ARTICLE

Management of hypertension in pregnancy

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SUMMARY

Hypertensive disorders of pregnancy are common and can result in maternal and fetal morbidity and mortality. Women may have chronic hypertension, or develop hypertension during pregnancy.

Management involves close maternal and fetal surveillance. If an antihypertensive drug is needed, prescribe one that is safe in pregnancy.

Pre-eclampsia is a hypertensive disorder of pregnancy. Women at high risk of pre-eclampsia should start aspirin 150 mg daily at 12–16 weeks gestation and continue until 36 weeks gestation, to reduce the risk of preterm delivery.

There are long-term cardiovascular and mortality risks associated with pregnancies complicated by gestational hypertension and pre-eclampsia. Ongoing cardiovascular and metabolic risk surveillance should be undertaken by the woman's general practitioner.

Introduction

In a normal pregnancy, blood pressure falls in the first trimester. The fall reaches a maximum of 10–15 mmHg (systolic) in mid-pregnancy, and returns to pre-pregnancy levels by term. Hypertensive disorders of pregnancy affect approximately 5–10% of pregnancies in Australia. These disorders are associated with both maternal and fetal morbidity and mortality.

Hypertension

Hypertension is defined as a systolic blood pressure 140 mmHg or above, or diastolic blood pressure 90 mmHg or above. This should be confirmed over four hours with repeated measures, or after overnight rest, to determine if there is true hypertension. Severe hypertension is classified as a systolic blood pressure 160 mmHg or above, or a diastolic blood pressure 110 mmHg or above. Severe hypertension (160/110 mmHg or above) requires urgent management in hospital.

Hypertensive disorders of pregnancy can be divided into four categories:

- chronic hypertension
  - primary
  - secondary
- gestational hypertension
- pre-eclampsia and eclampsia
- pre-eclampsia superimposed on chronic hypertension.

Chronic hypertension

Chronic hypertension predates the pregnancy or is first diagnosed before 20 weeks gestation. It includes both primary hypertension and less commonly secondary hypertension, related to an underlying cause, such as kidney disease. Routine testing for secondary causes is not recommended in pregnancy, but should be considered postpartum. For pregnant women with chronic hypertension, the initial recommended tests are:[1-3]

- full blood count
- urea, creatinine and electrolytes
- liver function tests
- uric acid
- urinalysis and microscopy
- urine protein:creatinine ratio (to establish a baseline)
- ECG.

Chronic hypertension is associated with adverse maternal and fetal outcomes:

- superimposed pre-eclampsia – 25%
- preterm delivery – 28%
- fetal growth restriction – 17%
- perinatal death – 4%.[4]

Some women have white-coat hypertension. This is defined as a clinic blood pressure of at least 140/90 mmHg, but with normal blood pressure outside the clinic. It is diagnosed by 24-hour

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ambulatory blood pressure monitoring or home blood pressure monitoring. White-coat hypertension is not entirely benign and is associated with an increased risk of pre-eclampsia (8%).[5] Generally, treatment is not required if the clinic blood pressure is below 160/110 mmHg and the out-of-office blood pressure remains normal.

Management

Women with chronic hypertension may be taking antihypertensive drugs before conception or conceive while taking them. Some of these drugs are contraindicated or not recommended in pregnancy (Table 1).[6] Table 2 lists oral antihypertensive drugs that are safer in pregnancy.[2,6]

The mainstay of management of chronic hypertension in pregnancy is regular maternal review and strict blood pressure control. Often the physiological fall in blood pressure in the first trimester will allow for a reduction or cessation of antihypertensive drug therapy.

Optimal management includes maintaining the blood pressure around 110–140/85 mmHg, regular assessment for the development of pre-eclampsia and close surveillance of fetal growth and wellbeing. Signs and symptoms suggestive of pre-eclampsia include headache, visual changes, epigastric or right upper quadrant pain and oedema (see Box). Assessment also includes careful blood pressure measurement, ideally using automated office or a liquid crystal sphygmomanometer, and testing for proteinuria. Home blood pressure monitoring may form part of this assessment. Proteinuria is defined as a spot urine protein:creatinine ratio above 30 mg/mmol or urine protein excretion above 300 mg/24 hours. Dipstick urinalysis (automated or visual) is most commonly used to screen for proteinuria, with a 'negative' or 'trace' result being normal. One plus (1+) or more on dipstick is sensitive, but inaccurate and should be further evaluated with a spot urine protein:creatinine ratio.

Table 1 **Antihypertensive drugs to avoid in pregnancy**

Antihypertensive class	Advice	Potential adverse effects	Recommendation
ACE inhibitors	Contraindicated	Teratogenic in the second and third trimester resulting in fetal anuria, oligohydramnios, hypocalvaria, intrauterine growth restriction and patent ductus arteriosus, death	Stop drug ideally before conception or at diagnosis of pregnancy
Angiotensin receptor blockers	Contraindicated	Teratogenic in the second and third trimesters, fetal anuria, oligohydramnios, hypocalvaria, intrauterine growth restriction, patent ductus arteriosus, death	Stop drug ideally before conception or at diagnosis of pregnancy
Diuretics	Avoid	Maternal hypovolaemia, fetal hypoglycaemia, thrombocytopenia, hyponatraemia and hypokalaemia	Use an alternative antihypertensive
Beta blockers (other than labetalol)	Avoid	Fetal bradycardia, intrauterine growth restriction (atenolol)	Use an alternative antihypertensive
Calcium channel antagonists (other than nifedipine and diltiazem)	Avoid	Maternal hypotension and fetal hypoxia	Use an alternative antihypertensive

Table 2 **Antihypertensive drugs that can be safely used in pregnancy**

Antihypertensive drug*	Class/action	Dose	Adverse effects
Labetalol	Beta blocker	100 mg twice a day – 400 mg three times a day	Bradycardia, bronchospasm, headache
Nifedipine controlled release	Calcium channel antagonist	30 mg daily – 60 mg twice a day	Headache (first-dose effect), flushing, tachycardia, peripheral oedema
Methyldopa	Central action	250 mg twice a day – 750 mg three times a day	Depression, dry mouth, sedation, rarely haemolysis and hepatitis
Hydralazine	Vasodilator	25 mg three times a day – 50 mg three times a day	Flushing, headache, lupus-like syndrome
Prazosin	Alpha blocker	0.5 mg twice a day – 5 mg three times a day	Orthostatic hypotension

* Although oxprenolol is safe, it is no longer available in Australia.

Gestational hypertension

Gestational hypertension is the development of hypertension at or after 20 weeks gestation, in the absence of other features of pre-eclampsia (see Box). Gestational hypertension is associated with an increased risk of developing pre-eclampsia (up to 25%, depending on the gestation at presentation), as well as the future development of cardiovascular disease.[1-3] Fetal growth restriction is not typically a feature of gestational hypertension.

Management

Regular blood pressure monitoring is necessary to ensure the blood pressure remains at 110–140/80–90 mmHg. There should be regular assessment for the development of pre-eclampsia and close surveillance of fetal growth and wellbeing. Once the blood pressure is controlled, gestational hypertension may continue to be managed with outpatient care, under close and regular review.

Pre-eclampsia

Pre-eclampsia is a complex multisystem disorder of pregnancy arising from abnormal placentation, resulting in an imbalance of angiogenic and anti-angiogenic factors, oxidative stress and immunological involvement. The maternal response to this is thought to involve systemic vascular endothelial dysfunction. Pre-eclampsia may be superimposed on chronic hypertension, or present as new onset hypertension, arising at or after 20 weeks gestation, with the presence of one or more of the typical clinical features (see Box).[1,2]

Risk factors for pre-eclampsia include maternal age, primiparity, previous pre-eclampsia, multiple gestation, prolonged interpregnancy interval and assisted reproduction therapies. Other factors are underlying renal disease or hypertension, antiphospholipid syndrome, systemic lupus erythematosus, diabetes and a maternal body mass index (BMI) above 30 kg/m^2.

Adverse maternal outcomes include eclampsia, stroke, multiorgan failure, major haemorrhage and death. Fetal complications of pre-eclampsia include growth restriction, preterm delivery, placental abruption and perinatal death.

Management

Whether pre-eclampsia is new onset or superimposed on chronic hypertension, a multidisciplinary approach optimises maternal and fetal outcomes as delivery is the only definitive cure. There is a balance between the welfare of the growing fetus and the ongoing risk of maternal complications. Management should occur at a specialist centre with the required protocols and expertise because inpatient care is usually required.

For severe hypertension urgent management is indicated and drugs are required to rapidly lower blood pressure (Table 3). An infusion of magnesium sulphate can be considered as it reduces the rate of seizure by 50% (Table 4).[7]

Prediction and prevention

A number of options are available in the first trimester for predicting the risk of pre-eclampsia. These include using maternal blood pressure and risk factors or combined prediction models using additional tests of placental growth factor and doppler imaging of the uterine artery. These tests are readily available and consideration needs to be given to how they could be integrated into antenatal care. In Australia, however, the cost effectiveness of combined first trimester screening for pre-eclampsia has yet to be evaluated.

Although there is no current method of preventing pre-eclampsia, aspirin is recommended for women considered to be at high risk because of maternal risk factors or by clinical prediction models. The ASPRE trial used combined first trimester screening and found a 62% reduction in preterm pre-eclampsia at less than 37 weeks gestation in women who took aspirin 150 mg daily.[8] Women at high risk require early obstetric review, because starting aspirin before 16 weeks is most effective. If started for pre-eclampsia prophylaxis, aspirin should be continued until

Box Features of pre-eclampsia and eclampsia

Renal
- proteinuria – spot urine protein:creatinine ratio 30 mg/mmol or more
- acute kidney injury with serum creatinine >90 micromol/L
- oliguria: <80 mL/4 hours

Haematological
- thrombocytopenia – platelet count <100,000/microlitre
- haemolysis
- disseminated intravascular coagulation

Hepatic
- raised serum transaminases (alanine aminotransferase or aspartate aminotransferase >40 IU/L)
- severe right upper quadrant or epigastric pain

Neurological
- eclamptic convulsion
- sustained clonus (hyperreflexia is commonly found and not diagnostic)
- severe headache
- visual disturbance – photopsia, scotomata, cortical blindness
- stroke

Pulmonary oedema

Uteroplacental dysfunction with fetal growth restriction, abnormality on doppler imaging of the umbilical artery, stillbirth

Table 3 **Urgent treatment of severe hypertension* in pregnancy**

Drug	Dose	Route	Onset of action	Adverse effects
Hydralazine	5–10 mg	Intravenous bolus repeated after 20 min if blood pressure remains >160/110 mmHg	20 min	Flushing, headache, nausea, hypotension, tachycardia
Labetalol	20–80 mg	Intravenous bolus over 2 min, repeat after 10 min if blood pressure remains >160/110mmHg	5 min	Bradycardia, hypotension, fetal bradycardia
Labetalol	200 mg	Oral	30–45 min	Bradycardia, bronchospasm, headache
Nifedipine†	10 mg	Oral	30–45 min	Headache, flushing

* Severe hypertension is 160/110 mmHg or above.
† This formulation is no longer available in Australia.

Table 4 **Seizure prophylaxis and treatment of eclampsia**

Drug	Dose	Route	Onset of Action	Adverse effects
Magnesium sulphate	4 g	Intravenous bolus over 20 min followed by 1 g/hour infusion, typically continued for 24 hours	20 min	Flushing, respiratory depression Caution in renal impairment as magnesium is excreted renally and toxicity may occur

36 weeks gestation. Aspirin reduces the risk of preterm birth, fetal growth restriction and fetal death, but may increase postpartum bleeding.[9,10]

Women with an inadequate dietary calcium intake may have an increased risk of pre-eclampsia. They should aim to achieve the recommended daily allowance (1000 mg daily) through diet or calcium supplementation to reduce the risk.[11]

Postpartum management

After delivery, hypertension typically resolves within 12 weeks for women with gestational hypertension or pre-eclampsia. If this does not occur, consideration should be given to investigation for primary or secondary hypertension. Regular monitoring of blood pressure postnatally should occur, with down titration of antihypertensive drugs when the systolic blood pressure drops below 120 mmHg. For women with chronic hypertension, the decision to return to their usual antihypertensive treatment will depend on its compatibility with breastfeeding, and their future pregnancy plans. It would be reasonable to transition them back to their usual treatment early, provided they remain aware of the importance of review before future pregnancies to ensure it will be safe to use.

The antihypertensive drugs that are safe in pregnancy are also safe in breastfeeding. However, given that methyldopa is associated with a 30% risk of depression, it is usually stopped postpartum. ACE inhibitors, particularly enalapril, have very low concentrations in breast milk and are often used during lactation. Angiotensin receptor blockers are not recommended due to a lack of available safety information.

Long-term implications

Gestational hypertension and pre-eclampsia are associated with a two- to fourfold increase in the future risk of cardiovascular disease. Women may develop hypertension, stroke, diabetes, venous thromboembolic disease or chronic kidney disease. Cardiovascular events such as stroke may occur in middle age. Given these risks, and the cumulative risks associated with several pregnancies complicated by severe pre-eclampsia, or preterm delivery, preconception counselling before future pregnancies is recommended.

Women with a history of hypertension in pregnancy require indefinite follow-up. They are recommended to have annual reviews of blood pressure, fasting lipids and blood glucose. Counselling on a healthy lifestyle and diet, maintenance of an optimal BMI, smoking cessation and regular exercise are essential for optimising long-term health outcomes.[12-14] <

Conflicts of interest: none declared

Q:

SELF-TEST QUESTIONS

True or false?

1. Angiotensin receptor blockers should not be used during pregnancy and lactation.
2. Women at high risk of pre-eclampsia should avoid taking aspirin after the first trimester of pregnancy.

Answers on page 177

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