NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Diagnostics Assessment Programme

PlGF-based testing to help diagnose suspected pre-eclampsia (update of DG23)

Final scope

November 2020

1 Introduction

In February 2020, following a review proposal it was determined that NICE diagnostics guidance 23 on PlGF-based testing to help diagnose suspected pre-eclampsia should be updated. During the development of the review proposal it was identified that further data on PlGF-based tests is now available that may address research recommendations in the original guidance, therefore an update to the guidance is needed.

A glossary of terms and a list of abbreviations are provided in appendices A and B.

2 Description of the technologies

This section describes the properties of the diagnostic technologies based on information provided to NICE from the companies and information available in the public domain. NICE has not carried out an independent evaluation of this description.

2.1 Purpose of the medical technology

The PlGF tests measure the amount of placental growth factor (PlGF) in blood plasma or serum. PlGF is a protein involved in placental angiogenesis (the development of new blood vessels). In pre-eclampsia, a condition that is thought to be related to problems with the development of the placenta, levels of PlGF can be abnormally low. In normal pregnancy, PlGF levels rise and peak at 26 to 30 weeks gestation so the failure of PlGF levels to rise during pregnancy may be an indicator of placental dysfunction. In addition, some PlGF-based tests also measure soluble FMS-like tyrosine kinase-1 (sFlt-1), an anti-angiogenic protein which is thought to disable proteins, such as PlGF, which are associated with blood vessel formation. In women who develop pre-eclampsia, the levels of sFlt-1 may be higher than those seen in normal

pregnancy. The tests are intended for use in conjunction with clinical judgement and other existing diagnostic tests, to aid the diagnosis of pre-eclampsia. This assessment will look at the use of the tests in the second and third trimesters only. Some of the tests can be used in the first trimester but this is outside of the scope.

Using the PlGF tests in addition to current clinical practice could help in making decisions about the care of women with suspected pre-eclampsia. For example, they could allow women who have pre-eclampsia ruled out with the PlGF test to receive outpatient care instead of being admitted to hospital for observation.

2.2 Product properties

2.2.1 Triage PlGF Test (Quidel)

The Quidel Triage PLGF Test is a fluorescence immunoassay to be used with the Quidel Triage Meter for the quantitative determination of Placental Growth Factor (PLGF) in EDTA anticoagulated plasma specimens. The company state that it can be used at the point of care and in the laboratory. The test is used in conjunction with other clinical information as an aid in the diagnosis of preterm pre-eclampsia and as an aid in the prognosis of delivery, in women presenting with signs and symptoms of pre-eclampsia after 20 weeks and prior to 35 weeks of gestation.

In addition to the test kits, the following equipment is required:

- Quidel Triage MeterPro
- Triage MeterPlus
- Quidel Triage PLGF Control Level 1
- Quidel Triage PLGF Control Level 2

The test has a limit of detection of 9 picograms/millilitre and a measurable range of 12 to 3000 picograms/millilitre. The test takes less than 30 minutes to run.

Table 1 Recommended cut-offs for the Triage PlGF Test

Result	Classification	Interpretation
PlGF < 12pg/mL	Test positive – highly abnormal	Highly abnormal and suggestive of patients with severe placental dysfunction and at increased risk for preterm delivery
PlGF ≥12 pg/mL and <100pg/mL	Test positive – abnormal	Abnormal and suggestive of patients with placental dysfunction and at increased risk for preterm delivery
PlGF ≥100 pg/mL	Test negative – normal	Normal and suggestive of patients without placental dysfunction and unlikely to progress to delivery within 14 days of the test.

2.2.2 Elecsys immunoassay sFlt-1/PlGF ratio (Roche)

The Elecsys immunoassay sFlt-1/PlGF ratio measures the relative amounts of PlGF to soluble FMS-like tyrosine kinase-1 (sFlt-1; also known as VEGFR1) in serum samples from women with suspected pre-eclampsia. The ratio is formed by combining the results from 2 electrochemiluminescence immunoassays (the Elecsys PlGF and Elecsys sFlt-1 assays) which are compatible with the Roche Cobas e automated clinical chemistry analysers.

The sFlt-1/PlGF ratio is intended for use as an aid in the diagnosis of pre-eclampsia in conjunction with other diagnostic and clinical information. In addition the sFlt-1/PlGF ratio is intended for use as an aid in short-term prediction of preeclampsia (rule-out and rule-in) in pregnant women with suspicion of preeclampsia in conjunction with other diagnostic and clinical information.

In addition to the test kits, the following equipment is required:

- PlGF CalSet, for 4 x 1.0 mL
- sFlt-1 CalSet, for 4 x 1.0 mL
- PreciControl Multimarker, for 6 x 2.0 mL
- cobas e analyzer

The Elecsys sFlt-1 assay has a limit of detection of 10 picograms/millilitre (measuring range 10 to 85,000 picograms/millilitre) and a limit of quantitation of 15 picograms/millilitre. The Elecsys PlGF assay has a limit of detection of 3 picograms/millilitre (measuring range 3 to 10,000 picograms/millilitre) and a limit of quantitation of 10 picograms/millilitre.

Table 2 Recommended cut-offs for the Elecsys immunoassay sFlt-1/PlGF ratio

	sFlt-1/PlGF ratio

Aid in diagnosis of pre-eclampsia	Week 20^{+0} to week 33^{+6}	Rule out cut-off	33
		Rule in cut-off	85
	Week 34^{+0} to delivery	Rule out cut-off	33
		Rule in cut-off	110
Short-term prediction of pre-eclampsia (week 24^{+0} to 36^{+6})		Rule out*	≤38
		Rule in**	>38

* rule out pre-eclampsia for one week; ** rule-in pre-eclampsia within 4 weeks

2.2.3 DELFIA Xpress PlGF 1-2-3 test / DELFIA Xpress sFlt-1 kit (PerkinElmer)

The DELFIA Xpress PlGF 1-2-3 can be used stand-alone test or together with DELFIA Xpress sFlt-1 test.

The DELFIA Xpress PlGF 1-2-3 is intended for the quantitative determination of PlGF in maternal serum using the 6000 DELFIA® Xpress clinical random access screening platform. The kit is described as being an aid in screening pregnant women for pre-eclampsia in all trimesters of pregnancy. In the second and third trimester, the company state that PlGF can be used for screening for risk of pre-eclampsia together with other relevant clinical information.

This DELFIA Xpress sFlt-1 kit is intended for the quantitative determination of sFlt-1 in maternal serum using the 6000 DELFIA® Xpress random access immunoanalyzer. The ratio of sFlt-1/PlGF may be used as an aid in diagnosis of pre-eclampsia and for short term prediction of suspected pre-eclampsia together with other biochemical and clinical information.

In addition to the test kits, the following equipment is required:

- 6000 DELFIA Xpress random access immunoanalyzer
- Wash Concentrate
- DELFIA Inducer

Using the DELFIA Xpress PlGF 1-2-3 test alone, the process time for first results is 30 minutes. Using both DELFIA Xpress PlGF 1-2-3 and sFlt-1 together takes approximately 31,5 minutes for the first sFlt-1/PlGF ratio result. The instrument is able to process samples simultaneously, leading to approximately 40 results per hour throughput.

The company state that the recommended cut-off values for the DELFIA Xpress PlGF 1-2-3 test alone are:

- Higher than 150 pg/ml: rule out pre-eclampsia,
- From 50 to 150 pg/ml: follow up,

- Below 50 pg/ml: rule in and deliver within 14 days (50% of women).

If using DELFIA Xpress 1-2-3 in combination with DELFIA Xpress sFlt-1 (for sFlt-1/PlGF ratio), the company state that:

- Published cut-offs for the sFlt-1/PlGF ratio are not directly transferable to the ratios of DELFIA Xpress sFlt-1 and PlGF 1-2-3 assays.
- Each laboratory must validate their own cut-offs for management of pre-eclampsia in women with suspected pre-eclampsia.
- Published cut-offs can only be used as guidance.
- For aid in diagnosis and for short term prediction of pre-eclampsia, using cut-offs validated in the laboratory, the sFlt-1/PlGF ratio results may be categorized to:
    - Low (ratio below low cut off): rule out
    - Intermediate to follow-up
    - Increased (ratio above increased cut off): rule in

The DELFIA Xpress PlGF 1-2-3 assay has a limit of detection of 1.9 picograms/millilitre and a limit of quantitation of 3.3 picograms/millilitre (measuring range 1.9 to 4000 picograms/millilitre). The DELFIA Xpress sFlt-1 has a limit of detection of is 3.79 picograms/millilitre and a limit of quantitation of 7.6 picograms/millilitre (measuring range 3.79 to 19500 picograms/millilitre).

2.2.4 BRAHMS sFlt-1 Kryptor / BRAHMS PlGF plus Kryptor PE ratio (ThermoFisher)

The BRAHMS PlGF plus Kryptor test can be used as a stand-alone test or together with BRAHMS sFlt-1 Kryptor test.

The BRAHMS sFlt-1 Kryptor / BRAHMS PlGF plus Kryptor PE ratio is formed by combining the results from 2 automated immunofluorescent sandwich assays, the BRAHMS sFlt-1 Kryptor and BRAHMS PlGF plus Kryptor assays. The assays are indicated for the quantitative determination of sFlt-1 and PlGF in serum samples and are compatible with the BRAHMS Kryptor compact plus analyser and the Kryptor Gold immunoanalyser. The BRAHMS sFlt-1 Kryptor / BRAHMS PlGF plus KRYPTOR PE ratio is intended to be used to confirm or exclude diagnosis of pre-eclampsia after 20 weeks gestation.

When using the Kryptor Gold Immunoanalyser it takes 29 minutes for the first BRAHMS sFlt-1 Kryptor / BRAHMS PlGF plus Kryptor ratio result, and then a further 90 seconds for each additional result

In addition to the test kits, the following equipment is required:

- BRAHMS PlGF plus KRYPTOR CAL

- BRAHMS sFlt-1 KRYPTOR CAL 1/CAL 2
- BRAHMS PlGF plus KRYPTOR Control 1/2/3
- BRAHMS sFlt-1 KRYPTOR Control 1/2/3
- BRAHMS KRYPTOR compact PLUS Consumables

The BRAHMS sFlt-1 Kryptor assay has a limit of detection of 22 picograms/millilitre (measuring range 22 to 90,000 picograms/millilitre) and a limit of quantitation of 34 picograms/millilitre. The BRAHMS PlGF plus Kryptor assay has a limit of detection of 3.6 picograms/millilitre (measuring range 3.6 to 7000 picograms/millilitre) and a limit of quantitation of 6.9 picograms/millilitre.

The company state that a ratio of more than 85 is suggestive of pre-eclampsia and suggests a high-risk pregnancy.

3 Target conditions

Gestational hypertension and pre-eclampsia

3.1 Background

Pre-eclampsia is a condition which can affect women who are pregnant and most frequently occurs during the second half of pregnancy. It is thought to be associated with placental dysfunction, whereby blood flow through the placenta is reduced. Pre-eclampsia is characterised by maternal hypertension and proteinuria, and may also cause restricted growth in the fetus. It is thought to affect up to 6% of pregnancies (NHS UK 2018), and if not detected and monitored, pre-eclampsia can develop into eclampsia, a potentially life-threatening convulsive condition, which affects around 1 in 4000 pregnancies in the UK (NHS UK 2018). Pre-eclampsia may also result in HELLP syndrome, disseminated intravascular coagulation, stroke or organ dysfunction. Women who have hypertension or pre-eclampsia during pregnancy may also have a higher risk of complications from placental abruption. It is also thought that those who develop pre-eclampsia during pregnancy may be at greater risk of cardiovascular disease later in life.

According to the NHS digital's Hospital Admitted Patient Care Activity 2019-20 data, there were 10,547 admissions to hospital for pre-eclampsia and 211 for eclampsia between April 2019 and April 2020. However, a clinical expert cautioned that there may be some uncertainty in these data as they may not have captured everyone admitted with pre-eclampsia. Some women may have been classed as hypertensive disease admissions and so the actual number of pre-eclampsia admissions may be higher. Gestational hypertension (new hypertension presenting after 20 weeks of pregnancy without significant proteinuria) and pre-eclampsia may impact upon the fetus, placing them at

increased risk of intrauterine growth restriction, prematurity and intrauterine death. It is estimated that around 1,000 babies die each year because of pre-eclampsia and associated early delivery (NHS UK).

Pre-eclampsia is frequently asymptomatic and may only be detected through routine antenatal testing. Symptoms of pre-eclampsia include severe headache, problems with vision, severe pain just below the ribs, vomiting, and sudden swelling of the hands or face.

Pre-eclampsia

The NICE hypertension in pregnancy guideline defines pre-eclampsia as new onset of hypertension (over 140 mmHg systolic or over 90 mmHg diastolic) after 20 weeks of pregnancy and the coexistence of 1 or more of the following new-onset conditions:

- proteinuria (urine protein:creatinine ratio of 30 mg/mmol or more or albumin:creatinine ratio of 8 mg/mmol or more, or at least 1 g/litre [2+] on dipstick testing) or
- other maternal organ dysfunction:
    - renal insufficiency (creatinine 90 micromol/litre or more, 1.02 mg/100 ml or more)
    - liver involvement (elevated transaminases [alanine aminotransferase or aspartate aminotransferase over 40 IU/litre] with or without right upper quadrant or epigastric abdominal pain)
    - neurological complications such as eclampsia, altered mental status, blindness, stroke, clonus, severe headaches or persistent visual scotomata
    - haematological complications such as thrombocytopenia (platelet count below 150,000/microlitre), disseminated intravascular coagulation or haemolysis
- uteroplacental dysfunction such as fetal growth restriction, abnormal umbilical artery doppler waveform analysis, or stillbirth.

The International Society for the Study of Hypertension in Pregnancy (ISSHP) 2014 statement defines pre-eclampsia as new-onset of hypertension (≥ 140 mmHg systolic, or ≥ 90 mmHg diastolic) with the coexistence of one or more of the following new-onset conditions:

- proteinuria (urine protein creatinine ratio of ≥ 30 mg/mmol [0.3 mg/mg] or >300 mg/day or at least 1 g/L ['2 + '] on dipstick testing),
- renal insufficiency (creatinine ≥ 90umol/L),
- liver involvement (elevated transaminases at least twice the upper limit of normal ± right upper-quadrant or epigastric abdominal pain),

- neurological complications (eclampsia, blindness, hyperreflexia with clonus, severe headaches, persistent visual scotomata),
- haematological complications (platelet count ≤ 150 x 10^9 per litre, disseminated intravascular coagulation, haemolysis),
- evidence of uteroplacental dysfunction with fetal growth restriction.

The ISSHP statement does not recommend diagnosing pre-eclampsia that is superimposed on chronic hypertension on the basis of a rise in blood pressure alone. For women with underlying essential hypertension, superimposed pre-eclampsia can be diagnosed when one or more of the above features of preeclampsia occur in addition to the hypertension.

Clinical experts also suggested that in practice there may be additional symptoms that would be considered indicative of pre-eclampsia. These include new nausea with or without vomiting after 20 weeks, new (rapid onset) hand or facial oedema, and shortness of breath.

Suspected pre-eclampsia

Clinical experts commented that women who are suspected of having pre-eclampsia (that is, women presenting with symptoms or signs which could be attributable to pre-eclampsia) but who do not meet the full criteria of the condition (as described above) would be considered to have suspected pre-eclampsia. For example, women with new-onset hypertension but without another new-onset condition, such as proteinuria. There may be some variation in practice across in NHS in terms of who would be considered to have suspected pre-eclampsia; for example, whether proteinuria alone (without hypertension) would be sufficient.

For pregnant women with chronic hypertension, pre-eclampsia will be suspected if there is a worsening of blood pressure (or if hypertension is being managed but with increasing dose of anti-hypertensive treatment) or if blood pressure does not increase but there is another indication of possible pre-eclampsia (such as proteinuria).

Clinical experts noted that there may be less value to a PlGF-based test for women with severe hypertension, because they would likely be admitted to hospital to manage the condition (as per the NICE hypertension in pregnancy guideline; see table 4 below). While in hospital, routine blood tests such as creatinine and tests of liver function would be used make a diagnosis of pre-eclampsia, alongside the hypertension that the patient was admitted for.

Pregnant women presenting with suspected pre-eclampsia often have one or more clinical signs or symptoms which may be caused by other underlying

health conditions and which may not be directly attributable to pre-eclampsia. The assessment of suspected pre-eclampsia therefore represents a significant diagnostic challenge and often requires a large degree of clinical judgement to determine whether a definitive diagnosis of pre-eclampsia is appropriate. A clinical expert commented that the diagnosis is subjective and dynamic, especially in women with underlying medical disease (such as hypertension, renal disease, diabetes or autoimmune disease).

The clinical diagnosis of pre-eclampsia is often not clear and the thresholds used for clinical features such as blood pressure to indicate pre-eclampsia will miss many cases of true disease. For example, a small number of women will develop signs or symptoms of pre-eclampsia without hypertension(that is, with blood pressure less than140/90mmHg).

3.2 Diagnostic and care pathway

Since the NICE diagnostic guidance on PlGF-based testing to help diagnose suspected pre-eclampsia published, the NICE guidance on hypertension in pregnancy has been updated.

3.2.1 Identifying and managing the risk of developing pre-eclampsia

The NICE antenatal care guideline recommends that blood pressure measurement and urinalysis for protein should be carried out at each antenatal visit to screen for pre-eclampsia. The guideline also recommends determining risk factors for pre-eclampsia at the booking appointment (by 10 weeks of pregnancy).

The NICE hypertension in pregnancy guideline describes risk factors for pre-eclampsia. Women with either 1 high risk factor, or more than 1 moderate risk factor for pre-eclampsia, take 75-150 mg of aspirin daily from 12 weeks gestation until the birth of the baby.

The NICE hypertension in pregnancy guideline also includes recommendations on the assessment of proteinuria in hypertensive disorders of pregnancy. These include thresholds for significant proteinuria. In addition to antenatal surveillance for hypertension and proteinuria, the NICE antenatal care and hypertension in pregnancy guidelines recommend advising women who are pregnant to see a healthcare professional immediately if they experience symptoms of pre-eclampsia. Symptoms include:

- severe headache
- problems with vision, such as blurring or flashing before the eyes
- severe pain just below the ribs
- vomiting

- sudden swelling of the face, hands or feet.

3.2.2 Management of chronic hypertension in pregnancy

The NICE hypertension in pregnancy guideline includes recommendations on the management of chronic hypertension in pregnancy. Antenatal appointments should be scheduled based on the individual needs of the person and her baby. This may include weekly appointments if hypertension is poorly controlled or every 2 to 4 weeks if hypertension is well-controlled.

Planned early birth before 37 weeks should not be offered to women with chronic hypertension whose blood pressure is lower than 160/110 mmHg, with or without antihypertensive treatment, unless there are other medical indications.

3.2.3 Management of pregnancy with gestational hypertension

The NICE hypertension in pregnancy guideline includes recommendations on the management of gestational hypertension in pregnancy. These are summarised in table 3.

Table 3 Management of pregnancy with gestational hypertension (table 1 from the NICE hypertension in pregnancy guideline)

	Degree of hypertension	
	Hypertension: blood pressure of 140/90–159/109 mmHg	**Severe hypertension: blood pressure of 160/110 mmHg or more**
Admission to hospital	Do not routinely admit to hospital	Admit, but if BP falls below 160/110 mmHg then manage as for hypertension
Antihypertensive pharmacological treatment	Offer pharmacological treatment if BP remains above 140/90 mmHg	Offer pharmacological treatment to all women
Target blood pressure once on antihypertensive treatment	Aim for BP of 135/85 mmHg or less	Aim for BP of 135/85 mmHg or less
Blood pressure measurement	Once or twice a week (depending on BP) until BP is 135/85 mmHg or less	Every 15–30 minutes until BP is less than 160/110 mmHg
Dipstick proteinuria testing [a]	Once or twice a week (with BP measurement)	Daily while admitted

Blood tests	Measure full blood count, liver function and renal function at presentation and then weekly	Measure full blood count, liver function and renal function at presentation and then weekly
PlGF-based testing	Carry out PlGF-based testing on 1 occasion (in accordance with NICE guidance) if there is suspicion of pre-eclampsia	Carry out PlGF-based testing on 1 occasion (in accordance with NICE guidance) if there is suspicion of pre-eclampsia
Fetal assessment	Offer fetal heart auscultation at every antenatal appointment Carry out ultrasound assessment of the fetus at diagnosis and, if normal, repeat every 2 to 4 weeks, if clinically indicated Carry out a CTG only if clinically indicated (See section 3.2.6)	Offer fetal heart auscultation at every antenatal appointment Carry out ultrasound assessment of the fetus at diagnosis and, if normal, repeat every 2 weeks, if severe hypertension persists Carry out a CTG at diagnosis and then only if clinically indicated (See section 3.2.6)
[a] Use an automated reagent-strip reading device for dipstick screening for proteinuria in a secondary care setting. Abbreviations: BP, blood pressure; CTG, cardiotocography; PlGF, placental growth factor.		

Planned early birth before 37 weeks should not be offered to women with gestational hypertension whose blood pressure is lower than 160/110 mmHg, unless there are other medical indications.

3.2.4 Management of pregnancy with pre-eclampsia

The NICE hypertension in pregnancy guideline recommends carrying out a full clinical assessment at each antenatal appointment for women with pre-eclampsia, and offer admission to hospital for surveillance and any interventions needed if there are concerns for the wellbeing of the woman or baby. The guideline also recommends considering using either the fullPIERS or PREP-S validated risk prediction models to help guide decisions about the most appropriate place of care (such as the need for in utero transfer) and thresholds for intervention.

Table 4 summarises the recommendation on the management of pregnancy with pre-eclampsia from the guideline.

Table 4 Management of pregnancy with pre-eclampsia (table 2 from the NICE hypertension in pregnancy guideline)

	Degree of hypertension

	Hypertension: **blood pressure of 140/90–159/109 mmHg**	**Severe hypertension:** **blood pressure of 160/110 mmHg or more**
Admission to hospital	Admit if any clinical concerns for the wellbeing of the woman or baby or if high risk of adverse events suggested by the fullPIERS or PREP-S risk prediction models	Admit, but if BP falls below 160/110 mmHg then manage as for hypertension
Antihypertensive pharmacological treatment	Offer pharmacological treatment if BP remains above 140/90 mmHg	Offer pharmacological treatment to all women
Target blood pressure once on antihypertensive treatment	Aim for BP of 135/85 mmHg or less	Aim for BP of 135/85 mmHg or less
Blood pressure measurement	At least every 48 hours, and more frequently if the woman is admitted to hospital	Every 15–30 minutes until BP is less than 160/110 mmHg, then at least 4 times daily while the woman is an inpatient, depending on clinical circumstances
Dipstick proteinuria testing [a]	Only repeat if clinically indicated, for example, if new symptoms and signs develop or if there is uncertainty over diagnosis	Only repeat if clinically indicated, for example, if new symptoms and signs develop or if there is uncertainty over diagnosis
Blood tests	Measure full blood count, liver function and renal function twice a week	Measure full blood count, liver function and renal function 3 times a week
Fetal assessment	Offer fetal heart auscultation at every antenatal appointment Carry out ultrasound assessment of the fetus at diagnosis and, if normal, repeat every 2 weeks Carry out a CTG at diagnosis and then only if clinically indicated (See section 3.2.6)	Offer fetal heart auscultation at every antenatal appointment Carry out ultrasound assessment of the fetus at diagnosis and, if normal, repeat every 2 weeks Carry out a CTG at diagnosis and then only if clinically indicated (See section 3.2.6)

[a] Use an automated reagent-strip reading device for dipstick screening for proteinuria in a secondary care setting.

Abbreviations: BP, blood pressure; CTG, cardiotocography.

3.2.5 Timing of birth

The NICE hypertension in pregnancy guideline recommends recording maternal and fetal thresholds for planned early birth before 37 weeks in women with pre-eclampsia. A senior obstetrician should be involved in any decisions on timing of birth for women with pre-eclampsia. Recommendations on the timing of birth in women with pre-eclampsia are summarised in table 5.

Table 5 Timing of birth in women with pre-eclampsia

Weeks of pregnancy	**Timing of birth**
Before 34 weeks	Continue surveillance unless there are indications for planned early birth. Offer intravenous magnesium sulfate and a course of antenatal corticosteroids in line with the NICE guideline on preterm labour and birth.
From 34 to 36 +6 weeks	Continue surveillance unless there are indications for planned early birth. When considering the option of planned early birth, take into account the woman's and baby's condition, risk factors (such as maternal comorbidities, multi-fetal pregnancy) and availability of neonatal unit beds. Consider a course of antenatal corticosteroids in line with the NICE guideline on preterm labour and birth.
37 weeks onwards	Initiate birth within 24–48 hours.

3.2.6 Fetal monitoring

The NICE hypertension in pregnancy guideline has recommendations on fetal monitoring for women with chronic hypertension, gestational hypertension and pre-eclampsia.

Women with pre-eclampsia or severe gestational hypertension, should have a care plan that includes the timing and nature of future fetal monitoring, fetal indications for birth and if and when antenatal corticosteroids should be given, and plans for discussion with neonatal paediatricians and obstetric anaesthetists.

3.2.7. *Medical management of severe hypertension, severe pre-eclampsia or eclampsia in a critical care setting*

The NICE hypertension in pregnancy guideline provides recommendations on the management of severe hypertension, severe pre-eclampsia or eclampsia in a critical care setting. These include that, if early birth is considered likely

within 7 days in women with pre-eclampsia, offer a course of antenatal corticosteroids in line with the NICE guideline on preterm labour and birth. There are also criteria to consider when referring women with severe hypertension or severe pre-eclampsia to the appropriate critical care setting.

3.3 Use of PlGF-based tests in the NHS

NICE diagnostics guidance 23 recommends use of the Triage PlGF test and the Elecsys immunoassay sFlt-1/PlGF ratio, used with standard clinical assessment and subsequent clinical follow-up, to help rule-out pre-eclampsia in women presenting with suspected pre-eclampsia between 20 weeks and 34 weeks plus 6 days of gestation. This recommendation was included in the NICE hypertension in pregnancy guideline.

Clinical experts commented that the use of PlGF-tests to help diagnose women with *suspected* pre-eclampsia was the most appropriate place to assess use of the test. If a person exhibits sufficient signs and symptoms to make a diagnosis of pre-eclampsia (as per definitions in section 3.1) then the PLGF-based tests are unlikely to add value in helping diagnose the condition.

Clinical experts highlighted that if an initial PlGF-based test is negative for pre-eclampsia, it would be appropriate to do another test at a later time if there was a worsening or new-onset of signs or symptoms of possible pre-eclampsia. That is, if the person had suspected pre-eclampsia again.

Repeat testing may be considered for a person who had an initial PlGF-based test that was negative for pre-eclampsia and who had no further subsequent indications of the condition (for example, worsening blood pressure or new-onset symptoms). NICE diagnostics guidance 23 included a recommendation for further research on the use of repeat PlGF-based testing, with standard clinical assessment, in women presenting with suspected pre-eclampsia between 20 weeks and 34 weeks plus 6 days of gestation, who have had a negative PlGF-based test result that was used to rule-out pre-eclampsia (see recommendation 6.1).

3.4 Patient issues and preferences

Pre-eclampsia may be associated with significant maternal and fetal morbidity. Babies of women with pre-eclampsia are at risk of stillbirth or complications arising from premature birth. The quality of life of women with pre-eclampsia may be substantially impacted by anxiety arising from having a condition which can deteriorate rapidly, and which could require them to decide whether to prolong their pregnancy or opt for a premature birth. Women who have had pre-eclampsia during pregnancy may also have

reduced quality of life in the longer-term. Previous adverse pregnancy outcomes may lead to increased anxiety in subsequent pregnancies, and in some cases a decision to not complete their family. The risk and experience of pre-eclampsia can also lead to substantial anxiety for the family of pregnant women.

Use of tests which are intended to aid the diagnosis of suspected pre-eclampsia may identify women who are at low risk of developing pre-eclampsia, who may therefore be managed more conservatively, preventing inpatient hospital stays and increased anxiety. Use of the test may also provide additional information to permit planning for a pre-term birth and reduce anxiety in women who have borderline results from blood pressure and proteinuria monitoring.

4 Comparator

No use of PlGF-based testing to help diagnose pre-eclampsia and make decisions about care.

5 Scope of the assessment

Table 6 Scope of the assessment

Decision question	What is the clinical and cost-effectiveness of the Triage PlGF test, Elecsys immunoassay sFlt-1/PlGF ratio, DELFIA Xpress PlGF 1-2-3 test (with or without DELFIA Xpress sFlt-1 test) and BRAHMS sFlt-1 Kryptor / PlGF plus Kryptor PE ratio when used in addition to clinical assessment for the diagnosis of pre-eclampsia in the second and third trimesters of pregnancy?
Populations	Women between 20 weeks and 36 weeks and 6 days of pregnancy who have suspected pre-eclampsia. If data permits, subgroup analyses could be done for women: • Between 20 weeks and 34 weeks plus 6 days of pregnancy • Between 35 weeks and 36 weeks and 6 days of pregnancy • With chronic hypertension • With severe hypertension (BP of 160/110 mmHg or more) • With pre-existing or gestational diabetes • With renal disease • With an autoimmune disease

	• With a multiple pregnancy (for example, twin or triplet pregnancy) Test results may be impacted by ethnicity and maternal weight, where data are available these variables should be taken into account.
Interventions	Use of the following tests to help diagnose pre-eclampsia and make subsequent decisions about care (in addition to any clinical assessments): • Triage PlGF test • Elecsys immunoassay sFlt-1/PlGF ratio • DELFIA Xpress PlGF 1-2-3 test with or without DELFIA Xpress sFlt-1 test • BRAHMS sFlt-1 Kryptor / PlGF plus Kryptor PE ratio Use of the interventions should be assessed when used once per episode of suspected pre-eclampsia, and when the interventions are also used for repeat testing of women who have had an initial PlGF-based test for suspected pre-eclampsia that was negative, and who have no additional signs or symptoms of possible pre-eclampsia.
Comparator	No further assessment (that is, beyond clinical assessments already done, such as blood pressure measurement, urinalysis and fetal monitoring) to help make a decision about a diagnosis of pre-eclampsia and subsequent decisions about care.
Healthcare setting	Secondary care
Outcomes	Intermediate measures for consideration may include: • Diagnostic accuracy (including positive and negative predictive values) • Concordance between tests • Prognostic accuracy • Time to test result • Impact of test result on clinical decision making • Test failure rate • Time to diagnosis • Proportion of women diagnosed with pre-eclampsia • Time to onset of pre-eclampsia and/or eclampsia • Proportion of women returned to less intensive follow-up • Number of women admitted to hospital / Length of in-patient hospital stay • Time to delivery

	• Gestation at diagnosis of pre-eclampsia • Use of antihypertensive drugs
	Clinical outcomes for consideration may include: • Maternal morbidity and mortality • Fetal morbidity and mortality • Neonatal morbidity and mortality
	Patient-reported outcomes for consideration may include: • Health related quality of life
	Costs will be considered from an NHS and Personal Social Services perspective. Costs for consideration may include: • Costs of equipment, reagents and consumables • Cost of staff and associated training • Medical costs arising from testing and care such as hospital stay • Medical costs arising from adverse events including those associated with false test results and inappropriate treatment
	The cost-effectiveness of interventions should be expressed in terms of incremental cost per quality-adjusted life year.
Time horizon	The time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared.

6 Other issues for consideration

If a PLGF-based test can be done at the point of care (that is, rather than having to send a sample to a laboratory) this may reduce the time to a diagnosis of pre-eclampsia. This can be particularly beneficial if the laboratory doing the test is not on-site. A clinical expert highlighted that if the sample is done late in the day it may not be transported to an off-site laboratory until the following day. Quicker results will allow changes to care plans to be made more rapidly, potentially at the same appointment as the test was done, rather than having to provide results through a follow-up phone call.

7 Potential equality issues

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others.

Pregnancy and maternity are protected characteristics in the Equality Act (2010). Pregnant women who have pre-existing conditions such as

autoimmune disease, chronic kidney disease or diabetes may be at a higher risk of developing pre-eclampsia. People of African-Caribbean origin may be at increased risk of severe adverse pregnancy outcomes.

Levels of PlGF may differ according to ethnicity and maternal weight.

8 Potential implementation issues

Use of PlGF-based tests in a near patient setting may require changes to the existing infrastructure in antenatal clinics and maternity units. The feasibility of centrifuging blood in a near patient setting will also need to be considered.

Where PlGF-based tests are used in a laboratory setting, changes to laboratory infrastructure may be required to ensure that test turnaround times facilitate same day assessment of women presenting with suspected pre-eclampsia. Use of PlGF-based tests in either a near patient or laboratory setting would also require the development of both internal and external quality assurance processes.

Antenatal services will need to develop local protocols to facilitate the introduction of PlGF-based testing into the care pathway for women presenting with suspected pre-eclampsia.

9 Authors

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Appendix A Glossary of terms

Automated reagent-strip reading device
A point of care device for assessing proteinuria. Results obtained from an automated strip reading device need to be confirmed by spot urinary protein:creatinine ratio or 24 hour urine collection. The results from an automated strip reading device provide a crude estimation of protein concentration, where 1+ is equal to 30 milligrams/decilitre.

Cardiotocography
Fetal heart rate monitoring.

Chronic hypertension
Hypertension that is present at the booking visit, or before 20 weeks, or if the woman is already taking antihypertensive medication when referred to maternity services. It can be primary or secondary in aetiology

Eclampsia
A convulsive condition associated with pre-eclampsia.

fullPIERS
Risk estimation model developed and validated with the aim of identifying the risk of fatal or life-threatening complications in women with pre-eclampsia within 48 h of hospital admission for the disorder.

Gestational hypertension
New hypertension presenting after 20 weeks of pregnancy without significant proteinuria.

HELLP syndrome ('H' – haemolysis, 'EL' – elevated liver enzymes, 'LP' – low platelet count)
A rare liver and blood clotting disorder that can develop as a complication of pre-eclampsia. It is most likely to occur immediately after the delivery, but can appear any time after 20 weeks of pregnancy, and in rare cases before 20 weeks.

Hypertesnsion
Blood pressure of 140 mmHg systolic or higher, or 90 mmHg diastolic or higher.

Pre-eclampsia
New onset of hypertension (over 140 mmHg systolic or over 90 mmHg diastolic) after 20 weeks of pregnancy and the coexistence of 1 or more of the following new-onset conditions:

- proteinuria (urine protein:creatinine ratio of 30 mg/mmol or more or albumin:creatinine ratio of 8 mg/mmol or more, or at least 1 g/litre [2+] on dipstick testing) or

- other maternal organ dysfunction:
    - renal insufficiency (creatinine 90 micromol/litre or more, 1.02 mg/100 ml or more)
    - liver involvement (elevated transaminases [alanine aminotransferase or aspartate aminotransferase over 40 IU/litre] with or without right upper quadrant or epigastric abdominal pain)
    - neurological complications such as eclampsia, altered mental status, blindness, stroke, clonus, severe headaches or persistent visual scotomata
    - haematological complications such as thrombocytopenia (platelet count below 150,000/microlitre), disseminated intravascular coagulation or haemolysis

- uteroplacental dysfunction such as fetal growth restriction, abnormal umbilical artery doppler waveform analysis, or stillbirth. [Definition from NICE hypertension in pregnancy guideline]

PREP-S
An externally validated survival regression based prognostic model predicting the risk of complications in early-onset pre-eclampsia at various timepoints following diagnosis until 34 weeks of pregnancy.

Proteinuria
The presence of a detectable level of protein in the urine. Initially, this is determined by an automated reagent-strip reading device and confirmed, and quantified, by either a spot urinary protein:creatinine ratio or 24 hour urine collection. A significant level of proteinuria is considered to be more than 300 milligrams per day or a protein:creatinine ratio of 30 milligrams/millimole.

Severe hypertension
Blood pressure over 160 mmHg systolic or over 110 mmHg diastolic.

Severe pre-eclampsia
Pre-eclampsia with severe hypertension that does not respond to treatment or is associated with ongoing or recurring severe headaches, visual scotomata, nausea or vomiting, epigastric pain, oliguria and severe hypertension, as well as progressive deterioration in laboratory blood tests such as rising creatinine or liver transaminases or falling platelet count, or failure of fetal growth or abnormal doppler findings

Soluble FMS-like tyrosine kinase-1 (sFlt-1)
A protein which is thought to disable proteins that aid the development of new blood vessels. It is produced by variety of tissues and binds to circulating vascular endothelial growth factor and PlGF, reducing the effects of these proteins on the developing placenta.

Appendix B Abbreviations

BP	Blood pressure
CTG	cardiotocography
ISSHP	International Society for the Study of Hypertension in Pregnancy
mmHg	Millimetre of mercury
PlGF	Placental growth factor
sFlt-1	Soluble FMS-like tyrosine kinase-1

Appendix C References

NHS digital (2020) Hospital Admitted Patient Care Activity 2019-20, England

NHS UK (2018) Pre-eclampsia https://www.nhs.uk/conditions/pre-eclampsia/