Management of chronic hypertension in pregnancy

Almost all pregnant women who present with hypertension during the first 20 weeks of gestation are likely to have chronic hypertension. However, the normal physiological fall in blood pressure during the first and second trimesters can make it difficult to diagnose chronic hypertension in women whose blood pressure before the pregnancy was unknown.

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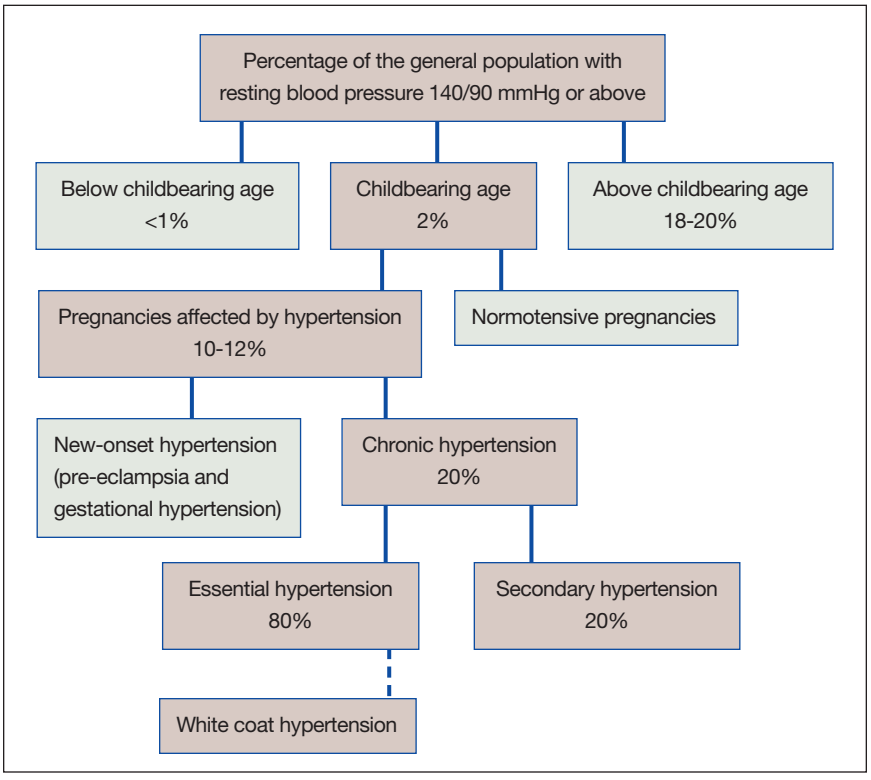
Up to 20% of the adult population are affected by hypertension, defined as a resting blood pressure of 140/90 mmHg or above. The prevalence of hypertension increases with age.[1] An estimated 2% of Australian women of childbearing age are hypertensive and, of the 10 to 12% of pregnancies affected by elevated blood pressure, one in five (20%) is related to chronic hypertension.

Virtually all pregnant women who present with hypertension during the first 20 weeks of gestation are likely to have chronic hypertension. However, because of the physiological fall in blood pressure during the first and second trimesters, it can be difficult to diagnose chronic hypertension in women whose blood pressure before pregnancy is unknown. Of those women diagnosed with chronic hypertension, at least 80% will have essential hypertension (Figure 1). However, an

IN SUMMARY

- **About 10 to 12% of pregnancies are complicated by hypertension; 20% of these are due to chronic hypertension.**
- **Pre-eclampsia is the most likely event to complicate the pregnancy of a woman with chronic hypertension.**
- **Tests are indicated in all women with known chronic hypertension to assess the severity of the hypertension and to investigate possible secondary causes.**
- **Antihypertensive treatment is recommended when the systolic or diastolic blood pressure consistently reaches or exceeds 160 mmHg and 100 mmHg, respectively. Admission to hospital or an antenatal day-assessment unit may be required for pregnant women with such blood pressure levels.**
- **The decision to treat intermediate blood pressures of 140 to160 mmHg (systolic) or 90 to 100 mmHg (diastolic) is based on clinical opinion. Admission to hospital or an antenatal day-assessment unit is recommended for pregnant women with these blood pressures if new-onset proteinuria develops.**
- **Methyldopa and labetalol are currently the agents of choice in hypertensive pregnant women due to their efficacy and safety profile.**



PHOTOLIBRARY

Figure 1. Causes of hypertension in pregnancy.

underlying cause should be investigated in all cases, as essential hypertension remains a diagnosis of exclusion.

Common secondary causes of chronic hypertension are listed in Table 1.[2-5] Absence of these conditions suggests a diagnosis of essential hypertension; however, it is important to remember that complete appraisal of possible secondary causes may have to be deferred until after delivery.

An additional cause of apparent hypertension in pregnancy is 'white coat hypertension'. The frequency and significance of this condition in pregnancy has not been defined; however, one study suggests that it is present in over 30% of women diagnosed with essential hypertension. It may also be associated with an increased incidence of pre-eclampsia compared with normotensive women.[6] Similarly, an elevated 24-hour mean pulse pressure – even in women who have normal measured systolic and diastolic pressures – has also been found to predict complications in pregnancy, including gestational hypertension and pre-eclampsia.[7]

Significance of chronic hypertension in pregnancy

It is important to distinguish between mild and severe hypertension. There is no consensus on the diagnosis of the former; however, most authors agree that systolic and diastolic pressures above 170 mmHg and 110 mmHg, respectively, represent severe hypertension.[8,9] Studies in pregnant and nonpregnant women have demonstrated a reduction in stroke and other cardiovascular complications when antihypertensive treatment is initiated at or above these levels.[10,11] Although the gestational risks associated with chronic hypertension (e.g. superimposed pre-eclampsia, intrauterine fetal growth restriction and stillbirth, placental abruption and premature delivery) are increased, outcomes correlate more closely with elevated uric acid levels and proteinuria than with blood pressure levels.[12-19] The exception appears to be cases of severe and uncontrolled hypertension during the first trimester, when fetal and maternal morbidity and mortality are markedly increased.[20]

Other indicators of poor prognosis include:

- previous severe pre-eclampsia in women with chronic hypertension
- failure of blood pressure to fall during the second trimester
- the presence of secondary hypertension
- a history of longstanding severe hypertension
- pre-existing chronic kidney disease.

Table 1. Causes of secondary hypertension in pregnancy

Chronic kidney disease

The most important renal disorders to consider are glomerulonephritis, reflux nephropathy and adult polycystic kidney disease. It is important to assess the degree of renal impairment and the prognosis of the underlying renal disease when determining the risk in relation to pregnancy. The risk associated with kidney disease may be substantially greater than that associated with the hypertension.[2,3]

Renal artery stenosis

Renal artery stenosis is usually due to fibromuscular dysplasia in young women.[4]

Systemic disease with renal manifestations

Diabetes mellitus and systemic lupus erythematosus are the most common conditions. The extent of other organ involvement also determines the degree of risk associated with pregnancy.

Endocrine disorders

Endocrine causes of hypertension include phaeochromocytoma, Cushing's syndrome and primary hyperaldosteronism. Although rare, phaeochromocytoma has grave prognostic implications for both maternal and fetal welfare.[5] Measurement of fasting plasma free metanephrines or 24-hour urinary catecholamines should be considered in women with very labile or severe hypertension. Measurement of renin and aldosterone concentrations during pregnancy is problematic.

Aortic coarctation

Rare, but more likely in younger women.

Clinical features

A detailed history and physical examination are essential in seeking a possible cause for the chronic hypertension or, equally importantly, ascertaining new-onset hypertension. Known pre-existing hypertension, treated or untreated, can be most helpful, particularly if an elevated blood pressure is evident before 30 weeks' gestation.

It is imperative to determine if there is a family history of hypertension or renal disease. A history of urinary infection, renal colic, haematuria and/or proteinuria should be sought, and women questioned about their drug ingestion (including hormonal preparations) prior to the pregnancy. A history of rash, arthritis or diabetes may point to a systemic disease, while episodic palpitations, headache or flushing may suggest a phaeochromocytoma.

Physical examination should include blood pressure measurements (Korotkoff sounds I and V) while the woman is seated. Blood pressure should be measured in both arms using an appropriately sized cuff, and the femoral pulses should be palpated. Auscultation in the epigastrium and over the renal angles posteriorly may be of value for diagnosing renal artery stenosis (Figure 2). Evidence of any systemic disease should be recorded. Examination should also ascertain evidence of end-organ damage due to hypertension. This requires examination of the precordium for left ventricular hypertrophy, urinalysis and optic fundoscopy.

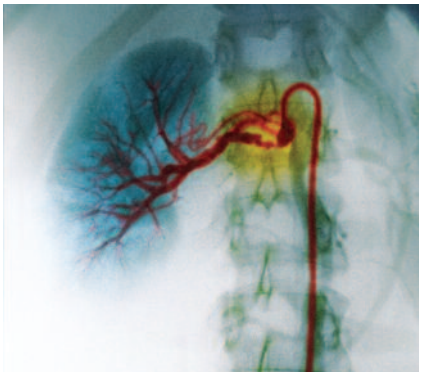


Figure 2. Renal artery stenosis, a cause of secondary hypertension in pregnancy.

Recent studies have suggested that 24-hour ambulatory blood pressure appraisal may have application in the diagnosis and management of women with chronic hypertension in pregnancy. This option can be considered, particularly if the diagnosis of hypertension is in doubt.[6,7]

Preconception counselling

Ideally, women who have hypertension and/or renal disease should be seen and investigated, a diagnosis established, and the underlying condition stabilised prior to a planned pregnancy. The potential risks of pregnancy can be discussed at this time and an assessment made of the likely prognosis. Also at this time, the risks of perinatal morbidity and mortality and the potential for deterioration of any underlying kidney disease should be fully explained to those women with significant prenatal renal dysfunction (a serum creatinine of 130 µmol/L or greater).[21]

Clinical and laboratory monitoring

Tests should be performed in all women with known chronic hypertension to assess the severity of the hypertension, ascertain if there is any end-organ damage and investigate possible causes of the hypertension. Appropriate tests are outlined in Table 2.

Pregnant women with chronic hypertension, whether essential or secondary, should be observed frequently during their pregnancy by an obstetrician and a physician who are familiar with the management of pre-eclampsia and hypertension

Table 2. Recommended investigations for pregnant women with hypertension

- **Urinalysis for protein, blood and glucose.** If proteinuria is evident on dipstick analysis, a spot urine collection for measurement of the urinary protein:creatinine ratio or a 24-hour urinary protein collection should be obtained.
- **Direct urinary microscopy.** Performed to detect the presence of casts, and white and red blood cells (including red cell morphology).
- **Midstream urine culture**
- **Blood tests.** These include measurement of electrolytes, creatinine, uric acid and blood glucose; full blood examination; and other tests (measurement of antinuclear antibodies, C3 or C4 complement fractions, or HbA_{1C}) as clinically indicated.
- **ECG**
- **Renal ultrasound and Doppler studies.** These should be considered, particularly if the hypertension is severe, proteinuria is identified or a renal bruit is evident.
- **Twenty-four-hour urine collection.** For estimation of catecholamine excretion if there is a concern regarding a possible phaeochromocytoma. At least two consecutive collections are advised. Where available, plasma free metanephrines are a suitable alternative.

during pregnancy.

Statistically pre-eclampsia, which is often causatively associated with intrauterine growth restriction, is the most likely event to complicate the pregnancy of a woman with chronic hypertension. Early detection and appropriate management of this complication assumes the highest priority after 20 weeks' gestation. Table 3 summarises the monitoring of hypertension in pregnant women.

Admission to hospital or an antenatal day-assessment unit is recommended for women with a confirmed systolic blood pressure over 160 mmHg or a diastolic blood pressure over 100 mmHg. This approach is also recommended for women who have less severe hypertension (a systolic blood pressure between 140 and 160 mmHg and/or a diastolic blood pressure between 90 and 100 mmHg) if the hypertension is accompanied by newly developed proteinuria at any stage of the pregnancy. This enables assessment of maternal and fetal welfare and facilitates discussion among all parties involved so that pharmacological treatment can be commenced under close supervision. Before labour and delivery, review by an obstetric anaesthetist is also recommended, particularly if the woman is obese.

Drug treatment

The continued administration or initiation of antihypertensive therapy in women with chronic hypertension in pregnancy (except for the acute treatment of severe hypertension) remains controversial. The physiological fall in blood pressure that manifests during the first half of pregnancy in most women may allow antihypertensive medication to be reduced or withdrawn. Although treatment is associated with a significant reduction in severe hypertension-related morbidity, it has not been shown to alter the risk of superimposed pre-eclampsia, preterm delivery, placental abruption or perinatal death.[22-24]

To initiate or increase drug therapy at too low a blood pressure level may result in a large number of women being unnecessarily exposed to medication and, depending on the drug used, result in compromised fetal growth and development. It should be recognised that over 20% of unselected normal pregnancies, usually late in the third trimester, can record a maximum prenatal blood pressure of at least 140/90 mmHg.[9] Thus, the clinician needs to be aware that a single reading in a consultation room may not be representative of future readings. Pregnant women with borderline hypertension (according to gestational age) may therefore benefit from increased vigilance, either at a day-assessment unit or by instigating 24-hour ambulatory blood pressure monitoring. The latter can help determine the blood pressure pattern before treatment is initiated.

The decision to initiate drug treatment in a pregnant woman with chronic hypertension depends on several factors in addition to the blood pressure level itself. These factors include:

- whether the patient has renal or cardiovascular disease, or is at risk of target organ damage
- whether the patient has a past history of stroke
- the stage of gestation.

Most authors would agree that treatment should be started when, on careful and reproducible appraisal, the blood pressure reaches or exceeds a systolic pressure of 160 mmHg or a diastolic pressure of 100 mmHg. For systolic pressures between 140 and 160 mmHg, or diastolic pressures between 90 and 100 mmHg, direct evidence of a benefit from treatment is lacking, although appropriate studies are limited. The decision to treat patients who have these intermediate blood pressure levels will therefore be opinion-based, after consideration of such factors as the consistency and trend of the hypertension, the presence of systemic disease and the gestational age of the fetus. In the third trimester, an increase in the requirement for antihypertensive therapy should be anticipated.

As is evident from the above discussion, the appropriate target blood pressure for pregnant women with hypertension has not been and perhaps, given the multiple variables involved, cannot be strictly defined. Logically, for a given patient,

a commonsense approach will be to maintain levels safely below those which prompted the initiation of treatment.

Choice of antihypertensive medication

Drugs that have been used for many years in pregnant women with some measure of safety are noted in Table 4. Labetalol (Presolol, Trandate) and methyldopa (Aldomet, Hydopa) have been used most often, followed by other β-blockers, hydralazine (Alphapress, Apresoline) and, more recently, calcium-channel blockers, prazosin (Minipress, Pressin) and clonidine (Catapres 150).

Methyldopa and clonidine

Methyldopa is the drug that has been most studied in pregnancy and has the best safety and efficacy profile.[25-27] It has been shown to maintain uteroplacental blood flow and fetal haemodynamics[28] and is considered first-line therapy for chronic hypertension in pregnancy. However, it should not be used in women who have a history of depression or are currently depressed.

Clonidine is a centrally active vasodilator like methyldopa; few studies have evaluated its efficacy or safety in pregnancy.

Labetalol

Labetalol, a β-blocker with some α-adrenoreceptor-blocking activity, is now widely used because of its efficacy and safety profile. It has been shown to be as effective as methyldopa. Although studies have not documented adverse fetal effects with labetalol, there are as yet no follow-up safety trials (as exist for methyldopa) in children whose mothers received labetalol while pregnant to justify its use ahead of methyldopa.[29-31]

Hydralazine

Hydralazine is often used parenterally in hypertensive emergencies but can also be administered orally. It can result in headache, palpitations and dizziness when used alone and hence it is often administered with methyldopa or a β-blocker. It appears safe and efficacious for chronic treatment, although long-term studies are lacking. High doses and protracted use can be associated with a lupus-like syndrome.

Other β-blockers

There is evidence of differential effects among the β-blockers when used in pregnancy. Maternal therapy with atenolol (a cardioselective drug with no intrinsic sympathomimetic activity) was associated with impaired fetal growth in two studies, especially when used before the third trimester. Distinct from this is the beneficial effect on fetal growth found with oxprenolol (Corbeton), a nonselective agent possessing intrinsic sympathomimetic activity.[32-35] Thus, drugs within a pharmacological class may not always have identical effects and the findings for one drug cannot always be extrapolated to others within the class. In general, it would appear that β-blockers are best reserved for treatment during the third trimester.

Calcium-channel blockers

Of the calcium-channel blockers, nifedipine (Adalat, Addos, Adefin, Nifehexal, Nyefax) has been used extensively for the acute lowering of blood pressure in late pregnancy, but in large doses it may inhibit uterine contractions.[36,37] It can also produce a marked drop in blood pressure when given in combination with magnesium sulphate in an emergency situation and should be used with care in this context.

Although nifedipine is not recommended for use during early pregnancy, recent data have shown no evidence of a major teratogenic risk with calcium-channel blockers taken in early pregnancy.[38] Nifedipine has been used successfully for chronic hypertension in pregnancy without adverse effects, although no difference has been observed in maternal or fetal outcomes in these studies.[39,40]

ACE inhibitors

ACE inhibitors (and, by association through mode of action, angiotensin-receptor blockers) are contraindicated in pregnancy. They have been associated with an increased risk of fetal, particularly cardiovascular, malformations in early pregnancy, and other adverse sequelae late in pregnancy.[41]

Table 3. Monitoring hypertensive women during pregnancy

- Record any symptoms and enquire about fetal movements at each visit.
- Perform a physical examination at each visit, including measurement of blood pressure (with an appropriately sized cuff) and assessment of uterine size.
- Refer the patient for an obstetric ultrasound early in the pregnancy to confirm the gestational age of the fetus. Additional scans can be obtained as clinically indicated.
- Order biochemical and haematological tests (as outlined in Table 2) at the initial visit. Some tests will need repeating according to clinical demands. In particular, women with underlying chronic kidney disease should have renal function assessed regularly. In other women, repeat testing for proteinuria may be of value for the detection of superimposed pre-eclampsia (particularly later in the second and third trimesters).
- Collect a urine sample for urinalysis to detect protein in the urine at each visit. If the test is positive at any visit, an accurate 24-hour urine protein estimation (ideally) or measurement of a spot urinary protein:creatinine ratio should be performed.

Table 4. Summary of antihypertensive drugs commonly used in pregnancy*

Drug	Dose	Action	Contraindications*	Practice points*
Methyldopa	250-750 mg tds	Central	Depression	Slow onset of action over 24 hours. Dry mouth, fatigue and blurred vision may occur, which usually settle with time
Labetalol	100-400 mg tds	β-blocker with mild vasodilator (α-blocker) effect	Asthma, chronic airflow obstruction and heart block	Headache, nausea and scalp tingling may occur, which usually resolve within 24 to 48 hours. Not available for IV use in Australia
Oxprenolol	40-160 mg tds	β-blocker		Bradycardia and bronchospasm may occur
Hydralazine	25 mg (po); 5–10 mg (IV bolus)	Peripheral vasodilator	Concurrent systemic lupus erythematosus or past rash	May aggravate hyper-reflexia and tachycardia. Often used peripartum
Nifedipine	20 mg bd; 60 mg daily (slow release)	Calcium-channel antagonist	Aortic stenosis	Headache, flushing, tachycardia, peripheral oedema and red shins may occur
Prazosin	0.5–5 mg tds	α_1- blocker		First dose effect: orthostatic hypotension

* Refer to full prescribing information for each drug for complete listings of contraindications and precautions. It should be remembered that evidence-based data are limited for most agents and their use is sometimes indicated despite the stated risk. Nonetheless, the clinician should carefully address the relevant issues for each patient before commencing treatment with any agent (see text).

Delivery

Decisions regarding the delivery of a baby when a woman has hypertension are complex. Careful consideration is required in each case, with consultation between the obstetric, medical, paediatric, midwifery and anaesthetic members of the team caring for the woman. Such decisions are determined by fetal and/or maternal factors.

Timing

The general principle is that the pregnancy should be allowed to proceed as far as possible provided that both maternal and fetal wellbeing is maintained. In many women with chronic hypertension, blood pressure remains well controlled and no fetal or maternal problems mandating premature delivery arise. In such cases it is usual for the pregnancy to be allowed to continue, under close supervision, with the aim of vaginal delivery at term. In other cases, and almost always in the setting of superimposed pre-eclampsia, early delivery is necessitated by the occurrence of one or more of a number of 'endpoints' representing fetal or maternal compromise.

Occasionally, the patient's blood pressure becomes impossible to control despite maximal doses of medications. This can occur in the absence of proteinuria, fetal abnormalities or other features of pre-eclampsia. In these cases, delivery may be necessary to prevent likely maternal cerebral haemorrhage, the indication being 'failed blood pressure control'.

Mode of delivery

The mode of delivery should be determined by obstetric considerations. If there is evidence of fetal compromise the obstetrician will usually favour caesarean section. The vaginal route of delivery is favoured unless delivery is required urgently, such as in cases of fetal distress, antepartum haemorrhage or severe pre-eclampsia.

Regional anaesthesia is extremely helpful in most cases, and caesarean section should be performed under regional block unless there is maternal coagulopathy (most often thrombocytopenia) or other unusual factors. Despite the undoubted utility of an epidural block, it does not provide complete blood pressure control and so usual monitoring and hypertension therapy should be continued.

Location

Delivery should be conducted in a centre with adequate facilities to care for the mother with severe hypertension or other features of severe pre-eclampsia, and for preterm infants.

Postpartum management

For many women with chronic hypertension, a period of instability follows delivery for seven to 14 days, during which time it may be extremely difficult to achieve adequate blood pressure control.

continued

This instability is more pronounced in women who have sustained superimposed pre-eclampsia, but is also seen in those who do not have this complication.

Typically, the blood pressure will be exaggerated on the second or third day after delivery and will remain sustained for several days thereafter. It is often necessary to increase medication or commence new antihypertensive therapy at this time. The use of methyldopa postpartum should be avoided because of the risk of aggravating postnatal depression. An elevated risk of eclampsia remains for up to about five days postpartum, after which time it is much less common.

Conclusion

Chronic hypertension in pregnancy is not uncommon; its incidence is likely to be increasing as women defer pregnancy until they are older. The clinician needs to distinguish between new-onset and chronic hypertension and be aware of possible secondary causes – chronic kidney disease in particular. Specific treatment targets remain unclear, but avoidance of severe hypertension, familiarity with appropriate antihypertensive agents, early awareness of superimposed pre-eclampsia, and recognition of the need for a team approach to management are crucial to the long-term wellbeing of mother and child. Postpartum, the blood pressure is often labile, and it can be several weeks before it stabilises. MT

A list of references is available on request to the editorial office.

COMPETING INTERESTS: None.

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