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ARTICLE

Antihypertensive drug therapy for women with non-severe hypertensive disorders of pregnancy: a systematic review and meta-analysis

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Abstract

Hypertensive disorders of pregnancy (HDP) represent a frequent disorder among pregnancies. Women with severe hypertension in pregnancy are at increased risk of maternal complications and require antihypertensive drug therapy. This study aimed to systematically review randomized control trials of antihypertensive drug(s) treating non-severe hypertension during pregnancy to estimate the effectiveness and safety of this intervention. On May 8, 2018, we searched PubMed, Cochrane Library, and Ichu-Shi with no restriction on publication year. We selected randomized control trials that involved women with HDP being treated with antihypertensive drug(s) as intervention. Fourteen trials (1804 women) were identified for meta-analysis. There were no significant differences in the risk of maternal death (373 women; risk ratio (RR) 0.70; 95% confidence interval (CI) 0.04 to 11.45), proteinuria (1214 women; RR 1.00; 95% CI 0.67 to 1.49), side effects (360 women; RR 2.69; 95% CI 0.32 to 22.64), cesarean section (1239 women; RR 0.97; 95% CI 0.82 to 1.15), neonatal and birth death (1548 women; RR 0.80; 95% CI 0.43 to 1.49), preterm birth (904 women; RR 0.86; 95% CI 0.53 to 1.39), or small for gestational age infants (1082 women; RR 1.04; 95% CI 0.66 to 1.63) with antihypertensive drug therapy versus placebo or no treatment. The current review suggests that antihypertensive drug therapy does not reduce or increase the risk of maternal or perinatal outcomes. Further studies are needed to build reliable estimates of the effectiveness and safety of antihypertensive drug therapy for women with HDP.

Keywords Hypertension · Pregnancy · Antihypertensive

Introduction

Hypertensive disorders of pregnancy (HDP) is a frequent disorder, with a reported incidence of 10% to 15% among pregnancies [1]. HDP is a leading cause of maternal/fetal morbidity and mortality, the most common being preeclampsia-eclampsia [2]. The definition of HDP includes preeclampsia-eclampsia, chronic hypertension, chronic hypertension with superimposed preeclampsia, and gestational hypertension [3]. Gestational hypertension is defined as sustained systolic blood pressure (BP) of 140 mmHg or higher and/or diastolic BP of 90 mmHg or higher with onset after 20 weeks of gestation in the absence of proteinuria. Chronic hypertension is defined as preexisting hypertension or hypertension diagnosed before 20 weeks of gestation.

Sustained severe hypertension in pregnancy is considered to be a risk factor for maternal and perinatal complications. On the other hand, excessive BP lowering may cause dizziness or fetal distress. There is consensus that severe hypertension (defined as a sustained systolic BP of 160 mmHg or higher and/or diastolic BP of 110 mmHg or higher) during pregnancy should be treated

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to decrease the maternal and perinatal risk of complications [3]. However, the role of antihypertensive drug therapy for non-severe hypertension during pregnancy (defined as a systolic BP of 140 to 159 mmHg and/or diastolic BP of 90 to 109 mmHg) remains unclear. Thus, this study aimed to systematically review and meta-analyze available data from randomized controlled trials on the effect of antihypertensive drug therapy for non-severe hypertension during pregnancy.

Methods

The methods for this systematic review were developed according to recommendations from the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) statement [4]. No ethical approval was required.

Literature search

We searched Medline (PUBMED), the Cochrane Central Register of Controlled Trials (CENTRAL), and Ichu-Shi (Japanese). We limited the search from their earliest entries until May 8, 2018. Searches of exploded MeSH terms "Hypertension, Pregnancy-Induced" and the text words "Hypertensi or High Blood Pressure" and "therap or treatment or pharmacotherapy or antihypertensi" and "Randomized Controlled Trial" (Medline) and "Antihypertensive Agents" (CENTRAL) were performed individually. There were language restrictions for Japanese and English (Medline). Reference lists from identified trials and review articles were manually scanned to identify any other relevant studies (Supplementary Appendix).

Study selection criteria

Two reviewers (S.O and J.S) independently and in duplicate screened the titles and abstracts of all identified studies using a priori selection criteria. Subsequently, reviewers independently assessed eligibility of the full texts of potentially eligible studies. Reviewers resolved discrepancies through discussion. We included randomized controlled trials that compared non-severe hypertension during pregnancy (defined as a systolic BP of 140 to 169 mmHg and/or diastolic BP of 90 to 109 mmHg). Comparisons were of one or more antihypertensive drug-(s) with placebo, with no antihypertensive drug. Women were included regardless of whether they had proteinuria or not, and irrespective of previous antihypertensive treatment or whether the pregnancy was singleton or multiple.

Data extraction

The titles, abstracts and selected full texts generated from the literature search were independently screened by 2 of the authors (S.O. and J.S.). The authors were not masked to the results of the study or the authors. Where 2 articles published results from the same study, individual pertinent outcomes were extracted from both articles. The following outcome measures were recorded for each study: maternal death, proteinuria (1+ or more or 300 mg/L or 5 g/24 h), side effects (rash, headache, vertigo, generalized weakness, lethargy, diarrhea), cesarean section, neonatal and birth death, preterm birth (defined as less than 36 or 37 completed week's gestation), and small for gestational age infants. The PRISMA statement was considered and observed for all procedures and reporting.

Study quality assessment

Two reviewers (S.O. and J.S.) independently assessed the risk of bias of each trial using the Risk of Bias tool, which was developed by Cochrane [5]. The risk bias in each of following domains was assessed: random sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting, and other factors.

Statistical method

We carried out statistical analyses using Review Manager Version 5.2 (RevMan 5.2) software (Nordic Cochrane Centre, Copenhagen, Denmark). All outcomes were analyzed on an intention-to-treat bias. Meta-analysis was performed using a fix-effects model when there was more than 1 study with analyzable data. The initial analysis of treatment effects was performed by antihypertensive agent (treat) versus placebo or no treatment (control). Treatment effects are presented as estimated differences in mean or risk ratio with 95% confidence interval (CI). Forest plots ware constructed to graphically represent the results. Heterogeneity was measured using the inconsistency (I^2) statics, which estimates the percentage of total variation across trials that can be attributed to heterogeneity rather than chance. I^2 values of less than 25% and more than 75% represent low and high inconsistency, respectively [6]. P values of less than 0.05 were considered statistically significant. No other units of analysis were used in this review.

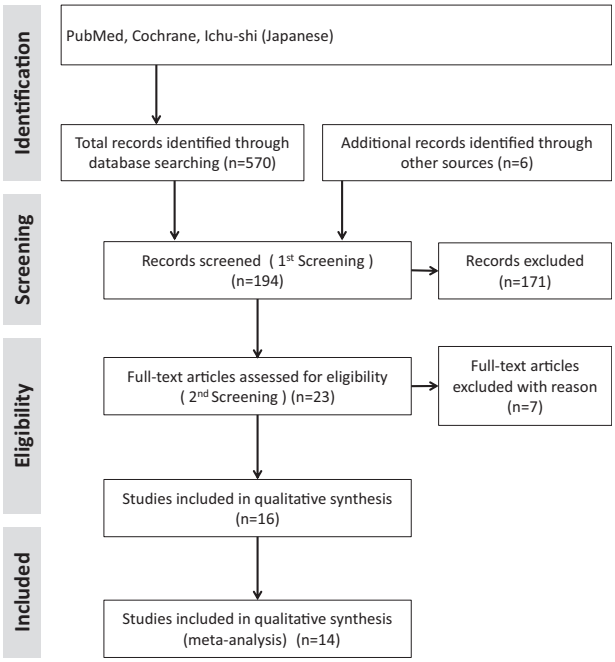

Fig. 1 The PRISMA flow diagram of the study selection

Results

Description of the included studies

From three databases, 617 potential studies were identified. We identified 6 additional candidate studies by reviewing bibliographies of included articles. After removal of duplicates, the initial search generated 194 titles and abstracts for review. From reading abstracts, 171 articles were excluded on the basis of study design, and 23 full-text articles were retrieved. Of those, 14 articles met the final inclusion criteria and formed the basis of this systematic review. The study selection process is shown in Fig. 1. The characteristics of the included studies are described in Table 1.

Fourteen trials (1804 women) were included in this review. Of these, 7 (790 women) were conducted in European countries [7–13], 4 (640 women) in the USA [14–17], and 3 (374 women) in other countries [18–20]. One trial was published in the 1970s [12], 4 in the 1980s [10, 11, 14, 17], 7 in the 1990s [7–9, 13, 15, 16, 20], and 2 after the year 2000 [18, 19]. The antihypertensive drugs used in these trials included: alpha agonists (methyldopa), beta blockers (atenolol, labetalol, oxprenolol), and a calcium channel blocker (isradipine). Six trials were placebo-controlled studies of a single antihypertensive drug (537 women) [7, 8, 10, 11, 13, 14], and 8 were studies of a single antihypertensive drug or 2 antihypertensive drugs compared to no drug treatment (1267 women) [9, 12, 15–20].

Effect of intervention: antihypertensive drugs versus none

Overall, 14 trials with a total of 1804 women compared an antihypertensive drug with placebo or no antihypertensive drug.

Maternal outcomes

Only 3 small trials reported maternal death (373 women; risk ratio (RR) 0.70; 95% CI 0.04 to 11.45) (Fig. 2a). There is no overall difference in the risk of proteinuria in the 9 trials (1214 women) reporting this outcome (RR 1.00; 95% CI 0.67 to 1.49) (Fig. 2b). Drug changes due to maternal side effects were reported in 4 small trials (360 women). Although the maternal side effects tended to be more apparent in women treated with antihypertensive drugs, there was no statistically significant difference (RR 2.69; 95% CI 0.32 to 22.64) (Fig. 2c). There was also no overall difference in the 8 trials (1239 women) reporting cesarean section (RR 0.97; 95% CI 0.82 to 1.15) (Fig. 2d).

Perinatal outcomes

Of the perinatal outcomes, neonatal and birth death was reported in 12 trials (1548 women) (RR 0.80; 95% CI 0.43 to 1.49) (Fig. 3a), preterm birth in 5 trials (904 women) (RR 0.86; 95% CI 0.53 to 1.39) (Fig. 3b), and small for gestational age infants in 9 trials (1082 women) (RR 1.04; 95% CI 0.66 to 1.63) (Fig. 3c). There is no clear evidence of an overall difference in the risk of these outcomes.

Risk of bias in the included studies

Risk of bias of the 14 trials was assessed in 7 areas. Methods for generating the random sequence were described 8 trials [7, 9, 10, 15–18, 20]. Inadequate methods were used in 2 trials [9, 18]. There were high risks of performance bias (blinding of participants and personnel) in 7 trials due to the open label nature of the study [9, 12, 15–19]. Two trials reported losses of greater than 10% of randomized women and were assessed as "high risk" for attrition bias [13, 16]. The shapes of the funnel plots in all outcomes did not reveal any evidence of obvious asymmetry. A representative funnel plot shows the symmetric distribution of the studies that evaluated the RR of the neonatal and birth death when comparing antihypertensive drugs or none (Fig. 4). Details of risk of bias are presented in Fig. 5. Although there was moderate to high inconsistency among trials in all outcomes, except for neonatal and birth death, there was no substantial variation in the effect estimates across studies, and there was a clear overlap of CIs among trials.

Table 1 Characteristics of the studies Included in the meta-analysis

Author, year, country	Methods	Participants	Interventions	Outcomes included in Meta-analysis
Blake, 1991, Ireland	• Participants allocated randomely to antihyper-tensive treatment or no antihypertensive treatment • Allocation concealment: card with "test" or "control" sealed in envelopes, shuffled and then numbered in sequence • Open label	• BP ≧ 140/90 mmHg at < 38 weeks' gestation without proteinuria	• Treatment: atenolol 50–100 mg/day and/or methyldopa 750–2250 mg/day • Control: no antihypertensive	• Proteinuria • Neonatal and birth death • Small for gestational-age infants
Butters, 1990, UK	• Double-blind randomized placebo controlled trial	• Systolic BP 140–170 mmHg and diastolic BP 90 to 110 mmHg at 12–24 weeks' gestation • Excluded: contraindication to beta blockers	• Treatment: atenolol 50–200 mg/day • Control: placebo	• Side effect • Neonatal and birth death • Small for gestational-age infants
Elhassan, 2002, Sudan	• Participants allocated randomely to antihyper-tensive treatment or no antihypertensive treatment • No information on allocation concealment • Open label	• Diastolic BP 90–109 mmHg at 28–36 weeks' gestation	• Treatment: methyldopa 750–4000 mg/day • Control: no antihypertensive	• Maternal death • Cesarean section • Neonatal and birth death
Molvi, 2012, India	• Participants allocated randomely to antihyper-tensive treatment or no antihypertensive treatment • Allocation concealment: mixed sealed envelopes containing the assigned intervention, 3-arm study • Open label	• BP 140–159/90–109 mmHg at 20–38 weeks' gestation without proteinuria • Excluded: Chronic hypertension, diabetes, known medical/ psychiatric disorders, multiple pregnancy, congenital abnormality	• Treatment: (1) labetalol 200–2500 mg/day, (2) methyldopa 500–2000 mg/day • Control: no antihypertensive	• Maternal death • Proteinuria • Cesarean section • Neonatal and birth death • Preterm birth • Small for gestational-age infants
Pickles, 1989, UK	• Double-blind randomized placebo controlled trial	• Systolic BP 140–160 mmHg and diastolic BP 90 to 105 mmHg at 20–38 weeks' gestation without proteinuria • Excluded: history of hypertension, renal, metabolic, cardiovascular, respiratory or collagen disease	• Treatment: labetalol 100–200 mg/day • Control: placebo	• Side effect • Neonatal and birth death • Preterm birth • Small for gestational-age infants
Pickles, 1992, UK	• Participants allocated randomely to antihyper-tensive treatment or no antihypertensive treatment • Allocation concealment: numbered, sealed opaque envelopes • Open label	• Diastolic BP > 90 mmHg at 20–39 weeks' gestation without proteinuria • Excluded: psychoneurosis, cardiac abnormality, diabetes, asthma, contraindication to beta blockers	• Treatment: labetalol 200–1200 mg/day • Control: no antihypertensive	• Proteinuria • Cesarean section • Neonatal and birth death
Plouin, 1990, Caribbean	• Double-blind randomized placebo controlled trial	• Diastolic BP > 84 mmHg at 20–36 weeks' gestation • Excluded: history of hypertension, type I diabetes, congestive heart failure, cardiac blocl, asthma	• Treatment: oxprenolol 160–320 mg/day, hydralazine 50–100 mg added if necessary to keep diastolic BP < 86 mmHg • Control: placebo	• Maternal death • Proteinuria • Side effect • Cesarean section • Neonatal and birth death • Preterm birth • Small for gestational-age infants

Table 1 (continued)

Author, year, country	Methods	Participants	Interventions	Outcomes included in Meta-analysis
Redman, 1976, UK	• Participants allocated randomely to antihyper-tensive treatment or no antihypertensive treatment • No information on allocation concealment • Open label	• BP ≧ 140/90 mmHg • Excluded: diabetes, multiple-pregnancy, > 32 weeks' gestation	• Treatment: methyldopa 750–4000 mg/day • Control: no antihypertensive	• Neonatal and birth death
Rubin, 1983, UK	• Double-blind randomized placebo controlled trial	• Systolic BP 140–170 mmHg and diastolic BP 90 to 110 mmHg • Excluded: contraindication to beta blockers	• Treatment: atenolol 100–200 mg/day • Control: placebo	• Proteinuria • Neonatal and birth death • Small for gestational-age infants
Shibai, 1987, USA	• Participants allocated randomely to antihyper-tensive treatment or hospitalization alone • Allocation concealment: physician drew a sealed envelope containing assignment • Open label	• Systolic BP 140–160 mmHg and diastolic BP 90 to 110 mmHg at 26–34 weeks' gestation • Excluded: associated medical and obstetrical complications	• Treatment: labetalol 300–2400 mg/day + hospitalization • Control: hospitalization alone	• Proteinuria • Neonatal and birth death
Shibai, 1990, USA	• Participants allocated randomely to antihyper-tensive treatment or no antihypertensive treatment • Allocation concealment: envelope randomization, 3-arm study • Open label	• Chronic mild-moderate hypertension at 6–13 weeks' gestation	• Treatment: (1) methyldopa 750–4000 mg/day, (2) labetalol 300–2400 mg/day • Control: no antihypertensive	• Cesarean section • Neonatal and birth death • Preterm birth • Small for gestational-age infants
Shibai, 1992, USA	• Participants allocated randomely to antihyper-tensive treatment or bed rest alone • Allocation concealment: physician drew a sealed envelope containing assignment • Open label	• Systolic BP 140–160 mmHg and/or diastolic BP 90 to 110 mmHg at 26–36 weeks' gestation • Excluded: associated medical and obstetrical complications or fetal compromise	• Treatment: nifedipine 40–120 mg/day • Control: bed rest alone	• Proteinuria • Cesarean section • Neonatal and birth death • Preterm birth • Small for gestational-age infants
Weits, 1987, USA	• Double-blind randomized placebo controlled trial	• BP > 140/90 mmHg at < 34 weeks' gestation without proteinuria	• Treatment: methyldopa 750–2000mg/day • Control: placebo	• Proteinuria • Side effect • Neonatal and birth death • Small for gestational-age infants
Wide Swensson, 1995, Sweden	• Double-blind randomized placebo controlled trial	• Diastolic BP 95–100 mmHg at 26–37 weeks' gestation • Excluded: history of alcohol or drug abuse	• Treatment: isradipine 10 mg/day • Control: placebo	• Cesarean section • Neonatal and birth death

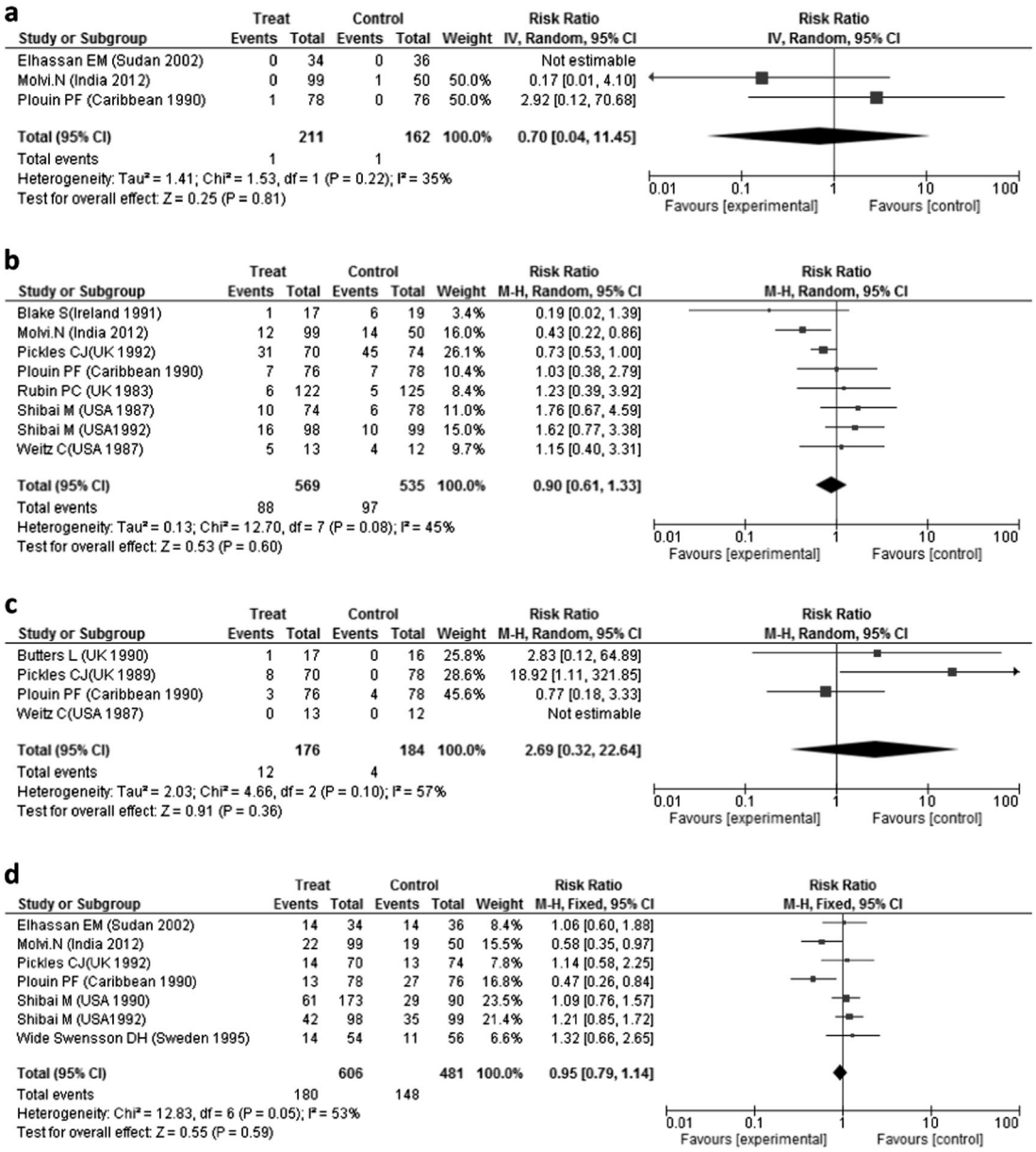

Fig. 2 Meta-analysis of maternal outcomes: antihypertensive drug versus placebo or no antihypertensive drug. **a** Maternal death. **b** Proteinuria. **c** Side effects. **d** Cesarean section for hypertensive disorders of pregnancy. Boxes and horizontal lines represent risk ratios and 95% confidence intervals (CIs) for each trial. The size of each box is proportional to the weight of that trial result. Diamonds represent the 95% CIs. Treat, antihypertensive drug; Control, placebo or no antihypertensive drug

Discussion

In this review, we pooled studies that examined the effects of antihypertensive drugs on non-severe hypertension during pregnancy. There was no evidence to suggest that antihypertensive drug therapy reduced or increased the risk of maternal death, proteinuria, side effects, cesarean section, neonatal and birth death, preterm birth, or small for gestational age infants. Although antihypertensive drug therapy resulted in reduced risk for developing severe hypertension, there were no differences in the risk for eclampsia, stroke, or HELLP (hemolysis, elevated liver enzymes, and low platelets) syndrome when antihypertensive drug therapy was compared with the control (data not shown). In all outcomes, except for cesarean section, very small numbers of outcome events resulted in imprecise estimates. The quality of evidence was low, which was attributed to serious inconsistency and imprecision.

It is widely accepted that women with severe hypertension during pregnancy are at increased risk of fatal

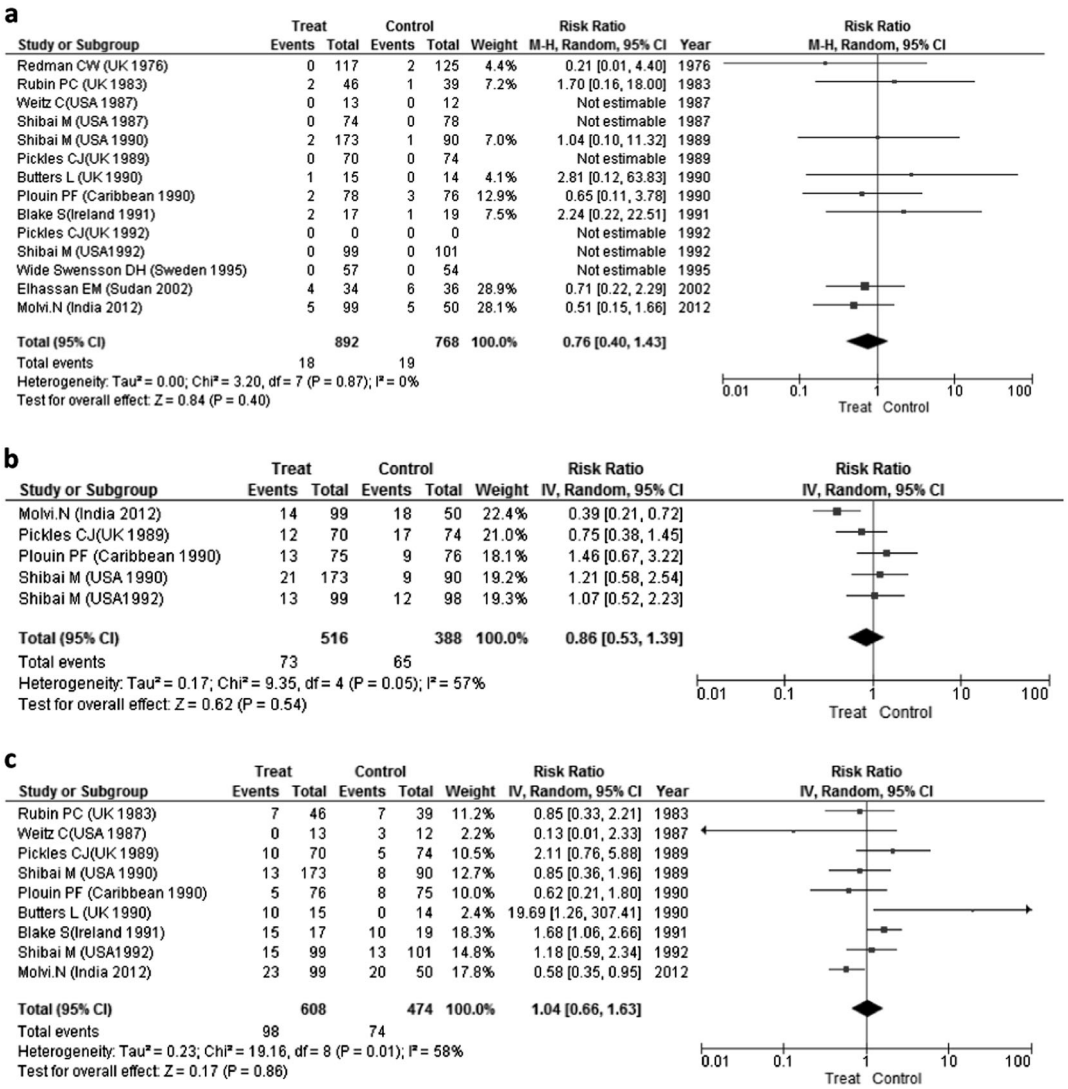

Fig. 3 Meta-analysis of perinatal outcomes: antihypertensive drug versus placebo or no antihypertensive drug. **a** Neonatal and birth death. **b** Preterm birth. **c** Small for gestational age infants. Boxes and horizontal lines represent risk ratios and 95% confidence intervals (CIs) for each trial. The size of each box is proportional to the weight of that trial result. Diamonds represent the 95% CIs. Treat, antihypertensive drug; Control, placebo or no antihypertensive drug

intracranial hemorrhage and require urgent and effective antihypertensive drug therapy [21, 22]. However, excessive BP lowering may impair placental vascularization and fetal development. Therefore, the benefits of antihypertensive drug therapy for women with HDP are to be weighed against the potential risk of fetal distress in the event of excessive BP lowering. Consistent with our results, a previous systematic review and meta-analysis revealed that there was not enough evidence to show the benefit of antihypertensive drugs for mild to moderate hypertension during pregnancy [23]. Moreover, the CHIPS trial, which randomized women with non-severe pregnancy hypertension to a diastolic BP target of 100 mmHg ("less tight" control) versus 85 mmHg ("tight" control), showed no significant between-group differences in the risk of pregnancy loss, high-level neonatal care, or overall maternal complications [24].

Limitations

This review has some limitations. First, the trials included in the study showed a relatively low level of quality because half of them failed to conduct a double-blind technique. Because almost all outcome data are only available from a small number of studies, reporting bias also needs to be taken into consideration. Second, no trials included in this review had a long-term follow-up. Women with HDP have been reported to be at high risk of later

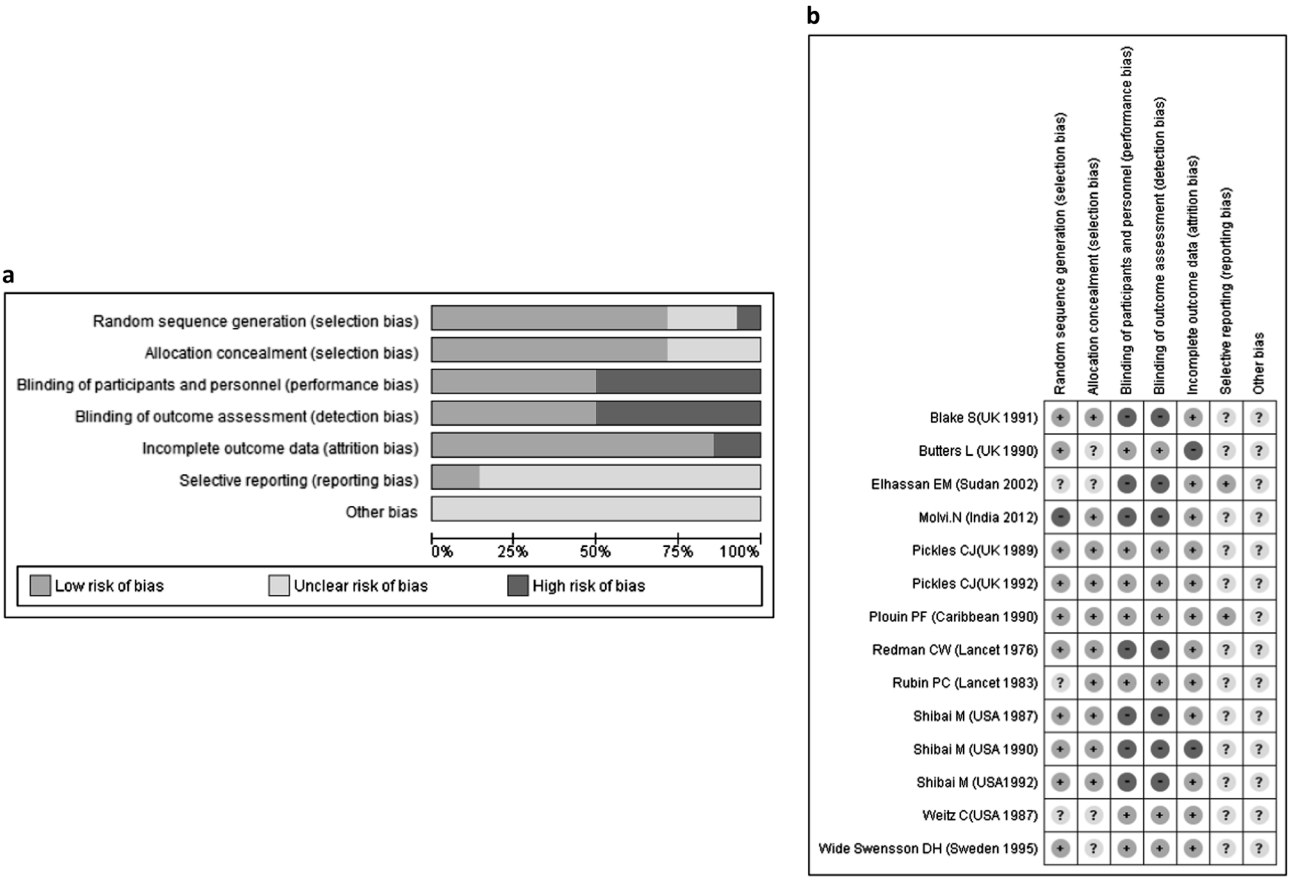

Fig. 4 Risk of bias assessment of each study included in the meta-analysis. **a** Risk of bias graph: a review of the author's assessments about each risk of bias item, presented as percentages of all included studies. **b** Risk of bias summary: a review of the author's assessments about each risk of bias item for each included study. +, low risk;?, unclear risk; and −, high risk

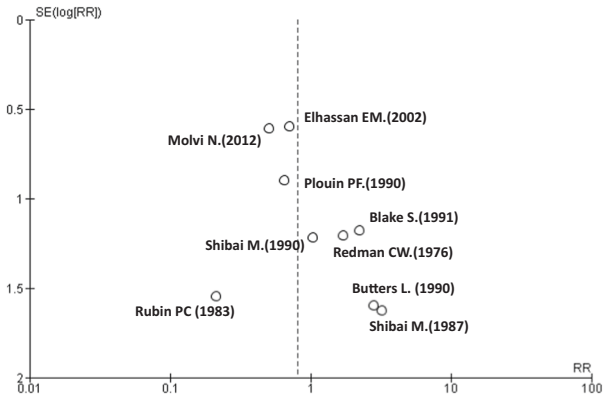

Fig. 5 Funnel plot comparing neonatal and birth death difference between studies. Open circles represent trials included in the meta-analysis. The dotted line in the center indicates the summary of the risk ratio. RR risk ratio; SE standard error

cardiovascular diseases, chronic kidney disease, and diabetes mellitus [25, 26]. However, the effects of antihypertensive drug therapy on the future cardiovascular and renal risk for mothers, as well as long-term child health, including attention deficit hyperactivity disorder, allergic diseases, and cardiovascular diseases after non-severe hypertension during pregnancy, are unknown. Third, the risks for maternal and/or perinatal outcomes of chronic hypertension might be different from those of gestational hypertension. However, because many trials included women with hypertensive disorders of pregnancy regardless of type of hypertension at trial entry, we could not evaluate the outcomes separately.

Conclusion

The current review suggests that antihypertensive drug therapy does not reduce or increase the risk of maternal death, proteinuria, side effects, cesarean section, neonatal and birth death, preterm birth, or small for gestational age infants. The quality of evidence was low. Therefore, it remains undetermined whether antihypertensive drug therapy for non-severe hypertension during pregnancy is worthwhile. Further studies are needed to build reliable estimates of the effectiveness and safety of antihypertensive drug therapy for women with HDP.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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