

Current best practice in the management of hypertensive disorders in pregnancy

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Abstract: Preeclampsia is a potentially serious complication of pregnancy with increasing significance worldwide. Preeclampsia is the cause of 9%–26% of global maternal mortality and a significant proportion of preterm delivery, and maternal and neonatal morbidity. Incidence is increasing in keeping with the increase in obesity, maternal age, and women with medical comorbidities entering pregnancy. Recent developments in the understanding of the pathophysiology of preeclampsia have opened new avenues for prevention, screening, and management of this condition. In addition it is known that preeclampsia is a risk factor for cardiovascular disease in both the mother and the child and presents an opportunity for early preventative measures. New tools for early detection, prevention, and management of preeclampsia have the potential to revolutionize practice in the coming years. This review presents the current best practice in diagnosis and management of preeclampsia and the hypertensive disorders of pregnancy.

Keywords: preeclampsia, eclampsia, gestational hypertension, blood pressure, pregnancy screening, management, treatment, outcome

Epidemiology

Preeclampsia is a global health problem of increasing significance.^{1,2} Preeclampsia complicates 2%–8% of all pregnancies, contributes to 15% of preterm deliveries, and between 9% and 26% of maternal deaths worldwide.³ In the most recent confidential inquiry into maternal mortality in the UK, 22 of 107 direct maternal deaths from 2006 to 2008 were related to preeclampsia and eclampsia.⁴

The incidence of preeclampsia is increasing with the global increase in maternal age, obesity, assisted reproductive techniques, and medical comorbidities that predispose to preeclampsia, such as diabetes, hypertension, and renal disease. Preeclampsia is more common in Afro-Caribbean women, multifetal gestation, and primigravidas.⁵

Although in simple terms, preeclampsia is understood to arise from failure of the normal development of the maternal–fetal interface in the placenta,^{6–8} the pathogenesis of the disease is not well established. Rapid advances in understanding in recent decades have opened up new avenues of exploration in screening for and prevention of preeclampsia, with the potential of significantly improving outcomes in the future. It is now clear that the onset of the disease is multifactorial, and interventions for prevention and management of preeclampsia will necessarily have to address a wide range of factors through lifestyle and diet modification and multidisciplinary care.

Preeclampsia is a risk to health not only in the immediate peripartum period – women who have suffered from preeclampsia are at increased risk of cardiovascular disease throughout life,^{9–12} and children born from pregnancies affected by

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preeclampsia are more likely to suffer from metabolic syndrome, cardiovascular disease, and hypertension at earlier ages.¹³ Optimizing management of hypertensive disorders in pregnancy is a major step toward improving population health worldwide.

Hypertensive disorders in pregnancy

Hypertensive disorders of pregnancy can be subclassified into four groups – chronic hypertension, gestational hypertension, preeclampsia, and superimposed preeclampsia in the setting of chronic hypertension, as laid out in the ACOG (American Congress of Obstetricians and Gynecologists) guideline.¹⁴ The International Society for the Study of Hypertension in Pregnancy (ISSHP) has published guidelines on diagnosis to establish global unity of meaning in referring to the various hypertensive disorders of pregnancy, with the most recent guidance being released in 2014. They include an additional category of white coat hypertension.¹⁵

Although each condition increases the risk of maternal and neonatal morbidity, the greatest risks are associated with a diagnosis of preeclampsia, either *de novo* or in the setting of chronic hypertension.^{16,17} The diagnostic criteria for these disorders vary somewhat among published international guidelines, particularly between the research and clinical setting, in the discrimination between preeclampsia and gestational hypertension, and in setting the definition of severe preeclampsia.^{14,15,18–20}

Diagnostic criteria Hypertension

Hypertension in pregnancy is defined as a blood pressure of greater than or equal to 140 mmHg (systolic) or 90 mmHg (diastolic) on at least two measurements, ideally separated by a period of rest.¹⁵ Severe hypertension is defined as a blood pressure of greater than 160/110 mmHg. Systolic hypertension of greater than 180 mmHg is a medical emergency.

The gold standard for measurement is a mercury sphygmomanometer;²¹ however these are increasingly being withdrawn from clinical use for health and safety reasons. Aneroid devices require regular calibration, the interval for which can be increased by using wall or trolley mounted devices that are less susceptible to loss of accuracy. If an automated device is used, it should have been validated for use in pregnancy.

Blood pressure should be measured with the woman at rest and the arm held at the level of the heart. If the woman is supine she should be in the left lateral position.²² An

appropriately sized cuff should always be used, with thigh cuffs used for women with arm circumferences greater than 41 cm. In pregnancy, diastolic pressure is measured at the 5th Korotkoff sound.

Proteinuria

Proteinuria is best measured using a 24-hour urine collection, although even this test is susceptible to user error.²³ A simultaneous 24-hour creatinine excretion measurement may assess the quality of the collection and aid in interpreting the results. Proteinuria is defined as total protein of >300 mg/day in the 24-hour collection. In practical terms, the delay inherent in obtaining a result makes this test suboptimal for facilitating rapid decision making about the need for delivery or admission in women with suspected preeclampsia.

A spot protein creatinine ratio (PCR) can be performed quickly on a single urine sample and provides a more rapid result that can facilitate efficient clinical management. A value greater than or equal to 30 mg/mmol is taken to indicate significant proteinuria.²³ A negative test has a high negative predictive value, but a positive test should always, in ideal circumstances, be followed up by a 24-hour urine collection, particularly if the PCR is in the nephrotic range (>230 mg/mmol).²³

Often in clinical practice, neither a 24-hour urine collection nor a spot PCR is available, and clinical management may be based on dipstick assessment for proteinuria. It is reasonable to initiate management of preeclampsia based on significant proteinuria on dipstick (>2+) when clinical suspicion is strong and no recourse to other testing is available. Caution should always be exercised in women where preeclampsia is strongly suspected with a negative urine dip because the sensitivity of dipstick testing is poor (negative predictive ratio 0.6),²³ and many cases would be missed if relying on dipstick testing alone.

Women who present with proteinuria without hypertension should be monitored for development of preeclampsia or other renal disease, but not treated as preeclamptic. As many as 51% of women presenting with proteinuria without hypertension will go on to develop preeclampsia in the remainder of pregnancy.²⁴

The hypertensive disorders of pregnancy

Pre-pregnancy hypertension

Any woman presenting at booking with hypertension may have preexisting hypertension. Many apparently healthy

women will not have accessed health care prior to booking in pregnancy, and hypertension may be a new finding at booking in the first trimester.

Blood pressure should be recorded either pre-pregnancy or in early pregnancy, before the nadir in blood pressure in the second trimester. A normal blood pressure may be recorded between 16 and 20 weeks, even in a woman with chronic hypertension, because of the systemic vasodilation in pregnancy, which may cause diagnostic uncertainty later in pregnancy when hypertension is detected for the first time if no earlier blood pressure is noted. In this situation it is best to manage as gestational hypertension and consider further investigations for an alternative underlying cause if the hypertension does not resolve after pregnancy.

These women require careful evaluation to rule out hypertension secondary to other underlying pathology before declaring them to have essential hypertension. In addition, “white coat hypertension” is recognized in pregnant women and, while not entirely benign, does not carry the same risks as true essential hypertension. Whereas as many as 22%–25% of women with chronic hypertension will develop preeclampsia in pregnancy, around half of all women with white coat hypertension will develop gestational hypertension and 8% will develop preeclampsia.²⁵ A 24-hour ambulatory monitoring may be indicated to confirm the diagnosis prior to commencing antihypertensive therapy.²⁴

Other women will have established chronic hypertension and may present in early pregnancy, already maintained on antihypertensive therapy. Ideally, women with existing hypertension should receive pre-conception counseling and stabilization on antihypertensive therapy appropriate for use in pregnancy. Women with chronic hypertension should receive early referral to an obstetric medicine service for the management of their pregnancy, as they are at increased risk of preeclampsia in pregnancy. According to the National Institute for Health and Care Excellence (NICE) guidance, these women should be offered low-dose aspirin from 12 weeks of gestation.¹⁸

Gestational hypertension

Hypertension detected for the first time after 20 weeks of pregnancy and in the absence of any other features of preeclampsia is classified as gestational hypertension. It is therefore necessary to perform an assessment for proteinuria, laboratory tests for organ dysfunction, and consider ultrasound assessment of fetal growth in all women presenting with asymptomatic new onset hypertension after 20 weeks.

There is a risk of progression to preeclampsia of around 25%,¹⁵ and women with gestational hypertension require monitoring throughout pregnancy. Hypertension carries a risk of cerebral hemorrhage, and the absence of proteinuria is not a reason to relax the treatment goals in controlling hypertension in pregnancy. These women are also at increased risk of future cardiovascular disease and may benefit from lifestyle and dietary advice to promote cardiovascular health.

Preeclampsia

The classical definition of preeclampsia has been new onset hypertension in pregnancy after 20 weeks with proteinuria (bearing in mind for both preeclampsia and gestational hypertension that the presentation may occur postpartum). As a disease with a highly diverse phenotypic spectrum, there are a number of presentations and there are inevitably patients who do not fit neatly into the classical definition. It can be particularly challenging in the setting of preexisting hypertension and/or renal disease to detect new onset preeclampsia; however, these women are those at highest risk of developing preeclampsia and its complications.

The most common presentation of preeclampsia is hypertension, detected at a routine antenatal visit in an asymptomatic woman. The common symptoms of preeclampsia may present late and, in the mild forms, overlap to some degree with normal pregnancy – epigastric pain, nausea and vomiting, peripheral and facial edema, headache with or without visual scotomas, and blurred vision. On examination, patients may be hyperreflexic with marked clonus, show an altered mental status, and have right upper quadrant tenderness on palpation. Most of these signs and symptoms will be present only in severe disease, and rapidly evolving symptoms should raise concern about impending severe disease.

Many patients clearly have a preeclampsia-like syndrome with similar prognosis and outcomes but have either no hypertension or no proteinuria. New onset hypertension may be combined with fetal growth restriction or development of hemolysis, elevated liver enzymes and low platelet (HELLP) syndrome, or eclampsia without proteinuria. Eclampsia may present with no previously documented hypertension or symptoms,²⁶ although women will usually be found to be hypertensive after admission with seizures. At the present time, all guidelines in use require hypertension in order to diagnose preeclampsia.^{14,15,18–20}

The ISSHP has recently elected to exclude proteinuria as a necessary condition to be met to establish the clinical diagnosis of preeclampsia in the presence of other maternal organ dysfunction or uteroplacental dysfunction.¹⁵ In a

research setting, to ensure specificity in included cases, it may be appropriate to maintain a requirement for proteinuria to be established. Older guidelines²⁷ include proteinuria as a necessary condition for the diagnosis of preeclampsia, but it is vital to recognize the breadth of presentation of this disease and not dismiss, for example, a severely hypertensive woman with marked intrauterine fetal growth restriction as having gestational hypertension. Most expert bodies now follow the ISSHP in defining preeclampsia as hypertension and any of proteinuria, organ dysfunction, or fetal growth restriction consistent with placental insufficiency.

Preeclampsia superimposed on preexisting hypertension

Hypertension alone is not sufficient to diagnose preeclampsia, and a rise in blood pressure and subsequent requirement for antihypertensive therapy in the third trimester is to be expected in women with essential hypertension. If women develop worsening hypertension in combination with either proteinuria, new organ dysfunction, or uteroplacental dysfunction, then preeclampsia may be diagnosed. In those women with long-standing hypertension and renal dysfunction, the diagnosis of preeclampsia is most problematic.

Severe preeclampsia

Most guidelines also include a subset of criteria to define those women with the most severe disease which can be used to target higher levels of medical and midwifery care at the patients most in need. Table 1 illustrates the criteria set for severe preeclampsia in several national guidelines.

Early onset preeclampsia is used as a marker of severity, which is appropriate given the greatly increased risk of maternal morbidity in pregnancies complicated by preeclampsia remote from term. The ACOG defines early onset as <35 weeks¹⁴ whereas the SOGC (Society of Obstetricians and Gynaecologists of Canada) uses <34 weeks.¹⁹

There is also disagreement about whether systolic hypertension of greater than 160 mmHg (SOGC/American Society of Hypertension [ASH]) or 170 mmHg (Royal College of Obstetricians and Gynaecologists [RCOG], Society of Obstetric Medicine of Australia and New Zealand [SOMANZ]) is the most appropriate limit for severe hypertension, but all agree that severe hypertension is a marker of severe preeclampsia.

The degree of proteinuria has, in the past, been included as a marker of severe disease. However, it is evident that simply the degree of proteinuria is not related to disease progression or outcomes. It is relevant to clinical management when proteinuria in the nephrotic range is detected, which should alert clinicians to a further risk of venous thromboembolism (VTE). It should be noted that preeclampsia itself increases the risk of VTE, particularly if associated with a period of bed rest or hospital admission, and appropriate thromboprophylaxis should be prescribed. The degree of proteinuria should not influence the timing of delivery or the decision to start antihypertensive treatment or magnesium sulfate.²⁸

Severe disease can develop rapidly, even in women previously classified as having “mild” disease. Worsening symptoms of abdominal pain, nausea and vomiting, and

Table 1 Diagnostic criteria of severe preeclampsia

	National Institute for Clinical Excellence (2010) (any of the features below in combination with hypertension and proteinuria)	American College of Obstetricians and Gynecologists (2013) (any of the below with known preeclampsia)	American Society of Hypertension (2008)
Symptoms	Headache Visual disturbance Vomiting Epigastric pain	Severe persistent right upper quadrant or epigastric pain Cerebral or visual disturbance	Headache Visual disturbance Abdominal pain
Signs	Papilloedema Clonus Liver tenderness	Pulmonary edema	Oliguria Early onset disease (<35 weeks) Nonreassuring fetal monitoring
Hypertension	Severe hypertension and proteinuria alone	Systolic BP >160 mmHg Diastolic BP >110 mmHg (on two occasions >4 h apart while on bed rest)	Diastolic >110 mmHg
Other maternal disorders	HELLP syndrome Platelets <100×10 ⁹ /L AST or ALT >70	Platelets <100×10 ⁹ /L Liver enzymes > twice normal concentration Progressive renal insufficiency	Elevated creatinine Nephrotic range proteinuria Elevated AST or LDH

Abbreviations: HELLP, hemolysis, elevated liver enzymes and low platelets; AST, aspartate transaminase; ALT, alanine transaminase; LDH, lactate dehydrogenase.

headache, while nonspecific, should always be taken seriously in a patient with known preeclampsia.¹⁸

Complications of hypertensive disorders of pregnancy

Preeclampsia is a multisystem disorder characterized by generalized endothelial damage, which can result in widespread end-organ damage. The presence of any of these features is a marker of severe disease, even with relatively mild hypertension. Of the maternal deaths attributable to preeclampsia in the last UK confidential inquiry, most were related to cerebral or hepatic complications. Two women died of ARDS (Acute respiratory distress syndrome).⁴ Table 2 summarizes the complications associated with preeclampsia by organ system.

HELLP syndrome

HELLP syndrome describes a constellation of Hemolysis (anemia with blood film evidence of hemolysis), Elevated Liver enzymes showing hepatic dysfunction (transaminitis greater than twice the normal range), and Low Platelets (platelet count of less than 150,000/dL).³

HELLP occurs in around 5% of preeclampsia cases²⁷ or 10%–20% of severe preeclampsia, and is associated with 1.1% maternal mortality and severe morbidity including disseminated intravascular coagulopathy, liver hematoma, liver failure, and renal failure.²⁹ Perinatal mortality rate is reported at 6%–17%.^{30,31} An initial minor derangement in transaminases and platelets can deteriorate rapidly, and blood tests should be repeated every 6–12 hours if the trend is worsening and the decision has been made to prolong pregnancy to allow administration of corticosteroids for fetal lung maturity. Corticosteroids are not currently used to attempt to treat HELLP syndrome.¹⁸ HELLP is, by definition, a marker of severe disease and requires multidisciplinary care, including hematology, renal, and hepatic physicians, and anesthetic involvement.

Renal impairment

Renal perfusion and filtration increase in normal pregnancy, and creatinine levels should therefore be lower than normal

in pregnancy.³² Creatinine level over 90 $\mu\text{mol/L}$ is a marker of severe disease, or sufficient evidence of organ dysfunction to diagnose preeclampsia in the presence of hypertension even without proteinuria.¹⁵

The glomerular endothelium may be directly damaged in preeclampsia, with a pathological finding of glomerular endotheliosis. In addition, the state of relative intravascular volume constriction can predispose to acute kidney injury. Renal impairment usually resolves with treatment of the preeclampsia. However, it may be worsened by the practice of fluid restriction in management of severe preeclampsia, and renal physicians should be involved where there is coexisting renal injury and pulmonary edema.

Pulmonary edema

Hypoalbuminemia leads to reduced oncotic pressure and relative intravascular volume depletion with significant interstitial fluid.³³ Women with preeclampsia are thus much more vulnerable to pulmonary edema, especially those with significant renal impairment. For this reason, careful fluid management is critical in all women with preeclampsia, and pulmonary edema secondary to iatrogenic fluid overload is a cause of maternal mortality in preeclampsia. It is common practice to restrict fluid intake in women with severe preeclampsia, but in the setting of concomitant renal injury, specialist nephrology advice may be required. Invasive monitoring in the setting of an intensive care unit is most appropriate for women with signs of pulmonary edema in preeclampsia.

Eclampsia/cerebral hemorrhage

The most feared complications of preeclampsia are cerebral. They were the cause of mortality in 14 of the 22 maternal deaths reported by the Centre for Maternal and Child Enquiries (CMACE) in the triennium 2006–2008⁴ and account for 10% of severe maternal morbidity.²⁶ Of the 14 maternal deaths, 5 were secondary to eclampsia and 9 secondary to intracranial hemorrhage.

Eclampsia literally means lightning, and it is the rapidity of the onset that is so concerning. Eclampsia refers to generalized tonic-clonic seizures in a pregnant or recently

Table 2 Complications of preeclampsia by organ system

Cardiorespiratory	Neurological	Renal	Hepatic	Hematological
ARDS	Eclampsia	Acute tubular necrosis	Periportal inflammation	Thrombocytopenia
Pulmonary edema	Cerebral thrombosis or hemorrhage	Acute kidney injury	Hepatic dysfunction	DIC
Cardiomyopathy	PRES	Glomerular endotheliosis	Hepatic hematoma/rupture	Microangiopathic hemolysis
Generalized edema	Altered mental status		Acute fatty liver of pregnancy	Venous thromboembolism

Abbreviations: ARDS, adult respiratory distress syndrome; DIC, disseminated intravascular coagulopathy; PRES, posterior reversible leukoencephalopathy syndrome.

delivered woman with no other attributable cause, and complicates 1%–2% of severe preeclampsia.²⁶ Search for an underlying cause should never delay initiation of treatment for eclampsia, and all generalized seizures in pregnancy after 20 weeks should be managed as eclampsia unless a clear alternate cause (head trauma or known epilepsy) is identified. Seizures can arise with no or minimal preceding symptoms and signs, or in a woman who has had stable “mild” disease for several weeks. The most common preceding symptoms are severe headache, visual disturbance, and nausea, and may be present in 79% of cases who go on to present with eclampsia. Eclampsia may be 10–30 times more common in developing countries, largely because of differences in the quality of antenatal monitoring.¹

Cerebral damage is caused by a failure of autoregulation related to endothelial damage, exacerbated by acute or large changes in the blood pressure. A common finding in eclampsia is posterior reversible leukoencephalopathy syndrome (PRES),³⁴ vasogenic edema in the posterior cerebral circulation, a finding also seen in hypertensive encephalopathy. The hypertension associated with eclampsia and PRES is often less severe than in nonpregnant hypertensive encephalopathy, and it is possible that the endothelial damage associated with preeclampsia predisposes to this syndrome even at lower blood pressure.³³

Differential diagnosis of preeclampsia

In a woman presenting with hypertension and any form of organ dysfunction, preeclampsia will always be the most likely differential diagnosis. However, many other conditions with microangiopathic effects can mimic elements of the preeclampsia phenotype. The management of these disorders may be different from that of preeclampsia, and misdiagnosis can have serious implications. For example, preterm delivery is not indicated in thrombotic thrombocytopenic purpura (TTP), and delivery of a fetus in a woman presenting at 28 weeks will create major risk for the fetus without conferring benefit on the mother. In addition, platelet transfusion in TTP carries a high risk of microvascular thrombosis and should be reserved for life-threatening bleeding.

The diagnostic challenge can be complicated by the possibility of preeclampsia coexisting with another disorder such as systemic lupus erythematosus.

Table 3 summarizes a range of conditions that can present with some of the features of preeclampsia. Acute fatty liver of pregnancy, thrombotic thrombocytopenic purpura,

Table 3 Differential diagnoses in severe preeclampsia by organ system

Vasculature
Pheochromocytoma
Hyperaldosteronism
Cushing's disease
Thyrototoxicosis
Aorta coarctation
Renal system
Lupus nephritis
Acute and chronic glomerulonephritis
Interstitial nephritis
Pyelonephritis
Liver
Acute fatty liver of pregnancy
Pregnancy cholestasis
Hyperemesis gravidarum
Cholecystitis
Cholangitis
Viral hepatitis
Acute pancreatitis
Gastritis
Gastric ulcer
Hemostasis
Benign thrombocytopenia of pregnancy
Thrombotic thrombocytopenic purpura
Hemolytic uremic syndrome
Idiopathic thrombocytopenic purpura
Antiphospholipid syndrome
Folate deficiency
Systemic lupus erythematosus
Septic or hemorrhagic shock
Respiratory system
Pneumonia
Pulmonary embolus
(Catastrophic) antiphospholipid syndrome
Cardiovascular system
Peripartum cardiomyopathy
Myocardial infarction or ischemia
Brain
Cerebral systemic lupus erythematosus
Epilepsy
Brain tumour
Cerebrovascular accident
Hypertensive encephalopathy
Metabolic disease
Eyes
Retinal arterial or venous thrombosis
Retinal ischemia
Retinal detachment
Persistent spasm of retinal vessels
Central serous retinopathy
Uveal melanoma
Choroidal osteoma

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hemolytic uremic syndrome and systemic lupus erythematosus are those microangiopathic diseases where the laboratory test results and clinical presentation may overlap so closely with severe preeclampsia as to be extremely challenging to definitively diagnose.

There are some additional symptoms and laboratory findings that may help to discriminate between these conditions – for example, acute fatty liver of pregnancy (AFLP) is associated with hypoglycemia, ammonemia, and jaundice in 50%–100% of cases.³⁵

Patients with suspected systemic lupus erythematosus should be tested for antinuclear or anti-dsDNA antibodies. Systemic lupus erythematosus patients who are also positive for antiphospholipid antibodies are at higher risk of microthrombotic events that can precipitate a clinical syndrome very similar to preeclampsia/HELLP. Serum complement levels may help determine if symptoms relate to a flare in disease activity.

Hemolysis and anemia are more common in TTP and hemolytic uremic syndrome (HUS), and von Willebrand factor multimers are more commonly elevated than in either AFLP or HELLP. The underlying pathology of TTP relates to a reduced activity of von Willebrand cleaving protease (a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13, also called ADAMTS13) which is detectable on testing. However, this test may not be available in standard hospital laboratories. Antibodies against ADAMTS13 are also detectable and the titers may determine whether management is by plasma exchange, immunosuppression, or splenectomy.

New diagnostic markers

New diagnostic tests are under evaluation to address some of the inadequacies in current tests and obscurities in presentation. Urinary albumin/creatinine ratios are routinely used outside of pregnancy to detect proteinuria, and may be superior to PCR, but have yet to be validated in pregnancy and preeclampsia.¹⁹ Other markers investigated include pregnancy-associated plasma protein A (PAPP-A), placental protein 13 (PP-13), homocysteine, asymmetric dimethylarginine (ADMA), uric acid, and leptin. None of these has adequate performance individually as a clinical test, but several groups have proposed models that include a number of factors in addition to maternal history and/or ultrasound markers to identify women at risk of preeclampsia.³⁶

As the pathogenesis of preeclampsia relates to an imbalance in the control of angiogenesis, a number of factors might be outside the normal range in the weeks leading

up to presentation with preeclampsia. Placental growth factor (PIGF) is a proangiogenic factor, and from as early as 11–13 weeks' gestation low levels are associated with the later development of preeclampsia.³⁷ sFlt-1 (soluble fms-like tyrosine kinase 1) is antiangiogenic and levels are elevated as much as 5 weeks prior to the clinical onset of disease.³⁸ Both have been evaluated as diagnostic tests but neither has sufficient sensitivity to be of use in clinical practice. Preliminary studies have evaluated the use of the sFlt-1/PIGF ratio as a diagnostic and screening test, and have found a high specificity and sensitivity, particularly for early onset disease.³⁹ Subsequent investigations have shown that it may be possible to discriminate between the hypertensive disorders of pregnancy with this ratio.⁴⁰ This approach provides the possibility of rapid testing to clarify a diagnosis of preeclampsia, but requires further testing and validation with larger numbers of patients.

Screening for preeclampsia

Preeclampsia is a serious disease and it is likely that early identification of those at risk would allow targeted surveillance and intervention, in order to improve the pregnancy outcomes for both mother and fetus. Low dose aspirin started in the first trimester in high risk women may reduce the risk of preeclampsia by up to 50%⁴¹ and may improve associated fetal and maternal outcomes.⁴² No other agents tested (progesterone or Vitamins D and E) have shown a reduction in risk of preeclampsia.⁴³ Calcium supplementation reduces the risk only in women who are deficient in dietary calcium.⁴⁴

With the introduction of aspirin as a prophylactic agent there is a package of intervention – aspirin and increased ultrasound and blood pressure monitoring – that can reduce the risk of preeclampsia and increase the chances of early detection in women determined to be at high risk. Now it is necessary to refine how we define who is at high risk.

Historically, screening took the form of regular blood pressure and urine checks throughout pregnancy for all women. In the UK today, NICE recommends using maternal history, age, body mass index, and number of fetuses to select women for treatment with aspirin.¹⁸ Unfortunately, for a population prevalence of 4% the positive predictive value of this model is low and would lead to nearly half of all women being screen positive.⁵ With a sensitivity of only 77%, a significant number of women who will develop preeclampsia are not detected with this model, so routine antenatal care still has to include regular blood pressure monitoring throughout later pregnancy. The maternal risk factors for preeclampsia

according to NICE, the World Health Organization (WHO), ACOG, and the SOGC are listed in Table 4.

A number of areas are under investigation and many show limited promise, but no single test can accurately predict preeclampsia, and most have poor positive predictive values. The strategy most commonly used is to identify a number of factors and combine these in a predictive model.

Abnormal uterine artery Dopplers at 20–22 weeks are strongly associated with risk of preeclampsia and intrauterine growth restriction and are in current use to identify high risk women for additional monitoring in later pregnancy. However, to obtain maximal benefit from aspirin treatment, a first trimester screening tool is needed, and although first trimester uterine artery Dopplers are associated with risk of later preeclampsia, this test in isolation is not sufficiently sensitive for use in directing aspirin therapy and later pregnancy monitoring.³⁶

A stepwise approach where women are identified as high risk in the first trimester and then reevaluated at the time of the mid-trimester anomaly scan is promising in terms of picking up most cases of early onset preeclampsia.⁴⁵ Combining first trimester uterine artery Doppler findings with maternal characteristics and serum markers in the manner of the first trimester fetal anomaly screening is likely to provide the best approach to first trimester screening for preeclampsia. No models have yet been successfully validated in clinical practice, but such research is urgently required.

Antenatal care of women with preeclampsia

Once preeclampsia has been diagnosed, subsequent management will be determined largely by gestation at presentation and markers of severity. The cure for preeclampsia is simple – delivery of the placenta will ultimately lead to

Table 4 Maternal risk factors for preeclampsia according to NICE, WHO, ACOG, and the SOGC

NICE (2010) ¹⁸	WHO (2011) ²⁰	ACOG (2013) ¹⁴	SOGC (2014) ^{*,19}
Previous hypertensive disease during a pregnancy*	Previous preeclampsia	Previous preeclampsia	Previous preeclampsia
Chronic kidney disease	Renal disease	Chronic renal disease	Preexisting renal disease
Autoimmune disease (including SLE/APS)	Autoimmune disease	SLE	APS
Type 1 or type 2 diabetes	Preexisting diabetes mellitus	Preexisting diabetes mellitus	Preexisting diabetes mellitus
Chronic hypertension	Chronic hypertension	Chronic hypertension	Preexisting hypertension
Multiple pregnancy	Multiple pregnancy	Multiple pregnancy	Multiple pregnancy
Nulliparity		Primiparity	First ongoing pregnancy (nulliparity)
Age 40 years or older		Age 40 years or older	Maternal age ≥ 40 years
Pregnancy interval of more than 10 years			Inter-pregnancy interval ≥ 10 years
Body mass index of ≥ 35 kg/m ² at booking		Obesity	Overweight/obesity
Family history of preeclampsia		Family history of preeclampsia	Family history of preeclampsia
			Family history of early-onset cardiovascular disease
			Lower maternal birthweight and/or preterm delivery
		History of thrombophilia	Heritable thrombophilias (factor V Leiden/protein S deficiency)
			Increased pre-pregnancy triglycerides
			Non-smoking
			Cocaine and methamphetamine
			Previous miscarriage at ≤ 10 weeks with same partner
			New partner
			Short duration of sexual relationship with current partner
		In vitro fertilization	Reproductive technologies
			Booking SBP ≥ 130 mmHg, or DBP ≥ 80 mmHg
			Vaginal bleeding in early pregnancy
			Gestational trophoblastic disease

Note: *Women are at increased risk if they have one of the risk factors in bold or ≥ 2 of the other risk factors.

Abbreviations: NICE, National Institute for Health and Care Excellence; WHO, World Health Organization; ACOG, American College of Obstetricians and Gynecologists; SOGC, Society of Obstetricians and Gynecologists of Canada; SLE, systemic lupus erythematosus; APS, anti-phospholipid antibody syndrome; SBP, systolic blood pressure; DBP, diastolic blood pressure.

resolution of the disease. The challenges of management are in balancing the maternal risks of continuing pregnancy against the maternal risks of intervention and the fetal risks of preterm delivery.

It is important to recognize that, although most guidelines include specific gestational cutoffs for expectant and interventional management, a continuum of risk exists. While opting to continue pregnancy, the goals of treatment are to maintain a safe blood pressure, monitor the mother for deteriorating disease and the fetus for signs of placental dysfunction and growth restriction.

Inpatient or outpatient management

ISSHP recommends admitting all women at diagnosis of preeclampsia¹⁵ to complete a full maternal and fetal assessment, stabilize blood pressure, and finalize a plan of care prior to considering outpatient follow-up and management. This is also recommended in the Pre-eclampsia Community Guideline (PRECOG) day-assessment unit guideline in use in the UK, which also lays out suggested investigation pathways for women with hypertension but not yet diagnosed with preeclampsia,⁴⁶ and in the WHO²⁰ and ACOG¹⁴ guidelines.

At diagnosis of preeclampsia, all women should be offered admission to hospital and ultrasound assessment of fetal well-being and Doppler studies of the umbilical artery performed. While an inpatient, women should have their risk of VTE assessed. The combination of pregnancy, preeclampsia and inpatient admission significantly increase the risk of VTE, so most patients should receive low molecular weight heparin for thromboprophylaxis, unless they have contraindications. All patients should have a full blood count, coagulation profile, and renal and liver function checked. Uric acid may be of benefit in confirming a diagnosis but is not related to maternal or fetal outcome, and a normal result does not rule out preeclampsia.⁴⁷

If blood pressure is persistently elevated (cutoff 150/100 mmHg), consideration should be given to the commencement of antihypertensive therapy.¹⁸ During admission, blood pressure should be checked at least 4-hourly, and a 24-hour urine collection for quantification of proteinuria should be performed if not already completed. It is reasonable to commence treatment on the basis of dipstick or PCR results, but a 24-hour urine collection is the gold standard for confirming the presence of proteinuria.

Women with stable blood pressure on treatment, normal laboratory studies, no concern about fetal well-being, and a good understanding of their condition are candidates for outpatient management. Outpatient management should be

undertaken in the context of a specialized day-assessment unit and extensive patient briefing on symptoms and signs that should prompt urgent presentation to hospital services (headache, abdominal pain, or vaginal bleeding) is necessary.

Maternal monitoring should include regular blood pressure measurement in a dedicated day-assessment unit. No subsequent quantification of proteinuria is necessary after significant proteinuria has been confirmed. Laboratory tests of biochemical and hematological parameters should be repeated 2–3 times a week, according to the severity and the progression of the disease.¹⁷

Fetal monitoring

All women diagnosed with preeclampsia should have ultrasound assessment of fetal growth, liquor volume, and umbilical artery Doppler. As long as pregnancy continues, scans should be repeated at fortnightly intervals.¹⁸

Mothers should be informed of the importance of self-monitoring of fetal movement and where to present if there are subjectively reduced fetal movements. There is no specific evidence related to kick charts or equivalent monitoring tools in preeclampsia, and as these women are at high risk of placental insufficiency it would be reasonable to perform ultrasound assessment at the first presentation with subjectively reduced fetal movement.

Lifestyle modification and patient education

There is no evidence to support the use of bed rest in the hypertensive disorders of pregnancy, and there is a probable harm from reduced mobility increasing the risk of thrombosis, infection, and psychosocial harm.⁴⁸ Women with preeclampsia should be offered advice on a healthy diet and light exercise, as for any other pregnant woman.

According to NICE guidance, patients should have their diagnosis explained to them clearly, the warning signs of progressive disease explained, and the appropriate contact points documented in the maternity notes.

Antihypertensive therapy

Antihypertensive therapy aims to reduce the risk of severe hypertension and cerebrovascular accidents, cardiovascular strain, and renal injury. The degree of hypertension at which to institute therapy is the subject of controversy. NICE guidance recommends commencing therapy when blood pressure exceeds 150/100 mmHg, with the aim

of maintaining blood pressure below this level, and the SOGC guidelines are similar.¹⁹ This is stressed in the Top 10 recommendations of the most recent CMACE report.⁴ Based on a review of maternal deaths in the UK, the authors stress that systolic hypertension should be treated seriously and that failure to do so was a feature of several maternal deaths from cerebral hemorrhage and aortic dissection.⁴

The ACOG guidelines are more conservative, citing concerns about the side-effects of antihypertensive therapy in pregnancy and the relative rarity of complications at blood pressures of 150/100 mmHg, and would recommend treatment only for blood pressure over 160/110 mmHg.¹⁴ The WHO guideline specified that the evidence is not yet sufficient to determine which strategy is preferable, but ongoing study will clarify this issue in the near future.²⁰ In all cases, care should be taken to avoid reducing the blood pressure below the lower limits (110/80 mmHg) which would lead to a risk of placental underperfusion.¹⁵

Choice of antihypertensive in moderate hypertension

NICE recommends that the first line antihypertensive should be labetalol. However, there is insufficient evidence as to which antihypertensive is most effective.⁴⁹ Acceptable and commonly used alternatives are methyldopa and nifedipine.

There is some evidence outside of pregnancy that beta blockers are less effective in controlling hypertension in Afro-Caribbean patients, who may have elevated renin levels

even at a young age.⁵⁰ This leads some to argue that, as these patients are likely to be resistant to labetalol, nifedipine should be the first line drug for them. Nifedipine may be more effective in controlling blood pressure than labetalol or hydralazine, but labetalol was associated with fewer adverse perinatal events, and remains generally the recommended first line antihypertensive.⁵¹

Angiotensin-converting enzyme (ACE) inhibitors and alpha blockers are not appropriate in pregnancy. Choice of antihypertensive should be guided by an individualized assessment of the patient and risk of adverse reactions. Multiple medications may be needed in women with persistent severe hypertension at the maximal dose of their first line antihypertensive. Table 5 outlines the commonly used antihypertensive drugs in the UK.

Treatment of severe disease

Severe hypertension

Severe hypertension (>160–170/100–110 mmHg) requires antihypertensive treatment. In the absence of symptoms suggestive of impending eclampsia it is reasonable to start with oral therapy, if tolerated by the mother. It can be a feature of essential or gestational hypertension, but may also represent progression to full preeclampsia. The patient should undergo a full evaluation, including urine and blood tests, to detect new onset preeclampsia. A systolic blood pressure of >180 mmHg is a medical emergency and should be controlled rapidly with intravenous antihypertensives. A maintenance infusion may be required. An important principle is to avoid causing relative hypotension and compromising uteroplacental circulation

Table 5 Antihypertensive drugs used in pregnancy and lactation

	Atenolol	Captopril	Enalapril
Mechanism	Beta blocker	ACE inhibitor	ACE inhibitor
Pregnancy	Avoid in first and second trimester. Associated with fetal growth restriction and bradycardia, reduces uteroplacental blood flow	No – associated with severe fetal anomaly, fetal nephropathy, and intrauterine death	No – associated with severe fetal anomaly, fetal nephropathy, and intrauterine death
Breast-feeding	No known evidence of harm (NICE). Second line after labetalol	Manufacturers advise avoid; however recommended by SOGC. No known evidence of harm (NICE)	Not for preterm infants. No known evidence of harm (NICE) Particularly for women needing cardiac/renal protection
Postnatal	Yes	Yes	Yes
Side-effects	Risk of fetal growth restriction and bradycardia in pregnancy	Cough	Cough
Contraindications	Asthma		

Abbreviations: ACE, angiotensin-converting enzyme; CTG, cardiotocography; NICE, National Institute for Health and Care Excellence; SOGC, Society of Obstetricians and Gynecologists of Canada.

while still reducing the blood pressure to a level not associated with cerebral adverse events. The target of treatment should be to maintain blood pressure at <150/100 mmHg.

Oral fast acting nifedipine, intravenous hydralazine, and labetalol are equally efficient for management of acute severe hypertension in pregnancy, so the choice should be guided by local protocols, clinician familiarity, and individualized patient risk profiles.⁴⁸

Blood pressure should be checked at least every 5 minutes while attempting to gain control, and if refractory consideration should be given to invasive monitoring. All women with severe hypertension should be managed in a minimum of a level 2 care bed until stable, whether or not management includes delivery.

Severe preeclampsia

Women with severe preeclampsia (as defined by the national guidelines described in Table 1) should be managed as inpatients with senior clinicians reviewing the plan of care on a daily basis. Before 34 weeks, the focus of care is on prolonging pregnancy as long as the mother is stable, in the interests of the fetus. Where some would advocate delivery within 24–48 hours of diagnosis of early onset stable severe preeclampsia (interventionist management), doing so increases neonatal morbidity with no proven maternal benefit. It is instead common practice to continue pregnancy until maternal condition cannot be stabilized safely (expectant management).⁵² Since delivery may become necessary rapidly, corticosteroids for fetal lung maturity should be considered at the diagnosis of severe early onset preeclampsia.

Women meeting the criteria for delivery would normally also merit treatment with magnesium sulfate.

Women who meet the criteria for the diagnosis of severe preeclampsia (Table 1) or have significant signs and symptoms of impending eclampsia (severe headache, clonus, neurological impairment) should be considered for treatment with magnesium sulfate for eclampsia prophylaxis. Magnesium sulfate is associated with a 50%–67% reduction in the risk of seizures, a reduction in the risk of maternal death, and may have some benefit to the baby.⁵³ The standard protocol is as described in the Collaborative Eclampsia Trial,⁵⁴ a 4 g loading dose with a maintenance infusion of 1 g/h. Treatment with magnesium sulfate requires at least level 2 care, with close monitoring, observation of urine output, respiratory rate, and deep tendon reflexes. After 34 weeks, the decision to deliver should be based on the condition of the mother and baby and any identifiable risk factors for progression of disease.

Eclampsia

Eclampsia is an obstetric emergency, and the first priority is to stabilize the mother through the application of a standardized ABCDE (airway, breathing, circulation, disability and evaluate) approach. Most eclamptic seizures are self-terminating; however, magnesium sulfate should be commenced as soon as possible if not already in progress, according to the protocol described above. If magnesium sulfate therapy has already commenced, a further bolus may be given, and the maintenance infusion may be increased to 2 g/h.⁵⁴ Hypertension should be controlled as outlined above, and the intravenous

Labetalol	Methyldopa	Hydralazine	Nifedipine
Beta blocker	Alpha 2 agonist	Vasodilator	Calcium channel blocker
Yes. Can be given intravenously for rapid control of severe resistant hypertension	Yes, including first trimester. Longest post-marketing surveillance data	Used intravenously for rapid blood pressure control. May be associated with neonatal thrombocytopenia. Long history of use. Avoid rapid intravenous bolus because of risk of hypotension	After 20 weeks. Available in short acting forms for rapid blood pressure control and long acting for long-term maintenance therapy. May be used simultaneously with magnesium sulfate. May inhibit labor
Manufacturers recommend avoid. Very small amounts in breast milk. No known evidence of harm (NICE)	No known evidence of harm (NICE)	Excreted in breast milk, at levels too low to be harmful	Manufacturers advise avoid, no known evidence of harm (NICE). Amounts in breast milk too small to be harmful.
Yes	NICE says avoid	Yes	Second line: Amlodipine
Tachycardia	Depression		Yes
	Reduced variability on CTG		Headache
	Methyldopa hepatitis		
Asthma	Mental health disorders		
	Hepatic disease		

route is preferable as the mother is likely to be in a state of altered consciousness. Recurrent seizures may warrant intubation and paralysis in order to maintain oxygenation.

Fetal monitoring is not a priority until the mother has been stabilized. Auscultation or cardiotocography will inevitably show a fetal bradycardia during and immediately after a seizure, but the primary interventions are seizure and blood pressure control, not delivery.

As soon as the mother's condition is judged stable she should be delivered by the most expedient route. In certain selected situations this may be achievable vaginally, but will most commonly be by Cesarean section. All women who have suffered an eclamptic seizure should be cared for in a level 3 setting.

Timing of delivery

The only cure for preeclampsia is delivery of the placenta, and all other management merely serves to stabilize the mother and enable the extension of pregnancy in the interests of the fetus. The timing of delivery is therefore guided by weighing the relative risks of preterm delivery to the fetus against the risks of continuing the pregnancy to the mother.

At any gestation, delivery is indicated for life-threatening maternal disease, which may take the form of severe refractory hypertension, eclampsia, placental abruption or rapidly deteriorating HELLP syndrome, or renal dysfunction. After the age of viability, delivery may also be indicated for serious fetal compromise with preterminal Doppler or CTG changes. If this is the primary indication for delivery at 24–26 weeks, a frank discussion with the parents regarding the poor prognosis for the baby, particularly in the setting of marked intra-uterine growth restriction, and the potential complications of preterm surgery, should be had before proceeding.

In all cases the mother should be stabilized before proceeding to delivery. Performing a category 1 Cesarean section immediately after an eclamptic seizure without full assessment of the mother and baby exposes her to severe risks associated with general anesthetic (failed intubation, severe hypertension, aspiration, further cerebral event), bleeding secondary to an undetected coagulopathy, and rushed, potentially complex, surgery with a higher risk of intraoperative damage to bladder and ureters. Once the mother is stable, any blood products ordered and the appropriate obstetric, anesthetic and neonatal team assembled, delivery can be accomplished safely, if it is indicated. If the patient is significantly preterm (<34 weeks) and delivery could be safely postponed for 12–24 hours, consideration should be given to the administration of corticosteroids for lung maturity.¹⁸

In the presence of stable disease without severe features before 34 weeks, delivery should not be undertaken. Between 34 and 37 weeks any features of worsening disease should prompt thorough review of the clinical case and consideration of delivery.

A clinical test to identify those women most at risk of serious adverse events in continued pregnancy would be invaluable to reduce the number of unnecessary preterm deliveries. Two models have recently been developed that may identify this group of patients. The fullPIERS model incorporates gestational age, chest pain or dyspnea, SpO₂, platelet count, creatinine, and aspartate transaminase and predicts adverse maternal outcomes within 48 hours and 7 days with an AUC (area under the curve) of 0.88 and >0.7 respectively.⁵⁵ This model has undergone external validation⁵⁶ and seems to perform well as a prediction tool but has not yet been tested in a clinical context as a decision making aid. A similar model has been developed in the context of low resource clinical settings incorporating physical findings and symptoms rather than the more specialized laboratory tests in the fullPIERS. The features included are parity, gestational age, systolic blood pressure, degree of proteinuria, vaginal bleeding with abdominal pain, headache and/or visual changes, and chest pain and/or dyspnea.⁵⁷ Predictive modeling along these lines may be improved in the future by the addition of biochemical or ultrasound markers and offer a significant opportunity for targeting intervention in a way that can optimize maternal and fetal outcomes.

Delivery need not be by Cesarean section if assessment shows a possibility of successful induction of labor with cervical ripening agents. Over half of all inductions before 35 weeks end in Cesarean section, and it would be inappropriate to continue an induction for 2–3 days in the presence of severe disease warranting delivery. However sometimes a vaginal delivery is achievable rapidly and may be preferable than the additional risks of bleeding, thrombosis, infection, and fluid management challenges associated with operative delivery.

After 37 weeks, any woman with gestational hypertension or mild to moderate disease should have delivery discussed with her. The HYPITAT⁵⁸ trial demonstrated that induction of labor at this gestation reduces the risk of adverse maternal events and carries no additional risk to the neonate. In addition, this strategy does not seem to increase the risk of Cesarean section, and the women most likely to benefit are those least favorable for induction.

The trial was conducted in a setting where women are not treated for hypertension <160/100 at term, and may

not be directly applicable to the UK population where antihypertensive therapy is offered for lower degrees of hypertension, as one of the outcomes was the occurrence of severe hypertension. It is also reasonable to offer antihypertensive treatment and continue pregnancy under close monitoring as long as blood pressure is controlled and there are no features of severe disease if that is the woman's wish.¹⁸ This should be clearly explained to the woman and, if she chooses to continue the pregnancy she should be offered regular follow-up in the hospital day-assessment unit, as outlined above, with regular fetal assessment, and a clear plan of care made for when induction of labor will be planned if no spontaneous labor has occurred.

Intrapartum care

Women with gestational hypertension or preeclampsia of any severity have a higher risk of placental insufficiency and subsequent fetal hypoxic stress during labor secondary to poor placental reserves. For this reason all women with hypertensive disorders in pregnancy should be advised to have continuous fetal monitoring in labor. Blood pressure should be measured hourly in labor, and any antihypertensive medication continued as previously prescribed. In women with severe preeclampsia, more frequent blood pressure measurement is required and consideration should be given to invasive monitoring, particularly if intravenous antihypertensive therapy is required.

An anesthetist should review every woman with hypertensive disease admitted in labor to assess her airway and make a contingency plan for emergencies. Early epidural or spinal analgesia reduces the risk of needing a general anesthetic for emergency intervention. Pharyngolaryngeal edema in preeclamptic patients increases the chances of failed intubation, and intubation increases the chances of severe hypertension and aspiration. Women with hypertensive disorders should not routinely receive a fluid preload prior to initiating epidural or spinal analgesia.¹⁸ Consideration should be given to the potential need for blood products based on the hematological and coagulation parameters as measured at the onset of labor. If platelets are $<50 \times 10^9/L$, falling rapidly, or there is associated coagulopathy, consideration should be given to ordering platelets and other blood products. Platelet transfusion is required if platelets fall below $20 \times 10^9/L$ around delivery, whatever the mechanism. There is no indication to limit the length of the second stage if the blood pressure is stable and well controlled. However, in the event of severe uncontrolled hypertension or neurological symptoms, elective instrumental delivery may be recommended.

Ergometrine and oxytocin are in common use as uterotonics for the active management of the third stage of labor. However, ergometrine should be avoided for women with known hypertensive disease of any kind, even if blood pressure is normal at the time of delivery. Several maternal deaths have been provoked by the hypertension associated with ergometrine use.⁴ This should not preclude the use of ergometrine in the event of severe postpartum hemorrhage at the discretion of senior clinical staff.

Postnatal care

Although delivery is the cure for preeclampsia and the related disorders, resolution is not immediate and many women may initially deteriorate after delivery, or re-present some days later with worsening disease. Women being managed in Level 2 or 3 care should be maintained there for at least 24 hours postpartum, and magnesium sulfate that has been commenced prior to delivery should be continued to 24 hours postdelivery.

Postpartum hypertension

In normal pregnancy, blood pressure falls immediately post-delivery and peaks 3–6 days postdelivery. In hypertensive women this is also the case, and women frequently experience a further spike in their blood pressure several days postpartum. In fact, 32%–44% of all eclampsia occurs postpartum.⁵⁹ Preeclampsia can present for the first time postpartum, and for that reason blood pressure measurement should continue to be part of the full postnatal check for all women, regardless of their history in pregnancy. There is no benefit in routine testing of urine for proteinuria because of the inevitable contamination of the urine with lochia that will render the results uninterpretable. If a woman with no previous history of preeclampsia presents with hypertension and other features of disease, a catheter specimen of urine for dipstick or PCR may be of limited use in establishing a diagnosis.

Other factors that can cause or exacerbate hypertension postpartum are pain, anxiety, the use of certain drugs (nonsteroidal anti-inflammatory drugs [NSAIDs], and ergometrine), and fluid overload in labor. These factors should be assessed and analgesia and fluid management adjusted as necessary prior to altering antihypertensive management. NSAIDs should be avoided in women with known hypertensive disease because of the risk of exacerbating both hypertension and any renal injury.

The same targets for control of hypertension apply as in pregnancy – the aim should be to control the blood pressure at less than 150/100 mmHg if on medication. If any new

features of severe disease develop, mothers should be moved to a higher level of care and consideration given to administering at least 24 hours of magnesium sulfate as eclampsia prophylaxis. Any woman with a new onset severe headache, with or without neurological symptoms, should be assessed to evaluate the possibility of postpartum stroke or venous thrombosis.

Choice of antihypertensive

No antihypertensive drugs are licensed for use in breast-feeding, so most evidence is based on observational studies and expert opinion. In addition to the drugs used in pregnancy, the ACE inhibitors Enalapril and Captopril have been shown to be safe and effective in breast-feeding women (Table 5). They are particularly appropriate for women needing renal or cardiac protection because of their pre-pregnancy comorbidities.

Methyldopa is the drug of choice for the Medicines and Healthcare Products Regulatory Agency (MHRA) because of a long history of use, but is usually avoided by clinicians because of its side-effect profile, including depression and sedation, as recommended by NICE.¹⁷

Outpatient management

If the blood pressure is stable and well controlled, and there are no other features of severe disease women may be discharged to community care. For the 1st week, blood pressure should be checked at least every other day, and then weekly. The antihypertensive medication can be reduced and then stopped by the primary care provider when target blood pressures are achieved.

For most women, hypertension will resolve within the 1st week postpartum.⁶⁰ Hypertension that persists more than 6 weeks postpartum usually represents a pathology not directly associated with pregnancy such as essential hypertension or underlying endocrine, neurological, or renal disease. These women should have their hypertension confirmed with ambulatory monitoring and referred for investigation for a secondary cause for their hypertension as suggested in the guidelines for new onset hypertension in young adults. Proteinuria that persists beyond 6–12 weeks postpartum may also warrant further investigation, particularly in the setting of early onset preeclampsia, the group of women most likely to have underlying renal disease.

Future health risks and screening

All women who have had a hypertensive complication in pregnancy should receive postnatal counseling regarding the management of future pregnancies. For women

with gestational hypertension, the risk of recurrence of hypertension in the next pregnancy is 16%–47% and the risk of preeclampsia is 2%–7%. For women with preeclampsia, the risk of recurrence is 16% if they delivered at term, 25% if they delivered before 34 weeks, and 55% if they delivered before 28 weeks.⁵⁹

These women should be advised to book early in their next pregnancy for consideration of starting low-dose aspirin as prophylaxis against preeclampsia. They should also have more frequent blood pressure and urine dipstick monitoring in pregnancy, particularly approaching the gestation at which symptoms commenced in the index pregnancy. Women on long-term antihypertensive therapy should be counseled to stabilize blood pressure on medications safe to use in the first trimester, prior to attempting to conceive.

Women who have had preeclampsia and delivered before 34 weeks should be screened for antiphospholipid syndrome.¹⁸ All women who have had any element of hypertensive disease in pregnancy or the puerperium have an increased risk of cardiovascular disease in the future. The associated adverse outcomes demonstrated by meta-analysis are increased risk of cardiovascular disease, chronic hypertension, venous thromboembolism, and cerebrovascular disease.^{9–12}

The obstetric team at discharge and the primary care physician in the community have an opportunity to counsel women at this point about their future risk and offer simple lifestyle modification suggestions to help reduce future risk. Weight loss, smoking cessation, low salt, and regular exercise may be recommended as a matter of common sense. However, no evidence yet exists that these measures can improve long-term outcomes in these women.

In conclusion, this review presents the current best practice in diagnosis and management of preeclampsia. New tools for early detection, prevention, and management of preeclampsia have the potential to revolutionize practice in the coming years.

Disclosure

The authors report no conflicts of interest in this work.

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