Methods of prediction and prevention of pre-eclampsia: systematic reviews of accuracy and effectiveness literature with economic modelling

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Executive summary

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Background

Pre-eclampsia is part of a spectrum of conditions known as the hypertensive (high blood pressure) disorders of pregnancy and is defined as hypertension and proteinuria detected for the first time in the second half of pregnancy (after 20 weeks’ gestation). Pre-eclampsia complicates 2–8% of pregnancies and may have serious effects on mother and child, which makes it an important threat to public health in both developed and developing countries. Once women are identified to be at high risk, they can be targeted for more intensive antenatal surveillance and prophylactic interventions. This report contains a health technology assessment of current strategies for risk stratification and prevention to guide clinical practice and future research in this field.

Objectives

The aim of the project was to identify combinations of test and treatments that would predict and help prevent pre-eclampsia. This study completed three distinct pieces of work to contribute to this goal:

- a series of systematic reviews on the accuracy of tests for the prediction of pre-eclampsia
- a series of systematic reviews of effectiveness of interventions with potential to reduce the number of cases of pre-eclampsia
- a health economic evaluation, including an economic model, of the combined effect of tests and interventions and their cost-effectiveness.

Methods

Protocols were developed for test accuracy and effectiveness systematic reviews which used up-to-date review methods, including searches without language restrictions, study quality assessment and meta-analysis where appropriate. Although there was a slight variation between the search end-date of different systematic reviews, searches were generally conducted to January 2005 at least. For test accuracy reviews, literature was identified from several sources, including databases: PubMed (MEDLINE), EMBASE (Ovid), The Cochrane Library (DARE, CCTR), MEDION, contact with experts including the Cochrane Pregnancy and Childbirth Group and checking of reference lists of accuracy review articles and papers that were eligible for the systematic reviews included in this report. Included were cohort and case-control studies of pregnant women where the test under review was performed before the 25th week of gestation and compared with the reference standard of pre-eclampsia and a $2 \times 2$ table was reported or could be calculated. Quality assessment was based on QUADAS criteria. Meta-analyses used a bivariate approach.

Effectiveness reviews were conducted under the auspices of the Cochrane Pregnancy and Childbirth Group. Studies were identified from the Cochrane Central Register of Controlled Trials (CENTRAL), the Cochrane Pregnancy and Childbirth Group’s trials register, MEDLINE, EMBASE, handsearches of 30 journals and conference proceedings and reference lists of trial reports. Included were randomised or quasi-randomised controlled trials of the relevant intervention compared with placebo, no treatment or usual care in pregnant women that measured pre-eclampsia as an outcome. Quality assessment was as described in the Cochrane Handbook. Meta-analyses estimating relative risk (RR) were conducted in Review Manager software, using a fixed effects models or random effects if heterogeneity was detected.

For the economic evaluation, the model structure used was a decision tree constructed in DATA Treeage software. An NHS perspective was chosen. Four options (test no-one and treat all, test all and treat no-one, test all and treat only with positive test and test all and treat all) were compared with test no-one and treat no-one. Inputs to the model were test accuracy and effectiveness systematic review meta-analysis results, test accuracy and intervention costs, cost of pre-eclampsia as an outcome and the prevalence of pre-eclampsia. The primary analysis used point estimates of key parameters of all tests and the most effective interventions. Extensive deterministic and probabilistic sensitivity analyses were
conducted. The outputs were incremental cost-effectiveness ratios for test and treatment combinations.

Results

Main findings of test accuracy reviews
There were 27 tests reviewed [body mass index (BMI), α-fetoprotein, cellular and total fibronectin, foetal DNA, haemoglobin, haematocrit, human chorionic gonadotrophin, oestriol, uric acid, urinary calcium excretion, urinary calcium/creatinine ratio, several forms of proteinuria/albuminuria and several flow velocity waveforms of Doppler uterine artery]. The quality of studies and the accuracy of tests were generally poor. Some tests appeared to have high specificity, but at the expense of compromised sensitivity. Only a few tests reached specificities above 90%. These were BMI > 34, α-fetoprotein and uterine artery Doppler (bilateral notching). The only Doppler test with a sensitivity of over 60% was resistance index and combinations of indices. Kallikreinuria had a sensitivity of over 80%. Cellular and total fibronectin and kallikreinuria were found to have specificities above 90%. However, these estimates were based on single studies. Also, a few tests not commonly found in routine practice, such as kallikreinuria and sodium dodecyl sulfate polyacrylamide gel electrophoresis proteinuria, seemed to offer the promise of high sensitivity, without compromising specificity, but these too would require further investigation.

Main findings of effectiveness reviews
Sixteen systematic reviews of interventions are presented in this report, of which 15 provided estimates of effectiveness in preventing pre-eclampsia. The quality of included studies was variable; many reviews included only small, poor-quality trials and a small number of reviews included large, well-designed trials. The largest review was of antiplatelet agents, primarily low-dose aspirin, and included 51 trials (36,500 women). This was the only review where the intervention was shown to prevent both pre-eclampsia [RR 0.81, 95% confidence interval (CI) 0.75 to 0.88] and its consequences for the baby (death, preterm birth and small for gestational age). Calcium supplementation also reduced the risk of pre-eclampsia (12 trials, 15,206 women, RR 0.48, 95% CI 0.33 to 0.69) but with some uncertainty about the impact on outcomes for the baby. The only other intervention associated with a reduction in RR of pre-eclampsia was rest at home, with or without a nutritional supplement, for women with normal blood pressure. However, this review included just two small trials (106 women) and its results should be interpreted with caution. Although the review of antioxidant agents (vitamins C and E in particular) presented here reports a reduction in the relative risk of pre-eclampsia, two large trials have subsequently reported their results. In the recently updated Cochrane review, the effect on pre-eclampsia is no longer statistically significant.

Main findings from the economic evaluation
The cost of most of the tests was modest, ranging from £5 for blood tests such as serum uric acid to approximately £20 for Doppler tests. Similarly, the cost of most interventions was also modest. In contrast, the best estimate of additional average cost associated with an average case of pre-eclampsia was high at approximately £9000.

The results of the modelling revealed that prior testing with the test accuracy sensitivities and specificities identified appeared to offer little as a way of improving cost-effectiveness. Based on the evidence reviewed, none of the tests appeared sufficiently accurate to be clinically useful and the results of the model favoured no-test/treat-all strategies.

The treatments included in the main analysis were rest at home, antiplatelets, antioxidants and calcium as these were the interventions where the RRs and 95% CIs showed they were unlikely to be associated with a worse outcome of pre-eclampsia frequency. However, if the results of the updated Cochrane review on antioxidants had been available when the economic model was run, antioxidants would not have been so included.

Rest at home without any initial testing was the most cost-effective ‘test–treatment’ combination, delivering the greatest reduction in number of cases of pre-eclampsia at virtually zero additional cost (to the NHS). Calcium supplementation to all women, without any initial testing, was the second most cost-effective. The costs averted as a result of this reduction in cases of pre-eclampsia greatly exceed the cost of the calcium supplementation. Paradoxically, antiplatelet agents, the treatment about which there was greatest certainty of effectiveness, did not feature among the cost-effective options highlighted. This was because the size of the effect on number of cases of pre-eclampsia prevented, on current evidence, was smaller than the effect of rest at home and calcium supplementation. Thus, the very low cost
associated with antiplatelet agents was outweighed by the higher number of pre-eclampsia cases and the high associated cost. Calcium was more costly compared with antiplatelets but had fewer cases of pre-eclampsia and was therefore shown to be relatively much more cost-effective by the economic model.

All three main predictions of the economic model were affected by uncertainty. However, effective treatments (RR < 0.7) with modest costs (<£50) applied to all women without prior testing were likely to be preferred from the perspective of cost-effectiveness. Threshold analyses conducted in the economic model suggested that tests with upper range costs would need substantially improved sensitivities (assuming best level of specificity achieved in any test was maintained). The economic model provided little support that any form of Doppler test has sufficiently high sensitivity and specificity to be cost-effective for the early identification of pre-eclampsia. The economic model also suggested that the pattern of cost-effectiveness was no different in high-risk mothers than the low-risk mothers considered in the base case.

**Conclusions**

None of the tests evaluated is sufficiently accurate, in our opinion, to suggest its routine use in clinical practice. Calcium and antiplatelet agents, primarily low-dose aspirin, are the interventions shown to prevent pre-eclampsia. The most cost-effective approach to reducing pre-eclampsia is likely to be the provision of an effective, affordable and safe intervention applied to all mothers without prior testing to assess levels of risk. However, we believe that it is probably premature to suggest the implementation of a treat-all intervention strategy such as advice to rest or pharmacological interventions such as low-dose aspirin or calcium supplementation at present. However, the feasibility and acceptability to women of offering universal application of interventions could be explored. Some consideration needs to be given to whether the health service should continue to do certain tests whose main perceived value is to help identify pre-eclampsia when their usefulness is questionable.

**Recommendations for further research**

Rigorous evaluation is needed of tests with modest cost whose initial assessments suggest that they may have high levels of both sensitivity and specificity. Similarly, there is a need for high-quality, adequately powered randomised controlled trials to investigate whether interventions such as advice to rest are indeed effective in reducing pre-eclampsia. In future, an economic model should be developed which considers not just pre-eclampsia, but other related outcomes, particularly those relevant to the infant such as perinatal death, preterm birth and small for gestational age. Such a modelling project should make provision for primary data collection on the safety of interventions and their associated costs.

**Publication**

The Health Technology Assessment (HTA) Programme, part of the National Institute for Health Research (NIHR), was set up in 1993. It produces high-quality research information on the effectiveness, costs and broader impact of health technologies for those who use, manage and provide care in the NHS. ‘Health technologies’ are broadly defined as all interventions used to promote health, prevent and treat disease, and improve rehabilitation and long-term care.

The research findings from the HTA Programme directly influence decision-making bodies such as the National Institute for Health and Clinical Excellence (NICE) and the National Screening Committee (NSC). HTA findings also help to improve the quality of clinical practice in the NHS indirectly in that they form a key component of the ‘National Knowledge Service’.

The HTA Programme is needs-led in that it fills gaps in the evidence needed by the NHS. There are three routes to the start of projects.

First is the commissioned route. Suggestions for research are actively sought from people working in the NHS, the public and consumer groups and professional bodies such as royal colleges and NHS trusts. These suggestions are carefully prioritised by panels of independent experts (including NHS service users). The HTA Programme then commissions the research by competitive tender.

Secondly, the HTA Programme provides grants for clinical trials for researchers who identify research questions. These are assessed for importance to patients and the NHS, and scientific rigour.

Thirdly, through its Technology Assessment Report (TAR) call-off contract, the HTA Programme commissions bespoke reports, principally for NICE, but also for other policy-makers. TARs bring together evidence on the value of specific technologies.

Some HTA research projects, including TARs, may take only months, others need several years. They can cost from as little as £40,000 to over £1 million, and may involve synthesising existing evidence, undertaking a trial, or other research collecting new data to answer a research problem.

The final reports from HTA projects are peer-reviewed by a number of independent expert referees before publication in the widely read journal series *Health Technology Assessment*.

Criteria for inclusion in the HTA journal series

Reports are published in the HTA journal series if (1) they have resulted from work for the HTA Programme, and (2) they are of a sufficiently high scientific quality as assessed by the referees and editors.

Reviews in *Health Technology Assessment* are termed ‘systematic’ when the account of the search, appraisal and synthesis methods (to minimise biases and random errors) would, in theory, permit the replication of the review by others.

The research reported in this issue of the journal was commissioned by the HTA Programme as project number 01/64/04. The contractual start date was in January 2004. The draft report began editorial review in August 2006 and was accepted for publication in August 2007. As the funder, by devising a commissioning brief, the HTA Programme specified the research question and study design. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors’ report and would like to thank the referees for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

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