Assessment of pre-eclampsia: a change in clinical practice at the John Radcliffe Hospital

Oxford University Hospitals NHS Foundation Trust

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Background

Oxford University Hospitals NHS Foundation Trust (OUH) in numbers (2018-2019)[1]

Turnover of **£1.073 billion**
Employed **3,779 nurses/midwives** and **1,829 doctors**
A total of **7,585 babies** were delivered

OUH hospitals in Oxford serve an Oxfordshire population of 655,000.
OUH specialised services serve approximately 2.5 million people within the local authority areas of Oxfordshire, Buckinghamshire, Milton Keynes, Berkshire, Swindon, Gloucestershire, Northamptonshire and Warwickshire.

Disease burden

Hypertensive disorders, including pre-eclampsia (PE), affect approximately 8 - 10% of pregnancies in the UK.[2] Uncertainty in the diagnosis and prognosis of PE may lead to late diagnosis or, more frequently, unnecessary hospitalisation of women who do not go on to develop the condition.[3] The cause of PE is not fully understood; however, there is growing evidence that angiogenic factors such as placental growth factor (PlGF) and soluble fms-like tyrosine kinase-1 (sFlt-1) play a major role in the development of the condition.[4]

Diagnosis and management of PE (current situation in the UK)

Routine antenatal appointments in the UK involve the assessment of clinical signs and symptoms, including blood pressure and urine protein concentration. Women with suspected PE (often identified at regular community midwife or GP visits) are usually referred to hospital for further assessment. This visit to the hospital combines repeat checks of blood pressure and urine protein, clinical signs and symptoms, and a suite of blood tests including kidney function, electrolytes, full blood count, transaminases, and bilirubin (as per NICE guideline NG133).[5] However, the diagnosis of PE is often challenging due to the non-specificity of these tests and healthcare professionals must therefore rely on their own clinical judgement and patient history.[6]

Unmet medical needs and current challenges

Unfortunately, the presence and severity of hypertension and proteinuria are poor predictors of maternal or neonatal complications.[7,8,9] As such, there is an unmet need for additional measures to aid in the diagnosis of PE, particularly for the short-term prediction or rule-out of PE in pregnant women who are suspected to be at risk of PE.[10]

Opportunity for change

Scientific evidence

Specific biomarkers for PE have been identified, they include soluble fms-like tyrosine kinase (sFlt-1) and placental growth factor (PlGF).[7,11] These markers have been validated in a large number of studies demonstrating that high levels of sFlt-1 and low levels of PlGF are indicators of placental dysfunction, which is clearly implicated in the pathogenesis of PE.[12-14] sFlt-1 is released by the placenta and appears to be a major disease-causing molecule in PE.[15] One of the key actions of sFlt-1 is to bind to other circulating angiogenic factors, including PlGF.[11] Therefore, an elevated sFlt-1 is associated with reduced free PlGF in the circulation. The Elecsys® sFlt-1/PlGF ratio test allows direct measurement of both sFlt-1 and PlGF, which provide valuable information for clinicians when deciding on the most appropriate management of women with suspected PE.

Rationale for change

The John Radcliffe Hospital is a tertiary referral centre set up to serve the Thames Valley region and South Midlands. It provides tertiary referral centre services for maternity, obstetrics and neonatology; patients who are unwell and preterm are transferred to the centre. Therefore, there are a significant number of patients with either PE or suspected PE attending the unit. The lack of accuracy of the routinely used clinical signs and symptoms prompted a rationale for assessing the use of sFlt-1/PlGF ratio in a clinical trial setting. The trial (INSPIRE)[8] was designed to assess patients with suspected symptoms and signs of PE. Patients that fulfilled the criteria for eligibility were approached and consented to have sFlt-1/PlGF ratio measurements in addition to their routine blood tests. sFlt-1/PlGF ratio test requests were sent to the biochemistry lab at the John Radcliffe Hospital to be analysed.

The results were randomised to either being revealed to the clinical team or not. Those patients who did not have a revealed result were treated under standard clinical management, and those patients who had a revealed result were treated according to standard clinical management and an algorithm built around the ratio.

The INSPIRE trial

Design and key results

The INSPIRE trial showed that use of the test significantly improved risk stratification of patients with suspected disease.[8]

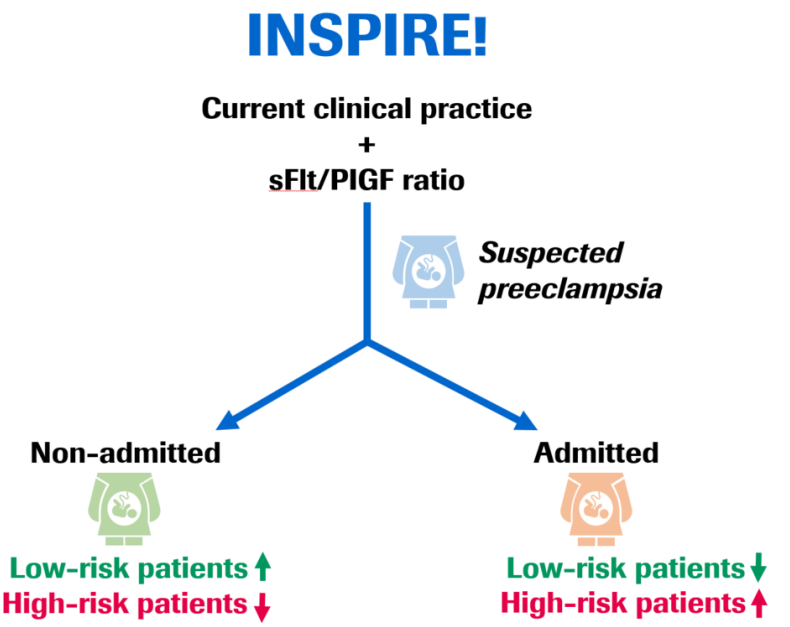


Figure adapted from Cerdeira, et al. (2019).[8]

The figure shows the outcomes in the reveal arm of the study, when the sFlt-1/PlGF ratio was made available to the clinician and this informed the decision whether to admit the woman at suspected risk of PE to hospital or not.

Importantly, adopting the ratio meant that the patients who did develop PE remained in hospital and of the patients who were sent home, none of them developed PE. The ratio in combination with standard clinical management identified 100% of the patients that later developed PE, whereas standard clinical management (non-reveal), by the same clinical team, identified 83%.[8] The trial also provided some insights into the ability of the test to segregate between high and low risk patients.

"Using the test, we were able to identify a cohort of women who had smaller babies, worse blood results, more neonatal intensive care admissions and lower APGAR scores".*[8]

Dr. Sofia Cerdeira, NIHR academic Clinical Lecturer

In general, patients in the reveal arm that were admitted were more likely to have elevated indicators of a higher risk group. This showed the test was able to segregate women by risk more accurately than standard clinical practice. At the end of this trial, the clinicians within the John Radcliffe Hospital expressed concern that the test was no longer available to support clinical decisions and as a body, requested that the test was incorporated into routine practice, as it was found to be of significant clinical value. This then instigated the design of a business case to implement the ratio test.

*This is currently not among the intended uses of the Elecsys® sFlt-1/PlGF ratio test, please refer to package inserts on Roche DiaLog[16] (Elecsys® PlGF catalogue number 05144671190; Elecsys® sFlt-1 catalogue number 05109523190).

The laboratory perspective

The laboratory's awareness of the sFlt-1/PlGF ratio was initiated through an approach from the department of obstetrics to support a study of their value in clinical care. The lab reviewed the method availability on the **cobas e** 411 analyzer to assess the level of difficulty in adopting this test for this study. Professor Tim James (Head Biomedical Scientist in Clinical Biochemistry) says "The automated **cobas**® Elecsys® immunoassay for sFlt-1 and PlGF was easy to set up on the **cobas e** 411 analyzer and a standard laboratory verification was performed. The lab at John Radcliffe Hospital was the first undertaking such a verification in the UK and therefore, we were vigilant around two specific areas. The first being the reproducibility of the test and therefore study samples were analysed in duplicate and assessment of between batch imprecision was undertaken. Secondly, lack of reference material on which to assess accuracy."

As an alternative approach, samples from patients with known PE and those known not to have PE were obtained and analysed as part of the verification. This gave confidence to the laboratory that the test was performing reliably and in accordance with the designated purpose, i.e. prediction of PE. Through discussions with the department of obstetrics, study requirements were ascertained (e.g. reveal vs non-reveal), a small group of lab staff were trained to undertake the test, and started the trial. The within laboratory turnaround for the clinical study was about one hour. This meant the tests were available in the same time frame as routine biochemistry when assessing the patient. Communication channels were direct to the laboratory staff designated to undertake the test (As the clinical implementation of the test was rolled out, there were separate discussions about turnaround times, which are discussed later in the document. Currently – twice daily).

The business case

In order to drive the implementation process forward, the John Radcliffe Hospital team put together a business case. This was drawn up very closely between the department of obstetrics and the department of biochemistry, to fully reflect the cost of providing a result rather than purchasing a kit. These costs will vary depending on whether the lab in question already has Roche Diagnostics Limited equipment in use and are dependent on the number of normal deliveries and the PE patient case mix. Thus, an individual figure will be recommended for each unit contemplating a tailored business case. The design of the Oxford business case was built around the clinical need and the evidence from the INSPIRE trial. Initially efforts for the business case was built on reducing patient bed stay based upon the strong negative predictive value of the test.[3] Whilst this approach was clearly a potent financial argument, these savings were non-recoverable costs since they did not allow the immediate closure of beds within wards and reduction of staff resources. Consequently, an alternative approach was developed to identify true avoided costs (recoverable costs).

This subsequent analysis showed that the principal driver of cost of admission in addition to the bed stay costs was the cost of ultrasound and cardiotocograph (CTG) analysis as well as the cost of follow up monitoring and testing. The redesigned business case showed a reduction in the requirement of scans for patients who did not have a high ratio, as well as the reduction in the need for follow-up. This cost analysis proved cost neutral. Consequently, this approach, which combined quality and safety improvements concurrent to overall cost neutrality was welcomed and the business case was approved at a senior management level, and progression to implementation was agreed.

Implementing the change

Education

Lectures and teaching sessions were offered on a repetitive basis to midwifery staff, junior doctors, and consultants to educate on the use and benefits of using the ratio test. This recurrent training allowed people to understand what the ratio was measuring, what the value of the ratio was, what the ratio meant, and what they were meant to do with the ratio with reference to the clinical algorithm. There was also a strict and very important caveat to the process: The ratio was not a substitute for clinical assessment on the patient and that the clinical assessment of the patient would override the ratio.

Alongside this local education there was engagement with the Oxford Academic Health Science Network (AHSN), which ran concomitantly. The Oxford AHSN had a mandate to improve adoption of new technologies and were very interested in the concept of rolling out sFlt-1/PlGF testing for PE. This facilitated education in the more peripheral hospitals and allowed the John Radcliffe Hospital to obtain key contacts in both the department of biochemistry and obstetrics who would champion the test in each of those local hospitals.

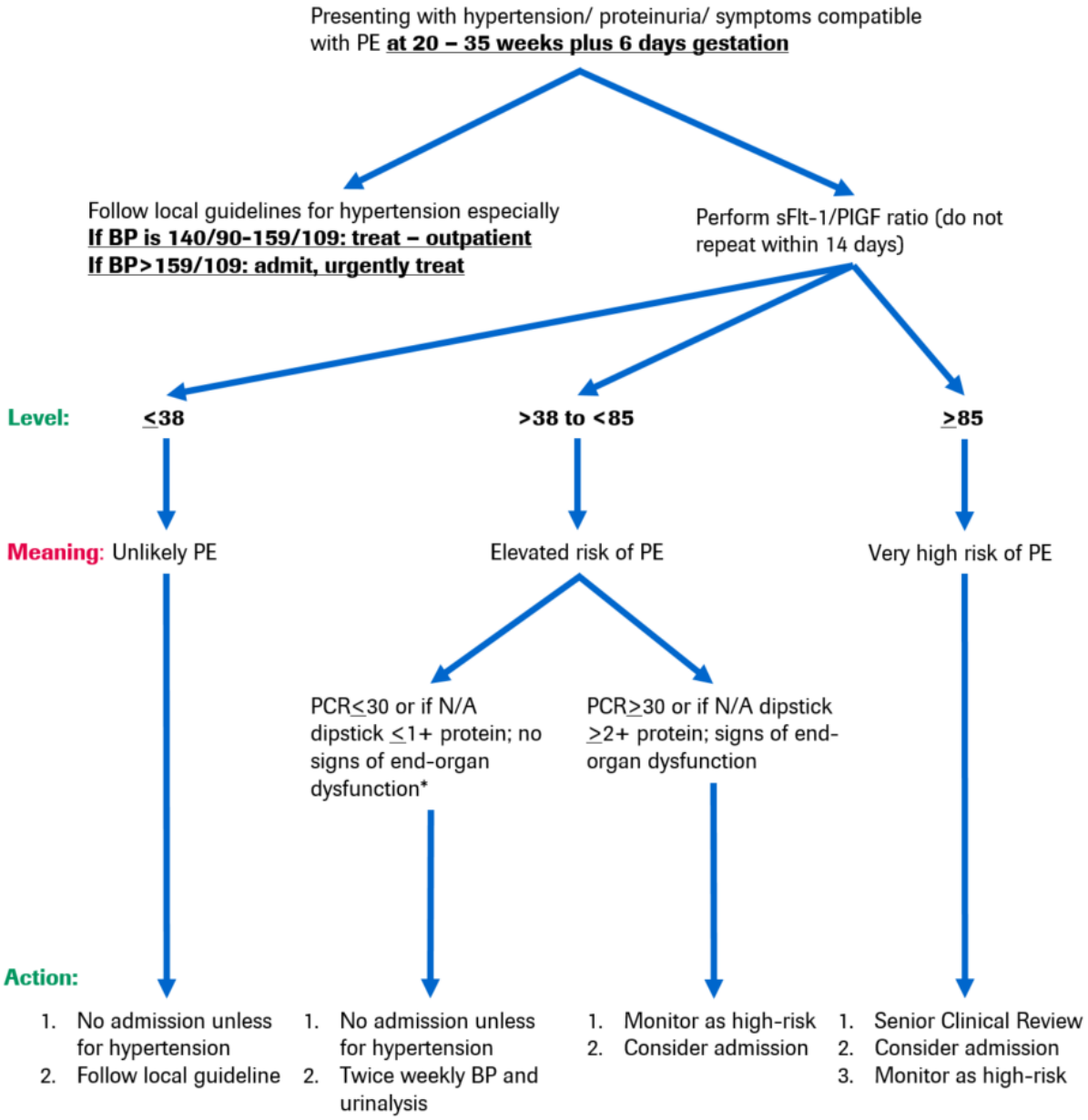
Algorithm

A clinical algorithm was created which took into account the positive and negative predictive values of the INSPIRE trial performed and thus divided the sFlt-1/ PlGF into three areas of risk based on the ratio:

- A ratio of less than or equal to 38 as determined in the PROGNOSIS study[13], which from our trial INSPIRE[8] showed that those patients had a less than 0.4% risk of developing PE within the following seven days. There was <3% risk of developing PE over the following four weeks. This meant that the clinicians could confidently send these patients home, within this time frame.
- Patients with a ratio above 85 had a 55% chance of developing PE within the following seven days. This provided strong evidence that these patients should be followed up with senior review and a strong consideration for admission.
- The patients with a ratio higher than 38 and less than 85 had a 20% chance of developing PE within the following seven days and thus an enhanced programme of surveillance was designed. This focused on the presence or absence of protein in urine so, if the ratio was between the lower and the outer figures and they had no proteinuria, a light touch policy of surveillance was implemented, whereas if the patient had proteinuria or signs of end-organ disease, then a higher level of surveillance was recommended.

The Algorithm

Clinical algorithm used by OUH for women (out-patients) at suspected risk of pre-eclampsia (PE):



BP: blood pressure; **PCR:** protein to creatinine ratio; **PE:** preeclampsia

Notes:

This guideline should be regarded as additional to local hypertension/ PE guidelines and should not replace them. sFlt-1/ PlGF ratio DOES NOT predict hypertension, which may be life threatening in absence of PE. Local/ national hypertension guidelines should be followed, and ultrasound and steroids should be considered as per local guidelines.

*Determined as per ISSHP criteria; (creatinine >90 umol/L, elevated transaminases 2x normal +/- severe RUQ/epigastric pain; eclampsia, altered mental status, blindness, stroke, or more commonly hyperreflexia when accompanied by clonus, severe headaches when accompanied by hyperreflexia, persistent visual scotomata; thrombocytopenia, DIC, haemolysis; foetal growth restriction).

This algorithm was shared within the Thames Valley network, and the Oxford AHSN was instrumental in disseminating that protocol. This meant that everybody within the region would be following the same approach and therefore avoiding the risk of having different cut offs and thus the risk of inappropriate admission or inappropriate discharge. As doctors were moving around hospitals as part of their rotation, the familiarity of the test meant that they could move to a new hospital without the need to re-train. Designing the algorithm with the benefit of the INSPIRE[8] data took also into account NICE DG23[17] and the decision was made to initiate testing between 24 and 34+6 weeks gestation.

This is not because they did not believe the test has a value greater than that gestation (PROGNOSIS study and INSPIRE trial include patients up to 37 weeks), but so to educate clinicians and the midwives in appropriate use of the test before rolling the test out to later gestations. If testing across all gestational ages was implemented in one go, there was a risk of inappropriate and excessive usage without education.

"The ratio test added an element of substantiation to the situation which we couldn't have otherwise done"

Dr Manu Vatish, Senior Clinical Fellow and Consultant in Obstetrics

The laboratory perspective

Once the John Radcliffe Hospital had achieved financial approval for initiating the test, a discussion with the clinical biochemistry department took place, regarding the appropriate timing and turnaround time for the ratio test as a routine service. It was clear that this needed to be a phased approach. This initially focused on Monday to Friday 8am to 8pm, which is when it was thought the majority of admissions would come from the community midwives and GPs to the hospital. As the Roche Diagnostics Limited analyser was in the screening laboratory section rather than the core 24/7 laboratory, a decision to run a twice-daily batch analysis was made which developed into a continuously available eight to eight service. This was with the caveat that, if a subsequent audit revealed an unmet need for more frequent testing or testing later on into the evening, or weekend then this could be discussed with the senior hospital managers with the benefit of audit data.

Patient cases

Case one

First pregnancy
24 weeks plus 3 days of gestation
Moderately elevated blood pressure (144/95 mmHg)
No proteinuria
sFlt-1/PlGF ratio test: 623

Her blood pressure was moderately elevated, and the scan showed the baby was small, following the algorithm she received a ratio test that gave a number of 623. As a result, she was closely monitored and developed severe PE about a week and a half following the ratio test. The baby was delivered, but the advantage of having that ratio was that they had admitted her, scanned her, given her antenatal corticosteroids to improve foetal maturity, and then were ready with the magnesium sulphate to help improve the neurological outcome for the baby when she required delivery. This asymptomatic patient might well have been sent home without the benefit of ratio and might have presented in extremis.

Case two

Second pregnancy
28 weeks of gestation
sFlt-1/PlGF ratio: 6

Severe PE in the last pregnancy and severe HELLP syndrome. Based on this past experience, the mother kept measuring her own blood pressure (140/90mmHg) at home and then attending the hospital, as she was anxious and very concerned that she might develop PE again. Carrying out the ratio test on this lady, the midwife on call was able to reassure her that she was well as it was very low (ratio=6) and she could go home. Dr Manu Vatish (Senior Clinical Fellow and Consultant in Obstetrics) said “the ratio test added an element of substantiation to the situation which we couldn’t have otherwise done”.

Looking to the future

Challenges and practical learns

Dr Manu Vatish said “Firstly it is important that the department of obstetrics engages with the biochemistry lab at a very early time point in the gestation of the proposed implementation, as these departments are usually housed in completely different directorates, they have a different management structure and a different set of financial umbrellas. Within the Oxford network, they found that there is engagement and collaboration at every level of the Obstetrics and laboratory departments. Secondly, initiating a conversation about budget as early as possible. Depending on the financial arrangements in place at any individual trust, there may be silo budgets, and block contracts, which preclude development to new markers from laboratory services. Therefore, jointly written business cases are more likely to succeed. It is advisable to start with a clear objective that is aligned with the Trust focus e.g. bed saving on non-recoverable costs basis.

The business case needs to be tailored to the appropriate financial model of the Trust, and so independent of the conversation between the department of obstetrics and the department of biochemistry. It is important to talk to finance colleagues and understand whether the particular Trust works to recoverable or non-recoverable costs savings and tailor the business case accordingly. Consideration will need to be made in regards to the primary provider of laboratory automation and contractual obligations in relation to that, as this will influence within laboratory options and sample workflow. Engaging and working closely with the local AHSN would help to identify and reach out to the most appropriate collaborators.”

Looking forward

The John Radcliffe Hospital is currently carrying out an audit that would enable them to draw conclusions regarding the penetration and performance of the test. The number of tests that they have performed so far are in line with what they expected. An internal audit has confirmed the 100% negative predictive value of the test that they showed in the INSPIRE trial. They are currently benchmarking practice pre-test implementation in order to evaluate the efficacy of the test.

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Company Registration Number: 571546

Date of preparation: May 2020.
Document number: MC-CY-00038

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