

Original Article

Comparison of aspirin combined with low molecular weight heparin versus aspirin alone for habitual abortion: a systematic review and meta-analysis of randomized controlled trials

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Abstract: Background: The efficacy of aspirin combined with low molecular weight heparin in the treatment of habitual abortion is controversial. The efficacy of aspirin combined with low molecular weight heparin versus aspirin alone for habitual abortion is still unclear. Aim: The purpose is to compare the efficacy of low molecular weight heparin therapy versus aspirin monotherapy for habitual abortion. Methods: The PubMed, EMBASE, Cochrane Library, Web of Science, Chinese National Knowledge Infrastructure (CNKI) and Chinese Biology Medicine (CBM), VIP database and Wanfang database were searched to identify randomized controlled trials (RCTs) about aspirin combined with low molecular weight heparin in the treatment of habitual abortion without date or language restrictions (last search up to April, 2016) and reference lists of relevant reviews were checked to identify additional studies. We calculated relative risk (RR) with 95% confidence interval (CI) using Stata 14.0 software. Results: The results of meta-analysis suggested that combination therapy improved the live birth rate [RR, 1.18, 95% CI, (1.06, 1.31), $I^2=0\%$, $P=0.002$] and significantly reduced abortion rate [RR, 0.55, 95% CI, (0.44, 0.69), $I^2=2.1\%$, $P=0.000$] compared with aspirin monotherapy. Conclusion: Combination therapy shows benefic effects in the treatment of women with habitual abortion and is better than aspirin alone therapy. Further study is required to confirm these findings.

Keywords: Aspirin, low molecular weight heparin, habitual abortion, systematic review, meta-analysis, randomized controlled trials

Introduction

Habitual abortion, a primary healthy problem, 5% of women who are reproductive age have two or more abortions and about 1% have three abortions or more. There is still unexplained about most of habitual abortions, without effective therapy [1]. The morbidity of recurrent spontaneous abortion is 3%~5%, and its risk factors include genetics, hormones or metabolism, uterine anatomy, abnormal immune function, thrombophilia, infections, etc [2, 3]. Over the past 30 years, there have been a variety of treatment options, such as aspirin, hepa-

rin, plasma exchange, glucocorticoid, immunoglobulin and other joint or separate applications [4]. A increasing number of clinical trials report the efficacy of aspirin (ASA) combined with low molecular weight heparin (LMWH) in the treatment of habitual abortion. Bing Han et al [5] and Wen Cao et al [6] showed that the clinical effect of ASA combined with LMWH in the treatment of habitual abortion is very well. ASA combined with LMWH therapy can significantly improve the patients' pregnancy cycle and the live birth rate. However, Laskin et al [7] showed that ASA combined with LMWH therapy shows no incremental benefit compared to ASA alone

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therapy. One trial [8] indicated that both ASA combined with LMWH and ASA alone can't improve the live birth rate compared with placebo in the treatment of women with unexplained habitual abortion. In addition, Greer indicated that antithrombotic therapy should not be recommended for unexplained habitual abortion [9]. Thus, the efficacy of ASA combined with LMWH in the treatment of habitual abortion is controversial. The efficacy of ASA combined with LMWH versus ASA alone for habitual abortion is still unclear. We did a systematic review of randomized controlled trials which compared the efficacy of ASA combined with LMWH therapy and ASA monotherapy because of the increasing interest in combination therapy.

Methods

Search strategy

In accordance with the PRISMA guidelines [10], we identified studies by a literature search of PubMed, EMBASE, Cochrane Library, Web of Science, Chinese National Knowledge Infrastructure (CNKI) and Chinese Biology Medicine (CBM), VIP database and Wanfang database without date or language restrictions (last search up to April, 2016). Relevant search terms were as follows: "abortion habitual", "habitual abortion", "habitual abortions", "miscarriage, recurrent", "miscarriages, recurrent", "recurrent miscarriage", "recurrent miscarriages", "abortion, recurrent", "abortions, recurrent", "recurrent abortion", "recurrent abortions", "aspirin", "acetylsalicylic acid", "acid, acetylsalicylic", "2-(acetyloxy) benzoic acid", "acetylsalicylic", "aloxiprim", "colfarit", "dispril", "easprin", "ecotrin", "endosprin", "magnecyl", "micristin", "polopirin", "polopiryna", "solprin", "solupsan", "zorprin", "acetysal", "heparin, low molecular weight", "LMWH", "low molecular weight heparin", "low-molecular-weight heparin", "random*" and "randomized controlled trial". We also checked reference lists of relevant reviews for additional search. All titles and abstracts from the initial search were imported Endnote X7 to screen eligible studies.

Inclusion and exclusion criteria

Studies were included in this systematic review by the following terms: (1) RCTs; (2) aspirin plus low molecular weight heparin and aspirin were

randomly grouped into combination therapy group and aspirin monotherapy group; (3) at least one outcome (number of live births, number of abortions, complications, adverse events); (4) sample size not less than 20. In addition, we also excluded observational studies, comments, reviews, meeting papers, letter to editor, studies without aspirin monotherapy group, and studies without original data.

Data extraction

Two authors (Guan JZ and Du QC) independently chose the following included publication data: the first authors' name, year of publication, number of patients, patient characteristics, study design, combination therapy group (dosage, duration), aspirin monotherapy group (dosage, duration), outcomes (number of live births, number of abortions, complications, adverse events). Extracted data were transferred into Microsoft Excel 2010 and were checked carefully by us. For studies with insufficient information and unclear information, we contacted the corresponding authors to verify the data. All discordant results were resolved by discussion and consensus.

Quality assessment

Two authors (Guan JZ and Du QC) independently assessed risk of bias in the included studies using RCTs tool for assessing quality and risk of bias which was recommended by Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0, containing random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting and other bias [11]. Each terms has three options (low risk, high risk and unclear risk). All discordant results were resolved by discussion and consensus or referral to the third author (Yuan SF).

Statistical analysis

All statistical analyses were performed using Stata 14.0 software. All outcomes were dichotomous variables and were analyzed by using the relative risk (RR) with 95% confidence interval (CI) computed using the Mantel Haenszel method (fixed or random models). I-square (I^2) test was carried out to evaluate the impact of study heterogeneity on the results of the meta-

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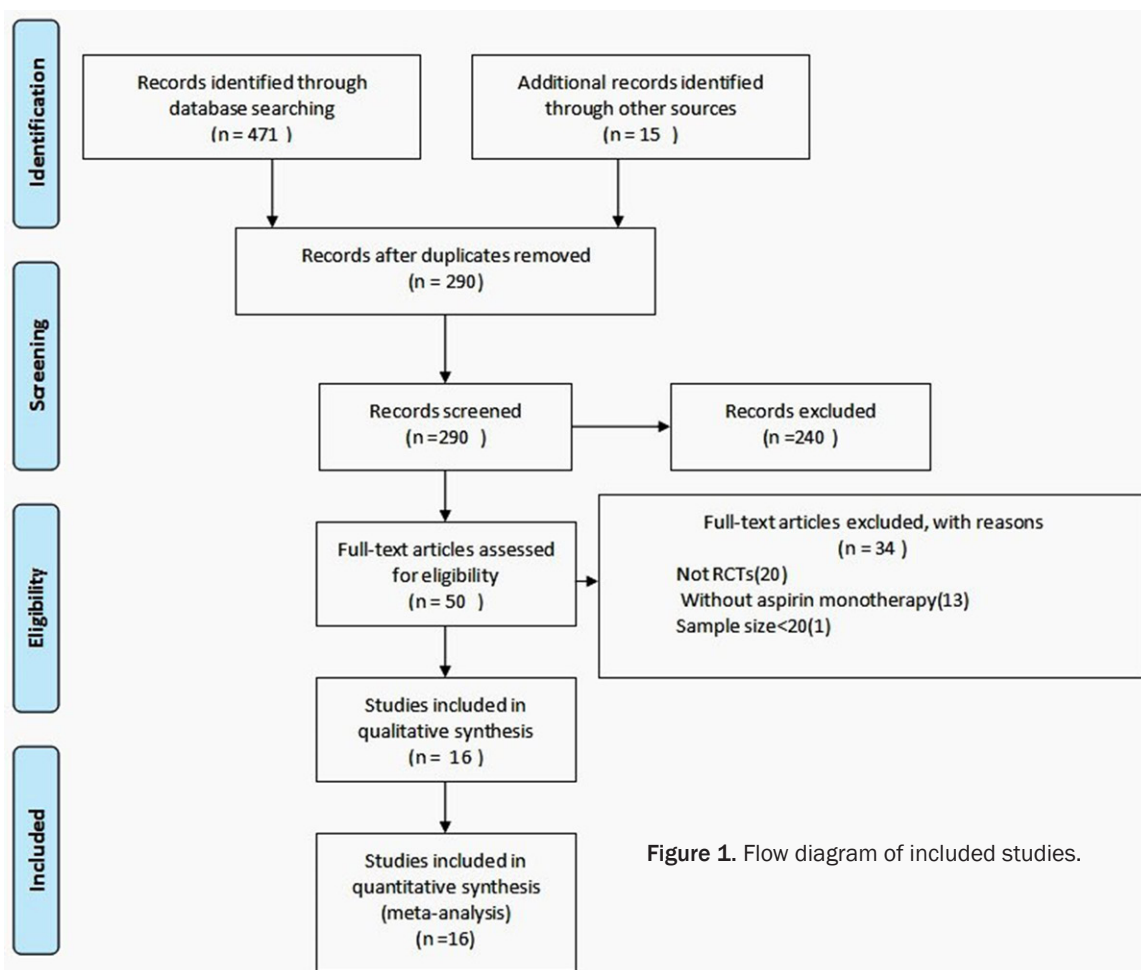


Table 1. Characteristics of included studies

Study (year)	N (C/M)	Mean age	Intervention	Duration
Laskin CA 2009	88 (45/43)	C: 34.6 M: 33.8	C: aspirin (80 mg/day) + LMWH (5000 IU/day) M: aspirin (80 mg/day)	35 weeks
Kaandorp CP 2010	243 (123/120)	C: 34 M: 35	C: aspirin (80 mg/day) + LMWH (2850 IU/day) M: aspirin (80 mg/day)	36 weeks
Visser J 2011	139 (76/63)	C: 31.6 M: 32.0	C: aspirin (100 mg/day) + LMWH (40 mg/day) M: aspirin (100 mg/day)	37 weeks
Zhou X 2011	61 (31/30)	C: 34 M: 33	C: aspirin (100 mg/day) + LMWH (5000 IU/day) M: aspirin (100 mg/day)	NR
Zhang YH 2011	54 (27/27)	28	C: aspirin (25 mg/day) + LMWH (5000 IU/day) M: aspirin (25 mg/day)	NR
Cao W 2012	80 (40/40)	25.4	C: aspirin (75 mg/day) + LMWH (5000 IU/day) M: aspirin (75 mg/day)	2 months
Zhou X 2012	61 (31/30)	C: 35 M: 34	C: aspirin (100 mg/day) + LMWH (5000 IU/day) M: aspirin (100 mg/day)	NR
Han B 2014	60 (30/30)	C: 30.41 M: 31.09	C: aspirin (75 mg/day) + LMWH (NR) M: aspirin (75 mg/day)	2 months
Elmahashi 2014	150 (75/75)	C: 27.3 M: 26.5	C: aspirin (75 mg/day) + LMWH (0.4 ml/day) M: aspirin (75 mg/day)	34 weeks
Wang L 2014	62 (31/31)	26.9	C: aspirin (25 mg/day) + LMWH (75 mg/day) M: aspirin (25 mg/day)	1 month

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Peng FM 2015	56 (28/28)	C: 30.2 M: 30.5	C: aspirin (100 mg/day) + LMWH (5000 IU/day) M: aspirin (100 mg/day)	NR
Zhang G 2015	118 (59/59)	C: 28.47 M: 29.15	C: aspirin (75 mg/day) + LMWH (5000 IU/day) M: aspirin (75 mg/day)	NR
Meng XW 2015	70 (35/35)	C: 29.5 M: 28.5	C: aspirin (100 mg/day) + LMWH (5000 IU/day) M: aspirin (100 mg/day)	NR
Sun Y 2015	70 (35/35)	C: 33.12 M: 32.56	C: aspirin (75 mg/day) + LMWH (5000 IU/day) M: aspirin (75 mg/day)	2 months
Tang HQ 2015	60 (30/30)	32.6	C: aspirin (25 mg/day) + LMWH (5000 IU/day) M: aspirin (25 mg/day)	2 months
Jin PP 2016	50 (25/25)	C: 27.0 M: 28.1	C: aspirin (75 mg/day) + LMWH (5000 IU/day) M: aspirin (75 mg/day)	2 months

Notes: C: combination therapy; M: aspirin monotherapy; NR: not report.

Table 2. Risk of bias summary of included studies

Study (year)	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias
Laskin CA 2009	Unclear	High	High	High	Low	Low	Low
Kaandorp CP 2010	High	Unclear	Unclear	Unclear	Low	Low	Low
Visser J 2011	High	Low	Low	Low	Low	Low	Low
Zhou X 2011	High	Unclear	Unclear	Unclear	Low	Low	Unclear
Zhang YH 2011	Unclear	Unclear	Unclear	Unclear	Low	Low	Unclear
Gao W 2012	Unclear	Unclear	Unclear	Unclear	Low	Low	Unclear
Zhou X 2012	Unclear	Unclear	Unclear	Unclear	Low	Low	Low
Han B 2014	Low	Unclear	Unclear	Unclear	Low	Unclear	Unclear
Elmahashi 2014	Low	Unclear	Unclear	Unclear	Low	Unclear	Low
Wang L 2014	Unclear	Unclear	Unclear	Unclear	Low	Unclear	Low
Peng FM 2015	Low	Unclear	Unclear	Unclear	Low	Low	Low
Zhang G 2015	Low	Unclear	Unclear	Unclear	Low	Low	Low
Meng XW 2015	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Low
Sun Y 2015	Unclear	Unclear	Unclear	Unclear	Low	Low	Low
Tang HQ 2015	High	Unclear	Unclear	Unclear	Low	Low	Low
Jin PP 2016	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Low

Notes: Low: low risk of bias; High: high risk of bias; Unclear: unclear risk of bias.

analysis. If severe heterogeneity occurred (I^2 was more than 50%), the random models were chosen. The fixed effect models were chosen when I^2 was less than 50% [11]. Sensitivity analysis was performed by deleting each study individually to evaluate the quality and consistency of the results. Publication bias was assessed using funnel plot.

Results

The initial literature search identified 486 articles. There were 290 articles after removing duplicates. Fifty articles were required to read full text. Finally, a total of 16 studies [5-8, 12-23] were included in this systematic review

after detailed evaluation. Detailed search steps for studies included in this systematic review are shown in **Figure 1**. Characteristics of included studies were summarized in **Table 1**. Risk of bias summary is shown in **Table 2**.

The results of meta-analysis showed that ASA combined with LMWH therapy improved the live birth rate [RR, 1.18, 95% CI, (1.06, 1.31), $I^2=0\%$, $P=0.002$] (**Figure 2**) compared with ASA monotherapy. ASA combined with LMWH therapy significantly reduced abortion rate [RR, 0.55, 95% CI, (0.44, 0.69), $I^2=2.1\%$, $P=0.000$] (**Figure 3**) compared with ASA monotherapy. A summary of pooled results is shown in **Table 3**. Heterogeneity among studies was very low, and

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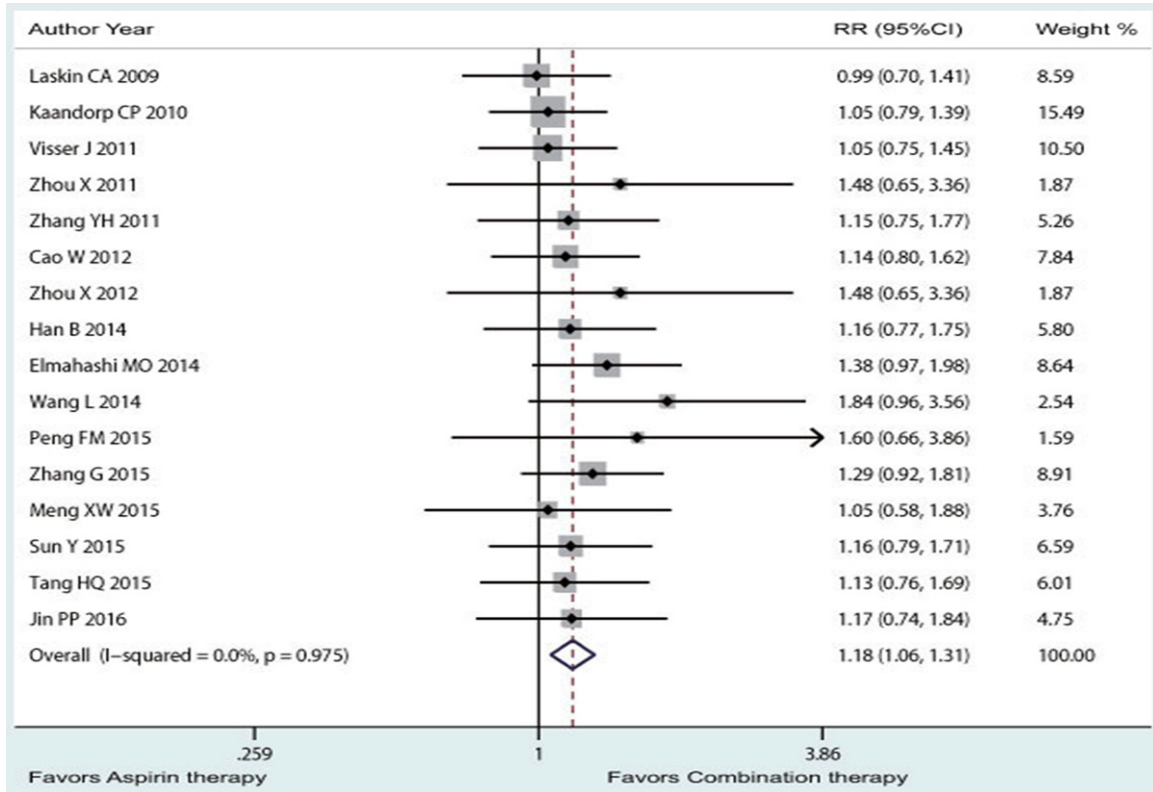


Figure 2. Relative risk 95% (confidence interval) in live birth rate between combination therapy and aspirin monotherapy.

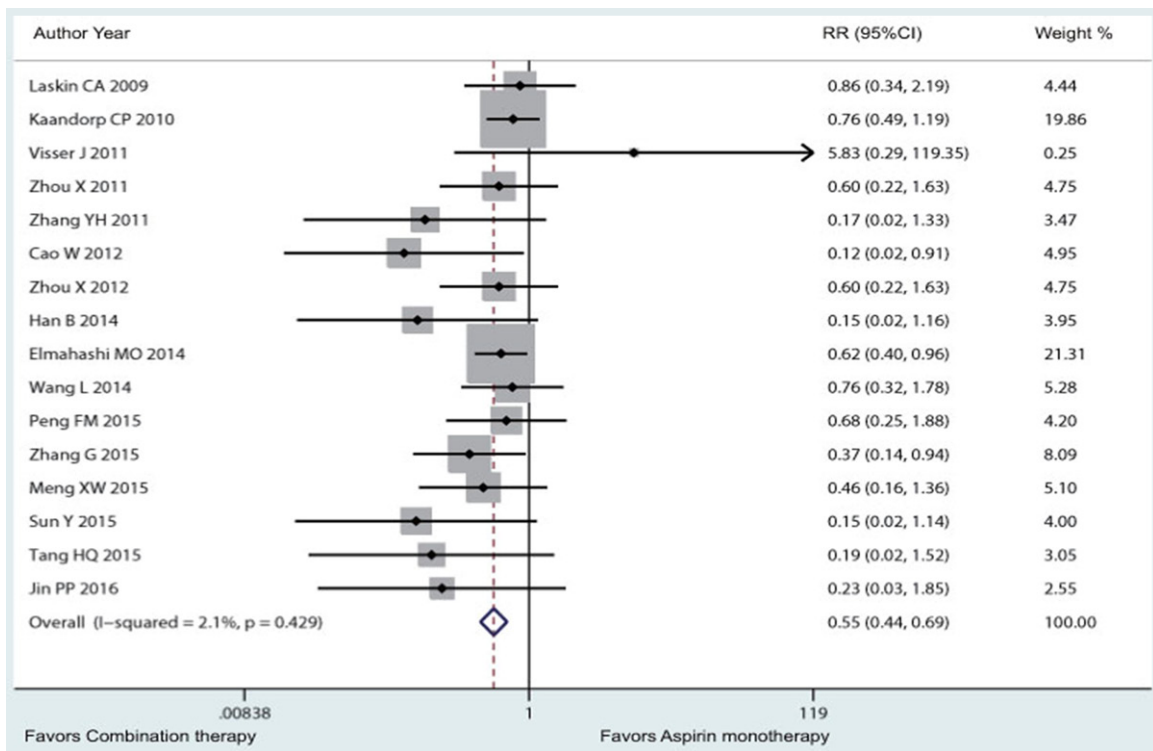


Figure 3. Relative risk 95% (confidence interval) in abortion rate between combination therapy and aspirin monotherapy.

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Table 3. Pooled results of meta-analysis: a summary

Outcome	RR	95% CI	I ² statistic (%)
Live birth rate	1.18	1.06-1.31	0
Abortion rate	0.55	0.44-0.69	2.1%

Notes: RR: relative risk; CI: confidence interval.

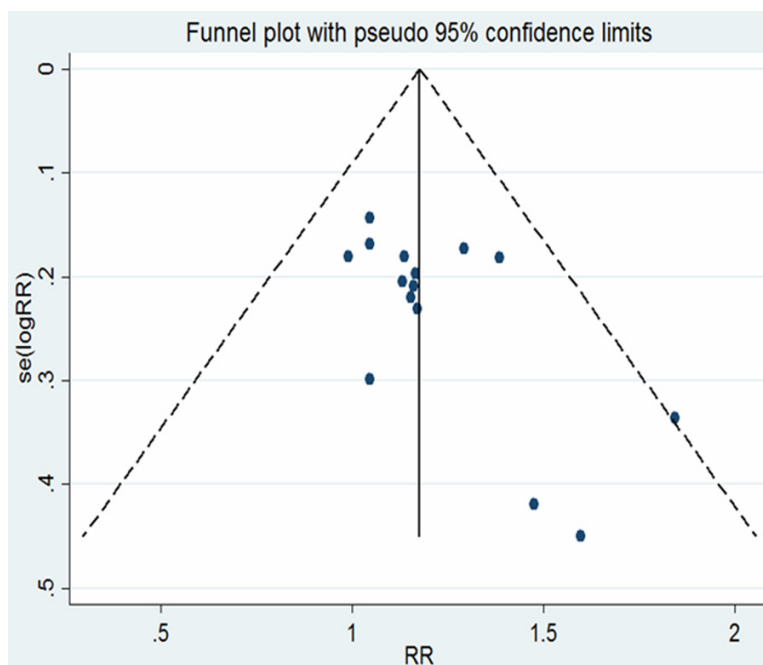


Figure 4. Funnel plot in the live birth rate.

the fixed models were chosen. Most studies reported complications and adverse events but they were various. In addition, complications and adverse events were not reported in detail, so we did not compare these outcomes.

We assessed the effect of each study on the pooled results by deleting each study individually. The result of sensitive analysis showed that the stability of results had no significant changes, which validated the rationality and reliability of this meta-analysis.

The funnel plot was applied for examining publication bias of studies included in the live birth rate in this meta-analysis. Funnel plots (**Figure 4**) showed that there was publication bias.

Discussion

This is the latest systematic review about comparison of aspirin combined with low molecular weight heparin versus aspirin alone for habitual

abortion. We found the combination therapy resulted in improving live birth rate and reducing abortion rate.

One trial [8] of included trials reported complications of early pregnancy, including miscarriage, ectopic pregnancy, termination of pregnancy, gestational age at miscarriage and the following maternal adverse events: thrombocytopenia, swelling or itching at injection site, need to change heparin formulation, nose-bleed, bruising, gastrointestinal problem, hematuria, bleeding gums. One trial [23] of included trials reported pregnancy complications (preeclampsia, abruptio placentae) and minor vaginal bleedings. Some trials of included trials reported adverse events, such as gastro-intestinal tract response, anaphylaxis, osteoporosis, thrombocytopenia. Most trials of included trials did not report complications and adverse events in detail.

A meta-analysis [24] showed that there were no significant differences in live birth rate [OR, 1.7, 95% CI (0.72, 4.0), I²=0%], first-trimester miscarriages [OR, 0.69, 95% CI (0.22, 2.16)], prematurity [OR, 0.99, 95% CI (0.4, 2.08)], preeclampsia [OR, 1.49, 95% CI (0.63, 3.5)] and small for gestational age babies [OR, 2.08, 95% CI (0.96, 4.47)] between comparison of aspirin combined with low molecular weight heparin versus aspirin alone, but their meta-analysis only included four RCTs. There was lack of credibility in such a small number of studies. Moreover, two meta-analysis [25, 26] indicated that combination therapy significantly increased the birth rate compared with aspirin monotherapy, but both of them were small in size. Roberge et al [27] showed that low-dose aspirin combined with LMWH could reduce the prevalence of preeclampsia and birth of small for gestational age in women with history preeclampsia. Our systematic review included more RCTs than the previous systematic

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reviews and meta-analysis. We believe that our study is the systematic review and meta-analysis with the largest sample size so far for comparison of aspirin combined with low molecular weight heparin versus aspirin alone for habitual abortion, including 16 studies (1442 patients). Heterogeneity among studies was very low, so we did not explore the source of heterogeneity using subgroup analysis or meta regression. To sum up, we believe that our systematic review can provide clinicians or patients with some useful informations about therapy of habitual abortion.

There are several limitations in our systematic review. Firstly, there was publication bias in this meta-analysis. Secondly, most included studies had poor methodological quality. Many unfinished studies which we can't get; a potential limitation for any meta-analysis is caused by such a relatively small number of available trials. The lack of gray literature, including presentations, unpublished data, government reports, other traditional or nontraditional sources of evidence is another limitation in this meta-analysis.

In conclusion, this limited systematic review indicates combination therapy shows benefic effects in the treatment of women with habitual abortion. Combination therapy is better than aspirin alone therapy. Therefore, combination therapy should be recommended for clinical application. Further study is required to assess the efficacy of aspirin combined with low molecular weight heparin in the treatment of women with habitual abortion.

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Disclosure of conflict of interest

None.

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