

How to manage hypertension in pregnancy effectively

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The hypertensive disorders of pregnancy (HDP) are a leading cause of maternal mortality and morbidity in both well and under-resourced settings. Maternal, fetal, and neonatal complications of the HDP are concentrated among, but not limited to, women with pre-eclampsia. Pre-eclampsia is a systemic disorder of endothelial cell dysfunction and as such, blood pressure (BP) treatment is but one aspect of its management. The most appropriate BP threshold and goal of antihypertensive treatment are controversial. Variation between international guidelines has more to do with differences in opinion rather than differences in published data. For women with severe hypertension [defined as a sustained systolic BP (sBP) of ≥ 160 mmHg and/or a diastolic BP (dBP) of ≥ 110 mmHg], there is consensus that antihypertensive therapy should be given to lower the maternal risk of central nervous system complications. The bulk of the evidence relates to parenteral hydralazine and labetalol, or to oral calcium channel blockers such as nifedipine capsules. There is, however, no consensus regarding management of non-severe hypertension (defined as a sBP of 140–159 mmHg or a dBP of 90–109 mmHg), because the relevant randomized trials have been underpowered to define the maternal and perinatal benefits and risks. Although antihypertensive therapy may decrease the occurrence of BP values of 160–170/100–110 mmHg, therapy may also impair fetal growth. The potential benefits and risks do not seem to be associated with any particular drug or drug class. Oral labetalol and methyldopa are used most commonly, but many different β -adrenoceptor blockers and calcium channel blockers have been studied in clinical trials.

Introduction

The hypertensive disorders of pregnancy (HDP) are common. According to population-based data, 7–9% of pregnancies are complicated by hypertension, defined as a diastolic blood pressure (dBP) ≥ 90 mmHg and/or a systolic BP (sBP) of ≥ 140 mmHg [1].

The HDP are important because they are a leading cause of maternal and perinatal mortality and morbidity, worldwide [2]. Most of the morbidity is concentrated among pregnancies complicated by pre-eclampsia/eclampsia, which is the leading or second-leading cause of maternal death in the UK [2], Canada [3] and the developing world [4]. In addition, for every woman who dies, approximately 20 others suffer severe morbidity [4].

Pre-eclampsia complicates 2% of pregnancies. Pre-eclampsia is classically defined as proteinuria and gestational (pregnancy-induced) hypertension after 20 weeks [1]. More inclusive definitions are advocated by Canadian and Australasian guidelines, which define pre-eclampsia as gestational hypertension with proteinuria and/or either a maternal end-organ complication(s) (e.g. eclampsia) or fetal involvement [5, 6] (http://www.somanz.org/pdfs/somanz_guidelines_2008.pdf). An additional 1% of pregnancies are complicated by pre-existing hypertension (defined as hypertension with onset before pregnancy or before 20 weeks), and 5–6% by isolated gestational hypertension [5].

Hypertension in pregnancy is also classified as severe or non-severe. Severe hypertension is variably defined as a

BP of $\geq 160/110$ mmHg and non-severe (or 'mild-moderate') as a BP of $140/90$ – $159/109$ mmHg. As with all patients, accurate measurement of BP is critical. The recommended technique is as advocated outside pregnancy, with sitting BP being particularly important in order to bring the gravid uterus off the inferior vena cava. Few automated BP measurement devices on the market have been validated for use in pregnancy and pre-eclampsia specifically, such as the Dinamap ProCare® [7], Microlife 3BTO® [8] and WatchBP® [9]. Those that have been validated have usually received a grade A/B rating for pre-eclampsia (according to the British Hypertension Society protocol), but clinically important variability in measurement has been demonstrated and remains relevant to the individual woman [10]. In general, automated devices underestimate BP in pre-eclampsia by 5 mmHg, with large variations in systolic (SD of 8 mmHg) and diastolic BP (SD of 7 mmHg) [9, 10].

Antihypertensive therapy

Drug metabolism changes significantly in pregnancy, largely resulting in increased clearance and decreased pharmacological effect. The increased glomerular filtration rate associated with pregnancy will enhance the apparent oral clearance of drugs such as atenolol, the primary disposition of which is dependent on renal filtration [11]. Calcium channel blockers are substrates of the enzyme CYP3A which is upregulated in pregnancy such that the expected area under the curve (AUC) may be 50% of that seen with the same dose outside pregnancy [12]. Metoprolol, propranolol and clonidine are substrates of CYP2D6 which is also upregulated in pregnancy resulting in substantially reduced serum concentrations [13, 14]. The presence of relatively common CYP2D6 polymorphisms for slow and ultra-rapid metabolizers further complicates the anticipated response to CYP2D6 substrates in pregnancy. Labetalol is metabolized through conjugation to glucuronide metabolites. Conjugation also appears to be upregulated in pregnancy such that labetalol has a reported half-life of 1.7 h following oral ingestion [15].

The impact of changes in metabolism should be considered when choosing a drug for therapy and when selecting appropriate dosing. The therapeutic effect of drugs such as β -adrenoceptor blockers can be directly monitored by assessing changes in heart rate. Dosing frequency for many drugs will need to be increased. For example, one would not expect efficacy from a commonly used drug such as labetalol with a half-life of 1.7 h if dosed twice a day. Given a basic understanding of alterations of pharmacokinetics in pregnancy and clinical observations of drug effect (particularly at the end of a dosed interval), the practicing clinician can make reasonable adjustments in dose and dosed interval to achieve a desired effect.

Severe hypertension

There is consensus that sustained severe hypertension in pregnancy should be treated as it is considered to be a risk factor for maternal end-organ complications (such as stroke), independent of pre-eclampsia [5, 6, 16]. In fact, many of the serious maternal (e.g. pulmonary oedema, abruption) and perinatal complications (e.g. preterm delivery and perinatal death) are more common among women with severe gestational hypertension without proteinuria than those women with non-severe gestational hypertension with proteinuria [17, 18].

A sBP threshold of 160 mmHg has been suggested as a more appropriate threshold for defining severe maternal hypertension, based on a case series of 28 women with pre-eclampsia and stroke [19]. In this series, 96% of women had a sBP ≥ 160 mmHg immediately prior to their stroke, but only 13% had a dBP ≥ 110 mmHg. This series has been criticized for its potentially biased ascertainment of cases and its small sample size, which precludes use of a statistical model that could confirm the independent importance of sBP by adjusting for dBP and other important covariates.

The 2003–2005 UK Confidential Enquiry into Maternal and Child Health (CEMACH) report found that the second most common cause of maternal death was pre-eclampsia/eclampsia (18 deaths representing 0.85/100 000 maternities) [2]. Twelve of these deaths were due to stroke (10 intracranial haemorrhage) and in 13, the most common source of sub-standard care was failure of effective antihypertensive therapy. The CEMACH report concluded that 'Systolic blood pressures over 160 mmHg must be treated' and this recommendation has been reflected in subsequently published Canadian and UK guidelines, including the recently published National Institute of Health and Clinical Excellence (NICE) guideline in August 2010 [5] (<https://guidance.nice.org.uk/CG107>). A dBP of ≥ 110 mmHg must of course also be treated, even when sBP is < 160 – 170 mmHg.

Almost all severe hypertension in pregnancy is without clear hypertension-related end-organ dysfunction and as such, most episodes are classified as hypertensive 'urgencies'. How to classify the seriousness of headache and visual symptoms is unclear. Both are very common among women admitted to hospital with pre-eclampsia (i.e. 30% and 19%, respectively), yet, the incidence of adverse central nervous system outcomes in this group is rare (0.3%) [20]. Also, headache is a well-recognized side effect of medications used in pre-eclampsia, such as nifedipine.

General principles

Most episodes of severe hypertension in pregnancy can be managed without an arterial line. Based on extrapolation of the approach outside pregnancy, mean arterial BP should be lowered by no more than 25% over minutes to

hours, and then further lowered if necessary to 160/100 mmHg over hours. In selected cases, hypertensive urgencies may be treated with oral agents, which have peak drug effects in 1–2 h (e.g. oral labetalol or intermediate acting nifedipine), recognizing that gastric emptying may be delayed or unreliable among women in active labour [21].

Any associated factors that may be contributing to the severe hypertension should be addressed. These include pain, upset and inadequate levels of antihypertensive therapy related to delayed gastric emptying in labour. Epidural analgesia may also be beneficial by producing peripheral vasodilatation.

Observational literature emphasises that hypotension may result from use of any rapid acting agents in women with pre-eclampsia, which is not surprising as they are intravascularly volume depleted [22]. As the uteroplacental circulation does not autoregulate blood flow, precipitous falls in maternal BP may be associated with fetal heart rate abnormalities and monitoring is prudent (http://www.somanz.org/pdfs/somanz_guidelines_2008.pdf). There are limited data on the pharmacological effects of antihypertensives on fetal heart rate or pattern in human pregnancy [23]. Similarly to the uteroplacental circulation, the maternal cerebrovasculature may not autoregulate blood flow in the setting of severe hypertension particularly when mean arterial pressure exceeds 140 mmHg (e.g. BP of 180/120 mmHg) in the previously normotensive patient [24]. The basic principle to apply in clinical practice is 'start low' (with regards to dose) and 'go slow' (in terms of repeating doses).

Agents for treatment of severe hypertension

Thirty trials (3446 women) have compared one antihypertensive with another. These trials have been systematically reviewed in two high quality publications and there have been three recently published trials (<http://guidance.nice.org.uk/CG107>).

The two relevant quantitative reviews had some analytic differences. One compared each type of antihypertensive with the other, based on the assumption that the pharmacology of the drugs would have an impact on outcomes [25]. The second review compared hydralazine with other antihypertensives, based on hydralazine being the traditional drug of first choice, and the assumption that the lowering of BP would be more important than the mechanism by which that is achieved (as is the situation outside pregnancy). In addition, this approach would maximize statistical power while still enabling potential differences to be explored by subgroup analysis [26].

Most trials have compared parenteral hydralazine with either labetalol (six trials) or oral calcium channel blockers (nine trials). Another trial has compared intravenous labe-

talol with oral nicardipine. These are the medications used most commonly to treat severe hypertension in pregnancy and as such, these data are most informative for clinical practice. However, additional comparisons from small randomized trials include hydralazine vs. either diazoxide, ketanserin (four trials), urapidil (two trials) or prostacyclin, labetalol vs. either methyldopa or mini-dose diazoxide, magnesium sulphate vs. either nitrates or nimodipine and nifedipine capsules vs. either intermediate-acting nifedipine, nitroglycerin, chlorpromazine, or prazosin [25, 27–29].

When hydralazine was compared with other antihypertensives together, parenteral hydralazine was associated with more adverse effects including maternal hypotension, Caesarean section and fetal heart rate abnormalities ($n = 21$ trials, 1085 women) [26]. When compared with parenteral labetalol specifically in a subgroup analysis, hydralazine was a more effective antihypertensive [26]. A subsequently published trial found no between-group difference in persistent severe hypertension (5% in each group) but maternal hypotension occurred in 2/100 women treated with hydralazine compared with 0/100 treated with labetalol [29]. It should be noted that labetalol was associated with more neonatal bradycardia which required intervention in one of six affected babies in the relevant trial [30], and a similar result was seen in a subsequently published labetalol vs. hydralazine trial [29].

When hydralazine has been compared with calcium channel blockers (nine trials), hydralazine was a less effective antihypertensive in one review [25] with the relevant subgroup analysis of the other review consistent with this [26]. Hydralazine was also associated with more fetal heart rate abnormalities [26]. There have been no new relevant trials.

When labetalol has been compared with calcium channel blockers (1 trial, 60 women), no between-group differences in outcomes have been seen.

The potential advantages of orally administered antihypertensive therapy for severe hypertension are worth pondering. Maternity care providers are not always immediately available in the delivery suite to administer parenteral agents to women with severe hypertension. Although labetalol has been administered parenterally in published trials, it has been given orally in an initial dose of 200 mg for hypertensive urgencies as part of an overall management strategy, with good reported outcomes [21]. Relevant preparations of nifedipine for treatment of severe hypertension include the capsules (used in all but one of the relevant trials) and the intermediate acting tablet [31]. Most trial publications did not specify whether capsules were bitten prior to swallowing. Although use of a 5 mg (vs. 10 mg) dose may decrease anxiety about a precipitous fall in BP as was seen with use of 10 mg capsules in older patients, there are no published comparative studies. For severe hypertension, there is no published literature on use of the extended release preparation of nifedipine, peak

Table 1

Doses of most commonly used agents used for treatment of a BP of $\geq 160/110$ mmHg hypertension (reproduced with permission from Magee *et al.* SOGC 2008) [5]

Agent	Dosage	Comments
Labetalol	Start with 20 mg i.v.; repeat 20–80 mg i.v. every 30 min Alternative: i.v. infusion of 1–2 mg min ⁻¹ to a maximum of 300 mg (then switch to oral)	Best avoided in women with asthma. Parenteral labetalol may cause neonatal bradycardia but this is not a major problem in clinical practice
Nifedipine	5–10 mg capsule to be bitten and swallowed, or just swallowed, every 30 min 10 mg PA tablet every 45 min to a maximum of 80 mg day ⁻¹	There are three types of nifedipine preparations [i.e. capsules, intermediate-release tablets (PA), and slow-release tablets (SL)] with which all staff must be familiar. Nifedipine capsules cause a reflex increase in sympathetic tone which is best avoided in women for whom increased myocardial oxygen demands could be dangerous (e.g. coronary artery disease), or in the setting of fixed valvular obstruction.
Hydralazine	Start with 2–5 mg i.v.; repeat every 30 min in doses up to 10 mg, or 0.5–10 mg h ⁻¹ i.v., to a maximum of 20 mg i.v. (or 30 mg i.m.)	May increase the risk of maternal hypotension. Hydralazine causes a reflex increase in sympathetic tone which is best avoided in women for whom increased myocardial oxygen demands could be dangerous (e.g. coronary artery disease), or in the setting of fixed valvular obstruction.

concentrations of which rise gradually following oral ingestion and peak at 6 h. Outside pregnancy, recommendations have been made to treat markedly elevated BP with immediate combination oral therapy [32].

In response to withdrawal of the 10 mg nifedipine capsule from Australasia, Brown *et al.* compared the intermediate acting nifedipine 10 mg tablet with the 10 mg capsule in a small trial of 64 women [31]. The primary outcome of treatment success at 90 min was achieved in more than 75% of women in both groups, although a maternal BP <110/80 mmHg at anytime was more common with the 10 mg capsule (35%) compared with the 10 mg tablet (9%). The tablet is now being withdrawn from some drug markets. There have also been case reports of neuromuscular blockade with contemporaneous use of nifedipine and magnesium sulphate, but the risk was estimated to be <1% in a single centre, controlled study and complete data synthesis [33]; blockade is reversed with 10 g of intravenous calcium gluconate which is immediately available in all delivery suites.

Magnesium sulphate has been advocated in obstetrics to decrease BP. The relevant observational literature is limited, with reports of no decrease, or transient decreases in BP, at 30 min after 2–5 g of intravenous magnesium sulphate, with/without ongoing infusion, usually in the setting of pre-eclampsia [5]. Although a sustained lowering of BP cannot be anticipated following a magnesium sulphate bolus, the potential for a transient lowering of BP 30 min after administration should be considered when antihypertensives are co-administered. Magnesium sulphate should be otherwise administered for proven indications, such as eclampsia prophylaxis and treatment.

Low dose diazoxide (15 mg i.v.), an arterial vasodilator, compared favourably with hydralazine 5 mg i.v. in a randomized controlled trial of 124 women [27].

Nitroglycerin (glyceryl trinitrate) is primarily venodilatory. Women with pre-eclampsia are usually intravascularly

volume depleted, so nitroglycerin would not be a logical first choice of antihypertensive in women with severe hypertension and pre-eclampsia. No adverse clinical effects were demonstrated in small studies [34, 35].

For refractory hypertension in intensive care, sodium nitroprusside can be used. The theoretical concerns are well known: light-sensitive, requires careful monitoring and has the potential to cause fetal cyanide toxicity. A published review of case reports (22 women, 24 fetuses) documented stillbirths among five of 18 women treated antenatally (27.8%) with nitroprusside, although the authors could not attribute these deaths to fetal cyanide toxicity [36].

A comment should be made regarding the choice of antihypertensive agent and its potential to cause cerebral vasodilatation. In posterior reversible encephalopathy syndrome (PRES), of which eclampsia (and possibly pre-eclampsia with neurological symptoms) is thought to be a form, acute elevations in BP result in forced dilatation of vascular smooth muscle (of cerebral arteries and arterioles), and increased blood–brain barrier permeability, promoting oedema formation [37]. Theoretically, it may be prudent to choose an antihypertensive that does not cause cerebral vasodilatation outside pregnancy, such as labetalol and nicardipine, rather than hydralazine or nifedipine [38]. However, basing antihypertensive choice on such considerations is not recommended. First, there are no data from pregnancy. Second, magnesium sulphate actually dilates the cerebral vasculature in animal studies, but magnesium prevents and treats eclampsia in human pregnancy [39, 40].

Table 1 lists the doses of the most commonly used antihypertensives for severe hypertension in pregnancy.

Following treatment of severe hypertension, oral antihypertensive therapy should usually be started to maintain BP, unless there was a clear, modifiable precipitant (such as the pain of labour). During labour, gastric emptying may be unreliable.

Postpartum, BP peaks on days 3–6, so consideration should be given to restarting antihypertensive therapy after delivery, particularly in women with pre-eclampsia in whom postpartum hypertension and pulmonary oedema are more common, possibly related to mobilization of extravascular fluid into the intravascular space. At minimum, BP should be measured after discharge (so as not to miss a clinically important peak) and certainly before the 6 week postpartum visit. Captopril may be used for severe postpartum hypertension without precluding breastfeeding; a transition to other ACE inhibitors such as enalapril may be made thereafter without precluding breastfeeding. Breastfeeding information is available free of charge in the Lactmed database (at <http://www.toxnet.nlm.nih.gov>). Management issues around postpartum hypertension and breastfeeding are discussed in detail in the NICE guidelines (<https://guidance.nice.org.uk/CG107>).

In summary, there is consensus that severe hypertension in pregnancy should be treated to decrease maternal risk. Parenteral hydralazine and labetalol and oral nifedipine have been best studied in randomized trials for this indication. No agent is clearly superior to others, although parenteral hydralazine may be associated with more maternal hypotension and adverse fetal heart rate effects.

Non-severe hypertension

At present, the literature is not robust enough to guide decision making about optimal use of antihypertensives for non-severe hypertension in pregnancy. Most of the relevant randomized trials were published in the 1980s and 1990s and they were primarily small and inadequately powered to examine important outcomes [41].

Different expert committees have reviewed the same literature and published different guidelines [5, 6, 16, 42]. Advice to initiate antihypertensive therapy varies from a threshold sBP of 140–159 mmHg and/or a dBP of 90–109 mmHg, with treatment goals, when specified, ranging from 110–140 mmHg systolic and 80–105 mmHg diastolic [5, 6, 16, 42]. Some recommendations vary based on considerations such as associated co-morbidities, including pre-gestational (but not gestational) diabetes or renal disease.

We are aware of 31 RCTs (3462 women) that have examined the impact of differential BP control on maternal and perinatal outcomes in the setting of non-severe pre-existing ($n = 7$ trials) or gestational ($n = 25$ trials) hypertension. Different systematic reviews [41, 43–47] have reached the same conclusion: there is insufficient evidence on which to base treatment of non-severe hypertension in pregnancy in order to optimize outcome for the baby and minimize maternal risk.

In the relevant trials that addressed whether normalization (treatment) of maternal hypertension is beneficial, antihypertensive treatment was compared with

placebo/no therapy. In the ‘treatment’ groups of cited trials, women were randomized to antihypertensive therapy to achieve a dBP <90 mmHg. In the placebo or ‘no therapy’ arms, antihypertensive therapy was administered only if BP rose to 160–170/100–110 mmHg.

Antihypertensive therapy decreased the risk of severe hypertension (RR 0.50, 95% CI 0.41, 0.61, 19 trials, 2409 women, NNT 9–17). There was no reported maternal stroke and no difference in outcomes otherwise associated with a hypertensive crisis in pregnancy (e.g. preterm birth or Caesarean section) [41]. There was one maternal death in the antihypertensive therapy group due to refusal to accept antihypertensive therapy for severe hypertension [48].

There is ongoing debate about whether antihypertensive therapy impairs intra-uterine fetal growth, and if so, whether this effect is restricted to β -adrenoceptor blocker therapy. By meta-analysis, no increase in small for gestational age (SGA) infants was seen overall for antihypertensive drug vs. placebo/no therapy trials (RR 1.04, 95% CI 0.84, 1.27, 19 trials, 2437 women) although there was a trend for the β -adrenoceptor blocker subgroup (RR 1.38, 95% CI 0.99, 1.92, nine trials, 904 women). It is unlikely, however, that any adverse effects of antihypertensive therapy are attributable to use of β -adrenoceptor blockers. These drugs have been studied most extensively for treatment of non-severe hypertension in pregnancy and relevant analyses have the greatest statistical power to find between-group differences in outcomes when compared with placebo/no therapy. β -adrenoceptor blockers had no significant effect on the incidence of SGA infants when compared with methyldopa (RR 0.99, 95% CI 0.57, 1.70, $n = 5$ trials, 478 women). Meta-regression analysis of trials described a significant relationship between greater antihypertensive-induced falls in mean arterial pressure and heightened risk of SGA infants [45, 46]. These data are consistent with the relationship between spontaneously lower BP (i.e. dBP <70 mmHg) and both lower birthweight and higher perinatal mortality in the general obstetric population [49], as well as better neurodevelopmental outcomes for preterm and term growth-restricted babies born to hypertensive (vs. normotensive) mothers [50, 51].

In summary, a large definitive trial is needed to identify optimal BP goals and therapy of non-severe maternal hypertension in pregnancy. The CHIPS Trial (Control of Hypertension In Pregnancy Study) is currently recruiting (<http://www.utoronto.ca/cmcr/chips>).

When antihypertensive therapy is prescribed, there is little to guide the choice of agent.

Methyldopa has become the reference drug in many guidelines, possibly related to the pioneering trial by Redman *et al.* of methyldopa vs. no antihypertensive in which children were followed up (by parental questionnaire) at the age of 7.5 years [52]. Subsequently, studies have demonstrated no adverse effects of nifedipine (110 children at 1 year) or atenolol (190 children at 18 months) on paediatric health or neurodevelopment. Data are too

Table 2Doses of most commonly used agents used for treatment of a BP of 140–159/90–105 mmHg (reproduced with permission from Magee *et al.* SOGC 2008) [5]

Agent	Dosage	Comments
Methyldopa	250–500 mg orally two to four times daily (max 2 g day ⁻¹)	There is no evidence to support a loading dose of methyldopa.
Labetalol	100–400 mg orally two to four times daily (max 1200 mg day ⁻¹)	Some experts recommend a starting dose of 200 mg orally twice daily.
Nifedipine	PA tablets (10–20 mg orally two to three times daily, max 180 mg day ⁻¹) or XL preparation (20–60 mg orally once daily, max 120 mg day ⁻¹)	Caution should be exercised in ensuring that the correct form of nifedipine has been prescribed.

BP, blood pressure.

limited to guide the choice of antihypertensive medication for women with non-severe hypertension [41] and interest in this topic continues [53].

In the most recent meta-analysis of one antihypertensive drug vs. another for non-severe hypertension, 19 trials (1282 women) were included [41]; the same dBp goal was applied to women in both treatment groups. The most common comparison was a β -adrenoceptor blocker with methyldopa (14/19 trials). β -adrenoceptor blockers (and labetalol particularly) may be more effective antihypertensives than is methyldopa (RR 0.75, 95% 0.58, 0.94, 10 trials, 539 women), but no other differences in outcomes were demonstrated (19 trials, 1282 women) [41].

Table 2 lists the doses of the most commonly used antihypertensives for non-severe hypertension.

Fetal programming effects

There is growing evidence that reduced fetal growth rate is associated with cardiovascular risk markers and disease in adulthood. This has been shown to be true in varied populations worldwide and across the spectrum of normal and low birthweight [54]. As an adaptive mechanism, the fetus responds to the *in utero* environment by changes in regulation of the genome, so-called 'epigenetic' change. These changes are permanent, and although adaptive in fetal life, they may be maladaptive postnatally. Although we do not know whether antihypertensive therapy has a fetal programming effect, this is an area of active interest and this has served to fuel caution around antihypertensive treatment of non-severe hypertension in pregnancy.

Conclusion

The HDP include the systemic disorder of pre-eclampsia. This highlights that all hypertension in pregnancy is not just hypertension and that BP management with antihypertensive therapy is but one aspect of the management of women with a HDP. Women with severe hypertension in pregnancy should be treated with antihypertensive therapy. Treatment of non-severe hypertension is still very

controversial based on the lack of clarity around relative maternal and perinatal benefits and risks, as well as concerns about fetal programming effects. Both close collaboration among maternity care providers and active participation in research will be required to optimize the care of these women and babies.

Competing Interests

There are no competing interests to declare.

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REFERENCES

- 1 Saftlas AF, Olson DR, Franks AL, Atrash HK, Pokras R. Epidemiology of preeclampsia and eclampsia in the United States, 1979–1986. *Am J Obstet Gynecol* 1990; 163: 460–5.
- 2 Lewis G, ed. The Confidential Enquiry into Maternal and Child Health (CEMACH). Saving Mother's Lives: Reviewing Maternal Deaths to Make Motherhood Safer – 2003–2005. The Seventh Report on Confidential Enquiries into Maternal Deaths in the United Kingdom. London: CEMACH, 2007.
- 3 Health Canada. Special Report on Maternal Mortality and Severe Morbidity in Canada – Enhanced Surveillance: the Path to Prevention. Ottawa: Minister of Public Works and Government Services Canada, 2004.
- 4 Khan KS, Wojdyla D, Say L, Gulmezoglu AM, Van Look PF. WHO analysis of causes of maternal death: a systematic review. *Lancet* 2006; 367: 1066–74.
- 5 Magee LA, Helewa M, Rey E, Cote AM, Douglas J, Gibson P, Gruslin A, Lange I, Leduc L, Logan AG, Smith GN, STIRRHS Pre-eclampsia Scholars, Cardew S, Firoz T, Moutquin J-M,

- von Dadelszen P. SOGC Clinical Practice Guideline: diagnosis, evaluation, and management of the hypertensive disorders of pregnancy. *JOGC* 2008; 30: S1–48.
- 6 Brown MA, Hague WM, Higgins J, Lowe S, McCowan L, Oats J, Peek MJ, Rowan JA, Walters BN. The detection, investigation and management of hypertension in pregnancy: executive summary. *Aust N Z J Obstet Gynaecol* 2000; 40: 133–8.
 - 7 De Greeff A, Ghosh D, Anthony J, Shennan A. Accuracy assessment of the Dinamap ProCare 400 in pregnancy and preeclampsia. *Hypertens Pregnancy* 2010; 29: 198–205.
 - 8 Reinders A, Cuckson AC, Lee JT, Shennan AH. An accurate automated blood pressure device for use in pregnancy and pre-eclampsia: the Microlife 3BTO-A. *BJOG* 2005; 112: 915–20.
 - 9 Chung Y, De Greeff A, Shennan A. Validation and compliance of a home monitoring device in pregnancy: microlife WatchBP home. *Hypertens Pregnancy* 2009; 28: 348–59.
 - 10 Villar J, Say L, Shennan A, Lindheimer M, Duley L, Conde-Agudelo A, Merialdi M. Methodological and technical issues related to the diagnosis, screening, prevention, and treatment of pre-eclampsia and eclampsia. *Int J Gynaecol Obstet* 2004; 85 (Suppl. 1): S28–41.
 - 11 Hebert MF, Carr DB, Anderson GD, Blough D, Green GE, Brateng DA, Kantor E, Benedetti TJ, Easterling TR. Pharmacokinetics and pharmacodynamics of atenolol during pregnancy and postpartum. *J Clin Pharmacol* 2005; 45: 25–33.
 - 12 Hebert MF, Easterling TR, Kirby B, Carr DB, Buchanan ML, Rutherford T, Thummel KE, Fishbein DP, Unadkat JD. Effects of pregnancy on CYP3A and P-glycoprotein activities as measured by disposition of midazolam and digoxin: a University of Washington specialized center of research study. *Clin Pharmacol Ther* 2008; 84: 248–53.
 - 13 Buchanan ML, Easterling TR, Carr DB, Shen DD, Risler LJ, Nelson WL, Mattison DR, Hebert MF. Clonidine pharmacokinetics in pregnancy. *Drug Metab Dispos* 2009; 37: 702–5.
 - 14 Claessens AJ, Risler LJ, Eyal S, Shen DD, Easterling TR, Hebert MF. CYP2D6 mediates 4-hydroxylation of clonidine in vitro: implication for pregnancy-induced changes in clonidine clearance. *Drug Metab Dispos* 2010; 38: 1393–6.
 - 15 Rogers RC, Sibai BM, Whybrew WD. Labetalol pharmacokinetics in pregnancy-induced hypertension. *Am J Obstet Gynecol* 1990; 162: 362–6.
 - 16 Report of the National High Blood Pressure Education Program Working Group on High Blood Pressure in Pregnancy. *Am J Obstet Gynecol* 2000; 183: S1–22.
 - 17 Buchbinder A, Sibai BM, Caritis S, Macpherson C, Hauth J, Lindheimer MD, Klebanoff M, Vandorsten P, Landon M, Paul R, Miodovnik M, Meis P, Thurnau G, for the National Institute of Child Health and Human Development Network of Maternal-Fetal Medicine Units BM. Adverse perinatal outcomes are significantly higher in severe gestational hypertension than in mild preeclampsia. *Am J Obstet Gynecol* 2002; 186: 66–71.
 - 18 Hauth JC, Ewell MG, Levine RJ, Esterlitz JR, Sibai B, Curet LB, Catalano PM, Morris CD. Pregnancy outcomes in healthy nulliparas who developed hypertension. Calcium for Preeclampsia Prevention Study Group. *Obstet Gynecol* 2000; 95: 24–8.
 - 19 Martin JN Jr, Thigpen BD, Moore RC, Rose CH, Cushman J, May W. Stroke and severe preeclampsia and eclampsia: a paradigm shift focusing on systolic blood pressure. *Obstet Gynecol* 2005; 105: 246–54.
 - 20 Yen TW, Payne B, Qu Z, Hutcheon JA, Lee T, Magee LA, Walters BN, von Dadelszen P, for the PIERS Study Group. Using clinical symptoms to predict adverse maternal and fetal outcomes in women with pre-eclampsia: data from the PIERS (Pre-eclampsia Integrated Estimate of RiSk) Study. *JOGC* 2011; in press (MS# 10-09-180.R1).
 - 21 Tuffnell DJ, Jankowicz D, Lindow SW, Lyons G, Mason GC, Russell IF, Walker JJ. Outcomes of severe pre-eclampsia/eclampsia in Yorkshire 1999/2003. *BJOG* 2005; 112: 875–80.
 - 22 Duley L, Williams J, Henderson-Smart DJ. Plasma volume expansion for treatment of women with pre-eclampsia. *Cochrane Database Syst Rev* 2000; (2): CD001805.
 - 23 Waterman EJ, Magee LA, Lim KI, Skoll A, Rurak D, von Dadelszen P. Do commonly used oral antihypertensives alter fetal or neonatal heart rate characteristics? A systematic review. *Hypertens Pregnancy* 2004; 23: 155–69.
 - 24 Neill TA, Hemphill JC. Reversible posterior leukoencephalopathy syndrome. *UpToDate* 2010, Version 18.2.
 - 25 Duley L, Henderson-Smart DJ, Meher S. Drugs for treatment of very high blood pressure during pregnancy. *Cochrane Database Syst Rev* 2006; (3): CD001449.
 - 26 Magee LA, Cham C, Waterman EJ, Ohlsson A, von Dadelszen P. Hydralazine for treatment of severe hypertension in pregnancy: meta-analysis. *BMJ* 2003; 327: 955–60.
 - 27 Hennessy A, Thornton CE, Makris A, Ogle RF, Henderson-Smart DJ, Gillin AG, Child A. A randomised comparison of hydralazine and mini-bolus diazoxide for hypertensive emergencies in pregnancy: the PIVOT trial. *Aust N Z J Obstet Gynaecol* 2007; 47: 279–85.
 - 28 Manzur-Verastegui S, Mandeville PB, Gordillo-Moscoso A, Hernandez-Sierra JF, Rodriguez-Martinez M. Efficacy of nitroglycerine infusion versus sublingual nifedipine in severe pre-eclampsia: a randomized, triple-blind, controlled trial. *Clin Exp Pharmacol Physiol* 2008; 35: 580–5.
 - 29 Vigil-De Gracia P, Lasso M, Ruiz E, Vega-Malek JC, de Mena FT, Lopez JC. Severe hypertension in pregnancy: hydralazine or labetalol. A randomized clinical trial. *Eur J Obstet Gynecol Reprod Biol* 2006; 128: 157–62.
 - 30 Garden A, Davey DA, Dommissie J. Intravenous labetalol and intravenous dihydralazine in severe hypertension in pregnancy. *Clin Exp Hypertens B* 1982; 1: 371–83.
 - 31 Brown MA, Buddle ML, Farrell T, Davis GK. Efficacy and safety of nifedipine tablets for the acute treatment of severe hypertension in pregnancy. *Am J Obstet Gynecol* 2002; 187: 1046–50.

- 32** Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL Jr, Jones DW, Materson BJ, Oparil S, Wright JT Jr, Roccella EJ. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. *JAMA* 2003; 289: 2560–72.
- 33** Magee LA, Miremadi S, Li J, Cheng C, Ensom MH, Carleton B, Cote AM, von Dadelszen P. Therapy with both magnesium sulfate and nifedipine does not increase the risk of serious magnesium-related maternal side effects in women with preeclampsia. *Am J Obstet Gynecol* 2005; 193: 153–63.
- 34** Cetin A, Yurtcu N, Guvenal T, Imir AG, Duran B, Cetin M. The effect of glyceryl trinitrate on hypertension in women with severe preeclampsia, HELLP syndrome, and eclampsia. *Hypertens Pregnancy* 2004; 23: 37–46.
- 35** Neri I, Valensise H, Facchinetti F, Menghini S, Romanini C, Volpe A. 24-hour ambulatory blood pressure monitoring: a comparison between transdermal glyceryl-trinitrate and oral nifedipine. *Hypertens Pregnancy* 1999; 18: 107–13.
- 36** Sass N, Itamoto CH, Silva MP, Torloni MR, Atallah AN. Does sodium nitroprusside kill babies? A systematic review. *Sao Paulo Med J* 2007; 125: 108–11.
- 37** Euser AG, Cipolla MJ. Magnesium sulfate for the treatment of eclampsia: a brief review. *Stroke* 2009; 40: 1169–75.
- 38** McCoy S, Baldwin K. Pharmacotherapeutic options for the treatment of preeclampsia. *Am J Health Syst Pharm* 2009; 66: 337–44.
- 39** Duley L, Carroli G, Belizan J, Gonzalez L, Campodonico L, Bergel E, Taillades P, Ayers S, Wincott L, Gallagher K, Fredrick K, Reynolds J, Adadevoh S, Atallah A, George K, Grant A, Mahomed K, Mehta S, Mmiro F, Moodley J, Neilson J, Sheth S, Walker G, Chalmers I, Collins R, Munjanja S, Redman C, Elbourne D. Which Anticonvulsant for Women with Eclampsia – Evidence from the Collaborative Eclampsia Trial. *Lancet* 1995; 345: 1455–63.
- 40** Duley L, Farrell B, Spark P, Roberts B, Watkins K, Bricker L, Wang L, Armstrong N, Tivnin M, Salih N, Hurst A, Smyth R, Cooper S, Wilson A, Bowler U, Notman J. Do women with pre-eclampsia, and their babies, benefit from magnesium sulphate? The Magpie Trial: a randomised placebo-controlled trial. *Lancet* 2002; 359: 1877–90.
- 41** Abalos E, Duley L, Steyn D, Henderson-Smart D. Antihypertensive drug therapy for mild to moderate hypertension during pregnancy. *Cochrane Database Syst Rev* 2007; (1): CD002252.
- 42** Brown MA, Lindheimer MD, de Swiet M, Van Assche A, Moutquin JM. The classification and diagnosis of the hypertensive disorders of pregnancy: statement from the International Society for the Study of Hypertension in Pregnancy (ISSHP). *Hypertens Pregnancy* 2001; 20: IX–XIV.
- 43** Magee LA, Ornstein MP, von Dadelszen P. Fortnightly review: management of hypertension in pregnancy. *BMJ* 1999; 318: 1332–6.
- 44** Magee LA, Duley L. Oral beta-blockers for mild to moderate hypertension during pregnancy. *Cochrane Database Syst Rev* 2000; (4): CD002863.
- 45** von Dadelszen P, Magee LA. Fall in mean arterial pressure and fetal growth restriction in pregnancy hypertension: an updated meta-regression analysis. *JOGC* 2002; 24: 941–5.
- 46** von Dadelszen P, Ornstein MP, Bull SB, Logan AG, Koren G, Magee LA. Fall in mean arterial pressure and fetal growth restriction in pregnancy hypertension: a meta-analysis. *Lancet* 2000; 355: 87–92.
- 47** Magee LA. Review: drugs for mild-to-moderate hypertension in pregnancy reduce risk for severe hypertension but not preeclampsia. *ACP J Club* 2007; 147: 9.
- 48** Plouin PF, Breart G, Llado J, Dalle M, Keller ME, Goujon H, Berchel C. A randomized comparison of early with conservative use of antihypertensive drugs in the management of pregnancy-induced hypertension. *Br J Obstet Gynaecol* 1990; 97: 134–41.
- 49** Steer PJ, Little MP, Kold-Jensen T, Chapple J, Elliott P. Maternal blood pressure in pregnancy, birth weight, and perinatal mortality in first births: prospective study. *BMJ* 2004; 329: 1312.
- 50** Chen XK, Wen SW, Smith G, Yang Q, Walker M. Pregnancy-induced hypertension and infant mortality: Roles of birthweight centiles and gestational age. *BJOG* 2007; 114: 24–31.
- 51** McCowan LM, Pryor J, Harding JE. Perinatal predictors of neurodevelopmental outcome in small-for-gestational-age children at 18 months of age. *Am J Obstet Gynecol* 2002; 186: 1069–75.
- 52** Cockburn J, Moar VA, Ounsted M, Redman CW. Final report of study on hypertension during pregnancy: the effects of specific treatment on the growth and development of the children. *Lancet* 1982; 1: 647–9.
- 53** Pasker-de Jong PC, Zielhuis GA, van Gelder MM, Pellegrino A, Gabreels FJ, Eskes TK. Antihypertensive treatment during pregnancy and functional development at primary school age in a historical cohort study. *BJOG* 2010; 117: 1080–6.
- 54** Barker DJ. Human growth and cardiovascular disease. *Nestle Nutr Workshop Ser Pediatr Program* 2008; 61: 21–38.