Hypertension in pregnancy

Fergus P McCarthy
Louise C Kenny

Abstract
Hypertension is a common complication of pregnancy and remains a major cause of maternal and perinatal morbidity and mortality worldwide. Hypertensive disorders vary from mild gestational hypertension to severe pre-eclampsia, which remains one of the leading causes of maternal death in the UK. Although there have been major advances in understanding the pathophysiology of the disease in recent years, interventions to prevent hypertensive disorders in pregnancy have had disappointing results. Due to their unpredictable nature and potential poor outcomes, patients with hypertensive disorders of pregnancy warrant cautious care with consultant involvement to optimise both maternal and foetal outcomes.

Keywords eclampsia; hypertension; pregnancy; pre-eclampsia

Introduction
Hypertension is a frequently encountered complication of pregnancy and has a number of possible aetiologies. In the UK, the number of maternal deaths from hypertension in pregnancy has fallen steadily over the past few decades, as have the complication rates. However, hypertensive disorders remain a major cause of maternal and perinatal morbidity and mortality worldwide. The Confidential Enquiry into Stillbirths and Deaths in Infancy report cites one in six stillbirths as occurring in pregnancies complicated by maternal hypertension. Interventions to prevent hypertensive disorders in pregnancy (including pre-eclampsia) in the general population have been disappointing and the mainstay of treatment involves close antenatal supervision of mother and foetus and timely delivery to prevent deterioration of the condition and subsequent morbidity and mortality.

Hypertension in pregnancy

Classification and diagnosis of hypertension
The classification of hypertension in pregnancy by Davey and MacGillivray remains the most widely accepted and appropriate classification (Table 1).

Classification of hypertension in pregnancy

A New-onset hypertension and/or proteinuria in pregnancy
1. Gestational hypertension (without proteinuria)
2. Gestational proteinuria (without hypertension)
3. Pre-eclampsia (hypertension with proteinuria)

B Chronic hypertension and renal disease
1. Chronic hypertension without proteinuria
2. Chronic renal disease (proteinuria with or without hypertension)
3. Chronic hypertension with superimposed pre-eclampsia (i.e. with new-onset proteinuria in pregnancy)

C Unclassified
1. Hypertension and/or proteinuria noted when first presentation is after 20 weeks
2. As above, when noted for the first time during pregnancy, labour or puerperium and there are insufficient background data to permit a diagnosis from category A or B above

Women who are hypertensive and pregnant must be subdivided into those with:
• chronic hypertension
• pregnancy-induced or gestational hypertension (PIH). Women with PIH are subdivided further:
• the majority have non-proteinuric PIH, a condition associated with minimal maternal or perinatal mortality/morbidity
• a minority have the major pregnancy complication of pre-eclampsia.

Pre-eclampsia is associated with significant maternal and perinatal morbidity and mortality. As such, it is imperative that every effort is made to accurately classify women with hypertension in pregnancy as having chronic hypertension, non-proteinuric PIH or pre-eclampsia as the aetiology and management of the three conditions is very different.

PIH
Gestational or pregnancy-induced hypertension is a rise in the blood pressure in the absence of proteinuria after 20 weeks gestation. True non-proteinuric PIH does not appear to be associated with an increase in maternal or foetal morbidity. However, the risk of progression from PIH to pre-eclampsia is approximately 20–30% and, therefore, vigilance is required.

Chronic hypertension
Chronic hypertension is defined as hypertension preceding pregnancy. Blood pressure falls in the first and second trimesters. Therefore, women with high blood pressure before the 20th week of pregnancy are assumed to have pre-existing or essential hypertension. As many women of reproductive age only present for the first time when pregnant, chronic hypertension is often revealed in the first half of pregnancy. Approximately 90% of cases of chronic hypertension are considered to be essential. Secondary causes, which account for approximately 10% are listed in Table 2. In women presenting with hypertension in the first half of pregnancy

Fergus P McCarthy MRCPI is at the Anu Research Centre, Cork University Maternity Hospital, Wilton, Cork, Ireland.

Louise C Kenny PhD MRCOG is at the Anu Research Centre, Cork University Maternity Hospital, Wilton, Cork, Ireland.
It is important to look for an underlying cause. These investigations should at least include:
- urine analysis (looking for blood, protein or glucose)
- urea and electrolytes
- renal tract ultrasound.

Women with underlying renal disease are at significantly increased risk of poor pregnancy outcome and require multidisciplinary care.

### Treatment of chronic hypertension in pregnancy

The use of antihypertensive drugs in the hypertensive women without renal impairment is considered by some to be beneficial in preventing sudden increases in blood pressure, cerebral haemorrhage or hypertensive encephalopathy. However, a clear benefit of antihypertensive agents in mild-to-moderate chronic hypertension remains unproven, as treatment does not prevent placental abruption or superimposed pre-eclampsia, or influence perinatal outcome. There are differing opinions regarding the timing of initiation of treatment in hypertensive disorders in pregnancy. This is compounded by the fact that a single blood pressure of 140/90 mmHg or above is not uncommon in pregnancy and was reported in nearly 40% of pregnant women in one study, while persistent high blood pressure occurs in approximately 12–22% of pregnancies. Until recently, the focus remained on treating elevated blood pressure based on the diastolic reading with groups recommending treatment for sustained diastolic blood pressures of greater than 105–110 mmHg. There is now, however, increasing awareness on the importance of increases in, as well as the absolute values of, systolic blood pressure.

All pregnant women with a systolic blood pressure of 160 mmHg or more require antihypertensive treatment. Consideration should also be given to initialising treatment at lower pressures if the overall clinical picture suggests rapid deterioration and/or where the development of severe hypertension can be anticipated.

In the triennium 2003–2005, the single most serious failing in the clinical care provided for mothers with pre-eclampsia was the inadequate treatment of their systolic blood hypertension. In several cases this resulted in a fatal intracranial haemorrhage. Systolic hypertension was also a key factor in most of the deaths from aortic dissection.

There are multiple antihypertensive agents available that may be used in pregnancy. These can be used independently or in conjunction with a second or third agent.

Labetolol is a popular first-line antihypertensive of choice in the treatment of hypertension. Labetolol is a combined β-adrenoceptor blocker that also blocks α-adrenoceptors. Ordinary β-adrenoceptor blockers are unsuitable for producing a quick antihypertensive effect because a quick fall in blood pressure triggers a compensatory sympathetic discharge that increases the peripheral vascular resistance via α-adrenoceptors. Blocking the β-adrenoceptors alone cannot prevent this compensatory response, but the addition of an α-adrenoceptor blocker can. It is this action that renders labetolol suitable for gaining quick control of the blood pressure. Labetolol, like all β-adrenoceptors, is contraindicated in women with a history of asthma.

Nifedipine is a calcium-channel blocker that has, in recent years, gained popularity in the treatment of chronic hypertension in pregnancy. Data suggest that it is safe, however, cumulative evidence is not as extensive as with older drugs such as labetolol and methyldopa. The principal side effect is headache, which can be severe, last for several days after commencing treatment and may return after increasing the dose. Use of the long-acting once-daily preparation improves compliance.

A-Methyldopa (a centrally acting α-adrenergic agonist that inhibits vasoconstricting impulses from the medulla oblongata) has traditionally been the most commonly used agent for the control of blood pressure during pregnancy. Its safety has been well established both in pregnancy and in the long-term follow-up of infants. One of the most frequent side effects is sedation, which can be profound. This is often poorly tolerated and leads to unpredictable compliance. However, α-methyldopa remains the preferred agent of the National High Blood Pressure Education Programme. Angiotensin-converting enzyme (ACE) inhibitors and angiotensin-receptor blockers and diuretics should be avoided in pregnancy. Diuretics may reduce uteroplacental perfusion.

Second- and third-trimester exposure to ACE inhibitors appears to be fetotoxic, producing foetal hypocalvaria and renal defects. The cause of these defects seems to be related to foetal hypotension and reduced renal blood flow. Anuria associated with oligohydramnios can produce foetal limb contractures, craniofacial deformations and pulmonary hypoplasia. Intrauterine growth restriction, prematurity, persistence of a patent ductus arteriosus, severe neonatal hypotension, neonatal anuria and neonatal or foetal death have all been observed with the use of these drugs, and they should, therefore, be discontinued preconceptionally or as early in the first trimester as possible.

Angiotensin-receptor blockers are newer agents that have not been formally studied in pregnancy; they are probably best avoided given their common pathway with ACE inhibitors.

<table>
<thead>
<tr>
<th>Causes of secondary chronic hypertension</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Idiopathic</strong></td>
</tr>
<tr>
<td>Vascular disorders</td>
</tr>
<tr>
<td>Renovascular hypertension</td>
</tr>
<tr>
<td>Aortic coarctation</td>
</tr>
<tr>
<td>Endocrine disorders</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
</tr>
<tr>
<td>Hyperthyroidism</td>
</tr>
<tr>
<td>Hypothyroidism</td>
</tr>
<tr>
<td>Phaeochromocytoma</td>
</tr>
<tr>
<td>Acromegaly</td>
</tr>
<tr>
<td>Cushing’s syndrome</td>
</tr>
<tr>
<td>Conn’s syndrome</td>
</tr>
<tr>
<td>Renal disorders</td>
</tr>
<tr>
<td>Renal failure resulting from:</td>
</tr>
<tr>
<td>Diabetic nephropathy</td>
</tr>
<tr>
<td>Reflux nephropathy</td>
</tr>
<tr>
<td>Chronic glomerulonephritis</td>
</tr>
<tr>
<td>Nephritic and nephrotic syndrome</td>
</tr>
<tr>
<td>Polycystic kidney</td>
</tr>
<tr>
<td>Systemic lupus erythematosus</td>
</tr>
<tr>
<td>Systemic sclerosis</td>
</tr>
<tr>
<td>Polyarteritis nodosa</td>
</tr>
<tr>
<td>Rheumatoid disease</td>
</tr>
<tr>
<td>Connective tissue disorders</td>
</tr>
<tr>
<td>Systemic sclerosis</td>
</tr>
<tr>
<td>Systemic sclerosis</td>
</tr>
<tr>
<td>Systemic sclerosis</td>
</tr>
<tr>
<td>Systemic sclerosis</td>
</tr>
</tbody>
</table>
Pre-eclampsia

Introduction
Pre-eclampsia is a major cause of maternal and perinatal mortality and morbidity worldwide causing 15% of all direct maternal deaths in the UK and a 5-fold increase in perinatal mortality with iatrogenic prematurity being the main culprit. The incidence of pre-eclampsia and its complications have decreased significantly in the UK since 1992 (Table 3).

Pre-eclampsia is defined by the International Society for the Study of Hypertension in Pregnancy as gestational hypertension of at least 140/90 mmHg on two separate occasions measured at least 4 hours apart accompanied by significant proteinuria of at least 300 mg in a 24-hour collection of urine, arising de novo after the 20th week of gestation in a previously normotensive woman and resolving completely by the 6th post-partum week. It usually occurs during the second half of pregnancy and complicates 2% to 8% of pregnancies. Pre-eclampsia is twice as common in primigravid women as in women having second or later pregnancies. Women who become pregnant with donor eggs are at increased risk of developing pre-eclampsia while particular men are at increased risk of fathering a pre-eclamptic pregnancy. Table 4 highlights other risk factors for pre-eclampsia.

Pre-eclampsia also carries implications in adult life, with offspring of affected pre-term pregnancies demonstrating poor growth in childhood and an increased risk of hypertension, heart disease and diabetes.

Pathophysiology of pre-eclampsia
The individual stages in the pathogenesis of pre-eclampsia are generally well accepted. However, debate continues regarding the primary precipitating factor. Two theories, the two-stage process and the continuum theory, have emerged to explain the primary precipitating factor. The continuum theory proposes that pre-eclampsia is an exaggerated form of the inflammatory response and endothelial cell dysfunction as key features in the pathogenesis of pre-eclampsia. This endothelial dysfunction appears to occur as a result of oxidative stress and is mediated by high levels of free radicals and low levels of antioxidants as supported by the observation that markers of oxidative stress are present in the maternal circulation of affected women (Table 5).

Management of pre-eclampsia
Investigations and monitoring of the pre-eclamptic patient should include the following.

• Full blood count – this may demonstrate a raised haematocrit (indicating haemoconcentration) and thrombocytopenia (which is an indicator of severe pre-eclampsia). Thrombocytopenia may also occur as a result of HELLP syndrome (haemolysis, elevated liver enzymes and low platelets).

• Urea and electrolytes – uric acid is a particularly sensitive measure of pre-eclampsia and perinatal outcome but it is only of clinical significance if the levels are increasing or are very high.

• Urine analysis with a 24-hour urine collection – significant proteinuria is the most important clinical variable predicting both maternal and perinatal outcome.

• Ultrasound – increased foetal surveillance with ultrasound biometry.

Pre-eclampsia can occasionally be managed conservatively. Maternal and foetal monitoring should continue until foetal maturity has been achieved, at which stage the cervix is assessed with Bishops scoring and, if favourable, induction of labour is carried out.

Severe disease necessitates inpatient care with a close monitoring of the symptoms, signs and biochemical parameters. In extreme prematurity, transfer to hospital with adequate neonatal facilities (with steroid administration to enhance lung maturity) is indicated. Severe pre-eclampsia presenting prior to foetal viability is an indication for termination of pregnancy.
Management of hypertension in pregnancy

Screening
- Women should be screened for signs of hypertension using BP checks and urinalysis monthly until 30 weeks gestation, fortnightly from 30 weeks gestation and weekly from 36 weeks gestation
- If elevated BP +/- proteinuria refer for admission or monitoring in antenatal day unit

Maternal assessment
- Repeat (at least 4-hourly) BP measurement
- Quantitative measurement of protein in urine (pre-eclampsia = >0.3 g protein 24-hour urine collection)
- Platelet count, serum uric acid concentration, and liver function tests (alanine and aspartate aminotransferase levels)
- Coagulation screen if altered liver function

Antihypertensive therapy
- Consider admission, monitor closely and treat if BP is persistently above 160/100 mmHg

Anticonvulsant therapy
- If convulsions occur, use magnesium sulphate (intravenously or intramuscularly)
- In cases of severe pre-eclampsia, consider prophylactic magnesium sulphate

Foetal management
- Give prophylactic steroids if the duration of gestation is less than 34 weeks
- Perform an ultrasound assessment of foetal weight on initial presentation and repeat fortnightly
- Doppler ultrasonographic assessment of umbilical blood-flow velocity if evidence of growth restriction
- Regular cardiotocography (CTG/non-stress tests)
- Ultrasonography at least twice a week for liquor volume
- Multidisciplinary approach regarding timing and mode of delivery

Post-partum care
- Continued close monitoring of the mother by experienced carers
- If on magnesium therapy, continue for at least 24 hours post-partum until stable
- Careful fluid balance (total 80 ml/hour intake) and early use of diuretics if pulmonary oedema secondary to fluid overload is suspected
- Decrease dose of antihypertensive agents as indicated. Avoid sudden cessation immediately post-partum as rebound hypertension likely

Follow-up
- Long-term follow-up to make sure that the blood pressure falls (within 6 weeks post-partum) and suitable referral if it does not
- Discussion about the illness and the significance for the future
- Recommend pre-conceptual counselling for future pregnancies

BP, blood pressure; CTG, cardiotocography.

Table 5

| BP, blood pressure; CTG, cardiotocography. | REVIEW |

The optimum time of delivery is of crucial importance and remains a balance between the risks of major complications to the mother and intrauterine growth retardation in the foetus against the risks of delivery and prematurity to the foetus. The mode of delivery is a balance between Caesarean section and vaginal delivery. Caesarean section is a better option for rapid deteriorating maternal and foetal condition, or alternatively for those remote from term with an unfavourable cervix. Epidural analgesia may be beneficial by preventing the increase of catecholamine release, in order to prevent further elevations of blood pressure during uterine contractions. It may also allow a more controlled second stage.

Oral antihypertensive are discussed above. In severe pre-eclampsia, there are two antihypertensive regimens to choose from.

- Labetolol (200 mg) can be given orally prior to or in the absence of intravenous access; if there is no response within 30 minutes, a second oral dose can be given. If there is no initial response to oral therapy or if it is not tolerated, a bolus of 50 mg given intravenously over at least 5 minutes can be administrated, repeated to a maximum of 200 mg, at 10-minute intervals. Following this, or as treatment for moderate hypertension, a labetolol infusion can be commenced (5 mg/ml at 4 ml/hour via a syringe pump, the infusion rate being doubled every 30 minutes to a maximum of 32 ml (160 mg)/hour until the blood pressure has dropped and stabilised at an acceptable level). Labetolol is contraindicated in women with asthma and should be used with caution in cardiac disease.
- Hydralazine is given by bolus infusion (10–20 mg over 10–20 minutes measuring the blood pressure every 5 minutes). This may be followed by an infusion (40 mg hydralazine in 40 ml normal saline, which should run at 1–5 ml/hour (1–5 mg/hour)).

In pre-eclampsia, magnesium sulphate is indicated as the first-line anticonvulsant. Formal clinical review should occur every 4 hours, observing for side effects (motor paralysis, absent reflexes, respiratory depression and cardiac arrhythmia). The
Eclampsia
Eclampsia refers to the occurrence of one or more generalised convulsions and/or coma in the setting of pre-eclampsia and in the absence of other neurological conditions. The UK Obstetric Surveillance System (UKOSS) reported an estimated incidence of 26.8 cases per 100,000 maternities, 36% of which occurred post-partum. A total of 99% of women in the UKOSS study were treated with magnesium sulphate in accordance with national guidelines. The benefit of magnesium sulphate in the prevention of eclampsia has been well demonstrated and magnesium sulphate has been shown to halve the risk of eclampsia among women with pre-eclampsia. Table 6 indicates the diagnostic criteria for eclampsia. Cerebral haemorrhage has been reported to be the most common cause of death in patients with eclampsia and stroke is known to be the most common cause of death (45%) in women with HELLP syndrome.

Post-partum management of hypertension in pregnancy
Blood pressure rises progressively over the first 5 postnatal days, peaking on days 3–6 after delivery. Research has focused on the antenatal complications, for both mother and baby, and the risks and benefits of administering antihypertensive therapy prior to delivery. There is very little information on how best to manage post-partum hypertension, regardless of type or severity, to optimise maternal safety and minimise hospital stay. The true prevalence of post-partum hypertension is difficult to ascertain, but the importance of monitoring women in the puerperium was highlighted by the Confidential Enquiry into Maternal and Child Health, in which roughly 10% of maternal deaths due to a hypertensive disorder of pregnancy occurred in the post-partum period. In the 1997–1999 triennial report, one of 15 deaths was attributed to severe hypertension that developed only post-partum in a woman with antenatal pre-eclampsia. Women with post-partum hypertension may also experience longer hospital stays and, possibly, heightened anxiety about their recovery.

In most cases of gestational hypertension and pre-eclampsia there is a rapid and complete resolution within 6 weeks of delivery of the foetus. Patients requiring antihypertensives can be weaned off slowly and medications should not be stopped suddenly as there may often be a rebound hypertension.

Postnatal follow-up
Women who have had pre-eclampsia should be educated regarding their increased risk of development of cardiovascular disease, renal disease and cardiovascular risk factors for several years following pregnancy and regular blood pressure checks with their general practitioner should be recommended. Women with severe pre-eclampsia have an increased risk of recurrence in their next pregnancy but the disorder is generally less severe and manifests 2–3 weeks later than in the first pregnancy.

Women with essential hypertension should be encouraged to present for pre-conceptual counselling as antihypertensive medications such as ACE inhibitors are contraindicated in pregnancy and should be changed pre-conceptually. The use of low-dose aspirin in women with chronic hypertension moderately reduces the risk of developing superimposed pre-eclampsia, intrauterine growth retardation and perinatal death, and should be offered to all women at an early booking visit. The findings from the CLASP trial do not support routine treatment with aspirin of all women at risk of pre-eclampsia.

Conclusion
Hypertensive disorders are one of the most common complications of pregnancy and may be associated with significant maternal and foetal morbidity and mortality. Although the aetiology of these disorders is becoming increasingly better understood, interventions to prevent hypertensive disorders of pregnancy have had poor results. The mainstay of treatment remains the use of antihypertensive medications, the use of magnesium sulphate in the prevention of eclampsia and multidisciplinary input to ensure a timely delivery.

Diagnostic criteria used for eclampsia

Any woman with convulsion(s) during pregnancy or in the first 10 days post-partum, together with at least two of the following features within 24 hours of the convulsion(s):

- Hypertension (a booking diastolic pressure of <90 mmHg, a maximum diastolic of ≥90 mmHg and a diastolic increment of ≥25 mmHg)
- Proteinuria (at least + protein in a random urine sample or ≥0.3 g in a 24-hour collection)
- Thrombocytopenia (platelet count of less than 100 x 10^9/l)
- Raised plasma alanine aminotransferase concentration (≥42 IU/l) or an increased plasma aspartate aminotransferase concentration (≥42 IU/l)

Table 6

FURTHER READING


Acknowledgements

This review has been revised and updated from an earlier one which appeared in this journal (formerly entitled Current Obstetrics & Gynaecology) in Volume 16, Issue 6 pp 315–320, by F Soydemir and L Kenny.

Practice points

- Automated blood pressure devices may underestimate the blood pressure in pregnancy and, therefore, caution should be exercised in their use
- Labetolol remains the antihypertensive of choice. Methyldopa and nifedipine may be used as second- or third-line agents
- Systolic blood pressures over 160 mmHg should be treated
- Anaesthetists should anticipate an additional rise in blood pressure at intubation in women with severe pre-eclampsia who are undergoing Caesarean section under general anaesthesia and take measures to avoid a speed that compromises maternal wellbeing, even when there are concerns about foetal wellbeing
- Syntometrine should not be given for the active management of the third stage if the mother is hypertensive, or her blood pressure has not been checked
- Post-partum, women should be counselled appropriately regarding their risk of recurrence of pre-eclampsia as well as their increased risk of developing cardiovascular and renal disease