

# Maternal and neonatal outcomes of preeclamptic and normotensive women who underwent cesarean section under spinal Anesthesia: Systematic review and Meta-Analysis

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## Research

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## Abstract

**Background:** preeclampsia is very challenging for anesthetists due to the heterogeneous clinical spectrum of the disease characterized by hypertension, risk of hypotension, high risk of aspiration, and difficult airway. Therefore, the Meta-Analysis is intended to provide evidence on maternal and neonatal outcomes of preeclamptic parturient.

**Methods:** A comprehensive strategy was conducted in PubMed/Medline, Science Direct, and Cochrane from January 2000 to May 2020 without language restriction. The Heterogeneity among the included studies was checked with forest plot and  $I^2$  test. Observational and experimental studies reporting maternal and neonatal outcomes among preeclamptic and normotensive women were included.

**Results:** The Meta-Analysis revealed that pooled incidence of hypotension was reduced by thirty-eight percent in preeclamptic as compared to normotensive parturient, RR=0.62(95% confidence interval (CI): 0.52 to 0.75)

**Conclusion:** The Meta-Analysis revealed that the incidence of hypotension was lower in preeclamptic women when compared to normotensive women. The included studies were low to a very low quality of evidence which entails further randomized controlled trials.

**Registration:** This systematic review and meta-analysis was registered in Open science Network on June 6, 2020, and the registration is available at <https://osf.io/jcedt/>.

## 1. Introduction

Preeclampsia is a multisystem, highly variable disorder unique to pregnancy that typically occurs after 20 weeks of gestation and associated with significant maternal and neonatal morbidity and mortality worldwide (1–3). Maternal and neonatal mortality related to Preeclampsia is due to problems with cardiovascular, acute liver injury, hypoplacental perfusion, thrombocytopenia, and neurologic sequelae (4–10).

Several risk factors are mentioned in different works of literature including but not limited to chronic hypertension, diabetes mellitus, obesity, history of preeclampsia, primi-gravida, renal disease, autoimmune disease, older maternal age, multiple pregnancy, infection, genetic factors, and high altitude. However, studies revealed that smoking showed a protective effect in preeclampsia(5, 11).

Evidence showed that preeclampsia is associated with several maternal catastrophic problems in later life which include, ischemic heart disease, type 2 diabetes mellitus hypertension, and thromboembolism events. Besides, preeclampsia caused intrauterine retardation and preterm delivery which is associated with higher rates of infant respiratory distress syndrome, sepsis, broncho-pulmonary dysplasia, and neurodevelopmental disability in childhood (2, 5, 12, 13).

Despite a tremendous effort made by World Health Organization (WHO), the United Nations Children's Fund (UNICEF), the United Nations Population Fund (UNFPA), World Bank Group, the United Nations Population Division (UNPD) and other stakeholders strived to achieve the Millennium Development goals(14); the maternal and neonatal mortality is still very high(4, 15–23).

It is estimated that the global maternal mortality by the year 2015 was more than 303,000, and low and middle-income countries accounted for approximately 99% of the global maternal deaths. The sub-Saharan Africa countries alone accounting for 66% (201 000 while the Southern Asia region accounted for 66 000 maternal mortality in 2015(14).

More than 300, 000 mothers lost their lives worldwide due to pregnancy and pregnancy-related problems every year, and 99% (302,000) of them are from low and middle-income countries(24). Preeclampsia is the second leading cause of maternal mortality which accounted for 10%-15% of maternal and neonatal death and 15% of preterm deliveries worldwide, and the majority of deaths were from low and middle-income countries (4, 7, 17, 25–27).

A systematic review and meta-analysis showed that the global incidence of preeclampsia was 4.6%, and European, American, and African regions accounted for 17%, 9%, and 4% respectively(17).

A World Health Organization systematic analysis revealed that preeclampsia is the second cause of maternal death following hemorrhage accounted for 14% (343, 000) of global maternal death. It is the major cause of maternal death in developed regions counted for 12.9%( 19000) maternal death while Sub-Saharan Africa, Asia, and Latin America accounted for more than fifty percent of maternal mortality associated with hypertensive disorder of pregnancy(23).

A systematic review by Sobhy et al including 44 studies from low and middle-income countries showed that the risk of death from anesthesia in women undergoing obstetric procedures was

### 1.2 Per 1000 women who are responsible for 2-8% of all maternal deaths(4).

Management of preeclampsia is very challenging for anesthetists due to the heterogeneous clinical spectrum of the disease characterized by hypertension, intravascular dehydration, risk of hypotension, thrombocytopenia, acute liver injury, high risk of aspiration and difficult airway (17, 28–30).

Recent evidence showed that spinal anesthesia is associated with better maternal and neonatal outcomes as compared to general anesthesia (31–38). However, spinal anesthesia is associated with hypotension, nausea and vomiting, and cardiac arrest (39–43).

Observational studies showed that the hemodynamic impacts of spinal anesthesia are well tolerated in preeclamptic parturient as compared to none preeclamptic parturient (32, 35–38, 44). However, the body of evidence is still in demand on maternal and neonatal effects of spinal anesthesia in the

preeclamptic parturient. Therefore, this systematic review and Meta-Analysis is intended to provide evidence on maternal and neonatal outcomes of preeclamptic parturient that underwent cesarean section under spinal anesthesia.

## 2. Methods

### 2.1. Eligibility criteria

#### 2.1.1. Types of studies

All observational (cohort, case-controlled and cross-sectional) and experimental (randomized controlled trials, quasi-experimental, and cross-over) studies comparing maternal and neonatal outcomes in preeclamptic and none preeclamptic parturient who underwent cesarean section under spinal anesthesia without any language restriction from January 2000 up to January 2020 were incorporated.

#### 2.1.2. Types of participants

The participants were all preeclamptic and none preeclamptic pertinent who underwent cesarean sections under spinal anesthesia were included.

#### 2.1.3. Outcomes of interest

The primary outcomes of interests were incidence of hypotension, lowest mean arterial blood pressure, systolic blood pressure, and diastolic blood pressure, Apgar score at first and fifth minutes. A total vasopressor requirement, heart rate variability, total fluid requirement, and blood loss were the secondary outcomes.

#### 2.1.4. Context

This systemic review and Meta-Analysis incorporated all studies conducted globally and reporting outcomes of maternal and neonatal outcomes in preeclamptic and none preeclamptic parturient who underwent cesarean section under spinal anesthesia.

#### 2.1.5. Inclusion criteria

All observational (cohort, case-controlled and cross-sectional) and experimental (randomized controlled trials, quasi-experimental, and cross-over) studies conducted globally from January 2000 to January 2020 without language restriction which were published and unpublished articles were included.

#### 2.1.6. Exclusion criteria

Studies conducted among either preeclampsia or normotensive women alone to assess neonatal outcomes; studies that did not report relevant data; systematic and clinical reviews were excluded.

## 2.2. Search strategy

The search strategy was intended to explore all available published and unpublished studies on maternal and neonatal outcomes of preeclamptic and normotensive women undergoing cesarean section under spinal anesthesia. A three steps search strategy was employed from January, 200 to May 2020 without language restriction. An initial search on PubMed/Medline, Science direct and Cochrane library were carried out followed by an analysis of the text words contained in Title/Abstract and indexed terms. A second search was undertaken by combining free text words and indexed terms with Boolean operators. The third search was conducted with the reference lists of all identified reports and articles for additional studies. Finally, the additional and grey literature search was conducted on Google scholars up to ten pages. The result of the search strategy was presented with the Prisma flow chart (Fig. 1). The search strategy on PubMed/Medline was conducted as follows:

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Cesarean section[Title/Abstract] OR (caesarean section[Title/Abstract]) OR (cesarean delivery[Title/Abstract]) OR (operation[Title/Abstract]) AND (preeclampsia[Title/Abstract]) OR(preeclampsia[Title/Abstract])OR(hypertension[Title/Abstract])OR(pregnancy[Title/Abstract])AND(normotensive[Title/Abstract])OR(nonepreeclampsia[Title/Abstract])OR(hemodynamic[Title/Abstract]) OR (Apgar score[Title/Abstract]) OR (PH[Title/Abstract]) OR (Umbilical[Title/Abstract]) AND (vasopressor[Title/Abstract]) OR (ephedrine[Title/Abstract])OR(phenylephrine[Title/Abstract])OR(norepinephrine [Title/Abstract])
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## 2.3. Data extraction

The data from each study were extracted by SM and GM independently extracted the data with Microsoft excel format and imported for analysis in R software version 3.6.1 and Review manager version 5.3. Author, publication year, the mean age of participants, sample size, Country, types of study design, the incidence of hypotension and mean/ standard deviation of mean arterial blood pressure, systolic blood pressure, diastolic blood pressure, vasopressor requirement first and fifth minutes Apgar scores in each group were extracted.

## 2.4. Assessment of methodological quality

The methodological quality of the studies was assessed using the Newcastle-Ottawa Scale (NOS)(45). The criteria include three categories with a maximum score of nine points. The first is the 'selection' category which accounts for a maximum of four points, the second category is 'comparability' with a maximum point of two and the third category is 'outcome of interest' which counts a maximum of three points. The studies were categorized as high, moderate, and low quality if the total score is 7–9, 5–6, and 0–4 respectively. Studies with moderate to high methodological quality were included for data extraction (supplemental Table 1). The disagreements between the Authors appraising the articles were resolved through discussion.

## 2.5. Grading the quality of evidence

The overall qualities of evidence for the studied outcome were evaluated using the GRADE system (Grading of Recommendations Assessment, Development, and Evaluation)(46, 47). The system incorporates study quality (risk of bias), inconsistency (comparison of effect estimates across studies), indirectness (applicability of the population, intervention, comparator and outcomes to the clinical decision), imprecision (certainty of confidence interval) and high probability of publication bias. The overall quality of evidence was categorized as follows by evaluating and combining the above five parameters for the incidence of hypotension, vasopressor requirement, Apgar score, lowest systolic, mean arterial, and diastolic pressure.

- **Effective interventions:** indicated that the review found high-quality evidence of effectiveness for an intervention.
- **Possibly effective interventions:** indicated that the review found moderate-quality evidence of effectiveness for an intervention, but more evidence is needed.
- **Ineffective interventions:** indicated that the review found high-quality evidence of lack of effectiveness (or harm) for an intervention.
- **Probably ineffective interventions:** indicated that the review found moderate-quality evidence suggesting a lack of effectiveness (or harm) for an intervention, but more evidence is needed.
- **No conclusions possible:** indicated that the review found low or very low-quality evidence or insufficient evidence to comment on the effectiveness or safety of an intervention.

## 2.6. Data analysis

The pooled incidence of hypotension, lowest systolic blood pressure, diastolic blood pressure, mean arterial blood pressure, and the vasopressor requirement was determined with a fixed-effect model as there was no substantial heterogeneity. The Heterogeneity among the included studies was checked with forest plot,  $\chi^2$  test,  $I^2$  test, and the p-values. Substantial heterogeneity among the included studies was investigated with subgroup analysis and meta-regression. Sensitivity analysis was done to evaluate the influential studies and further analysis was made after removing the outliers.

Publication bias was checked with a funnel plot and the objective diagnostic test was conducted with Egger's correlation, Begg's regression tests, and Trim and fill method. Furthermore, moderator analysis was carried out to identify the independent predictors of maternal and neonatal outcomes. The results were presented based on the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA)(48).

## 3. Results

### 3.1. Protocol and registration

The systematic review and meta-analysis were conducted based on the Preferred Reporting Items for Systematic and Meta-analysis (PRISMA) protocols(48). This systematic review and meta-analysis was registered in Open science Network on June 6, 2020, and the registration is available at <https://osf.io/jcedt/>.

### 3.2. Characteristics of included studies

A total of 852 articles were identified from different databases as described in the methodology section with the Prisma flow diagram (Fig. 1). Twenty-three articles were selected for evaluation after the successive screening. Thirteen Articles with 848 participants comparing maternal and neonatal outcomes in preeclamptic and normotensive women undergoing cesarean section under spinal anesthesia were included (Table 1) and the rest were excluded with reasons (49–59).

The included studies were published from 2003–2018 with sample size ranged from 20 to 136.

The twelve included studies were conducted in Brazil (one study), Ethiopia (one study), Iran (one study), India (four studies), UK (one study), Macedonia (1 study), Finland (one study) and France (two studies).

Eleven of the included studies reported data for the primary outcomes while only one study didn't report quantitative data for primary and secondary outcomes.

The majority of included studies were conducted on different types of surgical specialties (eighteen studies) while five, two, one, and two studies were conducted on cancer, cardiac, obstetrics, and orthopedics respectively.

The majority of the included studies reported hemodynamic changes, Apgar scores, and vasopressor requirements among the groups. Nine studies reporting the incidence of hypotension while eight studies reported vasopressor requirements. Six studies used ephedrine and two studies preferred phenylephrine vasopressor for prevention and management of hypotension between the groups. The lowest mean systolic, diastolic, and arterial blood pressure was reported in ten and eight studies respectively. The neonatal outcome was evaluated with Umbilical PH, first and fifth minute Apgar score. Six studies reported the first and fifth minute Apgar scores while only one study reported Umbilical Blood PH.

Table 1  
description of included studies

Author	Year	Country	Sample	Design	Quality score
Aya et al(44)	2003	France	60	Prospective Cohort	8
Aya et al(32)	2005	France	136	Prospective Cohort	8
Clark et al(60)	2005	UK	40	Prospective Cohort	8
Tihtonen et al(37)	2006	Finland	20	Prospective Cohort	6
Mendes et al(61)	2011	Brazil	40	Prospective Cohort	5
Saha et al(36)	2013	India	60	Prospective Cohort	5
Mitra et al(38)	2016	India	100	Prospective Cohort	6
Nikooseresht et al(35)	2016	Iran	80	Prospective Cohort	9
Goel et al(62)	2017	India	50	Prospective Cohort	7
Chowdhury et al(50)	2018	India	62	Prospective Cohort	6
Sivevski et al(63)	2019	Macedonia	78	Prospective Cohort	7
Alemayehu et al(64)	2020	Ethiopia	122	Prospective Cohort	7

### 3.3. Meta-Analysis

This systematic review and Meta-Analysis was intended to provide evidence on the incidence of maternal and neonatal outcomes among preeclampsia and normotensive women undergoing cesarean section under spinal anesthesia.

#### 3.3.1. Incidence of hypotension

The incidence of hypotension was reported in nine studies. The Meta-Analysis revealed that pooled incidence of hypotension was reduced by thirty-eight percent in preeclamptic as compared to normotensive parturient, RR = 0.62(95% confidence interval (CI): 0.52 to 0.75, 9 studies, 696 participants) (Fig. 2).

**Figure 2** Forest plot for the incidence of hypotension comparing preeclamptic and normotensive parturient: individual cohorts and meta-analysis. Events, the total numbers with events (incidence of hypotension) in the intervention (preeclampsia) and control (normotensive) groups; Total, the total numbers of participants in the intervention and control groups; Weight, sample size contribution of the study relative to the pooled sample size of the meta-analysis; M-H, Mantel-Hansel methods.

#### 3.3.2. Lowest mean arterial blood pressure

The Meta-Analysis revealed that the lowest mean arterial blood pressure increased by 23 mmHg in preeclamptic as compared to normotensive parturient, MD = 22.72( 95% confidence interval(CI): 14.96 to 30.49, 8 studies, 686 participants) (Fig. 3).

**Figure 3.** Forest plot for lowest MAP comparing preeclamptic and normotensive parturient: individual cohorts and meta-analysis. Mean the lowest MAP (mean arterial blood pressure) in the intervention (preeclampsia) and control (normotensive) groups; Total, the total numbers of participants in the intervention and control groups; Weight, sample size contribution of the study relative to the pooled sample size of the meta-analysis; M-H, Mantel-Hansel methods.

#### 3.3.3. Lowest mean systolic and diastolic blood pressure

The Meta-Analysis included nine studies reporting the lowest mean systolic blood pressure between preeclampsia and normotensive women. The pooled mean systolic blood pressure increased by twenty-nine percent in preeclamptic women as compared to normotensive women, MD = 28.64(95% confidence interval(CI): 20.19 to 37.09, 9 studies, 726 participants) (Fig. 4). Besides, the Meta-Analysis showed that diastolic blood pressure was maintained in preeclamptic women as compared to normotensive women, MD = 17.91(95% confidence interval(CI): 11.31 to 24.52, 10 studies, 766participants) (supplemental Fig. 1).

#### 3.3.4. First minute Apgar score

The Meta-Analysis showed that the first minute Apgar score was lower in preeclamptic women as compared to normotensive women, MD=-0.88(95% confidence interval(CI): -1.29 to -0.47, 6 studies, 444 participants) (Fig. 5). However, the systematic review and Meta-Analysis didn't show a significant difference between preeclamptic and normotensive women on the fifth minute Apgar score, MD= -0.25(95% confidence interval (CI): -0.69 to 0.29, 6 studies, 444 participants) (supplemental Fig. 2).

#### 3.3.5. Vasopressor requirements

The majority of the included studies reported the amount of vasopressor consumed between the groups. The ephedrine and phenylephrine requirement reduced in preeclamptic women when compared to normotensive women as depicted with the Meta-Analysis, MD=-6.78(95% confidence interval (CI): -8.14 to

-5.41, 6 studies, 434 participants) and MD=-100.34 (95% confidence interval (CI): -117.41 to -83.27, 2 studies, 150 participants) respectively (**supplemental Fig. 3**).

### 3.4. Sensitivity analysis and publication bias

Sensitivity analysis was conducted to identify the most influential study on the pooled summary effect and we didn't find significant influencing the summary effect.

Publication bias was investigated with funnel plot asymmetry and Egger's regression, Begg's rank correlation test, and trim fill method. The trim fill showed that two large standard error studies were missed but the rank correlation test didn't show a significant difference (P-value < 0.1194) (**Fig. 6**).

**Figure 6** Funnel plot and trim fill funnel plot to assess publication bias. The vertical line indicates the effect size whereas the diagonal line indicates the precision of individual studies with a 95% confidence interval.

## 4. Discussion

The maternal and neonatal mortality among preeclamptic women was very high. Anesthesia-related maternal mortality among preeclamptic women accounted for 20% (4). Recent evidence studies showed that maternal and neonatal outcomes in preeclamptic women were superior in spinal anesthesia as compared to general Anesthesia (53, 65–69). However, hypotension and bradycardia were the most common undesirable consequences of spinal anesthesia particularly in hemodynamically unstable patients (31, 70–72).

Observational studies showed that spinal anesthesia is better tolerated in stable preeclamptic women as compared to normotensive parturient who underwent cesarean section under spinal anesthesia (16, 32, 36–38, 44, 50, 63, 64). But there is no high-quality evidence supporting the superiority of hemodynamic stability in preeclamptic to normotensive women under Spinal Anesthesia.

Therefore, this systematic review and Meta-Analysis was intended to provide evidence on maternal and neonatal outcomes of preeclamptic women as compared to normotensive who underwent cesarean section under spinal anesthesia

The Systematic review and Meta-Analysis revealed that the incidence of hypotension was higher in normotensive when compared to preeclamptic a woman which is in line with included observational studies (16, 32, 35–37, 44, 50, 63, 64). However, prospective cohort studies by Mendes et al and Mitral et al didn't show a significant difference between the groups on the incidence of hypotension (38, 61). The possible explanation for this discrepancy might be due to the small sample size with observational studies where different confounders were not controlled appropriately.

The Meta-analysis showed that the mean systolic, diastolic, and arterial blood pressures were better in preeclamptic women as compared to normotensive women. This finding is comparable with included individual studies but contrary to a study by Mendes et al where mean arterial blood pressure didn't show significant differences between the groups.

The Meta-Analysis also revealed that the first Apgar score was better in normotensive women as compared to preeclamptic women that are in line with observational studies conducted (35, 44) but other observational studies by (32, 61) showed a different result where the first Apgar score was not different between the groups. This discrepancy might be due to the inclusion of a small sample size which is observational in which confounding is unavoidable. However, the fifth minute Apgar score didn't show the significant difference which is in line with all included studies.

The systematic review and Meta-Analysis showed that the vasopressor requirement was higher in normotensive women when compared to preeclamptic counterparts who are in line with all included studies except one study by Mendes et al where the requirement of ephedrine dose requirement didn't show a significant difference between normotensive and preeclamptic women.

### 4.1. Quality of evidence

The systematic review and meta-analysis included only prospective Cohort studies. The methodological quality of included studies was moderate to high quality as depicted with the Newcastle-Ottawa Scale (NOS) for meta-analysis of Cohort studies. The overall quality of evidence was graded with GRADEpro online software for the outcomes including the incidence of hypotension, mean systolic blood pressure, mean diastolic blood pressure, mean arterial blood pressure, first Apgar score and vasopressor requirement. The GRADEpro summary table showed that the overall quality of evidence was low to very low (**supplemental Table 2**).

### 4.2. Limitation of the study

The review incorporated Cohort studies with small sample size and some of the included studies didn't report relevant outcomes that limit the precision of effects size. The overall quality of evidence was low to very low which entails randomized controlled trials with large sample size to provide conclusive evidence.

### 4.3. Implication for practice

Body of evidence revealed that maternal and neonatal mortality related to Anesthesia was very high particularly with preeclampsia and eclampsia. The right choice of anesthetic management is very crucial to reduce preventable maternal and neonatal outcomes. Spinal anesthesia showed better outcomes as compared to general anesthesia in stable preeclamptic women despite the catastrophic hemodynamic impacts of spinal anesthesia. However, high-quality randomized trials with high power are required before providing a strong recommendation.

## 4.4. The implication for further research

The Meta-analysis revealed that maternal and neonatal outcomes were better in preeclamptic women as compared to normotensive women. However, all of the included studies were observational studies with small sample size and the overall quality of evidence was low to very low which entails further randomized controlled trial studies with high power.

## 5. Conclusion

The Meta-Analysis revealed that the incidence of hypotension was lower in preeclamptic women when compared to normotensive women. However, the first Apgar score was better in normotensive when compared to preeclamptic women. The included studies were low to a very low quality of evidence which entails further randomized controlled trials with a large sample size.

## Declarations

## Ethics approval and consent to participate

Not applicable

## Consent for publication

Not applicable

## Availability of data and materials

Data and material can be available where appropriate.

## Competing interests

The authors declare that there are no competing interests

## Funding

No funding was obtained from any organization

## Authors' contributions

SA conceived the idea and designs the study. GM involved in searching strategy, data extraction, quality assessment, analysis, and manuscript preparation. All Authors have read and approved the manuscript

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## Figures

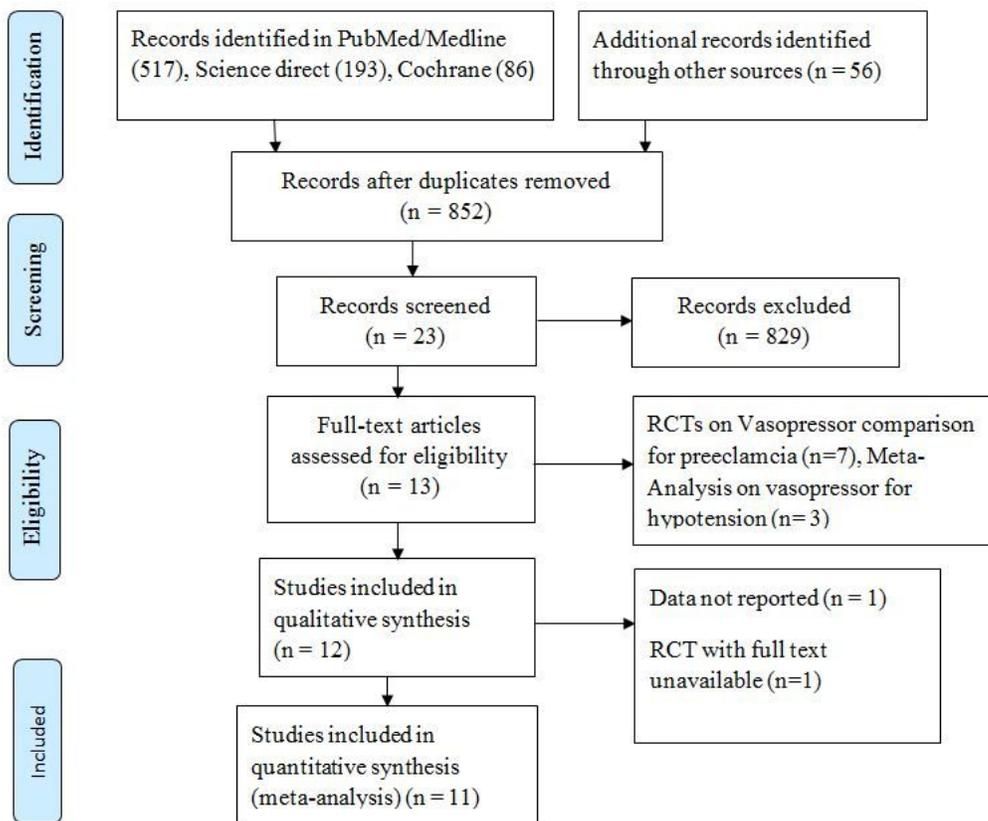


Figure 1

Prisma flow chart

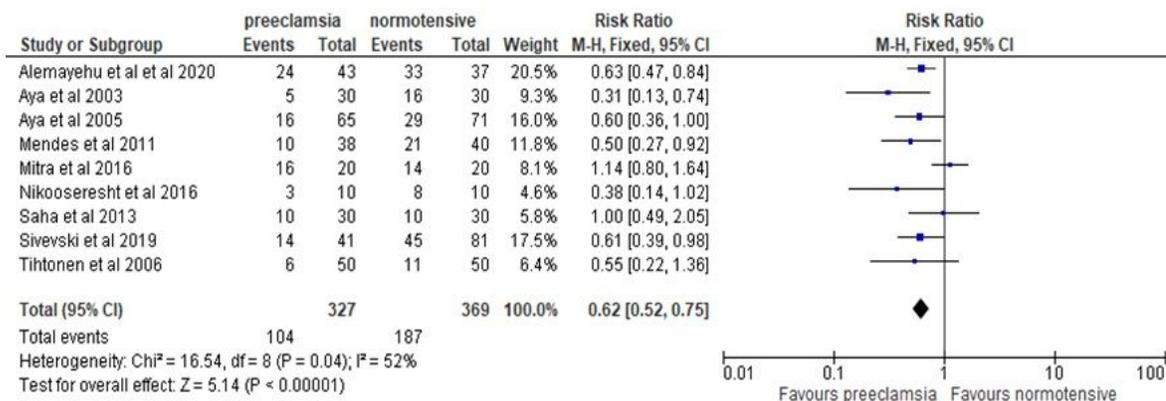


Figure 2

Forest plot for the incidence of hypotension comparing preeclamptic and normotensive parturient: individual cohorts and meta-analysis. Events, the total numbers with events (incidence of hypotension) in the intervention (preeclampsia) and control (normotensive) groups; Total, the total numbers of participants in the intervention and control groups; Weight, sample size contribution of the study relative to the pooled sample size of the meta-analysis; M-H, Mantel-Hansel methods.

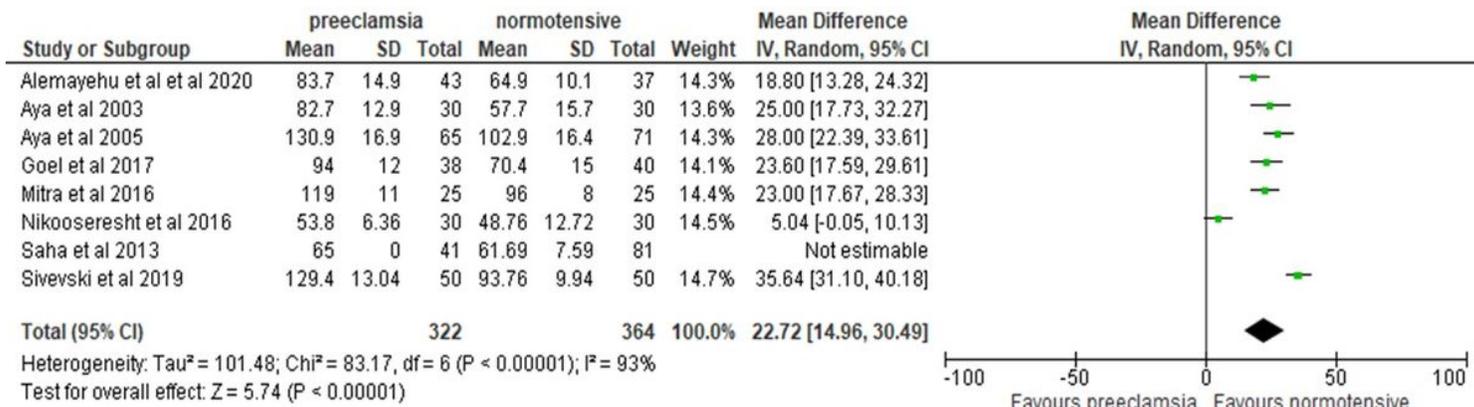


Figure 3

Forest plot for lowest MAP comparing preeclamptic and normotensive parturient: individual cohorts and meta-analysis. Mean the lowest MAP (mean arterial blood pressure) in the intervention (preeclampsia) and control (normotensive) groups; Total, the total numbers of participants in the intervention and control groups; Weight, sample size contribution of the study relative to the pooled sample size of the meta-analysis; M-H, Mantel-Hansel methods.

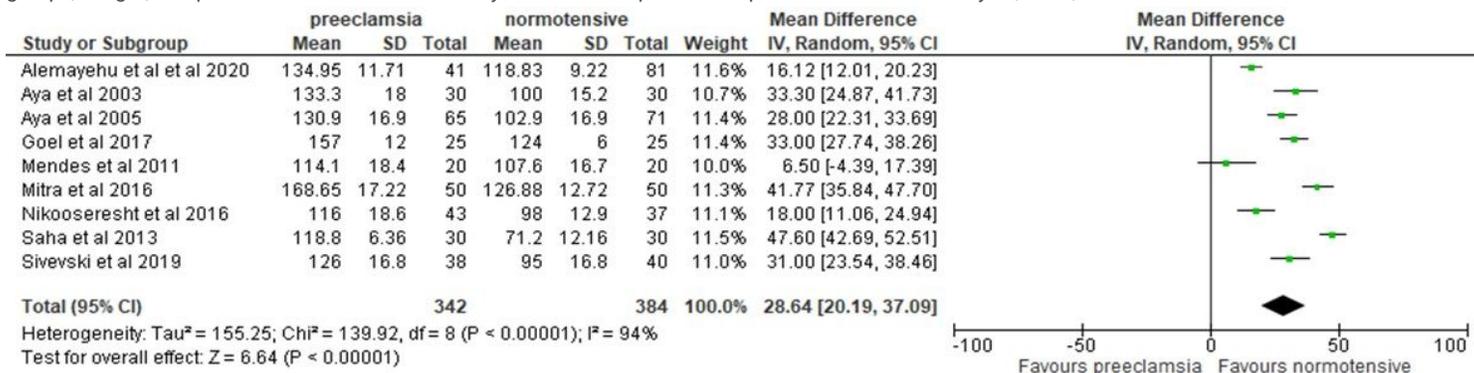
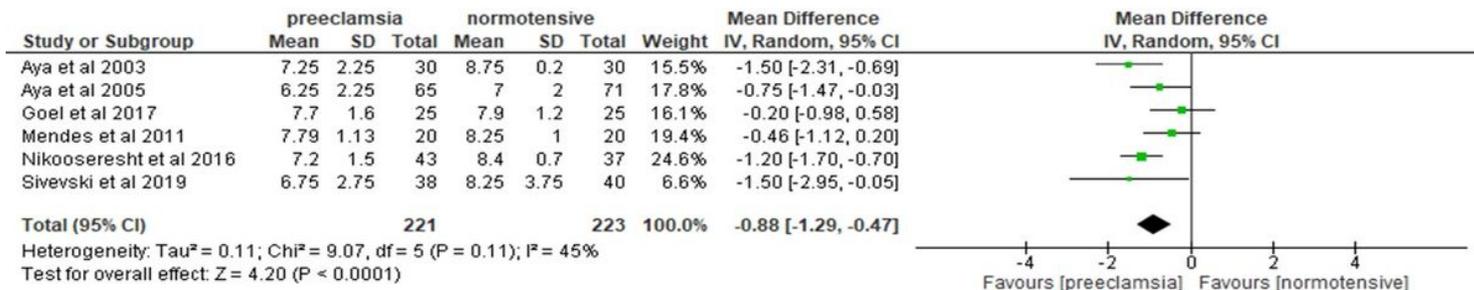
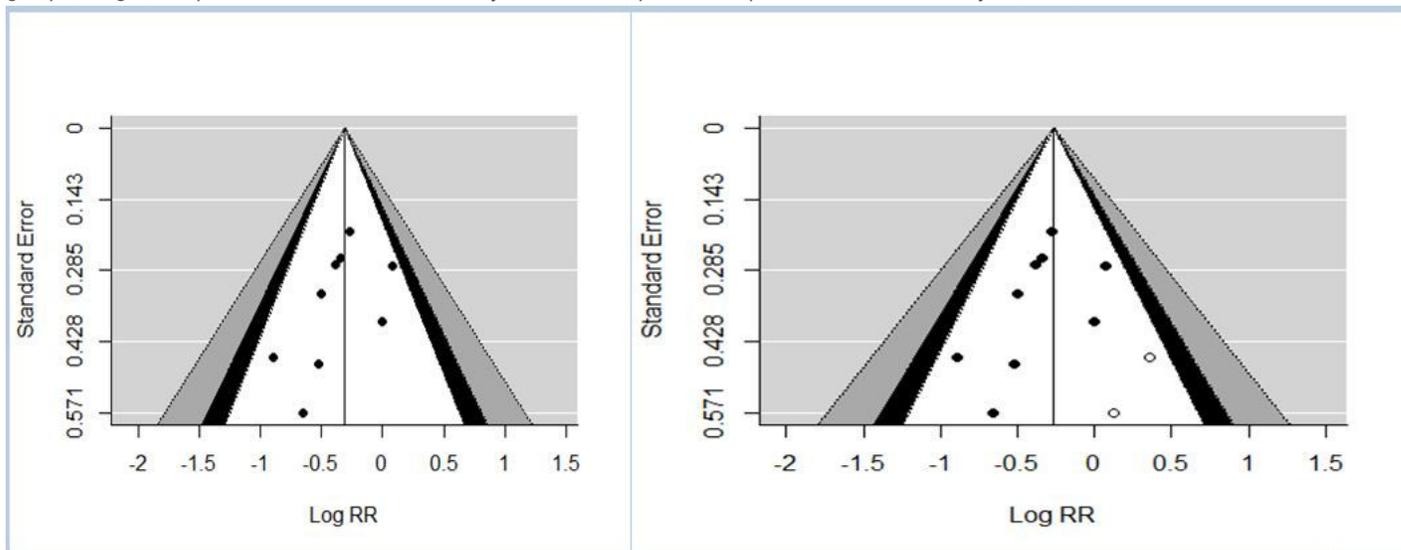


Figure 4

Forest plot for systolic blood pressure comparing preeclamptic and normotensive parturient: individual cohorts and meta-analysis. Mean the mean lowest SBP (lowest systolic blood pressure) in the intervention (preeclampsia) and control (normotensive) groups; Total, the total numbers of participants in the intervention and control groups; Weight, sample size contribution of the study relative to the pooled sample size of the meta-analysis; M-H, Mantel-Hansel methods.



**Figure 5**  
 Forest plot for first minute Apgar score comparing preeclamptic and normotensive parturient: individual cohorts and meta-analysis. Mean the First minute Apgar score in the intervention (preeclampsia) and control (normotensive) groups; Total, the total numbers of participants in the intervention and control groups; Weight, sample size contribution of the study relative to the pooled sample size of the meta-analysis; M-H, Mantel-Hansel methods.



**Figure 6**  
 Funnel plot and trim fill funnel plot to assess publication bias. The vertical line indicates the effect size whereas the diagonal line indicates the precision of individual studies with a 95% confidence interval.

## Supplementary Files

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