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Systematic review

Oral antihypertensive therapy for severe hypertension in pregnancy and postpartum: a systematic review

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Background Pregnant and postpartum women with severe hypertension are at increased risk of stroke and require blood pressure (BP) reduction. Parenteral antihypertensives have been most commonly studied, but oral agents would be ideal for use in busy and resource-constrained settings.

Objectives To review systematically, the effectiveness of oral antihypertensive agents for treatment of severe pregnancy/postpartum hypertension.

Search strategy A systematic search of MEDLINE, EMBASE and the Cochrane Library was performed.

Selection criteria Randomised controlled trials in pregnancy and postpartum with at least one arm consisting of a single oral antihypertensive agent to treat systolic BP ≥ 160 mmHg and/or diastolic BP ≥ 110 mmHg.

Data collection and analysis Cochrane RevMan 5.1 was used to calculate relative risk (RR) and weighted mean difference by random effects.

Main results We identified 15 randomised controlled trials (915 women) in pregnancy and one postpartum trial. Most trials in pregnancy compared oral/sublingual nifedipine capsules (8–10 mg) with another agent, usually parenteral hydralazine or labetalol. Nifedipine achieved treatment success in most women, similar to hydralazine (84% with nifedipine; relative risk [RR] 1.07, 95% confidence interval [95% CI] 0.98–1.17) or labetalol (100% with nifedipine; RR 1.02, 95% CI 0.95–1.09). Less than 2% of women treated with nifedipine experienced hypotension. There were no differences in adverse maternal or fetal outcomes. Target BP was achieved ~ 50% of the time with oral labetalol (100 mg) or methyldopa (250 mg) (47% labetelol versus 56% methyldopa; RR 0.85 95% CI 0.54–1.33).

Conclusions Oral nifedipine, and possibly labetalol and methyldopa, are suitable options for treatment of severe hypertension in pregnancy/postpartum.

Keywords Antihypertensive therapy, hypertensive disorders of pregnancy, oral agents, pregnancy, severe hypertension.

Linked article This article is commented on by Norton ME, p 1220 in this issue. To view this mini commentary visit http://dx.doi.org/10.1111/1471-0528.12738. The article has journal club questions by Duffy JMN, p.1219 in this issue.

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Background

International guidelines define severe pregnancy hypertension as systolic blood pressure (sBP) ≥ 160–170 mmHg and/or diastolic BP (dBP) ≥ 110 mmHg.[1–3] Severe hypertension is the only modifiable end-organ complication of pre-eclampsia, the most dangerous of the hypertensive disorders of pregnancy (HDP). However, severe hypertension may occur in association with any of the HDP, and either antenatally, intrapartum or postpartum.

It is widely accepted that women with severe hypertension are at increased risk of stroke and, as such, must have their BP lowered.[4,5] In the latest report from the Centre for Maternal and Child Enquiries (CMACE) in the UK (2006–08), failure to treat sustained severe hypertension was identified as the most common cause of substandard

care of women with pre-eclampsia who die in the UK;[5] 12 of the 18 women who died from pre-eclampsia suffered from severe hypertension-related intracerebral haemorrhage or cerebral infarction.

All international pregnancy hypertension guidelines recommend immediate treatment of severe pregnancy hypertension, a recommendation endorsed as 'strong' by the World Health Organization (WHO).[6] While severe pregnancy hypertension is a 'hypertensive urgency' that requires treatment, it is appropriate to lower BP over hours (and certainly within 24 hours) and this could be achieved with oral or parenteral antihypertensive therapy.

Traditionally, severe hypertension has been treated with short-acting parenteral antihypertensive agents, most frequently, intravenous hydralazine or labetalol.[7–9] These agents have been most widely studied in randomised controlled trials (RCTs), although systematic reviews have failed to reveal clear differences between agents.[10,11] Parenteral agents require more resources than do oral antihypertensive agents, in terms of equipment (i.e. intravenous tubing, syringes and needles) and personnel (as administration is by nurses or often, doctors). Also, parenteral agents require more monitoring and supervision because they are rapidly-acting and have the potential to lower BP within minutes and cause maternal hypotension and fetal compromise.

Oral therapy would be particularly attractive for community or office treatment of severe hypertension (while organising transport to facility) or in resource-constrained settings.

The objective of this systematic review was to assess the effectiveness of oral antihypertensive therapy for treatment of severe pregnancy or postpartum hypertension by reviewing relevant RCT evidence.

Methods

We undertook a comprehensive search for RCTs of oral antihypertensives for severe hypertension in pregnancy or postpartum, with no limitation on year of publication. The search strategy included the following databases: Medline using Pubmed, Excerpta Medica Database (Embase), the Cochrane Central Register of Controlled Trials (CCRCT), Cochrane Database of Systematic Reviews (CDSR), and Database of Abstracts of Reviews (DARE) up to 9 July 2012. In addition, we also searched bibliographies of retrieved papers and the authors' personal files. For trials in and outside pregnancy, abstracts without accompanying articles were included if they otherwise met inclusion criteria. Trials with quasi-randomisation were excluded.

The complete search strategy is summarised in Table 1. In brief, to identify RCTs, the search terms used were: 'antihypertensive agents', 'oral or sublingual', 'hypertension', 'hypertensive urgency', 'hypertensive emergency', 'hypertensive encephalopathy' and 'randomised controlled trials'. The search was limited to 'pregnancy, postpartum and puerperium'. Criteria for inclusion were severe hypertension (defined as a sBP $\geq$ 160 mmHg, dBP $\geq$ 110 mmHg, and/or mean arterial BP $\geq$ 127, either as inclusion criteria or as mean BP at enrolment), use of oral or sublingual antihypertensive therapy in at least one of the treatment arms, and at least one relevant measure of effectiveness within 24 hours of drug administration, as all guidelines state that BP must be lowered within that time frame.

All HDP were included and there were no language restrictions. Outcomes were adapted from published systematic reviews: the Cochrane Pregnancy & Childbirth Group for trials in pregnancy/postpartum, and the Brazilian Cochrane Centre for treatment of hypertensive urgencies (see Table S1).[10] We defined the postpartum period as up to 42 days after delivery. Maternal outcomes in pregnancy and postpartum included: caesarean delivery, placental abruption and maternal end-organ complications closely associated with pre-eclampsia (e.g. eclampsia). Perinatal outcomes included adverse effects on fetal heart rate, stillbirth, Apgar scores at 1 and 5 minutes, neonatal death and admission to a neonatal intensive care unit. Outcomes definitions were documented at data abstraction and considered as potential sources of between-study variation in outcomes. For duplicate publications, the most complete data set was used for any given outcome.

The quality of each trial was evaluated independently by two reviewers using the Cochrane Risk of Bias assessment tool (Table 2). Data were abstracted independently by two reviewers (LAM and TF) and discrepancies were resolved by discussion. The included trials were presented descriptively, and then the Cochrane Review Manager 5.1 was used for statistical analysis. Data were entered by subgroup according to the type of antihypertensive in each arm. We determined heterogeneity between studies by: examining the forest plot (of relative risk [RR] for each trial) and using the I^2 statistic. When heterogeneity between trials was found, we sought to explain it by examining differences in study design, women enrolled, intervention administered and/or outcomes definitions. The summary statistic was RR (and 95% confidence interval [95% CI]) by random effects model. For continuous variables, the weighted mean difference and 95% CI were used (random effects model). In addition, we calculated risk difference (RD), a measure of absolute effect that is both sensitive to between-trial differences in absolute event rates and inclusive of data from all trials, even those without reported events in either treatment arm.

The manuscript was prepared in accordance with the PRISMA checklist.[11] A protocol of the systematic review was not published.

Table 1. Search strategy

	Medline	Embase	CDRT
Antihypertensive medications	Antihypertensive agents OR calcium channel blockers	Exp antihypertensive agent/OR exp calcium channel blocking agent/	
Oral or sublingual therapy	Oral* or sublingual* or sub-lingual*	Exp oral drug administration/ OR exp sublingual drug administration/OR (oral* or sublingual* or sub-lingual*).mp. OR li.fs. OR po.fs	
Hypertensive disorder	Hypertensive Encephalopathy[mh] OR hypertension/complications[mh] OR hypertens* urgenc* OR hypertens* emerg* OR Hypertensive Encephalopathy OR (severe and hypertension) OR (hypertensive and crisis) OR (acute and hypertens*) OR (acute and treatment and hypertension) OR (acute and blood and pressure and lowering and effect) OR (malignant and hypertension) OR (accelerat* and hypertension) OR (hypertensive and encephalopat*)	Exp hypertensive crisis/OR (hypertension cris* OR hypertens* urgenc* OR hypertens* emerg* OR Hypertens* Encephalopat* OR severe hypertens* OR acute hypertens* OR malignant hypertens* OR accelerat* hypertens*).mp.	Hypertension cris* or hypertens* urgenc* or hypertens* emerg* or Hypertens* Encephalopat* or severe hypertens* or acute hypertens* or malignant hypertens* or accelerat* hypertens*
Randomised controlled trials	Controlled trial [pt] OR controlled clinical trial [pt] OR clinical trial [pt] OR randomized controlled trials [mh] OR random allocation [mh] OR double-blind method [mh] OR single-blind method [mh] OR ("clinical trial" [tw]) OR ((single*[tw] OR doubl*[tw] OR trebl*[tw] OR tripl*[tw]) AND (mask*[tw] OR blind*[tw])) OR placebos[tw] OR randomi*[tw] OR research design[mh:noexp] OR comparative study[pt] OR Evaluation Studies[PT] OR Evaluation Studies as Topic[mh] OR follow-up studies[mh] OR prospective studies[mh] OR control[tw] OR control[tw] OR controls[tw] OR controll* OR prospective*[tw] OR volunteer*[tw]	Exp "randomized controlled trial (topic)"/OR exp randomization/ OR double blind procedure/OR single blind procedure/OR clinical trial/OR (single mask* OR doubl* mask* OR trebl* mask* or tripl* mask* or singl* blind* OR doubl* blind* or trebl* blind* or tripl* blind*).mp. OR (placebo* or randomi*).mp. OR exp evaluation/OR exp follow up/ OR exp prospective study/OR (control* or prospective* OR volunteer*).mp. OR exp comparative study/OR Applied Limits: [clinical trial or randomized controlled trial or controlled clinical trial])	
Pregnancy (additional terms for trials in pregnancy and postpartum)	Pregnancy [mh] OR Pregnan* OR Gestation* OR pregnant women[mh] OR Pregnancy Complications[mh] OR "Postpartum Period"[Mesh] OR Puerperium OR postpartum OR "Peripartum Period"[Mesh] OR Peripartum* OR Perinatal Care[mh] OR perinatal	Exp pregnancy/OR Pregnan*.mp. or Gestation*.mp. OR exp pregnant woman/OR exp pregnancy complication/OR exp puerperium/ OR postpartum.mp. OR Peripartum Period.mp. or exp perinatal period/OR Peripartum*.mp. OR exp perinatal care/OR perinatal.mp. OR exp pregnancy disorder/	Pregnan* or Gestation* or puerper* or postpart* or Peripart* or perinat*
Filter	Humans	Humans	

Results

Pregnancy and postpartum

Of 465 papers identified, 16 published from 1982 to 2011 met eligibility criteria: 15 in pregnancy[12–29] (914 women) (one of which was a three-armed trial)[26] and one a postpartum trial (38 women)[24] (Figure 1). Two abstracts were later published as full studies.[28,29] The reasons for exclusion were: no randomisation,[30,31] enrolment of women with nonsevere hypertension,[32] failure to identify one

Table 2. Study quality

Study	Sequence generation	Allocation concealment (selection bias)	Blinding	Selective outcome reporting	Incomplete outcome data
Pregnancy					
Australia 2002 (Brown)	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Unclear risk
Brazil 1992 (Martins-Costa)	Low risk	Unclear risk	Low risk	Unclear risk	Unclear risk
Brazil 1994 (Mesquita-Duley)	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Unclear risk
Iran 2002 (Aali)	Unclear risk	Low risk	Unclear risk	Unclear risk	Unclear risk
Iran 2011 (Rezaei)	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Unclear risk
Malaysia 2011 (Raheem)	Low risk	Unclear risk	Unclear risk	Unclear risk	Unclear risk
Mexico 1989 (Walss-Rodriguez)	Low risk	Low risk	Unclear risk	Unclear risk	Unclear risk
Mexico 1993 (Walss-Rodriguez)	Low risk	Low risk	Unclear risk	Unclear risk	Unclear risk
New Zealand 1992 (Duggan)	Unclear risk	Unclear risk	Low risk	Unclear risk	Unclear risk
South Africa 1989 (Seabe)	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Unclear risk
South Africa 2000 (Hall)	Low risk	Low risk	High risk	Unclear risk	Unclear risk
USA 1999 (Vermillion and Scardo)	Low risk	Low risk	Low risk	Unclear risk	Unclear risk
England 1982 (Moore)	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Unclear risk
Argentina 1990a (Voto)	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Unclear risk
Argentina 1990b (Voto)	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Unclear risk
Mexico 1998 (Vargas)	Unclear risk	Unclear	Unclear risk	Unclear risk	Unclear risk

antihypertensive treatment arm as administered orally or parenterally,[33] and inability to obtain abstracts for review (despite contacting our local libraries and the Cochrane library).[34,35]

Trials were generally small with a median of 50 women (range 20–150). There was a wide range of HDP type at inclusion, most commonly pre-eclampsia deemed to be severe, of onset at < 34 weeks of gestation, or complicated by eclampsia (nine trials); fewer trials enrolled women with any HDP (three trials), gestational hypertension (two trials) or an unspecified HDP (one trial). Gestational age at enrolment varied, as follows: > 20 weeks (two trials), ≥ 24 weeks (four trials), > 28 weeks (four trials), < 34 weeks (one trial), < 36 weeks (two trials), or was not stated (two trials). The median BP values at enrolment in the intervention and control arms were 167/109 mmHg versus 169/114 mmHg, respectively. When specified, the BP treatment goal was usually a dBP < 110 mmHg (seven trials) or < 100 mmHg (three trials), to be achieved over a short time frame: 20 minutes,[15] 90 minutes[12] or 120 minutes.[13,18,21]

The quality of each trial was fair at best (Table 2). An unclear risk of bias was seen for most trials for sequence generation (8 out of 15), allocation concealment (9 out of 15) and masking (10 out of 15), and incomplete outcome data (14 out of 15). An unclear risk of bias was seen for all trials for selective outcome reporting.

Nifedipine

Twelve RCTs compared oral/sublingual nifedipine capsules or tablets (5–10 mg, 724 women) with another agent. Most compared nifedipine with intravenous hydralazine (5–20 mg, seven trials, 350 women)[13,14,16,19–21] or intravenous labetalol (20 mg, two trials, 100 women).[17,23] Other trials compared short-acting nifedipine with oral nifedipine 10 mg prolonged action (PA) tablets (one trial),[12] oral prazosin 1 mg (one trial)[22] or intravenous/intramuscular chlorpromazine 12.5 mg (one trial).[18] The postpartum RCT (38 women) compared sublingual nifedipine with intravenous hydralazine.[24]

Nifedipine was administered as a capsule (eight trials), tablet (three trials; one was a comparison of capsule versus tablet), or the formulation was unclear (two trials). Nifedipine was administered by capsule puncture/biting ($n = 4$), swallowing of capsule whole ($n = 1$), or by an unclear method ($n = 3$).

Nifedipine capsules (10 mg orally), compared with nifedipine PA tablets (10 mg orally), were associated with more maternal hypotension (< 110/80 mmHg) at 90 minutes (35% versus 9%; RD 0.26, 95% CI 0.07–0.46, one trial, 64 women).[12] No fetal deaths were reported in either arm. The absolute rate of hypotension with nifedipine capsules in this trial (35%) was higher than that seen in the six other nifedipine capsule trials of similar dosage (8–10 mg) where the rate of maternal hypotension was 3/158 women (absolute rate 1.90%, RD 0.01, 95% CI − 0.02 to 0.03; six trials).

When short-acting nifedipine was compared with intravenous hydralazine in pregnancy, there was no difference in effectiveness, as seen by: achievement of target BP (84% [nifedipine] versus 79% [hydralazine]; RR 1.07 95% CI 0.98–1.17; five trials, 273 women), the time taken to achieve the target BP (weighted mean difference

Figure 1. Literature search results.

−1.36 hours, 95% CI −6.64 to 4.14), or the need for a repeat dose(s) of antihypertensive (51% versus 55%; RR 0.97 95% CI 0.50–1.88; four trials, 246 women). Maternal hypotension was unusual and did not differ between groups (1.6% versus 0%; RD 0.00 95% CI −0.02 to 0.03; four trials, 246 women) (Figure 2). There were no maternal deaths reported (RD 0.00 95% CI −0.03 to 0.03; three trials, 96 women). There were no differences in perinatal outcomes reported (caesarean delivery, adverse fetal heart rate effects, Apgar score < 7 at 5 minutes, perinatal death, neonatal death or stillbirth) (see Table S2). One RCT (38 women) compared sublingual nifedipine with intravenous hydralazine postpartum, with no between-group differences demonstrated in the need for additional antihypertensive therapy (5% versus 28%; RR 0.18, 95% CI 0.02–1.40; one trial, 38 women).[35]

When short-acting nifedipine was compared with intravenous labetalol (two trials, 100 women), there was no difference in maternal or perinatal outcomes (see Table S3). Of particular note, there was no difference in achievement of successful treatment (RR 1.02, 95% CI 0.95–1.09, two trials, 100 women).

Nifedipine capsules, compared with oral prazosin, were associated with fewer Caesarean deliveries (64% versus 70%; RR 0.90, 95% CI 0.07–0.53, 150 women). Although not statistically significant, there appeared to be fewer stillbirths in the nifedipine group (6/75) compared with the oral prazosin group (13/74).

Labetalol and methyldopa

There was a single trial (74 women) that compared oral labetalol 100 four times daily with oral methyldopa 250 mg four times daily.[25] There was no difference in achievement of target BP (47% versus 56%; RR 0.85 95% CI 0.54–1.33) although the time over which BP was lowered was not stated. No between-group differences were seen in caesarean delivery (50% versus 59%; RR 0.85, 95% CI 0.56–1.30) or perinatal death (5% versus 0%; RD 0.05 95% CI − 0.03 to 0.14).

A three-arm trial compared oral methyldopa with either oral atenolol (50–200 mg) or ketanserin (80–120 mg).[26] This trial did not report on effectiveness in lowering BP. Perinatal outcomes did not differ between the groups (see Table S4).

Other antihypertensive agents

One small trial (36 women) compared sublingual isosorbide with parenteral magnesium sulphate and found no difference between groups in requirements for additional antihypertensive therapy (0% versus 17%; RR 0.14, 95% CI 0.01–2.58) although there were fewer caesarean deliveries in the sublingual isosorbide group (16% versus 89%; RR 0.19, 95% CI 0.07–0.53).[27]

Discussion

Main findings

Based on RCTs in pregnancy and postpartum, we found that a single oral agent can adequately lower BP when

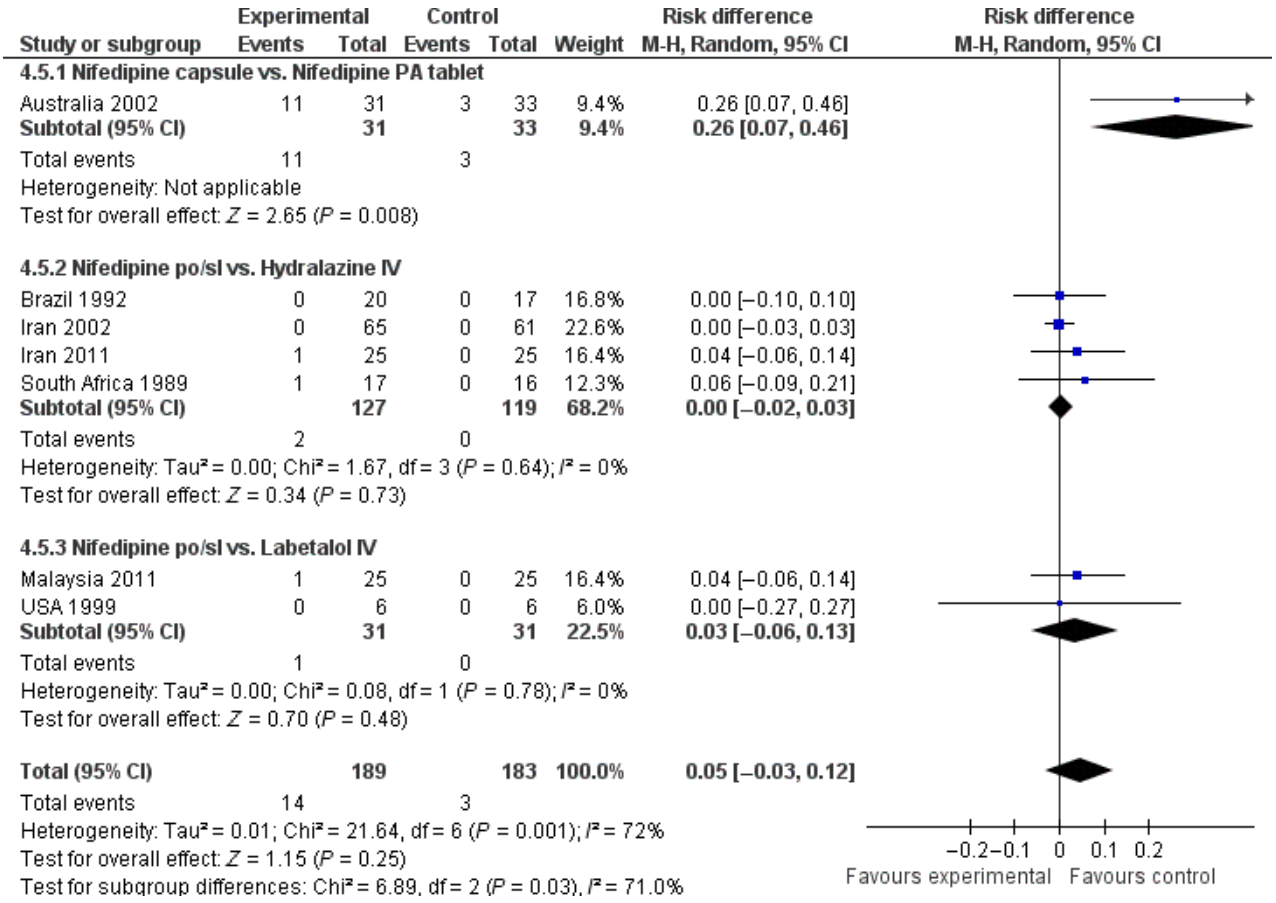

Figure 2. Maternal hypotension.

compared with parenteral agents. In particular, oral nifedipine (10 mg), compared with parenteral hydralazine or labetalol, is a suitable oral agent for treatment of severe hypertension in pregnancy or postpartum, with: similar and high treatment success rates (of at least 84%); low rates of maternal hypotension (< 2%, 3/158 women in six trials comparing nifedipine with either intravenous hydralazine or labetalol); and similar maternal and perinatal outcomes. Although there was one 10-mg nifedipine capsule versus 10-mg PA tablet trial that did report more hypotension with the capsule formulation, the absolute rates of hypotension were high in both arms of this trial (35% in the capsule arm and 9% in the 10-mg tablet arm) compared with the six other nifedipine capsule trials of similar dosage (3/158, 1.90%); also, that hypotension was not necessarily associated with adverse clinical effects.

The few, small comparative trials of other antihypertensive agents in pregnancy/postpartum preclude any firm conclusions. However, the limited data suggest that oral labetalol and methyldopa may be effective in approximately 50% of pregnant women. Caution should be exercised if considering use of oral prazosin given its association with more caesarean deliveries and, possibly, stillbirths.

Strengths

We captured a large number of studies of oral antihypertensive treatment of severe hypertension in pregnancy/postpartum, given our search of multiple sources and no language restriction. We also defined and presented absolute rates of treatment success.

Weaknesses

The first limitation of our review is that we had a meaningful body of RCTs for the nifedipine versus other antihypertensive (particularly intravenous hydralazine in pregnancy) comparisons, but all others were underpowered to find important between-group differences in outcomes given the limited number and size of trials. Second, our results are limited by poor to fair study quality.

Interpretation

To our knowledge, this is the first systematic review to specifically examine oral antihypertensive therapy for severe

hypertension in pregnancy and postpartum. There are, however, other meta-analyses of trials of short-acting parenteral agents that include oral nifedipine in pregnancy/postpartum, and the results of the oral nifedipine versus parenteral hydralazine subgroup are consistent with our analysis.[9,10]

Outside pregnancy, American guidelines recommend that antihypertensive therapy be initiated with two oral agents for treatment of severe hypertension. This recommendation is based on the multi-factorial nature of the BP elevation and the limited (but variable) average BP reduction of 9.1 mmHg in sBP and 5.5 mmHg in dBP achieved after treatment with any one agent.[36] In pregnancy, initiating antihypertensive therapy with a single agent may be more appropriate given the intravascular volume depletion associated with both severe hypertension and pre-eclampsia,[37] and the potential for fetal compromise if BP is lowered too quickly. In the regional pre-eclampsia guidelines from Yorkshire, UK, labetalol 200 mg is administered orally before intravenous access is secured, with a repeat dose given if no response is seen after 30 minutes.[38] The 2010 UK National Institute for Health and Clinical Excellence (NICE) Hypertension in Pregnancy guideline recommends oral labetalol or nifedipine for the treatment of severe hypertension in women during pregnancy or after birth.[2]

Our review presents reasonable options for oral antihypertensive therapy of severe hypertension in pregnancy or postpartum. First, options are key as there may be contraindications to use of a given drug (or women may already be on high doses of an oral agent when they present with severe hypertension). For example, there are published concerns about heightened cardiovascular morbidity/mortality associated with use of short-acting nifedipine outside pregnancy,[39,40] and neuromuscular blockade with contemporaneous use of magnesium sulphate and nifepidine in pregnancy (although the risk was estimated to be < 1% in a controlled study that incorporated data from RCTs).[41] The usefulness of beta-blockers may be limited in areas where reactive airways disease is prevalent and air quality is poor (such as in Pakistan).[42–44] Second, options for oral antihypertensive therapy are available; the 2012 Priority Medicines for Mothers and Children, a list of essential life-saving medications for women and children, has included methyldopa and hydralazine as antihypertensive agents, and nifedipine is also listed (albeit as a tocolytic).[45] All of these medications are on the essential medicines lists of most low- and middle-income countries.[46] Finally, based on proven effectiveness for treatment of severe hypertension outside pregnancy, there may be other treatment options that have not been studied in pregnancy or particularly, postpartum. For example, captopril is acceptable for use during breastfeeding and is known to be an effective agent for severe hypertension outside pregnancy.[47,48]

Conclusion

Severe hypertension in pregnancy and postpartum should be treated to decrease the risk of maternal stroke. Oral agents would be particularly appropriate in the outpatient setting while arranging transfer to hospital or in resource-constrained institutions, such as busy delivery suites in high-income settings or any maternity care facility in low- and middle-income countries where the vast majority of HDP-related maternal complications occur.

The oral antihypertensive agent for which there is the most evidence for treatment of severe hypertension in pregnancy/postpartum is nifedipine (10 mg). Labetalol (100 mg) and methyldopa (250 mg) are reasonable second-line options based on far more limited data. The choice of an oral antihypertensive agent for a given woman will be driven by many considerations, such as practitioner familiarity, efficacy, low-risk of maternal hypotension, duration of action, compatibility with magnesium sulphate, and no important contraindications with regards to concomitant medical conditions.

Future trials should focus on head to head comparisons of oral agents, particularly nifedipine, labetalol and methyldopa; one such trial is underway (http://gynuity.org). Studies should also focus on early treatment of severe hypertension in the community, particularly in low- and middle-income countries where delays in triage and transport could make antihypertensive treatment extremely important for stroke prevention.

Disclosure of interests

None declared.

Contribution to authorship

TF and LAM were responsible for data abstraction, data entry and execution of the manuscript. KM, CPSBC librarian, performed the literature search. All authors reviewed and edited the manuscript.

Details of ethics approval

This was a systematic review of published literature, so ethics approval was not required.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Relevant outcomes in trials of oral antihypertensive therapy for severe hypertension.

Table S2. Nifedipine per os/sublingual versus hydralazine intravenous: caesarean delivery and major perinatal outcomes.

Table S3. Nifedipine per os/sublingual versus labetalol intravenous: maternal and perinatal outcomes.

Table S4. Methyldopa versus other agents: maternal and perinatal outcomes.

Data S1. Powerpoint slides summarising the study.

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