Comparative efficacy and safety of antihypertensive agents in preeclampsia and gestational hypertension uncontrolled and their long-term effects on offspring

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Abstract

Background: Hypertensive disorder of pregnancy (HDP), a common obstetric complication that seriously threatens maternal and infant health. The current clinical treatment drugs include methyldopa, calcium channel blockers, etc. In order to provide evidence-based medicine for the treatment and medication of gestational hypertension, this study compared the efficacy and safety of different drugs in the treatment of gestational hypertension through network meta-analysis. Methods: Search and select relevant articles in the published and unpublished available data from Controlled Trials, PsycINFO, CINAHL,, etc. To assess the efficacy and safety of HDP treatment, 4 primary outcomes [SBP, DBP, perinatal fetal deaths, and NICU cases] and 9 secondary outcomes were selected. Results: 50 articles with 8212 participants were included. Low molecular weight heparin (LMH), Labetalol + LMH and Labetalol + Methyldopa can reduce DBP, and Ambrisentan + Methyldopa can prevent the occurrence of severe hypertension. Methyldopa and Atenolol were associated with lower rates of preterm birth, and Nifedipine, Methyldopa as well as Labetalol reduced the incidence of placental abruption. Ambrisentan + Nifedipine, Methyldopa, Labetalol + Nimodipine, Labetalol + LMH, Labetalol and LMH significantly reduced the incidence of postpartum complications. Magnesium sulfate (SM) and SM+ LMH can prolong the mean gestational age, LMH and Kethyldopa can reduce perinatal fetal death. Conclusions: LMH, labetalol, Methyldopa, labetalol in combination with LMH, and labetalol in combination with Methyldopa have better efficacy and safety.

Introduction

Hypertensive disease of pregnancy (HDP) includes gestational hypertension, pregnancy complicated with

chronic hypertension, chronic hypertension complicated with preeclampsia, preeclampsia and eclampsia, mainly manifested as hypertension and proteinuria, which is a common obstetric complication[1, 2]. Epidemiological studies show that the incidence of hypertensive diseases in pregnancy is 5.2-8.2%[3], and increases with the increasing maternal age and increasing occurrence rate of obesity, diabetes[4, 5], anxiety[6]and depression, and pregnancy complications[7, 8]. This disease seriously threatens the safety and health of mothers and infants, as one of the important causes of increased risk and death of pregnant women, fetuses and newborns. Relevant clinical data show that hypertensive disease in pregnancy can lead to an increase in the incidence of cesarean section, teratogenesis, maternal death, premature delivery, stillbirth, neonatal intensive care unit, and small for gestational age[9, 10]. For pregnant women with gestational hypertension disease, the risk of developing classic cardiovascular risk factors including renal insufficiency, dyslipidemia, diabetes and subclinical atherosclerosis during the third trimester of pregnancy, on average, is two times higher than that of women with normal pregnancy, and the prevalence and incidence depend on the severity of hypertensive disease during pregnancy[11]. Furthermore, due to poor intrauterine growth, hypertensive disorders in pregnancy may result in long-term vascular[12-14], cognitive and psychiatric sequelae[15, 16], and atopic disorders[17] in offspring. Existing antihypertensive drugs include Methyldopa, calcium channel blockers, beta blockers and diuretics[18]. As angiotensin converting enzyme inhibitors and angiotensin receptor blockers have been established to have teratogenic effects, their use in pregnant women is prohibited. At present, drugs commonly used in the treatment of hypertension during pregnancy include labeolol, methyldopa and nifedipine[19, 20]. However, there are no clear guidelines or consensus on the clinical decision of the treatment of hypertensive diseases in pregnancy. The choice of antihypertensive therapy in pregnancy is still controversial. In order to provide evidence-based medical basis for the treatment and medication of hypertensive diseases in pregnancy, this study compared different drugs in curative effect and safety of gestational hypertension disease by network meta-analysis.

Methods

This study follows the PRISMA (Preferred Reporting Item for Systematic Reviews and Meta-Analyses) statement for network meta-analyses (Supplementary Table 1). This systematic review was pre-registered in the International Prospective Database of Systematic Reviews (PROSPERO), revision document (CRD42022296086), and did not require ethical approval as it involved completed study results. Author statements, all supporting data are available in the article and its supplementary materials.

Search strategy and data extraction

We searched Controlled Trials, PsycINFO, CINAHL, PubMed, LILACS database, MEDLINE, Embase, MEDLINE In-Process, the websites of regulatory agencies, and international registers for published and unpublished, double-blind, randomised controlled trials from their inception to January 2, 2022, without language restrictions. The search terms we used were 'gestational hypertension', 'eclampsia', 'preeclampsia', 'treatment', 'drug' and their corresponding synonyms. The search results were independently screened by 2 reviewers (XC and WF) who searched and reviewed the full text of all relevant reports. Data were extracted by 3 reviewers (JZ, BL and XY) using review-specific forms. Disagreements were resolved through mutual consultation or consultation with a third investigator until consensus was reached.

Selection criteria

Studies will be included if they met the following criteria: (1) randomized controlled trials (RCTs) of antihypertensives for pregnancy hypertension, regardless of pregnancy hypertension type, previous antihypertensive treatment, or multiple gestation; (2) pregnant women aged 18 years or older with systolic blood pressure $>$ 140mmHg and/or diastolic blood pressure $>$ 90mmH and able to swallow oral medication of gestation (including pregnant women with preeclampsia); (3) antihypertensive therapy was any pharmacological intervention to lower blood pressure (BP), regardless of route of administration or place of care, and comparators were placebo, no antihypertensive, or another antihypertensive;(4) Treatment duration was [?] 5 days and the minimum follow-up period was 10 months. The exclusion criteria were: (1) non-RCTs, studies with insufficient data, duplicated publications, conference reports, systematic reviews; (2) the treatment plan of

the experimental group is only traditional Chinese medicine treatment or diet treatment.

Outcome measures

The main outcomes of this network meta-analysis were mean systolic blood pressure (SBP) after medication, mean diastolic blood pressure (DBP) after medication, perinatal fetal deaths, and the number of Neonatal Intensive Care Unit (NICU) cases.

The secondary outcomes included postpartum complications, mean gestational age, cesarean section, fetal distress, placental abruption, preeclampsia, small-for-gestational-age infants, and preterm births.

For continuous variables (ie, mean systolic blood pressure and mean diastolic blood pressure after medication), the difference from baseline (mean change) and its standard deviation (SD) at the end of treatment for treatment and comparison groups were extracted[21]. For dichotomous outcomes (ie, perinatal fetal death, preterm birth, number of NICU cases, small for gestational age, fetal distress, etc.), the total number of patients (N) and the number of patients with events (r) were extracted[22].

Quality assessment

Individual studies were assessed for risk of bias according to the Cochrane Handbook method for systematic reviews of interventions[23]. The following domains were assessed: random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective reporting (reporting deviations), and other deviations[24]. The overall risk of bias will be determined as low (all items are low risk, or at least 5 items are low risk and the remaining 2 items are unclear), unclear (>2 items with unclear risk), and high ([?]1 recommended high bias in the quality dimension). Two investigators independently assessed risk of bias for included studies. If there is any disagreement, it will be decided by consensus of the arbitration panel[25].

Network meta-analysis

Network evidence maps were constructed using STATA17.0 software. Differences between interventions were compared using Bayesian network meta-analysis. Results were presented as pooled estimates of odds ratio (OR) or weighted mean difference (WMD) (95% CI)[26]. We used a concordance model and an inconsistency model to assess the overall level of inconsistency of the study[27]. In addition, we used node splitting to determine local consistency between direct and indirect evidence[28]. To explain OR or WMD, the surface area under the cumulative ranking curve (SUCRA) was used to assess the ranking of each treatment modality. The value of SUCRA ranges from 1 to 0, with an area of 1 representing the best and an area of 0 representing the worst[29]. However, the interpretation of SUCRA needs to be interpreted with caution based on the existence of a statistical difference. We excluded articles at high risk of bias to assess the robustness and reliability of our trial results. We used funnel plots to assess whether our study was subject to publication bias[30].

Results

The outcomes of literature search are described in Appendix 1. Our search identified N=7152 publications, from electronic databases (N=7086), the relevant Cochrane review (N=12), and Citation searching (N=54), and 105 potentially qualified articles were retrieved. The majority of them were excluded due to duplicate publications, records flagged as ineligible by automated tools, etc. Subsequently, the articles that did not meet the inclusion criteria were excluded. Specifically, 7 studies were non-RCTs, 31 studies used only traditional Chinese medicine treatment or diet treatment, while 13 studies had a minimum follow-up period of less than 10 months. In addition, 2 studies retrieved by other methods were replicated with studies retrieved by database. Finally, a total of 50 articles[31-80] with 8212 participants were included in this study (Figure 1). Figure 2 shows the assessment of risk of bias with the Cochrane Risk of Bias tool.

Study selection

The methodological characteristics of the included studies are presented in Table 1. The meta-analysis was based on 4 studies included in review and 46 reports of included studies. The majority of studies recruited patients from Asia (56.9%) and Europe (21.6%), while 6 studies (11.8%) included patients from North America, 3 studies (5.9%) from Africa and the remaining 2 studies from Panama and Argentina. Magnesium sulfate (SM) was administered primary therapy in all study patients in 13 studies, and aspirin was used for preeclampsia prophylaxis in high-risk women in 6 studies. The main characteristics of patients are summarized in Table 2.

Network Characteristics

For current clinically commonly used drugs for the treatment of hypertension and each primary outcome, the number of trials in each analysis ranged from 10 to 34, with 2418 to 5840 participants. 41 trials had 2 treatment arms and 9 trials had 3 treatment arms each, except for 1 trial which had 4 treatment arms. Node-splitting analyses were performed to test inconsistencies in network of all outcome indicators. The results indicated that there is no significant difference between the direct and indirect analysis results ($P > 0.05$), suggesting that a consistency model should be applied to perform the meta-analysis. Figure 3 and Figure 4 shows the network of eligible comparisons for the pooled maternal outcomes and neonatal outcomes.

Main Outcomes

Perinatal fetal death

As for perinatal fetal death, there were 34 RCTs (5887 patients) compared the effectiveness of 15 drug regimens with placebo included in total. There was a statistically significant reduction in perinatal fetal death for LMH (OR, 0.27, 95% CI, 0.09–0.81), Kethyldopa (OR, 0.05, 95% CI, 0.00–0.81) versus Placebo. On the basis of the SUCRA, Kethyldopa (SUCRA: 88.1%) ranked first among all the treatments, followed by magnesium sulphate (SM) combined with low molecular weight heparin (LMH) (SUCRA: 82.9%). OR for perinatal fetal death from network meta-analysis was shown in Supplementary Table 2. SUCRA results were demonstrated in Table 3.

Neonatal Intensive Care Unit (NICU) cases

In NICU cases, there were 13 RCTs (2347 patients) compared the effectiveness of 5 drug regimens with placebo included in total. There was a reduction in NICU cases for LMH (OR, 0.59, 95% CI, 0.21–1.65), Labetalol (OR, 0.79, 95% CI, 0.36–1.74), Methyldopa (OR, 0.69, 95% CI, 0.40–1.20), Nifedipine (OR, 0.83, 95% CI, 0.41–1.68), Pravastatin (OR, 0.47, 95% CI, 0.10–2.30) versus Placebo, but none of these results were statistically significant. In the SUCRA, the top three of all treatments were Pravastatin (SUCRA: 71.2%), LMH (SUCRA: 64.2%) and Methyldopa (SUCRA: 59.9%). OR for NICU cases from network meta-analysis was shown in Supplementary Table 3. SUCRA results were demonstrated in Table 3.

SBP

In terms of the primary efficacy measure, SBP, a total of 22 RCTs (2395 patients) compared the effectiveness of 12 drug regimens with placebo. The results showed that Nifedipine (WMD, 2.15, 95% CI, 2.51–6.81) were statistically inferior to placebo. The results also presented that AlphaMethyldopa (WMD, -1.70, 95% CI, -7.54–4.15), Atenolol (WMD, -1.08, 95% CI, -4.15–1.98), Ketanscrin (WMD, -0.97, 95% CI, -6.81–4.88), LMH (WMD, -0.19, 95% CI, -3.07–2.68), Labetalol combined with LMH (WMD, -0.56, 95% CI, -6.39–5.27), Labetalol combined with Methyldopa (WMD, -1.30, 95% CI, -4.82–2.22), Methyldopa (WMD, -2.32, 95% CI, -5.59–0.95), Oxprenolol (WMD, -2.11, 95% CI, -8.05–3.84), SM (WMD, -0.36, 95% CI, -3.72–3.00), SM combined with LMH (WMD, -0.44, 95% CI, -3.80–2.92) were superior to placebo, while Labetalol (WMD, 1.28, 95% CI, -1.80–4.35) were inferior to placebo, but the above results were not statistically significant. According to the SUCRA, Labetalol combined with LMH (80.0%), Labetalol combined with Methyldopa (69.2%), and Alphanmethyldopa (67.0%) had the highest probabilities of being the best treatment options. WMD for SBP from network meta-analysis was shown in Supplementary Table 4. SUCRA results were demonstrated in Table 3.

DBP

In terms of the primary efficacy measure, DBP, a total of 15 RCTs (1715 patients) compared the effectiveness of 10 drug regimens with placebo. The results showed that LMH (WMD, -3.41, 95% CI, -4.79—2.02), Labetalol combined with LMH (WMD, -2.99, 95% CI, -4.48—1.51) and Labetalol combined with Methyldopa (WMD, -1.29, 95% CI, -2.15—0.43) were statistically superior to placebo. The results also presented that Alphamethyldopa (WMD, -0.44, 95% CI, -1.93–1.05), Labetalol (WMD, -0.77, 95% CI, -1.62–0.09) and Nifedipine (WMD, -0.05, 95% CI, -1.26–1.16) were superior to placebo, while Atenolol (WMD, 0.06, 95% CI, -0.74–0.86), Ketanscrin (WMD, 0.43, 95% CI, -1.06–1.92), Methyldopa (WMD, 0.52, 95% CI, -0.45–1.50), and Oxprenolol (WMD, 0.52, 95% CI, -1.03–2.08) were inferior to placebo, but the above results were not statistically significant. According to the SUCRA, LMH (98.0%), Labetalol combined with LMH (91.3%), and Labetalol combined with Methyldopa (74.2%) had the highest probabilities of being the best treatment options. WMD for DBP from network meta-analysis was shown in Supplementary Table 5. SUCRA results were demonstrated in Table 3.

Additional outcome

Postpartum complications

A total of 17 RCTs (3985 patients) compared the efficacy of 7 drug regimens with placebo on small for postpartum complications. Compared to Placebo, Ambrisentan combined with Nifedipine (OR, 0.21, 95% CI, 0.11–0.39), Methyldopa (OR, 0.17, 95% CI, 0.11–0.25), Labetalol combined with Nimodipine (OR, 0.04, 95% CI, 0.04–0.18), Labetaloll combined with LMH (OR, 0.14, 95% CI, 0.04–0.47), Labetalol(OR, 0.22, 95% CI, 0.13–0.37) and LMH (OR, 0.40, 95% CI, 0.20–0.83) significantly reduced the incidence of postpartum complications. According to the SUCRA, Labetalol combined with Nimodipine (98.1%) had the highest probabilitie of being the best therapeutic options. OR for postpartum complications from network meta-analysis was shown in Supplementary Table 6. SUCRA results were demonstrated in Table 3.

Mean gestational age

A total of 24 RCTs (3161 patients) compared the efficacy of 14 drug regimens with placebo on the secondary efficacy measure, mean gestational age. The results showed that LMH combined with SM (WMD, 2.25, 95% CI, 1.06–3.45) and SM (WMD, 1.48, 95% CI, 0.29–2.67) were statistically superior to placebo. As for the SUCRA, LMH combined with SM (99.4%), SM (90.0%), and LMH (73.5%) were more likely to be the best treatment option. WMD for Mean gestational age from network meta-analysis was shown in Supplementary Table 7. SUCRA results were demonstrated in Table 3.

Cesarean section

A total of 24 RCTs 4769 patients) compared the efficacy of 12 drug regimens with placebo on cesarean section. Compared to Placebo, Pravastatin (OR, 2.90, 95% CI, 0.07–117.54), Nifedipine (OR, 1.09, 95% CI, 0.33–3.57), Methyldopa (OR, 1.42, 95% CI, 0.62–3.26) and Labetalol (OR, 1.04, 95% CI, 0.30–3.63) increased the incidence of cesarean section, while SM combined with LMH (OR, 0.17, 95% CI, 0.01–2.94), SM (OR, 0.35, 95% CI, 0.05–2.55), Oxprenolol (OR, 0.84, 95% CI, 0.10–7.38), Labetalol combined with Nimodipine (OR, 0.31, 95% CI, 0.03–3.40), Labetalol combined with Methyldopa (OR, 0.19, 95% CI, 0.01–3.15), LMH (OR, 0.77, 95% CI, 0.21–2.80), Kethyldopa (OR, 0.72, 95% CI, 0.10–5.11) and Atenolol (OR, 0.48, 95% CI, 0.11–2.03) reduced the incidence of cesarean section. However, the above results were not statistically significant. According to the SUCRA, SM combined with LMH (79.4%), Labetalol combined with Methyldopa (77.2%) and Labetalol combined with Nimodipine (70.6%) had the highest probabilities of being the best therapeutic options. OR for cesarean section from network meta-analysis was shown in Supplementary Table 8. SUCRA results were demonstrated in Table 3.

Fetal distress

A total of 10 RCTs (1354 patients) compared the efficacy of 7 drug regimens with placebo on fetal distress.

Compared to Placebo, Pravastatin (OR, 1.20, 95% CI, 0.42–3.41), Nifedipine (OR, 1.79, 95% CI, 0.54–5.97), Methyldopa (OR, 1.15, 95% CI, 0.68–1.94) and Labetalol (OR, 1.40, 95% CI, 0.60–3.25) increased the incidence of fetal distress, while SM (OR, 0.10, 95% CI, 0.01–1.95), Labetalol combined with Nimodipine (OR, 0.08, 95% CI, 0.00–1.59) and LMH (OR, 0.79, 95% CI, 0.36–1.73) reduced the incidence of fetal distress. However, there was no statistically significant difference between drugs and Placebo. According to the SUCRA, Labetalol combined with Nimodipine (SUCRA: 90.2%) ranked first among all the treatments, followed by SM (SUCRA: 87.1%). OR for fetal distress from network meta-analysis was shown in Supplementary Table 9. SUCRA results were demonstrated in Table 3.

Placental abruption

A total of 13 RCTs (2514 patients) compared the efficacy of 7 drug regimens with placebo on placental abruption. Compared to Placebo, Nifedipine (OR, 0.32, 95% CI, 0.12–0.84), Methyldopa (OR, 0.23, 95% CI, 0.14–0.38) and Labetalol (OR, 0.33, 95% CI, 0.14–0.78) significantly reduced the incidence of placental abruption. According to the SUCRA, SM (82.7%), Methyldopa (72.6%) had the highest probabilities of being the best therapeutic options. OR for placental abruption from network meta-analysis was shown in Supplementary Table 10. SUCRA results were demonstrated in Table 3.

Preeclampsia cases

A total of 21 RCTs (5105 patients) compared the efficacy of 11 drug regimens with placebo on the additional efficacy measure, preeclampsia cases. The results showed that the incidence of preeclampsia after treatment with SM combined with LMH (OR, 1.00, 95% CI, 0.01–80.02), SM (OR, 1.00, 95% CI, 0.01–80.02), LMH (OR, 1.00, 95% CI, 0.01–78.85) were the same as with placebo. Compared to Placebo, Nifedipine (OR, 1.75, 95% CI, 0.32–9.47), Methyldopa (OR, 1.23, 95% CI, 0.52–2.93), Labetalol (OR, 1.11, 95% CI, 0.35–3.48), Furosemide (OR, 1.93, 95% CI, 0.09–43.25) and Aspirin (OR, 1.21, 95% CI, 0.02–58.57) increased the incidence of preeclampsia, while Kethyldopa (OR, 0.58, 95% CI, 0.08–4.43), Atenolol (OR, 0.25, 95% CI, 0.06–1.15) and Amlodipine (OR, 0.91, 95% CI, 0.12–6.86) reduced the incidence of preeclampsia. However, the above results were not statistically significant. When it comes to SUCRA, Atenolol (SUCRA: 83.9%) ranked first among all the treatments, followed by Kethyldopa (SUCRA: 63.6%). OR for preeclampsia cases from network meta-analysis was shown in Supplementary Table 11. SUCRA results were demonstrated in Table 3.

Small for gestational age neonates (SGA)

A total of 11 RCTs (3479 patients) compared the efficacy of 4 drug regimens with placebo on SGA. The results showed that the incidence of SGA after treatment with Methyldopa (OR, 1.00, 95% CI, 0.56–1.76) was the same as with placebo. Compared to Placebo, Nifedipine (OR, 1.12, 95% CI, 0.35–3.61) and Labetalol (OR, 1.24, 95% CI, 0.57–2.72) increased the incidence of SGA, while Atenolol (OR, 0.24, 95% CI, 0.05–1.07) reduced the incidence of SGA. However, the above results were not statistically significant. According to the SUCRA, Atenolol (97.1%) have the highest probabilities of being the best therapeutic options. OR for SGA from network meta-analysis was shown in Supplementary Table 12. SUCRA results were demonstrated in Table 3.

Preterm births

A total of 21 RCTs (5223 patients) compared the efficacy of 8 drug regimens with placebo on preterm births. Compared to Placebo, Methyldopa (OR, 0.57, 95% CI, 0.35–0.94) and Atenolol (OR, 0.03, 95% CI, 0.01–0.09) significantly reduced the incidence of preterm births. According to the SUCRA, Atenolol (98.8%) had the highest probabilities of being the best therapeutic options. OR for Preterm births from network meta-analysis was shown in Supplementary Table 13. SUCRA results were demonstrated in Table 3.

Severe hypertension

A total of 10 RCTs (2711 patients) compared the efficacy of 5 drug regimens with placebo on the additional efficacy measure, severe hypertension. Compared to Placebo, Ambrisentan combined with Methyldopa

(OR, 0.31, 95% CI, 0.14–0.13) significantly reduced the incidence of severe hypertension. According to the SUCRA, Methyldopa (68.8%), Kethyldopa (68.2%), Labetalol (61.2%) and Nifedipine (60.7%) had the highest probabilities of being the best therapeutic options. OR for severe hypertension from network meta-analysis was shown in Supplementary Table 14. SUCRA results were demonstrated in Table 3.

Sensitivity analyses

The sensitivity analyses were consistent with the primary analysis results. The results were shown in Supplementary Table 15 and Table 16. 1-4.

Publication bias

The funnel plots were shown in Supplementary Figure 1-4.

Discussion

The present meta-analysis collected current data on the treatment of chronic hypertension in pregnancy and compared the efficacy and safety of all drugs that are routinely used in the clinic. High quality evidence suggested that the combination of Ambrisentan and Methyldopa can prevent the occurrence of severe hypertension. Moreover, LMH alone, Labetalol combined with LMH and Labetalol combined with Methyldopa can reduce DBP in pregnant women, but no drugs can reduce SBP in pregnant women, Nifedipine is even inferior to placebo in reducing SBP. None of the drugs analyzed in this study could reduce the incidence of preeclampsia. Despite the limited data available, Methyldopa and Atenolol were associated with significantly lower rates of preterm birth, and Nifedipine, Methyldopa as well as Labetalol significantly reduced the incidence of placental abruption. Based on the RCTs included in this analysis on primary antihypertensive therapy for gestational hypertension, Ambrisentan combined with Nifedipine, Methyldopa, Labetalol combined with Nimodipine, Labetalol combined with LMH, Labetalol and LMH significantly reduced the incidence of postpartum complications. This network meta-analysis also shows that SM alone or combined with LMH can prolong the mean gestational age, and both LMH and Kethyldopa can reduce perinatal fetal death. But there was no evidence that drugs (vs. placebo/no treatment) have a statistically significant effect on other maternal outcomes (including caesarean) or perinatal outcomes (including SGA, neonatal intensive care unit admission, and fetal distress), although effect estimates were imprecise. It is obvious that LMH, labetalol, Methyldopa, labetalol in combination with LMH, and labetalol in combination with Methyldopa have better efficacy and safety.

Retrospective analyses of existing studies on the control of gestational hypertension indicated that severe hypertension is associated with higher rates of miscarriage, neonatal unit admissions, and low birth weight[81]. Many national and international guidelines generally recommend drug therapy to normalize gestational blood pressure in patients with gestational hypertensive disorders whose blood pressure cannot be controlled through diet[82]. Treatment options include calcium channel blockers, beta-blockers, Methyldopa or multidrug therapy[83], and Labetalol is currently recommended as first-line therapy[84, 85]. The results of our analysis also show that SM, Labetalol, Methyldopa alone or in combination with other drugs (such as LMH, Ambrisentan, etc.) are generally superior to placebo/no treatment in terms of efficacy, however, the safety problems of drug treatment cannot be ignored. Our findings are consistent with conventional meta-analyses refuting beta-blocking drugs, reporting that alpha- and beta-blocker (Labetalol) exposure may increase the risk of SGA[86]. Although the result was not statistically significant, several studies have shown that the use of drugs to block beta receptors during pregnancy is associated with higher rates of low birth weight and very low birth weight infants[87]. There are several mechanisms by which blockade of beta receptors affects fetal growth[88], the most notable of which is that they lower blood pressure by inhibiting adrenergic receptors, slowing heart rate, reducing myocardial contractility. However, its negative inotropic effect may reduce the cardiac output of the mother and the fetus[89], thereby affecting placental perfusion and fetal development, and even causing neonatal ventricular malformations, cardiovascular and neural tube defects, cleft lip or cleft palate, etc. Especially, there is a greater risk of using Labetalol during the month. Furthermore, Labetalol may exacerbate bronchospasm and should not be used in pregnant women with poorly controlled asthma[90]. Also, there is a risk of hypoglycemia following Labetalol exposure[91]. But these effects were absent in pa-

tients exposed to Methyldopa. Still, concerns about Methyldopa persist, as the drug is thought to increase the risk of postpartum depression[92].

It is well known that in non-pregnant women with hypertension, lower doses of 2 or more drugs that work in different ways are more effective and safer than single drug use (especially high doses)[93, 94]. However, for hypertensive pregnant women, different outcome measures have different interpretations on the selection of monotherapy or drug combination and how to combine drugs. Neither Labetalol plus LMH nor Labetalol plus Methyldopa reduced DBP as much as LMH alone, but only ambrisentan plus Methyldopa reduced the incidence of severe hypertension in this analysis. In reducing the incidence of perinatal fetal death, LMH or Kethyldopan alone is more feasible. LMH combined with SM is more effective in prolonging gestational age than SM alone. Nifedipine, Methyldopa or Labetalol alone can significantly reduce the incidence of placental abruption, Methyldopa or Atenolol alone can reduce the risk of preterm birth, while the effect of combined medication on placental abruption and premature birth was not statistically significant. In terms of reducing the incidence of postpartum complications, the effects from large to small are Labetalol combined with Nimodipine, Labetalol combined with LMH, Methyldopa, Ambrisentan combined with Nifedipine, Labetalol, LMH. Simply, SM or Labetalol in combination with other drugs is superior in prolonging gestational age and reducing postpartum complications, while in reducing the incidence of placental abruption, preterm birth, and perinatal fetal death, the single drug treatment regimen is better.

The choice of treatment should be individualized based on the phenotype (eg, race and age, comorbidities) and physiology (eg, heart rate, blood glucose) of patients with gestational hypertension[1, 95], in addition to focusing on pregnancy outcomes assessed in RCTs. On the other hand, the availability of drugs also needs to be considered[96]. Many South American countries have not obtained the production and sales license of labetalol[97], and only a few countries such as the United Kingdom and Australia produce methyldopa[98].

In conclusion, for patients with gestational hypertension, in order to reduce the risk of mother and fetus, it is necessary to take timely drug treatment. SM, Labetalol and Methyldopa are currently the best drugs in clinical use for the treatment of hypertensive disorders in pregnancy. It is recommended that in the absence of contraindications, SM should be used as the basic treatment drug, combined with Labetalol or Methyldopa to treat hypertensive pregnant women. At the same time, the treatment plan should be adjusted according to the actual situation of each patient to individualized drug delivery. During drug treatment, it is necessary to closely monitor the blood glucose, cardiac output, mood, etc. of pregnant women, as well as growth and development, cardiac output and other related indicators of fetal.

Strengths and limitations of the study

This meta-analysis retrieved all available evidence in this field through multiple approaches, and evaluated the efficacy of 18 drugs alone or in combination on hypertensive disorders in pregnancy. The population assessed was representative and sufficient, covering 13 outcomes, almost all of the possible outcomes of hypertensive disorders in pregnancy, and thus providing real-world evidence that is directly relevant to clinical practice.

However, interpretation of caesarean section results may be problematic due to a lack of information on elective and emergency surgery rates. Moreover, the few included studies only addressed certain endpoints, notably NICU cases, severe hypertension, placental abruption, SGA, fetal distress, and therefore, the effects of drugs on these results will need to be replicated in more clinical studies before firm conclusions can be drawn. At the same time, studies on SM and LMH are almost exclusively conducted in Asian populations, so the evaluation of these two drugs is imperfect.

Conclusion

It is suggested that Nifedipine may increase the risk of SBP in pregnant women when used in the treatment of hypertensive diseases of pregnancy and Ambrisentan combined with Methyldopa can prevent the occurrence of severe hypertension. Drugs such as SM and Labetalol can improve multiple pregnancy outcomes for both the mother and the fetus. SM, Labetalol and Methyldopa are recommended as the priority drugs for the clinical treatment of hypertensive pregnant women. However, in clinical drug selection, the specific

conditions of different patients (including physiological period and economic conditions, etc.) must be taken into account to provide individualized treatment.

Abbreviations: BP=blood pressure, DBP=diastolic blood pressure, HDP= Hypertensive disease of pregnancy, LMH=low molecular weight heparin, NICU= Neonatal Intensive Care Unit, OR=odds ratio, PROSPERO=International Prospective Database of Systematic Reviews, PRISMA= Preferred Reporting Item for Systematic Reviews and Meta-Analyses), RCTs=randomized controlled trials, SBP= systolic blood pressure, SD=standard deviation, SUCRA= urface area under the cumulative ranking curve, SM=magnesium sulphate, WMD= weighted mean difference

Disclosure statement

All authors declare that they have no competing interests.

Data availability

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

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Author contributions

XC, WF and JZ conceived and designed the study. BL, WJ and HH selected the articles and extracted the data. DT wrote the first draft of the article. XY interpreted the data and wrote the article's final version. All authors agreed with the results and conclusions of this article. XC, WF and XY took responsibility for the integrity of the data and the accuracy of the data analysis, including and especially any adverse effects.

Modification of the protocol

If we need to amend this protocol, we will give the date of each amendment, describe the change and give the rationale in this section. Changes will not be incorporated into the protocol.

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