Placental growth factor (alone or in combination with soluble fms-like tyrosine kinase 1) as an aid to the assessment of women with suspected pre-eclampsia: systematic review and economic analysis

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Scientific summary

Placental growth factor in cases of suspected pre-eclampsia

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Pre-eclampsia (PE) is a potentially serious condition affecting up to 5% of pregnancies, most frequently after 20 weeks of gestation. If undetected and untreated it may result in serious maternal and neonatal complications. Suspected PE affects health services by necessitating regular monitoring, testing and treatment. Uncertainty around PE prediction increases the economic burden on the NHS as a result of unnecessary antenatal admissions, fetal monitoring and preterm delivery associated with false-positive diagnoses. Women with PE have longer inpatient stays and their neonates require longer neonatal intensive care unit (NICU) stays than babies born to women without PE. Suspected PE may affect pregnant women through hospitalisation, loss of work days or anxiety. The only cure for PE is to deliver the placenta (and, therefore, the baby), so women are monitored until the optimum time for delivery.

In current practice, the presence or absence of hypertension and proteinuria aid diagnosis of PE, but these markers do not accurately identify or exclude disease with poor pregnancy outcome. Blood tests that could potentially predict PE have recently been developed. These measure the levels of two proteins in blood: placental growth factor (PlGF), which occurs in abnormally low levels in women with PE; and soluble fms-like tyrosine kinase 1 (sFlt-1), which occurs in abnormally high levels in women with PE. However, the diagnostic accuracy and cost-effectiveness of these tests are unclear. The tests specified in the National Institute for Health and Care Excellence (NICE) scope, and included in this diagnostic assessment and economic evaluation, are the Triage® (Alere, Inc., San Diego, CA, USA) PlGF test, the DELFIA® Xpress PlGF 1-2-3 test (PerkinElmer, Wallac Oy, Turku, Finland), the Elecsys® sFlt-1 to PlGF ratio test (Roche Diagnostics GmbH, Mannheim, Germany) and the BRAHMS® sFlt-1 Kryptor/BRAHMS PlGF plus Kryptor PE ratio (Thermo Fisher Scientific GmbH, Hennigsdorf, Germany).

Objectives

The aim was to evaluate the accuracy and cost-effectiveness of biomarker tests at identifying PE for women presenting with suspected PE between 20 weeks and 36+6 weeks of gestation who have received blood pressure assessment and qualitative (dipstick) proteinuria assessment. Specific objectives were to determine the accuracy and cost-effectiveness of the Triage PlGF test, Elecsys sFlt-1 to PlGF ratio test, DELFIA Xpress PlGF test and BRAHMS Kryptor sFlt-1 to PlGF ratio test for the diagnosis of PE in the second and third trimesters of pregnancy:

- in addition to standard clinical assessment
- as a replacement for quantitative proteinuria tests.

Methods

Systematic review of test accuracy

A systematic review of diagnostic and prognostic accuracy evidence was undertaken following a peer-reviewed protocol. Searches were based on a comprehensive search strategy. Bibliographic databases including MEDLINE, EMBASE, Web of Science and The Cochrane Library and Database of Abstracts of Reviews of Effects were searched for English-language references in March 2015, and these searches were updated in July 2015. Conferences, websites, systematic reviews and confidential company submissions were also obtained, and reference lists of identified relevant documents were checked. Studies were eligible if they included women with suspected PE in weeks 20–37 of pregnancy, and reported accuracy of
at least one of the specified tests for identifying PE quantitatively relative to standard clinical practice. Risks of bias and generalisability of the included studies were assessed using a modified version of the Quality Assessment of Diagnostic Accuracy Studies (QUADAS) instrument. Study selection, data extraction and critical appraisal were each performed by at least two reviewers, with any disagreements resolved through discussion. Data were synthesised narratively, with an option of conducting a preplanned meta-analysis if data were sufficiently homogeneous. An advisory group comprising five independent clinical experts informed the review by providing comments on draft versions of the protocol and final report.

Systematic review of economic studies
A systematic review of economic studies followed the same process as the review of test accuracy but with modified eligibility criteria for study designs and outcomes. Studies were included if they were full economic evaluations, assessing both costs and consequences, or cost studies for the specified biomarker tests. Outcomes were those consistent with full economic evaluations and cost studies, including intermediate outcomes (budget impact, cost per patient, cost per case of PE correctly managed), or final outcomes [life-years or quality-adjusted life-years (QALYs) gained]. Studies were critically appraised using standard checklists consistent with NICE criteria. Each step of the review was conducted by two health economists, with any disagreements resolved by discussion. Outcomes were synthesised narratively.

Economic evaluation
The External Assessment Group (EAG) developed a de novo decision-analytic model to assess the cost-effectiveness of PlGF tests or sFlt-1 to PlGF ratio tests for the diagnosis of PE when used in addition to standard clinical assessment compared with standard clinical assessment alone. The model was informed by the systematic review of economic studies, confidential company submissions and information provided by clinical experts and the advisory group. Test accuracy parameters and maternal and fetal outcomes were obtained from the systematic review of test accuracy studies, health-related quality of life (HRQoL) was obtained by a systematic search for HRQoL studies, and cost and resource parameters were obtained by targeted searches in relevant sources. The model is a decision tree incorporating the management of clinical symptoms of suspected PE, the timing and mode of delivery, and maternal and neonatal outcomes. Costs (2014, GBP) are evaluated from a NHS and Personal Social Services perspective. Given the analysis time horizon (under 1 year), no discounting was undertaken.

Results

Number and quality of test accuracy studies
Searches yielded 1972 unique bibliographic records, and a further 20 documents were identified through company submissions. After screening these, the systematic review included 12 documents that reported four unique studies: two used the Triage PlGF test and two employed the Elecsys sFlt-1 to PlGF ratio test. One of the included studies on the Triage test, PETRA, was unpublished and confidential when the present report was prepared; this is excluded from the present report, but was available to the EAG and the NICE Diagnostics Assessment Committee.

The three published studies generally rated well on QUADAS criteria, although all three studies had a high risk of clinical review bias. This is because only test results were used to diagnose PE in the primary studies, whereas in clinical practice test results would be interpreted in conjunction with hypertension, proteinuria and/or other signs or symptoms.

Test accuracy outcomes
Meta-analysis of sensitivity and specificity was not feasible because of the heterogeneity of the study populations and outcomes. Test accuracy outcomes differed among studies in terms of the test cut-off points employed, time periods of gestation covered, and time periods following testing to which the outcomes applied. The Triage PlGF test predicts PE requiring delivery within 14 days of testing (i.e. prognosis) for women presenting in weeks 20–35 and in weeks 35–37 of pregnancy, whereas the Elecsys

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sFlt-1 to PlGF ratio test is diagnostic, predicting rule-out or rule-in of PE within a specified number of weeks for women presenting at any time in weeks 20–37.

For the Triage PlGF test, data are available for test-positive cut-off points of < 100 pg/ml, < 12 pg/ml and < 5th percentile of PlGF concentration, but the < 12 pg/ml cut-off point had low sensitivity (≤ 63%). The < 100 pg/ml and < 5th percentile cut-off points both had high sensitivity (96%) for identifying women likely to develop PE requiring delivery within 14 days, when presenting with suspected PE up to 35 weeks of gestation. However, sensitivity was lower after 35 weeks of gestation (70% for the < 5th percentile cut-off point). Diagnostic accuracy outcomes for the Elecsys sFlt-1 to PlGF ratio are for three test cut-off points: 23, 38 and 85. However, the majority of data are from one study (PROGNOSIS) that employed the 38-week cut-off point. The PROGNOSIS study outcomes suggest that the Elecsys sFlt-1 to PlGF ratio is appropriate for rule-out of PE within 1 week of testing (sensitivity 85.7%, negative predictive value 99.1%) and for rule-in of PE within 4 weeks of testing (specificity 83.1%), although with a relatively high likelihood of false positives (positive predictive value 38.6%).

**Number and quality of economic studies**

Three documents were included in the systematic review of economic studies, which reported on three unique studies. These were cost analyses, focusing on potential savings in health sector resources through improved accuracy of diagnosis of PE. None of the three studies formally evaluated maternal or neonatal outcomes (other than admission to intensive care or to a special care baby unit, which were included in the cost analysis). These studies all have limitations, including that none measured health benefits, none adequately described and justified its resource costs, and none reported whether or not its model was validated. Owing to heterogeneity of the study designs and outcomes, meta-analysis was inappropriate and the results were synthesised narratively.

A further two cost studies for the Triage PlGF test and the Elecsys sFlt-1 to PlGF ratio test were provided in confidential company evidence submissions as part of the NICE Diagnostics Assessment process. These are not described in the current report, but were taken into consideration by the EAG when planning the de novo independent economic analysis.

**Results of the cost-effectiveness analysis**

The EAG cost-effectiveness model predicts that, when supplementing routine clinical assessment for rule-out and rule-in of PE in women with suspected PE, the Triage PlGF test and the Elecsys sFlt-1 to PlGF ratio test would both be cost-saving in weeks 20–35 of gestation and marginally cost-saving in weeks 35–37, but with a minuscule impact on QALYs. Cost differences slightly favour the Triage PlGF test for both gestational periods. The magnitude of savings is uncertain, but the tests remain cost-saving under worst-case assumptions. Length of NICU stay was the most influential parameter in sensitivity analyses. All other sensitivity analyses had negligible effects on results.

Scenario analyses assessing the effects of replacing quantitative proteinuria testing with biomarker testing, and assessing near-patient testing instead of central laboratory testing found negligible impacts on cost-savings for the biomarker tests.

**Discussion**

**Strengths of the evidence synthesis**

The current diagnostic assessment was based on a prespecified, peer-reviewed protocol. It included comprehensive literature searches in a wide variety of data sources undertaken by an experienced information specialist. The study selection and data extraction steps were based on standard pilot tested worksheets. Evidence was critically appraised using prespecified and internationally accepted criteria. Study selection, data extraction and critical appraisal were conducted by at least two reviewers to minimise
risks of errors and bias. All excluded full-text documents are listed with the reasons for exclusion. An independent advisory group informed the protocol, economic model and draft report.

**Limitations of the test accuracy evidence synthesis**
No head-to-head comparisons of relevant biomarker tests were identified. The included evidence base addresses only part of the decision problem, as no relevant studies were found for the DELFIA Xpress PI GF test or the BRAHMS Kryptor sFlt-1 to PI GF ratio test. No relevant studies have investigated the accuracy of PI GF-based tests when used as a replacement for proteinuria testing. Test accuracy studies were at high risk of clinical review bias. Meta-analysis was not possible because the studies employed different outcome measures, test cut-off points and gestational periods. Searches were limited to English-language references; however, we consider it unlikely that this resulted in us missing relevant evidence. The current report does not present information from confidential studies that were available to the EAG and NICE Diagnostics Assessment Committee. However, as explained in Chapter 6, the excluded information would not materially affect the conclusions.

**Limitations of the economic analysis**
Owing to lack of adequate diagnostic effectiveness data, only the Triage PI GF test and the Elecsys sFlt-1 to PI GF ratio test could be analysed. The economic analysis is based on several assumptions because of data insufficiency.

**Uncertainties**
Although data about clinical outcomes other than those related to diagnosing PE (maternal and fetal morbidity and mortality, emergency admission) were reported in some studies, heterogeneity between studies prevented useful assessment of test effects on these outcomes.

Data are lacking for women presenting before 30 weeks of gestation who are at high risk of adverse maternal and neonatal outcomes. There were also insufficient HRQoL data for women with gestational hypertension and PE. The EAG relied heavily on mapping algorithms from the Short Form questionnaire-36 items to provide European Quality of Life-5 Dimensions (EQ-5D) utility estimates. These appeared to overestimate EQ-5D utility scores compared with those measured directly using EQ-5D. However, as no studies have validated the EQ-5D for use in pregnancy or post-partum periods, we cannot rule out the possibility that EQ-5D might have underestimated HRQoL in these periods.

Data are lacking for long-term maternal and neonatal outcomes in women with gestational hypertension, in the general population of pregnant women who give birth preterm, and in high-risk subgroups of women with previous PE, multiple pregnancies, diabetes mellitus (pre-existing or gestational) or renal or autoimmune conditions.

**Conclusions**
The PI GF and sFlt-1 to PI GF ratio tests are currently used to predict PE in only a few UK hospitals. However, our results suggest that there would be clinical benefits and cost savings of using the Triage PI GF test or the Elecsys sFlt-1 to PI GF ratio test, when added to standard clinical assessment, for women presenting with suspected PE between 20 and 37 weeks of gestation. Sensitivity analyses indicate that replacing quantitative proteinuria testing with a PI GF test or a sFlt-1 to PI GF ratio test, or conducting the biomarker tests in a near-patient (e.g. antenatal clinic) setting (as opposed to a central laboratory), would have negligible impact on cost-effectiveness. The most appropriate location and type of testing would vary by local needs and local acquisition and maintenance costs for the test equipment. Investment in equipment and training will be required for any of the biomarker tests to be employed in NHS practice. Further information on the DELFIA Xpress PI GF test and the BRAHMS Kryptor sFlt-1 to PI GF ratio test would be helpful to allow adequate evaluation of their potential test accuracy and cost-effectiveness compared with the Triage PI GF test and the Elecsys sFlt-1 to PI GF ratio test.
Research recommendations
Observational research studies are needed to clarify long-term fetal, neonatal and maternal outcomes for women diagnosed with PE and the utilities associated with these.

Pragmatic research studies should clarify how the PlGF test and sFlt-1 to PlGF ratio test influence key decisions in a clinical setting.

Head-to-head comparisons of PlGF-based tests would help to clarify which test(s) could be most cost-saving for the NHS. This would require that the tests employ the same diagnostic or prognostic end points and cover the same periods of gestation. Such studies should be designed so as to minimise bias, pragmatically reflect UK clinical practice, include women with suspected PE between 20 and 30 weeks of gestation (in addition to other gestational age groups) and employ definitions of PE that are consistent with those employed in UK clinical practice.

Study registration
This study is registered as PROSPERO CRD42015017670.

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This report

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