ARTICLE

Hypertensive disorders of pregnancy

SUMMARY

Hypertensive disorders of pregnancy are common and represent a spectrum of disease ranging from chronic and gestational hypertension to eclampsia. They are associated with increased risk of both adverse maternal and fetal outcomes.

Drug treatment is generally reserved for moderate or severe hypertension. Pre-eclampsia–eclampsia can be life-threatening and requires urgent investigation and intervention. There are limited data about the safety of many hypertensive drugs in pregnancy. ACE inhibitors and angiotensin receptor blockers should be avoided.

Women who have had any hypertensive disorder in pregnancy have an increased cardiovascular risk. They require long-term follow-up.

Introduction

Hypertensive disorders affect 10–22% of pregnancies and have been classified into four conditions, reflecting potential differences in aetiology and pregnancy outcomes:[1,2]

- chronic hypertension
- gestational hypertension
- pre-eclampsia–eclampsia
- pre-eclampsia superimposed on chronic hypertension.

The incidence of these disorders is not entirely clear, but pre-eclampsia is thought to affect 5–8% of pregnancies. Chronic hypertension accounts for approximately 20% of the cases of high blood pressure seen in pregnancy.[1,3]

Chronic hypertension

Chronic hypertension is diagnosed when hypertension is confirmed before pregnancy or before 20 weeks gestation (blood pressure >140 mmHg systolic and/or >90 mmHg diastolic).[3] However, chronic hypertension is frequently diagnosed when high blood pressure fails to resolve post-partum. Women with chronic hypertension require careful monitoring during pregnancy as they have an increased risk of adverse events, including superimposed pre-eclampsia, placental abruption, fetal growth restriction, premature delivery and stillbirth.[3]

Pre-pregnancy counselling and management of chronic hypertension is essential. Some commonly prescribed antihypertensive drugs are contraindicated or best avoided before conception and during pregnancy (Table 1). These include ACE inhibitors, angiotensin receptor antagonists, diuretics and most beta blockers.[3,4]

Where indicated, it is advisable to look for secondary causes of hypertension before conception, as normal physiological changes in pregnancy can make many of these screening tests difficult to interpret. If this is not possible, with the exception of phaeochromocytoma, further investigation is often best deferred until the postpartum period. In all cases, preconception assessment for proteinuria (with urine protein:creatinine ratio) is recommended as a baseline measurement.

Treatment

With the exception of acute, severe hypertension, treatment with antihypertensive drugs during pregnancy remains controversial. In many cases, the

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

ANTIHYPERTENSIVE	ADVICE	POTENTIAL ADVERSE EVENTS
ACE inhibitors	Contraindicated	Teratogenic in first trimester Fetal renal dysfunction, oligohydramnios and skull hypoplasia in second and third trimesters
Angiotensin receptor blockers	Contraindicated	Teratogenic in first trimester Fetal renal dysfunction and oligohydramnios in second and third trimester
Diuretics	Avoid	Fetal electrolyte disturbances, reduction in maternal blood volume
Beta blockers (except labetalol and oxprenolol)	Avoid	Fetal bradycardia, long-term use of atenolol associated with fetal growth restriction
Calcium channel antagonist (except nifedipine)	Avoid	Maternal hypotension and fetal hypoxia

physiological fall in blood pressure that occurs during the first trimester leads to normalisation without the need for medication. There is no direct evidence that continued treatment of chronic hypertension leads to a reduction in the risk of adverse pregnancy events.[3] Benefits appear to be confined to reducing severe hypertension (≥170/110 mmHg), however most centres start or continue antihypertensive drugs when blood pressure exceeds 160 mmHg systolic and/or 100 mmHg diastolic on more than one occasion.[3] Table 2 outlines the antihypertensive drugs most commonly used in pregnancy.[3,4]

Blood pressure reduction to 140–160 mmHg systolic and 90–100 mmHg diastolic are acceptable treatment goals. Stricter blood pressure control may be associated with fetal growth restriction, presumed to be related to relative placental hypoperfusion. Importantly, women need to be carefully monitored for any signs of pre-eclampsia which may include worsening hypertension and new or worsening proteinuria (see Box). Repeated assessment of fetal wellbeing and growth is appropriate, although given that there are no guidelines, the frequency of monitoring is usually at the discretion of the woman's treating obstetrician.

Gestational hypertension

Gestational hypertension is defined as:

- new onset of hypertension after 20 weeks gestation
- no other features to suggest pre-eclampsia (see Box)
- normalisation of blood pressure within three months postpartum.

Gestational hypertension is associated with adverse pregnancy outcomes. These are more common if it presents earlier in the pregnancy, if it progresses to pre-eclampsia or if hypertension is severe (≥170/110 mmHg).[3]

Although rare, phaeochromocytoma can initially present in pregnancy. It can be fatal. Investigation is needed if there are any other features to suggest a phaeochromocytoma (for example paroxysmal hypertension, episodic headache and sweating), or if the onset of hypertension occurs early in the pregnancy or is severe. Plasma or urinary metanephrines (catecholamine metabolites) tend not be affected by the physiological changes of pregnancy and are useful as screening investigations.[5]

The benefits of treating mild to moderate hypertension are limited to the prevention of severe hypertension and appear to have no effect on the potential for adverse pregnancy outcomes. The indications for treatment with antihypertensive drugs, goals of therapy and the choice of drug are similar to the treatment of chronic hypertension in pregnancy (Table 2). Up to 25% of women who develop hypertension in pregnancy will eventually be diagnosed with pre-eclampsia, even if no other manifestations are present initially. Regular monitoring of blood pressure, and investigation for proteinuria and other features of pre-eclampsia (up to once or twice per week) is reasonable.[3]

By definition, gestational hypertension should resolve within three months postpartum and the patient can generally be weaned off antihypertensive drugs within weeks. If hypertension has not resolved within three months, an alternative diagnosis – for example chronic (essential or potentially secondary) hypertension – needs to be considered. There is a risk of recurrence in subsequent pregnancies so increased monitoring will be required.

Pre-eclampsia, eclampsia and superimposed pre-eclampsia

The aetiology of pre-eclampsia is unclear although a combination of maternal and placental factors are likely to contribute. Abnormal placental formation, resulting in aberrant angiogenic factor production and systemic endothelial dysfunction, as well as genetic and immunological factors, are thought to play a role. Risk factors include nulliparity, age less than 18 or more than 40 years, a past history of pre-eclampsia and maternal medical comorbidities (hypertension, diabetes mellitus, renal disease, obesity, antiphospholipid antibodies or other thrombophilia and connective tissue disease).[6] Pre-eclampsia is associated with fetal growth restriction, preterm delivery, placental abruption and

Box **Features of pre-eclampsia**

Hypertension with onset after 20 weeks gestation
Renal manifestations
Significant proteinuria
Serum creatinine >90 micromol/L (or renal failure)
Oliguria
Haematological manifestations
Disseminated intravascular coagulation
Thrombocytopenia
Haemolysis
Hepatic manifestations
Raised serum transaminases
Severe right upper quadrant or epigastric pain
Neurological manifestations
Eclamptic seizure
Hyperreflexia with sustained clonus
Severe headache
Persistent visual disturbances
Stroke
Pulmonary oedema
Fetal growth restriction
Placental abruption

perinatal death.[7] Severe pre-eclampsia has the potential for progression to eclampsia, multi-organ failure, severe haemorrhage and rarely maternal mortality.

Pre-eclampsia is a disorder with many manifestations. New onset hypertension after 20 weeks gestation and proteinuria are the most common presenting features. A urine dipstick for proteinuria can be a useful screening test, but is confounded by high false positive and false negative rates. If there is any uncertainty, assessment of the urine protein:creatinine ratio is advised. Peripheral oedema is no longer considered a diagnostic feature of pre-eclampsia as it is neither a sensitive nor specific sign. Other clinical manifestations are outlined in the Box, with their presence suggesting severe pre-eclampsia.

The presence of severe pre-eclampsia mandates urgent review. A multidisciplinary team approach (obstetrician, midwife, neonatologist, anaesthetist and physician) is often required. Delivery is the only definitive management for pre-eclampsia. The timing of delivery is dependent on the gestational age and well-being of the fetus and the severity of the pre-eclampsia. The pregnancy is rarely allowed to go to term. Management of pre-eclampsia before 32 weeks gestation should occur in specialist centres with sufficient expertise and experience. Severe hypertension may require parenteral antihypertensive drugs (such as hydralazine), which should only be given in a suitably monitored environment (birth suite or high dependency unit). Intravenous magnesium sulfate is given for the prevention of eclampsia in severe cases.[8]

Although pre-eclampsia progressively worsens while the pregnancy continues, outpatient management may be considered in selected cases. The antihypertensive drugs used in pre-eclampsia are the same as those used to treat chronic and gestational hypertension (Table 2).[3] The treatment goals for blood pressure control are also the same (140–160 mmHg systolic and 90–100 mmHg diastolic). Although widely advised in the past, there is little evidence to support bed rest. Given the potential for venous thromboembolism from immobilisation, bed rest is generally only advised with severe, uncontrolled hypertension.[9]

Postpartum management and secondary prevention

Most of the manifestations of pre-eclampsia resolve within the first few days or weeks postpartum. The features of pre-eclampsia, including hypertension, may worsen before they improve. Rarely the first manifestations occur postpartum. Frequent review of blood pressure during this period is essential, for example once to twice weekly. Antihypertensive doses are reduced or ceased when the blood pressure falls to less than 140/90 mmHg. Home blood pressure monitoring with an automated device can be helpful to avoid hypotension. This is a common occurrence, as the features of pre-eclampsia and therefore antihypertensive requirements can recede precipitously. Like gestational hypertension, if the blood pressure does not normalise within three months consider an alternative diagnosis. It is also important to confirm that proteinuria has resolved.

Pre-eclampsia can recur in subsequent pregnancies with the most prominent risk factors being previous severe or early onset pre-eclampsia or chronic hypertension. The use of low-dose aspirin has been shown to be safe and beneficial in decreasing this risk in women with a moderate to high risk of pre-eclampsia. Aspirin is therefore generally advised in subsequent pregnancies. It is started at the end of the first trimester and can be safely continued until the third trimester, with most centres ceasing therapy at 37 weeks gestation. Calcium supplements (1.5 g/day) may be of benefit, particularly in women at risk for low dietary calcium intake. The administration of vitamin C and E supplements has not been shown to be beneficial and may be harmful.[3]

Table 2 **Relatively safe antihypertensive drugs in pregnancy**

ANTIHYPERTENSIVE	CLASS	STARTING DOSE	MAXIMUM DOSE	IMPORTANT ADVERSE EFFECTS
Labetalol	Beta blocker	100–200 mg twice a day	400 mg three times a day	Bradycardia, bronchospasm, transient scalp tingling
Oxprenolol	Beta blocker	40–80 mg twice daily	80–160 mg twice daily	Bradycardia, bronchospasm
Nifedipine	Calcium channel antagonist	10 mg twice a day, 30 mg daily controlled release	20–40 mg twice a day, 120 mg daily controlled release	Severe headache, peripheral oedema
Methyldopa	Centrally-acting	250 mg twice a day	500 mg four times a day	Sedation, light-headedness, dry mouth, nasal congestion, haemolytic anaemia, depression
Hydralazine	Vasodilator	25 mg twice a day	50–200 mg total daily dose	Flushing, headache, lupus-like syndrome
Prazosin	Alpha blocker	0.5 mg twice a day	3 mg total daily dose	Postural hypotension

Antihypertensive drugs postpartum

The choice of antihypertensive drugs depends on whether breastfeeding is attempted. When the woman wishes to breastfeed, consideration must be given to potential transfer of the drug into breast milk. Most drugs safely used in pregnancy are excreted in low amounts into breast milk and are compatible with breastfeeding. Table 3 shows antihypertensive drugs to use or avoid during lactation.[4] Should there be no desire to breastfeed and adequate contraception is used, the choice of antihypertensive drug is the same as for any other non-pregnant patient.

Long-term follow-up

Pre-eclampsia and gestational hypertension appear to be associated with an increased long-term risk of cardiovascular disease, including hypertension, ischaemic heart disease, stroke and venous thromboembolism.[10] There may also be a small increased risk of chronic renal failure and thyroid dysfunction after pre-eclampsia.[11,12] Annual assessments of blood pressure and at least five-yearly assessments for other cardiovascular risk factors are advisable.[3] Thyroid and renal function should also be measured intermittently.

Conclusion

Pregnancies affected by hypertensive disorders require careful monitoring due to the increased risks of adverse pregnancy outcomes. New onset hypertension in pregnancy warrants consideration of pre-eclampsia. Antihypertensive drugs for all forms of hypertensive disorder of pregnancy tend to be reserved for persistent or severe hypertension. Many standard antihypertensive drugs are contraindicated in pregnancy and lactation. In women at moderate to high risk for recurrent pre-eclampsia, prophylaxis with low-dose aspirin and calcium supplements in subsequent pregnancies may be of benefit. Long-term follow-up, particularly in regard to cardiovascular risk, is important in women with a history of hypertensive disorders in pregnancy.

Conflict of interest: none declared

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SELF-TEST QUESTIONS

True or false?

3. Aspirin can be used to prevent the recurrence of pre-eclampsia in future pregnancies.

4. Gestational hypertension increases the risk of future cardiovascular disease.

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Table 3 **Antihypertensive drugs during breastfeeding**

CLASS	DRUGS CONSIDERED SAFE	AVOID – POTENTIALLY HARMFUL, NO OR LIMITED DATA
Beta blockers	Propranolol, metoprolol, labetalol	Avoid atenolol, no data for other beta blockers
Calcium channel antagonists	Nifedipine	More limited data for diltiazem and verapamil – may be safe; avoid other calcium channel blockers
ACE inhibitors	Captopril, enalapril	Other ACE inhibitors
Angiotensin receptor blockers	None	No data
Thiazide diuretics	None	Limited data
Other	Methyldopa, hydralazine	Limited data for prazosin, consider alternatives

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FURTHER READING

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