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Comparison of the efficacy and safety of phloroglucinol and magnesium sulfate in the treatment of threatened abortion

A meta-analysis of randomized controlled trials

Shaofei Yuan, MS[a], Fengli Gao, MS[a], Zhong Xin, MS[a], Haijun Guo, MS[a], Suqin Shi, MS[a], Lei Shi, MS[b], Xia Yang, MSc[c], Jingzhi Guan, MS[d,*]

Abstract

Background: To compare the clinical efficacy and safety of phloroglucinol (PHL) and magnesium sulfate (MS) in the treatment of threatened abortion through systematic review.

Methods: Foreign databases, such as the Cochrane Library, PubMed and EMBASE, and Chinese databases, including the China Biology Medicine disc (SinoMed), China National Knowledge Infrastructure (CNKI), Chongqing VIP (VIP) and WanFang Data, were searched. Published randomized controlled trials (RCTs) documents obtained from these databases were included if they were associated with the research objective. The search timeframe was from the beginning of the establishment of each database to May 2018. Document selection, data abstraction and document quality evaluation were independently performed by 2 investigators. A combined analysis of the data was performed for those documents that fulfilled the study requirements; Rev Man 5.3 and Stata 12.0 software were used to compare and analyze the 2 drugs in terms of the total effective rate (TER), rate of adverse events, time required to relieve uterine contractions, onset time, time of complete relief of uterine contraction symptoms, medication duration and length of hospital stay.

Results: A total of 21 RCT trials were included in the present research, according to the inclusion criteria. However, the quality of the included studies was low. The meta-analysis suggested that the TER and drug onset time of PHL were higher than those for MS, while the rate of adverse events, the time required to relieve uterine contractions, time to complete relief of uterine contraction symptoms, drug continuous treatment time and length of hospital stay were shorter than those for MS.

Conclusion: The clinical efficacy of PHL is better than that of MS, and PHL obviously results in fewer adverse reactions than MS. However, due to poor quality of evidence, high quality, multi-center RCTs with large samples are required for further verification.

Abbreviations: CG = control group, CNKI = China national knowledge infrastructure, GI = glucose injection, MD = mean deviation, MS = magnesium sulfate, PHL = phloroglucinol, RCTs = randomized controlled trials, RG = research group, RR = relative risk, SCI = sodium chloride injection, SMD = standardized mean difference, TER = total effective rate, VIP = Chongqing VIP.

Keywords: magnesium sulfate, meta-analysis, phloroglucinol, threatened abortion

1. Introduction

Threatened abortion refers to minor vaginal hemorrhage before paroxysmal lower abdominal pain or backache with no cervical dilation, an intact fetal membrane, no discharge of pregnancy tissue, and fetal survival. Threatened abortion is the most common pattern of spontaneous abortion. In clinical practice, the rate of threatened abortion is up to 20%. With lifestyle and dietary habit changes, an increasingly severe environmental pollution, increased occupational and work stress among women, more elderly parturient women and the associated decline in oocyte quality, the occurrence rate of threatened abortion has increased annually,[1] which has attracted increasing attention from the medical world. How to effectively prevent threatened abortion following gestation has been a focus of most obstetricians and gynecologists. Threatened abortion involves complicated factors, and the common factors include fetal chromosomal abnormalities, immunologic dysfunction, inadequate luteal function, cervical dysfunction, and reproductive tract infections, as well as genetic, psychic and mental factors.[2,3] The diagnosis of threatened abortion may be confirmed by medical history (menopause, clinical concomitant symptoms, etc), B ultrasonography, and laboratory tests of β human chorionic gonadotropin (β-HCG), progesterone and oestrogen E2. The

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[a] Department of Pharmacy, The Second Affiliated Hospital of Baotou Medical College, Baotou, [b] Department of Pharmacy, Huhhot First Hospital, Yuquan District, Huhhot, Inner Mongolia, [c] Department of Pharmacy, Baogang Hospital (The Third Affiliated Hospital of Inner Mongolia Medical University), Kundulun District, Baotou, Inner Mongolia Autonomous Region, [d] Department of Pharmacy, Inner Mongolia International Mongolian Hospital, Hohhot, Inner Mongolia, China.

[*] Correspondence: Jingzhi Guan, Department of Pharmacy, Inner Mongolia International Mongolian Hospital, No. 83 Daxue East Road, Hohhot, Inner Mongolia 010065, China (e-mail: jingzhiguan_IMIMH@163.com).

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primary principle of treating threatened abortion is to inhibit uterine contractions using tocolytic agents, thereby improving the survival rate of the fetus after the gestation age reaches 28 weeks. With the rapid development of medical science, particularly genetics, increasingly more studies have confirmed that for most threatened abortions for non-fetal reasons, continuation of gestation and delivery is possible if fetus protection is provided in time, and the complications during childbirth and adverse outcomes of the newborn are similar to those of newborns from normal pregnant women.[4,5] Patients with late threatened abortion should use tocolytic agents as soon as possible. Currently, common drugs include uterine muscular relaxants,[6] anti-D immunoglobulin,[7] progesterone, dydrogesterone, β-HCG,[8] etc. The primary tocolytic agents are magnesium sulfate (MS), phloroglucinol (PHL), ritodrine hydrochloride, atosiban, etc. MS, a type of calcium ion antagonist, can inhibit smooth muscle spasm. MS is widely used in obstetrics departments to treat eclampsia, pre-eclampsia and threatened abortion. However, there have been no guidelines on the use of MS in treating threatened abortion at home and abroad. PHL is a type of myotropic, non-atropine, non-papaverine, pure smooth muscle spasmolytic. In recent years, PHL has received increasing attention and has been widely used in obstetrics and gynecology departments, gastric and intestine departments and urinary surgery due to its rapid action and less adverse reactions. After collection of the current data in China, a meta-analysis was performed to compare MS and PHL in terms of the clinical efficacy and adverse reactions in treating late threatened abortion, thereby providing relatively reliable guidance for the treatment of late threatened abortion in clinical practice.

2. Methods and analysis

2.1. Search strategy

This study used a method of retrieving published studies through computer retrieval from foreign medical databases (Cochrane Library, PubMed and EMBASE) and domestic databases (SinoMed, CNKI, VIP, Wanfang Data, etc). The search strategy was based on the combination of subject terms and free terms. The Chinese search terms were "Xianzhaoxingliuchan", "Xianzhaoliuchan", "Liusuanmei", "Jianbensanfen", etc. The English search terms included "Abortion, Threatened", "Threatened Abortion", "Phloroglucinol", "Magnesium sulfate", etc. All searches were performed in Chinese and English starting from the establishment of each database to April 15, 2018. A manual search of the relevant conference literature and collected papers published after 2010 was also conducted. A supplementary search was also performed, as necessary, to ensure a comprehensive literature collection. Table 1, http://links.lww.com/MD/D35 shows the literature search strategy.

2.2. Inclusion and exclusion criteria

2.3. Type of study

Randomized controlled trials (RCTs) regarding PHL and MS in the treatment of threatened abortion in Chinese or English were included, regardless of study blinding. This study is based on the preferred reporting items for systematic reviews and meta-analysis (PRISMA statement).

Subjects investigated:

(1) Patients were enrolled regardless of age, sex, and source. Diagnostic criteria were based on the 6th Edition of Gynecology and Obstetrics.[9]
(2) All included pregnant woman were healthy, excluding those with internal or surgical disease during pregnancy or drug combinations.
(3) The observation and control groups (CG) were comparable in gestational weeks, pregnant frequency and abortion frequency, with no statistically significant differences.

Exclusion criteria:

(1) The therapeutic measures did not meet the pre-defined inclusion criteria, and non-target drugs were used;
(2) non-RCT, such as reviews, retrospective studies, animal experiments, phase I clinical trials, etc;
(3) patients with inconsistent baseline data; and
(4) important data or reports were incomplete, and the correspondence author did not respond to inquiry.

Intervention: In the experimental group, an intravenous drip of 40 mg or 80 mg PHL was administered, the dripping speed and dosage were adjusted according to the uterine contractions, and the dosage should be no more than 400 mg within 24 hours. In the CG, after finishing an intravenous drip of 4–5 g MS within 30–60 minutes, a sustained intravenous drip of MS was maintained at a rate of 1–2 g, according to the uterine contractions, and the dosage should not exceed 30 g within 24 hours.

2.4. Outcome indicators

The following related indicators were statistically analyzed after treatment:

(1) the total effective rate (TER) (i.e., effectual, uterine contractions were obviously relieved or disappeared within 12 hours of medication; improved, uterine contractions were relieved to a certain degree within 24 hours of medication; and ineffective, symptoms showed no change or were even aggravated within 48 hours of medication); the total effective rate = (number of effectual cases + number of improved cases)/number of total cases × 100%;
(2) the rate of adverse reactions;
(3) the time to relief of uterine contractions;
(4) the complete relief of uterine contraction symptoms;
(5) the drug onset time;
(6) the duration of the drug treatment; and
(7) the length of hospital stay.

2.5. Data extraction

Two investigators extracted data based on the jointly designed literature data extraction table. The following data were extracted through a double abstraction process:

(1) basic information about the studies, including the title, author, journal and year, and selection level;
(2) study elements, including basic information about subjects, interventions, outcome measures, and design type; and
(3) experimental results, including the total number of participants completing the trial, type of data, and effective dose.

The consistency in study selection between the two evaluators was determined by the Kappa value. Any disagreement was

determined by a third party or through mutual discussion. If no consensus was reached due to inadequate information, the literature involved was listed as "to be evaluated", and a final decision was not made until enough information was obtained after contacting the author(s).

2.6. Quality evaluation

The present study was independently completed by 2 investigators using the bias risk assessment tool before crosschecking the quality of the included trials. The bias risks of the included papers were evaluated in terms of selection bias, performance bias, measurement bias, loss to follow-up bias, and report bias. Each evaluation was considered to suggest a high bias risk, low bias risk or uncertain risk. Disagreement between the 2 investigators in the literature evaluation was resolved through mutual discussion or by a third party.

2.7. Data analysis

The meta-analysis was performed using Stata 12.0 and Rev Man 5.3 software. In the present study, the enumeration data of outcome evaluation were statistically analyzed using the relative risk (RR) and 95% CI as effect sizes. Continuous data were analyzed using standardized mean difference (SMD) and 95% CI; if the same variability had different weights and measures, the data were analyzed by difference in the mean deviation (MD) and 95% CI. Variations in the included documents were called heterogeneity. The heterogeneity of these documents was assessed using the I^2 test, and $P > .1$ or $I^2 < 25\%$ was considered to suggest no statistically significant heterogeneity in the documents. Meta-analysis was performed using a fixed model. $P \geq .1$ or $25\% \leq I^2 \leq 50\%$ was considered to indicate moderate heterogeneity in the documents; $P < .1$ or $I^2 > 50\%$ was considered to suggest high heterogeneity. If data consolidation was clinically feasible, moderate heterogeneity, and high heterogeneity were analyzed using a random effects model, and sensitivity analysis[10] was performed to identify the source of heterogeneity and robustness of the test result. Publication bias was evaluated by Egger test (regression analysis). Obvious clinical heterogeneity was processed through subgroup analysis or sensitivity analysis, or only descriptive analysis was performed.

3. Results

3.1. Search results

In total, 99 relevant documents were found using the search strategy and data collection: the Cochrane Library (n=0), PubMed (n=0), Embase (n=0), SinoMed (n=59), CNKI (n=29), WanFang Data (n=21) and VIP (n=24). Forty-nine papers were obtained after duplicate checking by using reference management software Note express 2. Papers were ruled out after review of their titles and abstracts due to the following reasons: not associated with the present research (n=4), clinical and nursing document (n=1), review (n=1) and conference data with incomplete data (n=3). Then, the following papers were excluded: those not meeting the inclusion criteria (n=18) and repeated publications (n=1). Finally, 21 RCTs were included (see Fig. 1).

3.2. Study characteristics

A total of 21 RCTs[11–31] were included, involving in 1940 patients in total (including 979 cases in the experimental group and 961 cases in the control group). The 2 groups showed no statistically significant differences in baseline data, including age, gestational weeks, pregnancy frequency, and abortion frequency. The 2 groups were comparable, showing no obvious difference in the mean dosage between the different groups. These papers were published in 2009 (n=1),[12] 2012 (n=1),[13,14] 2013 (n=2),[15–18] 2014 (n=4), 2015 (n=2),[19,20] 2016 (n=4),[21–24] 2017 (n=7).[25–31]Table 1 shows the basic characteristics of these included studies.

3.3. Summary of the quality and bias risk of the trials included

The quality of the studies included was low, and they were described as RCTs. Four of the 21 included RCTs reported the specific randomization methods, and 2 of them[21,30] used wrong random grouping methods.[21,30] All studies failed to mention blinding implementation and randomization concealment. The bias risks of the 21 RCTs included were analyzed. See Figures 2 and 3.

3.4. Outcome measures

Total effective rate: A total of 21 studies reported the total effective rate.

Rate of adverse reaction: A total of 21 documents reported the rates of adverse reactions, including flush and fever in 16 documents, dizziness and headache in 16 documents, gastrointestinal discomfort in 14 documents, nausea and vomiting in 9 documents, thirst in 9 documents, perspiration in 8 documents, insomnia in 4 documents, lack of strength in 4 documents, and chest depression in 2 documents.

Time to relieve uterine contraction: A total of 9 documents reported the index. Drug onset time: a total of 7 documents in total reported the index.

The complete relief of uterine contraction symptoms: A total of 4 documents reported this index.

Drug continuous treatment time: A total of 3 documents reported the index.

Length of hospital stay: A total of 2 documents reported the index. The abovementioned outcome measures were analyzed, as shown below.

3.5. Total effective rate

Twenty-one studies involving 1940 patients (979 cases in the experimental group and 961 cases in the control group) reported the TER.[11–31] The heterogeneity analysis suggested moderate heterogeneity ($P=.019$, $I^2=43.3\%$). Using a random-effects model, the meta-analysis revealed that the ORR of PHL for threatened abortion was higher than that of MS. The results of the two groups showed a statistically significant difference [n=21, RR=0.11, 95% CI (0.05, 0.26), $Z=5.30$, $P=.000$] (see Fig. 4). A sensitivity analysis of the results of the included documents found that the combined effective dose showed no change from the original effective dose, suggesting that the meta-analysis result was relatively stable (see Fig. 5).

3.6. Adverse reaction rate

(1) Flush and redness. Sixteen of the included studies reported flush and redness.[12–14,16,17–22,24,25,28–31] These studies in-

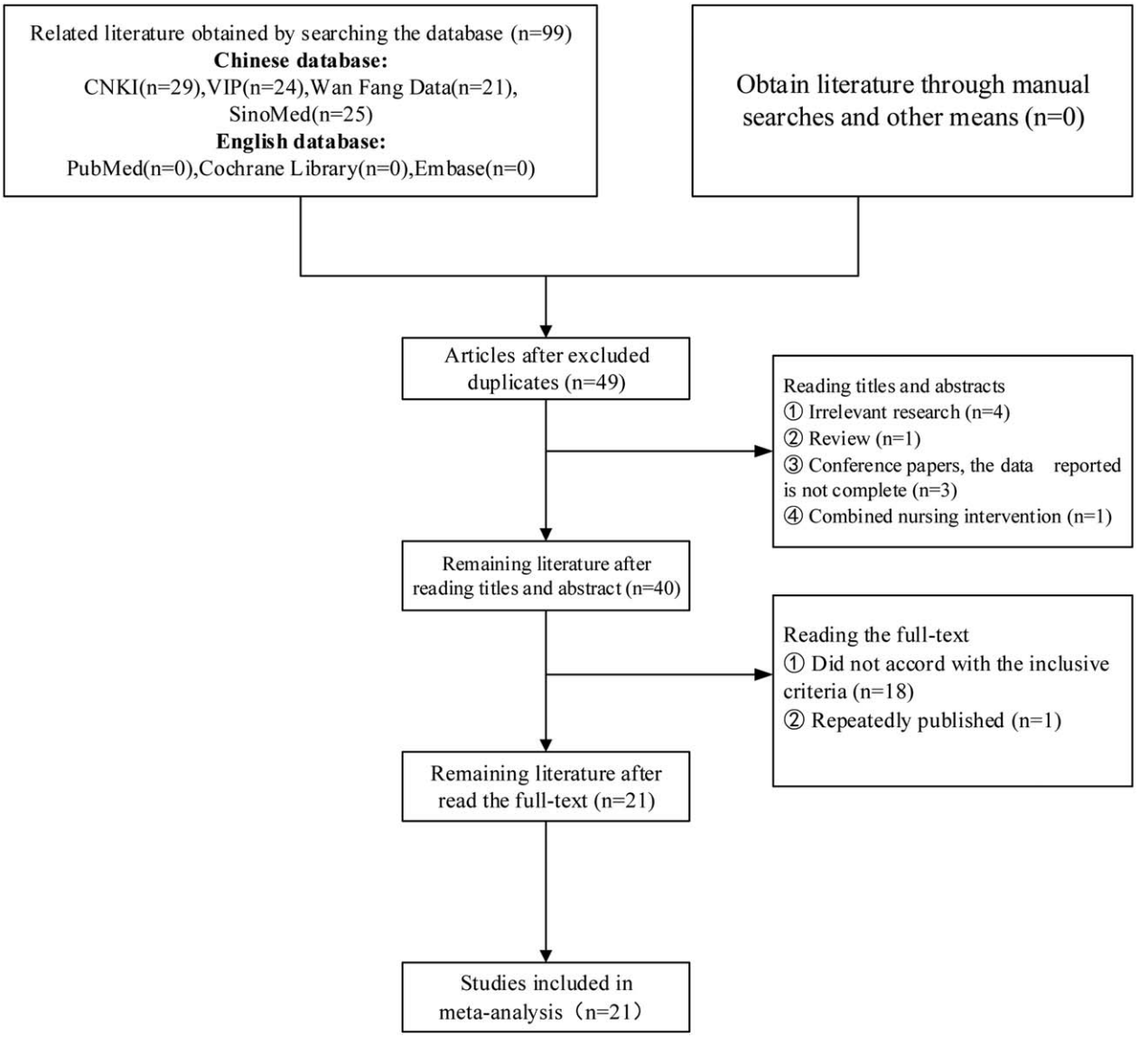

Figure 1. The document selection flowchart.

volved a total of 1544 patients (781 cases in the experimental group and 763 cases in the control group). The heterogeneity results suggested no heterogeneity ($P=.535$, $I^2=0.0\%$). Using a random-effects model, the meta-analysis showed that the occurrence rate of flush and redness of PHL was lower than that of MS, with a statistically significant difference [n=16, RR=0.09, 95% CI (0.05, 0.16), $Z=7.51$, $P=.000$]. See Figure 6.

(2) Dizziness and headache. Sixteen of the included studies reported dizziness and headache.[12–14,16–26,29,30] These studies involved in a total of 1496 patients (757 cases in the experimental group and 739 cases in the control group). The heterogeneity result suggested no heterogeneity ($P=.973$, $I^2=0.0\%$). Using a fixed-effects model, the meta-analysis showed that the occurrence rate of dizziness and headache of PHL was lower than that of MS, with a statistically significant difference [n=16, RR=0.15, 95% CI (0.08, 0.28), $Z=6.00$, $P=.000$]. See Figure 7.

(3) Gastrointestinal discomfort: Fourteen of the included studies reported gastrointestinal discomfort.[12–14,16–18,19,23–25,27,29–31] These studies involved a total of 1345 patients (679 cases in the experimental group and 666 cases in the control group). The heterogeneity result suggested no heterogeneity ($P=.856$, $I^2=0.0\%$). Using a fixed-effects model, the meta-analysis showed that the occurrence rate of gastrointestinal discomfort of PHL was lower than that of MS, with a statistically significant difference [n=14, RR=0.19, 95% CI (0.10, 0.36), $Z=5.10$, $P=.000$]. See Figure 8.

(4) Palpitation: Twelve of the included studies reported palpitation.[12,14,16,18,22,24,26–31] These studies involved a total of 1160 patients (582 cases in the experimental group and 578 cases in the control group). The heterogeneity result suggested no heterogeneity ($P=.987$, $I^2=0.0\%$). Using a fixed-effects model, the meta-analysis showed that the occurrence rate of palpitation of PHL was lower than that of MS, with a statistically significant

Table 1

The basic characteristics of the 21 included studies.

Inclusion research	Groups	Number of participants (cases)	Age (years)	Pregnancy time (weeks)	Number of abortions (times)	Number of pregnancies (times)	Intervention measures	Outcomes
Wang[11]	RG	30	27	21	1–2	1–2	PHL 80 mg + 5%GI 500 ml, 1 time/one day	②③④
	CG	30	28	22	1–2	1–2	MS 30 ml + 5%GI 500 ml, 2 times/one day	
Zhou and Chen[12]	RG	50	22–35	12–20	1–3	1–4	PHL 80 mg + 0.9% SCI 250 ml, 1time/one day	③④⑤⑥
	CG	50	22–35	12–20	1–3	1–4	25%MS 16 ml + 5%GI 100ml, 25%MS 16 ml + 5%GI 500ml	
Wei[13]	RG	40	22–33	12–20	–	–	PHL 80 mg + 0.9% SCI 250 ml, 1 time/one day	③④⑤⑥
	CG	40	23–33	12–20	–	–	25%MS 16 ml + 5%GI 100ml, 25%MS 30 ml + 5%GI 500ml	
Wu et al[14]	RG	58	23–36	20–27	1–3	1–4	PHL 200 mg + 5%GI 500 ml, 1–2times/one day	③④
	CG	58	23–36	20–27	1–3	1–4	25%MS 16 ml + 5%GI 100ml, 25%MS 60 ml + 5%GI 500ml	
Deng et al[15]	RG	50	23–35	20–27	1–2	1–2	PHL 120 mg + 5%GI 250 ml, 1–2times/one day	①②③④
	CG	50	23–35	20–27	1–2	1–2	25%MS 30 ml + 5%GI 500 ml, 2times/one day	
Wei and Lv[16]	RG	62	22–32	20–27	–	–	PHL 40 mg + 5%GI 500 ml, 1–2times/one day	③④⑦
	CG	58	22–32	20–27	–	–	25%MS 20 ml + 5%GI 100 ml, 25%MS 40 ml + 5%GI 500ml	
Zhong[17]	RG	25	21–41	12–22	–	–	PHL 200 mg + 5%GI 500 ml, 1time/one day	③④
	CG	25	20–39	13–21	–	–	25%MS 15g + 5%GI 500 ml, 1time/one day	
Zhu[18]	RG	40	22–36	16–27	–	–	PHL80/120 mg + 5%GI 500ml	③④⑤⑥
	CG	40	22–36	16–27	–	–	25%MS 16 ml + 5%GI 100 ml, 25%MS 30 ml + 5%GI 500ml	
Huang et al[19]	RG	69	19–37	12–20	–	–	PHL 80/120 mg + 5%GI 500ml	③④
	CG	60	18–35	12–20	–	–	25%MS 10 ml + 5%GI 100 ml, 25%MS 60 ml + 5%GI 1000ml	
Luo[20]	RG	65	21–39	29.1 ± 5.8	–	–	PHL 80/120 mg + 5%GI 500ml	①③④
	CG	60	23–41	28.7 ± 6.0	–	–	25%MS 20 ml + 5%GI 100 ml, 25%MS 30 ml + 5%GI 500ml	
Guan et al[21]	RG	40	36.8 ± 3.7	30.3 ± 4.2	–	2.3 ± 1.1	PHL 100 mg + 5%GI 500ml	③④
	CG	40	27.1 ± 3.8	30.8 ± 3.2	–	2.2 ± 1.1	25%MS 20 ml + 5%GI 100 ml, 25%MS 30 ml + 5%GI 500ml	
He[22]	RG	30	25–37	16–25	–	–	PHL 80/120 mg + 5%GI 500ml	③④⑦
	CG	30	24–39	14–26	–	–	25%MS 10 ml + 5%GI 100ml, 25%MS 60 ml + 5%GI 1000ml	
Jiang[23]	RG	48	27.1 ± 3.5	12–23	–	–	PHL 200 mg + 5%GI 250ml	①③④⑦
	CG	48	26.8 ± 3.3	12–24	–	–	25%MS 15 ml + 5%GI 100 ml, 25%MS 50 ml + 5%GI 1000ml	
Yang[24]	RG	50	22–36	<12	1–3	1–4	PHL 80 mg + 0.9%SCI 250ml	③④⑤⑥
	CG	50	22–36	<12	1–3	1–4	25%MS 30 ml + 5%GI 100 ml, 25%MS 30 ml + 5%GI 50ml	
Feng[25]	RG	30	27.2 ± 4.2	<20	2.8 ± 0.3	–	PHL 80 mg + 0.9%SCI 250ml	③④⑤⑥
	CG	30	27.5 ± 4.1	<20	2.5 ± 0.1	–	25%MS 16 ml + 5%GI 100 ml, 25%MS 30 ml + 5%GI 500ml	
Ge[26]	RG	30	22–37	22–28	–	–	PHL 40 mg + 5%GI 500ml	③④⑦
	CG	30	21–36	21–28	–	–	25%MS 20 ml + 5%GI 100 ml, 25%MS 40 ml + 5%GI 50ml	
Hu and Peng[27]	RG	40	22–32	11–19	–	–	PHL 80 mg + 0.9%SCI 250ml	③④⑥
	CG	40	21–33	11–19	–	–	25%MS1 6 ml + 5%GI 100ml	
Jin et al[28]	RG	55	20–33	22.8 ± 5.1	–	–	PHL 200 mg + 0.9%SCI 500ml	③④⑤
	CG	55	22–35	22.2 ± 5.1	–	–	25%MS 20 ml + 0.9%SCI 150 ml, 25%MS 40 ml + 0.9%SCI 500ml	
Lan et al[29]	RG	60	30.2 ± 3.3	16.4 ± 2.8	–	1.6 ± 0.3	PHL 80 mg + 0.9%SCI 250 ml, 1time/one day	③④⑥
	CG	60	30.5 ± 3.1	16.9 ± 2.9	–	1.9 ± 0.5	25%MS 30 ml + 5%GI 100ml	
Li[30]	RG	60	26.7 ± 7.2	15.2 ± 3.5	–	–	PHL 80 mg + 5%GI 250ml	③④⑤⑥
	CG	60	27.4 ± 6.9	16.3 ± 2.8	–	–	25%MS 16 ml + 5%GI 100 ml, 25%MS 16 ml + 5%GI 500ml	
Li[31]	RG	47	25.4 ± 3.3	14–20	–	–	PHL 80 mg + 0.9%SCI 250ml	③④⑤⑥
	CG	47	25.3 ± 2.9	14–20	–	–	25%MS 16 ml + 5%GI100 ml, 25%MS 30 ml + 5%GI 500ml	

① The duration of the drug treatment; ② The length of hospital stay; ③ The total effective rate; ④ The rate of adverse reactions; ⑤ The drug onset time; ⑥ The time to relief of uterine contractions; ⑦ The complete relief of uterine contraction symptoms.

CG = control group, GI = glucose injection, MS = magnesium sulfate, PHL = phloroglucinol, RG = research group, SCI = sodium chloride injection.

difference [n = 12, RR = 0.16, 95% CI (0.05, 0.44), $Z = 5.07$, $P = .000$]. See Figure 9.

(5) Nausea and vomiting: Nine of the included studies reported nausea and vomiting.[17,19–23,26,28,29] These studies involved in a total of 830 patients [the experimental group (422 cases) and the control group (408 cases)]. The heterogeneity result suggested no heterogeneity ($P = .435$, $I^2 = 0.0\%$). By using a fixed-effects model, the meta-analysis showed that the occurrence rate of nausea and vomiting of PHL was lower than that of MS, showing a statistically significant difference [n = 9, RR = 0.26, 95% CI (0.15, 0.47), $Z = 4.56$, $P = .000$]. See Figure 10.

(6) Dry mouth symptoms: Nine of the included studies reported dry mouth symptoms.[12–14,18,24,25,27,30,31] These studies involved a total of 830 patients (415 cases in the experimental group and 415 cases in the control group). The heterogeneity results suggested no heterogeneity ($P = .265$, $I^2 = 0.0\%$). Using a fixed-effects model, the meta-analysis showed that the occurrence rate of dry mouth symptom of PHL was lower than that of MS, with a statistically significant difference [n = 9, RR = 0.16, 95% CI (0.05, 0.44), $Z = 3.49$, $P = .000$]. See Figure 11.

(7) Perspiration: Eight of the included studies reported PHL.[12–14,18,24,25,30,31] These studies involved a total of 750 patients (375 cases in the experimental group and 375 cases in the control group). The heterogeneity results suggested no heterogeneity ($P = .966$, $I^2 = 0.0\%$). Using a fixed-effects model, the meta-analysis showed that the occurrence rate of perspiration of PHL

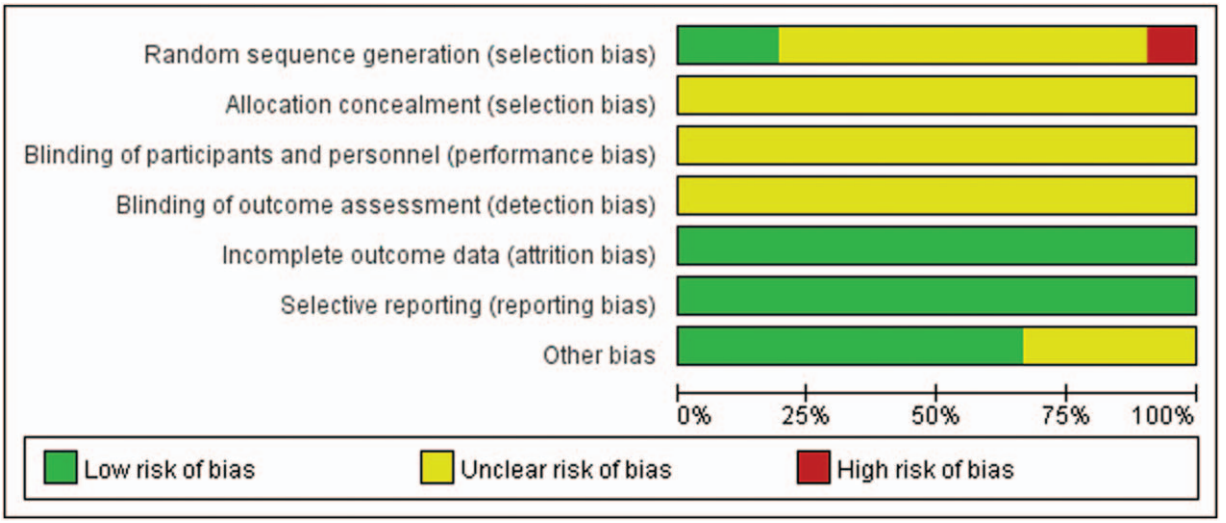

Figure 2. Risk of bias.

was lower than that of MS, with a statistically significant difference [n = 8, RR = 0.11, 95% CI (0.04, 0.28), $Z = 4.58$, $P = .000$]. See Figure 12.

(8) Insomnia: Among the studies included, 4 reported insomnia.[16,17,23,26] These studies involved in a total of 326 patients (165 cases in the experimental group and 161 cases in the control group). The heterogeneity results suggested no heterogeneity ($P = .560$, $I^2 = 0.0\%$). Using a fixed-effects model, the meta-analysis showed that the occurrence rate of insomnia of PHL was comparable to that of MS, showing no statistically significant difference [n = 4, RR = 0.42, 95% CI (0.11, 1.58), $Z = 1.29$, $P = .198$]. See Figure 13.

(9) Lack of strength: Four of the included studies reported a lack of strength in patients.[16,19,22,26] These studies involved a total of 369 patients (191 cases in the experimental group and 178 cases in the control group). The heterogeneity results suggested no heterogeneity ($P = .534$, $I^2 = 0.0\%$). Using a fixed-effects model, the meta-analysis showed that the occurrence rate of lacking in strength of PHL was shorter than that for MS, with a statistically significant difference [n = 4, RR = 0.34, 95% CI (0.13, 0.86), $Z = 2.28$, $P = .022$]. See Figure 14.

(10) Chest tightness: Two of the included studies reported chest tightness.[16,29] These studies involved a total of 240 patients (122 cases in the experimental group and 118 cases in the control group). The heterogeneity result suggested no heterogeneity ($P = .851$, $I^2 = 0.0\%$). Using a fixed-effects model, the meta-analysis showed that the occurrence rate of chest tightness of PHL was lower than that of MS, with a statistically significant difference [n = 2, RR = 0.16, 95% CI (0.02, 1.31), $Z = 1.71$, $P = .088$]. See Figure 15.

3.7. Time required to relieve uterine contractions

Nine of the included studies reported time required to relieve uterine contractions.[12,13,18,24,25,27,29–31] These studies covered 834 patients (417 cases in the experimental group and 417 cases in the control group). The results were moderately heterogeneous ($P = .158$, $I^2 = 32.5\%$). Using a random-effects model, the meta-analysis suggested that the time required to relieve uterine contractions for PHL was shorter than that for MS, with a statistically significant difference [n = 9, SMD = −0.22, 95% CI (−0.39, 0.05), $Z = 2.56$, $P = .010$]. See the results in Figure 16. A sensitivity analysis of the analysis results of the included documents found that the combined effective did not obviously change from the original effective dose, indicating the stability of the meta-analysis result (see Fig. 17).

3.8. Drug onset time

Seven of the included studies reported drug onset time.[12,13,18,24,25,30,31] These studies covered 634 patients (317 cases in the experimental group and 317 cases in the control group). The heterogeneity results suggested no heterogeneity ($P = .483$, $I^2 = 0.0\%$). Using a fixed-effects model, the meta-analysis suggested that the drug onset time of PHL was later than that of MS, with a statistically significant difference [n = 7, SMD = −0.25, 95% CI (0.09, 0.41), $Z = 3.13$, $P = .002$]. See the results in Figure 18.

3.9. The complete relief of uterine contraction symptoms

Four of the included studies reported the index.[16,22,23,26] These studies covered 336 patients (170 cases in the experimental group and 166 cases in the control group). The results were highly heterogeneous ($P = .000$, $I^2 = 91.9\%$). Using a random-effects model, the meta-analysis suggested that the time required for the complete relief of uterine contraction symptoms was shorter for PHL than for MS, showing a statistically significant difference [n = 4, SMD = −2.08, 95% CI (−3.05, 1.12), $Z = 4.24$, $P = .000$]. See the results in Figure 19. A sensitivity analysis of the results of the included documents found that the combined effective did not obviously change from the original effective dose, indicating the stability of the meta-analysis (see Fig. 20)

3.10. Drug continuous treatment time

Three of the included studies reported the index.[15,20,23] These studies covered 321 patients (163 cases in the experimental group and 158 cases in the control group). The results were highly heterogeneous ($P = .000$, $I^2 = 96.7\%$). Using a random-effects

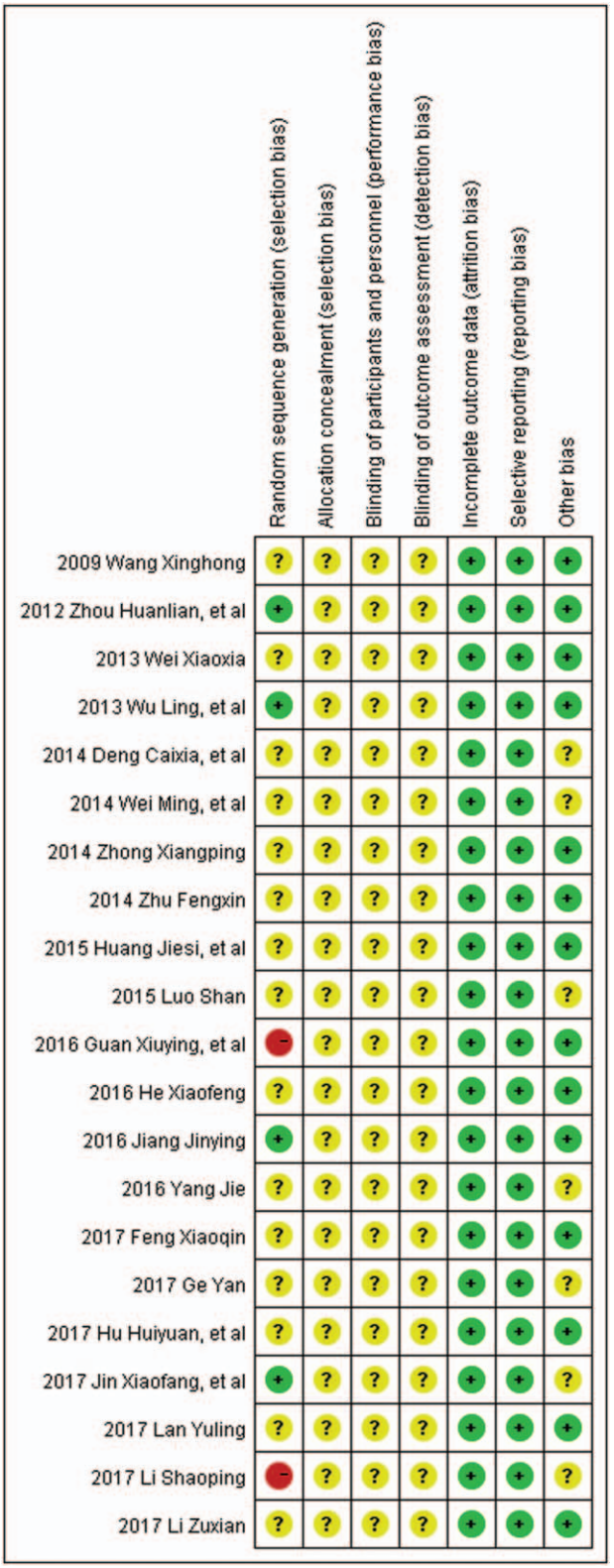

Figure 3. Risk of bias summary.

model, the meta-analysis suggested that the drug continuous treatment time of PHL was shorter than that of MS, with a statistically significant difference [n = 3, SMD = −1.51, 95% CI (−2.93, 0.09), $Z = 2.08$, $P = .038$]. See the results in Figure 21.

3.11. Length of hospital stay

Two of the included studies reported the index.[11,15] These studies covered 160 patients (80 cases in the experimental group and 80 cases in the control group). The results were highly heterogeneous ($P = .097$, $I^2 = 63.7\%$). Using a random-effects model, the meta-analysis suggested that the length of hospital stay of PHL was comparable to that of MS, with no statistically significant difference [n = 2, SMD = −0.27, 95% CI (−0.80, 0.26), $Z = 0.99$, $P = .323$]. See the results in Figure 22.

3.12. Publication bias

Egger test was performed to test the publication bias of two outcome measures (TER and time required to relieve uterine contractions) in more than 7 included studies, and $I^2 \geq 30$ using Stata 12.0 statistical software. The TER suggested certain publication bias ($P = .013 < .05$, 95% CI, 0.6333977, 4.670988). The results on the time required to relieve uterine contractions revealed no obvious publication bias ($P = .555 > .05$, 95% CI, −7.458848, 12.75799) (see Figs. 23 and 24).

4. Discussion

The occurrence rate of threatened abortion is high, and it is primarily early abortion. In particular, threatened abortion is more likely to happen in patients with a medical history of recurrent abortion. Some studies have shown that early vaginal hemorrhage is closely associated with perinatal hemorrhage and low-weight infant. Drug treatment can significantly lower the occurrence rate of antenatal hemorrhage, intrauterine fetal distress or low-weight infant.[32] Therefore, studying the clinical efficacy of drug treatments is of great significance.

The most striking characteristic of PHL is that such medicine can relieve smooth muscle spasm without causing a series of adverse reactions, avoid damage to cardiovascular functions, take effect rapidly and lead to high patient compliance.[33] Animal experimental studies have shown that PHL , which has no teratogenic action, carcinogenicity or mutagenicity, only acts on spasmodic smooth muscle and has the minimal effect on normal smooth muscle. Furthermore, its plasma concentration has a short half-life. PHL will be nearly entirely eliminated through metabolism 48 hours after intravenous or intramuscular injection.[34] Similar clinical applied studies have reported that the use of PHL plays an active role and achieves a definite curative effect in the abovementioned fields of gynecology and obstetrics without causing obvious adverse actions in mothers and infants. Thus, PHL is a safe, effective and dependable drug. The effective concentration of MS is close to the toxic concentration. As a result, MS often leads to palpitation, dizziness, nausea, rash and other adverse reactions during treatment, and frequent monitoring of magnesium concentration results in poor patient compliance and even refusal of treatment. In addition, the Food and Drug Administration believes that using magnesium for more than 7 days is likely to cause newborn hypocalcemia and bone changes. Therefore, the drug safety of MS injection during pregnancy has been downgraded from grade A to grade D (which refers to a drug that shows strong evidence of fetal damage, but the benefits to pregnant women outweigh the damage). In the present study, a total of 21 documents are included, and some discussions are provided below.

(1) Results: Although MS requires a shorter drug onset time than PHL in treating threatened abortion, the TEF, time required

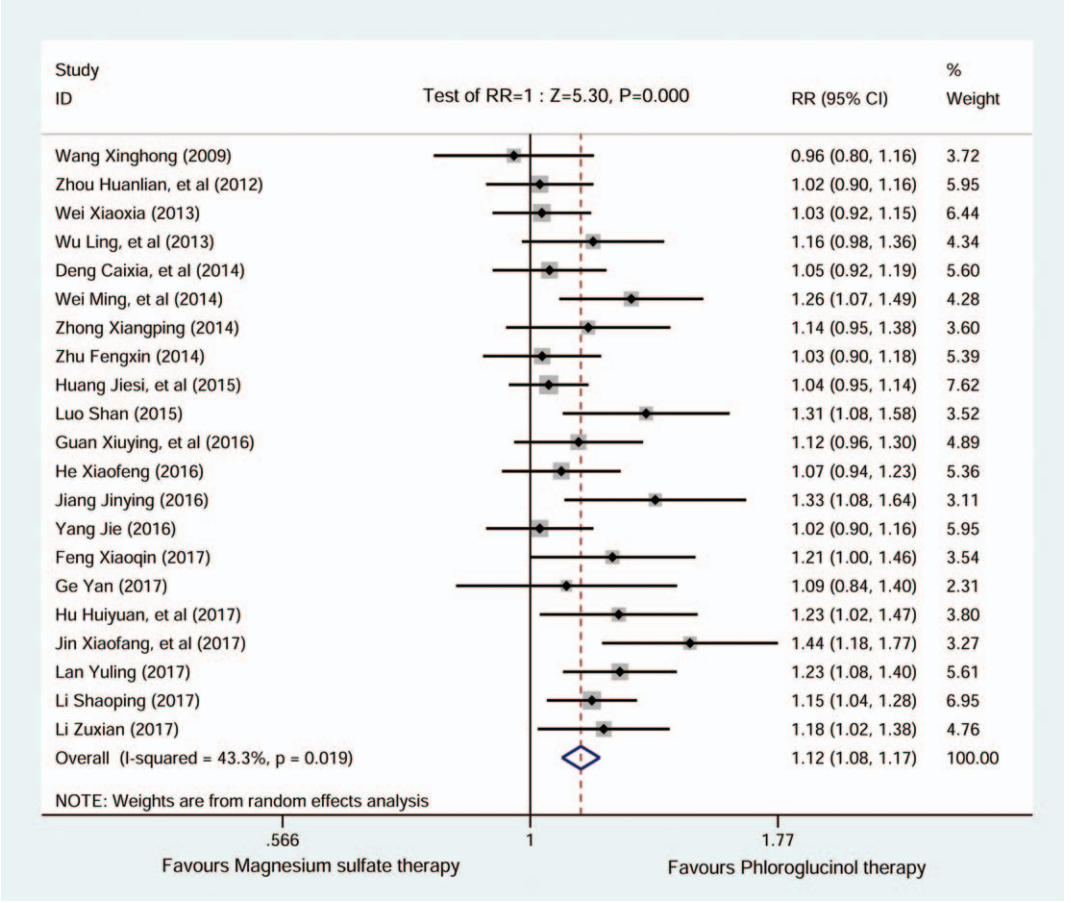

Figure 4. A forest map of the meta-analysis of the TER of phloroglucinol vs magnesium sulfate in the treatment of threatened abortion.

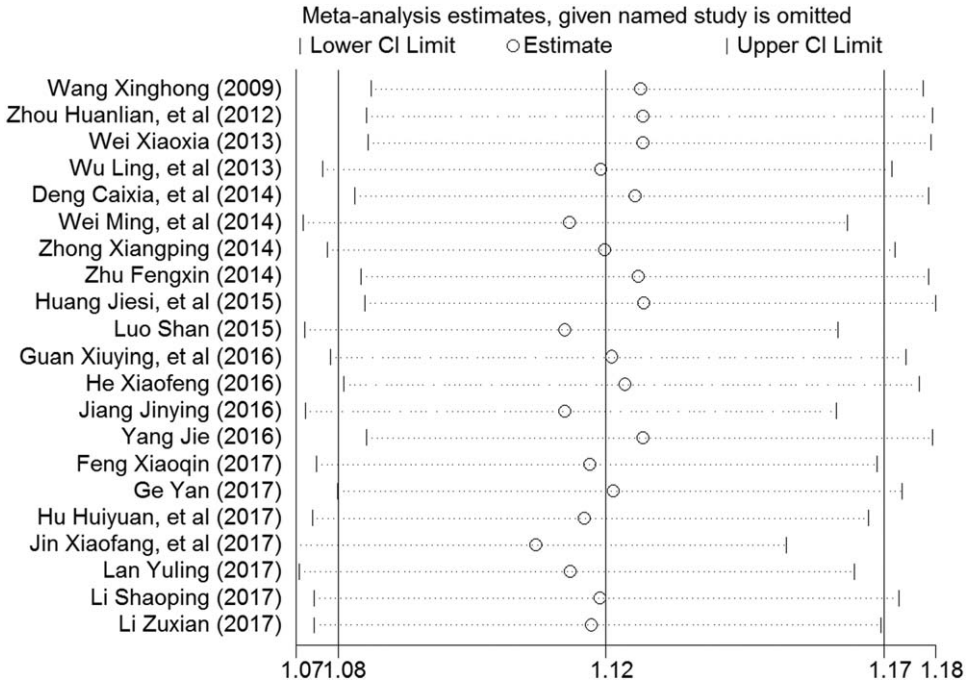

Figure 5. A sensitivity map of the TER of phloroglucinol versus magnesium sulfate in the treatment of threatened abortion.

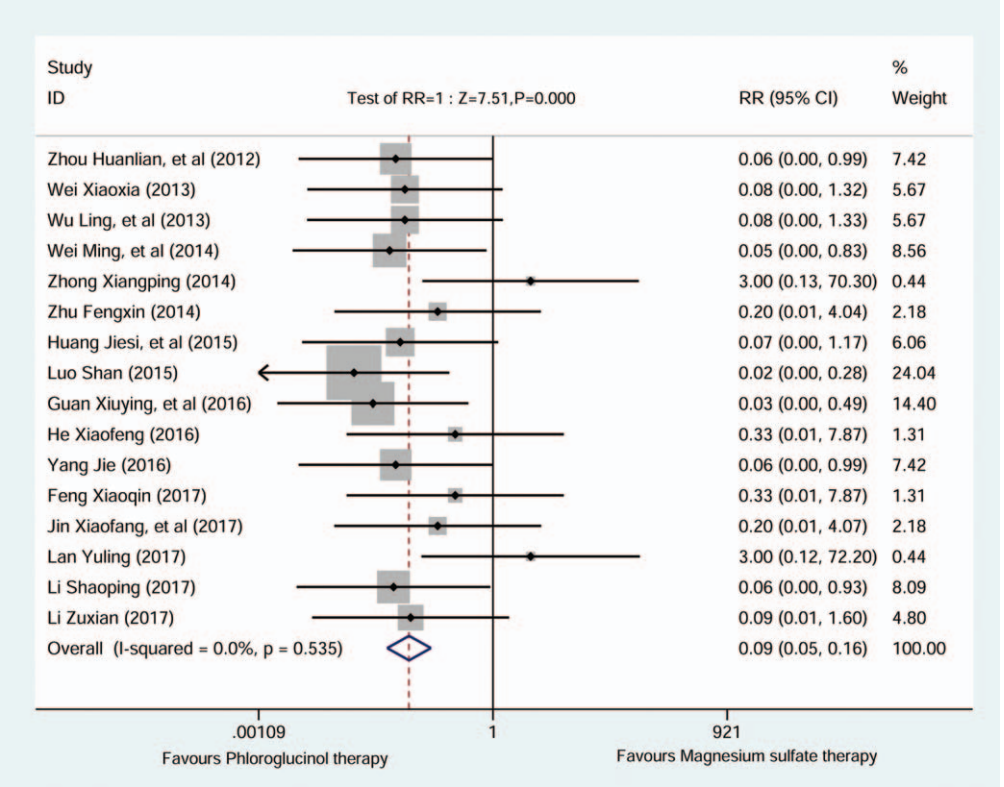

Figure 6. The results of the meta-analysis of the incidence rate of flush and redness associated with phloroglucinol vs magnesium sulfate in the treatment of threatened abortion.

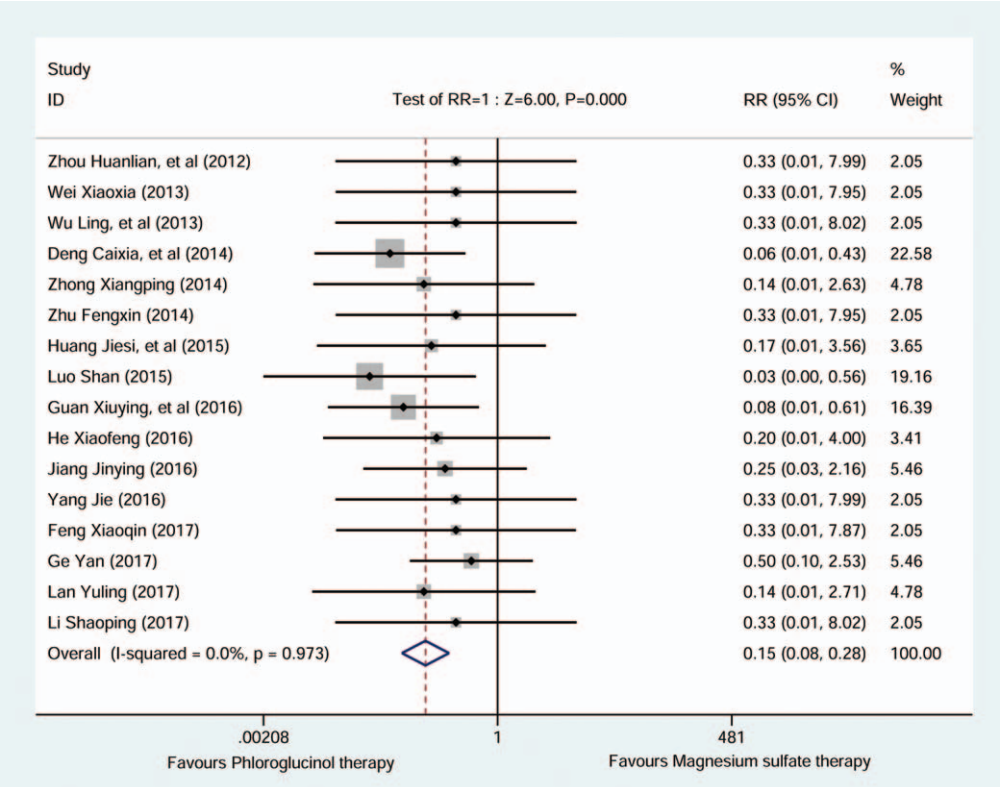

Figure 7. The results of the meta-analysis of the incidence rate of dizziness and headache associated with phloroglucinol vs magnesium sulfate in the treatment of threatened abortion.

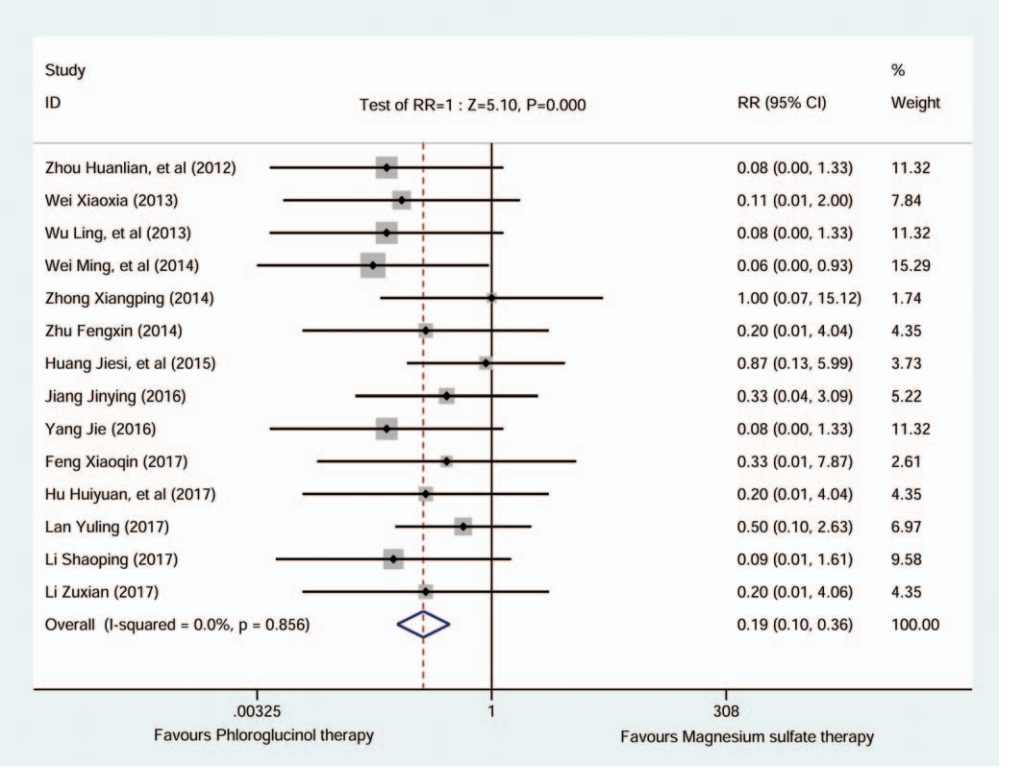

Figure 8. The results of the meta-analysis of the incidence rate of gastrointestinal discomfort associated with phloroglucinol vs magnesium sulfate in the treatment of threatened abortion.

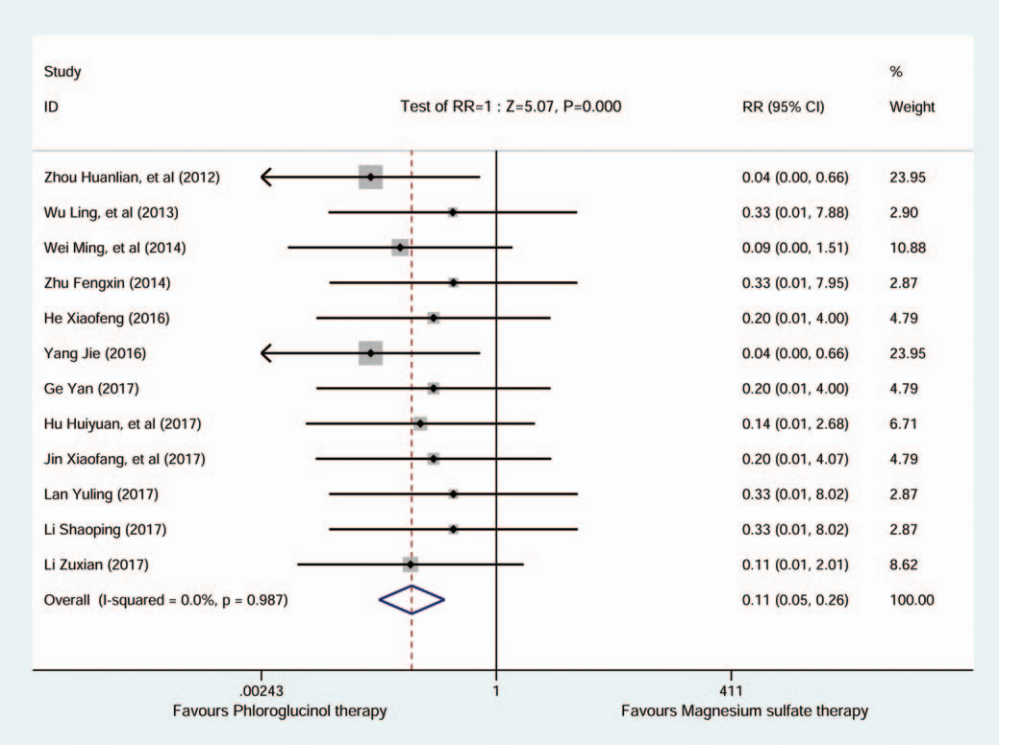

Figure 9. The results of the meta-analysis of the incidence rate of palpitation associated with phloroglucinol vs magnesium sulfate in the treatment of threatened abortion.

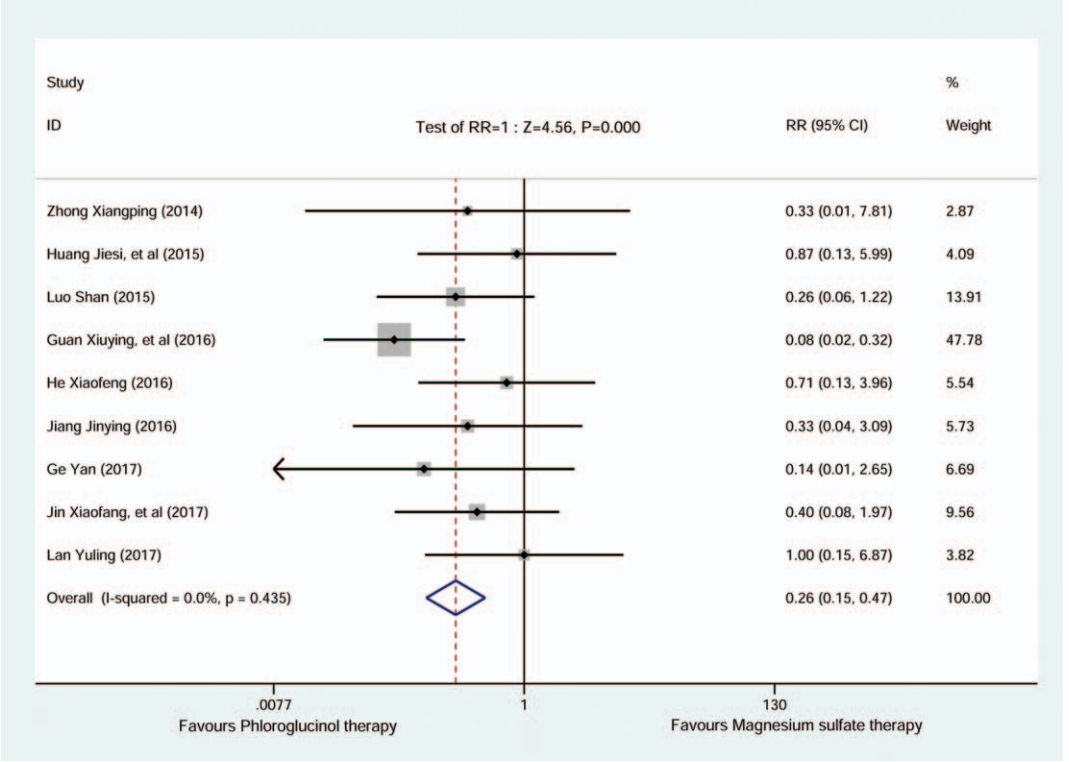

Figure 10. The result of the meta-analysis about the incidence rate of nausea and vomiting associated with phloroglucinol vs magnesium sulfate in the treatment of threatened abortion.

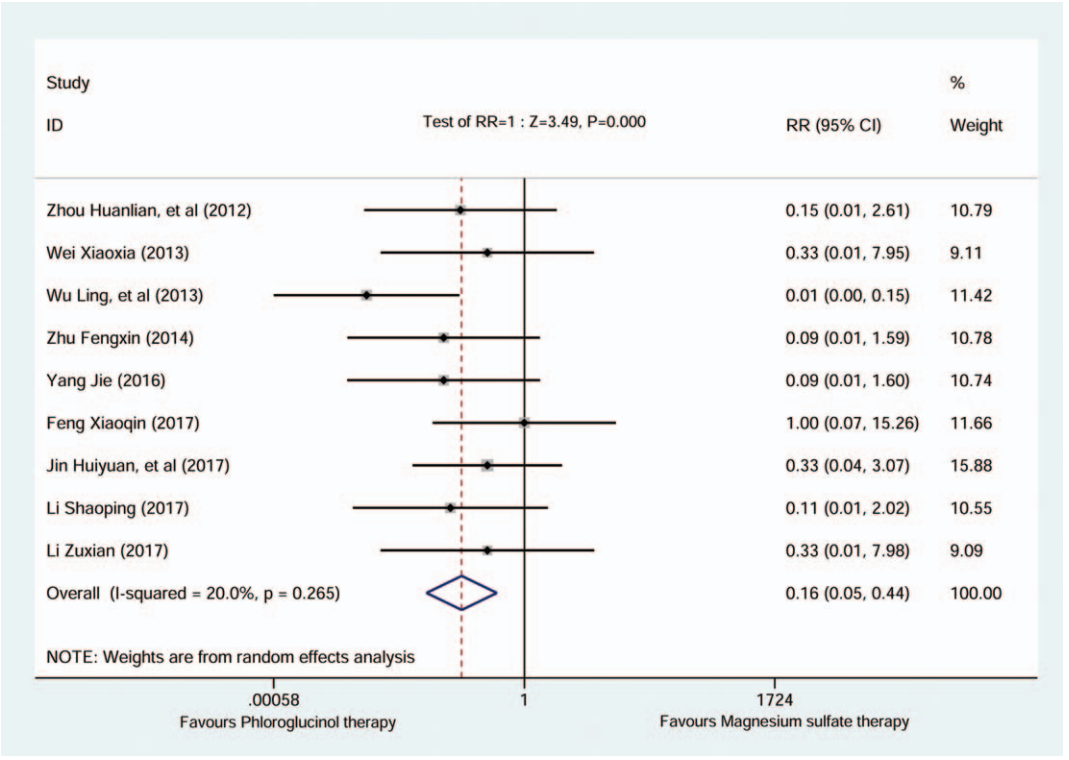

Figure 11. The results of the meta-analysis of the incidence rate of dry mouth associated with phloroglucinol vs magnesium sulfate in the treatment of threatened abortion.

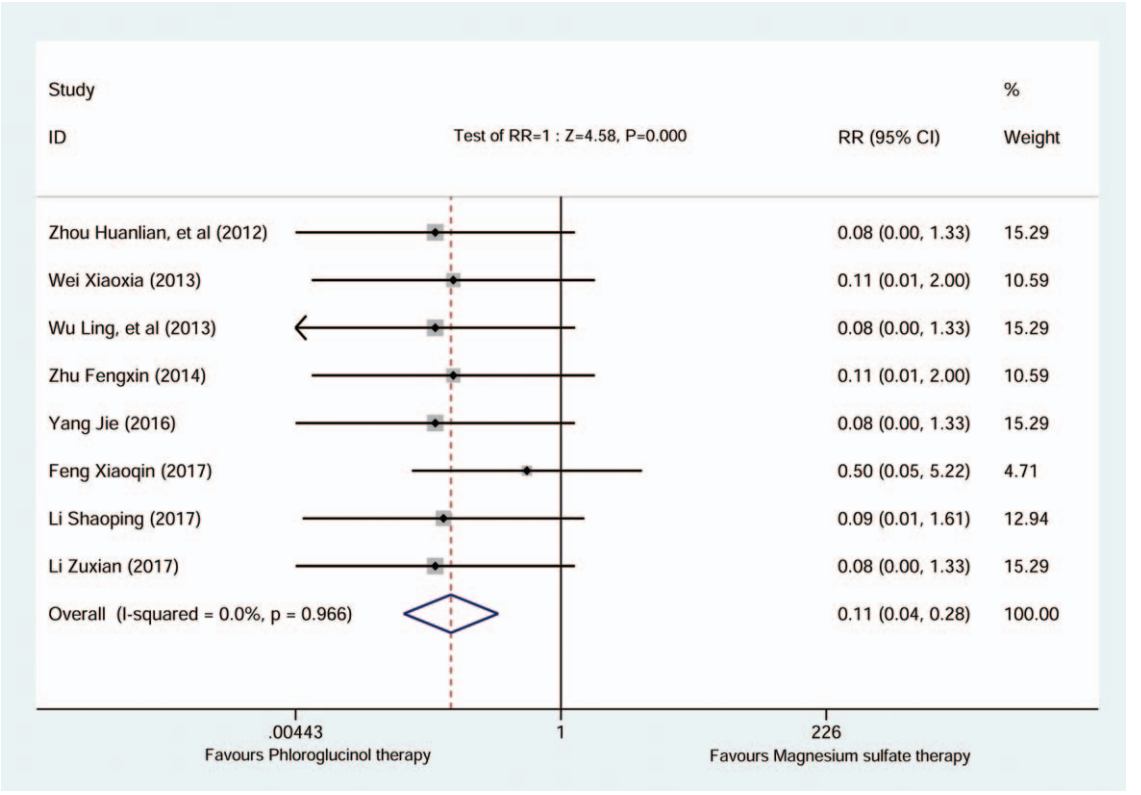

Figure 12. The results of the meta-analysis of the incidence rate of perspiration associated with phloroglucinol vs magnesium sulfate in the treatment of threatened abortion.

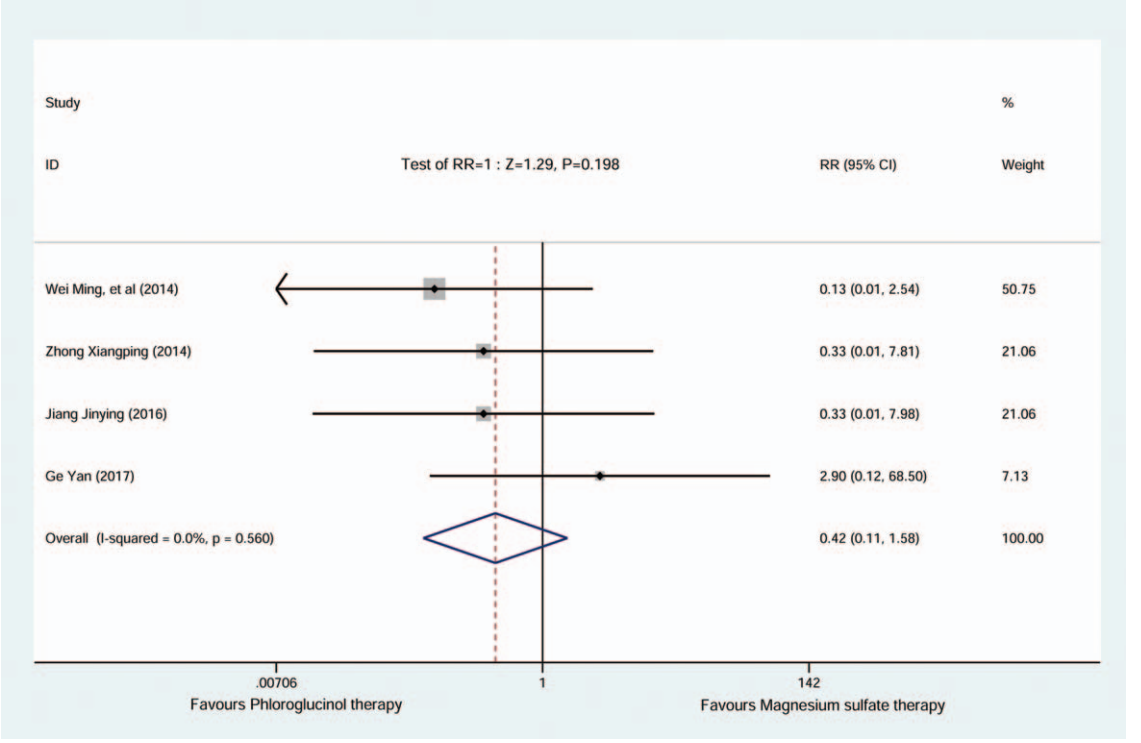

Figure 13. The results of the meta-analysis of the incidence rate of insomnia associated with phloroglucinol vs magnesium sulfate in the treatment of threatened abortion.

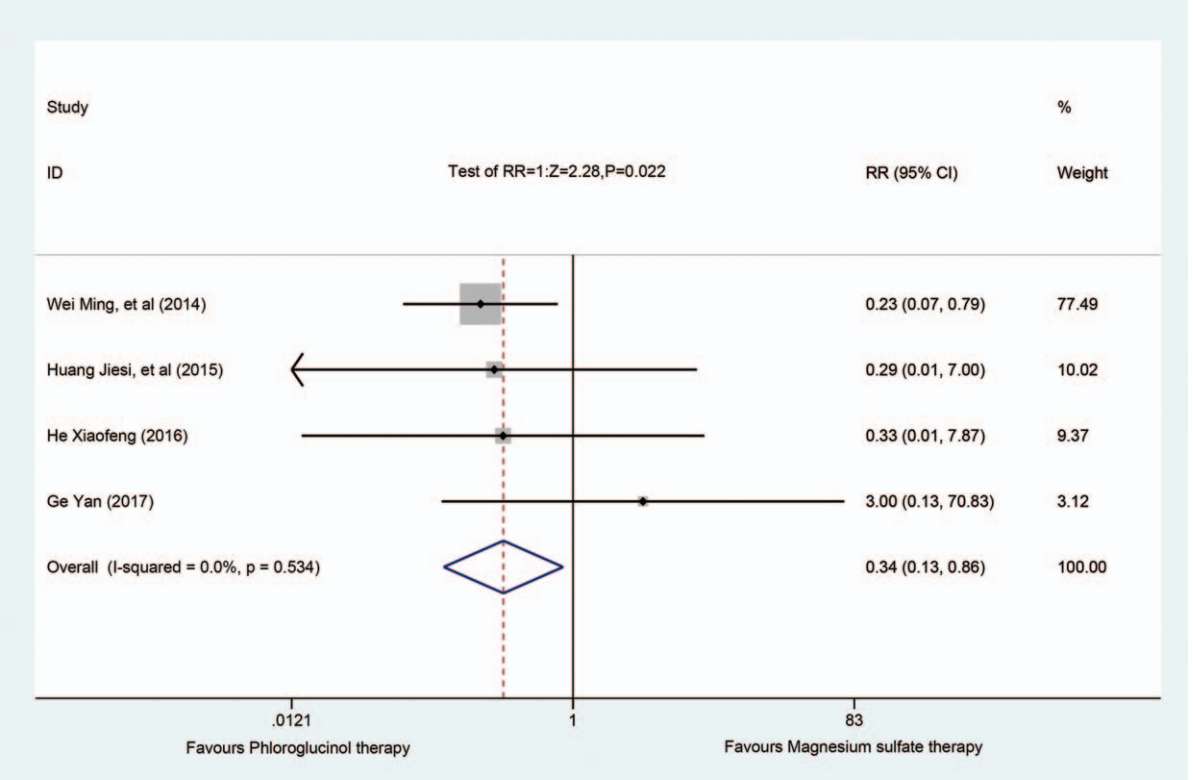

Figure 14. The results of the meta-analysis of the incidence rate of a lack of strength association with phloroglucinol vs magnesium sulfate in the treatment of threatened abortion.

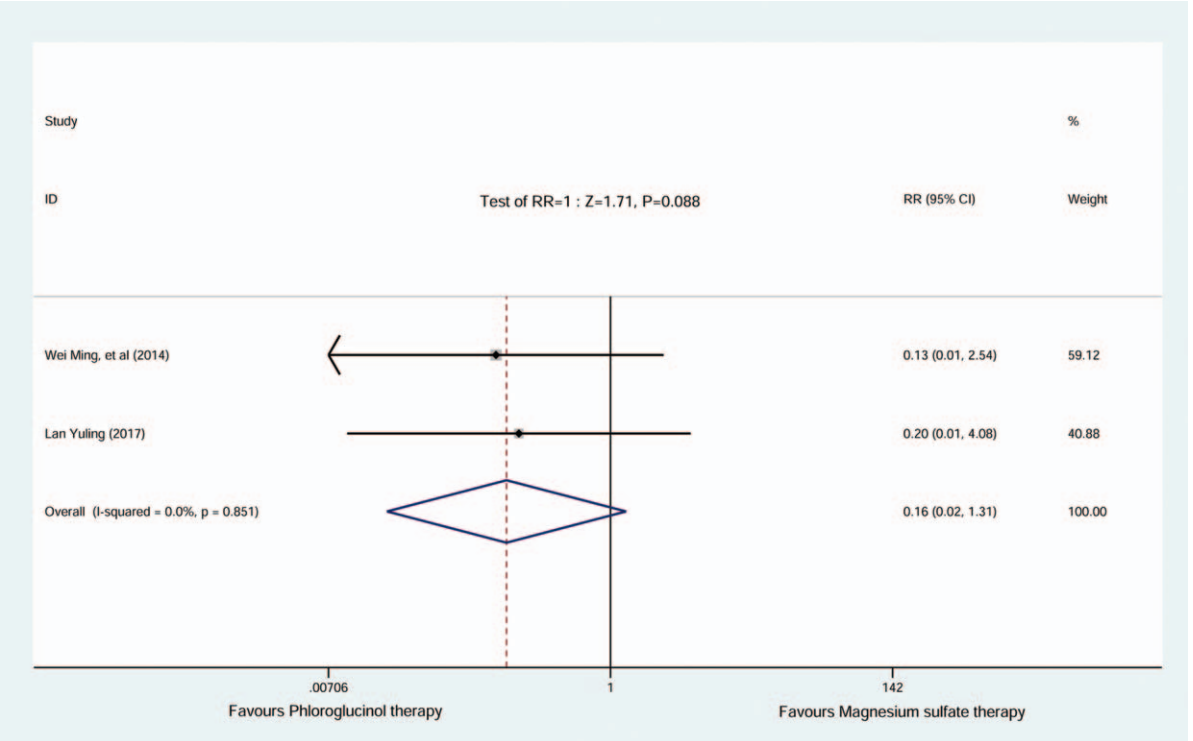

Figure 15. The results of the meta-analysis of the incidence of chest tightness associated with phloroglucinol vs magnesium sulfate in the treatment of threatened abortion.

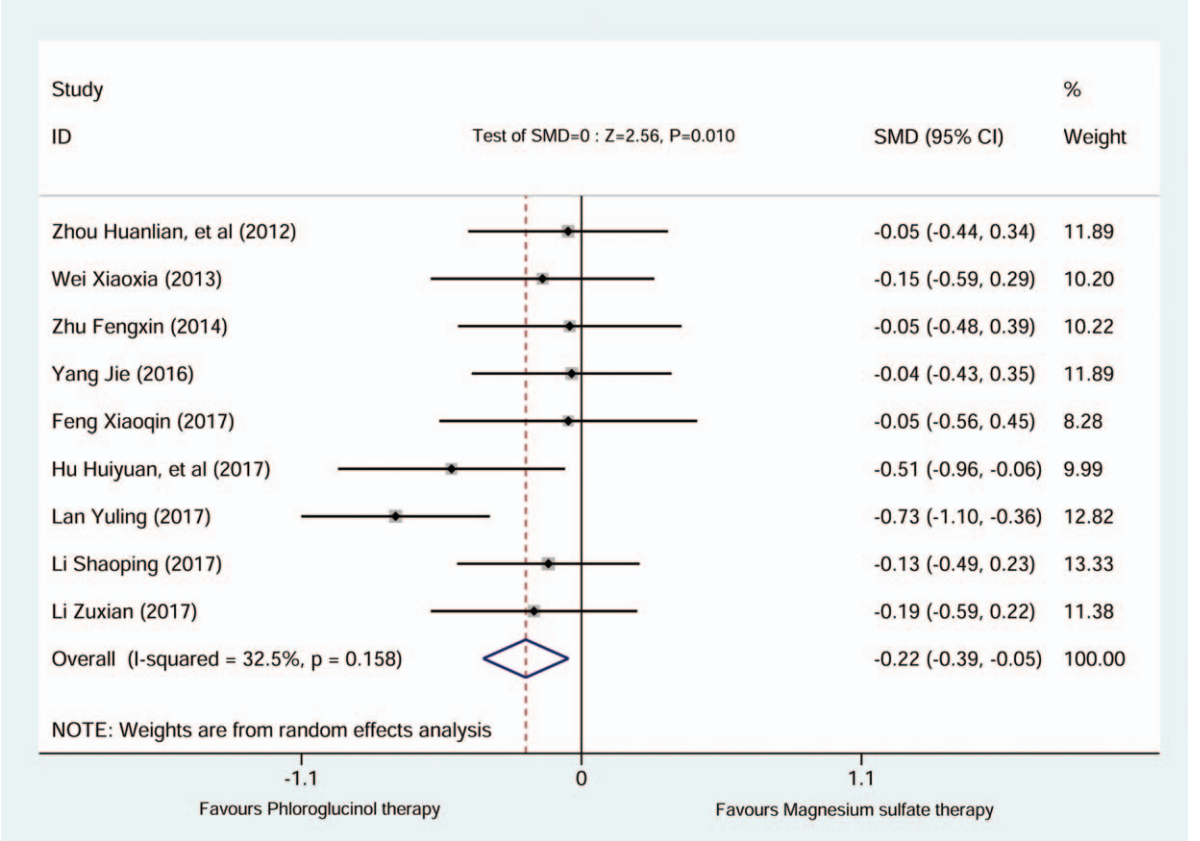

Figure 16. The results of the meta-analysis of the time required to relieve uterine contractions associated with phloroglucinol vs magnesium sulfate in the treatment of threatened abortion.

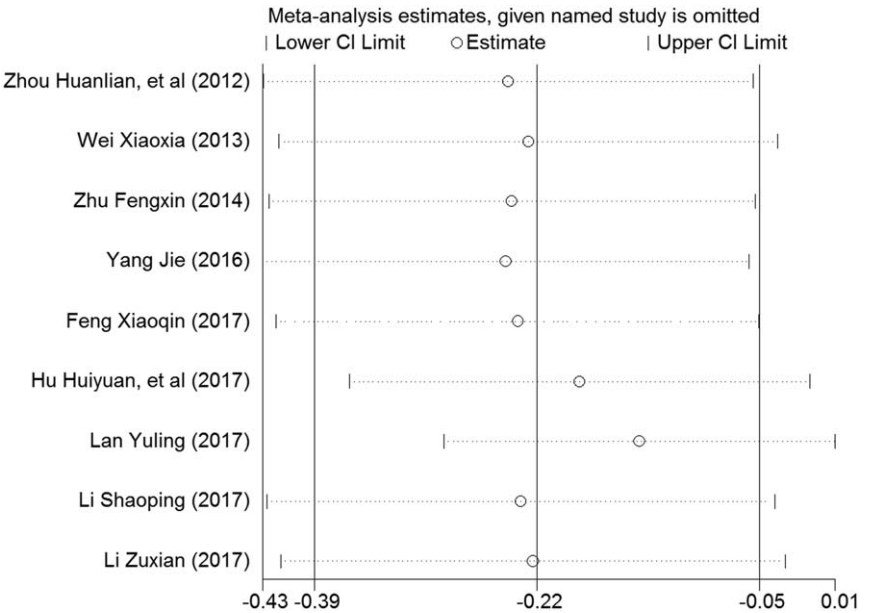

Figure 17. The sensitivity analysis results for the time required to relieve uterine contractions associated with phloroglucinol vs magnesium sulfate in the treatment of threatened abortion.

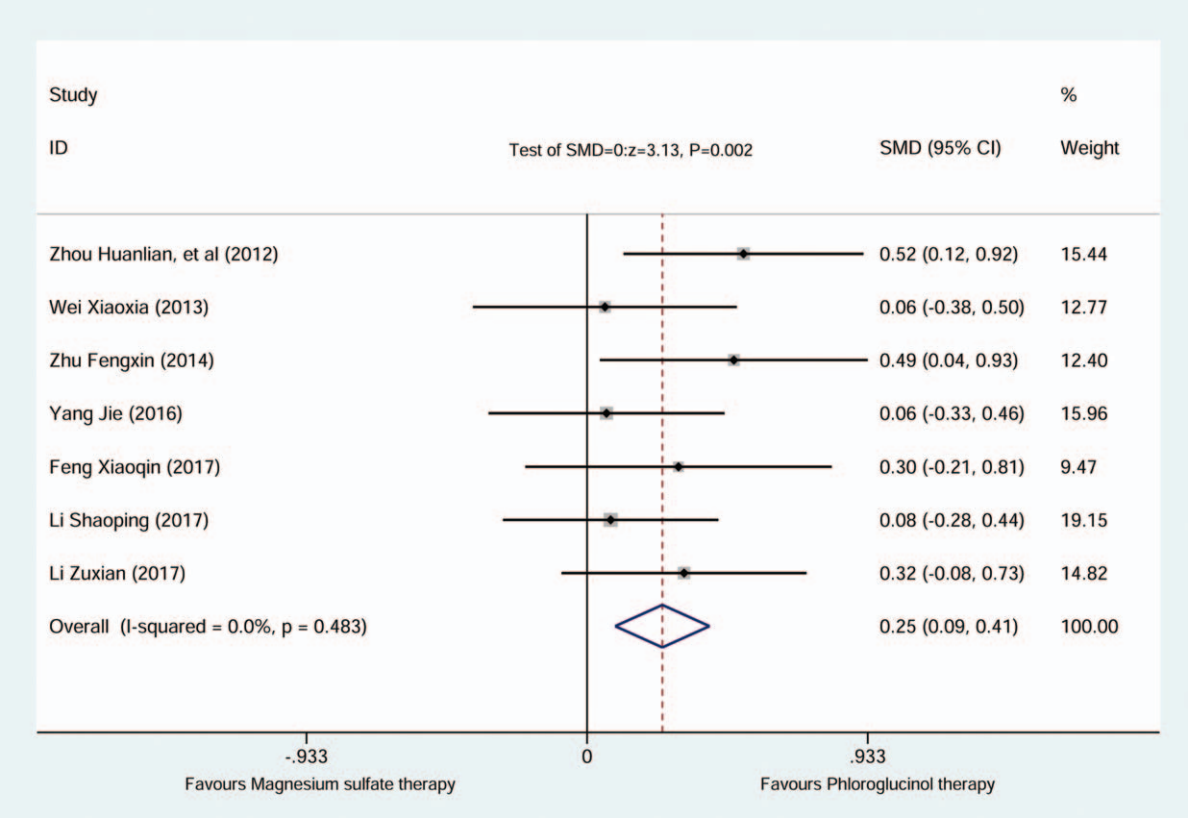

Figure 18. The meta-analysis results for the drug onset time of phloroglucinol vs magnesium sulfate in the treatment of threatened abortion.

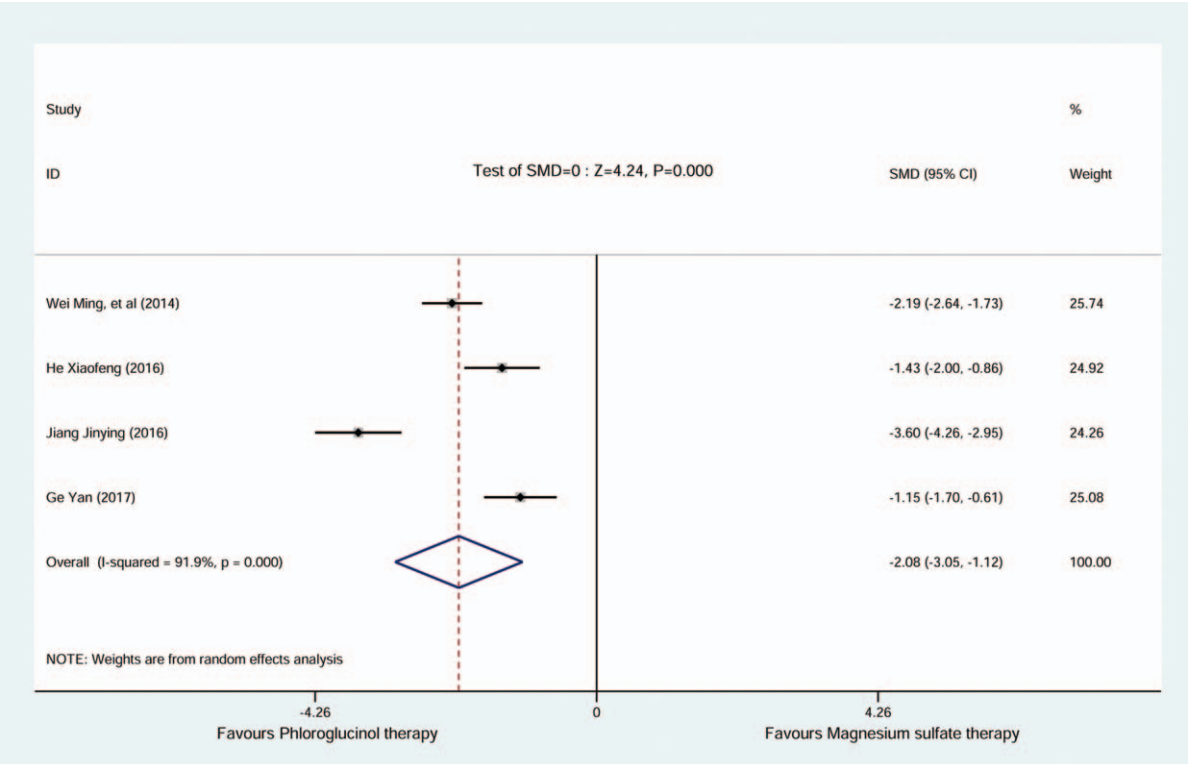

Figure 19. The results of the meta-analysis of the complete relief of uterine contraction symptoms after phloroglucinol vs magnesium sulfate in the treatment of threatened abortion.

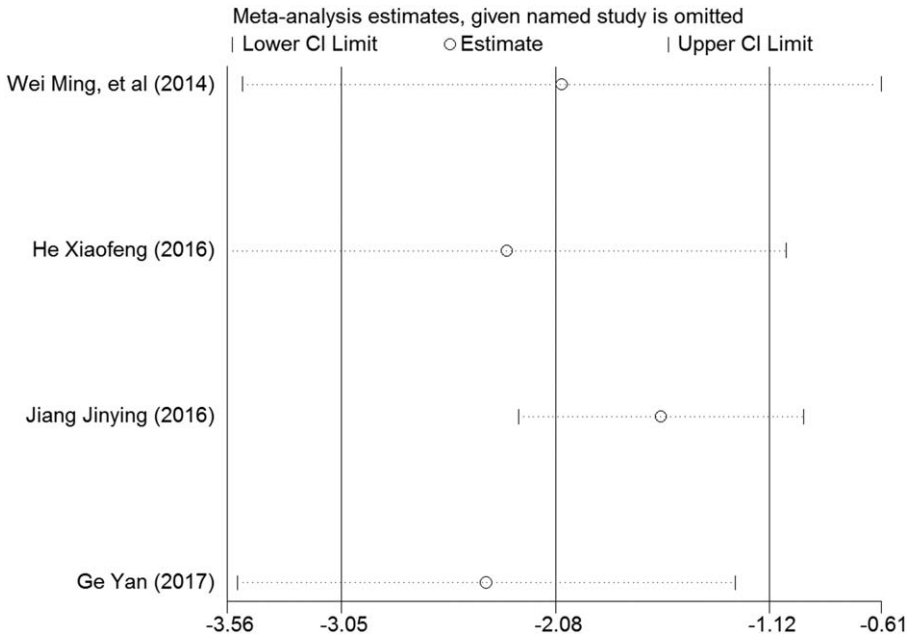

Figure 20. The sensitivity analysis of the results of the complete relief of uterine contraction symptoms after phloroglucinol vs magnesium sulfate in the treatment of threatened abortion.

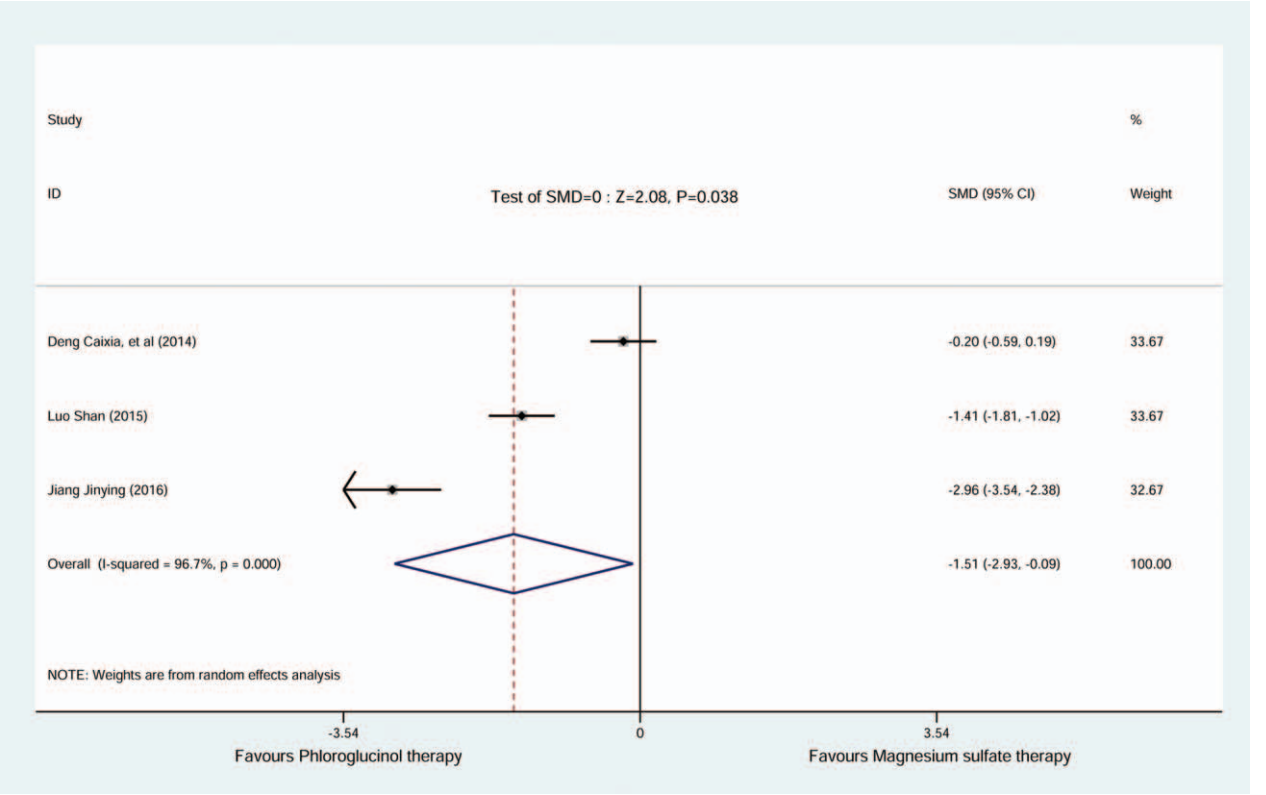

Figure 21. The results of the meta-analysis of the drug continuous treatment time of phloroglucinol vs magnesium sulfate in the treatment of threatened abortion.

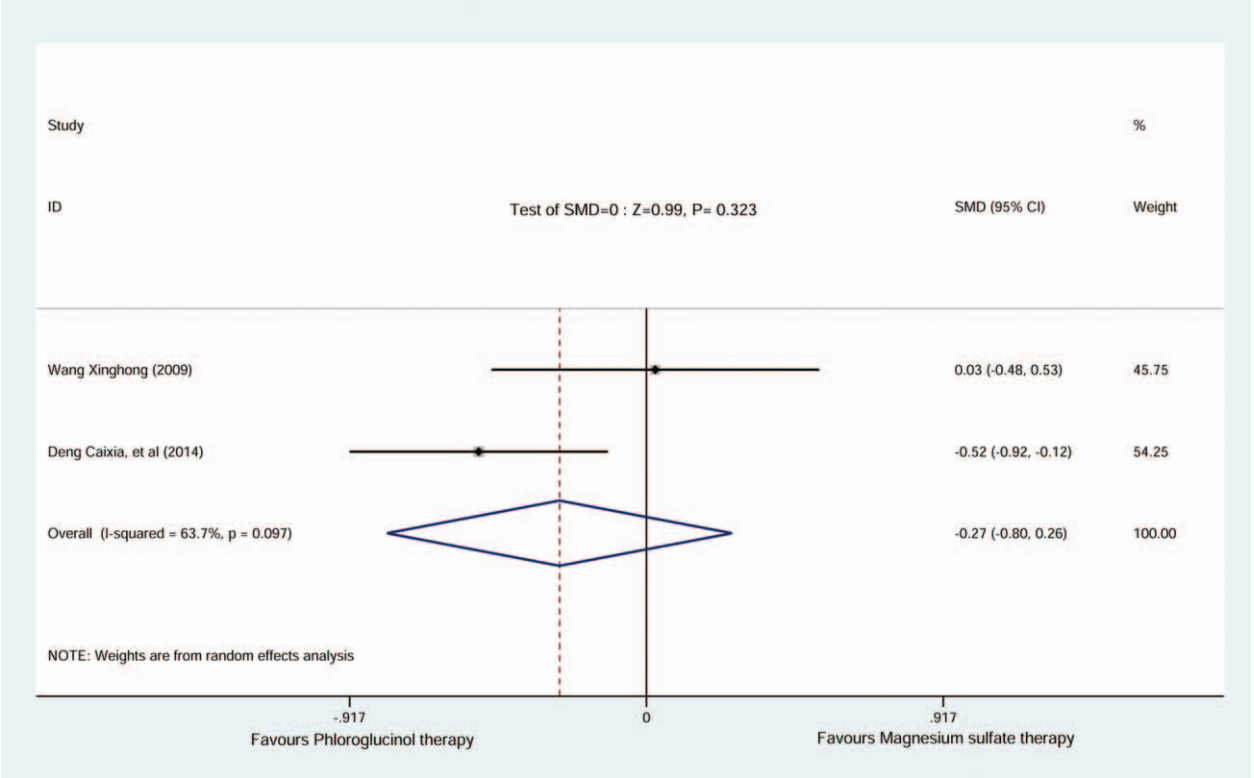

Figure 22. The results of the meta-analysis of the length of hospital stay after phloroglucinol vs magnesium sulfate in the treatment of threatened abortion.

to relieve uterine contractions, complete relief of uterine contraction symptoms, duration of drug treatment and length of hospital stay are better for PHL than for MS. More importantly, the adverse reaction rate is much lower for PHL than that for MS. Most independent trials have reported contrasting effects; however, some meta-analyses have suggested high heterogeneity. Although sources of heterogeneity have been explored through sensitivity analysis, it is difficult for many sensitivity analyses to identify exact sources of heterogeneity.

(2) Quality of evidence: Evidence-based medicine highlights the importance of evidence. The workgroup responsible for evaluating quality of evidence will have an important influence

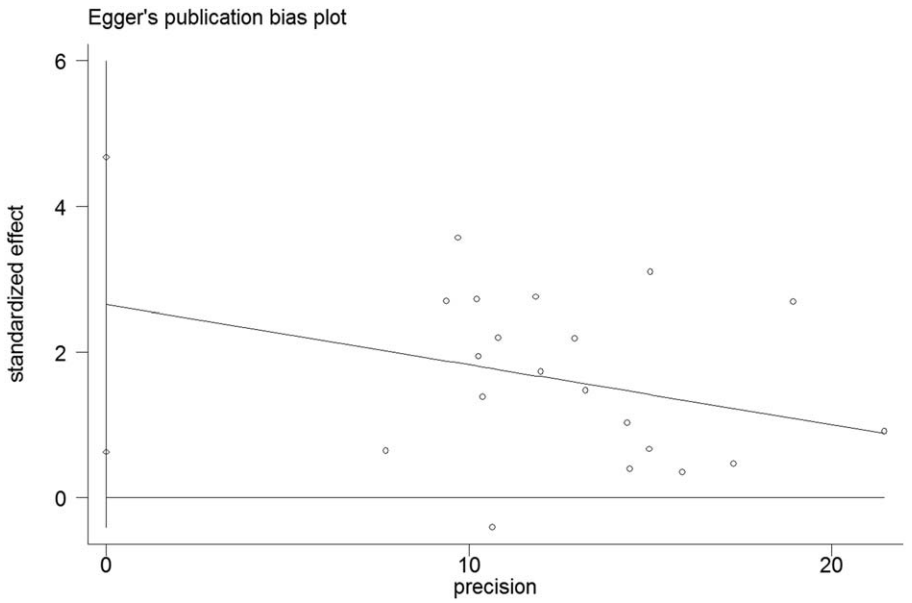

Figure 23. The TER of phloroglucinol vs magnesium sulfate, according to Egger test, in the treatment of threatened abortion.

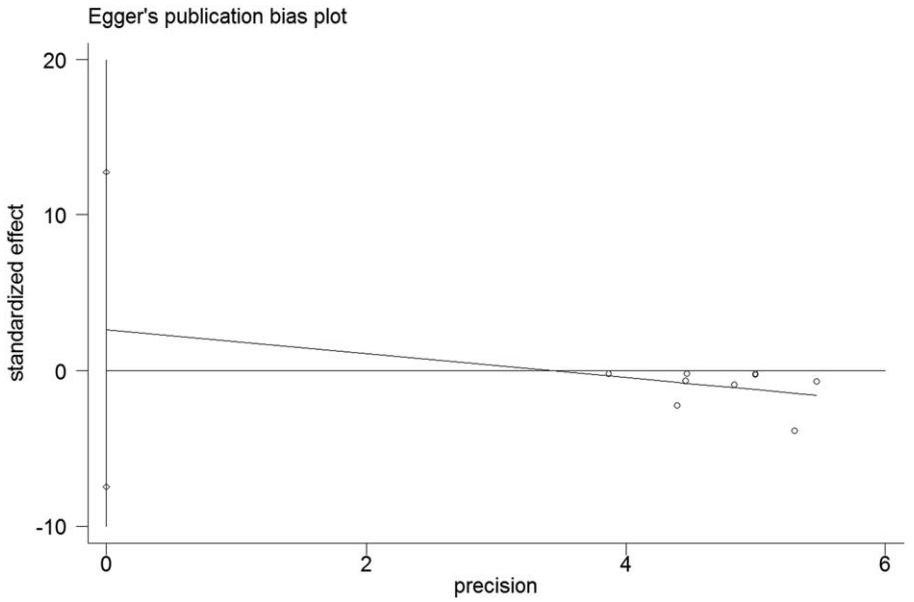

Figure 24. The time required to relieve uterine contractions associated with phloroglucinol versus magnesium sulfate, according to Egger test, in the treatment of threatened abortion.

on the validity of conclusion. In the present study, quality evaluation was performed using the RevMan 5.3 risk of bias table. There has been no completely reliable conclusion, however, due to the limited patient cases in the study and the poor methodological quality of the studies included.

(3) Potential bias in systematic review[35–37]: Although we have thoroughly searched multiple Chinese and English databases to ensure precision and recall, it is impossible for us to completely rule out the possibility that some important documents might have been overlooked. In addition, the studies in all documents were performed in China, and we note that the documents included from Chinese databases have reported no negative results, indicating the possibility that publication bias exists.

Limitations and advantages: Although PHL is expected to have a higher clinical application value than MS in the treatment of threatened abortion, its maternal-fetal safety in late threatened abortion necessitates a tremendous amount of research. To obtain more comprehensive data about the maternal-fetal influence of the drug, it is necessary to perform stratified RCT for threatened abortion of varying degrees at different gestational ages, improve the outcomes of mother and infant after the administration of tocolytic agent and provide long-term follow-up for newborn growth and development. Conclusions of meta-analyses are more convincing than the conclusions of individual clinical trials and serve as a reference for clinical decision-making. However, a meta-analysis still cannot substitute for large-scale, multicenter clinical RCT.

5. Conclusion

PHL can significantly control the symptoms of threatened abortion and shorten the treatment time without increasing the occurrence rate of adverse reactions compared to MS. However, the conclusion of the present study is limited by the small sample size. Thus, the results must be further verified by large-sample, multicenter, high quality clinical RCT.

Author contributions

Conceptualization: Jingzhi Guan.
Data curation: Shaofei Yuan, Jingzhi Guan.
Formal analysis: Fengli Gao, Zhong Xin.
Investigation: Haijun Guo, Suqin Shi.
Methodology: Shaofei Yuan, Fengli Gao, Lei Shi, Xia Yang, Jingzhi Guan.
Resources: Shaofei Yuan, Fengli Gao, Zhong Xin, Lei Shi.
Software: Shaofei Yuan, Fengli Gao, Xia Yang, Jingzhi Guan.
Supervision: Jingzhi Guan.
Writing – original draft: Shaofei Yuan, Fengli Gao, Zhong Xin, Haijun Guo, Suqin Shi, Lei Shi, Xia Yang.
Writing – review & editing: Jingzhi Guan.
Jingzhi Guan orcid: 0000-0002-3086-477X.

References

[1] Zhang Y. The progress of Chinese and Western medicine treatment for threatened abortion. Beijing J Tradit Chin Med 2009;28:566–9.
[2] Petriglia G, Palaia I, Musella A, et al. Threatened abortion and late-pregnancy complications: a case-control study and review of literature. Minerva Ginecol 2015;67:491–7.
[3] Kryvopustov OS, Dosenko VE. Pogesterone receptor gene polymorphisms as genetic risk factor of threatened abortion. Fiziol Zh 2016;62:60–4.
[4] Lee HJ, Park TC, Kim JH, et al. The influence of oral dydrogesterone and vaginal progesterone on threatened abortion: a systematic review and meta-analysis. Biomed Res Int 2017;2017:3616875doi: 10.1155/2017/3616875.
[5] Pabuccu R, Akar ME. Luteal phase support in assisted reproductive technology. Curr Opin Obstet Gynecol 2005;17:277.
[6] Lede R, Duley L, Karolinski A. Uterine muscle relaxant drugs for threatened miscarriage. Cochrane Database Syst Rev 2005;3:CD002857.
[7] Weinberg L. Use of anti-D immunoglobulin in the treatment of threatened miscarriage in the accident and emergency department. Emerg Med J 2001;18:444–7.
[8] Qureshi NS. Treatment options for threatened miscarriage. Maturitas 2009;65:35–41.
[9] Le J. Obstetrics and Gynecology· Sixth ed. Beijing: People's Medical Publishing House; 2005. 89–90.

[10] Zhang SH. Subgroup analysis and sensitive analysis should be set up reasonably in meta-analysis. Chin J Contemp Neurol Neurosurg 2016;16:1–2.
[11] Wang XH. Clinical observation on phloroglucinol in the treatment of 30 cases of late threatened abortion. Chin J N Clin Med 2009;2:1303–4.
[12] Zhou HL, Chen WJ. Clinical observation on the treatment of late threatened abortion after 20 weeks of pregnancy with phloroglucinol. Contemp Med 2012;18:9–10.
[13] Wei XX. Clinical observation of phloroglucinol in the treatment of threatened abortion before pregnancy. J Med Front 2013;22:202–3.
[14] Wu L, Liang XL, Zhu KY. Comparative analysis of the efficacy of three methods for the treatment of late threatened abortion. Jilin Med J 2013;34:244.
[15] Deng CX, Deng H, Jiang LX. Clinical effect of phloroglucinol in the treatment of advanced incipient abortion. China Pract Med 2014;9:37–8.
[16] Wei M, Lv Y. Clinical effects of Anbao, magnesium sulfate and phloroglucinol on treatment of threatened abortion after 20 weeks of gestation. J Trop Med 2014;14:81–3.
[17] Zhong XP. Analysis of the effect of phloroglucinol and magnesium sulfate in threatened abortion. Contemp Med 2014;20:82–3.
[18] Zhu FX. Clinical observation of phloroglucinol in the treatment of late-stage threatened abortion. Chin J Pract Med 2014;41:120–1.
[19] Huang JS, Liao ZL, Liu YH. Comparative analysis of adverse reactions of phloroglucinol and magnesium sulfate in the treatment of late-stage threatened abortion. Pharmacy Today 2015;25:210–1.
[20] Luo S. Phloroglucinol effect evaluation for the treatment of late abortions. China Med Pharmacy 2015;5:76–8.
[21] Guan XY, Zhou Y, Kuang XL. Clinical curative effect observation of phloroglucinol in treatment of late threatened abortion and threatened preterm labor. China Med Pharmacy 2016;6:71–3.
[22] He XF. Comparison of clinical efficacy of phloroglucinol and magnesium sulfate in the treatment of threatened abortion and premature labor. J Pract Gynecol Endocrinol 2016;3:116–7.
[23] Jiang JY. Clinical effect of combination of phloroglucinol and magnesium sulfate in the treatment of advanced threatened abortion. World Clin Med 2016;10:198–9.
[24] Yang J. Observe the effect of pyrophloroglucinol in the treatment of threatened abortion before pregnancy for 12 weeks. J North Pharmacy 2016;13:105–6.
[25] Feng XQ. Clinical observation on the treatment of late threatened abortion after 20 weeks of pregnancy with phloroglucinol. J Med Front 2017;7:93–4.
[26] Ge Y. Cmparison of clinical effects of Anbao, magnesium sulfate and phloroglucin in the treatment of threatened abortion after pregnancy for 20 weeks. China Contin Med Educ 2017;9:201–2.
[27] Hu HY, Peng Y. Clinical analysis of phloroglucin in treatment of threatened abortion after 20 weeks gestation. China Med Pharmacy 2017;7:78–80.
[28] Jin XF, Wang LP, Lu YD. Clinical effectiveness of magnesium sulfate comparing to phloroglucinol for treating threatened abortion. Chin J Family Plan 2017;25:247–9.
[29] Lan YL, Liu SF, Song YJ. Evaluation of the effectiveness of phloroglucinol in the clinical treatment of 60 cases of threatened abortion. China Pract Med 2017;12:143–4.
[30] Li SP. Clinical observation on threatened abortion before 20 weeks of pregnancy treated by two different medications. Contemp Med 2017;23:58–60.
[31] Li ZX. Clinical observation on the treatment of late threatened abortion after 20 weeks of pregnancy with phloroglucinol. China Health Care Nutr 2017;6:181.
[32] Sotiriadis A, Papatheodorou S, Makrydimas G. Threatened miscarriage: evaluation and management. BMJ 2004;329:152–155.
[33] Liang BK, Li YP, Luo XN, et al. Clinical efficacy and safety of phloroglucinol for promoting the progress of labor. Shenzhen J Integr Tradit Chin West Med 2017;27:153–4.
[34] Zhuang Y, Zhu X, Huang LL. The effect of phloroglucinol on pain in first-trimester surgical abortion: a double-blind randomized controlled study. Contraception 2010;81:157–60.
[35] Fairfield CJ, Harrison EM, Wigmore SJ. Duplicate publication bias weakens the validity of meta-analysis of immunosuppression after transplantation. World J Gastroenterol 2017;23:7198–200.
[36] Lin L, Chu H, Murad MH, et al. Empirical comparison of publication bias tests in meta-analysis. J Gen Intern Med 2018;33:1260–7. doi: 10.1007/s11606-018-4425-7.
[37] Chung VC, Wu X, Lu P, et al. Chinese herbal medicine for symptom management in cancer palliative care: systematic review and meta-analysis. Medicine (Baltimore) 2016;95:e2793doi: 10.1097/MD.0000000000002793.