American Journal of Clinical Case Reports

Research Article

# Efficacy and Safety of Pharmacological Treatments for Pregnancy-Induced Hypertension: A Systematic Review and Network Meta-Analysis

*Shuo Zhang[1,2], Kui-Wu Yao[2*], Zhen-Lin Chen[3,4], Jia-Jia Li[3], Shi-Jun Yue[3] and Yu-Ping Tang[3*]*

[1]*Graduate School, Beijing University of Chinese Medicine, Beijing 100029, China*

[2]*Guang'anmen Hospital, China Academy of Chinese Medical Sciences, Beijing 100053, China*

[3]*Key Laboratory of Shaanxi Administration of Traditional Chinese Medicine for TCM Compatibility, and State Key Laboratory of Research & Development of Characteristic Qin Medicine Resources (Cultivation), and Shaanxi Key Laboratory of Chinese Medicine Fundamentals and New Drugs Research, and Shaanxi Collaborative Innovation Center of Chinese Medicinal Resources Industrialization, Shaanxi University of Chinese Medicine, Xi'an 712046, Shaanxi Province, China*

[4]*International Programs Office, Shaanxi University of Chinese Medicine, Xi'an 712046, Shaanxi Province, China*

## Abstract

**Introduction:** To conducted a Bayesian network meta-analysis to determine the efficacy, safety and precision of pharmacological treatment for pregnancy-induced hypertension (PIH).

**Methods:** Randomized controlled trials were searched in 11 electronic databases from their establishment to October 31, 2021. Randomized controlled trials which using drugs to treat women with hypertension during pregnancy were included. The traditional pair-wise meta-analysis was done by using Stata 15, and Bayesian network meta-analysis was done with Win BUGS version 14.3. The dichotomous and continuous variable were described by relative risk and mean difference, 95% confidence interval was used in all outcomes

**Results:** 47 trials were included with 5717 participants and 19 drugs. The traditional pair-wise meta-analysis was performed by using Stata 15 and Bayesian network meta-analysis was done with Win BUGS version 14.3. The results showed that nifedipine and hydralazine had the most significant effects on systolic blood pressure and diastolic blood pressure, respectively. Labetalol and nifedipine were the safest treatment for pregnant women, and methyldopa and labetalol were the safest treatment for newborns and fetuses, respectively.

**Conclusions:** This study was the first most large-scale and comprehensive research of pharmacological treatments for PIH. The results showed that nifedipine had good efficacy and no obvious adverse reactions. So we think that it should be firstly recommend for PIH treatment, especially for severe hypertension. Our findings will help experts develop new guidelines for PIH treatment to better guide clinical medication for protecting the health of pregnancy women and offspring.

**Keywords: Antihypertensive; Hypertension; Meta-analysis; Offspring; Pregnancy**

## Abbreviations

CrI: Credibility Intervals; DBP: Diastolic Blood Pressure; MD: Mean Difference; PIH: Pregnancy-Induced Hypertension; RR: Relative Risk; SBP: Systolic Blood Pressure; Who: World Health Organization

**Citation:** Zhang S, Yao K-W, Chen Z-L, Li J-J, Yue S-J, Tang Y-P. Efficacy and Safety of Pharmacological Treatments for Pregnancy-Induced Hypertension: A Systematic Review and Network Meta-Analysis. Am J Clin Case Rep. 2022;3(1):1053.



**Publisher Name**: Medtext Publications LLC

**Manuscript compiled:** Jan 20th, 2022

***Corresponding author:** Kui-Wu Yao, Guang'anmen Hospital, China Academy of Chinese Medical Sciences, Beijing 100053, China. E-mail: yaokuiwu@126.com

Yu-Ping Tang, Key Laboratory of Shaanxi Administration of Traditional Chinese Medicine for TCM Compatibility, Shaanxi University of Chinese Medicine, Xi'an 712046, Shaanxi Province, China, Tel/Fax: 0086-029-3818-4350; E-mail: yupingtang@sntcm.edu.cn

## Introduction

Pregnancy-Induced Hypertension (PIH) is a form of high blood pressure during pregnancy, which is defined as Systolic Blood Pressure (SBP) ≥140 mmHg and/or Diastolic Blood Pressure (DBP) ≥90 mmHg on the basis of measurements in office/clinic settings. And it may be divided into 3 grades: mild (SBP 140 ~ 149 mmHg and DBP 90 ~ 99 mmHg), moderate (SBP 150 ~ 159 mmHg and DBP 100 ~ 109 mmHg) and severe (SBP ≥ 160 and DBP ≥ 110 mmHg) [1]. Hypertensive disorders of pregnancy are classified into (1) chronic hypertension diagnosed before pregnancy or 20 weeks' gestation, (2) gestational hypertension diagnosed at ≥ 20 weeks, (3) pre-eclampsia defined as gestational hypertension with proteinuria or the end-organ manifestation consistent with pre-eclampsia [2]. According to the WHO, PIH affects approximately 5 to 10 percent of all pregnant women in the word and is the major cause of maternal, neonatal and fetal morbidity and mortality [3]. It remains the scourge of obstetrics practice as well. The identification of superimposed pre-eclampsia in pregnant women with chronic hypertension requires special vigilance, which is an extremely serious life-threatening episode in women [4]. A large number of pregnant and lying-in women died from PIH all

over the world [5], accounting for approximately 80% of maternal deaths. Antihypertensive treatment is recommended for women with chronic hypertension, as it has been suggested to reduce the risk of severe maternal hypertension. The common antihypertensive drugs for PIH include labetalol (a non-selective α and β blocker), nifedipine (a calcium channel blocker), methyldopa (anα2 adrenergic agonist) and hydralazine (a vasodilator) [6]. Thiazide diuretics are used occasionally during pregnancy [7]. Although these drugs have been used for several decades, there is no consensus on the relative efficacy and safety of drugs for pregnancy women with chronic hypertension. Currently, the main treatment strategy for PIH is only based on expert opinions and clinical observation without more evidences from randomized controlled trials [8]. It is a challenging task to comprehensively analyze the current clinical evidences on the efficacy and safety of pharmacological treatments for PIH by using traditional meta-analysis methods due to the lack of head-to-head trials that directly compare certain treatments among existing trials. Bayesian network meta-analysis enables the comparison of multiple interventions to incorporate clinical evidence from both direct and indirect treatment comparisons in a network of treatments and associated trials [9], which can quantify the effects of different interventions on the treatment of the same disease, and rank the effectiveness of a certain outcome index, so as to help decision makers choose the best treatment plan [10-12]. Although some published meta-analyses have also studied the efficacy and safety of drug treatment for PIH [13,14], the results only showed that clinical efficacy of several drugs was similar without comprehensive sequencing of drugs, and they cannot guide clinical precision medication. So it is important to conduct a comprehensive network meta-analysis to rank the compacting drugs and draw a systematic conclusion. This study aimed to comprehensively evaluate the precise efficacy and safety of pharmacological treatments for PIH and to find out the therapeutic characteristics of each drug. And the effects of each drug on the mother, fetus and newborn were fully considered, which filled a crucial gap in precision medicine. Our findings will help experts to improve guidelines for PIH.

## Methods

This Bayesian network meta-analysis was conducted and reported following the PRISMA [15] with Cochrane methodology [16]. This study has been registered and the PROSPERO number is CRD42020205069.

### Literature search

From the establishment of each electronic databases to October 31, 2021, randomized controlled trials using medicine to treat PIH were searched in the following 11 electronic databases: Medline, Embase, Cochrane Library, PubMed, Web of Science, Springer link, ClinicalTrials.gov, the Chinese National Knowledge Infrastructure, Chinese Biomedical Literature Database, Wan fang Database and Weipu Database. A supplementary manual search was performed for relevant references of PIH. MeSH terms were used, and trials will be included if the title, original title, abstract, name of substance word, subject heading word, keyword, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word or unique identifier contained both "gestational" or "pregnant" or "pregnancy" and "random". All literature searches were limited to pregnant women with hypertension. And we do not specify the language and status of publications in our literature search. Additionally, we manually searched bibliographies of included trials and related articles for additional references.

### Inclusion criteria

**Types of studies:** This network meta-analysis included randomized controlled trials, in which some drugs were used to treat PIH. Trials were excluded if: (a) they were not randomized; (b) no control group was used; (c) no drugs aimed to reduce blood pressure; (d) they had indeterminacy of measurement index outcome criterion; (e) no data could be extracted from the outcomes in the trial; (f) case reports, reviews, experience sharing, etc.; (g) they were animal experiments; (h) repeatedly published articles and plagiarized studies.

**Types of participants:** This study included women with hypertension during pregnancy, defined as SBP greater than 140 to 169 mmHg and DBP more than 90 mmHg. Women were chosen regardless of prior antihypertensive treatment, proteinuria, single pregnancy or multiple pregnancies. And we have no restrictions on race. However, women were excluded if they gave birth before the trial began or had other medical conditions.

**Types of interventions:** Trials comparing antihypertensive drugs with placebo or different antihypertensive drugs were included. Trials were excluded if the same drug was compared among different dosage forms. Trials that contained the drugs which aimed at reducing the risk of PIH progressing to pre-eclampsia but were not antihypertensive ones were also excluded.

**Types of outcome measures:** The primary outcome was defined as blood pressure which included SBP and DBP, as well as maternal adverse reaction. The secondary outcomes included clinical effect, mean arterial pressure, mean pulse, fetal adverse reactions and neonatal adverse reactions.

### Study selection and data extraction

Two researchers who participated in training and calibration exercises before starting the screening processes independently screened the titles and abstracts of potential eligible trials which were in duplicate, then they retrieved independently and reviewed the full text of the possible trials in duplicate based on the inclusion and exclusion criteria and compared their results. If there was disagreement, they agreed through discussion, or submitted it to a third party for evaluation. The screening process was conducted in Endnote X9. Then according to the inclusion and exclusion criteria mentioned above, the two researchers used standardized tables to independently extract data in duplicate from all eligible trials. In case of disagreement, they agreed through discussion or submitted it to a third party.

### Assessment of risk of bias

Two reviewers assessed the methodological quality of each included study independently by using ROB 2.0, which comprised the following 7 aspects: random sequence generation, allocation concealment, blind method, incomplete result data, selective reporting, and other biases. The quality assessment results of each item can be divided into three grades: "low risk", "high risk" and "unclear". The more rigorous the design and the higher the methodological quality of each RCT, the lower the risk coefficient. If none of the above 7 aspects was reported in the trial, the aspect was considered to be "unclear". When necessary, the consensus on this issue was studied with the help of a third party.

### Data analysis

The traditional pair-wise meta-analysis was done by using Stata 15 (StataCorp, College Station, TX, USA) and Bayesian network meta-

analysis was done with Win BUGS version 14.3 (MRC Biostatistics Unit, Cambridge, UK). Both the continuous and dichotomous outcomes were derived from the included trials without any conversion. The dichotomous outcomes were described by Relative Risk (RR) and 95% Credibility Intervals (CrI), and Mean Difference (MD) and 95% CrI were used to describe the effect value of the inter-group comparison. Heterogeneity was determined according to the results of $I^2$ test. $I^2$< 50% indicated the low heterogeneity of inter-study, and the fixed effect model was adopted. Furthermore, the random effect model was adopted when $I^2$> 50% [17]. Direct estimates of any two interventions were obtained by pooling data from clinical trials which compared the same interventions face to face. And the mixed treatment comparison estimates of interventions were obtained by combining direct clinical trial data for comparative interventions with the indirect estimates between the interventions through a common comparator. Normal prior distributions, non-informative uniform and 3 different sets of starting values were used to fit the model 4 chains, 2.5 initial values scaling, 20000 tuning iterations, 50000 simulation iterations and 10 thinning interval were used to obtain the posterior distributions of model parameters. Subgroup analysis was used to evaluate the therapeutic effects among different drugs. Inverted funnel plots and Egger's regression test were used to determine publication bias when the number of included studies exceeded 10 in the network meta-analysis [18].

## Results

### Study selection

Based on the above retrieval strategy, a total of 2614 potentially relevant trials were retrieved from 11 electronic databases, and 1725 trials were retrieved after 889 duplicates were deleted. After screening the titles and abstracts, 1412 articles were excluded because they did not comply with the inclusion criteria, and 313 trials initially met the predetermined requirements and their full texts were read for detailed assessment. Finally, 47 trials were included for meta-analysis [19-65]. The PRISMA flow diagram of literature retrieval process was shown in Figure 1. All included trials have been published as full article.

### Study characteristics

Table 1 summarized the basic characteristics of the eligible 47 trials, all of which were published in English. And a total of 5717 women with PIH and 19 drugs were included. Sample sizes ranged from 16 to 894. In these 47 trials, 8 were multicenter randomized controlled ones [22,25,27,28,31,38,52,58], and 7 were three-arms ones [22,25,36,40,57,59,64]. Figure 2 provided the network plot of all the trials included and each outcome. Figure 3 showed the pooled hazard ratios of different drugs for outcomes. In addition, the specific percentage ranking of competing drugs was revealed in Table S1, and the drug ranking histogram was shown in Figure S1.

### Risk of bias

The methodological quality of 47 eligible trials was summarized in Table S2, and the criteria in the Cochrane Handbook for Systematic Reviews of Interventions were used to assess the risk of bias in the study [16]. Although all included trials were declared randomized, 10 trials did not report the adequate sequence generation, 1 trial was drawn by lottery and 1 used medical order, which might lead to high risk. 23 and 21 trials did not report whether allocation concealment and the blind method were used respectively. Figure 3 provided the funnel plot of the trials, indicating that there was no obvious publication bias in the trials. Most of the outcomes showed small heterogeneity between

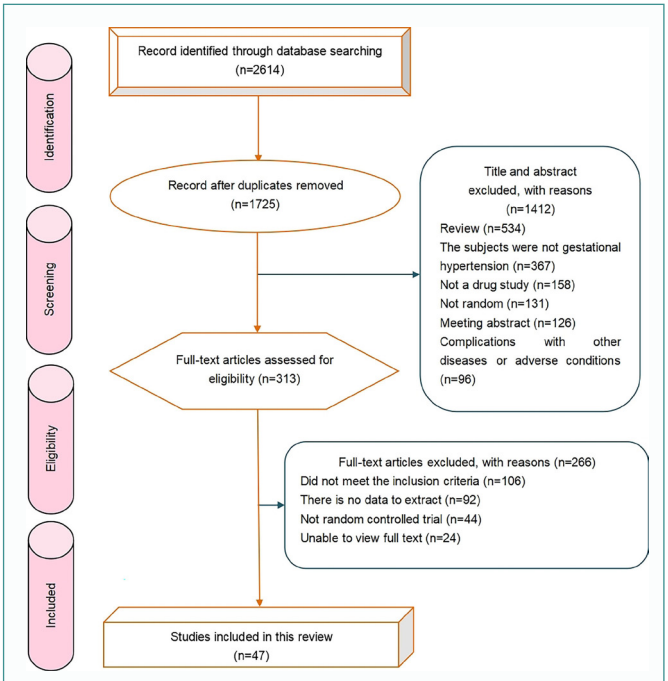



**Figure 1**: PRISMA flow diagram of literature selection.

included trials, but a few showed slightly higher heterogeneity, which may be related to the usage among different races.

### Outcomes

**Blood pressure:** The levels of SBP and DBP at baseline and after intervention were reported in 19 trials of 1695 patients [20,24,27,28,31,32,37,40,44-46,48,50,57,58,60,62-64]. These trials contained a total of 13 antihypertensive drugs. Figure S3 and 4 provided the forest plots for the network meta-analysis of each relevant drug. Only one trial comparing nicardipine with labetalol exhibited an obvious difference in SBP (MD,0.55; 95% CrI,0.04 to 1.07) [50], and the meta-analysis found that using hydralazine alone could lower DBP better than its combination with pindolol (MD,-0.83; 95% CrI,-1.45 to -0.22) [60]. Although agnesium sulfate could remarkably reduce SBP (MD,1.36; 95% CrI,0.99 to 1.73) and DBP (MD,1.74; 95% CrI,1.34 to 2.13) comparing to nifedipine [20], SBP (MD,-4.35; 95% CrI,-5.56 to -3.05) and DBP (MD,-4.00; 95% CrI,-5.23 to -2.78) were significantly decreased in methyldopa group compared with pindolol [62], all of which contained only one trial. In comparison to placebo, metoprolol established a significant lowering effect on DBP (MD, 0.89; 95% CrI, 0.32 to 1.46) [63], and oxprenolol could reduce more SBP (MD, 1.55; 95% CrI, 1.16 to 1.93) and DBP (MD, 1.75; 95% CrI, 1.35 to 2.15), 64 but labetalol showed a poor efficacy in SBP (MD, -1.81; 95% CrI, -2.27 to -1.34) and DBP (MD, -1.99; 95% CrI, -2.47 to -1.51) [40]. The results of network meta-analysis showed that nifedipine was the most effective drug for reducing SBP, followed by methyldopa, labetalol and hydralazine. And it also identified that hydralazine had the most significant effects for decreasing DBP.

**Maternal adverse reaction:** Maternal adverse reactions referred to all adverse reactions that occurred to pregnant woman in each trial. 41 trials involving 5396 patients and 19 kinds of drugs reported maternal adverse reaction [19,21-23,25-30,32-43,45-53,55-64], the forest plots of the network meta-analysis of all relevant drugs were exhibited in Figure S5. Meta-analysis identified that maternal adverse

**Table 1:** Characteristic of the 47 trials included in the Bayesian network meta-analysis.

| Author(s) | Country | Race | Gestational weeks | Age | Sample size (experimental/ control) | Time frame (y) | Contrast drugs | Outcome measures |
|---|---|---|---|---|---|---|---|---|
| Sahai | India | Black | ≥ 34 weeks | 20-45 years | 30/30 | 2016.10-2017.9 | nifedipine *vs.* labetalol | neonatal and fetal adverse reaction |
| Xiang | China | Yellow | 24-36 weeks | 21-42 years | 59/59 | 2017.4-2018.6 | magnesium sulfate + nifedipine *vs.* magnesium sulfate | blood pressure, clinical effect, |
| Easterling | India | Black | ≥ 28 weeks | ≥ 18 years | 298/295/301 | 2015.4-2017.8 | nifedipine *vs.* labetalol *vs.* methyldopa | clinical effect, neonatal adverse reaction |
| Jamil | India | Black | ≥ 28 weeks | 21.2±5.2/20.86±4.2 years | 30/30 | 2008.9-2010.4 | nifedipine*vs.* labetalol | neonatal adverse reaction |
| Salama | Egypt | White/ Black | 6-10 weeks | 20-40 years | 166/160/164 | 2017.8-2018.8 | methyldopa *vs.* nifedipine *vs.* placebo | maternal, neonatal and fetal adverse reaction |
| Wen and Li | China | Yellow | 28-39 weeks | 20-34 years | 80/80 | 2016.9-2018.2 | phentolamine + nifedipine + magnesium sulfate *vs.* magnesium sulfate | clinical effect, maternal and neonatal adverse reaction |
| Gainder | India | Black | 26-40weeks | NR | 15/15 | 2012.7-2013.11 | nifedipine *vs.* labetalol | blood pressure |
| Patel | India | Black | ≥ 28 weeks | NR | 76/76 | 2015.12-2016.11 | labetalol *vs.* hydralazine | blood pressure, mean arterial pressure, maternal and neonatal adverse reaction |
| Wajid | Pakistan | White | ≥ 20 weeks | 20-35 years | 165/165 | NR | Labetalol *vs.* hydralazine | maternal adverse reaction |
| Khan | Pakistan | White | 24-37 weeks | ≥ 15 years | 39/39 | 2012.11-2013.4 | labetalol *vs.* hydralazine | blood pressure and mean arterial pressure |
| Sharma | India | Black | ≥ 24 weeks | 18-45 years | 30/30 | 2014.12-2015.9 | nifedipine *vs.* hydralazine | maternal and neonatal adverse reaction |
| Shabnum | Pakistan | White | ≥ 20 weeks | 20-35 years | 50/50 | 2016.8-2017.1 | labetalol *vs.* hydralazine | maternal adverse reaction |
| Webster | The UK | White | ≥ 20 weeks | ≥ 18 years | 56/58 | 2014.8-2015.10 | labetalol *vs.* nifedipine | blood pressure, mean arterial pressure, maternal and neonatal adverse reaction |
| Liu | China | Yellow | 3-15 weeks | 18-50 years | 50/48 | 2012.10-2015.10 | aspirin *vs.* placebo | maternal and fetal adverse reaction |
| Sabir | Pakistan | White | ≥ 20 weeks | 25.2±4.68/25.1±5.11 years | 50/50 | 2014.11-2015.11 | nifedipine *vs.* hydralazine | maternal and fetal adverse reaction |
| Singh | India | Black | ≥ 34 weeks | < 30 years | 50/50 | 2013.10-2015.9 | labetalol *vs.* hydralazine | blood pressure, mean arterial pressure, pulse, maternal and fetal adverse reaction |
| Bijvanka | The Netherlands | White | ≤ 32 weeks | ≥ 18 years | 15/15 | NR | ketanserin *vs.* dihydralazine | clinical effect, maternal, neonatal and fetal adverse reaction |
| Delgado | Panama | White/ Black | ≥ 24 weeks | 26.3±7.1/26.5±6.8 years | 130/131 | 2012.7-2013.5 | labetalol *vs.* hydralazine | blood pressure, mean arterial pressure and maternal adverse reaction |
| Gracia | Panama | White/ Black | ≤ 20 weeks | 34.1±5.3/34.5±4.8 years | 21/20/29 | 2010.1-2012.9 | furosemide *vs.* amlodipine *vs.* aspirin | maternal, neonatal and fetal adverse reaction |
| Shekhar | India | Black | ≥ 24 weeks | 18-45 years | 30/30 | 2012.10-2013.4 | labetalol *vs.* nifedipine | maternal, neonatal and fetal adverse reaction |
| Dhali | India | Black | ≥ 22 weeks | 20-35 years | 50/50 | NR | labetalol *vs.* nifedipine | maternal and neonatal adverse reaction |
| Lakshmi | India | Black | ≥ 28 weeks | 23.4±3.8/ 24.6±3.3 years | 50/50 | 2008.9-2010.4 | labetalol *vs.* nifedipine | maternal, neonatal and fetal adverse reaction |
| Molvi | India | Black | 20-38 weeks | 25.66±2.76/25.18±4.08/24.94±2.59 years | 50/49/50 | 2005.8-2007.1 | labetalol *vs.* methyldopa *vs.* placebo | blood pressure, maternal, neonatal and fetal adverse reaction |
| Verma | India | Black | 20-40 weeks | NR | 45/45 | NR | labetalol *vs.* methyldopa | maternal and neonatal adverse reaction |
| Baggio | Brazil | White/ Black | 20-32 weeks | 28.4±7.8/31.0±7.8 years | 8-Aug | NR | labetalol *vs.* hydralazine | blood pressure |
| Rezaei | Iran | White | ≥ 24 weeks | 18-45 years | 25/25 | NR | nifedipine *vs.* hydralazine | maternal and neonatal adverse reaction |
| Bharathi | India | Black | ≥ 20 weeks | NR | 25/25 | 2006.7-2007.7 | nifedipine *vs.* methyldopa | blood pressure and maternal adverse reaction |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Neri | Italy | White | ≤ 16 weeks | 34.4±4.1/33.7±3.8 years | 40/39 | 2006.9-2008.6 | L-arginine *vs.* placebo | blood pressure, maternal and neonatal adverse reaction |
| Facchinetti | Italy | White | 24-36 weeks | 32.8±5.4/32.6± 4.9 years | 40/40 | 2001.1-2002.6 | L-arginine *vs.* placebo | blood pressure, maternal and neonatal adverse reaction |
| Vigil-De | Panama | White/ Black | NR | 31.3±5.5/29.9±5.9 years | 40/42 | NR | labetalol *vs.* hydralazine | maternal adverse reaction |
| Vigil-De | Panama | White/ Black | ≥ 24 weeks | 29.3±6.8/29.9±6.4 years | 100/100 | 2003.12-2004.11 | labetalol *vs.* hydralazine | maternal, neonatal and fetal adverse reaction |
| Elatrous | Tunisia | Black | ≥ 24 weeks | ≥ 18 years | 30/30 | 1995.1-1996.1 | nicardipine vs. labetalol | blood pressure, clinical effect and maternal adverse reaction |
| Vermillion | The US | White | ≥ 24 weeks | 18-45 years | 25/25 | NR | nifedipine *vs.* labetalol | maternal, neonatal and fetal adverse reaction |
| Parazzini | Italy | White | 12-34 weeks | 31.3±5.6/31.2±5.6 years | 132/129 | NR | nifedipine *vs.*placebo | maternal, neonatal and fetal adverse reaction |
| Howarth | Africa | Black | 25-34 weeks | 20-38 years | 20/9 | NR | urapidil *vs.* dihydralazine | maternal adverse reaction |
| Hirsch | Israel | White | ≤ 35 weeks | 33±5/33±6 years | 15/12 | NR | pindolol *vs.* placebo | neonatal adverse reaction |
| El-Qarmalawi | Kuwait | White | ≥ 20 weeks | 24.3±1.7/25.2±1.7 years | 54/50 | NR | labetalol *vs.* methyldopa | maternal and neonatal adverse reaction |
| Hjertberg | Sweden | White | 25-34 weeks | 20-38 years | 7/7/2008 | 1986-1987 | labetalol + hydralazine *vs.* labetalol *vs.* hydralazine | maternal and neonatal adverse reaction |
| Martins-Costa | Brazil | White/ Black | NR | 21±4/21±6 years | 20/17 | NR | nifedipine *vs.* hydralazine | blood pressure, pulse and maternal adverse reaction |
| Moodley and Gouws | Africa | Black | ≥ 33 weeks | 21.45±4.13/ 21.52±5.04 years | 22/25 | NR | epoprostenol *vs.* dihydralazine | blood pressure, pulse, maternal and neonatal adverse reaction |
| Sibai | The US | White | 11.2±0.2/11.2±0.2/ 11.3±0.2weeks | 30.9±0.7/28.9±0.7/ 29.0±0.6 years | 87/86/90 | NR | methyldopa *vs.* labetalol *vs.* placebo | maternal and neonatal adverse reaction |
| Ellenbogen | Israel | White | 27-33 weeks | 30.4±1.94/ 28.39±1.54 years | 16/16 | 1982.1-1984.2 | pindolol *vs.* methyldopa | blood pressure and maternal adverse reaction |
| Michael | Australia | White | 25-38 weeks | 24.5±9.5/22.3±7.6 years | 45/45 | 1974-1983 | diazoxide *vs.* labetalol | clinical effect, maternal, neonatal and fetal adverse reaction |
| Rosenfeld | Israel | White | ≤ 36 weeks | 20-44 years | 23/21 | NR | pindolol + hydralazine *vs.* hydralazine | blood pressure, pulse, maternal and neonatal adverse reaction |
| Wichman | Sweden | White | ≤ 37 weeks | 27±5/28±5 years | 26/26 | 1981.1-1983.4 | metoprolol *vs.* placebo | blood pressure and maternal adverse reaction |
| Fidler | Canada | White | 30.9±7.5/29.9±8.5/ 30.5±7.9weeks | 29±6/30±6/28±6 years | 50/50/96 | NR | oxprenolol *vs.* methyldopa *vs.* placebo | blood pressure, maternal and fetal adverse reaction |
| Gallery | Australia | White | NR | 28.5±0.74/27.7±0.95 years | 27/25 | NR | oxprenolol *vs.* methyldopa | neonatal and fetal adverse reaction |

NR: Not Reported

reaction in the nifedipine group decreased significantly comparing to magnesium sulfate (RR, 1.88; 95% CrI, 1.31 to 2.70) [23]. And compared with methyldopa, there was an obvious lowering effect on maternal adverse reaction for pindolol (RR, 0.43; 95% CrI, 0.22 to 0.83) [62]. It was also found that hydralazine combined with pindolol could produce fewer adverse reactions than hydralazine alone (RR, 2.74; 95% CrI, 1.04 to 7.19) [60]. In comparison to placebo, maternal adverse reaction was significantly lower in the aspirin group (RR, 0.37; 95% CrI, 0.14 to 0.96) [34], but oxprenolol could product more smaternal adverse reactions (RR, 3.75; 95% CrI, 2.51 to 5.59) [64]. The Bayesian network meta-analysis identified that treating PIH with labetalol or nifedipine had fewer maternal adverse reactions than methyldopa.

**Clinical effect:** The clinical effect standard was divided into cure, apparent efficacy, effectiveness and ineffectiveness. Except for ineffectiveness, all indicators were used to evaluate the clinical effect, which were reported in 6 trials involving 1352 participants and 9 drugs [20,23,25,35,50,61]. Figure S6 showed the forest plots of the network meta-analysis of all relevant drugs. The meta-analysis revealed that methyldopa had more remarkable clinical effect than nifedipine in the treatment of PIH (RR, 1.09; 95% CrI, 1.01 to 1.19) [25]. Compared with diazoxide, labetalol exhibited a significant improvement on clinical effect (RR, 1.35; 95% CrI, 1.10 to 1.67) [61]. The Bayesian network meta-analysis identified that treating PIH with labetalol or nifedipine had fewer maternal adverse reactions than methyldopa. Due to the small number of trials which reported clinical effect, a closed ring was not formed in the network plot, moreover, mixed treatment comparison and drug sequencing could not be performed.

**Mean arterial pressure:** Only 5 trials reported mean arterial pressure, which contained 705 patients and 3 kinds of drugs

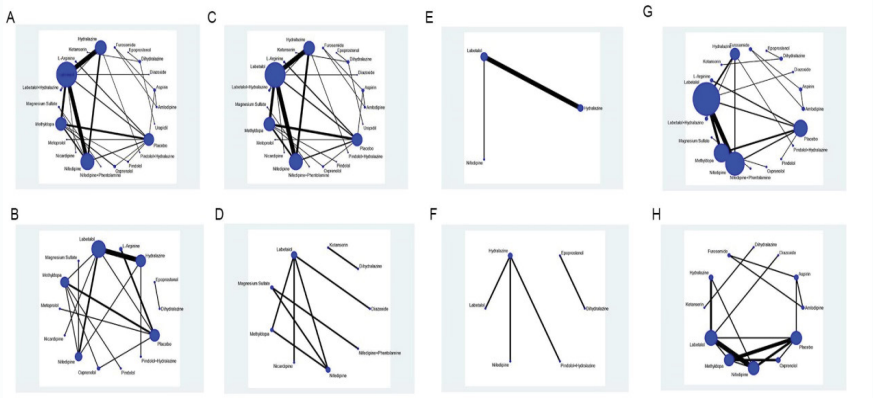


**Figure 2**: Network plot of the comparisons for the Bayesian network meta-analysis. (A) total, (B) blood pressure, (C) maternal adverse reaction, (D) clinical effect, (E) mean arterial pressure, (F) pulse, (G) neonatal adverse reaction, (H) fetal adverse reaction.

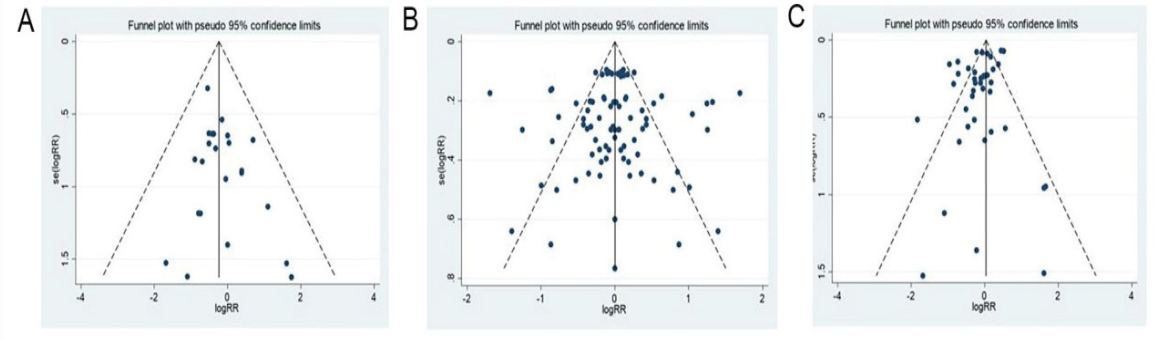



**Figure 3**: Funnel plots of the trials for outcomes. (A) fetal adverse reaction, (B) maternal adverse reaction, (C) neonatal adverse reaction.

[27,28,31,32,37]. The forest plots were shown in Figure S7. Meta-analysis identified that there was no obvious difference on mean arterial pressure among the included drugs. Mixed treatment comparison and drug sequencing were not performed, because a closed ring was not formed in the network plot.

**Pulse:** Pulse was only reported in 4 trials, which included 228 patients and 6 drugs [32,57,58,60], and Figure S8 exhibited the forest plots of the network meta-analysis. Labetalol had an obvious lowing effect on pulse compared with hydralazine (MD, -1.38; 95% CrI, -1.82 to -0.95) [32], and the effect of hydralazine combined with pindolol on pulse improvement was more significant than that of single use (MD, 3.44; 95% CrI, 2.50 to 4.39) [60]. And in comparison to dihydralazine, meta-analysis showed that epoprostenol had a remarkable decrease on pulse (MD, -0.90; 95% CrI, -0.15 to -0.30) [57]. It should be noted that the mixed treatment comparison and drug sequencing were not performed because there was no closed ring in the network plot.

**Neonatal adverse reaction:** Neonatal adverse reactions referred to all adverse reactions that happened to newborn in each trial. 29 included trials involved 3985 participants and 17 drugs in total reported neonatal adverse reactions [19,21-23,25,27-29,35,36,38-43,45,48,49,51,52,54-57,59-61,65]. The forest plots of the network meta-analysis of all relevant drugs were exhibited in Figure S9. An obvious lowing effect on neonatal adverse reaction of labetalol was identified compared with diazoxide (RR, 1.25; 95% CrI, 1.07 to 1.45) [61]. In comparison to nifedipine, neonatal adverse reaction was significantly lower in the methyldopa group (RR, 0.66; 95% CrI, 0.50 to 0.86) [22,25]. And meta-anlysis evaluated that using nifedipine to treat PIH could greatly reduce more neonatal adverse reaction than magnesium sulfate (RR, 6.25; 95% CrI, 2.28 to 17.14) [23], and in comparison to placebo, L-arginine caused less neonatal adverse reactions (RR, 0.55; 95% CrI, 0.32 to 0.92) [45]. The Bayesian network meta-analysis revealed that treating PIH with methyldopa produced the least neonatal adverse reactions followed by nifedipine, labetalol and hydralazine.

**Fetal adverse reaction:** Fetal adverse reactions referred to all adverse reactions that happened to fetuses in each trial. And a total of 2106 patients and 11 drugs were reported in 16 trials [19,22,32-36,38,40,41,47,51,52,61,64,65]. Figure S10 showed the forest plots of all relevant drugs. However, there was no obvious difference among included drugs according to traditional meta-analysis. The Bayesian network meta-analysis showed that treating PIH with labetalol had the least fetal adverse reactions. Nifedipine and hydralazine had similar effects on fetal adverse reactions, but both were inferior to labetalol and superior to methyldopa and other drugs.

## Discussion

The efficacy and safety of pharmacological treatments for PIH were evaluated by Bayesian network meta-analysis. 47 trials containing 5717 participants and 19 drugs were included. The network meta-analysis identified that nifedipine and hydralazine were the most effective drugs for reducing SBP and DBP, respectively. Dihydralazine

could increase clinical effect compared with ketanserin, and methyldopa had more significant clinical effect than nifedipine in the treatment of PIH. In comparison to hydralazine alone, its combination with pindolol could increase pulse, while combing with labetalol could lower pulse. And epoprostenol could reduce the number of pulses less than dihydralazine. The Bayesian network meta-analysis showed that treating PIH with labetalol or nifedipine had the least maternal adverse reactions. Labetalol could reduce neonatal adverse reaction compared with diazoxide. And methyldopa had an obvious lowing effect in comparison to nifedipine. Treating PIH with methyldopa produced the least neonatal adverse reactions followed by nifedipine, labetalol and hydralazine. Additionally, labetalol had the least fetal adverse reactions. The study was unique in many ways, including its comprehensiveness, the large-scale search, the novelty of discovery and the transparent approach. Some previous meta-analyses studied the efficacy and safety of drug treatment for PIH, most of which take the time to reach the target blood pressure as the standard of efficacy, but because the target blood pressure was not the same in different trials, the exact efficacy cannot be well reflected. This study comprehensively evaluated the efficacy of each drug and their efficacy characteristics from the aspects of blood pressure, clinical efficacy, mean arterial pressure and pulse. Our conclusions could guide clinical precision medication according to patients' specific conditions such as blood pressure and pulse. In terms of safety, they only focused on a certain point of adverse reactions caused by drugs including headache, so it was impossible to comprehensively assess the effects of drugs on the mother, fetus and newborn. This study attached great importance to the safety of drugs, and drugs for various adverse reactions to maternal, fetal and neonatal were summarized. We discussed the influence of drugs on three aspects at the same time, and systematically evaluated the adverse effects of each drug on maternal, fetal and neonatal characteristics, so as to select drugs according to the specific situation of mother and fetus. In addition, their results only showed that several drugs had similar clinical efficacy, without comprehensive sequencing of drugs, so it is impossible to guide clinical precision medication. This study performed a comprehensive analysis based on the sequencing of drugs in each outcome, and systematically evaluated the efficacy and safety of drugs, which was of certain help to the modification of the guidelines. Nowadays, with the increase of elderly mothers and more standardized pregnancy management examinations, the number of patients with PIH has increased significantly in the trend of early onset and severity [66]. The harm to pregnant women, newborns and fetuses was serious and long-term. The presence of eclampsia could be fatal to the pregnant women, and women with eclampsia in their first pregnancy showed a higher risk of developing eclampsia in their second pregnancy [67]. In addition, it could increase the risk of birth defects and cardiovascular disease in offspring. There was a clear correlation between PIH and genetic metabolic diseases, related organs and developmental diseases of the nervous system of newborns. And it could affect long-term cognitive development of the newborns and lead to behavioral sequelae [68,69]. So it remained a serious threat to both maternal and perinatal health. In view of this harm, special care should be taken in the treatment of PIH, and particular attention should be paid to various adverse reactions that may be caused by the drug. This study summarized the current commonly used drugs for PIH treatment in clinical practice and found out the therapeutic characteristics of each drug. In this study, the serious impacts of adverse reactions on the treatment of PIH were fully taken into account. Compared with improving clinical efficacy, significantly reducing adverse reactions was the preferred factor for drug selection. Most previously published meta-analyses of drug therapy for PIH have considered only one aspect of adverse reactions, such as headache, and did not conduct a detailed and systematic review of possible adverse reactions to the mother, fetus and newborn. This study systematically analyzed the adverse reactions of drugs to mothers, fetuses and newborns, and drew comprehensive conclusions to better select drugs based on the actual and specific conditions of pregnant women with PIH, so as to meet their greatest needs. This study found that Nifedipine was the most effective drug to reduce SBP and could produce the least maternal adverse reactions, and it also showed great advantages in reducing neonatal and fetal adverse reactions. Hydralazine was the most effective drug in lessening DBP, but it was not really able to avoid some adverse reactions. Although labetalol was not the best drug for lowering blood pressure, it produced the fewest maternal and fetal adverse reactions. Methyldopa had a favorable clinical effect for PIH and the minimal neonatal adverse reactions, but it was not optimal in terms of avoiding maternal and fetal adverse reactions. Other drugs had less effects on the treatment of PIH and/or more obvious adverse reactions than the above ones. Therefore, compared with most drugs, nifedipine, hydralazine, labetalol and methyldopa are not only clinically effective, but also safe. Their safety had significant advantages in maternal, fetal and neonatal aspects, and they were the first choice for the clinical treatment of PIH. Because nifedipine had good efficacy and no obvious adverse reactions, it is believed to be firstly recommend for PIH treatment, especially for severe hypertension. Of course, pregnant women with mild to moderate hypertension may also use labetalol in view of its fewest adverse reactions. Nifedipine have the effect of antagonizing calcium channels, it can block the calcium ion inflow caused by vascular smooth muscle cell spasm degree. While lowering blood pressure, it can control or even avoid various risks caused by systemic small blood vessel spasm, and play a stable role in lowering blood pressure, so as to restore the normal circadian rhythm of blood pressure. It can not only prevent preterm delivery, but also play the protective role of target organs in many ways [70]. It has little effect on the cardiac system and is completely reversible after withdrawal without rapid tolerability [71]. Therefore, nifedipine is considered more suitable for PIH than other drugs, because it may act through a combination of mechanisms, which can not only reduce blood pressure and protect maternal target organs, but also relieve the resistance of blood perfusion required by placental blood vessels and ensure the stability of placental function with a positive effect on the normal development and growth of the fetus in utero. Research may be needed to consider the optimization of drug selection for PIH treatment, because the drugs that we had identified to be the best for each outcome of efficacy and safety in treating PIH were not the part of existing guidelines in many countries. Most of the guidelines emphasized early prevention and treatment, but drug choice was not clear. Therefore, we recommended that the guidelines should increase the choice of drugs with particular emphasis on adverse reactions including pregnant women, newborns and fetuses. Some drugs that were likely to cause adverse reactions should be used with caution or prohibition, especially when considering childbirth. The formulation of specific drug selection in clinical research may require further investigation of all drug rankings that we had determined in the study. There were some important strengths in this study. Methodologically, our study benefits from the rigorous methods, the breadth of our search, the duplicate and independent screening, our meticulous data

abstraction process used, and the comprehensiveness of analytical indicators. In the study, the Bayesian network meta-analysis was used to compare therapies indirectly when no head-to-head trial existed, and more accurate evaluation for efficacy was obtained by jointly assessing direct and indirect comparisons. Also, we mapped drug sequencing figures 10s through single and mixed analysis, further ranked the competing drugs and summed up the best one for that outcome. Several limitations of this study should be acknowledged. Since the target blood pressure identified in each eligible trial was not the same, the step-down time to reach standard was not selected for judging efficacy in our study. But we believed that the blood pressure, clinical effect, mean arterial pressure and pulse should be enough to determine the efficacy of drugs. Potential limitations of the included studies were related to the inconsistency and variability across eligibility criteria in the original studies, as well as the variability in study design, study type, sample size and definitions of the PIH factors, which led to a high risk of bias in some of the included trials, and there were some methodological heterogeneity. In addition, there were a certain statistical and clinical heterogeneity in some outcomes of the study, which may be related to the drug dose and racial differences. Although our study had obtained the sequencing of efficacy and safety of the drugs, the most appropriate dose for each drug was still unclear, which needed to be further clarified in future studies. In conclusion, multiple outcomes were used to systematically evaluate the efficacy of pharmacological treatment for PIH in this study, and we focused on a comprehensive consideration of diversified adverse reactions, so as to determine the precise efficacy and safety of each drug for PIH treatment. This study analyzed the characteristics of pharmacological treatments for PIH and identified the most optimal drug for each outcome including lowering blood pressure, as well as reducing maternal, neonatal and fetal adverse reactions, which filled a crucial gap in precision medicine. Our findings will help experts to improve guidelines for PIH. As a result, nifedipine, hydralazine, labetalol and methyldopa had good clinical efficacy, and their safety had significant advantages in maternal, fetal and neonatal aspects, so they may be used preferentially in PIH treatment according to the situation. Nifedipine had good efficacy with no obvious adverse reactions, therefore, it is believed to be firstly recommend for PIH treatment, especially for severe hypertension. Our findings will help inform guidelines for PIH treatment and future research.

## Funding Sources

The authors thank grants from Key Research and Development Program of Shaanxi (2019ZDLSF04-05) and the National Natural Science Foundation of China (81773882, 81974522, 81974584). This research was also financially supported by Subject Innovation Team of Shaanxi University of Chinese Medicine (2019-YL10).

## Author Contributions

Shuo Zhang, Kui-Wu Yao and Yu-Ping Tang were responsible for the conception and design of the study; Shuo Zhang, Zhen-Lin Chen and Jia-Jia Li conducted the statistical analysis, drew the tables and pictures, and drafted the manuscript; Shuo Zhang, Zhen-Lin Chen and Shi-Jun Yue retrieved the database, screened the trials, extracted the data, and evaluated the methodological quality; and all authors critically revised the manuscript and approved the final version.

## References

1. Kintiraki E, Papakatsika S, Kotronis G, Goulis DG, Kotsis V. Pregnancy-induced hypertension. Hormones (Athens). 2015;14(2):211-23.
2. Magee LA, von Dadelszen P. State-of-the-art diagnosis and treatment of hypertension in pregnancy.Mayo Clin Proc. 2018;93(11):1664-77.
3. Rosas-Peralta M, Borrayo-Sánchez G, Madrid-Miller A, Ramírez-Arias E, Pérez-Rodríguez G. Hypertension during pregnancy: the challenge continues. Rev Med Inst Mex Seguro Soc. 2016;54:s90-s111.
4. Vest AR, Cho LS. Hypertension in pregnancy. Curr Atheroscler Rep. 2014;16(3):395.
5. Wildman K, Bouvier-Colle MH. Maternal mortality as an indicator of obstetric care in Europe. BJOG. 2004;111(2):164-9.
6. American College of Obstetricians and Gynecologists. Task Force on Hypertension in Pregnancy, Hypertension in pregnancy, Report of the American College of Obstetricians and Gynecologists' task force on hypertension in pregnancy. Obstet Gynecol. 2013;122(5):1122-31.
7. Sutton ALM, Harper LM, Tita ATN. Hypertensive disorders in pregnancy. Obstet Gynecol Clin North Am. 2018;45(2):333-47.
8. Kattah AG, Garovic VD. The management of hypertension in pregnancy. Adv Chronic Kidney Dis. 2013;20(3):229-39.
9. Catalá-López F, Tobías A, Cameron C, Moher D, Hutton B. Network meta-analysis for comparing treatment effects of multiple interventions: an introduction. Rheumatol Int. 2014;34(11):1489-96.
10. Ades AE, Sculpher M, Sutton A, Abrams K, Cooper N, Welton N, et al. Bayesian methods for evidence synthesis in cost-effectiveness analysis. Pharmacoeconomics. 2006;24(1):1-19.
11. Sutton A, Ades AE, Cooper N, Abrams K. Use of indirect and mixed treatment comparisons for technology assessment. Pharmacoeconomics. 2008;26(9):753-67.
12. Song F, Altman DG, Glenny AM, Deeks JJ. Validity of indirect comparison for estimating efficacy of competing interventions: empirical evidence from published meta-analyses. BMJ. 2003;326(7387):472.
13. Alavifard S, Chase R, Janoudi G, Chaumont A, Lanes A, Walker M, et al. First-line antihypertensive treatment for severe hypertension in pregnancy: A systematic review and network meta-analysis. Pregnancy Hypertens. 2019;18:179-87.
14. Sridharan K, Sequeira RP. Drugs for treating severe hypertension in pregnancy: a network meta-analysis and trial sequential analysis of randomized clinical trials. Br J Clin Pharmacol. 2018;84(9):1906-16.
15. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. J Clin Epidemiol. 2021;134:178-189.
16. Cochrane Handbook for Systematic Reviews of Interventions [computer program]. Version 5.2.
17. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ. 2003;327(7414):557-60.
18. Sedgwick P, Marston L. How to read a funnel plot in a meta-analysis. BMJ. 2015;16:h4718.
19. Sahai R, Nidhi A, Ranjan R, Lal S. Comparative study of oral nifedipine versus intravenous labetalol in severe hypertension in pregnancy: a randomized controlled study. Indian J Obstet Gynaecol Re. 2020;7:75-80.
20. Xiang CP, Zhou XG, Zheng XX. Magnesium sulfate in combination with nifedipine in the treatment of pregnancy-induced hypertension. Pak J Med Sci. 2020;36(2):21-5.
21. Easterling T, Mundle S, Bracken H, Parveka S, Mool S, Magee LA, et al. Oral antihypertensive regimens (nifedipine retard, labetalol, and methyldopa) for management of severe hypertension in pregnancy: an open-label, randomised controlled trial. Lancet. 2019;394(10203):1011-21.
22. Subiya J, Sengupta M, Saha C. Oral nifedipine versus intravenous labetalol in hypertensive emergencies of pregnancy-a randomised trial. J Evolution Med Dent Sci. 2019;8:3588-92.
23. Salama M, Rezk M, Gaber W, Hamza H, Marawan H, Gamal A, et al. Methyldopa versus nifedipine or no medication for treatment of chronic hypertension during pregnancy: a multicenter randomized clinical trial. Pregnancy Hypertens. 2019;17:54-8.

24. Wen J, Li WJ. Effect of magnesium sulfate combined with phentolamine and nifedipine for gestational hypertension and serum levels of LIF and apelin. J Coll Physicians Surg Pak. 2019;29(3):231-4.

25. Gainder S, Thakur M, Saha S, Prakash M. To study the changes in fetal hemodynamics with intravenous labetalol or nifedipine in acute severe hypertension. Pregnancy Hypertens. 2019;15:12-15.

26. Patel P, Koli D, Maitra N, Sheth T, Vaishnav P. Comparison of efficacy and safety of intravenous labetalol versus hydralazine for management of severe hypertension in pregnancy. J Obstet Gynaeco India. 2018;68(5):376-81.

27. Wajid R, Majeed T, Mahmood Z. To compare the side effects of intravenous labetalol vs. intravenous hydralazine in management of pregnancy induced hypertension. Pak J Med Health Sci. 2018;12:1563-6.

28. Khan A, Hafeez S, Nasrullah F. Comparison of hydralazine and labetalol to lower severe hypertension in pregnancy. Pak J Med Sci. 2017;33(2):466-70.

29. Sharma C, Soni A, Gupta A, Verma A, Verma S. Hydralazine vs. nifedipine for acute hypertensive emergency in pregnancy: a randomized controlled trial. Am J Obstet Gynecol. 2017;217(6):687.e1-e6.

30. Shabnum T, Amna S,Tanzila Y. Comparison of maternal hypotension after administration of labetalol versus hydralazine in treating patients having severe pregnancy induced hypertension. Pak J Med Health Sci. 2017;11:541-3.

31. Webster L, Myers J, Nelson-Piercy C, Harding K, Cruickshank JK, Watt-Coote I, et al. Labetalol versus nifedipine as antihypertensive treatment for chronic hypertension in pregnancy: a randomized controlled trial. Hypertension. 2017;70(5):915-22.

32. Liu F, Zhao M, Wang M, Yang HL, Li L. Effect of regular oral intake of aspirin during pregnancy on pregnancy outcome of high-risk pregnancy-induced hypertension syndrome patients. Eur Rev Med Pharmaco. 2016;20(23):5013-6.

33. Sabir S, Yasmin S, Abbas G. Comparison of oral nifedipine with intravenous hydralazine for acute hypertensive emergencies of pregnancy. J Postgrad Medical Inst. 2016;30:328-30.

34. Singh R, Singh S, Agarwal M, Anand S, Yadav NK. Comparative study of efficacy and safety of intravenous labetalol and intravenous hydralazine in managing hypertensive emergencies in pregnancy. J SAFOG. 2016;8:185-8.

35. Bijvank S, Visser W, Duvekot J, Steegers EA, Edens MA, Roofthooft DW, et al. Ketanserin versus dihydralazine for the treatment of severe hypertension in early-onset preeclampsia: a double blind randomized controlled trial. Eur J Obstet Gynecol Reprod Biol. 2015;189:106-11.

36. Delgado DPS, Velarde R, Reyes O, De LOK. Hydralazine vs. labetalol for the treatment of severe hypertensive disorders of pregnancy. a randomized, controlled trial. Pregnancy Hypertens. 2014;4(1):19-22.

37. Gracia PD, Dominguez L, Solis A. Management of chronic hypertension during pregnancy with furosemide, amlodipine or aspirin: a pilot clinical trial. J Matern-fetal Neo M. 2014;27(13):1291-4.

38. Shekhar S, Sharma C, Thakur S, Verma S. Oral nifedipine or intravenous labetalol for hypertensive emergency in pregnancy: a randomized controlled trial. Obstet Gynecol. 2013;122(5):1057-63.

39. Dhali B, Bhattacharya S, Ganguly R, Bandyopadhyay S, Mondal M, Dutta M. A randomized trial of intravenous labetalol & oral nifedipine in severe pregnancy induced hypertension. Int J Reprod Contracept Obstet Gynecol. 2012;1:42-6.

40. Lakshmi B, Dasari P. Oral nifedipine versus intravenous labetalol in hypertensive urgencies and emergencies of pregnancy: a randomized clinical trial. Obstet Med. 2012;5(4):171-5.

41. Molvi S, Mir S, Rana V, Jabeen F, Malik A. Role of antihypertensive therapy in mild to moderate pregnancy-induced hypertension: a prospective randomized study comparing labetalol with alpha methyldopa. Arch Gynecol Obstet. 2012;285(6):1553-62.

42. Verma R, Lahon K, Tonpay S, Kale VJ. A comparative randomised controlled parallel group study of maternal, fetal and neonatal outcomes of labetalol versus methyldopa in the treatment of new onset hypertension during pregnancy. Int J Pharma Bio Sci. 2012;3:201-11.

43. Baggio M, Martins W, Calderon A, Berezowski AT, Marcolin AC, Duarte G, et al. Changes in fetal and maternal doppler parameters observed during acute severe hypertension treatment with hydralazine or labetalol: a randomized controlled trial. Ultrasound Med Bio. 2011;37(1):53-8.

44. Rezaei Z, Sharbaf F, Pourmojieb M, Youefzadeh-Fard Y, Motevalian M, Khazaeipour Z, et al. Comparison of the efficacy of nifedipine and hydralazine in hypertensive crisis in pregnancy. Acta Med Iran. 2011;49(1):701-6.

45. Bharathi K, Prasad K, Jagannath P, Nalini KS. A comparison of nifedipine with methyldopa for control of blood pressure in mild to moderate pregnancy induced hypertension. J Clin Diagn Res. 2010;4:2406-9.

46. Neri I, Monari F, Sgarbi L, Berardi A, Masellis G, Facchinetti F. L-arginine supplementation in women with chronic hypertension: impact on blood pressure and maternal and neonatal complications. J Matern-fetal Neo M. 2010;23(12):1456-60.

47. Facchinetti F, Saade G, Neri I, Pizzi C, Longo M, Volpe A. L-arginine supplementation in patients with gestational hypertension: a pilot study. Hypertens Pregnancy. 2007;26(1):121-30.

48. Vigil-De GP, Ruiz E, López J, de Jaramillo I, Vega-Maleck J, Pinzón, J. Management of severe hypertension in the postpartum period with intravenous hydralazine or labetalol: a randomized clinical trial. Hypertens Pregnancy. 2007;26(2):163-71.

49. Vigil-De GP, Lasso M, Ruiz E, Vega-Malek J, de Mena Ft, LópezJc. Severe hypertension in pregnancy: hydralazine or labetalol. A randomized clinical trial. Eur J Obstet Gynecol Reprod Bio. 2006;128(1-2):157-62.

50. Elatrous S, Nouira S, OuanesBesbes L, Marghli S, Boussarssar M, Sakkouhi M, et al. Short-term treatment of severe hypertension of pregnancy: prospective comparison of nicardipine and labetalol. Intens Care Med. 2002;28(9):1281-6.

51. Vermillion S, Scardo J, Newman R, Chauhan S. A randomized, double-blind trial of oral nifedipine and intravenous labetalol in hypertensive emergencies of pregnancy. Am J Obstet Gynecol. 1999;181(4):858-61.

52. Parazzini F, Benedetto C, Bortolus R, Ricci E, Marozio L, Donvito V, et al. Nifedipine versus expectant management in mild to moderate hypertension in pregnancy. Briti J Obstet Gynaecol. 1998;105(7):718-22.

53. Howarth G, Seris A, Venter C, Pattinson R. A randomized controlled pilot study comparing urapidil to dihydralazine in the management of severe hypertension in pregnancy. Hypertens Pregnancy. 1997;16:213-21.

54. Hirsch M, Bar J, Bott-Kanner G, Kaplan B, Fuchs J, Ovadia J. Effect of the beta-adrenergic blocker pindolol on platelet function in chronic hypertensive pregnancy. Hypertens Pregnancy. 1996;15:193-202.

55. El-Qarmalawi A, Morsy A, al-Fadly A, Obeid A, Hashem M. Labetalol vs. methyldopa in the treatment of pregnancy-induced hypertension. Int J Gynaecol Obstet. 1995;49(2):125-30.

56. Hjertberg R, Faxelius G, Belfrage P. Comparison of outcome of labetalol or hydralazine therapy during hypertension in pregnancy in very low birth weight infants. Acta Obstet Gyn Scan. 1993;72(8):611-5.

57. Martins-Costa S, Ramos J, Barros E, Bruno R, Costa C, Goldin J. Randomized, controlled trial of hydralazine versus nifedipine in preeclamptic women with acute hypertension. Clin Exp Hyperten Part B Hypertens Pregnancy. 1992;11:25-44.

58. Moodley J, Gouws E. A comparative study of the use of epoprostenol and dihydralazine in severe hypertension in pregnancy. Br J Obstet Gynaecol. 1992;99(9):727-30.

59. Sibai B, Mabie W, Shamsa F, Villar M, Anderson G. A comparison of no medication versus methyldopa or labetalol in chronic hypertension during pregnancy. Am J Obstet Gynecol. 1990;162(4):960-6.

60. Ellenbogen A, Jaschevatzky O, Davidson A, Anderman S, Grunstein S. Management of pregnancy-induced hypertension with pindolol-comparative study with methyldopa. Int J Gynaecol Obstet. 1986;24(1):3-7.

61. Michael C. Intravenous labetalol and intravenous diazoxide in severe hypertension complicating pregnancy. Aust NZ J Obstet Gyn. 1986;26(1):26-9.

62. Rosenfeld J, Bott-Kanner G, Boner G, Nissenkorn A, Friedman S, Ovadia J, et al. Treatment of hypertension during pregnancy with hydralazine monotherapy or with combined therapy with hydralazine and pindolol. Eur J Obstet Gynecol Reprod Bio. 1986;22(4):197-204.

63. Wichman K, Karlberg B, Ryden G. Metoprolol in the treatment of mild to moderate hypertension in pregnancy-effects on the mother. Clin Exp Hypertens Part B Hypertens Pregnancy. 1985;4:141-56.

64. Fidler J, Smith V, Fayers P, De Swiet M. Randomised controlled comparative study of methyldopa and oxprenolol in treatment of hypertension in pregnancy. Br Med J. 1983;286(6382):1927-30.

65. Gallery E, Saunders D, Hunyor S, György A. Randomised comparison of methyldopa and oxprenolol for treatment of hypertension in pregnancy. Brit Med J. 1979;1(6178):1591-4.

66. Spencer-Jones J. Make every mother and child count. S Afr Med J. 2005;95(6):382-4.

67. Cho GJ, Kim LY, Min KJ, Sung YN, Hong SC, Oh MJ, et al. Prior cesarean section is associated with increased preeclampsia risk in a subsequent pregnancy. BMC Pregnancy Childb. 2015;15:24.

68. Johnson S, Evans TA, Draper ES, Field DJ, Manktelow BN, Marlow N, et al. Neurodevelopmental outcomes following late and moderate prematurity: apopulation-based cohort study. Arch Dis Child Fetal Neonatal Ed. 2015;100(4):F301-308.

69. Talge NM, Holzman C, Egeren LAV, Symonds LL, Scheid, JM Senagore PK, et al. Late-preterm birth by delivery circumstance and its association with parent-reported attention problems in childhood. J DevBehavPediatr. 2012;33(5):405-15.

70. Brown MJ, Palmer CR, Castaigne A, de Leeuw PW, Mancia G, Rosenthal T, et al. Morbidity and mortality in patients randomized to double-blind treatment with a long-acting calcium-channel blocker or diuretic in the international nifedipine GITS study: Intervention as a Goal in Hypertension Treatment (INSIGHT). Lancet. 2000;356(9227):366-72.

71. De Souza AR, Amorim MR, Costa AR. Nifedipine antihypertensive treatment effects in pre-eclampsia. Acta Med Port. 2008;21(4):351-8.

## Supplementary Files

**Table S1:** Specific percentage ranking in terms of competing drugs in each outcome.

**A**

| Drug | Rank 1 | Rank 2 | Rank 3 | Rank 4 |
|---|---|---|---|---|
| Hydralazine | 0.02 | 0.07 | 0.17 | 0.74 |
| Labetalol | 0.08 | 0.2 | 0.59 | 0.12 |
| Methyldopa | 0.2 | 0.52 | 0.17 | 0.11 |
| Nifedipine | 0.7 | 0.21 | 0.06 | 0.03 |

From rank1 to 4, the drugs became less effective.

**B**

| Drug | Rank 1 | Rank 2 | Rank 3 | Rank 4 |
|---|---|---|---|---|
| Hydralazine | 0.43 | 0.2 | 0.21 | 0.16 |
| Labetalol | 0.09 | 0.28 | 0.3 | 0.33 |
| Methyldopa | 0.31 | 0.25 | 0.23 | 0.21 |
| Nifedipine | 0.18 | 0.28 | 0.25 | 0.3 |

From rank1 to 4, the drugs became less effective.

**C**

| Drug | Rank 1 | Rank 2 | Rank 3 |
|---|---|---|---|
| Labetalol | 0.2 | 0.41 | 0.39 |
| Methyldopa | 0.52 | 0.24 | 0.24 |
| Nifedipine | 0.28 | 0.35 | 0.38 |

From rank1 to 3, the drugs caused fewer adverse reaction.

**D**

| Drug | Rank 1 | Rank 2 | Rank 3 | Rank 4 |
|---|---|---|---|---|
| Hydralazine | 0.47 | 0.18 | 0.19 | 0.16 |
| Labetalol | 0.3 | 0.43 | 0.23 | 0.04 |
| Methyldopa | 0.05 | 0.09 | 0.2 | 0.65 |
| Nifedipine | 0.18 | 0.3 | 0.37 | 0.15 |

From rank1 to 4, the drugs caused fewer adverse reaction.

**E**

| Drug | Rank 1 | Rank 2 | Rank 3 | Rank 4 |
|---|---|---|---|---|
| Hydralazine | 0.25 | 0.22 | 0.23 | 0.29 |
| Labetalol | 0.32 | 0.37 | 0.23 | 0.08 |
| Methyldopa | 0.25 | 0.15 | 0.2 | 0.4 |
| Nifedipine | 0.18 | 0.26 | 0.33 | 0.23 |

From rank1 to 4, the drugs caused fewer adverse reaction.

(A) aystolic blood pressure, (B) diastolic blood pressure, (C) maternal adverse reaction, (D) neonatal adverse reaction, (E) fetal adverse reaction.

**Table S2:** Methodology quality of the 47 included trials according to the Cochrane handbook.

| References | A | B | C | D | E | F |
|---|---|---|---|---|---|---|
| (Sahai) | - | - | - | - | - | - |
| (Xiang) | - | - | - | - | - | - |
| (Easterling) | - | - | - | - | - | - |
| (Jamil) | - | ? | ? | - | - | - |
| (Salama) | - | - | - | - | - | - |
| (Wen and Li) | - | ? | ? | - | - | - |
| (Gainder) | - | ? | ? | - | - | - |
| (Patel) | - | - | - | - | - | - |
| (Wajid) | - | ? | ? | - | - | - |
| (Khan) | - | - | - | - | - | - |
| (Sharma) | - | - | - | - | - | - |
| (Tariq) | + | ? | ? | - | - | - |
| (Webster) | - | - | - | - | - | - |
| (Liu) | + | ? | ? | - | - | - |
| (Sabir) | ? | ? | ? | - | - | - |
| (Singh) | ? | ? | ? | - | - | - |
| (Bijvanka) | - | - | - | - | - | - |
| (Delgado) | - | ? | ? | - | - | - |
| (Gracia) | - | - | - | - | - | - |
| (Shekhar) | - | - | - | - | - | - |
| (Dhali) | - | - | - | - | - | - |
| (Lakshmi) | - | - | - | - | - | - |
| (Molvi) | - | - | - | - | - | - |
| (Verma) | - | ? | ? | - | - | - |
| (Baggio) | - | - | - | - | - | - |
| (Rezaei) | ? | ? | ? | - | - | - |
| (Bharathi) | ? | ? | ? | - | - | - |
| (Neri) | - | - | - | - | - | - |

| | | | | | | |
|---|---|---|---|---|---|---|
| (Facchinetti) | - | - | - | - | - | - |
| (Vigil-De) | ? | ? | ? | - | - | - |
| (Vigil-De) | - | - | - | - | - | - |
| (Elatrous) | - | - | - | - | - | - |
| (Vermillion) | - | - | - | - | - | - |
| (Parazzini) | - | - | - | - | - | - |
| (Howarth) | - | - | - | - | - | - |
| (Hirsch) | - | ? | ? | - | - | - |
| (El-Qarmalawi) | - | ? | ? | - | - | - |
| (Hjerteerg) | ? | ? | ? | - | - | - |
| (Martins-Costa) | - | - | - | - | - | - |
| (Moodley and Gouws) | - | ? | ? | - | - | - |
| (Sibai) | - | - | - | - | - | - |
| (Ellenbogen) | ? | ? | ? | - | - | - |
| (Michael) | ? | ? | ? | - | - | - |
| (Rosenfeld) | ? | ? | ? | - | - | - |
| (Wichman) | - | ? | - | - | - | - |
| (Fidler) | - | ? | ? | - | - | - |
| (Gallery) | ? | ? | ? | - | - | - |

A: adequate sequence generation; B: allocation concealment; C: blinding; D: incomplete outcome data; E: selective reporting; F: other bias; +: high risk; -: low risk; ?, unclear

A

| | | | |
|---|---|---|---|
| **Hydralazine** | 0.93 (-1.04, 3.29) | 1.77 (-1.76, 5.93) | 2.59 (-0.87, 6.33) |
| -0.93 (-3.29, 1.04) | **Labetalol** | 0.85 (-2.31, 4.24) | 1.67 (-1.48, 4.91) |
| -1.77 (-5.93, 1.76) | -0.85 (-4.24, 2.31) | **Methyldopa** | 0.86 (-2.12, 3.61) |
| -2.59 (-6.33, 0.87) | -1.67 (-4.91, 1.48) | -0.86 (-3.61, 2.12) | **Nifedipine** |

B

| | | | |
|---|---|---|---|
| **Hydralazine** | -0.46 (-2.33, 1.13) | -0.18 (-3.09, 2.65) | -0.35 (-2.98, 2.20) |
| 0.46 (-1.13, 2.33) | **Labetalol** | 0.28 (-2.15, 2.80) | 0.11 (-1.96, 2.35) |
| 0.18 (-2.65, 3.09) | -0.28 (-2.80, 2.15) | **Methyldopa** | -0.19 (-2.38, 2.14) |
| 0.35 (-2.20, 2.98) | -0.11 (-2.35, 1.96) | 0.19 (-2.14, 2.38) | **Nifedipine** |

C

| | | |
|---|---|---|
| **Labetalol** | 1.21 (0.40, 3.44) | 1.03 (0.40, 2.43) |
| 0.82 (0.29, 2.50) | **Methyldopa** | 0.84 (0.25, 2.76) |
| 0.98 (0.41, 2.52) | 1.19 (0.36, 3.98) | **Nifedipine** |

D

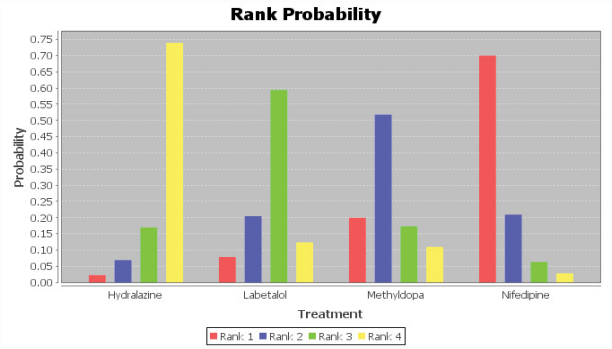
| | | | |
|---|---|---|---|
| **Hydralazine** | 0.95 (0.30, 2.81) | 0.59 (0.14, 2.26) | 0.84 (0.24, 2.60) |
| 1.06 (0.36, 3.32) | **Labetalol** | 0.62 (0.25, 1.44) | 0.88 (0.43, 1.71) |
| 1.70 (0.44, 7.01) | 1.62 (0.69, 3.94) | **Methyldopa** | 1.43 (0.51, 3.76) |
| 1.19 (0.38, 4.11) | 1.13 (0.58, 2.34) | 0.70 (0.27, 1.96) | **Nifedipine** |

E

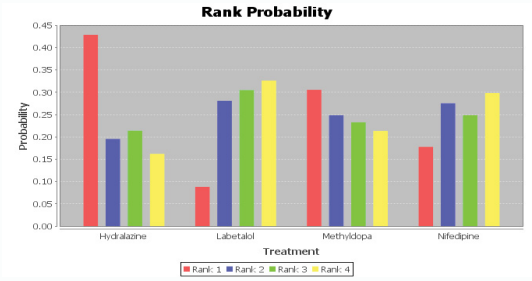
| | | | |
|---|---|---|---|
| **Hydralazine** | 1.17 (0.38, 4.37) | 0.87 (0.14, 7.06) | 0.99 (0.27, 5.21) |
| 0.85 (0.23, 2.65) | **Labetalol** | 0.76 (0.14, 3.80) | 0.82 (0.36, 2.58) |
| 1.15 (0.14, 7.20) | 1.32 (0.26, 7.12) | **Methyldopa** | 1.10 (0.25, 5.98) |
| 1.01 (0.19, 3.65) | 1.22 (0.39, 2.80) | 0.91 (0.17, 3.98) | **Nifedipine** |

**Figure S1**: Pooled hazard ratios for competing drugs in each outcome. The column treatment is compared with the row treatment, numbers in parentheses indicate 95% credible intervals, Figure A and B used RR, Figure C,D and E used MD. When the entire 95% confidence interval does not contain 0 or 1, the RR or MD is statistically significant. (A) systolic blood pressure, (B) diastolic blood pressure, (C) maternal adverse reaction, (D) neonatal adverse reaction, (E) fetal adverse reaction.

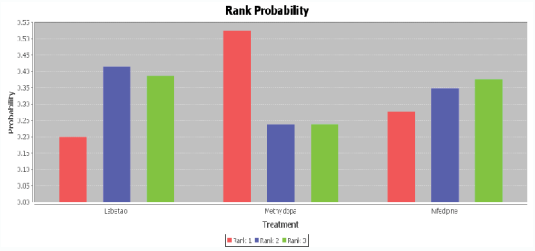
A



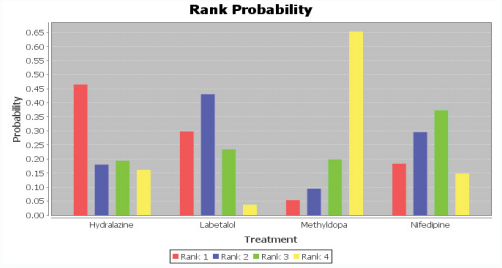

B




C




D




E

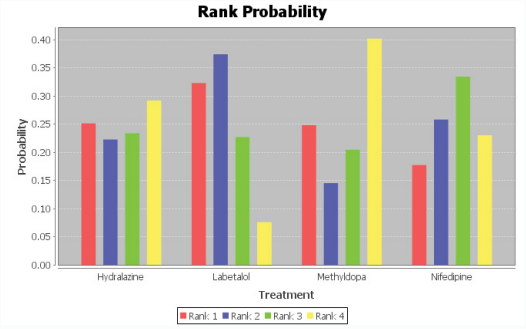



**Figure S2**: Rank probability of competing drugs in each outcome. (A) systolic blood pressure, (B) diastolic blood pressure, (C) maternal adverse reaction, (D) neonatal adverse reaction, (E) fetal adverse reaction.

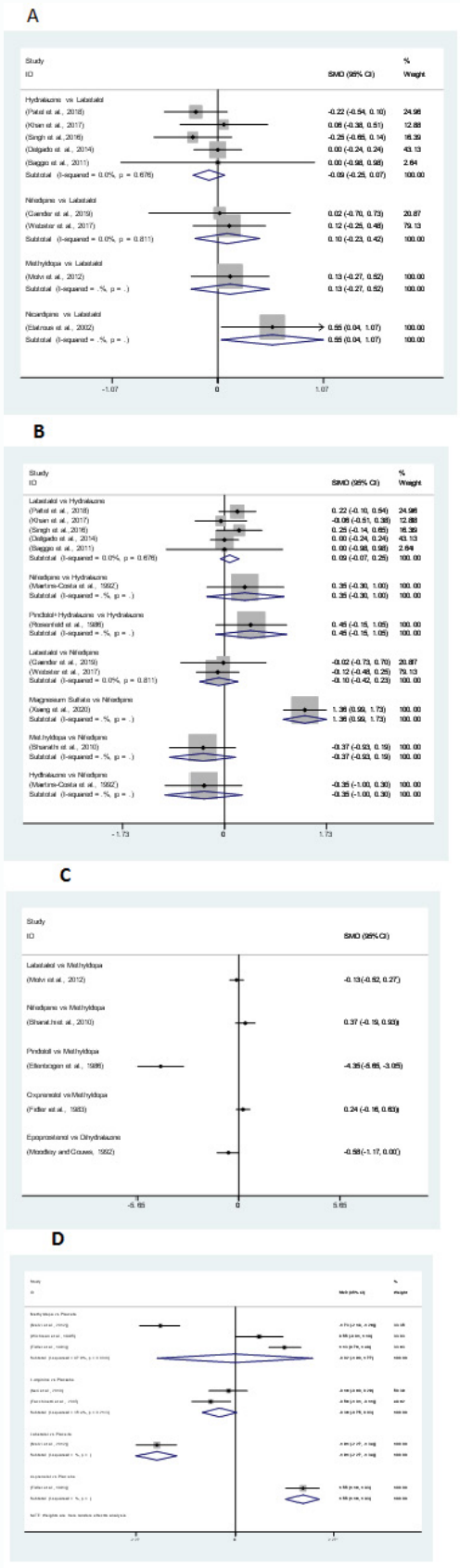



**Figure S3**: Forest plots for systolic blood pressure by Bayesian network meta-analysis and traditional meta-analysis. (A) drugs *vs.* labetalol, (B) drugs *vs.* hydralazine or nifedipone, (C) drugs *vs.* methyldopa or dihydralazine, (D) drugs *vs.* placebo.

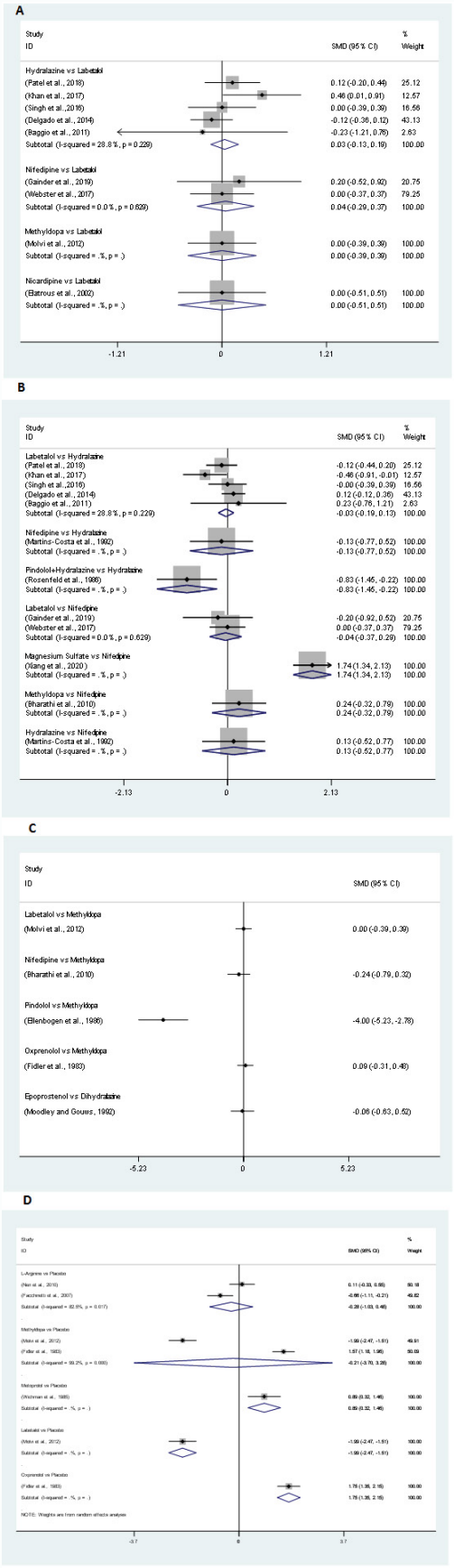



**Figure S4**: Forest plots for diastolic blood pressure by Bayesian network meta-analysis and traditional meta-analysis.(A) drugs vs. labetalol, (B) drugs *vs.* hydralazine or nifedipone, (C) drugs vs. methyldopa or dihydralazine, (D) drugs vs. placebo.

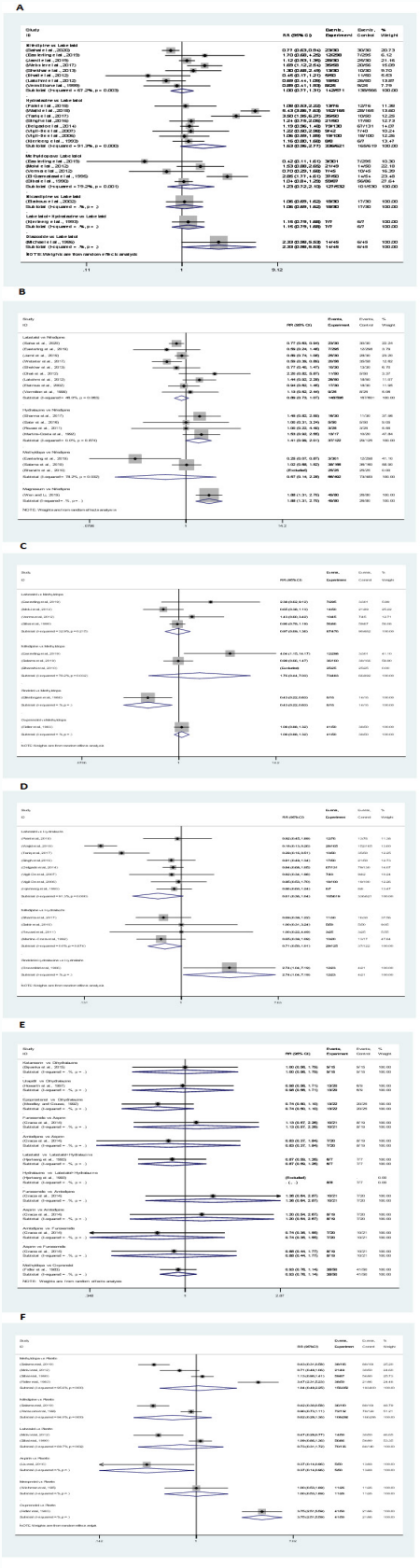


**Figure S5**: Forest plots for maternal adverse reactions by Bayesian network meta-analysis and traditional meta-analysis. (A) drugs *vs.* labetalol, (B) drugs *vs.* nifedipone, (C) drugs *vs.* methyldopa, (D) drugs *vs.* hydralazine, (E) drugs *vs.* others, (F) drugs *vs.* placebo.

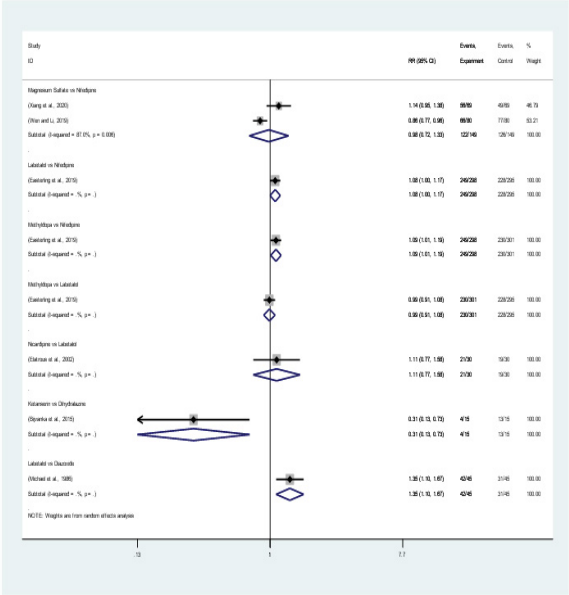


**Figure S6**: Forest plots for clinical effect by Bayesian network meta-analysis and traditional meta-analysis.

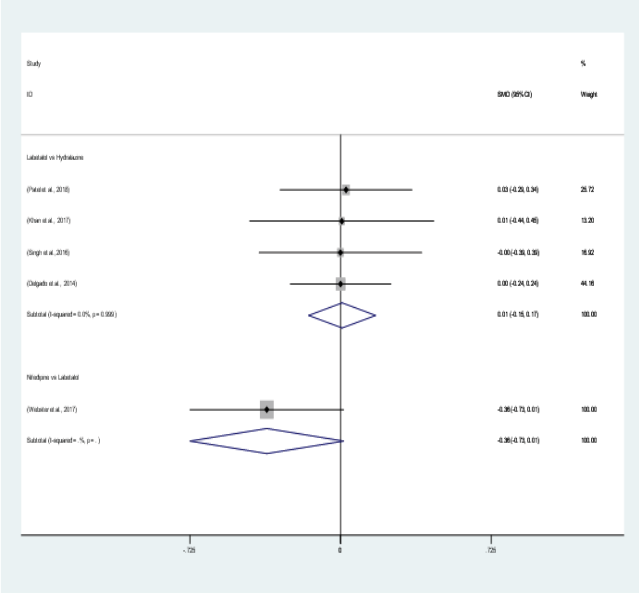


**Figure S7**: Forest plots for mean arterial pressure by Bayesian network meta-analysis and traditional meta-analysis.

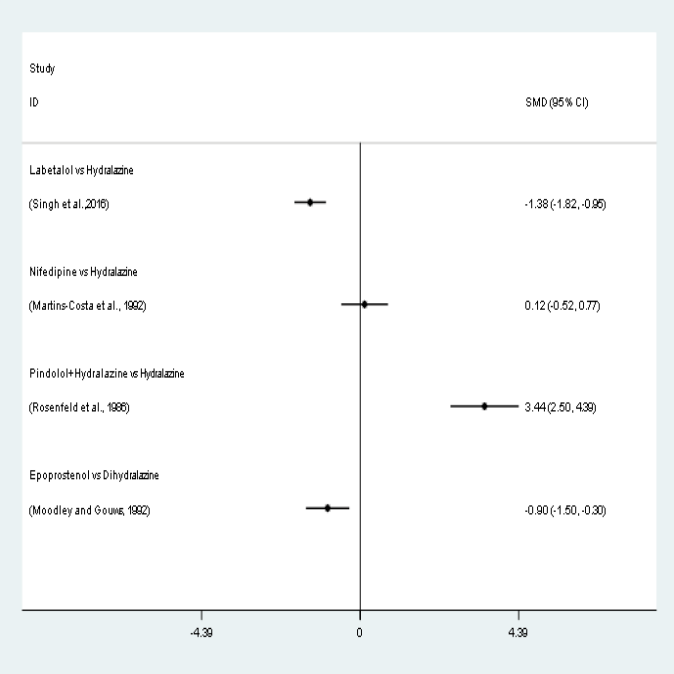
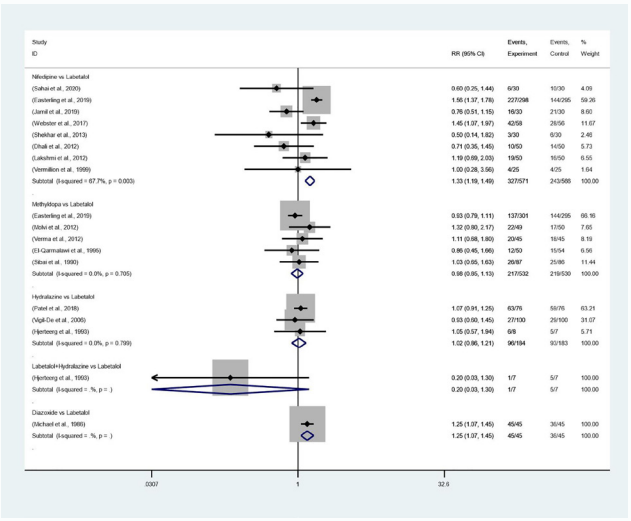
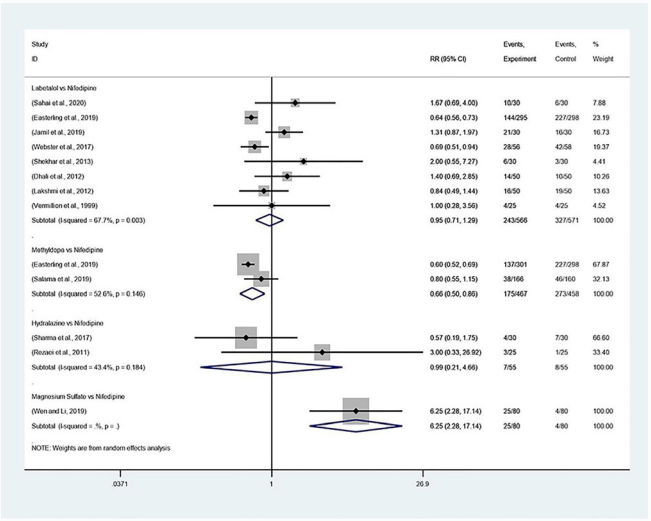
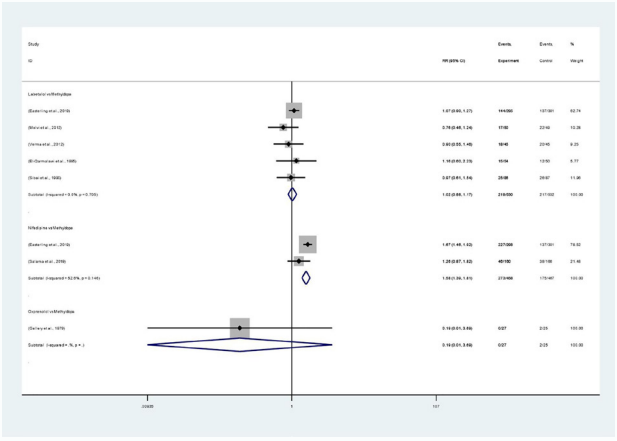
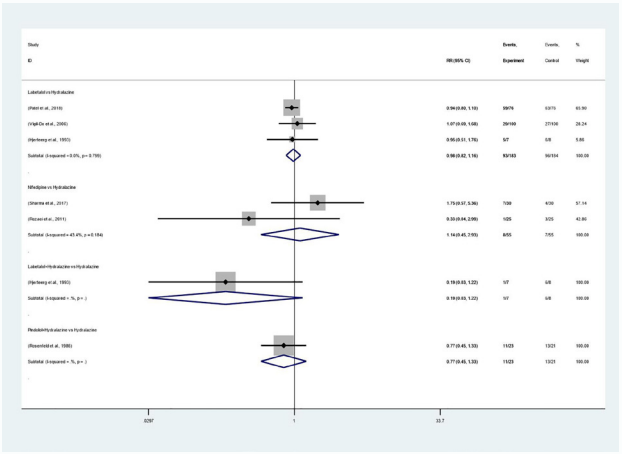


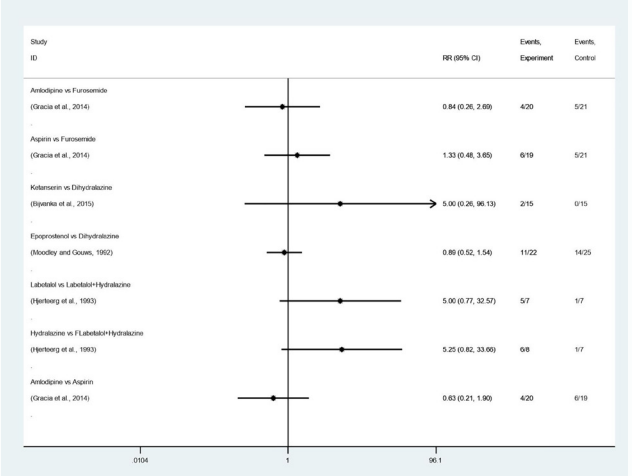

**Figure S8**: Forest plots for pulse by Bayesian network meta-analysis and traditional meta-analysis.











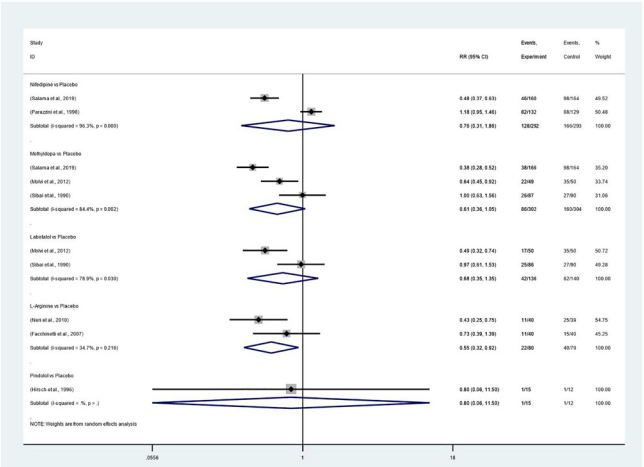


**Figure S9**: Forest plots for neonatal adverse reactions by Bayesian network meta-analysis and traditional meta-analysis. (A) drugs *vs.* labetalol, (B) drugs *vs.* nifedipone, (C) drugs *vs.* methyldopa, (D) drugs *vs.* hydralazine, (E) drugs *vs.* others, (F) drugs *vs.* placebo.

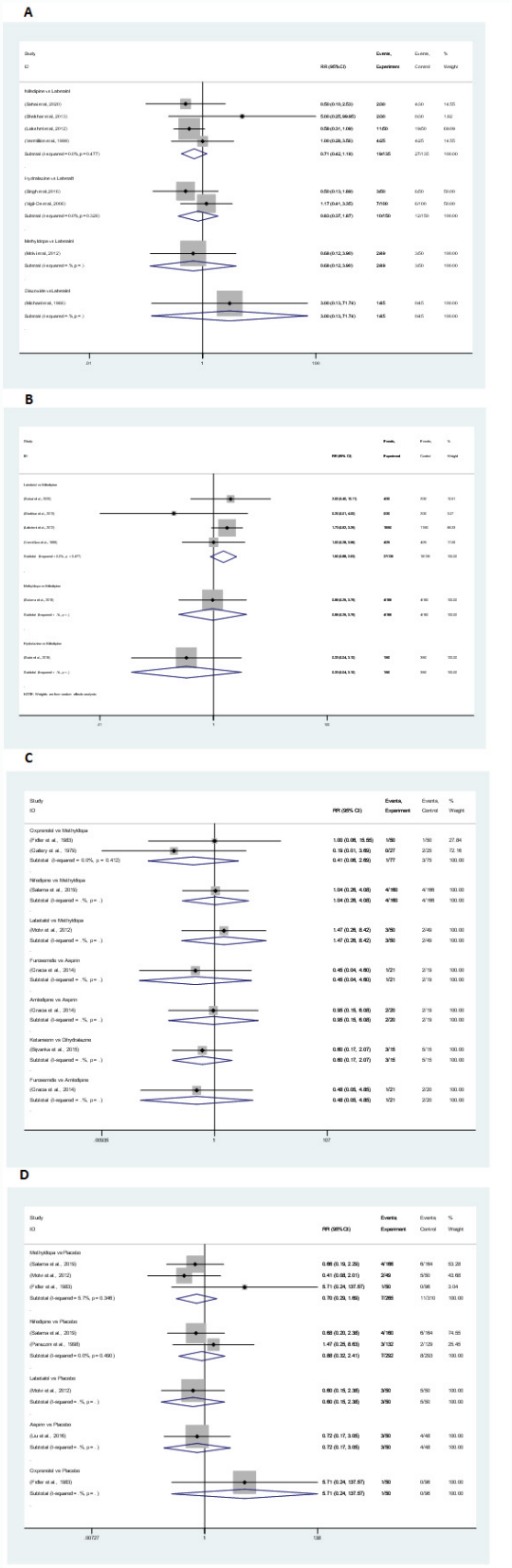



**Figure S10**: Forest plots for fetal adverse reactions by Bayesian network meta-analysis and traditional meta-analysis. (A) drugs *vs.* labetalol, (B) drugs *vs.* nifedipone, (C) drugs *vs.* others, (D) drugs *vs.* placebo.