progesterone, allylestrenol, serumβ-Human Chorionic Gonadotropin, vitamin E, folic acid and glucose. As shown in Table 2, the included RCTs have the following basic characteristics.

3.3. Results of the risk of bias assessment

Random numbers were generated in twenty trials (ten using a random number table, two using flip of a coin, and nine using random sampling). Only one trial used treatment method to generate random numbers [26]. The allocation concealment method is not mentioned in all RCTs. The assessors and analysts were blinded in two trial [10,24]. There was probably no selective reporting or other biases in any of the trials. Detailed information of the risk of bias assessment are shown in Figures S1-S2.

3.4. Evaluations of the outcomes

3.4.1. Human chorionic gonadotropin

Human chorionic gonadotropin were available from 13 RCTs (1212 patients) [8,11,16,17,19,21,25,28,31–35]. Compared with the control conditions, human chorionic gonadotropin was significantly improved in the experimental group [MD 19.33 IU/ml, 95% CI (15.84, 22.81), $P < 0.00001$], and there was statistical heterogeneity between studies ($I^2 = 99\%$). The comparison of treatment time into subgroups showed that there were no significant differences (Fig. 2).

3.4.2. Total effective rate

The total effective rate were available from 23 controlled trials (2411 patients) [8,10,11,16–35]. Each study was consistent ($P = 0.85$, $I^2 = 0\%$). The random effect model was used for analysis. Compared with the control conditions, the total effective rate was significantly improved in the experimental group (RR 1.19, 95% CI (1.15–1.23), $P < 0.00001$) (Fig. 3).

3.4.3. Progesterone

Progesterone was available from 16 RCTs (1643 patients) [8,10,11,16,17,19,21,23–25,28,31–35]. Compared with the control conditions, progesterone was significantly improvement in the experimental group [MD 7.14 ng/ml, 95% CI (6.14, 8.13), $P < 0.00001$], and there was statistical heterogeneity ($I^2 = 93\%$). The comparison of treatment time into subgroups showed that there were significant differences, the effect of treatment time ≦2 weeks was much better (treatment time of ≦2 week vs > 2 week: MD 7.56 ng/ml vs 5.72 ng/ml, test for subgroup analysis: $P = 0.003$), which is shown in Fig. 4.

3.4.4. Estradiol

The level of estradiol was available from 8 RCTs (762 patients) [8,16,17,20,31–33,35]. Compared with the control conditions, the

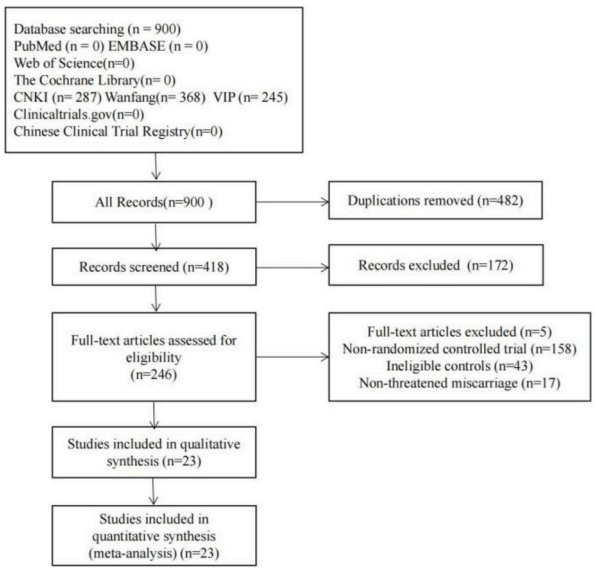

Fig. 1. Flow diagram of studies included in the systematic review and meta-analysis.

Table 2
Baseline characteristics of the included studies.

Inclusion research	Groups	Sample size	age (year)	Pregnancy time (week)	Intervention measures	Intervention times (week)	Outcome index
CHEN 2022	TG	25	29.53 ± 2.74	11.57 ± 0.4	Zishen Yutai Pill (5 g, po, tid)+progesterone injection (20 mg, im, qd)	2	a,b,c,d,e,f
	CG	25	29.52 ± 2.5	11.52 ± 0.8	progesterone injection (20 mg, im, qd)	2	
Chen 2014	TG	40	28.6 ± 3.1	<12	Zishen Yutai Pill (5 g, po, tid)+progesterone pill (20 mg, po, bid)	2	a,c
	CG	40	28.6 ± 3.1	<12	progesterone pill (20 mg, po, bid)	2	
Dong 2021	TG	50	28.37 ± 3.26	7.68 ± 1.25	Zishen Yutai Pill (5 g, po, tid)+progesterone capsules (200 mg, po, pd)	2	a,b,c
	CG	50	28.15 ± 3.38	8.15 ± 1.27	progesterone capsules (200 mg, po, pd)	2	
Han 2018	TG	30	29.13 ± 0.79	7.53 ± 0.35	Zishen Yutai Pill (5 g, po, tid)+progesterone injection (40 mg, im, qd)	3	a,b,c,d
	CG	30	28.76 ± 0.69	7.7 ± 0.35	progesterone injection (40 mg, im, qd)	3	
Hu 2018	TG	50	24.32 ± 4.93	<12	Zishen Yutai Pill (5 g, po, tid)+progesterone injection (40 mg, im, bid)+Progesterone capsules (0.1 g, po, tid)+Vitamin E (0.1 g, po, bid)	2	a,b,c,d
	CG	50	24.32 ± 4.93	<12	progesterone injection (40 mg, im, bid)+ Progesterone capsules (0.1 g, po, tid)+Vitamin E (0.1 g, po, bid)	2	
Huang 2017	TG	40	29.75 ± 3.24	6.45 ± 0.39	Zishen Yutai Pill (5 g, po, tid)+allylestrenol tablet (5 mg, po, tid)	2	a
	CG	40	29.37 ± 3.45	6.46 ± 0.40	allylestrenol tablet (5 mg, po, tid)	2	
Huang 2018	TG	37	27.3 ± 3.2	<12	Zishen Yutai Pill (5 g, po, tid)+progesterone injection (40 mg, im, qd)+Vitamin E (0.1 g, po, bid)	>2	a,c
	CG	37	27.0 ± 2.9	<12	progesterone injection (40 mg, im,qd)+Vitamin E (0.1 g, po, bid)	>2	
Huang 2021	TG	32	27.28 ± 2.41	9.53 ± 0.53	Zishen Yutai Pill (5 g, po, tid)+progesterone injection (20 mg, im, qd)	>2	a,b,d
	CG	32	28.84 ± 4.21	7.93 ± 1.41	progesterone injection (20 mg, im, qd)	>2	
Li 2021	TG	40	27.82 ± 3.24	6.85 ± 0.55	Zishen Yutai Pill (5 g, po, tid)+progesterone injection (20 mg, im, qd)	2	a,b,c,g,h
	CG	40	27.56 ± 3.21	6.83 ± 0.53	progesterone injection (20 mg, im, qd)	2	
Liu 2014	TG	84	22–37	5–9	Zishen Yutai Pill (5 g, po, tid)+progesterone injection (40 mg, im, qd)+Progesterone capsules (0.1 g, po, tid)+Vitamin E (0.1 g, po, bid)	>2	a
	CG	84	22–37	5–9	progesterone injection (40 mg, im, qd)+Progesterone capsules (0.1 g, po, tid)+Vitamin E (0.1 g, po, bid)	>2	
Liu 2019	TG	70	27.94 ± 2.53	6.94 ± 1.32	Zishen Yutai Pill (5 g, po, tid)+allylestrenol tablet (5 mg, po, tid)	1	a,c,e,f
	CG	71	28.22± ±2.62	6.83 ± 1.27	allylestrenol tablet (5 mg, po, tid)	1	
Mou 2019	TG	100	27.61 ± 1.01	8.01 ± 0.37	Zishen Yutai Pill (5 g, po, tid)+allylestrenol tablet (5 mg, po, tid)	1	a,c,e,f
	CG	100	27.46 ± 1.05	8.12 ± 0.43	allylestrenol tablet (5 mg, po, tid)	1	
Qiu 2021	TG	40	28.62 ± 4.71	7.84 ± 1.38	Zishen Yutai Pill (5 g, po, tid)+Dydrogesterone tablet (10 mg, po, bid)	>2	a,b,c,
	CG	40	28.84 ± 4.21	7.93 ± 1.41	Dydrogesterone tablet (10 mg, po, bid)	>2	
Tang 2015	TG	120	28 ± 2.6	6.14 ± 0.16	Zishen Yutai Pill (5 g, po, tid)+Progesterone capsules (150 mg, po, bid)	2	a
	CG	120	27 ± 2.9	6.43 ± 0.21	Progesterone capsules (150 mg, po, bid)	2	
Wang su 2016	TG	45	25.5 ± 4.5	<12	Zishen Yutai Pill (5 g, po, tid)+Progesterone capsules (150 mg, po, bid)	2	a
	CG	45	26.5 ± 6.5	<12	Progesterone capsules (150 mg, po, bid)	2	
Wang 2021	TG	50	27.5 ± 3.3	7.5 ± 0.7	Zishen Yutai Pill (5 g, po, tid)+progesterone injection (20 mg, im, qd)	2	a,b,c,g,h
	CG	50	27.1 ± 3.2	7.4 ± 0.6	progesterone injection (20 mg, im, qd)	2	

(*continued on next page*)

Table 2 (*continued*)

Inclusion research	Groups	Sample size	age (year)	Pregnancy time (week)	Intervention measures	Intervention times (week)	Outcome index
Wang jin 2016	TG	43	30 ± 3.36	11.15 ± 1.04	Zishen Yutai Pill (5 g, po, tid)+Chorionic gonadotropin for Injection (250 μg, im, pd)	2	a,e,f
	CG	43	28 ± 3.24	10.25 ± 1.94	Chorionic gonadotropin for Injection (250 μg, im, pd)	2	
Wu 2019	TG	20	27.28 ± 3.09	<12	Zishen Yutai Pill (5 g, po, tid)+progesterone injection (20 mg, im, qd)+Vitamin E (0.1 g, po, bid)	>2	a
	CG	20	27.31 ± 3.15	<12	progesterone injection (20 mg, im, qd)+Vitamin E (0.1 g, po, bid)	>2	
Xia 2016	TG	65	25.61 ± 3.6	9.02 ± 2.5	Zishen Yutai Pill (5 g, po, tid)+progesterone tablet (0.1 g,po, bid)+Vitamin E (0.1 g, po, bid)+Folic acid tablet (4 mg, po, pd)	2	a,b,c,d
	CG	65	24.79 ± 2.95	8.85 ± 2.6	progesterone tablet (0.1 g, po, bid)+Vitamin E (0.1 g, po, bid)+Folic acid tablet (4 mg, po, pd)	2	
Yang 2019	TG	45	25.54 ± 2.62	9.05 ± 0.35	Zishen Yutai Pill (5 g, po, tid)+Progesterone capsules (50 mg, po, tid)	>2	a,b,c,d
	CG	45	25.21 ± 2.34	9.21 ± 0.34	Progesterone capsules (150 mg, po, tid)	>2	
Zhang Mei 2019	TG	30	27.92 ± 5.33	6.75 ± 2.59	Zishen Yutai Pill (5 g, po, tid))+progesterone injection (20 mg, im, qd)	2	a,b,c,d
	CG	30	27.85 ± 5.41	6.64 ± 2.72	progesterone injection (20 mg, im, qd)	2	
Zhang Wen 2019	TG	45	25.40 ± 5.34	7.49 ± 0.41	Zishen Yutai Pill (5 g, po, tid)+progesterone injection (20 mg, im, qd)	2	a,b,c,d
	CG	45	26.27 ± 4.62	7.52 ± 0.55	progesterone injection (20 mg, im, qd)	2	
Zhao 2020	TG	104	28.07 ± 2.64	6.17 ± 1.40	Zishen Yutai Pill (5 g, po, tid)+progesterone capsules (150 mg, po, bid)+Vitamin E (0.1 g, po, bid)+Folic acid tablet (4 mg, po, pd)	2	a,b,c,d,g,h
	CG	104	27.92 ± 2.85	6.08 ± 1.35	progesterone capsules (150 mg, po, bid)+Vitamin E (0.1 g, po, bid)+Folic acid tablet (4 mg, po, pd)	2	

a.The total effective rate; b.Human chorionic gonadotropin; c. Progesterone; d. Estradiol; e. Abdominal pain; f. Vaginal bleeding; g. Fibrinogen; h. Hematocrit.

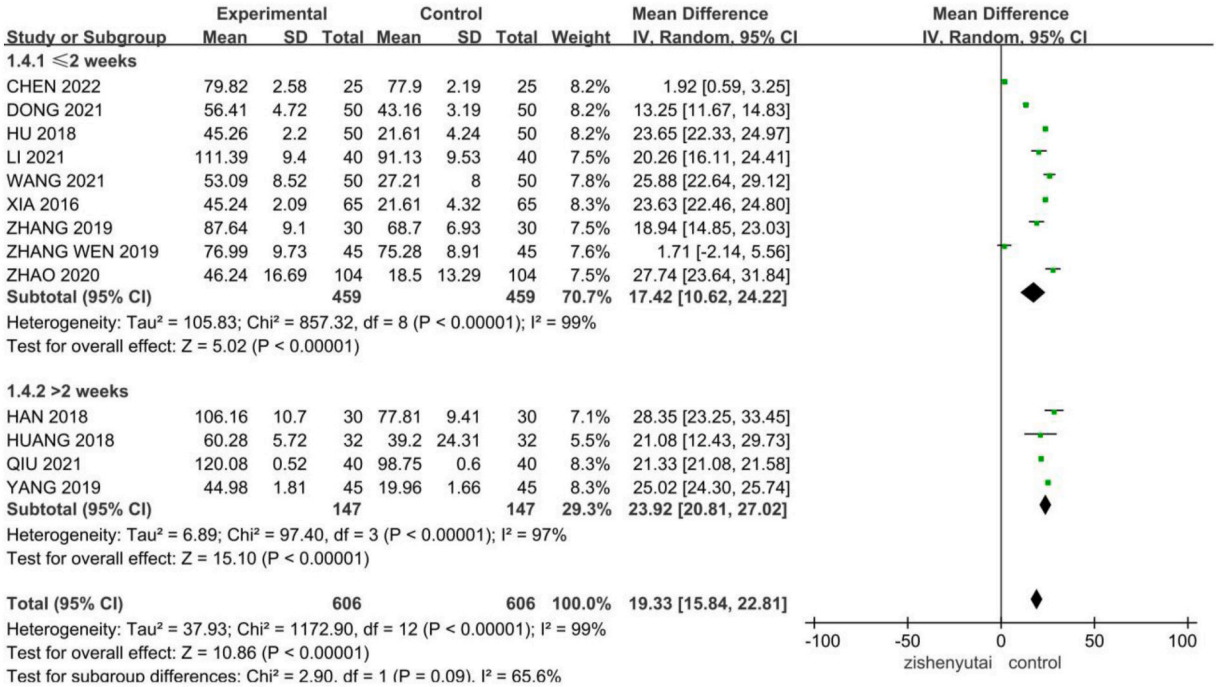

Fig. 2. Meta-analysis of the human chorionic gonadotropin (IU/mL).

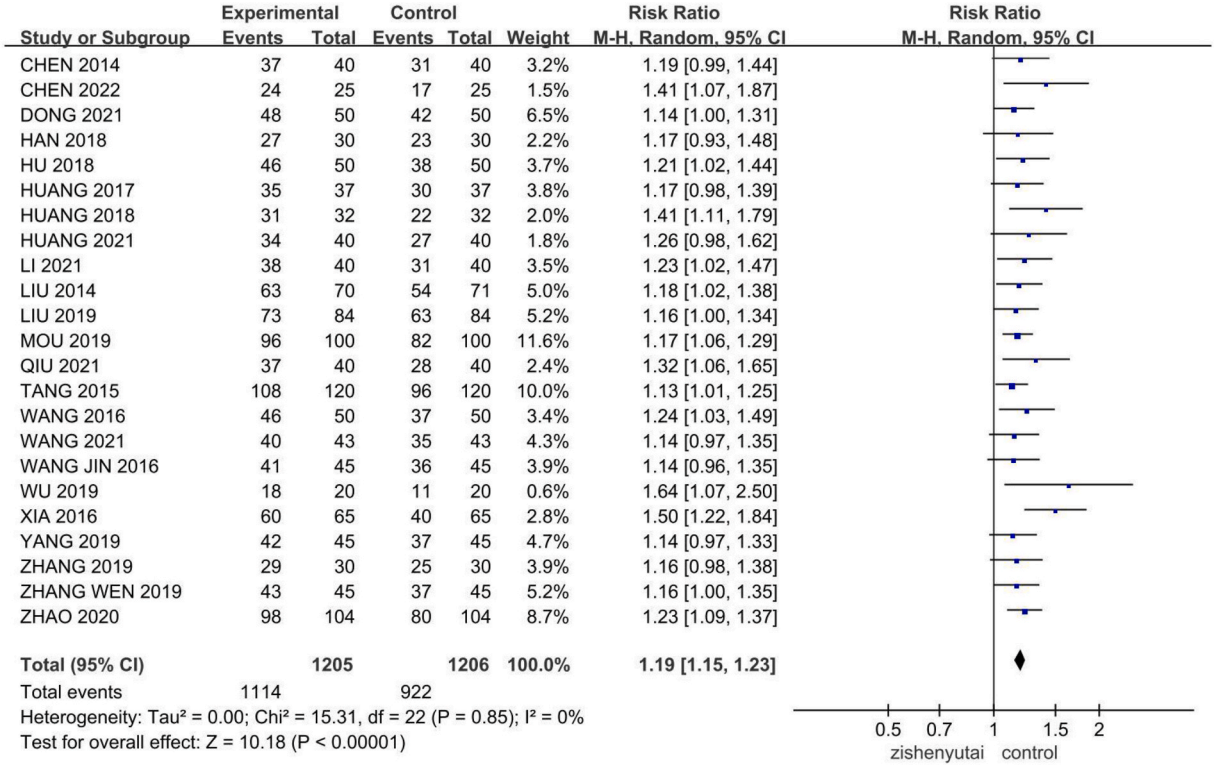

Fig. 3. Meta-analysis of the total effective rate (%).

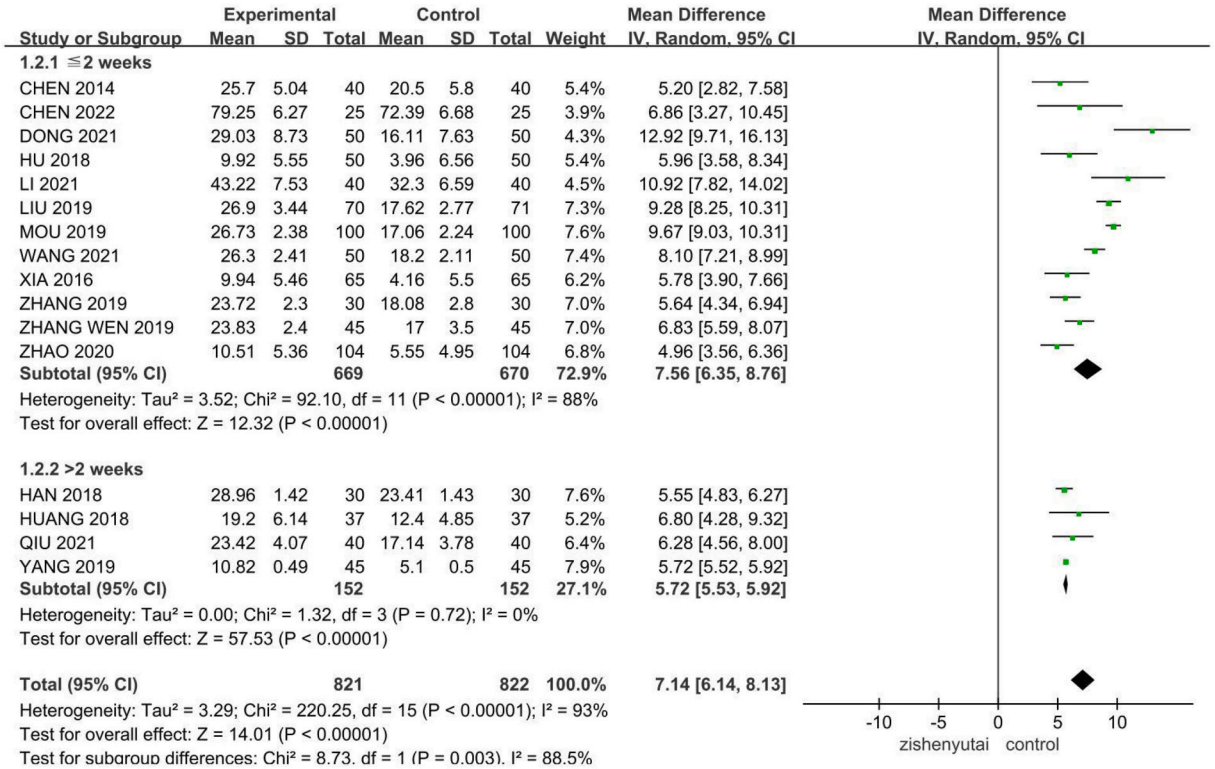

Fig. 4. Meta-analysis of the progesterone (ng/ml).

content of estradiol hormone was significantly enhanced in the experimental group [MD 33.69 pg/ml, 95% CI (27.42, 39.96), $P = 0.0002$], and there was statistical heterogeneity ($I^2 = 75\%$). The comparison of treatment time into subgroups showed that there were significant differences, and the effect of treatment time ≦2 weeks was more better (treatment time of ≦2 week vs > 2 week: MD 30.79 ng/ml vs 39.13 ng/ml, test for subgroup analysis: $P = 0.005$), which is shown in Fig. 5.

3.4.5. Duration of abdominal pain

The duration of abdominal pain was available from 4 RCTs (477 patients) [8,23,24,29]. Compared with the control conditions, the duration of abdominal pain was significantly slighter in the experimental group [MD -2.36 d, 95% CI (- 3.54, - 1.18)]; Heterogeneity test: $P < 0.00001$, $I^2 = 93\%$; Fig. 6). Subgroup analysis was not performed due to the small number of studies.

3.4.6. Duration of vaginal bleeding

The duration of vague bleeding were available from 4 RCTs (477 patients) [8,23,24,29]. Compared with the control conditions, the duration of vaginal bleeding was significantly lower in the experimental group [MD -1.94 d, 95% CI (- 2.93, - 0.94); Heterogeneity test: $P < 0.00001$, $I^2 = 90\%$; Fig. 7] Subgroup analysis was not performed due to the small number of studies.

3.4.7. Fibrinogen

Three RCTs (n = 388) reported fibrinogen [21,28,35]. As shown in Fig. 8, compared with the control conditions, the content of fibrinogen was significantly lower in the experimental group [MD -0.34 g/L, 95% CI (- 0.57, - 0.11); Heterogeneity test: $P = 0.12$, $I^2 = 53\%$]. Subgroup analysis was not performed due to the small number of studies.

3.4.8. Hematocrit

Three RCTs (n = 388) reported hematocrit [21,28,35]. As shown in Fig. 9, there was no statistically significant difference in hematocrit between the two groups [MD 0.68%, 95% CI (- 0.08, 1.44); Heterogeneity test: $P = 0.36$, $I^2 = 2\%$]. Subgroup analysis was not performed due to the small number of studies.

3.4.9. Safety evaluation

As shown in Table 3, eight trials reported adverse reactions, mainly including gastrointestinal and disturbed sleep [11,21,23–26,28,29]. There were one case of needle sickness and three cases of erythra in the study [11], four cases of edema in Mou's study [24], and two cases of edema in Liu et al.'s study [23]. There were no adverse events reported in the remaining trials, and remission was achieved without specific treatment.

3.4.10. Publication bias

Egger's test was used to quantify whether the funnel map had publication bias. The test results of human chorionic gonadotropin, the total effective rate, and progesterone were $P = 0.000$, $P = 0.040$ and $P = 0.001$ respectively; From the visual point of view of the funnel chart, human chorionic gonadotropin, the total effective rate, and progesterone are basically symmetrically distributed, which also suggests that there is little possibility of publication bias, which is shown by Figures S3-5.

4. Discussions

In the systematic reviews and meta-analysis, ZYP as a supplementary treatment, we extracted data from 23 studies (n = 2411) to comprehensively evaluate the efficacy and safety of ZYP in woman with TM. The results indicated that ZYP may improve the clinical symptoms in woman with TM, such as human chorionic gonadotropin the total effective rate, progesterone, estradiol, treatment time of abdominal pain, treatment time of vaginal bleeding, and fibrinogen. Moreover, ZYP has a low price and a high level of patient compliance, and it has no serious adverse effects. Although the clinical course of treatment is different, both treatment and control groups had similar efficacy in most outcomes. However, for progesterone in particular, the curative effect is significantly better with a ≦2 weeks treatment program than with >2 weeks, so the recommended duration of progesterone use is two weeks in order to optimize both cost-effectiveness and curative effects. For estradiol, the curative effect of >2 weeks is significantly better than that of ≦ 2 weeks, in terms of cost-effectiveness and curative effect, it is recommended that patients take estradiol for more than two weeks. And the recommended dosage of ZYP is 5 mg three times a day.

Retained products of conception refers to the phenomenon that trophoblastic tissue or placenta remains in the uterine cavity after pregnancy [36]. Most of the patients with retained products of conception are symptomatic. Common symptoms include abnormal uterine bleeding, pelvic pain, and fever [37]. Hysteroscopy is considered the gold standard for the diagnosis and treatment of intrauterine disorders [37]. A systematic review reported that hysteroscopic management of retained products of conception is effective and safe [37]. However, TM is bound to damage the endometrium. In order to minimize strauma to the healthy endometrium, ZYP usually treats TM at first-trimester pregnancy, which has both short- and long-term potential benefits.

This study has some limitations. 1) Many studies deviate from the standards for methodological quality and clinical trial reporting, leading to the lack of clarity in some trial publications. Therefore, the quality of information is degraded. 2) Only Chinese databases reported RCTs with ZYP, so the mete-analysis might have limitations. 3) There is significant heterogeneity in this systematic review and meta-analysis, which may be resulted from different doses, different administration methods, and severity of patients' conditions bring about high heterogeneity. 4) There was great heterogeneity among some outcome studies, but only some sources of heterogeneity were explained for progesterone and estradiol through subgroup analysis, and the sources of other heterogeneity were unclear.

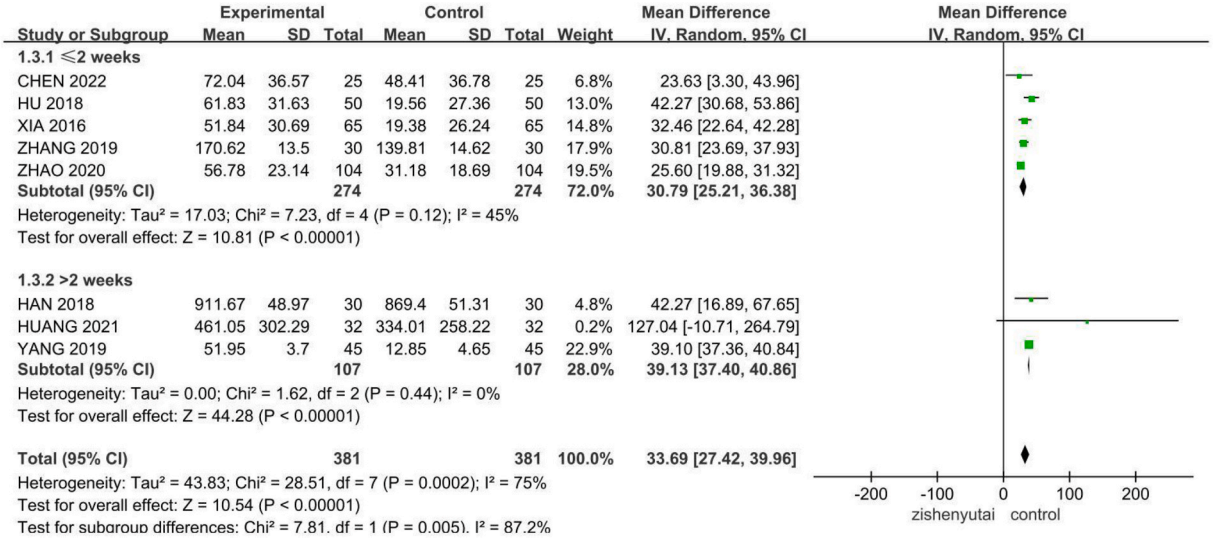

Fig. 5. Meta-analysis of the estradiol (pg/ml).

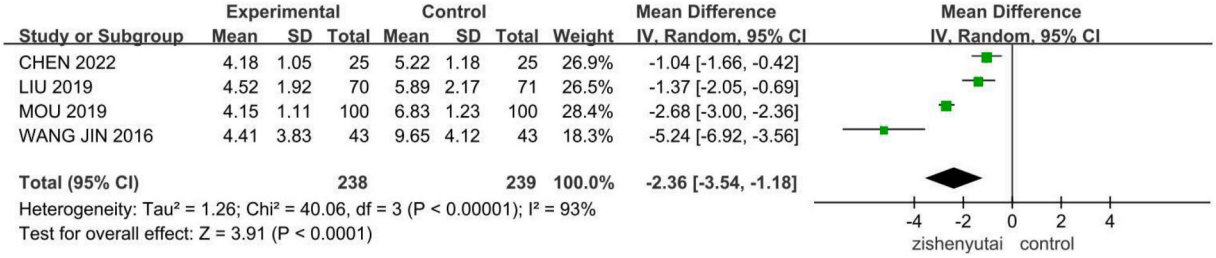

Fig. 6. Meta-analysis of the treatment length of time of abdominal pain(d).

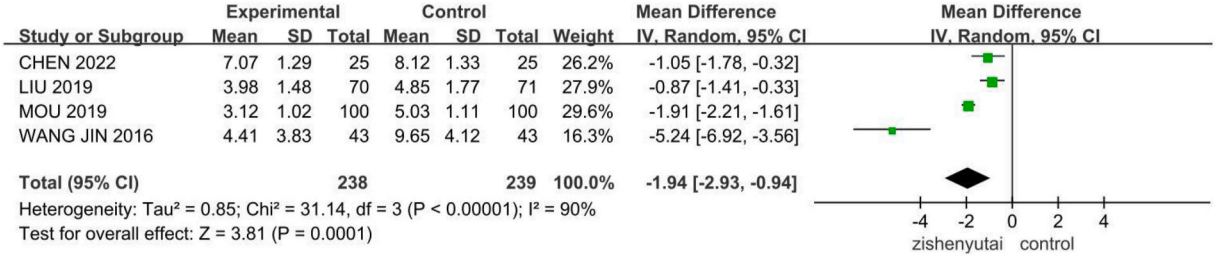

Fig. 7. Meta-analysis of the treatment length of time of vaginal bleeding(d).

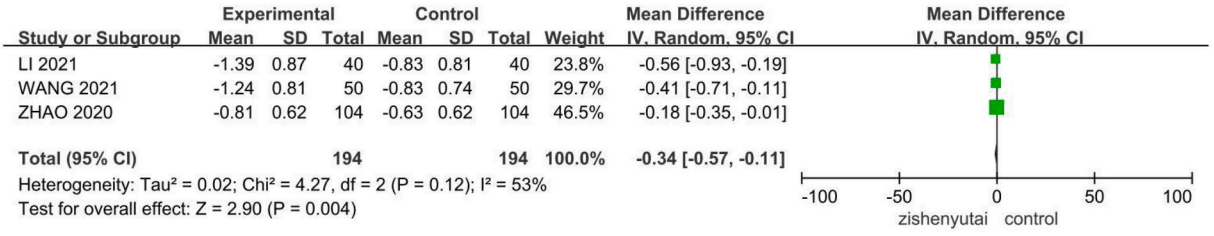

Fig. 8. Meta-analysis of the fibrinogen (g/L).

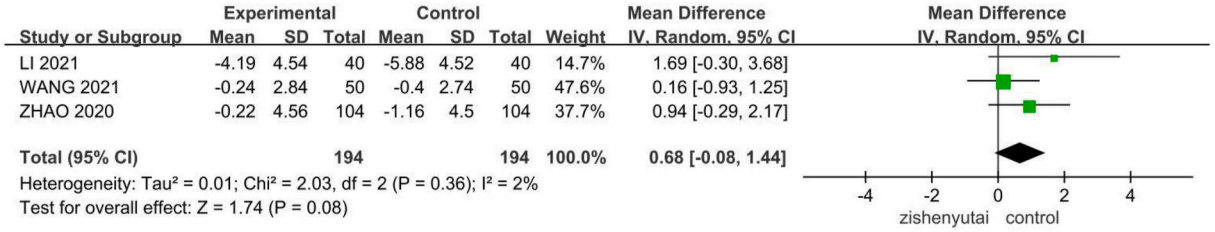

Fig. 9. Meta-analysis of the hematocrit (%).

Table 3
Condition of adverse reactions.

Study ID	Adverse reaction	Order of severity	Processing and conversion	Causal correlation
Dong 2014	Nausea, breast swelling, pain, dizziness, insomnia, rash	slight	No information	no
Mou 2019	Headache, nausea, and edema	slight	No information	no
Li 2021	Dry throat, diarrhea, constipation, and vomiting	slight	No information	no
Liu 2019	Dizziness, headache, nausea, Vomiting, dry throat, edema	slight	returning to normal after discontinuing medication	no
Tang 2015	Nausea, dry mouth, constipation	slight	returning to normal after discontinuing medication	no
Wang 2016	Nausea, restless sleep, constipation	slight	No information	no
Qiu 2021	Gastrointestinal reactions, rash, dizziness	slight	No information	no
Wang 2021	Diarrhea, Vomit, Constipation, Dry pharynx	slight	No information	no

5. Conclusion

ZYP showed significant improvement in AB patients compared with control group. As a safe, cost-effective, and convenient supplementary treatment, ZYP might be recommended for TM patients. However, future research should be conducted with reference to the aforementioned suggestions.

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Patient and public involvement

Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication

Not applicable.

Provenance and peer review

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Author contribution statement

All authors listed have significantly contributed to the development and the writing of this article.

Data availability statement

The data used to support the findings of this study are available from the corresponding author upon request.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper

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Abbreviations

CI	Confidence interval
MD	Mean difference
RR	Risk ratio
TM	Threatened miscarriage
ZYP	ZishenYutai Pill

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2023.e16213.

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