Hypertension in pregnancy: a review of therapeutic options

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Summary: Hypertensive disorders in pregnancy are common and can occur as a result of pre-existing hypertension or as new onset hypertension usually in the second half of pregnancy. In either situation there is potential for considerable perinatal and maternal morbidity and mortality. This review article aims to compare therapeutic options outlined in a selection of national guidelines and to look in more detail at the most commonly prescribed drugs – labetalol, methyldopa and nifedipine – with respect to their pharmacology and the evidence for their use in pregnancy. We will also consider the rationale for identifying and treating hypertension in pregnancy and the effect this can have on short- and long-term maternal and neonatal outcomes.

Keywords: hypertension, maternal–fetal medicine

INTRODUCTION

Hypertensive disorders in pregnancy can occur as a result of pre-existing hypertension or as new onset hypertension usually from the second half of pregnancy onwards. In either situation there is the potential for maternal and perinatal morbidity and mortality.

There are several considerations and aims of treating hypertension in pregnancy:

- (1) Prevention of serious maternal complications such as cerebral haemorrhage;
- (2) Disease progression in preeclampsia;
- (3) Perinatal outcome;
- (4) Long-term follow-up of children to mothers on antihypertensive treatment;
- (5) Long-term maternal cardiovascular risk identification.

The most recent United Kingdom Review of maternal deaths reported on the deaths of 22 women from preeclampsia and eclampsia.¹ Intracranial haemorrhage remains the leading cause of death in this group of women ($n = 9$). Failure of effective antihypertensive treatment is repeatedly highlighted within this report and there has been a gradual reduction in the upper limit of systolic blood pressure requiring effective antihypertensive treatment from 170 to 150 mmHg over subsequent reports.

Treatment of hypertension in pregnancy does not appear to alter disease progression in preeclampsia. A Cochrane review of randomized trials evaluated the role of antihypertensive therapy for mild-to-moderate hypertension during pregnancy.² It concluded that although there was a halving in the risk of developing severe hypertension with antihypertensive drugs (19 trials, 2409 women, relative risk 0.5, 95% confidence intervals 0.41–0.61), there was no overall difference in the risk of

proteinuria/preeclampsia when an antihypertensive drug was used compared with no treatment or placebo (22 trials, RR 0.97, 95% CI 0.83–1.13).

Furthermore, antihypertensive treatment of mild-to-moderate hypertension in pregnancy does not reduce the risk of perinatal adverse outcomes. Based on the hypothesis that less tight control may improve uteroplacental perfusion and fetal growth there is some concern that treatment may actually increase adverse perinatal outcomes. The Control of Hypertension in Pregnancy Study (CHIPS) aims to address this more comprehensively.³ This is a multicentre randomized controlled trial looking at non-severe non-proteinuric hypertension. It aims to answer whether 'less tight' control (target DBP 100 mmHg) versus 'tight' control (target DBP 85 mmHg) increases or decreases the likelihood of pregnancy loss or high-level neonatal care for more than 48 hours. Serious maternal outcomes will also be looked at but as secondary outcomes. This trial is currently in the process of recruiting.

There is now a strong body of literature supporting the fact that development of preeclampsia in pregnancy is a strong risk factor for later development of cardiovascular disease. In women who develop preeclampsia, necessitating delivery before 37 weeks, there is an eight-fold higher risk of death due to cardiovascular disease than in women without such a history.⁴ It is less clear as to how this information can be used usefully to reduce this risk.

This review aims to compare therapeutic options outlined in a selection of national guidelines, and to look in more detail at the most commonly prescribed drugs with respect to their pharmacology and the evidence for their use in pregnancy.

NATIONAL GUIDELINES

Several national guidelines have been published on the management of hypertension in pregnancy.^{5–7} Table 1 summarizes some aspects of the guidelines from the UK, Canada, Australia and New Zealand. There is consensus across these guidelines

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Table 1 Management of moderate/non-severe hypertension

	Thresholds for treatment of moderate/non-severe hypertension	Aim of treatment	Recommended drug treatment
United Kingdom (NICE) ⁸	Treat moderate hypertension, 150/100 to 159/109 mmHg	Maintain BP lower than 150/100 mmHg, 140/90 mmHg if secondary organ damage	First line labetalol
Canada (The Society of Obstetricians and Gynecologists of Canada ⁹)	Treat non-severe hypertension 140–159/90–109 mmHg	Aim to maintain sBP 130–155 mmHg and dBP 80–105 mmHg (130–139/80–89 if co-morbid conditions)	Second line methyldopa and nifedipine Choose from methyldopa, labetalol, other β -blockers (acebutolol, metoprolol, pindolol and propranolol), nifedipine
SOMANZ (Society of Obstetric Medicine of Australia and New Zealand ¹⁰)	Reasonable to consider treating 140–160/90–100 mmHg	No guidance given	First line – methyldopa, labetalol and oxprenolol Second line – hydralazine, nifedipine and prazosin

BP, blood pressure; sBP, systolic blood pressure; dBP, diastolic blood pressure

that severe hypertension requires immediate treatment because of the increased risk of maternal stroke. However, debate continues as to the thresholds at which moderate hypertension needs to be treated mainly because of concerns about worse perinatal outcomes in the infants of treated mothers. The differences in thresholds for treatment across the guidelines for the treatment of moderate hypertension reflect the lack of a clear evidence base, but it is hoped that the CHIPS can address this more fully following the publication of a pilot study. This study involved collaborating centres in the UK, Canada, Australia and New Zealand, which confirmed the feasibility of a large multicentre study to look at 'less tight' versus 'tight' blood pressure control.³

As to which individual agent might be best, a Cochrane review concluded that there is no clear evidence to recommend one antihypertensive over another for improving outcome for women with very high blood pressure during pregnancy.⁸ The authors recommend that until better evidence is available, the experience and familiarity of the clinician should determine as to which particular drug should be used. Therefore, the variations in the guidelines in Table 1 likely reflect local preference and experience. However, there are drugs that appear in all three of the national guidelines reviewed – labetalol, nifedipine and methyldopa – and each will be discussed in turn. Other antihypertensives and their possible role in managing hypertension in pregnancy are summarized in Table 2.

LABETALOL

Pharmacology

Labetalol is a β blocker used for treating hypertension since the 1970s. It possesses competitive α_1 and non-selective β adrenoceptor antagonist activity and low levels of intrinsic sympathomimetic activity. The α and β blocking effect contributes to the blood pressure-lowering effect while the β blocking properties prevents the reflex tachycardia seen with most α antagonists. At low doses its effect on β receptors predominates, being about a fifth of that of the β -blocking effect of propranolol. At intravenous doses of 50–100 mg or oral doses of 200–800 mg, a blood pressure drop of approximately 20% is observed in non-pregnant subjects.⁹ Administered acutely, labetalol reduces blood pressure rapidly with an associated decrease in total peripheral vascular resistance and a moderate reduction in heart rate and resting cardiac output. Chronic administration has been demonstrated to result in considerable reduction in blood pressure, total peripheral resistance, and a less-marked drop in heart rate and cardiac output, although with longer-term use (>5 years) this effect is lost.

Clinical use of labetalol

The main use of labetalol outside of pregnancy is in the management of hypertensive emergencies. The combination of its

Table 2 Other antihypertensive drugs

Class	Examples	Use in pregnancy	Role
ACE (angiotensin converting enzyme) inhibitors	Enalapril, captopril, ramipril, perindopril	Absolutely contraindicated (second/third trimester- oligohydramnios, fetal renal tubular dysplasia, neonatal renal failure)	Postnatal management of hypertension
A2RBs (angiotensin 2 receptor blockers)	Losartan, telmisartan, irbesartan	Absolutely contraindicated	Postnatal management of hypertension
Thiazide diuretics	Hydrochlorothiazide, bendroflumethiazide	Relatively contraindicated (neonatal thrombocytopenia, bone marrow suppression, electrolyte disturbance, jaundice and hypoglycaemia)	Postnatal management of hypertension
Loop diuretics	Furosemide, bumetanide	Relatively contraindicated	Specific role for treating oedema of cardiac origin
α -Blockers	Prazosin Doxazosin	Prazosin is safe and effective in pregnancy	Role in second and third trimesters
Potent vasodilators	Hydralazine	Safe throughout pregnancy – oral and intravenous preparations available	Role in management of severe hypertension as can be given in intravenous preparation

rapid onset of action and vasodilator properties ensure a prominent role in the management of accelerated hypertension. Although both the oral and intravenous routes have fast onset of action, the intravenous formulation allows for use in encephalopathic patients or in patients presenting with seizures or vomiting where the oral route is compromised. With a wide dosing range it can be titrated against blood pressure, limiting large fluctuations, and avoiding significant cerebral or renal hypoperfusion.

Short-term outcomes of labetalol in pregnancy

A Cochrane review of oral β blockers, including labetalol, for mild-to-moderate hypertension in pregnancy showed that compared with no therapy or placebo, β blockers were associated with an increase in small for gestational age infants.¹⁰ This association was strongest in a small study of 15 patients who took atenolol from the first trimester of pregnancy onwards. The conclusions that can be drawn from this study are limited because of its small size, but it may be that the effect is due to the drug being started in the first trimester or that it is an effect specific to atenolol which has no α_1 or intrinsic sympathomimetic activity. This Cochrane review also found that β blockers appear to be associated with an increase in neonatal bradycardia and a reduction in respiratory distress syndrome. Although few studies within the review reported on these outcomes, of the infants who developed bradycardia, none required treatment suggesting that it is not clinically significant. Finally, β blockers also have the potential to induce hypoglycaemia in the neonate.

Long-term outcomes of labetalol in pregnancy

Although labetalol has been in use for over three decades there is a paucity of data on long-term outcomes in children born to mothers taking it in pregnancy. A Dutch historical cohort study examined the functional development of 202 children born after treatment of mild-to-moderate gestational hypertension with labetalol versus methyl dopa, and no antihypertensive treatment.¹¹ Labetalol exposure *in utero* appeared to increase the risk of attention deficit hyperactivity disorder (ADHD) (OR 2.3; 95% CI 0.7–7.3) while methyl dopa exposure might influence sleep (OR 3.2; 95% CI 0.6–16.7). However, the findings were not statistically significant and in addition, the study had major methodological flaws such as failing to control for gestational age which impacts on the clinical interpretation. In a smaller prospective cohort study of 32 mother–child pairs with matched controls where labetalol had been taken antenatally, no adverse effect on neurocognitive development was seen.¹² Both these studies only assessed women who had gestational hypertension or preeclampsia. There remains no randomized controlled trial or well-conducted cohort study on the use of labetalol from the first trimester onwards.

OTHER β BLOCKERS

Oxprenolol, acebutolol, metoprolol, pindolol and propanolol are β blockers that are recommended as suitable antihypertensives in the Canadian and Australasian guidelines. The evidence for their safety and efficacy relates to clinical trials

carried out in the 1980s.^{13–16} In the context of hypertension in pregnancy, these drugs have been little studied since.

CALCIUM CHANNEL BLOCKERS: NIFEDIPINE

Pharmacology

Calcium channel blockers are classified into three groups according to their chemical structure: dihydropyridines, phenylalkylamines and benzothiazepines. Nifedipine is the prototype for the dihydropyridine group. Numerically this is the most important group as it contains the largest number of drugs.⁹

Calcium ions have a prominent role in many intracellular processes. In the cardiovascular system, an increase in intracellular ions triggers the actin–myosin interaction that causes myocardial and vascular smooth muscle cells to contract. Calcium channel blockers cause interference with the entry of calcium ions into cells by blocking voltage-gated calcium channels in cardiac and smooth muscles. The overall response relates to a combination of an arterial vasodilator effect, direct effects on cardiac conduction and contractility, and the indirect consequences of reflex activation of the sympathetic nervous system. The dominance of these effects varies between the different calcium antagonists.

Clinical use of nifedipine

The efficacy of nifedipine and other calcium channel blockers in reducing blood pressure is well established. There have been concerns raised about the safety of short-acting nifedipine preparations administered by the sublingual route because of their ability to precipitate angina in susceptible individuals. Furthermore, studies in the 1990s, including a meta-analysis of randomized controlled trials, highlighted that patients with acute myocardial infarction or unstable angina who had been previously treated with nifedipine were at an increased risk of death.¹⁷

The results from the above studies led to the withdrawal of short-acting rapid onset nifedipine capsules from the Australasian market. Brown *et al.*¹⁸ subsequently set out to determine whether the slower onset, longer-acting nifedipine preparations were as safe and effective as the short-acting, rapid onset nifedipine preparations for the acute treatment of severe hypertension in pregnancy. He concluded that although blood pressure was lowered further in those receiving the short-acting preparations, the effectiveness of treatment was similar between both groups. Fetal distress was uncommon but similar in both groups (3–4%).

Case reports have highlighted the risk of neuromuscular blockade when nifedipine is administered along with magnesium sulphate.¹⁹ However, a retrospective review of women who were given contemporaneous nifedipine and magnesium sulphate failed to reproduce this risk.²⁰

The large amount of data published showing a reduction in cardiovascular morbidity and mortality in those treated with calcium channel blockers outside of pregnancy relates to modern longer-acting calcium channel blockers.^{21,22}

Short-term outcomes of nifedipine in pregnancy

In a prospective cohort study of 78 women who took nifedipine from the first trimester onwards, there was no increased risk of

teratogenicity.²³ A randomized control trial allocated women who developed preeclampsia remote from term to treatment with nifedipine and bed rest versus bed rest alone.²⁴ While nifedipine reduced blood pressure, there was no effect on maternal hospitalization or perinatal outcome.

Long-term outcomes of nifedipine in pregnancy

There is no long-term outcome data for children born to mothers on nifedipine when it is used for the treatment of hypertension in pregnancy. However, there are two studies that evaluated several long-term outcomes in children born to mothers where nifedipine was used as tocolysis during pregnancy.^{25,26} A Dutch study looked at the long-term psychosocial and motor effects on children exposed *in utero* to nifedipine or ritodrine for the management of preterm labour. No long-term differences between the two groups were identified. Similarly, no difference in developmental scores at two years of age was found in children whose mothers were randomized to receive nifedipine versus those who received ritodrine.

CALCIUM CHANNEL BLOCKERS: VERAPAMIL AND DILTIAZEM

Verapamil and diltiazem are the prototype drugs for the phenylalkylamine and benzothiazepine groups of calcium channel blockers, respectively.⁹ These drugs also cause arterial vasodilation, but this affect is not as pronounced as that seen with the dihydropyridine group. In addition, these drugs have a direct effect on the heart resulting in a reduction in cardiac contractility and atrioventricular conduction.

Verapamil and diltiazem are not used routinely for the management of hypertension in pregnancy although they are believed to be safe.²⁷

METHYLDOPA

α -Methyldopa was developed in the 1950s and is an amino acid that was designed to block the action of the enzyme dopa-decarboxylase and thus prevent the formation of noradrenaline. However, it has since been shown that it is the active metabolite – α -methylnoradrenaline which stimulates the central α_2 receptors in the brainstem – which is responsible for the blood pressure-lowering effect.

Clinical use of methyldopa

Historically, methyldopa has been one of the most widely prescribed antihypertensives but its use has steadily declined because of the high incidence of central nervous system side-effects, most notably tiredness and sedation, combined with the introduction of newer antihypertensive agents. It retains a role as a second- or third-line therapy in patients intolerant or resistant to other antihypertensives. A Cochrane review looking at the role of methyldopa in primary hypertension reviewed 12 randomized controlled trials from which the authors concluded that methyldopa did reduce blood pressure. However, none of these studies reported on useful clinical outcomes such as the reduction in stroke with methyldopa treatment versus placebo.²⁸ Recent UK guidelines for managing hypertension in pregnancy have relegated methyldopa to a

second-line treatment. It retains a more prominent role in the guidelines of Canada and Australia and New Zealand where it is included as a first-line treatment. Use in the postnatal period is not recommended due to the risk of exacerbating depression.

Short-term outcomes of methyldopa in pregnancy

A Cochrane review of antihypertensive drug therapy for mild-to-moderate hypertension concluded that while methyldopa reduced blood pressure in pregnancy, β blockers appeared to be more effective than methyldopa in avoiding an episode of severe hypertension.² Other outcomes assessed in this review include development of preeclampsia, fetal deaths, preterm birth <37 weeks and small for gestational age. No differences were found when any hypertensive drug is used compared with methyldopa.

Long-term outcomes of methyldopa in pregnancy

A study published in the *Lancet* in 1982 looked at 195 children born to hypertensive women participating in a trial of methyldopa treatment.²⁹ It followed these children from birth to 71/2 years and found the frequency of problems with health, physical or mental handicap, sight, hearing and behaviour was the same in children of treated and untreated women.

ANGIOTENSIN-CONVERTING ENZYME (ACE) INHIBITORS AND ANGIOTENSIN II RECEPTOR ANTAGONISTS (AII RECEPTOR ANTAGONISTS)

Angiotensin-converting enzyme (ACE) inhibitors are effective antihypertensives and are recommended as a first-line treatment for younger, non-black patients.³⁰

Use of ACE inhibitors is contraindicated during the second and third trimesters of pregnancy as exposure during this gestation period is associated with a fetopathy; a group of conditions that includes oligohydramnios, intrauterine growth restriction, hypocalvaria, renal dysplasia and death. It is thought these effects are manifest due to either a direct or indirect effect on the fetal renin–angiotensin system. Because of the similar mechanism of action, angiotensin II receptor antagonists are also contraindicated.

In the late 1990s evidence was compiled from animal studies and cases reports that suggested use of ACE inhibitors in the first trimester was not associated with an increase in congenital malformations.³¹ Subsequently, in 2006 a cohort of 29,507 births were studied in whom 209 infants were exposed to ACE inhibitors in the first trimester.³² Compared with no exposure to antihypertensives in the first trimester there was a 2.7 times increase in the risk of congenital malformation in exposed infants. This increase in the congenital malformation rate was mainly due to malformations of the cardiovascular and central nervous systems.

A more recent study from California, looking at 466,754 mother–infant pairs, also observed a similar increase in the risk of cardiovascular malformations in the offspring of women who had used ACE inhibitors during the first trimester (odds ratio 1.54 [0.9–2.62]).³³ This increased risk, however, was not unique to ACE inhibitor use and a similar effect was seen in

women using other antihypertensive drugs (OR 1.52 [1.04–2.21]) as well as women with hypertension not on treatment (O.R 1.41 [1.3–1.53]). The authors concluded that it is the underlying hypertension that is the likely candidate for the increased malformation risk seen rather than the use of specific drugs in the first trimester.

α BLOCKERS

Prazosin is a α blocker that reduces peripheral vascular resistance by selective competitive inhibition of α_1 adrenergic receptors. Studies of the use of prazosin in pregnancy concentrate on evaluating its use as a second-line agent. In this context, it appears to be a safe and effective drug.^{34,35}

HYDRALAZINE

Hydralazine is a dilator of resistance vessels although how this is achieved is not entirely clear. Until recently, hydralazine was recommended as a first-line agent for the treatment of severe hypertension in pregnancy. A meta-analysis in 2003 showed that it was associated with some poorer maternal and perinatal outcomes than with other antihypertensives, particularly labetalol and nifedipine, with the authors concluding the evidence which did not support the use of hydralazine as a first-line treatment for severe hypertension.³⁶ Use of hydralazine does not feature in the most recent UK and Canadian Guidelines.

DISCUSSION

It is agreed that treatment of severe hypertension in pregnancy is required to reduce maternal complications, mainly cerebral haemorrhage. In contrast, when moderate hypertension is treated, there is no convincing evidence that disease progression in preeclampsia is altered and this combined with the possibility that there may be an increased risk of perinatal adverse events has made the decision when to start treatment difficult. Clarity on this issue has been achieved with the publication of three national guidelines.^{8–10} Each provides similar blood pressure thresholds when treatment should be commenced as well as outlining the aims of treatment. Particular emphasis is given in the UK and Canadian guidelines to treatment of hypertension in women with secondary organ damage and/or co-morbid conditions. Although blood pressure thresholds for instigating treatment are the same for both gestational and chronic hypertension, higher blood pressure reductions are sought in the latter group.

The final issue is which drug to use. Tables 3 and 4 outline the pharmacokinetics, side-effects and gestations when different antihypertensives can be used. These factors should all combine when choosing which particular drug to prescribe.

Ten different drugs are described within the three National Guidelines; however, labetalol, methyldopa and nifedipine feature in them all.

We agree that labetalol should remain the first drug to be considered when commencing antihypertensive treatment in pregnancy. It has a relatively quick onset of action, can be used in both the acute and chronic management of hypertension and can be continued safely in the postnatal period. A caution with labetalol, and with all other drugs with the exception of methyldopa, is the lack of robust long-term follow-up of

Table 3 Drug options for each trimester of pregnancy³⁸

Stage of pregnancy	Relatively contraindicated	Absolutely contraindicated	Suggested antihypertensives
First trimester		ACE inhibitors, A-II receptor antagonists	Methyldopa, labetalol, nifedipine, hydralazine
Second trimester	Beta blockers, diuretics	ACE inhibitors, A-II receptor antagonists	Methyldopa, nifedipine, labetalol, hydralazine
Third trimester	Beta blockers, diuretics	ACE inhibitors, A-II receptor antagonists	Methyldopa, nifedipine, labetalol, prazosin, hydralazine
Postnatal (safe for use when breast-feeding)	Methyldopa, A-II receptor antagonists*, amlodipine*, ACE inhibitors other than enalapril and captopril*		Labetalol [†] , nifedipine [†] , enalapril [†] , captopril [†] , atenolol [†] , metoprolol [†]

*Insufficient evidence on the safety of these drugs in babies receiving breast milk

[†]No known adverse effects on babies receiving breast milk⁵

children whose mothers took antihypertensive drugs during pregnancy. However, this is an insufficient reason for considering methyldopa a first-line drug mainly due to the issue that an alternative antihypertensive should be considered in the postnatal period. As arterial pressure rises for the first five days following delivery this is likely to be the case.³⁷ Additionally, methyldopa has a longer onset of action that does not allow for acute management of hypertension.

Nifedipine has a role in both the acute and chronic management of hypertension. It is generally safe and effective but can be poorly tolerated and for that reason we feel it should remain a second-line agent.

Table 4 Pharmacokinetics of commonly used antihypertensive agents in pregnancy

Drug	Timing of BP-lowering effect	Duration of action	Side-effects
Methyldopa	6–10 hours after oral administration*	Lasting up to 24 hours	Tiredness (up to 75% of patients), dreams may be affected, depression
Labetalol	2 hours after oral administration	Lasting 8–12 hours	Tiredness, bradycardia, nightmares
Nifedipine	10–15 minutes after oral administration	Lasting 3–4 hours	Headache, flushing, tachycardia, palpitations due to rapid onset of vasodilation. Reduced with the longer-acting preparations although 5–10% report ankle oedema
Modified release	1–2 hours after oral administration	Lasting up to 24 hours	

*There is no correlation between plasma concentration and antihypertensive effect. Peak levels of methyldopa are achieved 2–6 hours after oral administration. The plasma half-life is two hours. The lag between plasma concentration and blood pressure effect is consistent with the formation of an active metabolite

In contrast to the ever-expanding drug choice in the field of adult hypertension, the paucity of safety data for new agents restricts the choice available to clinicians managing hypertension in pregnancy. Nonetheless, the evidence of widespread and long-term use of the currently available therapies should allow for rational prescribing choices for this common condition.

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