The efficacy and safety of low dose aspirin combined with low-molecular-weight heparin in the treatment of preeclampsia: a meta-analysis and systematic review

Type
Research paper

Keywords
treatment, meta-analysis, aspirin, preeclampsia, dose, low molecular weight heparin

Abstract

Introduction
The role of low dose aspirin combined with low-molecular-weight heparin (LMWH) in the treatment of preeclampsia (PE) remains unclear. We aimed to assess the efficacy and safety of low dose aspirin combined with LMWH in PE treatment, to provide evidence for the clinical PE management.

Material and methods
We searched PubMed, et al databases for randomized controlled trials (RCTs) on the effects and safety of low dose aspirin and LMWH in the treatment of PE up to Jan 31, 2021. Two researchers strictly followed the inclusion and exclusion criteria to independently conduct the literature screening, data extraction and quality evaluation. We used RevMan 5.3 statistical software for synthesized analysis.

Results
A total of 8 RCTs involving 861 patients were included. The synthesized outcome indicated that the differences in systolic blood pressure (MD=- 10.61, 95%CI-13.19 ~ -8.02), diastolic blood pressure (MD=- 9.24, 95%CI-14.49 ~ -4.00), 24-hour urinary protein (MD= 2.24, 95%CI-3.97~ -0.50), PT (MD=1.42, 95%CI0.53 ~ -2.32), APTT (MD=2.91, 95%CI2.06~ 3.75), FIB (MD=-1.24, 95%CI-1.32~ -1.15), adverse perinatal outcomes (MD=0.41, 95%CI0.20~0.85) between the two groups were statistically significant (all p<0.05), the difference in the adverse reactions of pregnant women (MD=0.44, 95%CI0.18~1.10) between the two groups was not statistically significant (P=0.08). No publication bias was detected in all the synthesized outcomes (all P>0.05).

Conclusions
Low-dose aspirin combined with LMWH treatment of PE may be advantageous to improve blood pressure, 24-hour proteinuria and coagulation function, and it may reduce the adverse reactions in pregnant women without increasing adverse perinatal outcomes.
Title: The efficacy and safety of low dose aspirin combined with low-molecular-weight heparin in the treatment of preeclampsia: a meta-analysis and systematic review

Running title: aspirin and LMWH & preeclampsia

Authors: Chunfeng Wu⁷¹, Liling Li¹, Jiarong Zhang¹, Yang Song¹

¹, Department of Obstetrics, Maternal and Child Health Hospital of Longhua District, Shenzhen, China

⁷, Corresponding author

Corresponding to: Chunfeng Wu  iflpea8406284062@163.com

Address: No. 68, Huawang Road, Dalang Street, Longhua District, Shenzhen, China.

Telephone: 18646321726

Fax: 0012 1173 4016
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**Keywords:** dose; aspirin; low molecular weight heparin; preeclampsia; treatment; meta-analysis

**Background**

Preeclampsia (PE), as a kind of hypertension during pregnancy, is one of the important factors associated with maternal and perinatal death[1]. Studies[2, 3] have shown that among the factors leading to maternal death, PE ranks the third, second only to bleeding and thrombosis. It’s been reported[4, 5] that more than 60,000 pregnant women die of PE worldwide every year. PE has serious effects on both the mother and the fetus. If effective treatment is not carried out in time, complications such as pulmonary edema and placental abruption may occur in the mother; complications such as intrauterine growth restriction, premature delivery, respiratory distress syndrome and even death may occur in the fetus[6, 7]. At the same time, PE can also cause serious adverse effects on re-pregnancy, that is, women with a history of PE have 25% to 65% of possible recurrence of PE, 3% of placental abruption, and 10% of fetal growth limit[8-10]. Therefore, early diagnosis and effective treatment of PE is essential to the prognosis of patients.

At present, anticoagulant therapy is commonly used clinically. Aspirin and low molecular weight heparin (LMWH) are the most commonly used drug.[11] The effectiveness and safety of aspirin in the prevention and treatment of PE have been confirmed by a number of studies[12, 13], but there are still controversies regarding the effect and safety of LMWH in the prevention and treatment of PE. There are very few research reports about the applications of aspirin and LMWH in the treatment of PE. Therefore, the effects and safety of aspirin combined with LMWH in the treatment
of PE are still controversial. Therefore, this meta-analysis aimed to systematically evaluate the effectiveness and safety of aspirin combined with LMWH in the treatment of PE, and to provide evidence-based reference for the rational use of PE therapy in clinical practice.

**Methods**

We conducted and presented this meta-analysis in comply with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)[14].

**Search strategy**

We searched the potential related randomized controlled trials (RCTs) with reference to the search strategy formulated by the Cochrane Collaboration. We searched PubMed, EMBASE, Science Direct, Cochrane Central Register of Controlled Trials, China National Knowledge Infrastructure (CNKI), Weipu Database, Wanfang Database, Chinese Biomedical Literature Database for RCTs on the effects of low dose aspirin and LMWH in the treatment of PE. The search deadline was Jan 31, 2021. The search terms included: aspirin, low molecular weight heparin, LMWH, preeclampsia, and the search terms were combined according to the rules of different databases.

The search strategies were jointly formulated by two researchers. According to the established search strategy, the two researchers independently completed the inclusion of the literature, discussed and decided when there were differences, and finally integrated the collected information and data. Research screening process was as following: preliminary screening of the retrieved documents through the research title and abstract, then further screening through the full text, and finally in strict accordance with the literature inclusion criteria and exclusion criteria to determine the final inclusion of the literature.
The inclusion criteria for this meta-analysis were: (1) The patient was diagnosed as PE; (2) RCT study design; (3) The treatment method included the combined use of low dose aspirin and LMWH; (4) Aspirin dose $<150$ mg/d; (5) the outcome data could be extracted. The exclusion criteria for this meta-analysis were: (1) Animal experimental research, conference abstracts and review articles, retrospective research; (2) The studies that lack control group; (3) literatures that were repeatedly published.

Data extraction

Two authors independently evaluated and extracted the data, including: systolic blood pressure, diastolic blood pressure, 24-hour urinary protein, prothrombin time (PT), activated partial thromboplastin time (APTT), fibrinogen (FIB), the adverse perinatal outcomes and the adverse reactions of pregnant women.

Quality and bias evaluation

We used Cochrane's risk of bias assessment tool[15] to evaluate the quality and bias of the included RCTs. 7 items were designed to evaluate the risk of bias from the following 6 aspects: (1) sample selection (including random sequence generation and allocation hiding); (2) program implementation (including blinding researchers and subjects); (3) Outcome measurement (blind evaluation of study outcome); (4) Follow-up (completeness of outcome data); (5) Report (selective report of study results); (6) Other sources of bias. Each item was rated as "low risk", "high risk" and "unclear" according to the criteria.

Statistical methods

We used RevMan5.3 statistical software for meta-analysis. The odds ratio (OR) and its 95%
confidence interval (95% CI) were used as the statistics of the combined effect of the count data; the mean difference (MD) and its 95% CI were used as the statistics of the combined effect of the continuous data. The heterogeneity was evaluated by the chi-square test. If the heterogeneity difference between the studies was not statistically significant ($P > 0.10$ or $I^2 < 50\%$), the combined effect was analyzed by the fixed effects model; otherwise, the random effects model was used for the meta-analysis. In this study, $P < 0.05$ was considered statistically significant.

Results

Literature search results

We obtained 118 articles from the initial search. The we screened out 71 articles by screening titles, abstracts, and duplicate articles. We performed full-text reading of these articles for further screening, and finally included 8 RCTs [16-23]. The study selection process was shown in Figure 1.

Figure 1 PRISMA flow diagram of study inclusion

The characteristics of included RCTs

Amongst the 8 RCTs included, a total of 861 patients were involved. The basic characteristics of each study were shown in Table 1. Generally, the control group received conventional treatment, and the experimental group was treated with low-dose aspirin combined with LMWH on the basis of the treatment of control group.

<table>
<thead>
<tr>
<th>Table 1 The characteristics of included RCTs</th>
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</table>

Bias risk assessment

The evaluation results of the Cochrane bias risk assessment tool for 8 included RCTs were as
following: (1) Only 5 RCTs[16-18, 22, 23] described specific random sequence generation methods, but the other 3 RCTs[19-21] did not describe specific randomization methods; (2) None of the studies reported specific allocation concealment; (3) None of the studies reported the specific blinding settings; (4) None of the studies described blind evaluation of the outcome; (5) No missing data were found; (6) All pre-set indicators were reported, and no research with reporting bias was found; (7) No other biases were found. The quality and bias evaluation results of the included RCTs were shown in Figure 2 and 3.

Figure 2 Risk of bias graph

Figure 3 Risk of bias summary

Meta-analysis

Systolic blood pressure Four RCTs[16, 19, 21, 23] reported the systolic blood pressure. There was no statistical heterogeneity among the studies($I^2=44\%, P=0.15$). Therefore, a fixed effect model was used. The synthesized outcome indicated that the difference in systolic blood pressure between the two groups was statistically significant (MD=-10.61, 95%CI-13.19 ~ -8.02, P<0.001). See picture 4A.

Diastolic blood pressure Five RCTs[16-19, 23] reported the diastolic blood pressure. There was statistical heterogeneity among the studies($I^2=93\%, P<0.001$). Therefore, a random effect model was used. The synthesized outcome indicated that the difference in diastolic blood pressure between the two groups was statistically significant (MD=-9.24, 95%CI-14.49 ~ -4.00, P<0.001). See picture 4B.
24-hour urinary protein Five RCTs[16-19, 22] reported the 24-hour urinary protein. There was statistical heterogeneity among the studies ($I^2=99\%, P<0.001$). Therefore, a random effect model was used. The synthesized outcome indicated that the difference in 24-hour urinary protein between the two groups was statistically significant (MD=$-2.24$, 95% CI=$-3.97$ to $-0.50$, $P=0.01$). See picture 4C.

$PT$ Five RCTs[16, 18-20, 23] reported the PT. There was statistical heterogeneity among the studies ($I^2=94\%, P<0.001$). Therefore, a random effect model was used. The synthesized outcome indicated that the difference in PT between the two groups was statistically significant (MD=$1.42$, 95% CI=$0.53$ to $2.32$, $P=0.002$). See picture 4D.

Figure 4 The frost plot for synthesized outcomes

$APTT$ Five RCTs[16, 18-20, 23] reported the APTT. There was statistical heterogeneity among the studies ($I^2=56\%, P=0.06$). Therefore, a random effect model was used. The synthesized outcome indicated that the difference in APTT between the two groups was statistically significant (MD=$2.91$, 95% CI=$2.06$ to $3.75$, $P<0.001$). See picture 5A.

$FIB$ Four RCTs[16, 19, 20, 23] reported the FIB. There was no statistical heterogeneity among the studies ($I^2=38\%, P=0.18$). Therefore, fixed effect model was used. The synthesized outcome indicated that the difference in FIB between the two groups was statistically significant (MD=$-1.24$, 95% CI=$-1.32$ to $-1.15$, $P<0.001$). See picture 5B.

The adverse perinatal outcomes Four RCTs[16, 17, 19, 20] reported the adverse perinatal outcomes. There was statistical heterogeneity among the studies ($I^2=53\%, P=0.009$). Therefore, a random effect model was used. The synthesized outcome indicated that the difference in adverse
perinatal outcomes between the two groups was statistically significant (MD=0.41, 95% CI 0.20–0.85, P=0.02). See picture 5C.

The adverse reactions of pregnant women. Four RCTs [16, 17, 19, 21] reported the adverse reactions of pregnant women. There was no statistical heterogeneity among the studies (I² = 0%, P=0.65). Therefore, a random effect model was used. The synthesized outcome indicated that the difference in the adverse reactions of pregnant women between the two groups was not statistically significant (MD=0.44, 95% CI 0.18–1.10, P=0.08). See picture 5D.

Figure 5 The forest plot for synthesized outcomes

Publication bias

The funnel plot on the synthesized outcomes were presented in Figure 6. Even though the funnel plots were asymmetrical as it looked, no publication biases were detected in all the synthesized outcomes (all P>0.05).

Figure 6 The funnel plot for synthesized outcomes

Sensitivity analysis

We excluded RCTs on each result one by one to see that if the overall results would change, and we found that the overall results weren’t changed by exclusion of any included RCTs.

Discussions

It is estimated that 4%–5% of pregnant women in the world will suffer from eclampsia [24, 25]. PE brings a great burden to the morbidity and mortality of mothers and babies, and has an important influence on the premature delivery of the fetus and the long-term cardiovascular
disease of the mother[26]. The pathophysiological changes of PE include poor trophoblast infiltration, insufficient uterine spiral artery remodeling, decreased uterine placental perfusion, resulting in clinical manifestations of placental donor insufficiency, leading to insufficient blood supply to the placenta[27, 28]. In addition, this abnormal placenta formation leads to abnormal secretion of anti-angiogenesis and inflammatory proteins, which enter the maternal systemic circulation and damage the maternal systemic blood vessel function[29]. Therefore, the early prevention, detection and treatment of PE is of great significance to the prognosis of patients. Low-dose aspirin is considered the most effective preventive treatment, which can reduce the prevalence of early-onset PE in women. It is generally believed that it is safe for pregnant women to use low-dose aspirin because it will not unintentionally affect the pregnant woman and (or) her unborn fetus[30]. Some scholars[31, 32] believe that the main mechanism of low-dose aspirin is to inhibit platelet aggregation by inhibiting the production of thromboxane. Besides, low-dose aspirin has a direct positive effect on the villi trophoblast[33]. However, recent evidence[34] shows that low-dose aspirin prevents the development of preeclampsia by promoting the invasion and migration of trophoblast cells to the uterine artery, interfering with the production of cytokines, and stimulating the pro-angiogenic protein placental growth factor to prevent the development of preeclampsia, thereby inhibiting cell apoptosis and arterial remodeling. Studies[11, 35] have reported that low-dose aspirin taken by people at high risk of PE during gestational weeks 11-14 to 36 gestational weeks can significantly reduce the occurrence of preeclampsia. At the same time, when people with a high incidence of PE start taking aspirin and low molecular weight heparin before 16 weeks of pregnancy, it can effectively prevent PE[36]. The efficacy of aspirin and LMWH in the treatment of patients with preeclampsia remains to be
verified. It’s been reported that whether aspirin can improve the hypercoagulable state of pregnant
women is related to its dose. If the dose is too small, the effect is not obvious. However, excesseslly large doses can lead to increased adverse reactions such as bleeding in patients[37]. We have comprehensively evaluated the efficacy and safety of low-dose (<150 mg/d) aspirin combined with LMWH in the treatment of PE. The results have showed that the blood pressure and 24-hour urine protein in the combined drug use group have decreased significantly compared with the control group, and its coagulation function (PT, APTT, FIB) was also significantly improved compared with the control group. This suggests that the combination of low-dose aspirin and LMWH has a significant effect in the treatment of PE. The possible reason is that LMWH is a commonly used clinical anticoagulant with anti-inflammatory, anti-immune and protective effects on the vascular endothelium[38]. Its small molecule characteristics make it easy to be absorbed by the body and have a long half-life, and it can also lead to the reduction of platelets aggregation and will ultimately reduce the patient's thrombosis[39]. Aspirin can inhibit the production of thromboxane, the final product of prostaglandin, by inhibiting cyclooxygenase, which hinders the formation of thrombus, and ultimately improves the clinical symptoms of patients with PE[40]. In addition, studies[41, 42] have shown that the combination therapy improves the soluble vascular endothelial growth factor receptor in patients and reduces the level of ultrasound parameters of placental blood perfusion, and increases the expression of angiogenesis genes in the placenta. This suggests that on the basis of conventional treatment, low-dose aspirin combined with LMWH can improve blood flow in the uterine spiral artery and increase placental blood perfusion. Currently, There are many reports[43, 44] on the active management of the labour in women with hypertensive disorder or pre-eclampsia, based on our finding, the combined use of low-dose
aspirin and LMWH may be included for the active management of PE, which still needs further investigation in the future.

This study has the following limitations. Firstly, reports on the effects of aspirin combined with LMWH on PE in foreign countries are inconsistent. Most of the studies included in this meta-analysis are from China, and there is still a lack of high-quality research support from other regions. Secondly, the baseline characteristics of some of the included RCTs are incomplete, such as the lack descriptions of gestational age, pregnancy details, and the outcome indicators of the included RCTs are not all consistent. Besides, several studies[45-47] have reported the possible role of miRNAs in PE onset, both as increased or decreased expression in placenta or as maternal serum markers, which may be the important outcomes for the treatment evaluation of effects and safety, future studies focused more on the biological changes are needed. Thirdly, most outcome indicators in this present study are heterogeneous, limited by sample size, we cannot perform more subgroup analysis. Therefore, the results of this study need to be further verified by a rigorously designed, large-sample, multi-center randomized controlled trial.

**Conclusions**

In summary, the use of low-dose aspirin combined with LMWH in the treatment of PE may be beneficial to improve blood pressure, 24-hour proteinuria, and blood coagulation, and it may reduce the occurrence of adverse reactions of pregnant women without increasing adverse perinatal outcomes. Therefore, the effects and safety of low-dose aspirin combined with LMWH may provide a reference for the clinical treatment of PE. However, it is worth noting that the sample size of this meta-analysis is small, and the conclusions of this study need to be further elucidated in more high-quality studies with further in-depth analysis.
List of abbreviations

LMWH: low-molecular-weight heparin
PE: preeclampsia
RCTs: randomized controlled trials
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
CNKI: China National Knowledge Infrastructure
PT: Prothrombin time
APTT: activated partial thromboplastin time
FIB: fibrinogen
OR: odds ratio
95% CI: 95% confidence interval
MD: mean difference

Ethics approval and consent to participate
In this study, all methods were performed in accordance with the relevant guidelines and regulations. Ethics approval and consent to participate is not necessary since our study is meta-analysis.

Consent for publication
Not applicable.

Availability of data and materials
All data generated or analyzed during this study are included in this published article.

Competing interests
The authors declare that they have no competing interests.
Funding

None.

Author contributions

C W designed research; C W, L L, J Z, Y S conducted research; C W, L L analyzed data; C W wrote the first draft of manuscript; C W had primary responsibility for final content. All authors read and approved the final manuscript.

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None.

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**Figure legends**

430 Figure 1 PRISMA flow diagram of study inclusion

431 Figure 2 Risk of bias graph
Figure 3 Risk of bias summary

Figure 4 The frost plot for synthesized outcomes

Figure 5 The frost plot for synthesized outcomes

Figure 6 The funnel plot for synthesized outcomes
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<tr>
<th>Study</th>
<th>Sample size</th>
<th>Age(y)</th>
<th>Gestational weeks</th>
<th>Treatment</th>
<th>Sample size</th>
<th>Age(y)</th>
<th>Gestational weeks</th>
<th>Treatment</th>
<th>Follow-up period</th>
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<td>Qiao 2017</td>
<td>150</td>
<td>26.20±7.38</td>
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<td>25 mg<em>2 times/d aspirin + 5000 U</em> times/d LMWH</td>
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<td>65</td>
<td>28.40±4.90</td>
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<td>27.20±3.70</td>
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<td>Deng 2018</td>
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<td>27.08±3.46</td>
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<td>Hoorn 2016</td>
<td>16</td>
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<td>16</td>
<td>30.30±4.20</td>
<td>28.57±3.10</td>
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<td>During treatment, after childbirth</td>
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<td>Li 2019</td>
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<td>28.4±3.40</td>
<td>30.1±3.80</td>
<td>50 mg /d aspirin + 4000 U* times/d LMWH</td>
<td>28</td>
<td>28.90±3.70</td>
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<td>Lu 2018</td>
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<td>2019</td>
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<td>2019</td>
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<td>29.64±1.24</td>
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</table>

NA, not available; LMWH, low-molecular-weight heparin
Figure 1 PRISMA flow diagram of study inclusion

- Records identified through database searching (n = 112)
- Additional records identified through other sources (n = 6)

Records after duplicates removed (n = 107)

- Records screened (n = 107)
- Full-text articles excluded (n = 71); 9 not RCT; 17 inappropriate intervention; 1 duplicate publication; 1 low-quality report

- Full-text articles assessed for eligibility (n = 36)

Studies included in qualitative synthesis (n = 8)

Studies included in quantitative synthesis (meta-analysis) (n = 8)
Figure 2 Risk of bias graph
### Figure 3 Risk of bias summary

<table>
<thead>
<tr>
<th></th>
<th>Qiao 2017</th>
<th>Lu 2018</th>
<th>Li 2019</th>
<th>Li 2017</th>
<th>Hoorn 2016</th>
<th>Hong 2019</th>
<th>Feng 2019</th>
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<td>Incomplete outcome data (attrition bias)</td>
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</table>

Other bias

- Green circle indicates a low risk of bias.
- Yellow circle indicates unclear risk of bias.
- Red circle indicates a high risk of bias.
Figure 4 The frost plot for synthesized outcomes

### A. Forest plot for systolic blood pressure

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Experimental Mean</th>
<th>SD</th>
<th>Total</th>
<th>Control Mean</th>
<th>SD</th>
<th>Total</th>
<th>Mean Difference</th>
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<tbody>
<tr>
<td>Hong 2019</td>
<td>83.24</td>
<td>7.15</td>
<td>40</td>
<td>72.14</td>
<td>7.46</td>
<td>40</td>
<td>20.5%</td>
<td>-9.00 [-12.10, -5.70]</td>
</tr>
<tr>
<td>Hoorn 2016</td>
<td>83.42</td>
<td>7.41</td>
<td>16</td>
<td>93.2</td>
<td>8.04</td>
<td>16</td>
<td>17.8%</td>
<td>-9.78 [-15.36, -4.20]</td>
</tr>
<tr>
<td>Li 2017</td>
<td>86.43</td>
<td>8.59</td>
<td>65</td>
<td>90.51</td>
<td>9.48</td>
<td>62</td>
<td>20.6%</td>
<td>-5.06 [-8.23, -1.93]</td>
</tr>
<tr>
<td>Lu 2018</td>
<td>74.63</td>
<td>9.58</td>
<td>41</td>
<td>94.66</td>
<td>10.31</td>
<td>41</td>
<td>19.3%</td>
<td>-20.03 [-24.34, -15.72]</td>
</tr>
<tr>
<td>Qiao 2017</td>
<td>98.8</td>
<td>6.7</td>
<td>150</td>
<td>103.3</td>
<td>6.9</td>
<td>150</td>
<td>21.8%</td>
<td>-3.50 [-5.04, -1.96]</td>
</tr>
</tbody>
</table>

Total (95% CI): 312  
Heterogeneity: Tau² = 32.25, Chi² = 56.12, df = 4 (P < 0.0001); I² = 93%  
Test for overall effect: Z = 3.45 (P = 0.0003)

### B. Forest plot for diastolic blood pressure

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Experimental Mean</th>
<th>SD</th>
<th>Total</th>
<th>Control Mean</th>
<th>SD</th>
<th>Total</th>
<th>Mean Difference</th>
<th>IV, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Feng 2019</td>
<td>3.2</td>
<td>0.7</td>
<td>52</td>
<td>3.2</td>
<td>0.9</td>
<td>48</td>
<td>21.0%</td>
<td>0.00 [0.32, 0.32]</td>
</tr>
<tr>
<td>Hoorn 2016</td>
<td>0.32</td>
<td>0.02</td>
<td>16</td>
<td>0.41</td>
<td>0.02</td>
<td>16</td>
<td>20.2%</td>
<td>-0.09 [-0.10, -0.08]</td>
</tr>
<tr>
<td>Li 2017</td>
<td>2.47</td>
<td>1.02</td>
<td>65</td>
<td>2.95</td>
<td>1.06</td>
<td>62</td>
<td>20.0%</td>
<td>-0.48 [-0.84, -0.12]</td>
</tr>
<tr>
<td>Lu 2018</td>
<td>3.95</td>
<td>1.04</td>
<td>41</td>
<td>7.38</td>
<td>1.05</td>
<td>41</td>
<td>19.9%</td>
<td>-3.82 [-4.27, -3.37]</td>
</tr>
<tr>
<td>Qiao 2017</td>
<td>0.1</td>
<td>2.23</td>
<td>150</td>
<td>7</td>
<td>3.05</td>
<td>150</td>
<td>19.7%</td>
<td>-6.90 [-7.50, -6.30]</td>
</tr>
</tbody>
</table>

Total (95% CI): 324  
Heterogeneity: Tau² = 3.88, Chi² = 52.13, df = 4 (P < 0.0001); I² = 99%  
Test for overall effect: Z = 3.53 (P = 0.001)

### C. Funnel plot for 24-hour urinary protein

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Experimental Mean</th>
<th>SD</th>
<th>Total</th>
<th>Control Mean</th>
<th>SD</th>
<th>Total</th>
<th>Mean Difference</th>
<th>IV, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deng 2018</td>
<td>13.89</td>
<td>1.43</td>
<td>40</td>
<td>12.12</td>
<td>1.32</td>
<td>40</td>
<td>20.6%</td>
<td>1.77 [1.17, 2.37]</td>
</tr>
<tr>
<td>Hong 2019</td>
<td>13.87</td>
<td>1.14</td>
<td>40</td>
<td>12.05</td>
<td>1.18</td>
<td>40</td>
<td>20.5%</td>
<td>1.82 [1.31, 2.33]</td>
</tr>
<tr>
<td>Hoorn 2016</td>
<td>13.86</td>
<td>1.49</td>
<td>16</td>
<td>12.15</td>
<td>1.38</td>
<td>16</td>
<td>17.3%</td>
<td>1.71 [0.71, 2.71]</td>
</tr>
<tr>
<td>Li 2017</td>
<td>13.87</td>
<td>1.46</td>
<td>65</td>
<td>12.14</td>
<td>1.33</td>
<td>62</td>
<td>20.6%</td>
<td>1.73 [1.24, 2.22]</td>
</tr>
<tr>
<td>Qiao 2017</td>
<td>11.4</td>
<td>0.9</td>
<td>150</td>
<td>11.2</td>
<td>1.1</td>
<td>150</td>
<td>21.6%</td>
<td>0.20 [-0.03, 0.43]</td>
</tr>
</tbody>
</table>

Total (95% CI): 311  
Heterogeneity: Tau² = 0.95, Chi² = 69.44, df = 4 (P < 0.00001); I² = 94%  
Test for overall effect: Z = 3.11 (P = 0.002)

### D. Funnel plot for PT
### A Forest plot for APTT

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Experimental Mean</th>
<th>SD</th>
<th>Total</th>
<th>Control Mean</th>
<th>SD</th>
<th>Total</th>
<th>Weight</th>
<th>Mean Difference IV, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deng 2018</td>
<td>3.28</td>
<td>0.37</td>
<td>42</td>
<td>4.93</td>
<td>0.63</td>
<td>42</td>
<td>23.4%</td>
<td>-1.31 [-1.48, -1.14]</td>
</tr>
<tr>
<td>Hong 2019</td>
<td>3.24</td>
<td>0.37</td>
<td>40</td>
<td>4.36</td>
<td>0.35</td>
<td>40</td>
<td>27.7%</td>
<td>-1.12 [-1.28, -0.96]</td>
</tr>
<tr>
<td>Hoom 2016</td>
<td>3.23</td>
<td>0.36</td>
<td>16</td>
<td>4.34</td>
<td>0.4</td>
<td>16</td>
<td>9.9%</td>
<td>-1.11 [-1.37, -0.85]</td>
</tr>
<tr>
<td>Li 2017</td>
<td>3.27</td>
<td>0.35</td>
<td>65</td>
<td>4.58</td>
<td>0.41</td>
<td>62</td>
<td>39.0%</td>
<td>-1.31 [-1.44, -1.18]</td>
</tr>
</tbody>
</table>

Total (95% CI): 163

Heterogeneity: $I^2 = 4.86$, df = 3 ($P = 0.18$); $P = 38$

Test for overall effect: $Z = 29.22$ ($P < 0.00001$)

### B Forest plot for FIB

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Experimental Events</th>
<th>Control Events</th>
<th>Total</th>
<th>Mean Difference M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Feng 2019</td>
<td>18</td>
<td>52</td>
<td>19</td>
<td>0.81 [0.36, 1.82]</td>
</tr>
<tr>
<td>Hoom 2016</td>
<td>2</td>
<td>16</td>
<td>18</td>
<td>0.43 [0.07, 2.76]</td>
</tr>
<tr>
<td>Li 2017</td>
<td>19</td>
<td>65</td>
<td>84</td>
<td>0.47 [0.23, 0.96]</td>
</tr>
<tr>
<td>Lu 2018</td>
<td>8</td>
<td>41</td>
<td>49</td>
<td>0.16 [0.06, 0.42]</td>
</tr>
</tbody>
</table>

Total (95% CI): 174

Total events: 47

Heterogeneity: $I^2 = 0.28$, df = 3 ($P = 0.09$); $P = 53$

Test for overall effect: $Z = 2.40$ ($P = 0.02$)

### C Forest plot for the adverse perinatal outcomes

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Experimental Events</th>
<th>Control Events</th>
<th>Total</th>
<th>Mean Difference M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hoom 2016</td>
<td>1</td>
<td>16</td>
<td>17</td>
<td>0.20 [0.02, 0.32]</td>
</tr>
<tr>
<td>Li 2017</td>
<td>3</td>
<td>65</td>
<td>68</td>
<td>0.45 [0.11, 1.69]</td>
</tr>
<tr>
<td>Li 2019</td>
<td>3</td>
<td>28</td>
<td>31</td>
<td>1.00 [0.18, 5.44]</td>
</tr>
<tr>
<td>Lu 2018</td>
<td>0</td>
<td>41</td>
<td>41</td>
<td>0.19 [0.01, 0.49]</td>
</tr>
</tbody>
</table>

Total (95% CI): 150

Total events: 7

Heterogeneity: $I^2 = 1.63$, df = 3 ($P = 0.05$); $P = 0$

Test for overall effect: $Z = 1.76$ ($P = 0.08$)

### D Forest plot for the adverse reactions of pregnant women

Figure 5 The frost plot for synthesized outcomes
Figure 6 The funnel plot for synthesized outcomes