



GPs have key role in identifying women at risk of pre-eclampsia

McEwan M, Day A, Girling J. GPs have key role in identifying women at risk of pre-eclampsia.
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Abstract

Pre-eclampsia is an important cause of maternal morbidity and mortality. It is a multisystem disorder of pregnancy characterised by new onset hypertension after 20 weeks' gestation, usually accompanied by proteinuria. Women with either one high risk factor or two or more moderate risk factors for the development of pre-eclampsia should take 75-150 mg of aspirin daily from 12 weeks' gestation until delivery. If a urine dipstick is positive for protein, the amount should be quantified: a protein: creatinine ratio ≥ 30 mg/mmol is abnormal. There should be a high index of suspicion for pre-eclampsia if there is biochemical disturbance consistent with the diagnosis or evidence of fetal growth restriction when plotted on a customised growth chart. Women with severe hypertension ($\geq 160/110$ mm Hg), new onset hypertension with $\geq 1+$ proteinuria or any red flag symptoms should be referred for urgent obstetric review (within 4 hours). Women with new isolated non severe hypertension or $\geq 1+$ proteinuria should be referred for obstetric review, ideally within 24 hours. On discharge from hospital, women who are taking antihypertensive medication should have their BP measured every 1-2 days for 2 weeks until it has normalised. Women should see their GP 2 weeks postnatally to assess the need for ongoing antihypertensive treatment. BP, urinary protein and blood results (if previously abnormal) should be reviewed by their GP or hospital specialist at 6-8 weeks after birth.

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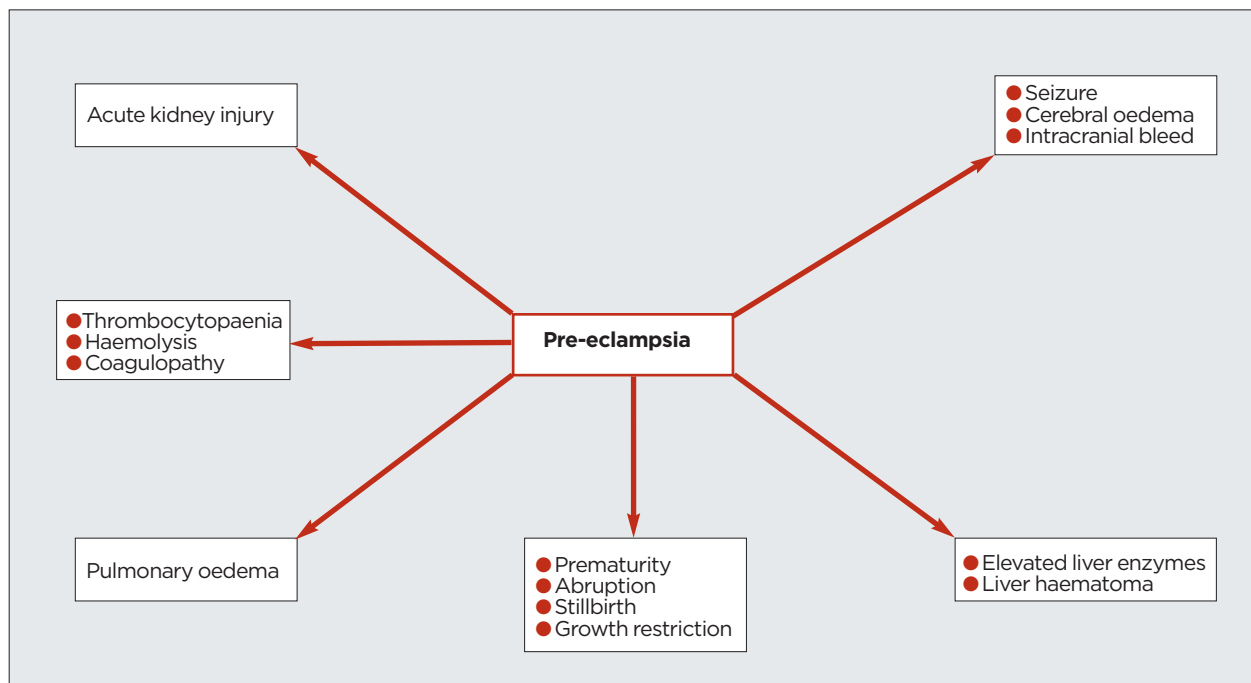
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FIGURE 1

Potential
complications of
pre-eclampsia



What are the risk factors for pre-eclampsia?



PRE-ECLAMPSIA IS AN IMPORTANT CAUSE OF MATERNAL MORBIDITY AND MORTALITY.¹

The incidence of pre-eclampsia is around 4% and is thought to be increasing.²

It is a multisystem disorder of pregnancy characterised by new onset hypertension after 20 weeks' gestation, usually accompanied by proteinuria.³ Other clinical features will depend on the systems involved (see figure 1, above).

The exact pathophysiology is not known but is thought to be a multifactorial interplay between the placenta and the maternal immune system.⁴

RISK FACTORS

Women with risk factors for pre-eclampsia should take 75-150 mg of aspirin from 12 weeks' gestation until the birth of the baby, see table 1, right.

There is some evidence that vitamin D supplementation in pregnancy has a role in the prevention of pre-eclampsia.

How should diagnosis be confirmed?

Table 1

Low dose aspirin therapy for women with risk factors for pre-eclampsia, adapted from NICE NG133⁵

Low dose aspirin is required from 12 weeks' gestation until birth for women with the following risk factors

High risk factors (one or more)

- Previous hypertensive disorder in pregnancy
- Autoimmune disease
- Type 1 or type 2 diabetes
- Chronic hypertension
- Chronic kidney disease

Moderate risk factors (two or more)

- First pregnancy
- Age 40 years or older
- BMI ≥ 35 kg/m² at first visit
- Interpregnancy interval > 10 years
- Family history of pre-eclampsia
- Multiple pregnancy

What are the long-term complications?

CHRONIC HYPERTENSION

Women with a diagnosis of chronic hypertension should have easy access to reliable contraception and be offered referral for pre-pregnancy counselling with a specialist in hypertensive disorders in pregnancy should they wish to conceive.⁵

If this has not already been carried out, women with chronic hypertension who are planning a pregnancy should be investigated for secondary causes of hypertension prior to conception.

Women taking angiotensin converting enzyme inhibitors (ACEi), angiotensin 2 receptor blockers (ARB) or diuretics should be advised to stop these medications within two days of confirmation of pregnancy as there is evidence of a risk of teratogenesis, and should be offered a suitable alternative, such as labetalol, nifedipine or methyldopa.^{5,6} Women should be encouraged to maintain a healthy weight, stop smoking and remain active.

There is a physiological fall in blood pressure (BP) of 15-20 mmHg during »

the first trimester of pregnancy, which is sustained until a return towards normal occurs in the third trimester. Therefore, women on antihypertensives may need to reduce the dose in early pregnancy. Furthermore, if the BP appears to be 'normal' at booking, the patient may in fact have chronic hypertension and may need treatment and close monitoring.

Pregnant women with chronic hypertension who are not already receiving antihypertensive medication should be offered treatment if they have a sustained systolic BP ≥ 140 mmHg or diastolic ≥ 90 mmHg. The treatment target should be $\leq 135/85$ mmHg.

ASSESSMENT

All women should be assessed for pre-eclampsia at every visit from 20 weeks' gestation. This should include: BP; urine dipstick for protein; fetal heart rate and from 26 weeks' gestation, symphyseal-fundal height (plotted on a customised growth chart).

If urine dipstick is positive for protein, the amount should be quantified. The traditional 24-hour urine collection has been superseded by a measurement of protein: creatinine ratio on a spot urine sample with the result available the same day; values ≥ 30 mg/mmol are

classed as abnormal.⁵ Once significant proteinuria has been confirmed, it is not usually necessary for the test to be repeated.

Other biochemical features that may be suggestive of pre-eclampsia include a rise in creatinine to ≥ 90 $\mu\text{mol/L}$; a fall in platelet count to below $150 \times 10^9/\text{L}$ or a rise in serum alanine transaminase to above 70 IU/L.⁵

Women should also be assessed for other signs and symptoms of pre-eclampsia (see red flags below).

Red flag symptoms include:

- Headache
- Vomiting
- Visual disturbance
- Epigastric pain
- Sudden onset swelling
- Shortness of breath
- Hyperreflexia

REFERRAL

Women with severe hypertension ($\geq 160/110$ mmHg), new onset hypertension with $\geq 1+$ proteinuria or any red flag symptoms should be referred for urgent obstetric review (within 4 hours). Those presenting with new isolated non severe hypertension or $\geq 1+$ proteinuria should be referred for obstetric review, ideally within 24 hours.

DIAGNOSIS

Traditionally, the diagnosis of pre-eclampsia was made only once a combination of hypertension and proteinuria had been confirmed. However, it is increasingly recognised that pre-eclampsia can present in the absence of significant proteinuria.⁵

There should be a high index of suspicion for pre-eclampsia in women presenting beyond 20 weeks' gestation with new onset, or deterioration, of chronic hypertension without proteinuria, if there is biochemical disturbance consistent with the diagnosis (see above) or evidence of fetal growth restriction. These women should be referred for obstetric input in order to consider further investigations regarding a possible diagnosis of pre-eclampsia.

Testing for placental growth factor (PIGF) is often done as a point of care test with the result available within an hour. The PELICAN trial demonstrated that this is a reliable rule-out test⁷ and the PARROT trial showed that PIGF can predict those women that are at high risk of requiring early delivery and can aid decisions regarding place of care and level of monitoring.⁸

PIGF testing reduces the time to diagnosis of pre-eclampsia and the incidence of adverse maternal outcomes.⁸ NICE recommends using this as a one-off test between 20 and 35 weeks' gestation.⁹

The PARROT-2 trial is currently underway to ascertain whether serial measurement could be of clinical benefit.¹⁰

For women in whom pre-eclampsia has been diagnosed, NICE recommends validated risk stratification scores (fullPIERS and PREP-s)^{5,11,12} in secondary care for predicting maternal adverse outcomes in early onset pre-eclampsia and helping to time delivery, although unlike PIGF testing, these risk scores do not predict fetal outcome.

MANAGEMENT

NICE guidance on the management of pre-eclampsia is summarised in table 2, left. There are regional differences in approach, most commonly regarding place of care. Many units routinely admit all patients with pre-eclampsia because of concerns about rapid deterioration, specifically placental abruption, eclampsia and intracranial haemorrhage (the main mechanism of maternal death in the context of pre-eclampsia).¹³

NICE recommends admitting women at high risk of adverse events, those with severe hypertension or where there are

Table 2

Management of pre-eclampsia, adapted from NICE NG133⁵

	Moderate hypertension 140/90-159/109 mmHg	Severe hypertension $\geq 160/110$ mmHg
Admission	If clinical concerns or high risk of adverse events	Admit
Treatment	Target for BP treatment $\leq 135/85$ Offer if BP remains 140/90 or higher	Target for BP treatment $\leq 135/85$ Offer to all women
BP measurement	At least every 48 hours until target BP reached, more often if an inpatient	Every 15-30 min until $< 160/110$ then at least 4 times a day
Blood tests (full blood count, liver function, renal function)**	At presentation and twice weekly	At presentation and three times a week ***
Fetal assessment	Fetal heart auscultation at every visit Ultrasound for growth at diagnosis and then every 2 weeks if it remains normal Cardiotocogram at diagnosis and then if clinically indicated	

**Clotting screen, serum urate and lactate dehydrogenase (if haemolysis is suspected) may occasionally be clinically useful

***In practice, frequency of blood testing is dependent on the clinical context and may be as frequent as every 6 hours in severe cases

key points

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Pre-eclampsia is an important cause of maternal

morbidity and mortality. It is a multisystem disorder of pregnancy characterised by new onset hypertension after 20 weeks' gestation, usually accompanied by proteinuria. Women with either one high risk factor or two or more moderate risk factors for the development of pre-eclampsia should take 75-150 mg of aspirin daily from 12 weeks' gestation until delivery.

Women with chronic hypertension who are planning

a pregnancy should be investigated for secondary causes of hypertension prior to conception. As there is a potential risk of teratogenesis, women taking ACEi, ARB or diuretics should stop these medications within 2 days of confirmation of pregnancy. They should be offered a suitable alternative such as labetalol, nifedipine or methyldopa.

If a urine dipstick is positive for protein, the amount should

be quantified: a protein: creatinine ratio ≥ 30 mg/mmol is abnormal. There should be a high index of suspicion for pre-eclampsia if there is biochemical disturbance consistent with the diagnosis or evidence of fetal growth restriction when plotted on a customised growth chart.

Women with severe hypertension ($\geq 160/110$ mm Hg),

new onset hypertension with $\geq 1+$ proteinuria or any red flag symptoms should be referred for urgent obstetric review (within 4 hours). Women presenting with new isolated non severe hypertension or $\geq 1+$ proteinuria should be referred for obstetric review, ideally within 24 hours. Placental growth factor testing reduces the time to diagnosis of pre-eclampsia and the incidence of adverse maternal outcomes; NICE recommends using this as a one-off test between 20 and 35 weeks' gestation.

NICE recommends admitting women at high risk of

adverse events, those with severe hypertension or where there are other concerns for the wellbeing of the woman or baby. However, many units routinely admit all patients with pre-eclampsia because of concerns about rapid deterioration, specifically placental abruption, eclampsia and intracranial haemorrhage. NICE recommends antihypertensive therapy if blood pressure remains $\geq 140/90$ mmHg, with labetalol first line. Delivery is recommended if there are serious maternal or fetal concerns, or by 37 weeks' gestation.

On discharge from hospital, women who are taking

antihypertensive medication should have their blood pressure measured every 1-2 days for 2 weeks until it has normalised. Women should see their GP 2 weeks postnatally to assess the need for ongoing antihypertensive treatment. Blood pressure, urinary protein and blood results (if previously abnormal) should be reviewed by their GP or hospital specialist at 6-8 weeks after birth.

other concerns for the wellbeing of the woman or baby.⁵

For BP control, NICE currently recommends treatment if BP remains $\geq 140/90$ mmHg with labetalol first line; nifedipine second line if labetalol is not suitable; methyldopa as a third option depending on the side effect profile and the woman's preference.⁵

The Giant PANDA trial is currently underway to compare nifedipine with labetalol for the treatment of hypertension in pregnancy.¹⁴

Delivery of the baby is the only 'cure' for confirmed pre-eclampsia, and is recommended if there are serious maternal or fetal concerns, or by 37 weeks' gestation if mother and baby seem well (or when the diagnosis is made, if later).^{3,5}

Prior to 34 weeks' gestation, expectant management is recommended because of the increased risk of the consequences of prematurity including respiratory distress syndrome and necrotising enterocolitis.¹⁵

In the absence of definite fetal or maternal indications for delivery, there is some debate regarding the timing of birth between 34 and 37 weeks' gestation. The PHOENIX trial¹⁶ demonstrated a significant reduction in adverse maternal outcomes with increased chance of vaginal birth without long-term neonatal morbidity (albeit with a small increased risk of neonatal unit admission) for women randomised to delivery at diagnosis compared with expectant management. The authors conclude that this should be discussed with the woman to determine the optimum timing of birth.

POSTNATAL CARE AND FOLLOW-UP

Women with pre-eclampsia may have a prolonged postnatal inpatient stay and will only be discharged once BP is $< 150/100$ mmHg, blood results are stable or improving, and they have no symptoms of pre-eclampsia.

Women who did not require antenatal antihypertensive treatment should be offered treatment if their BP is persistently $\geq 150/100$ mmHg.

If women are not breastfeeding, treatment of BP should follow the recommendations in the NICE guidance on hypertension in adults.¹⁷ In women who are breastfeeding, enalapril, amlodipine, or atenolol are used as once daily medications.

Women with pre-eclampsia will usually be prescribed low molecular weight heparin for prevention of venous thromboembolism and be offered

reliable contraception to start in the immediate postnatal period.¹⁸ On discharge, a written care plan should be provided including the following details:⁵

- Provision of follow-up care, including medical review and repeat blood tests
- Frequency of BP monitoring
- Thresholds for reducing or stopping treatment (usually 130/80 mmHg)
- Indications for referral to primary care for BP review
- Self-monitoring for symptoms

Women who are taking antihypertensive medication should have their BP measured every 1-2 days for two weeks until it has normalised. Women should see their GP two weeks postnatally to review BP and assess the need for ongoing antihypertensive treatment. This is also a good opportunity to discuss postnatal contraception if this has not been initiated prior to hospital discharge.

Women should have their BP, urinary protein and blood results (if previously abnormal) reviewed by their GP or hospital specialist at 6-8 weeks after birth.⁶ Women with persistently abnormal renal function or laboratory proven proteinuria at 3 months postnatal should be referred for an assessment for chronic kidney disease.⁵

Pre-eclampsia can occasionally present de novo in the first two postnatal weeks and may be atypical.¹⁹ Women with severe hypertension or red flags presenting should be referred for urgent obstetric review in hospital (within 4 hours).

LONG-TERM COMPLICATIONS

Women should be informed of their risk for pre-eclampsia recurrence and their lifetime cardiovascular risks at medical follow-up. Overall, women with pre-eclampsia have a risk of recurrence of 16%, however, the risk is 33% in those who deliver before 34 weeks' gestation and 23% for those who deliver between 34 and 37 weeks.⁵

Approximately 2% of women with pre-eclampsia will go on to develop chronic hypertension.⁵ They are twice as likely to die from a cardiovascular cause and have a 2- to 3-fold increased risk of a major cardiovascular event such as myocardial infarction or stroke.⁵ Pregnancy is therefore an excellent opportunity to counsel and support women to manage their modifiable cardiovascular risk factors, and to initiate appropriate ongoing monitoring.

Pre-eclampsia also increases risk in the offspring: in utero exposure to hypertension increases the risk of hypertension in adulthood by 2.5 times.²⁰ »

CONCLUSION

Although maternal mortality from pre-eclampsia has been reduced dramatically from the levels seen in the 1970s,¹³ it remains a common condition with a high burden of maternal and neonatal morbidity.

Novel methods of risk stratification such as angiogenic biomarker measurement show promise for improved diagnosis, and there is an increasing evidence base for BP control, place of care and timing of birth.

Primary care has an important role to play in pregnancy planning, early identification of at-risk women, detection of hypertensive disorders in pregnancy and short- and long-term postnatal follow-up of women with pre-eclampsia.

Competing interests: None

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Useful information

For healthcare professionals NICE

NG133. Hypertension in pregnancy: diagnosis and management www.nice.org.uk/guidance/ng133

For patients RCOG

Patient information leaflet on pre-eclampsia www.rcog.org.uk/globalassets/documents/patients/patient-information-leaflets/pregnancy/pi-pre-eclampsia.pdf

Action on pre-eclampsia

Support and information for those affected by pre-eclampsia <https://action-on-pre-eclampsia.org.uk>

Best Use of Medicines in Pregnancy

Patient information leaflets www.medicinesinpregnancy.org

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