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CLINICAL REVIEW:

Advances in the diagnosis of pre-eclampsia

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This CPD module was created in association with Roche Diagnostics Limited.

Learning Objectives

After reading this module and completing the online assessment, you should:

- Recognise the challenges associated with diagnosing pre-eclampsia.
- Understand the role of angiogenic factors in the pathogenesis of pre-eclampsia.
- Appreciate how placental growth factor (PlGF)-based tests can aid clinical decision making for women with suspected pre-eclampsia.

Questions

Visit our website to test your knowledge. Our questions cover:

- Risk factors for pre-eclampsia
- How pre-eclampsia develops
- NICE guidance on the use of PlGF-based blood tests.

This learning module can be used towards CPD for revalidation with the Nursing and Midwifery Council (NMC).

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Introduction

Pre-eclampsia affects between 2 and 5% of pregnancies in the UK.[1-3] It is traditionally diagnosed when a woman presents with new-onset hypertension and proteinuria after 20 weeks of pregnancy or soon after the birth of the baby.[4,5]

Early diagnosis is crucial and women thought to have pre-eclampsia require urgent admission for maternal and fetal assessment.[5] Diagnosis, however, can be challenging: clinical presentation can be variable and the disease often progresses over several weeks before a diagnosis is confirmed.[6]

Improved understanding of the underlying causes of pre-eclampsia has led to the development of new blood tests that can help to identify women at high risk of developing the disease, and to 'rule out' in the short-term those who are not.[5,7-9]

Pre-eclampsia carries significant risks to mum and baby

Pre-eclampsia is one of four hypertensive disorders of pregnancy (see Table 1).[10,11] Its effects are widespread, with the potential for damage to several vital organs including the liver, kidneys, brain and lung.[7] Symptoms can include sudden swelling of the face, hands and feet, upper abdominal pain, severe headaches and visual disturbances.[5]

Left undiagnosed and unmonitored, pre-eclampsia can progress to eclampsia (onset of seizures), HELLP syndrome (haemolysis, elevated liver enzymes and low platelets), disseminated intravascular coagulation, stroke and organ dysfunction.[5]

Women with pre-eclampsia require close monitoring in hospital, whereas women with chronic or gestational hypertension can be managed as outpatients, unless their blood pressure reaches or exceeds 160/110 mmHg.[5]

Table 1: Hypertensive disorders of pregnancy[10,11]

Chronic hypertension	High blood pressure that precedes pregnancy, is diagnosed within the first 20 weeks, or persists 12 weeks after delivery
Gestational hypertension	New-onset hypertension after 20 weeks' gestation without significant proteinuria
Pre-eclampsia	New-onset hypertension and proteinuria from 20 weeks' gestation
Chronic hypertension with super-imposed pre-eclampsia	Women with existing hypertension who then go on to develop pre-eclampsia

Pre-eclampsia can also place the fetus at greater risk of intrauterine growth restriction, prematurity and intrauterine death.[4] One half of women with severe pre-eclampsia give birth preterm.[7]

Diagnosis can be challenging

The International Society for the Study of Hypertension in Pregnancy (ISSHP) changed the diagnostic criteria for pre-eclampsia in 2014.[4] The revised definition is de novo hypertension developing after 20 weeks' gestation and the coexistence of one or more of the following new onset conditions:

- Proteinuria
- Other maternal organ dysfunction, e.g. renal insufficiency, liver involvement, neurological or haematological complications
- Fetal growth restriction.[4]

Diagnosis of pre-eclampsia is currently based on antenatal assessment of risk factors (see Table 2), routine monitoring of blood pressure and urine, and blood tests to monitor kidney and liver function and platelets.[5,10]

Table 2: Risk factors for the development of pre-eclampsia[5]

High risk	Moderate risk
• Hypertensive disease during a previous pregnancy • Chronic kidney disease • Autoimmune disease, such as systemic lupus erythematosus or antiphospholipid syndrome • Type 1 or type 2 diabetes • Chronic hypertension	• First pregnancy • Age > 40 years • Pregnancy interval of more than 10 years • BMI of 35kg/m^2 at first visit • Family history of pre-eclampsia • Multiple pregnancy

As pre-eclampsia is defined as new-onset hypertension, it is important to document the woman's blood pressure early in pregnancy as a baseline, before the pregnancy-related dip in blood pressure during the second trimester.[4]

Pre-eclampsia often progresses over several weeks before diagnosis. It can be unpredictable and clinical presentation is variable.[6] The presence of other pre-existing conditions can further complicate diagnosis.

Because hypertension and proteinuria can be poor predictors of disease onset and progression, a high proportion of women with signs and symptoms of pre-eclampsia may be hospitalised for observation unnecessarily.

Pre-eclampsia begins in the placenta

The causes of pre-eclampsia are not completely understood, but the disorder is thought to start in the placenta. In a normal pregnancy, the maternal uterine vessels supplying the placenta (spiral arteries) begin to change at about 10 weeks' gestation.[12] They dilate and lose their smooth muscle to become flaccid, large diameter vessels capable of transmitting increased volumes of blood to the placenta.[12,13]

In pre-eclampsia, the spiral arteries do not remodel. Instead, they remain narrow and highly resistant, and are unable to supply sufficient blood to the placenta.[12,13] To compensate for this reduced blood flow, the placenta releases substances into the maternal bloodstream to increase blood vessel permeability, blood pressure and the blood's tendency to clot.[14] These substances include antiangiogenic factors, such as soluble fms-like tyrosine kinase-1 (sFlt-1),[9,12] which cause vasoconstriction and endothelial damage throughout the body.[9]

Angiogenic: relating to blood vessel growth

Antiangiogenic: a substance that interferes with the formation of new blood vessels

Proangiogenic: a substance that promotes the formation of new blood vessels

ABOUT THE HEALTH PROFESSIONAL ACADEMY

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All our online CPD modules are developed in partnership with a team of leading academics, so you can be sure the module you've chosen is credible, referenced and up to date. All information by HPA is in line with guidance from the NHS, NICE and Royal Colleges, as well as Unicef's Baby Friendly Initiative.

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Placental growth factor (PlGF) is released by the placenta and has proangiogenic effects on the fetal and placental circulation.[15] In a normal pregnancy, PlGF levels increase during the first two trimesters and then decline until delivery.[9]

Levels of PlGF are found to be lower in women with pre-eclampsia. This may be due to decreased release of PlGF as a consequence of poor placental perfusion, as well as reduced free PlGF in the presence of increased sFlt-1, since sFlt-1 'disables' PlGF by binding to it.[15]

Importantly, the increased levels of sFlt-1 and decreased levels of PlGF seen in women with pre-eclampsia are not only evident at diagnosis, but also weeks in advance of its onset.[8,15] A high ratio of sFlt-1 to PlGF is associated with an increased risk of pre-eclampsia and may be a better predictor of risk than either PlGF or sFLT-1 on their own.[8]

This imbalance of proangiogenic and antiangiogenic factors is characteristic of pre-eclampsia: lowered PlGF levels and elevated sFLT-1 levels.

Early- and late-onset pre-eclampsia develop differently

Pre-eclampsia can be divided into early-onset (<34 weeks) and late-onset (>34 weeks). Each has a different pathophysiology.[9]

Early-onset or placental pre-eclampsia is thought to be caused by abnormal remodelling of the spiral arteries and insufficient blood supply to the placenta as already described. It is associated with fetal growth restriction or small-for-gestational-age babies, and confers a significantly higher chance of adverse outcomes for mother and baby.[16,17]

In late-onset or maternal pre-eclampsia, there is little evidence of abnormal artery remodelling. Instead it appears to be a mismatch between maternal supply and the demands of the growing fetus close to term.[9,16,18] In most cases of late-onset pre-eclampsia, babies are a normal size or large for gestational age.[16]

Altered levels of sFlt-1 and PlGF are seen in both early- and late-onset pre-eclampsia, although it is less pronounced in late-onset compared to early-onset pre-eclampsia.[16]

Blood tests that measure angiogenic factors can aid diagnosis

Simple PlGF-based blood tests are now being used in a few NHS organisations to aid diagnosis of suspected pre-eclampsia.[19] The latest NICE guidance recommends the use of PlGF-based blood tests to help rule-out pre-eclampsia in women between 20 weeks and 34 weeks plus 6 days' gestation.[5]

NICE recommends two PlGF-based tests:

- The Triage® PlGF test, which measures PlGF levels in a maternal blood plasma sample.[5]
- The Elecsys® immunoassay sFlt-1/PlGF ratio, which measures the amount of sFlt-1 relative to PlGF in maternal serum samples.[5]

The Elecsys® immunoassay sFlt-1/PlGF ratio is also supported by the Accelerated Access Collaborative* (AAC).[19]

*The AAC is a unique partnership between representatives of healthcare organisations – including NHS England, NICE and the Department of Health and Social Care – and the health technology industry. The purpose of the AAC is to get 'breakthrough' technologies to NHS patients more quickly.

The NICE guidance states that these tests should only be used to *rule-out* pre-eclampsia in the short term.[5] The negative predictive value (NPV) of the test is important when ruling out pre-eclampsia. NPV is expressed as a percentage and tells us the likelihood that a negative result represents a 'true' negative rather than a 'false' negative. Therefore, the higher the NPV, the greater the confidence that the woman does *not* have pre-eclampsia and can be managed at home for the short term.

The use of these tests – in conjunction with blood pressure monitoring, urine analysis, haematological tests and clinical judgment – could result in faster and more accurate diagnosis of pre-eclampsia and better risk assessment for adverse outcomes in women with suspected pre-eclampsia.[5] These tests also allow women in whom pre-eclampsia has been ruled out to return home instead of being admitted to hospital for monitoring, reducing stress for the woman and freeing up hospital beds.[5]

Box 1. Benefits of PlGF-based testing, as reported by NHS staff with experience of using test[20]

- Supports decision making on appropriate patient pathway.
- Provides reassurance to clinicians and pregnant women who are sent home that they do not have pre-eclampsia at that point.
- Reduces hospital admissions solely for monitoring.
- Helps to identify appropriate surveillance frequency when pre-eclampsia is ruled out.

For further training in pre-eclampsia, visit the APEC (Action on Pre-eclampsia) website: https://action-on-pre-eclampsia.org.uk/

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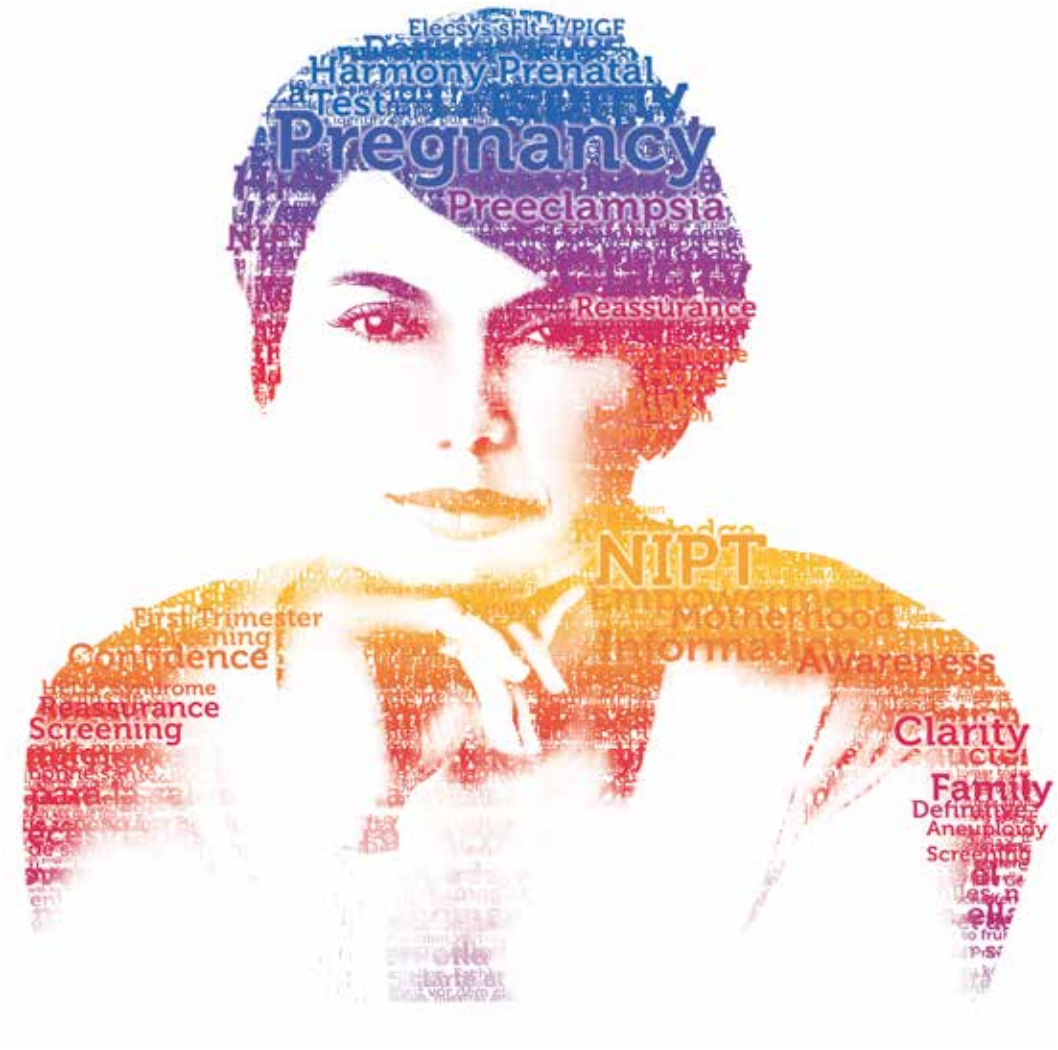

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