Placental Growth Factor based tests for the diagnosis of pre-eclampsia

August 2011

The Alere PIGF test and the Roche sFlt-1/PIGF ratio tests may provide a new way of diagnosing pre-eclampsia in pregnant women who have signs and symptoms of the condition. The Alere PIGF test measures a biomarker called placental growth factor (PIGF) and the Roche sFlt-1/PIGF ratio test measures PIGF and soluble FMS-like tyrosine kinase-1 (sFlt-1) in blood samples. It is claimed that these tests may provide earlier and more accurate diagnosis and therefore improved management of this potentially serious condition.

Background

Pre-eclampsia is a potentially life-threatening condition which occurs in an estimated 2.5-3% of pregnancies (an average of 32-38 cases per 100,000 population in 2009 in England & Wales). Severe pre-eclampsia is present in an estimated 0.5% of pregnancies and eclampsia (severe, life-threatening seizure) in 0.04%. Symptoms in the mother include newly increased blood pressure; protein in the urine; headaches; sudden swelling of the hands, feet or face; abdominal pain and vomiting. The developing baby may also be smaller than usual. The most severe complications of pre-eclampsia in the mother include HELLP syndrome (broken down blood cells, raised liver enzymes, and low levels of blood platelets); stroke and eclampsia. Severe complications for the baby include reduced growth; increased risk of developing breathing problems; premature birth; and stillbirth. Taking into consideration the risks to the mother and baby, early delivery of the baby (the only cure for pre-eclampsia) may be offered or recommended. Early-onset pre-eclampsia (20-34 weeks) is associated with more severe symptoms. Risk factors for pre-eclampsia include being aged 40 or over; a personal or family history of pre-eclampsia, no previous pregnancies, a multiple pregnancy, obesity, high blood pressure, stroke and diabetes.

In 2009-10, there were 13,731 admissions to hospital inpatient departments for pre-eclampsia and 354 admissions for eclampsia in England. Maternal deaths from pre-eclampsia are rare in the UK (under 20 per year in England in 2006-08), but most deaths were found to be associated with substandard care, caused by a failure to recognise the signs and symptoms of the condition. Pre-eclampsia is associated with an increased risk of stroke or heart problems in the mother later in life and it is estimated that 50% of women with severe pre-eclampsia will deliver prematurely (10% before 34 weeks). Stillbirths due to pre-eclampsia in 2007 were estimated at approximately 220 for England, Wales, Northern Ireland, Channel Islands and the Isle of Man.
**Current Practice**

Diagnosis of pre-eclampsia is currently made from a clinical assessment, measurement of blood pressure and detection of protein in the urine. Blood pressure and urine protein are routinely measured by the 10th week of pregnancy and at all subsequent antenatal visits. If blood pressure is raised or protein is detected in the urine, these levels are monitored more frequently and often this will involve hospitalisation for confirmation of diagnosis and initiation of expectant management. A uterine artery Doppler ultrasound may also be used in assessing the risk of developing pre-eclampsia. All women with severe high blood pressure which starts in pregnancy are also admitted to hospital. Importantly, these diagnostic criteria are not specific to pre-eclampsia and therefore women without this condition may undergo high levels of monitoring. One estimate is that about 5% of women who are not initially diagnosed with pre-eclampsia, are monitored because of raised blood pressure and ultimately, 15-20% of these women will get pre-eclampsia. Conversely, an estimated 10-20% of women with HELLP syndrome and 38% of women having their first seizure (eclampsia) will not have previously exhibited high blood pressure or protein in their urine.

**New Technology**

Two new tests which measure proteins associated with the development of the blood vessels of the placenta have been developed by Alere International and Roche Diagnostics Ltd. Levels of placental growth factor (PIGF), which normally rise during the first two trimesters and then decrease as pregnancy progresses, are lower throughout pregnancy in women with pre-eclampsia. Levels of soluble FMS-like tyrosine kinase-1 (sFlt-1), which normally increase in late pregnancy, are higher throughout pregnancy and rise at earlier stages of pregnancy in women with pre-eclampsia. These differences in levels between healthy pregnancies and those affected by pre-eclampsia may occur prior to onset of the condition. These new tests are designed for use in women with suspected pre-eclampsia, in addition to current practice, to increase the certainty of diagnosis. The test may need to be repeated at the discretion of the clinician during pregnancy.

**Alere PIGF test**

The Alere PIGF test measures PIGF levels in the plasma, using a fluorescence immunoassay technique. The Triage® meter, into which the test is inserted, provides an automated reading in 15 minutes which can be stored or transmitted. This test may be suitable for use in a point of care setting (for example, providing results during routine antenatal checks).

The Alere PIGF test was CE marked in September 2009 and is currently available in the UK, Europe and Australia. This test is currently being used only in evaluation studies in the UK and will initially be marketed for the diagnosis of early-onset pre-eclampsia. No cost information for this test was available for this brief.

**Roche sFlt-1/PIGF ratio test**

The Roche sFlt-1/PIGF ratio tests measure the relative amounts of PIGF and sFlt-1 (also known as VEGFR1) in a serum sample by ‘sandwich’ immunoassays using...
electrochemiluminescence. The test can be performed by either the Roche Elecsys® or Cobas® automated systems and the time taken to analyse the sample is 18 minutes. In one study, using the Roche Elecsys® instrument, the ratio of sFlt-1 and PlGF levels performed better at diagnosing pre-eclampsia than either PlGF or sFlt-1 alone13.

The Roche sFlt-1/PlGF ratio test was CE marked in the first quarter of 2009 and is currently available in the UK, Europe, Canada, Australia, most countries in Asia as well as all countries recognising the CE mark in Latin America14. It is not currently being used in the UK. The company state that the cost of this test will range approximately at the level of a PCR test. One study, sponsored by Roche, models the economic impact of using this test and concludes that the NHS would save £945 per pregnancy if it was used as an additional diagnostic tool in pre-eclampsia15.

Other than the two tests described above, there are currently no other biomarker tests available for clinical use in the UK for diagnosis of pre-eclampsia in women with suspected pre-eclampsia. The Alere PlGF and Roche sFlt-1/PlGF ratio tests are not intended for screening all pregnant women for pre-eclampsia but for further information on biomarker tests for screening, please see News Brief on Delfia® Xpress PlGF assay by PerkinElmer Inc (Autumn 2011).

Clinical Studies and Research Questions

Alere PlGF and Roche sFlt-1/PlGF Tests
In a study of 44 patients with pre-eclampsia (25 with early-onset pre-eclampsia) and 84 matched healthy patients, samples were tested with the Alere PlGF and Roche sFlt-1/PlGF tests16. The test was done without any knowledge of the clinical diagnosis. The Alere PIGF test was used with cut-off levels dependent on pregnancy stage and the Roche sFlt-1/PlGF test was used with a fixed cut-off (not dependent on the stage of pregnancy), as described by each product insert. The Alere PIGF test correctly identified 100% of early-onset pre-eclampsia cases and 96% of healthy cases. It also identified 77% of all pre-eclampsia cases and 47% of late-onset pre-eclampsia cases, whilst identifying 95% of healthy cases for each group. The Roche sFlt-1/PlGF test correctly identified 64% of early-onset pre-eclampsia cases, 59% of all pre-eclampsia cases and 53% of late-onset pre-eclampsia cases and 100% of healthy cases in all groups. When using pregnancy stage-dependent cut-off values, the Roche sFlt-1/PlGF test correctly identified 68% of early-onset cases, 57% of all pre-eclampsia cases, 42% of late-onset cases and 100% of healthy matched pregnancies in each group.

Alere PIGF Test
Data provided by the company, but as yet unpublished, describe a study of a cohort of 13 women with pre-eclampsia diagnosed before 35 weeks and 22 at 35 weeks or after, who were matched to 18 women in a control group12. For women diagnosed at 23-35 weeks, the company report that the test correctly identified 100% of pre-eclampsia cases and 100% of healthy cases, using a gestational age-dependent variable cut-off. The second cohort reported on consisted of 26 women diagnosed with pre-eclampsia before 35 weeks and 19 at 35 weeks or more, matched to 87 women in a control group. For women diagnosed between 21 and 35 weeks, the test
was reported as correctly identifying 100% of pre-eclampsia cases and 94% of healthy pregnancies, using the same variable cut-off for diagnosis.

A blinded evaluation of the Alere PIGF test as an aid in diagnosing pre-eclampsia and as a predictor of final pregnancy outcome in women with suspected pre-eclampsia is ongoing and is expected to include approximately 500 patients12. Clinical trials of America and Peacehealth have also commenced an evaluation of this test as part of a multicentre study addressing diagnosis and risk stratification in pre-eclampsia in the USA17.

**Roche sFlt-1/PlGF Test**

A study of 71 patients with pre-eclampsia and 280 matched healthy pregnancies initially used the samples of the healthy group to produce a reference level ratio of sFlt-1/PlGF, for diagnosing pre-eclampsia18. The test then correctly identified 82% of all 71 cases of pre-eclampsia (95% of the healthy pregnancies would give a negative test result at this cut-off). The test correctly identified early-onset pre-eclampsia in 89% of the 37 early-onset cases (when 97% of healthy pregnancies would have given a negative result) and 74% of 34 late-onset cases (when 89% of healthy pregnancies would have given a negative result).

The initial characterisation of sFlt-1/PIGF ratio levels in various types of hypertensive pregnancies has been reported at conference. The authors conclude that levels are significantly different in pre-eclampsia, chronic hypertension and pregnancy-induced hypertension and therefore there is potential for this test to differentiate between these conditions in the future19.

There are ongoing studies to evaluate the use of the Roche sFlt-1/PIGF test in diagnosing and predicting pre-eclampsia14.

Trials of these tests in differentiating pre-eclampsia from other conditions with similar symptoms and directly comparing these new tests with current practice alone will be valuable in further assessing their accuracy and potential impact on health outcomes. More data are required to determine whether a negative result from these tests may be used to safely exclude further monitoring of pregnant women, and the optimum frequency with which the test should be repeated during pregnancy.

**Potential Impact**

If these tests are proven to be sufficiently accurate at diagnosing pre-eclampsia, women with raised blood pressure but who do not have pre-eclampsia may potentially be spared stressful, unnecessary further investigations and monitoring in hospital, which may also release NHS resources. Increased certainty in diagnosis may lead to earlier and improved management of the condition in those with pre-eclampsia.

As the range of outcomes for pre-eclampsia varies greatly, of greater impact than diagnosis would be a test that predicts the likelihood of adverse outcomes in those with suspected pre-eclampsia. It is too soon to say whether the Alere PIGF and the Roche sFlt-1/PlGF ratio tests will be able to make such predictions.
References


