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ESSENTIALS High blood pressure (BP >140/90 mm Hg) complicates approximately 10% of pregnancies and may be due to white coat hypertension, chronic hypertension, gestational hypertension, or pre-eclampsia (de novo or superimposed on chronic hypertension). Pre-eclampsia occurs in 2–8% of pregnancies and remains a common cause of fetal and maternal death in developing countries. Maternal symptoms include headache/visual disturbances, breath- lessness, epigastric pain, and seizures (eclampsia); signs include pulmonary oedema, liver tenderness, hyper-reflexia/clonus, and papilloedema. Treatment of pre-eclampsia is by timely delivery of the fetus (and placenta) to minimize maternal complications and maxi- mize fetal gestational age, while avoiding morbidity and mortality. Pharmacological treatment to control hypertension is generally given when BP consistently exceeds 150 mm Hg (systolic) or 90 mm Hg (diastolic). Commonly used agents include labetalol, nifedipine, amlodipine, and α-methyldopa. ACEi, ARBs, and diuretics should not be used in pregnancy. Intravenous magnesium sulphate is given to women at risk of eclampsia. Introduction Hypertensive disorders in pregnancy are the commonest medical disorder complicating approximately 10% of pregnancies. These fig- ures are expected to rise with increasing maternal age and maternal co-morbidities such as obesity. Hypertension in pregnancy may be classified into white coat hypertension, chronic hypertension, gestational (or pregnancy-induced) hypertension or pre-eclampsia; de novo or superimposed on chronic hypertension (see Table 14.4.1). Pre-eclampsia, a pregnancy-specific condition associated with hypertension and proteinuria, complicates 2–8% of pregnancies. Over the past few decades within the United Kingdom, maternal deaths from hypertensive disorders in pregnancy have consistently declined. Nonetheless, worldwide they continue to contribute to maternal and perinatal morbidity and mortality. Hypertensive conditions are responsible for approximately one- third of severe maternal morbidity in pregnancy. Up to 5% of patients with severe pre-eclampsia require admission to intensive care and 8–10% of all preterm deliveries occur as a result of iatrogenic de- livery secondary to pre-eclampsia. More extreme prematurity (de- fined as delivery <34 weeks' gestation) occurs in approximately 1 in 250 (0.4%) women with pre-eclampsia—and fetal growth restriction as a result of pre-eclampsia occurs in a quarter of preterm births and up to 20% of term births. Epidemiology Around 2–8% of pregnancies are complicated by pre-eclampsia, which occurs

in nearly all cases during the second half of preg- nancy. Worldwide, approximately 10 million women develop pre- eclampsia annually. According to the World Health Organization, approximately 76 000 women die each year from hypertensive- related disorders in pregnancy. Although overall rates of pre- eclampsia remain static, rates of severe pre-eclampsia appear to have increased over recent decades. In the United Kingdom and Ireland in 2010–2012, pre-eclampsia was responsible for nine ma- ternal deaths giving a maternal mortality rate of 0.38 per 100 000 maternities. Worldwide, severe pre-eclampsia is commoner ran- ging from 4% of all deliveries up to 18% of all deliveries in some African countries. In Latin America, pre-eclampsia remains the leading cause of maternal death. In developing countries, women are seven times more likely to have a pregnancy complicated by pre-eclampsia compared with women in developed countries. Around 10–25% of these cases will result in maternal death. Furthermore, the condition increases perinatal mortality fivefold, largely through iatrogenic prematurity. Approximately 500 000 babies are thought to die annually as a result of hypertensive dis- orders. Post-partum, pre-eclampsia and its complications are a common reason for post-partum admission to high dependency or critical care. Aetiology • Pre-eclampsia occurs from impaired trophoblast differentiation and invasion in early pregnancy. This stimulates a sustained oxi- dative stress and a systemic inflammatory response. 14.4 Hypertension in pregnancy Fergus McCarthy

Section 14 Medical disorders in pregnancy 2584 • These processes are widely accepted to be influenced by both maternal and fetal genetic composition and environmental factors. • Risk factors for pre-eclampsia include advanced maternal age (greater than 40 years), a family history of pre-eclampsia, first pregnancy, previous hypertensive disease in pregnancy, chronic hypertension, chronic kidney disease, autoimmune diseases such as systemic lupus erythematosus, or antiphospholipid syndrome and diabetes. Pre-eclampsia results from impaired trophoblast differentiation and invasion in the first trimester. As a result of this impaired invasion trophoblast cells are unable to break down the muscularis layer of the spiral arterioles and this results in the development of a poorly formed and ultimately poorly perfused placenta. The uterine spiral artery invasion is limited to the proximal decidua and there is no endovascular trophoblast remodelling in 30–50% of the spiral ar- teries in the placental bed. This prevents the normal adaptation of spiral arteries to pregnancy and leads to a reduction in blood flow to the intervillous space and both placental hypoxia and ischaemia. The development of pre-eclampsia is thought to require additional maternal factors. These include environmental (such as obesity and diet) and genetic factors. All these contribute to widespread endothelial dysfunction, which is thought to cause proteinuria and hypertension. Many other factors have been shown to potentially contribute to the development of the syndrome of pre-eclampsia. Oxygen is a major regulator of trophoblast invasion and altered oxygen tension has been shown to control trophoblast differentiation down the extravillous trophoblast pathway. Most cases of pre-eclampsia are sporadic but genetic factors also play a role in disease development. Primigravid women with a family history of pre-eclampsia have a two- to fivefold increased risk of developing the disease com- pared with primigravid women with no history of pre-eclampsia. Placental hypoxia, which may result from the impaired tropho- blast invasion that occurs in pre-eclampsia, results in an imbal- ance between pro-angiogenic and antiangiogenic factors due to the excessive secretion of antiangiogenic factors such as soluble fms-like tyrosine kinase-1 (sFlt-1) and a reduction in the release of the pro-angiogenic factors vascular endothelial growth factor (VEGF) and placental growth factor (PlGF). In pre-eclampsia there is an increase in the levels of placental oxidative stress, and this oxidative stress may mediate endothelial cell dysfunction con- tributing to the pathophysiology of pre-

eclampsia. Other systems/ molecules implicated in the pathogenesis of pre-eclampsia include altered plasma levels of cell adhesion molecules (VCAM-1, ICAM- 1, and E-selectin), which are also significantly elevated in women with pre-eclampsia; altered plasma levels of nitric oxide; and reduced prostacyclin (PGI2), a potent antiplatelet and vasodilator compound. Pathogenesis/Pathology The clinical presentation of pre-eclampsia is varied but all of its fea- tures can be explained as responses to generalized endothelial dys- function. Headaches, seizures, visual symptoms, epigastric pain, and fetal growth restriction are the sequelae of endothelial dysfunction in the vasculature of target organs, such as the brain, liver, kidney, and placenta. In the cardiovascular system there is an increase in peripheral resistance, resulting in vasospasm and hypertension. Intravascular volume becomes reduced in pre-eclampsia. This is worsened by the endothelial damage which leads to increased vascular permeability, oedema, and a decrease in central venous/pulmonary wedge pres- sures. Haematologically, pre-eclampsia may result in a decrease in platelet count secondary to immunologically mediated consump- tion, but an increase in platelet aggregation and adhesion to vascular endothelial cells occurs. Activation of these cells causes the produc- tion of both inflammatory and oxidative mediators which further augment vascular dysfunction. It is rare for clotting problems to occur in the absence of thrombo- cytopenia. The levels of antithrombin, protein C, and protein S fall in pre-eclampsia as a result of increased consumption of clotting factors. In the hepatic bed vasoconstriction occurs which may lead to periportal fibrin deposition, haemorrhage, and hepatocellular ne- crosis. This may occur as part of the HELLP syndrome (haemolysis, elevated liver enzymes, and low platelet count). Rarely, hepatic in- farction with rupture of the liver capsule may occur. Enhanced vascular sensitivity to angiotensin II and norepineph- rine, resulting in vasoconstriction and hypertension occurs in pre-eclampsia. The enhanced sensitivity to angiotensin II may be secondary to increased bradykinin upregulation seen in pre-eclamptic patients. In pre-eclampsia there is a reduction in uric acid clearance due to impair- ment of tubular function. Proteinuria of intermediate selectivity occurs as a result of impaired glomerular filtration. The characteristic renal lesion of pre-eclampsia is glomerular endotheliosis, which involves Table 14.4.1 Classification of hypertension in pregnancy White coat hypertension Blood pressure readings ≥140/90 mm Hg but only when in a medical setting Chronic hypertension Blood pressure readings ≥140/90 mm Hg which predate the pregnancy or discovered at <20 weeks' gestation Gestational (or pregnancy induced) hypertension Blood pressure readings ≥140/90 mm Hg occurring after 20 weeks' gestation without proteinuria Pre-eclampsia; de novo or superimposed
on chronic hypertension Gestational hypertension (≥140/90 mm Hg on two separate occasions) at least four hours apart and associated with one of: • Proteinuria >300 mg in a 24-hour collection of urine or a protein creatinine ratio ≥30 mg/mmol on a spot urine or at least 1 g/litre (2+ on urine dipstick) • Other maternal organ dysfunction including renal impairment (creatinine >90 µmol/litre), hepatic involvement (elevated liver transaminases of at least twice upper value of normal), neurological complications (seizure) or haematological complications such as thrombocytopenia. • Uteroplacental dysfunction manifested by fetal growth restriction

 swelling of the glomerular endothelial cells and subendothelial fi- brinoid deposits, which may occlude capillary lumens. Cerebral vasoconstriction may occur in the brain resulting in focal ischaemia and abnormal electrical activity, which may trigger seizures (eclampsia). Eclampsia is the occurrence of one or more convulsions, not attributable to other pathology in a patient with pre-eclampsia. Previously pulmonary oedema, mainly as a result of iatrogenic fluid administration, was the main cause of mortality in women with

pre-eclampsia. Intracranial haemorrhage is now the leading cause of death in women with pre-eclampsia. Blindness which may be retinal or cortical in origin is a rare, but usually tem- porary complication of pre-eclampsia. Clinical features The clinical presentation of pre-eclampsia can vary; from the asymptomatic patient with incidental findings of hypertension and proteinuria, to the patient presenting with eclamptic seizures. Maternal symptoms and signs of pre-eclampsia may include: • severe headache and visual disturbances • epigastric pain • hyper-reflexia and/or clonus • papilloedema • pulmonary oedema • seizures • placental abruption (1–4%) • liver (right upper quadrant) tenderness • platelets under 100 × 109/litre • alanine amino transferase more than twice upper value of normal • creatinine more than 90 umol/litre Fetal effects include oligohydramnios and fetal growth restriction (up to 30%). Differential diagnosis Secondary causes of hypertension should be considered particularly if hypertension is diagnosed in the first half of pregnancy and appro- priate investigations performed if necessary as detailed in Table 14.4.2. In those women with pre-existing disease it may be extremely difficult to differentiate pre-eclampsia from worsening renal disease due to pre- existing hypertension and proteinuria. A low placental growth factor may help in this differentiation. Clinical investigations • Full blood count may show an elevated haematocrit occurring due to haemoconcentration and/or thrombocytopenia. • Urea and electrolytes may demonstrate elevated creatinine and/or uric acid. • Liver function tests may show elevated transaminases which may be part of a HELLP syndrome. Table 14.4.2 Secondary causes of hypertension (see Chapter 16.17.3) System Disease Key diagnostic test/clinical clues Vascular disorders Renovascular hypertension Renal bruit; renal ultrasound/CT angiography/MR angiography Aortic coarctation Hypertension in upper limbs/diminished or delayed femoral pulses; echocardiography Endocrine disorders Hyperparathyroidism Hypercalcaemia: abdominal pain, renal stones, nausea vomiting Hyperthyroidism Palpitations, weakness, sweating, anxiety, tremor, intolerance of heat; thyroid function tests Hypothyroidism Weight gain, lethargy; thyroid function tests Phaeochromocytoma Headache, palpitations, sweating; measurement of 24-hour urine fractionated catecholamines and metanephrines Acromegaly Macrognathia, enlargement of hands and feet; measurement of serum insulin-like growth factor-1 Cushing’s syndrome Central obesity, ecchymoses Cushingoid facies, proximal muscle weakness; initially measurement of ACTH Primary hyperaldosteronism Hypokalaemia, metabolic alkalosis; measurement of plasma renin and aldosterone concentrations Renal disorders Diabetic nephropathy Reflux nephropathy History of urinary tract infections Chronic glomerulonephritis Nephritic and nephrotic syndrome Nephrotic syndrome: heavy proteinuria (>3.5 g/day). Nephritic syndrome: variable degrees of proteinuria with the presence of red cells and/or white blood cells Polycystic kidney Family history, renal ultrasound Connective tissue disorders Systemic lupus erythematosus Oral ulcers, malar rash, arthritis discoid rash, photosensitivity, raised protein creatinine ratio, presence of ANA, anti-dsDNA, anti-Sm, and/or other extractable nuclear antigens Systemic sclerosis Skin thickening; anti-topoisomerase I, anticentromere, anti-RNA polymerase III antibodies Polyarteritis nodosa General symptoms including weakness, fever, arthralgia, fatigue, weight loss, and skin lesions. Systemic signs such as hypertension, renal insufficiency, or neurologic dysfunction

 • A coagulation screen (prothrombin time (PT), activated partial thromboplastin time (aPTT), and international normalized ratio (INR)) is indicated if platelet count and/or liver function tests are abnormal. • Urine analysis should be performed using either a 24-hour urine collection or protein creatinine ratio. A protein creatinine ratio greater than 30 mg/mmol is equivalent to a 24-hour urine excre- tion greater than 300 mg. • Ultrasound should be performed to estimate fetal weight (and outrule fetal growth restriction) and calculate

liquor volume and Doppler indices. This should be performed at the time of diagnosis and then fortnightly depending on the findings. In the presence of intrauterine growth restriction, increased frequency of surveillance is recommended with additional Doppler studies of middle cerebral artery and ductus venosus in addition to umbilical artery Dopplers. Prediction of pre-eclampsia The National Institute for Clinical Excellence (NICE) guidelines advise that none of the screening methods for pre-eclampsia have sufficient sensitivity and specificity to be used in clinical practice. Nonetheless, many assays are currently in use in clinical practice. Impedance to flow in the maternal uterine arteries normally de- creases as pregnancy progresses. Increased impedance in the uterine arteries is an early feature of pre-eclampsia detectable on ultrasound. This increased resistance is thought to reflect high downstream re- sistance due to defective invasion of spiral arteries and failure of these vessels to transform into low resistance vessels. In low-risk women, the risk of severe pre-eclampsia is best predicted by eleva- tion of the pulsatility index in the second trimester (sensitivity 78%, specificity 95%). In women at high risk of pre-eclampsia, the risk is best predicted by elevated resistance index in the second trimester (sensitivity 80%, specificity 78%). Placental growth factor (PlGF), one of the vascular endothelial growth factor family, is an angiogenic, proinflammatory factor pro- duced by trophoblast cells. It is involved in the regulation of vascular endothelial growth factor dependent angiogenesis and is thought to be a secondary marker for placental dysfunction. PlGF levels less than the fifth centile had high sensitivity (0.96; 95% CI 0.89–0.99) and negative predictive value (0.98; 0.93–0.99) for the need for de- livery due to the development of pre-eclampsia in the following two weeks; specificity was lower (0.55; 0.48–0.61). Other methods used to screen for pre-eclampsia include meas- urement of pregnancy-associated plasma protein A at 11–13 weeks' gestation. The ASPRE study used an algorithm that combines ma- ternal factors, mean arterial pressure, uterine artery pulsatility index and maternal serum pregnancy-associated plasma protein-A and placental growth factor at 11–13 weeks' gestation. This combined screening detected 76.6% of cases of preterm pre-eclampsia and 38.3% of term pre-eclampsia at a FPR of 10%. Treatment The treatment for pre-eclampsia remains timely delivery of the fetus (and placenta) to minimize maternal complications and maxi- mize fetal gestational age while avoiding morbidity and mortality. Pharmacological treatment is aimed at the control of hypertension. No disease-modifying drugs are currently available that target the placenta or pathophysiological processes causing pre-eclampsia. The risk of pre-eclampsia may be reduced by optimization of pre- pregnancy health. This may include adjustment of medications to optimize medical morbidities including renal disease, blood pres- sure control in those with chronic hypertension, weight loss, and cessation of potentially teratogenic agents such as warfarin and angiotensin-converting enzyme inhibitors. Low-dose (60–150 mg) aspirin has been shown to reduce the risk of development of pre-eclampsia in moderate to high-risk woman by approximately 10–15%. The ASPRE study was a multicenter, double- blind, placebo-controlled trial in which 1776 women with singleton pregnancies who were at high risk for preterm preeclampsia were randomly assigned to receive aspirin, at a dose of 150 mg per day, or placebo from 11 to 14 weeks of gestation until 36 weeks of gestation. Preterm preeclampsia occurred in 13 participants (1.6%) in the aspirin group, as compared with 35 (4.3%) in the placebo group (odds ratio in the aspirin group, 0.38; 95% confidence interval, 0.20 to 0.74; P=0.004). Calcium supplementation (≥1 g/day) in women with low calcium diets has been shown to reduce the chances of having a pregnancy complicated by pre-eclampsia. Recommendations regarding timing of delivery for women with pre-eclampsia are based largely around the HYPITAT studies. HYPITAT I, a randomized controlled trial, recruited patients with gestational hypertension or mild pre-eclampsia with a singleton pregnancy between 36 and 41 weeks' gestation. The primary out- come was a composite measure of maternal

morbidity and mortality. The trial randomized 756 patients to either induction of labour (n = 377 patients) or expectant management (n = 379). 117 (31%) women in the induction group developed poor maternal outcome com- pared with 166 (44%) women in the expectant group (relative risk 0.71, 95% CI 0.59–0.86, p <0.0001). As a result of this trial, induction of labour is advocated beyond 37 weeks' gestation in women with pre-eclampsia. The HYPITAT II trial, an open-label, randomized controlled trial, focused on women with nonsevere hypertensive disorders of pregnancy between 34 and 37 weeks of gestation. Women were randomly allocated to delivery (induction of labour or caesarean section) within 24 hours (immediate delivery) or expectant management until 37 weeks' gestation or deterioration of the mother or fetus. The primary outcomes were a composite of adverse maternal outcomes and neo- natal respiratory distress syndrome. The trial recruited 703 women and demonstrated that the composite adverse maternal outcome oc- curred in four (1.1%) of 352 women allocated to immediate delivery versus 11 (3.1%) of 351 women allocated to expectant monitoring (relative risk 0.36, 95% CI 0.12–1.11; p = 0·069). Respiratory distress syndrome was diagnosed in 20 (5.7%) of 352 neonates in the imme- diate delivery group versus six (1.7%) of 351 neonates in the expect- antly managed group (relative risk 3.3, 95% CI 1.4–8.2; p = 0·005). This trial demonstrated that the absolute risk of maternal morbidity under 37 weeks' gestation was low and earlier delivery significantly increased the risk of neonatal respiratory distress syndrome. As a re- sult, most would continue to advocate expectant management with monitoring until the clinical situation deteriorates. Generally, when blood pressure consistently exceeds 150 mm Hg systolic or 90 mm Hg diastolic treatment with antihypertensives is advocated but treatment should be individualized depending on the clinical picture. A systolic blood pressure over 160 mm Hg is a med- ical emergency requiring an immediate response due to the risk of haemorrhagic stroke.

14.4 Hypertension in pregnancy 2587 Commonly used antihypertensive agents in pregnancy are as follows; • Labetolol is a combined β- and α-adrenoceptor blocker. It may be used throughout pregnancy and in the postpartum period. Doses typically range from 100 mg twice daily to 400 mg four times daily. Labetolol is contraindicated in women with asthma. • Nifedipine is a calcium channel blocker. The main side effect is headache which is often most severe after starting the medication. Long-acting once-daily preparations may reduce the incidence of headache and help with compliance. The concomitant use of nifedi- pine and magnesium sulphate must be with caution due to the po- tential risk of serious adverse maternal effects such as hypotension. • Amlodipine is another calcium channel blocker which has the advantage of a once-daily dosage to help improve compliance. Its side effect profile is similar to nifedipine. • α-Methyldopa, a central acting α-adrenergic agonist, is a safe medication for use in pregnancy. However, it has a slow onset of action and at higher doses causes sedation and irritability. It should be stopped postnatally as it may cause postnatal depression. Angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and diuretics should not be used in pregnancy. Angiotensin converting enzyme inhibitors may result in fetal hypocalvaria and renal defects. These drugs have also been associated with growth restriction, prematurity, persistent patent ductus arteriosus, and neonatal anuria. Therefore, patients with pre-existing hypertension should be commenced on safe alternatives ideally preconception. In the case of severe hypertension, or when oral treatment is not possible, intravenous antihypertensives may also be used. The com- monest intravenous regimens are: • Labetolol given as a bolus of 50 mg over a minimum of five min- utes. This may be repeated to a maximum of 200 mg, at 10-minute intervals. A labetolol infusion can then be commenced to control blood pressure until oral medication can be administered or has had sufficient time to act.

The maintenance rate is 5 mg/ml at 4 ml/ hr via a syringe pump, which can be doubled every 30 minutes, up to a maximum of 32 ml (160 mg)/hour until the blood pressure has dropped and stabilized at an acceptable level. • Hydralazine is an alternative intravenous agent given by bolus in- fusion. The recommended dose is 5–20 mg over 10–20 minutes. This may be followed by a maintenance infusion, which runs at 40 mg hydralazine in 40 ml normal saline at a rate of 1–5 ml/hour (1–5 mg/hour). The Control of Hypertension in Pregnancy Study (CHIPS) was a ran- domized controlled trial in which women with hypertension in preg- nancy (pre-existing or pregnancy-induced but not pre-eclampsia) were randomized to either 'less tight' control (aiming for diastolic blood pressure of 100–105 mm Hg) or 'tight' control (aiming for a dia- stolic blood pressure of 80–85 mm Hg) of their hypertension. The trial demonstrated that women in 'less tight' compared with 'tight' con- trol groups had similar rates of adverse perinatal (31.4% vs. 30.7%) and maternal outcomes (3.7% vs. 2.0%), despite higher mean diastolic blood pressures by 4.6 mm Hg. However, severe hypertension (≥160/ 110 mm Hg) developed more frequently in 'less tight' (vs. 'tight') con- trol (40.6% vs. 27.5%). As a result, tight control of blood pressure is advocated to prevent potential adverse maternal outcomes. When a patient is at risk of eclampsia, magnesium sulphate is the pharmacological agent of choice. Initial treatment is with a loading dose of 4 grams. This is followed by a maintenance infusion of 1 g/hour continued for up to 24 hours after delivery. Signs of toxicity with mag- nesium sulphate include motor paralysis, absent reflexes, respiratory depression, and cardiac arrhythmia. If signs of toxicity occur magne- sium sulphate should be discontinued, and consideration given to ad- ministration of 10 ml 10% calcium gluconate slowly intravenously to counteract the toxicity. Ninety-seven per cent (97%) of magnesium sul- phate is excreted in the urine. As a result, when oliguria or acute kidney injury occur, the maintenance dose should be reduced or withheld. Prognosis/outcome While the severity of clinical presentation of pre- eclampsia is highly variable, outcomes are usually favourable when pre-eclampsia de- velops after 36 weeks' gestation. When preterm pre-eclampsia occurs (<34 weeks' gestation), the risk of adverse maternal and peri- natal outcome increases significantly. Outcomes are less favourable in women living in developing countries, regardless of gestation or severity of clinical presentation. With eclampsia 38% of fits occur antenatally, 18% intrapartum, and the remaining 44% postpartum, usually in the first 24–48 hours. Eclampsia has a high maternal and perinatal morbidity. Nearly one in 50 women with eclampsia die and the rate of stillbirths and neonatal deaths is 22.2/1000 and 34.1/1000, respectively. The most common cause of death in women dying with eclampsia is cerebral haemorrhage. The risk of progression from gestational hypertension to pre- eclampsia is approximately 20–30% and increased if the hyperten- sion appears at earlier gestations. Therefore, closer monitoring of these patients is essential. Women with chronic hypertension who become pregnant are at significantly increased risk of adverse pregnancy outcomes. A sys- tematic review demonstrated that women with chronic hyperten- sion had higher pooled incidences of multiple adverse pregnancy outcomes. As a result, heightened antenatal surveillance is required. Increased risks included: • superimposed pre-eclampsia (26%) • Caesarean section (41%) • preterm delivery less than 37 weeks' gestation (28%) • birth weight less than 2500 g (17%) • neonatal unit admission (21%) • perinatal death (4%) Those who have been diagnosed with severe pre-eclampsia are more likely to experience recurrence in their next preg- nancy. However, this is typically less severe with clinical presen- tation usually approximately two to three weeks later in gestation. Women who have experienced severe early onset pre- eclampsia necessitating delivery at less than 34 weeks, especially if complicated by growth restriction or late fetal loss, should undergo testing for antiphospholipid syndrome. It may be necessary to discuss the im- plications of these results on future pregnancies. Special

circumstances Women with pre-eclampsia are at high risk of fluid overload and subsequent pulmonary oedema. Fluid management should be

Section 14 Medical disorders in pregnancy 2588 closely monitored, and total input should not exceed 80 ml/hour (approximately 1 ml/kg/hr). Oxytocin, if required, should be used at high concentrations, and included as part of the total fluid input. When oliguria occurs, caution should be exercised, and boluses of fluid and diuretics avoided if possible. Most of these patients re- cover spontaneously, provided delivery is expedited. Following delivery and resolution of symptoms, women should be reviewed six to eight weeks postpartum to ensure resolution of hypertension and blood abnormalities. Women should also be debriefed in the case of complicated deliveries, educated re- garding modifiable risk factors, and counselled regarding their increased risk of later hypertension (3.7 times higher risk), cor- onary heart disease (2.2 times increased risk) and stroke (1.8 times higher risk). Areas of uncertainty, controversy,
and future developments The prediction of pre-eclampsia remains elusive with established assays having poor sensitivity and specificity. To date, no pharma- cological therapies exist for the prevention or treatment of pre- eclampsia. Statins for the treatment of pre-eclampsia are currently being trialled in randomized trials in the United States and United Kingdom. An increasing body of evidence supports the association of pre-eclampsia with long-term adverse cardiovascular health. It is unclear whether women with pre-eclampsia should be offered any interventions such as angiotensin-converting-enzyme (ACE) inhibitors, statins, or low-dose aspirin in the postpartum period to reduce these long-term risks. FURTHER READING Bramham K, et al. (2013). Postpartum management of hypertension. BMJ, 346, f894. Bramham K, et al. (2014). Chronic hypertension and pregnancy out- comes: systematic review and meta-analysis. BMJ, 348, g2301. Broekhuijsen K, et al. (2015). Immediate delivery versus expectant monitoring for hypertensive disorders of pregnancy between 34 and 37 weeks of gestation (HYPITAT-II): an open-label, random- ised controlled trial. Lancet, 385, 2492–501. Brown MA, Magee LA, Kenny LC, et al. (2018). Hypertensive dis- orders of pregnancy: ISSHP classification, diagnosis, and manage- ment recommendations for international practice. Hypertension, 72(1), 24–43. Koopmans CM, et al. (2009). HYPITAT study group. Induction of labour versus expectant monitoring for gestational hypertension or mild pre-eclampsia after 36 weeks' gestation (HYPITAT): a multicentre, open-label randomised controlled trial. Lancet, 374, 979–88. Magee LA, et al. (2015). Less-tight versus tight control of hypertension in pregnancy. N Engl J Med, 372, 407–17. National Institute for Health and Clinical Excellence (NICE) (2010). Hypertension in Pregnancy: The Management of Hypertensive Disorders During Pregnancy. https://www.nice.org.uk/guidance/CG107 Rolnik DL, Wright D, Poon LC, et al. (2017). Aspirin versus placebo in pregnancies at high risk for preterm preeclampsia. N Engl J Med, 377(7), 613–22.

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