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Review article

First-line antihypertensive treatment for severe hypertension in pregnancy: A systematic review and network meta-analysis

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ABSTRACT

Background: Hydralazine, labetalol, and nifedipine are the recommended first-line treatments for severe hypertension in pregnancy. While all three are effective, there is a lack of sufficient evidence regarding their comparative safety and efficacy.

Objective: To determine the comparative safety and efficacy of the first-line treatment options for severe hypertension in pregnancy.

Methods: A systematic search of Medline, Embase, and Cochrane Central Register of Controlled Trials up to May 31, 2018 was conducted. RCTs in pregnancy comparing a first-line antihypertensive agent to another first-line agent for the treatment of severe hypertension in pregnancy. Screening, data abstraction, and quality assessment were done by two independent reviewers. To estimate relative effects from all available evidence, a Bayesian network meta-analysis with vague priors was conducted.

Main Results: Of the 1330 publications identified, 17 RCTs comprised of a total of 1591 women met our selection criteria. For successful treatment of severe hypertension, nifedipine was found to be superior to hydralazine (OR 4.13 [95% CrI 1.01–20.75]) but not labetalol (OR 3.43 [95% CrI 0.94–19.95]). This was not associated with an increased risk for caesarean delivery or maternal side effects. There was no significant difference between labetalol and hydralazine.

Conclusions: Given the results of this systematic review and network meta-analysis, maternity care providers should feel comfortable initiating management of severe hypertension in pregnancy using oral nifedipine.

1. Introduction

It is estimated that hypertensive disorders of pregnancy (HDP) complicate 5–10% of pregnancies worldwide and account for 18% of maternal deaths [1,2]. HDPs are responsible for 25% of maternal deaths in Latin America and the Caribbean, 16% in developed countries, and 9% in Asia and Africa [3]. As the leading contributor to maternal and neonatal mortality and morbidity across the world [1], optimal treatment of HDPs represents an important avenue for scientific inquiry.

Severe hypertension in pregnancy is defined as systolic blood pressure (sBP) ≥160 mmHg and/or diastolic blood pressure (dBP) ≥110 mmHg [4]. Severe hypertension in pregnancy is associated with a number of serious adverse events for mother and child. It increases the risk of maternal morbidities, including: stroke, maternal-end organ damage, abnormal clotting, postpartum hemorrhage, and placental abruption. In addition, the fetus is at increased risk of intrauterine growth restriction, premature delivery, and low Apgar score [1,5–7]. Another serious concern is the development of severe hypertension into preeclampsia, the most dangerous of HDPs [8].

For severe hypertension in pregnancy, there is general consensus supporting immediate intervention with antihypertensive agents [4,8]. Current clinical practice guidelines (CPGs) recommend intravenous (IV) hydralazine, IV labetalol, and oral nifedipine as the first-line antihypertensive treatments [5,6,9–11]. While all three are effective

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antihypertensive medications, there is a lack of sufficient evidence regarding their comparative safety and efficacy [8,12,13].

Based on the current body of evidence, the decision of which first-line antihypertensive treatment to use is based on physician experience, convenience of use, local availability, and cost [8,12–14]. Since effective management of severe hypertension is vital for safe progression of pregnancy, a more evidence-based approach is necessary. Network meta-analyses (NMA) use direct and indirect evidence to strengthen treatment comparisons and allow for effect estimates between interventions that have not been compared head-to-head and for the estimation of the relative efficacy and safety of the interventions under investigation [15].

Therefore, we conducted a systematic review and NMA to determine the comparative effectiveness and safety of hydralazine, labetalol, and nifedipine for severe hypertension in pregnancy.

2. Methodology

2.1. Systematic search

We conducted a comprehensive systematic search of Medline (ovid), Embase (ovid), and Cochrane central register of controlled trials (CCRT) up to October 20, 2015, then updated until May 31, 2018. The search strategies used are outlined in Appendix S1. The Medline search strategy was verified by comparing the results with 10 RCTs known to be relevant and peer reviewed by an information specialist using PRESS [16].

2.2. Study selection, data extraction, and study quality assessment

Screening, data abstraction, and assessment of the quality of each study was done by paired independent reviewers (SA, RC or SA, AC). The quality of trials that met the selection criteria were assessed using the Cochrane Collaboration's 'Risk of bias' tool for randomized controlled trials [17]. Disagreements were resolved by consensus or a third independent reviewer (LG).

Included in this review were all randomized controlled trials (RCTs) for treatment of severe hypertension or hypertensive emergencies in pregnancy using any of the three agents of interest (labetalol, hydralazine, nifedipine), regardless of dosage or administration protocol. Although severe hypertension is formally defined by International Society for the Study of Hypertension in Pregnancy as sBP of $\geq$160 mmHg and/or dBP $\geq$110 mmHg, we broadened our criteria to also include studies that investigated hypertensive emergencies. Therefore, we included studies that had minimum blood pressure criteria of sBP of $\geq$160 mmHg and/or dBP $\geq$105 mmHg. The studies had to also report at least one outcome of interest. Studies were excluded if they did not have an accompanying full-text in English or French, had combination interventions, or were restricted to only postpartum management of severe hypertension.

The primary outcome of interest was successful treatment of hypertension, as defined by the study. The secondary outcomes of interest were divided into maternal and fetal outcomes. Secondary maternal outcomes included: persistent hypertension, maternal hypotension, composite maternal morbidity*, proteinuria, preeclampsia, eclampsia, placental abruption, emergency termination of pregnancy, caesarean delivery, admission to ICU, composite maternal side effects†, adverse events (AE), withdrawal due to adverse events (WDAE), and serious adverse events (SAE). Secondary fetal outcomes included: perinatal death, neonatal death, stillbirth, neonatal intensive care unit (NICU) admission, premature delivery, Apgar < 7 at 5 min, small for gestational age (SGA), and fetal arrhythmia.

During data abstraction, patient and trial characteristics as well as outcome definitions were recorded and later reviewed as possible sources of clinical or methodological heterogeneity. Statistical heterogeneity evaluated for the standard pairwise meta-analysis using I^2. For each outcome, network inconsistency was evaluated using an inconsistency plot.

3. Data synthesis

To estimate relative effects from all available evidence (direct and indirect), a Bayesian network meta-analysis with vague (non-informative) priors and a homogenous variance structure was conducted for outcomes with sufficient evidence. Relative effects were calculated as odds ratios (ORs) with 95% credible intervals (CrI) using both a fixed and random effects model. The analysis was done using 5000 burn-ins and 40,000 iterations with NetMetaXL – a Bayesian network meta-analysis tool that uses WinBUGS from within Microsoft Excel [18]. NetMetaXL was also used to generate NMA network diagrams, forest plots, and rankograms. Convergence was assessed using the Brooks-Gelman-Rubin method and visual analysis of trace plots. Deviance information criterion (DIC) and inconsistency plots were used to assess model fit [18,19]. For each outcome, surface under cumulative ranking curve (SUCRA) was used for treatment ranking.

To estimate the relative effect of all direct pairwise comparisons, a standard pairwise meta-analysis using random effects model was conducted [20]. Comparative effect sizes were calculated as ORs with 95% confidence intervals (CI).

In October 2015, this systematic review and network meta-analysis was registered on PROSPERO (CRD42015025839).

4. Results

4.1. Study characteristics

Of the 1330 publications identified, 17 RCTs comprising a total of 1591 women met the selection criteria (Fig. 1) [21–37].

Overall, there were 595 patients (37.4%) receiving labetalol, 598 (37.6%) receiving hydralazine, and 398 (25%) receiving nifedipine. All labetalol and hydralazine arms had an intravenous (IV) route of administration. Of the 11 trials with a nifedipine arm, nine orally administered nifedipine, one sublingually [21], and one used sublingual route for the first three doses but any further dose was given orally [23]. There were no trials with more than two arms; six trials (802 women) that compared labetalol to hydralazine [22,24,25,32,33,37], six trials (422 women) that compared hydralazine to nifedipine [21,23,26,28,34,35], and five trials (367 women) that compared labetalol to nifedipine [27,29–31,36]. The pairwise meta-analyses can be found in Appendix S2.

Selected characteristics of included trials are presented in Table 1. Of the trials that had a labetalol arm, three had a maximum administration dosage of 140 mg while the remaining had a maximum dosage of 300 mg. The hydralazine and nifedipine maximum dosages varied between 40–90 mg and 15–45 mg, respectively. Details of trial dosage protocols and target blood pressures are presented in Appendix S3. Most trials had at least one component of sBP $\geq$160 mmHg or dBP $\geq$110 mmHg as part of their inclusion criteria. There were two trials that studied "Hypertensive Emergencies" which were defined as some variation of "sustained sBP $\geq$170 mmHg and/or dBP $\geq$105 mmHg" [28,30] . These trials had dosage protocols and target blood pressures within the variation between most other trials.

There were four trials that investigated patients with severe preeclampsia. Of these, three compared hydralazine to nifedipine

* Composite of non-fatal cerebrovascular, cardiovascular, and cardiopulmonary events (stroke, myocardial infarction, angina, ischemia, arrhythmias, congestive heart failure, pulmonary edema), kidney failure, liver failure, and permanent eyesight loss.

† Composite of dizziness, nausea, vomiting, headache, tachycardia, bradycardia.

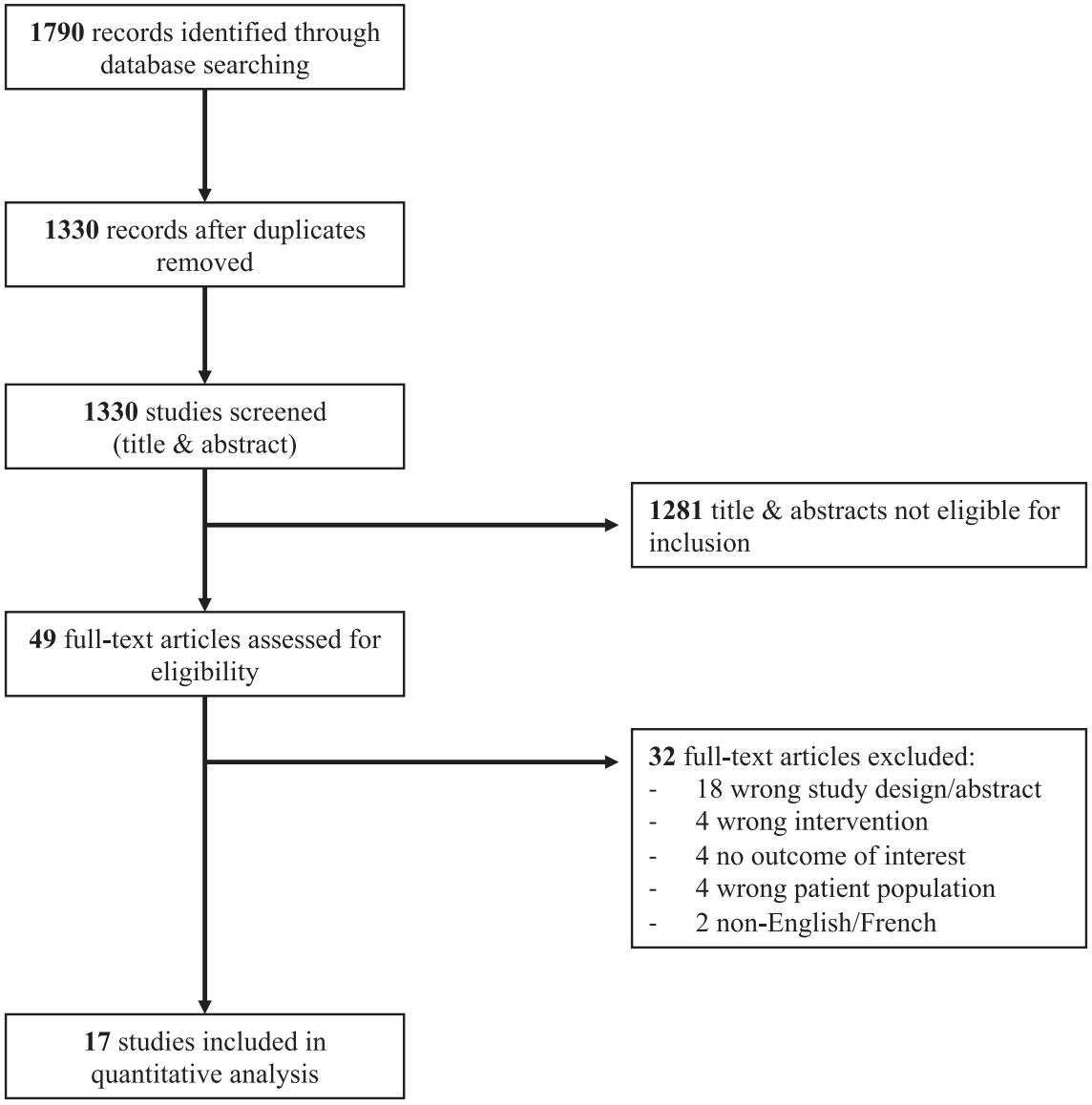

Fig. 1. PRISMA Flow Diagram – Literature Search and Screening Results.

[21,23,26] and one compared labetalol to nifedipine [36]. Of those comparing hydralazine to nifedipine, two administered the agent until time of delivery (no maximum dosage) [21,23] and one had an unclear dosage protocol [26].

Of the 17 studies, two recruited patients in the post-partum period [25,30]. *Vermillion et al.* enrolled during the intrapartum or within 24 h postpartum but did not report the number of patients in each category. *Mabie et al.* enrolled patients during pregnancy or in the puerperium, 19 of 60 received the randomized medication before delivery; 13/40 in the labetalol arm and 6/20 in the hydralazine arm.

For the network meta-analysis, the performance of both the fixed and random effects models were evaluated. The random effects models had a greater number of studies with a contribution to deviance close to one and therefore was the model used for analysis (Appendix S4).

4.2. Quality assessment

Amongst the included trials, there was a median sample size of 60 (range 30–275). The majority of studies had low or unclear risk of bias for most criteria (Appendix S5); ten out of 17 studies had a high risk of bias for both performance and detection bias, however, the effect on the results is unclear as most outcomes were objective in nature. Three studies showed high risk of attrition bias [21–23]. Based on the risk of bias assessment, the included trials were of poor to fair study quality.

The severe preeclampsia trials (Table 1) and variation in drug administration regimens (Appendix S3) between trials were identified as the primary source of clinical heterogeneity. When statistical heterogeneity was possible to assess, I^2 was < 30% in all cases except for labetalol vs nifedipine for composite maternal side effects (I^2 = 80%) and labetalol vs hydralazine for caesarean delivery (I^2 = 63%) (Appendix S2).

4.3. Blood pressure control

The network meta-analysis for successful treatment of severe hypertension consisted of eight trials with a total of 790 patients – 356 in the labetalol arm, 300 in the hydralazine arm, and 134 in the nifedipine arm (Appendix S6).

As presented in Fig. 2A, nifedipine was found to be superior to hydralazine (OR 4.13 [95% CrI 1.01–20.75]) but not labetalol (OR 3.43 [95% CrI 0.94–19.95]). There was no significant difference between labetalol and hydralazine.

There were 15 trials that reported on maternal hypotension and five trials that reported on persistent hypertension. Due to the low event

Table 1
Selected Characteristics of Included Trials.

Trial	Publication Year	Sample Size	Country	Gestational Age (Inclusion Criteria) Weeks	Type of Hypertension Definition	Maximum Total Administered Dosage (mg)		
						Labetalol (IV)	Hydralazine (IV)	Nifedipine (Oral)
Mabie	1987	60	United States	-	Severe Hypertension dBP ≥110 mmHg sustained for ≥30 min	300	Unclear	-
Vigil-De Gracia	2006	200	Panama	≥24	Severe Hypertension sBP ≥160 mmHg and/or dBP ≥110 mmHg	300	25	-
Delgado De Pasquale	2014	275	Panama	≥24	Severe Hypertension sBP ≥160 mmHg and/or dBP ≥110 mmHg	300	15	-
Morris	2016	30	United States	>20	Severe Hypertension (acute-onset, sustained) sBP ≥160 mmHg and/or dBP ≥110 mmHg for ≥15 min	140	30	-
Patel	2017	152	India	>28	Severe Hypertension sBP ≥160 mmHg and/or diastolic ≥110 mmHg	140	15	-
Tariq	2017	100	Pakistan	>20	Severe Hypertension Not defined; "as per operational definition"	300	30	-
Fenakel	1991	54	Israel	26-36	Severe Preeclampsia BP ≥160/110 on at least two occasions 3 hours apart with complete bed rest and one or more of: proteinuria (determined by dipstick), generalized edema, or hyperreflexia	-	No maximum	No maximum *Oral or Sublingual*
Martins-Costa	1992	37	Brazil	≥28	Severe Hypertension and Preeclampsia dBP ≥110 mmHg sustained for 50 minutes after bed rest on left side and significant proteinuria (≥300 mg in 24-hr collection urine, or a min of 3 pluses as measured by dipstick)	-	No maximum	No maximum
Aali	2002	126	Iran	>20	Severe Preeclampsia BP ≥160/110 and criteria of severe preeclampsia according to ACOG[21]	-	No maximum	No maximum *Sublingual*
Rezaei	2011	50	Iran	≥24	Hypertensive Emergency Sustained sBP ≥170 mmHg and/or dBP ≥105 mmHg	-	45	90
Sabir	2016	100	Pakistan	≥20	Severe Hypertension (Acute) sBP ≥160 and/or dBP ≥110mmHg	-	25	50
Sharma	2017	60	India	≥24	Severe Hypertension (Sustained) sBP ≥160 mm Hg or dBP ≥110 mm Hg on 2 separate occasions, ≥30 minutes apart	-	35	40
Vermillion	1999	50	United States	≥24	Hypertensive Emergency sBP ≥170 mmHg and/or dBP ≥105 mmHg sustained on repeat measurements 15 min apart	300	-	90
Raheem	2012	50	Malaysia	≥24	Hypertensive Emergency sBP ≥160 mmHg and/or dBP ≥110 mmHg on at least two occasions in the last 4 hrs	300	-	50
Shekhar	2013	60	India	≥24	Severe Hypertension (Sustained) sBP ≥160 mmHg and/or dBP ≥110 mmHg on two separate occasions, at least 30 min apart	300	-	50
Dhananjaya	2015	60	India	≥28	Hypertensive Emergency sBP ≥160 and/or dBP ≥110mmHg	300	-	50
Shi	2016	147	China	>30	Severe Hypertension and Preeclampsia sBP ≥160 and/or dBP ≥110mmHg, preeclampsia not defined	300	-	50

Gray shading: trial inclusion criteria is severe preeclampsia (which includes severe hypertension as part of the definition)

rate for both outcomes, an NMA was not performed (Table 2). In summary, the pooled incidence of hypotension was highest in the hydralazine group (7.55%) when compared to labetalol (1.68%) and nifedipine (0.57%). For persistent hypertension, nifedipine had the highest incidence (9.09%) when compared to hydralazine (6.64%) and labetalol (2.93%).

4.4. Caesarean delivery

The NMA consisted of ten trials with a total of 725 patients – 259 in the labetalol arm, 292 in the hydralazine arm, and 174 in the nifedipine arm (Appendix S6). The analysis showed no significant difference in caesarean delivery between any of the treatment comparisons (Fig. 2B).

4.5. Maternal side effects (composite)

The NMA consisted of 14 trials with a total of 1403 patients – 500 in the labetalol arm, 534 in the hydralazine arm, and 369 in the nifedipine arm (Appendix S6). The analysis showed no significant different in compose maternal side effects between any of the treatment comparisons (Fig. 2C).

4.6. Other maternal outcomes

SAE was reported by three studies. two comparing labetalol to nifedipine and one comparing hydralazine to nifedipine [21,29,36]. The incidence of events was zero for all groups. Similarly, eclampsia was reported by two studies, both with no incidence [23,24]. Other maternal outcomes that were had insufficient evidence for NMA are presented in Table 3. Preeclampsia as an outcome, emergency termination of pregnancy, and WDAE were not reported by any trials.

4.7. Fetal outcomes

There was a low event rate for perinatal death, neonatal death, stillbirth; Apgar < 7 at 5 min, and fetal arrhythmia also had low event rates (Tables 4 and 5) and therefore a network meta-analysis was not conducted.

Premature delivery and SGA were not reported by any of the trials. There was one trial that reported IUGR (fetal growth restriction) with 10 events (in 103 pregnancies) in the labetalol group and 8 events (in 102 pregnancies) in the hydralazine group [24].

4.8. Treatment rankings

Appendix S7 presents the rankogram and SUCRA for the reported outcomes. For successful treatment of hypertension, nifedipine is shown to have the highest probability of being ranked the first best (95.3%) while hydralazine has the highest probability of being ranked as the third best treatment (62.0%). The SUCRA for maternal side effects (composite) suggests hydralazine to have the lowest probability of being ranked as the best treatment (6.9%). There was no clear finding for caesarean delivery.

5. Discussion

5.1. Main findings

We have performed a network meta-analysis to assess the safety and efficacy of three widely used antihypertensive treatments in the context

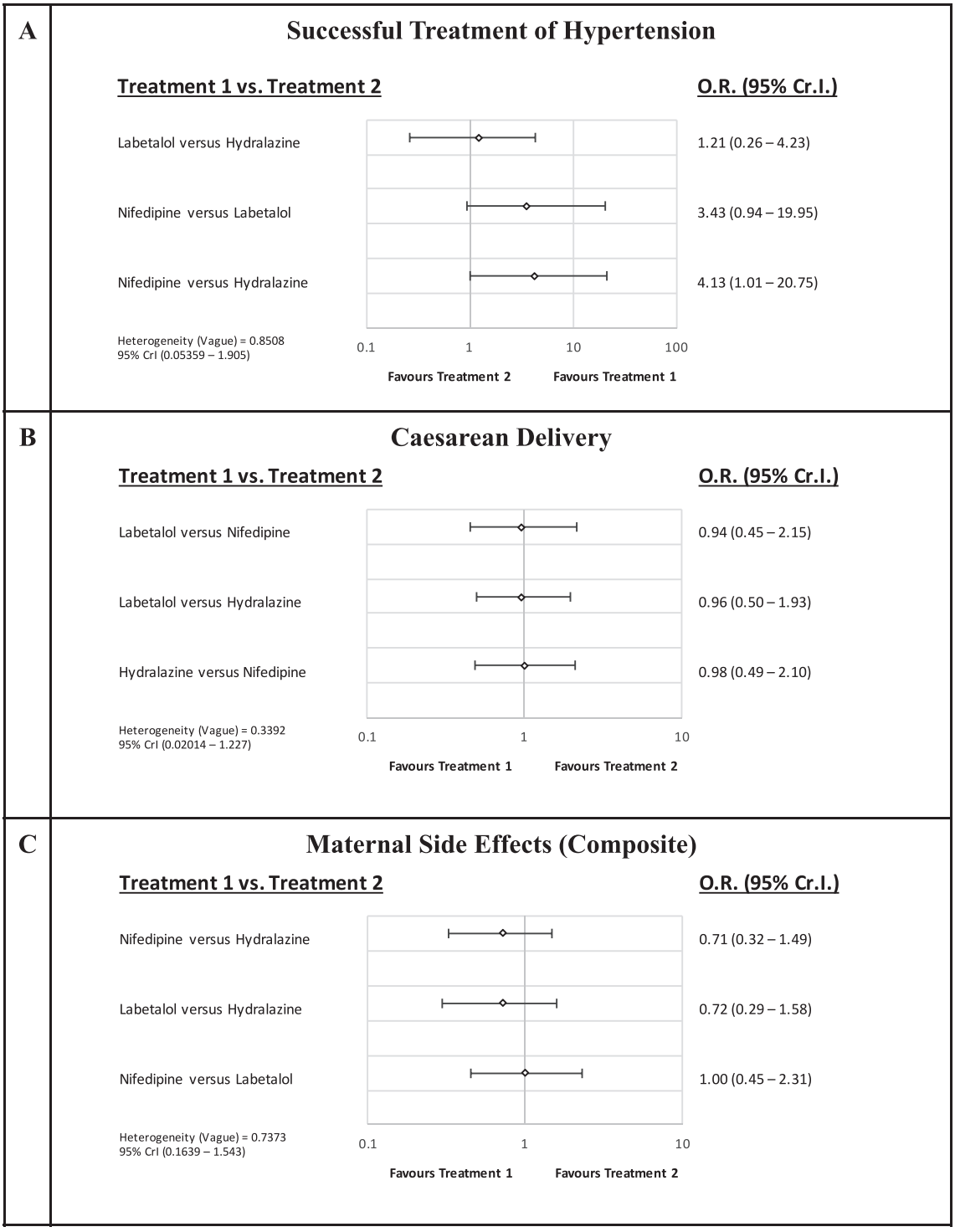

Fig. 2. Forest Plots for Network Meta-Analysis.

of severe hypertension in pregnancy. Through the use of both direct and indirect evidence, this systematic review suggests that oral nifedipine improves successful treatment of hypertension with no observed increase in risk for caesarean delivery or maternal side effects relative to IV hydralazine and with no significant difference to IV labetalol.

A recent trial comparing oral nifedipine to IV labetalol, consistent with our conclusion, shows no difference between the two drugs in successful treatment of severe hypertension [38]. It supports the use of nifedipine as it reports target BP to be achieved more rapidly and with fewer number of doses by nifedipine. This study was not included in our analysis as it was published after our search end-date.

A network meta-analysis by *Sridharan et al.* has also studied pharmacotherapy management of severe hypertension in pregnancy. Their inclusion criteria were different than our review in that they did not limit their analysis to first-line treatment options, and included trials that compared combination treatment (eg. *Ding et al.* comparing combination of nifedipine and resveratrol dual-therapy to nifedipine as monotherapy [39]). While their analysis included more interventions, they were unable to make conclusions for comparisons outside of hydralazine, labetalol, and nifedipine. Similar to our quality assessment,

Table 2
Maternal Hypotension and Persistent Hypertension (Raw Data).

Author (Publication Year)	# of Events / # of Patients		
	Labetalol	Hydralazine	Nifedipine
Maternal Hypotension			
Mabie (1987)	0/40	1/20	-
Vermillion (1999)	0/25	-	1/25
Aali (2002)	-	0/61	0/65
Vigil-De Gracia (2006)	0/100	2/100	–
Rezaei (2011)	–	0/25	1/25
Raheem (2012)	0/25	–	0/25
Shekhar (2013)	0/30	–	0/30
Delgado De Pasquale (2014)	0/131	0/130	–
Dhananjaya (2015)	0/30	–	0/30
Morris (2016)	0/15	0/14	–
Sabir (2016)	–	2/50	0/50
Shi (2016)	0/73	–	0/74
Patel (2017)	0/76	1/76	–
Sharma (2017)	–	1/30	0/30
Tariq (2017)	10/50	35/50	–
Total (Percentage)	**10/595 (1.68)**	**42/556 (7.55)**	**2/354 (0.57)**
Persistent Hypertension			
Vigil-De Gracia (2006)	5/100	5/100	–
Rezaei (2011)	–	11/25	5/25
Delgado De Pasquale (2014	2/131	6/130	–
Patel (2017)	2/76	2/76	–
Sharma (2017)	–	0/30	0/30
Total (Percentage)	**9/307 (2.93)**	**24/361 (6.64)**	**5/55 (9.09)**

Sridharan et al. found the evidence to be sub-optimal in quality primarily due to inclusion of studies with high risk of bias.

Similar to our findings, *Sridharan et al.* found no significant difference when comparing hydralazine and nifedipine to labetalol. For success of treatment, our results favored nifedipine compared to hydralazine (OR 4.13 [95% CrI 1.01–20.75]) while theirs found no difference (OR 2.1 [95% CI 0.9–5.2]). The reliability of both findings is unclear given the wide interval estimates.

While *Sridharan et al.* had the same primary outcome as our study, their secondary outcomes also included number of doses required and the time taken for successful treatment. The study found target BP to be achieved with fewer doses when using nifedipine compared to hydralazine with a mean difference (95% CI) of -0.4 (-0.8, -0.1) with no significant difference in time for achieving target blood pressure.

Their study's trial sequential analysis concluded sufficient evidence for the primary outcome when comparing hydralazine and nifedipine to labetalol, but insufficient evidence for the comparison between hydralazine and nifedipine.

Table 4
Perinatal Death, Neonatal Death, and Still Birth (Raw Data).

Author (Publication Year)	# of Events / # of Patients		
	Labetalol	Hydralazine	Nifedipine
Perinatal Death			
Fenakel (1991)	–	2/27	1/26
Shekhar (2013)	2/30	–	0/30
Morris (2016)	0/15	1/14	–
Neonatal Death			
Vigil-De Gracia (2006)	2/103	2/102	–
Shekhar (2013)	2/30	–	0/30
Shi (2016)	0/73	–	0/74
Sharma (2017)	–	0/30	0/30
Stillbirth			
Martins-Costa (1992)	0/30	–	0/30
Shekhar (2013)	–	0/17	2/20
Patel (2017)	3/76	4/76	–
Total (Percentage)	**9/357 (2.52)**	**9/266 (3.38)**	**3/240 (1.25)**

Table 5
Apgar Score < 7 at 5 min and Fetal Arrhythmia (Raw Data).

Author	# of Events / # of Patients		
	Labetalol	Hydralazine	Nifedipine
Apgar < 7 at 5 min			
Fenakel (1991)	–	2/27	1/26
Rezaei (2011)	–	0/25	0/25
Shekhar (2013)	2/30	–	1/30
Vermillion (1999)	2/14	–	1/15
Vigil-De Gracia (2006)	4/103	2/102	–
Shi (2016)	12/73	–	10/74
Patel (2017)	1/76	0/76	–
Sharma (2017)	–	1/30	2/30
Total (Percentage)	**21/296 (7.09)**	**5/260 (1.92)**	**15/200 (7.50)**
Fetal Arrhythmia			
Fenakel (1991)	–	0/27	1/26
Vermillion (1999)	1/14	–	2/15
Vigil-De Gracia (2006)	6/103	8/102	–
Rezaei (2011)	–	3/25	1/25
Sabir (2016)	–	3/50	1/50
Patel (2017)	12/76	21/76	–
Sharma (2017)	–	0/30	0/30
Total (Percentage)	**19/193 (9.84)**	**35/310 (11.3)**	**5/146 (3.42)**

The results of our study with respect to hydralazine and nifedipine are consistent with previous meta-analyses. The most recent Cochrane Collaboration review on drugs for treatment of very high blood pressure

Table 3
Other Maternal Outcomes (Raw Data).

Outcome	Author (Publication Year)	# of Events / # of Patients		
		Labetalol	Hydralazine	Nifedipine
Adverse Events (Minor)	Aali (2002)	–	10/61	11/61
Adverse Events	Shekhar (2013)	0/30	–	0/30
Adverse Events	Shi (2016)	14/73	–	11/74
Chest Pain	Shi (2016)	0/73	–	0/74
Convulsion	Patel (2017)	1/76	3/76	
HELLP	Dhananjaya (2015)	0/30	–	1/30
ICU Admission	Raheem (2012)	2/25	–	0/25
Kidney failure	Fenakel (1991)	–	1/25	2/24
Kidney failure	Dhananjaya (2015)	0/30	–	1/30
Kidney failure and pulmonary edema	Vigil-De Gracia (2006)	1/100	0/100	–
Palpitations	Raheem (2012)	0/25	–	1/25
Palpitations	Dhananjaya (2015)	2/30	–	10/30
Placental abruption	Vigil-De Gracia (2006)	1/100	2/100	–
Proteinuria	Dhananjaya (2015)	26/30	–	22/30
Shortness of Breath	Shi (2016)	0/73	–	0/74

during pregnancy found calcium channel blockers (nifedipine and nicardipine) to reduce the risk of persistent hypertension when compared to hydralazine [8].

Ultimately, the available literature suggests no greater harm with any one of the recommended first-line treatments. There is some evidence suggesting nifedipine's superiority and therefore should be further investigated in a well-designed randomized controlled trial.

One of the commonly reported adverse effects of hydralazine is hypotension which is concerning due to the association between feto-placental hypoperfusion [5]. Our study provides up-to-date evidence of the frequency of hypotension among the addressed interventions and confirms hydralazine as the intervention with the highest frequency; Labetalol 1.7%, Hydralazine 7.6%, Nifedipine 0.6%. We did not perform a meta-analysis due to the low event rates (Table 2).

In a systematic review which included one trial of 50 women, caesarean delivery risk was shown to be non-significant between those receiving nifedipine compared to labetalol [12]. This is consistent with the findings of our study which included direct evidence from a total of three trials with 139 women as well as indirect evidence from seven other trials.

In our study, there was no significant difference between maternal side effects of the interventions. This is in contrast to the meta-analysis of three trials and a total of 207 patients by *Shekhar et al.* which found nifedipine to be associated with fewer maternal side effects than labetalol [13]. Two of the three trials were included in our analysis. The third trial was not included as no full-text was identified. Our analysis included three trials that were not included in that meta-analysis. It is important that not all trials reported on all outcomes included in the composite. A core outcomes set for hypertension in pregnancy, similar to that which is being prepared for preeclampsia, would help improve the interpretability of results from meta-analyses on this topic [40].

One advantage of conducting a network meta-analysis is the ability to use SUCRA to provide comparative treatment ranking between three or more interventions. SUCRA provides a measure of the probability of a treatment to be ranked, compared to other treatments examined, as the most effective, second most effective, third most effective, etc. When examining the probability of being ranked number 1 (most effective treatment) we found that nifedipine had the highest probability to be the most effective at 95.3%. A potential interpretation can be phrased that nifedipine was shown to be most effective treatment in almost all of the Markov chain Monte Carlo simulations. A hypothesized clinical translation of this finding can be viewed as if the treating clinician has access to all the reviewed agents, providing nifedipine will likely provide the highest effectiveness in more than 95% of the patients given the medication. This can be contrasted to the decision to give labetalol or hydralazine where the expectation would be for them to be effective in 2–3% of the patients receiving this drug. Although that the difference between the probability to be ranked the number one drug (nifedipine) and the other two drugs is drastically different, as described previously by *Wang et al.*, it is important to be cautious in interpreting SUCRA findings as they can be misleading and imprecise [41]. Therefore, considering that the SUCRA does not provide a measure of potential uncertainty, it is difficult to ascertain if this difference is sufficiently and clinically meaningful.

Although we excluded trials exclusively studying the postpartum period, only one previous trial was identified that focused on the management of severe hypertension in the postpartum period [12,35,42]. This trial randomized 82 women with to IV labetalol or IV hydralazine and found no significant difference in treatment of severe hypertension or maternal side-effects. The 2019 ACOG Committee Opinion on management of acute-onset postpartum severe hypertension recommends IV labetalol and hydralazine as first-line treatments with extrapolation of safety of oral nifedipine based on trials that recruited in pregnancy. The National Institute for Health and Care Excellence 2019 recommendations propose treatment of hypertension in the postpartum period as an avenue for further research.

5.2. Strengths & limitations

There are several strengths associated with our study. Notably, this study uses direct and indirect evidence to evaluate the safety and efficacy of antihypertensive agents for severe hypertension in pregnancy. In addition, we have included a number of recent trials that have not previously been appraised or synthesized. Our study was also conducted in accordance to the Cochrane Handbook for Systematic Reviews of Interventions and the PRISMA-NMA statement [43].

The quantity of the available evidence and data did not facilitate conducting a robust network meta-analysis; as evident by the wide credible intervals demonstrated and the inability to perform a network meta-analysis on a number of pre-planned outcomes. The quality of the evidence informing our study is subject to a number of limitations as discussed in the results section. Our results are subject to poor to fair study quality and trials. In addition, we are unable to make a strong assessment of the safety profile of the treatments due to low event rates or poor reporting of safety outcomes.

Based on the information reported, the assessment of sources of clinical heterogeneity is limited. While most studies focused on women with severe gestational hypertension, four of the 18 studies limited their inclusion criteria to those with severe preeclampsia. Although severe hypertension (sBP $\geq$160 and/or dBP $\geq$110) is a component of both clinical conditions, preeclampsia is associated with significantly more adverse pregnancy outcomes than isolated gestational hypertension and thus, this may account for clinical heterogeneity. While most trials in the meta-analysis had a maximum number of dosages as part of their protocol, three of the four trials studying preeclampsia had no maximum dosage (Table 2). The findings of the individual trials were similar to others comparing the same two interventions (Appendix S2).

Another source of clinical heterogeneity was introduced by the two trials that studied "Hypertensive Emergencies". The blood pressure criteria for these trials (sustained sBP $\geq$170 mmHg and/or dBP $\geq$105 mmHg) falls within the criteria reported by ACOG Committee Opinion #767 ("acute-onset, severe hypertension [sBP of $\geq$160 mmHg and/or dBP $\geq$110 mmHg] that…is persistent for 15 min or more") but differs from the definition. Given the overlap in definition, a priori we broadened our inclusion criteria to include these trials. Importantly, these trials had dosage protocols and target blood pressures comparable to most other trials. The findings were similar to other trials (Appendix S2).

5.3. Interpretation

This systematic review provides a comprehensive summary of the evidence on first-line management of severe hypertension in pregnancy. While our network meta-analysis showed oral nifedipine to have better efficacy than IV hydralazine, a similar study did not find the relationship to be significant. In terms of safety, the current evidence, while limited, suggests a comparable safety profile between labetalol, hydralazine, and nifedipine; nifedipine has shown to have the lowest incidence of hypotensive episodes. As an inexpensive oral agent that does not require special storage, nifedipine also provides an economic advantage, and is more accessible for community care and resource-constrained settings. While maternity care providers should feel comfortable using oral nifedipine for management of severe hypertension, the relationship between nifedipine and hydralazine should be further investigated.

6. Conclusion

Given the results of this systematic review and the network meta-analysis, maternity care providers should feel comfortable initiating management of severe hypertension in pregnancy using oral nifedipine. Further efforts are needed on the direct comparison between nifedipine and hydralazine as well as educational and translational studies, and

evaluation of the implementation of nifedipine as first-line treatment for severe hypertension in pregnancy.

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Disclosure of interests

The authors declare no conflict of interest.

Contribution of authors

Sepand Alavifard contributed to the study conception, planning, performing the systemic review, network meta-analysis, and manuscript preparation.

Dr. Rebecca Chase contributed to performing the systematic review and preparation of this manuscript.

Andréanne Chaumont contributed to performing the systematic review and preparation of this manuscript.

Dr. Ghayath Janoudi contributed to the study conception, planning, data analysis, and manuscript preparation.

Dr. Andrea Lanes contributed to the study conception, planning, and manuscript preparation.

Dr. Mark Walker contributed to the study conception and planning, provided clinical expertise, and contributed to manuscript preparation.

Dr. Laura Gaudet contributed to the study conception and planning, provided clinical expertise, and contributed to manuscript preparation.

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Appendix A. Supplementary data

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