Pre-eclampsia and the anaesthetist

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Abstract

Pre-eclampsia is a multisystem disorder of pregnancy that forms an integral part of the spectrum known as hypertensive diseases of pregnancy, occurring after 20 weeks of gestation. Intracerebral haemorrhage, pulmonary, liver and renal dysfunction are recognized complications of pre-eclampsia that contribute to maternal morbidity and mortality. Measurement of specific maternal angiogenic factors such as placental growth factor (PlGF) and soluble FMS-like tyrosine kinase-1 (sFlt-1) may aid in the diagnosis of and management of this condition. Strict blood pressure control using anti-hypertensive medications, aspirin in the dose of 75–150 mg for prophylaxis antenatally, fluid restriction, magnesium sulphate for seizure prophylaxis and timely delivery remain the key strategies to decrease maternal morbidity. Neuraxial anaesthesia, provided the coagulation status is normal is the preferred technique for delivery. If general anaesthesia is used, emphasis should be on preparing for a difficult airway and ablation of the pressor response of laryngoscopy and intubation.

Keywords Anaesthesia; intracranial haemorrhage; magnesium sulphate; neuraxial; pre-eclampsia; pregnancy

Royal College of Anaesthetists CPD Matrix: 2B01, 2B02, 2B03, 2B05, 3B00

Learning objectives

After reading this article, you should be able to:

- classify pre-eclampsia
- state the risk factors and the manifestations of pre-eclampsia
- describe the anaesthetic management of a woman with pre-eclampsia

Introduction

Pre-eclampsia is a multisystemic hypertensive disorder occurring after 20 weeks of pregnancy. The incidence of pre-eclampsia in UK is estimated to be around 2–8%.[1] The mortality from hypertensive disorders of pregnancy has been significantly reduced in the period between 2009–2011 and 2012–2014. Eleven women died from 2009 to 2011 (0.42 per 100,000 maternities) whereas only three died from 2012 to 2014 (0.11 per 100,000 maternities). This is a positive reflection on the standard and provision of care for women with hypertensive disorders of pregnancy in UK. Intracranial haemorrhage remains the most common cause of death followed by hepatic complications. Reassuringly, no women died in relation to inappropriate fluid management (pulmonary oedema and renal failure).[2] Though mortality from pre-eclampsia is decreasing, maternal morbidity due the multisystemic nature of the disease and fetal morbidity (prematurity, small for gestation age (SGA), respiratory distress syndrome, stillbirth and death) necessitate a multidisciplinary approach in the diagnosis and management of this condition.

Diagnostic criteria

The updated diagnostic criteria for pre-eclampsia are listed in Box 1.

Eclampsia is defined as seizures that cannot be attributed to other causes in a woman with pre-eclampsia. It occurs in <1% of women with pre-eclampsia.

Pre-eclampsia needs to be differentiated from gestational hypertension, which is characterized by new onset of hypertension (>140/90 mmHg) after 20 weeks' gestation without significant proteinuria or end-organ damage and return of blood pressure within 6–12 weeks postpartum. Progression from gestational hypertension to pre-eclampsia occurs in almost 25% of women.

Chronic hypertension refers to hypertension before pregnancy or before 20 weeks' gestation without a known cause and persists after 12 weeks postpartum. It complicates between 1% and 5% of pregnancies but this is on the rise with increasing maternal age, increasing obesity and increase in vitro fertilization (IVF) pregnancies.

Pre-eclampsia superimposed on chronic hypertension is when a woman with chronic hypertension develops new signs or symptoms of pre-eclampsia.

Classification

Pre-eclampsia can be classified based on blood pressure measurements or based on gestation age though now it is agreed that there may be an overlap of these two.

Blood pressure measurements:

- mild – systolic blood pressure (SBP) 140–149 and or diastolic blood pressure (DBP) 90–99 mmHg
- moderate – SBP 150–159 or DBP 100–109 mmHg
- severe – SBP ≥160 mmHg or DBP ≥110 mmHg.

The other way of classifying is early-onset and late-onset pre-eclampsia as per gestation age:

- Early-onset pre-eclampsic (<34 weeks' gestation) – Early-onset pre-eclamptic women are more likely to develop severe pre-eclampsia (<1% of pre-eclamptic patients), HELLP syndrome (haemolysis, elevated liver enzymes, low platelet count) and eclampsia. Their fetuses are at higher risk of preterm delivery and death compared to late-onset pre-eclampsia. There is strong association between

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Pre-eclampsia (diagnostic criteria)

Hypertension diagnosed after 20 weeks of gestation, with previous normal blood pressure (BP), which returns to normal within 6—12 weeks postpartum.

1) High blood pressure

Systolic BP (SBP) ≥ 140 mmHg or
Diastolic BP (DBP) ≥ 90 mmHg on two occasions at least 4 hours apart or
SBP ≥160 mmHg or DBP ≥110 mmHg, confirmed within a short interval.
(Note — Automated devices may under estimate BP, Korotkoff phase 5 should be used to determine DBP)

PLUS

Proteinuria

≥ 300 mg per 24 hour urine collection or
Protein/Creatinine ratio ≥30 mg/mmol or
Dipstick reading of 1+ (only if other quantitative methods unavailable)

Or new onset of:

2) High blood pressure

Systolic BP (SBP) ≥ 140 mmHg or
Diastolic BP (DBP) ≥ 90 mmHg on two occasions at least 4 hours apart or
Systolic BP ≥ 160 mmHg or Diastolic BP ≥ 110 mmHg, confirmed within a Short interval.

PLUS

Any of the following severe features:

- Thrombocytopenia: Platelet count <100 x 109/L
- Renal Insufficiency: Serum creatinine >97 mmol/L or 2 x serum concentrations in the absence of other renal disease
- Impaired liver function: 2x normal blood concentrations of liver transaminases and/or severe persistent right upper quadrant or epigastric pain unresponsive to medication and without alternative diagnosis.
- Pulmonary oedema
- Cerebral/visual symptoms
- Utero-placental involvement

Box 1

African-American race, congenital anomalies and pre-existing hypertension with early-onset pre-eclampsia.

ii) Late-onset (≥34 weeks' gestation) — younger maternal age, nulliparity, diabetes mellitus and other maternal co-morbidities are associated with late-onset disease.

Pathogenesis, aetiology and risk factors

The main risk factors for pre-eclampsia are highlighted in Box 2[3]

The pathogenesis includes maternal and placental factors. During normal pregnancy, cytotrophoblasts invade the inner third of the myometrium, and spiral arteries lose their endothelium and most of their muscle fibers leading them to become low

Risk factors for pre-eclampsia

High risk factors (aspirin recommended if one or more present)

- History of pre-eclampsia especially when accompanied by adverse outcomes
- Type 1 or 2 diabetes
- Chronic hypertension
- Renal disease
- Autoimmune disease/antiphospholipid antibodies/factor V Leiden

Moderate risk factors (aspirin recommended if two or more present)

- Age >35 years
- First pregnancy
- Obesity
- Family history of pre-eclampsia (mother or sister)
- Pregnancy interval >10 years
- Socio-demographic characteristics (African race)

Box 2

resistance vessels. In pre-eclampsia this invasion by trophoblasts is deficient. This leads to inadequate perfusion of the placenta and release of substances such as free radicals, oxidized lipids, prostaglandins, cytokines and endothelial dysfunction. Inadequate perfusion of placenta also results in a decrease in pro-angiogenic factors, i.e. vascular endothelial growth factor (VEGF), placental growth factor (PlGF), placental protein 13(PP-13) and pregnancy associated plasma protein A (PAPP-A), and an increase in anti-angiogenic factors, i.e. soluble FMS-like tyrosine kinase1 (sFlt1) and soluble endoglin (sEng) and asymmetric dimethyl arginine (ADMA).[4] These anti-angiogenic factors cause maternal hypertension and other systemic changes.

Multiple theories are postulated for the abnormal placentation seen in pre-eclampsia. Genetic and immunological seem to be the most commonly accepted and are possibly interlinked. Factors favouring genetic theory include: family history of pre-eclampsia on either maternal or paternal side and a meta-analysis in 2013, which identified seven relevant gene variants in or near six genes associated with pre-eclampsia. More than 40% of pre-eclamptic women do not respond to traditional antihypertensive therapy. This has led to identify genetic polymorphisms of responders and non-responders.

Factors favouring the immunological theory include: limited exposure to paternal antigen supports immunological theory, as is seen in teenage mothers, conception by donor insemination, nulliparity and increased interpregnancy interval. A higher incidence of pre-eclampsia in autoimmune diseases supports immunological mechanisms. Meta analyses concluded that conception through oocyte donation has more than twofold higher rate of pre-eclampsia than women who conceived through other methods and more than fourfold higher rate of pre-eclampsia than women who conceived naturally. Recently it has been suggested that this condition could actually be a reflection of mismatch between the stimulus of fetal oxygen demand and response of maternal oxygen supply. Increased fetal oxygen demand as seen in conditions such as multi-parity and macrosomia and decreased maternal oxygen supply as seen in conditions such as chronic hypertension, diabetes, obesity, autoimmune conditions and renal disease lend support to this theory.[5]

Screening for pre-eclampsia

Patients at risk of developing pre-eclampsia are usually identified by the maternal risk factors based on NICE (National Institute for Health and Care Excellence) guidelines and appropriate aspirin prophylaxis instituted for this cohort. The SPREE (Screening Program for Pre-eclampsia) study highlighted that recording of maternal characteristics, medical history and measurements of mean arterial pressure (MAP), uterine artery pulsatility index (UtA-PI), serum placental growth factor (PlGF) and serum pregnancy-associated plasma protein-A (PAPP-A) in the first trimester can lead to better identification of women at high risk of developing preterm pre-eclampsia when compared to using NICE guidance and substantially reducing such risk through the prophylactic use of the appropriate dose of aspirin.[6]

In a prospective multicentre study of 287 women with suspected pre-eclampsia at <35 weeks' gestational age, low placental growth factor PIGF (<5th percentile or <100 pg/ml) was found to have high sensitivity and negative predictive value for determining which women are likely to need delivery within 14 days.[7] A recent study highlighted than a sFlt-1/PlGF ratio of 38 and below can rule out the development of pre-eclampsia within the next week with a negative predictive value of 99.3%, whereas a ratio above this cut-off value predicts the development of pre-eclampsia within 4 weeks with a positive predictive value of 36.7%.[8]

Prevention of pre-eclampsia

The proposed primary preventive therapy like oral antioxidants (i.e. vitamin C or E), dietary (e.g. salt) and bed rest lack proven efficiency. Recently, the high-dose folic acid trial to prevent pre-eclampsia failed to show any benefit in preventing this condition in women at high risk of developing pre-eclampsia.[9]

Aspirin remains the main-stay drug for prevention of pre-eclampsia. A dose of 75 mg/day has been recommended by NICE in high-risk patients (one high risk factor), and women with two or more moderate risk factors from 12 weeks of gestation till the birth of the baby.

Recent systematic review have highlighted that doses of 150 mg/day commenced from under 16 weeks till delivery is associated with a significant reduction in the prevention of pre-eclampsia, severe pre-eclampsia and fetal growth restriction.[10]

In countries with low dietary calcium (<600 mg/day), oral calcium intake of >1 g/day can reduce the incidence of pre-eclampsia though this regime is not used in UK.

Manifestations of pre-eclampsia

The end-organ damage that pre-eclampsia can potentially cause is highlighted in Table 1.

Management of pre-eclampsia

General management

To optimize patient outcome, early multidisciplinary management involving the anaesthetist, obstetrician and neonatologist should be initiated. Obstetric units in the UK admit women with pre-eclampsia routinely in obstetric high dependency units. The only curative treatment of the disease is delivery of the fetus and placenta; however this must be balanced with the risks of delivering a preterm baby.

Control of hypertension

Inadequate blood pressure control leading to intracranial haemorrhage still remains one of the key factors leading to maternal death. A SBP of ≥150 mmHg must be treated immediately within the hospital setting. Aim for a SBP <150 mmHg and for DBP between 80 and 100 mmHg.

Anti-hypertensive therapy with oral labetalol, nifedipine or alpha methyldopa is used for persistent mild to moderate hypertension during pregnancy. They reduce the risk of developing severe hypertension by 50% but with little evidence of a difference in the risk of pre-eclampsia. Angiotensin-converting enzyme inhibitors and angiotensin II receptor antagonists are contraindicated during pregnancy.

The treatment of severe hypertension is strongly recommended to minimize maternal and fetal morbidity. In 2013, a Cochrane meta-analysis (35 RCTs — 3573 women) showed insufficient evidence to preferentially recommend one antihypertensive agent over another in severe pre-eclampsia.[11] It concluded that until better evidence is available, the choice of antihypertensive should depend on the clinician's experience and familiarity with a particular drug; on what is known about adverse effects; and on women's preferences. The acceptable agents include labetalol, nifedipine and hydralazine. The first choice agent is oral labetalol. This can be given even before venous access is obtained. Labetalol is contraindicated in severe asthma and use in caution in women with pre-existing cardiac disease. The second-line anti-hypertensive medication (nifedipine or hydralazine) should be considered if labetalol has not reduced BP <160/105 mmHg. If oral therapy fails to achieve the desired outcome, intravenous (IV) therapy with labetalol and or hydralazine should be initiated. IV nicardipine is one of the newer agents that could be used to treat severe pre-eclampsia.

Treatment and prophylaxis of eclampsia

The Magpie trial has shown a 58% decrease in relative risk of eclampsia, when magnesium sulphate ($MgSO_4$) is used for seizure prophylaxis.[12] The regime in severe pre-eclampsia, along with the recommended monitoring and side effects are listed in Table 2.

$MgSO_4$ infusion when used prophylactically should continue for 24 hours postpartum. More recently it has been shown that there was no difference in maternal outcome when the infusion was stopped only 12 hours postpartum.

Fluid therapy

Fluid balance is aimed at avoiding fluid overload. Total IV input from all sources should be limited to 80 ml/hour. If syntocinon is used it should be in high concentration and the volume of fluid included in the total input.

Thromboprophylaxis

Women with pre-eclampsia are at increased risk of thromboembolic disease. All patients should have anti-embolic stockings and/or flowtrons and/or low molecular weight heparin (LMWH) while immobile as recommended by the Royal College of Obstetricians and Gynaecology (RCOG) guidelines.[13]

Manifestations of pre-eclampsia

Organ	Manifestation	Implication for Anaesthetists & Relevant Investigations
Central nervous system	Headache, visual changes, blindness, hyper-reflexia, clonus, cerebral oedema and seizures (eclampsia – 3/10000 deliveries). Seizures could occur antepartum (38–53%), intrapartum (18–36%) or postpartum (11–44%).	Complete neurological examination, fundoscopy Magnesium sulphate therapy CT scan head if recurrent fits
Airway	Oro-pharyngeal, laryngeal oedema	Assess airway, prepare for a difficult intubation in theatre
Respiratory	Pulmonary oedema, acute respiratory distress syndrome (ARDS)	Strict fluid balance, oxygen, fluid restriction, frusemide
Cardiovascular	Hypertension, pericardial effusions, pulmonary oedema Increased contractility, increased stroke Volume with vasoconstriction Diastolic dysfunction	Echocardiography, anti-hypertensive therapy, arterial line, CVP monitoring rarely necessary.
Haematological	HELLP – 1.6/10000 pregnancies (haemolysis, elevated liver enzymes low platelets) syndrome – 8% and 24% of cases with severe pre-eclampsia, DIC (disseminated intravascular coagulation) ELLP (elevated liver enzymes low platelets) – 1/10000 pregnancies	Monitor full blood count, peripheral smear, platelet count $<100{,}000 \times 10^9$/l, coagulation profile, Thrombo-elastography, LFTs (AST, ALT >70 IU, LDH >600 IU, Bilirubin >20 umol/l) and serum fibrinogen. Steroid therapy currently not recommended.
Hepatobiliary	Subcapsular haematoma, hepatic rupture	Monitor LFTs, US abdomen
Renal	Severe proteinuria >5g, oliguria and renal failure	Input output monitoring, serum uric acid Watch out for increasing metabolic acidosis and hyperkalemia
Uteroplacental	Oligohydroamnios, placental abruption	Antepartum haemorrhage Postpartum haemorrhage
Fetus	IUGR, pre-term birth, still birth	Fetal movements, fetal biophysical profile, amniotic fluid status, uterine artery Doppler measurements, uterine artery pulsatility index, CTG Antenatal steroids to enhance lung maturity Magnesium sulphate provides neuroprotection in preterm

CT, computerized tomography; SVR, systemic vascular resistance; AST, aspartate transaminase; ALT, alanine transaminase, US, ultrasound, IUGR, intrauterine growth retardation; CVP, central venous pressure; CTG, cardiotocography; LFT, liver function test.

Table 1

Postpartum, LMWH should be given daily following delivery until fully mobile, or for 10 days if delivered by Caesarean section. If the patient has had regional anaesthesia, LMWH should be given 4–6 hours after spinal or epidural catheter removal.

Monitoring

Patients suffering from severe pre-eclampsia should be monitored preferably in a high dependency unit. Monitoring should include regular BP measurements (every 15 minutes until stable, then half hourly), pulse oximetry and hourly urine output along with a fluid balance chart. Intra-arterial blood pressure monitoring is recommended in severe cases, where there is poor BP control, in patients on IV anti-hypertensive medication or when non-invasive BP monitoring is difficult. Echocardiography is recommended in patients who develop pulmonary oedema.

Laboratory tests include full blood count, clotting studies, serum electrolytes, renal and liver function tests repeated every 12 hours while on the protocol. In the event of clinical deterioration, more frequent testing may be required, e.g. every 6 hours.

Thromboelastography (TEG) and platelet function analyzer (PFA-100) can be used to monitor platelet function especially in thrombocytopenia and cases of HELLP syndrome. The K time, α

angle and MA (maximum amplitude) differ with worsening pre-eclampsia disease severity, indicating slower clot strengthening, and impaired fibrin cross-linking and clot strength on TEG. Increasing severity of pre-eclampsia was associated with increasing prolongation of closure time (CT), even in the presence of normal platelet counts on PFA 100.

Fetal wellbeing assessment involves continuous CTG, growth scan, liquor assessment and umbilical artery Doppler flow velocity waveforms.

Analgesia

The gold standard for labour analgesia in pre-eclampsia is epidural analgesia, although combined-spinal epidural (CSE) techniques have been also used. Epidural analgesia helps stabilize BP by dampening pain-mediated hypertensive responses. The presence of a functioning epidural catheter also allows for surgical anaesthesia for a caesarean section hence avoiding the risks of general anaesthesia (GA).

If neuraxial analgesic methods are contraindicated, a relatively recent option is remifentanil patient-controlled analgesia. Due to its quick onset and offset times, it is well suited to provide rapid analgesia for labour pain. Although a high proportion crosses the placenta, this is rapidly metabolized such that the risk of neonatal respiratory depression is low. Appropriate monitoring, continuous oxygen supplementation and one-to-one nursing should be in place due to the risk of maternal respiratory depression.

Postpartum haemorrhage (PPH)

Pre-eclampsia is a recognized risk factor for PPH. In the case of PPH, mechanical methods and pharmacological therapy with concentrated syntocinon (slow bolus and infusion) and prostaglandins (misoprostol and prostaglandin F2 analogues) should be considered. Ergometrine is contraindicated as it can precipitate a hypertensive crisis.

Anaesthetic management

Appropriate pre-operative assessment is mandatory in this group of patients with emphasis on airway assessment, blood pressure control and coagulation status. The preferred anaesthetic technique for caesarean section is neuraxial anaesthesia as it avoids the risks of a GA provided there are no contraindications. The options are single-shot spinal anaesthesia (SA), CSE and epidural anaesthesia. There is no evidence to indicate that any one of these is more favourable than the others. Low-dose aspirin (150 mg) does not increase the risk of neurological complications.[14]

SA and CSE can produce a period of hypotension although there is no evidence of this having any adverse effects on the mother or fetus. If anything, hypotension is less common compared to the normal pregnant population. It should be managed with vasopressors (e.g. phenylephrine) titrated to effect. Epidurals produce less hypotension; however, they have a slower onset time and the block produced is less reliable than SA.

Neuraxial techniques are contraindicated if patients are coagulopathic, one of the features of severe pre-eclampsia. Although there is no absolute cut off regarding the lower limit of platelet count, figures quoted are usually around the 80×10^9/L mark. The trends seem more important than an absolute value. Other indications of a GA include severe fetal distress, placental abruption, eclampsia and severe pulmonary oedema.

The aims with a GA are:

- Prepare for a difficult endotracheal intubation.
- Attenuate the pressor response to laryngoscopy, intubation, skin incision and extubation, which can lead to intra cranial haemorrhage and cardiac failure with pulmonary oedema.

A number of IV drugs have been used: alfentanil, remifentanil, fentanyl, esmolol, labetalol, glyceryl trinitrate (GTN), lidocaine and magnesium sulphate.

$MgSO_4$, can prolong the effects of non-depolarizing muscle relaxants and neuromuscular monitoring is recommended. The neonatologist should be informed if opioids have been given to attenuate pressor response.

Postpartum care

Blood pressure, urine output, platelet count, liver function tests and serum creatinine should be monitored post-delivery. Non-steroidal analgesics should be avoided in pre-eclampsia. Fluid restriction and anti-hypertensive therapy should be continued with the aim to decrease BP <150/100 mmHg.

Prior to hospital discharge, patients should be asymptomatic, BP $\leq$ 149/99 mmHg and blood tests stable or improving. A care plan should be made including follow up with appropriate health professional, BP monitoring and management and symptoms requiring medical review.

Magnesium sulphate regime

$MgSO_4$ regime	Monitoring	Side effects and antidote
Prophylaxis and treatment: Loading dose — 4 g intravenously (IV) over 5—10 minutes followed by a continuous infusion of 1 g/h for 24 hours or until 24 hours after delivery — whichever is the later If seizures occur a further 2 g of IV $MgSO_4$ is given and infusion increased to 1.5 g/h	Pulse, BP, ECG, Respiratory rate, pulse oximetry, hourly urine output and deep tendon reflexes/Clonus (every 4 hours) Monitoring Mg levels is not necessary with this regime If oliguria or renal dysfunction the infusion is decreased or stopped and Mg levels measured Toxicity apparent with Mg level >3.5 mmol/l	Flushing, nausea and vomiting, muscle weakness, absent or reduced tendon reflexes, respiratory depression, headache, hypotension, palpitations, dizziness, drowsiness or confusion $MgSO_4$ also potentiates neuromuscular blocking agents The antidote is 10 ml of 10% calcium gluconate given slowly intravenously

Table 2

All women should have a medical review 6–8 weeks after delivery and if anti-hypertensive treatment is still required, the woman should be referred for further investigation of cardiovascular and renal abnormalities. Women should also be informed of the risk of developing pre-eclampsia in future pregnancies (1 in 6 women will have it again in a future pregnancy) and the increased risk of developing hypertension and its screening in later life. ◆

REFERENCES

1 The Royal College of Obstetricians and Gynaecologists. Available from: https://www.rcog.org.uk/globalassets/documents/patients/patient-information-leaflets/pregnancy/pi-pre-eclampsia.pdf (accessed 25 March 2019).

2 On behalf of MBRRACE-UK. In: Knight M, Nair M, Tuffnell D, et al., eds. Saving lives, improving mothers' care – surveillance of maternal deaths in the UK 2012-14 and lessons learned to inform maternity care from the UK and Ireland confidential enquiries into maternal deaths and morbidity 2009-14 2016. Oxford: National Perinatal Epidemiology Unit, University of Oxford. Available from: https://www.npeu.ox.ac.uk/downloads/files/mbrrace-uk/reports/MBRRACE-UK%20Maternal%20Report%202016%20-%20website.pdf (accessed 25 March 2019).

3 National Institute for Health and Care Excellence NICE. Hypertension in pregnancy: the management of hypertensive disorders during pregnancy. Clinical guideline 107. January 2011. Available from: https://www.nice.org.uk/guidance/cg107, (accessed 25 March 2019).

4 Powe CE, Levine JR, Karumanchi RA. Pre-eclampsia, a disease of the maternal endothelium:the role of antiangiogenic factors and implications for later cardiovascular disease. *Circulation* 2011; **123:** 2856–69.

5 Dennis AT, Castro JM. Hypertension and haemodynamics in pregnant women – is a unified theory for pre-eclampsia possible? *Anaesthesia* 2014; **69:** 1183–9.

6 Tan MY, Wright D, Syngelaki A, et al. Comparison of diagnostic accuracy of early screening for pre-eclampsia by NICE guidelines and a method combining maternal factors and biomarkers: results of SPREE. *Ultra Obstet Gynecol* 2018; **51:** 743–50.

7 Chappell L, Duckworth S, Seed P, et al. Diagnostic accuracy of placental growth factor in women with suspected pre- eclampsia. *Circulation* 2013; **128:** 2121–31.

8 Zeisler H, Llurba E, Chantraine F, et al. Predictive value of the sFlt-1:PlGF ratio in women with suspected pre-eclampsia. *N Engl J Med* 2016; **374:** 13–22.

9 Wen SW, White RR, Rybak N, et al. Effect of high dose folic acid supplementation in pregnancy on pre-eclampsia (FACT): double blind, phase III, randomised controlled, international, multicentre trial. *Br Med J* 2018; **362:** k3478. https://doi.org/10.1136/bmj.k3478.

10 Roberge S, Nicolaides K, Demers S, Hyett J, Chaillet N, Bujold E. The role of aspirin dose on the prevention of pre-eclampsia and fetal growth restriction: systematic review and meta-analysis. *Am J Obstet Gynecol* 2017; **216:** 110–20.

11 Duley L, Meher S, Jones L. Drugs for treatment of very high blood pressure during pregnancy (review). *Cochrane Database Syst Rev* 2013; **31:** 7.

12 The Magpie Trial Collaboration Group. Do women with pre-eclampsia, and their babies, benefit from magnesium suphate? The Magpie trial: a randomised placebo-controlled trial. *Lancet* 2002; **359:** 1877–90.

13 Royal College of Obstetricians and Gynaecologists. Reducing the risk of thrombosis and embolism during pregnancy and the puerperium. Guideline 37a, April 2015.

14 Vela Vásquez RS, Peláez Romero R. Aspirin and spinal haematoma after neuraxial anaesthesia: myth or reality? *Br J Anaesth* 2015; **115:** 688–98.