Pre-eclampsia screening.

An evaluation of the applicability of the criteria for appraising the viability, effectiveness and appropriateness of a screening programme for pre-eclampsia, based on the HTA report – Meads CA et al. Methods of prediction and prevention of pre-eclampsia: systematic reviews of accuracy and effectiveness literature with economic modelling.(1)

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Introduction

This brief document was developed at the request of the UK National Screening Committee as a means of summarising the findings of the 2008 HTA report 'Methods of prediction and prevention of pre-eclampsia: systematic reviews of accuracy and effectiveness literature with economic modelling' (1). This document should be read as an appendix to the report.

The Condition

1. The condition should be an important health problem

Pre-eclampsia is a serious health problem. It is defined as the development of high blood pressure and proteinuria first detected in the second half of pregnancy (after 20 weeks gestation), and may have serious effects on both the mother and the child. Pre-eclampsia in the mother can lead to eclampsia, stroke, a syndrome of haemolysis, elevated liver enzymes and low platelets (HELLP syndrome) and disseminated intravascular coagulation, and is a major cause of maternal mortality. The effects on the baby include premature delivery of the baby, foetal growth restriction, developmental delay and chronic ill-health in childhood.

2. The epidemiology and natural history of the condition, including development from latent to declared disease, should be adequately understood and there should be a detectable risk factor, disease marker, latent period or early symptomatic stage.

Pre-eclampsia is part of a spectrum of conditions known as the hypertensive disorders of pregnancy. These conditions have a continuum with normal pregnancy. Further information on the epidemiology and natural history of the condition can be found in section 1 of the HTA report (1). Pre-eclampsia complicates between 2-8% of all pregnancies, and incidence is increased in women with risk factors such as maternal diabetes, chronic hypertension and renal disease.

For women with raised blood pressure only (gestational hypertension) the outcome is similar to normal pregnancy. If proteinuria develops, the condition is then pre-eclampsia and the outcome may be compromised. An estimated 10–25% of maternal deaths in developing countries are associated with pre-eclampsia or eclampsia as are 15% of the direct obstetric deaths in the UK

and USA. Perinatal mortality is increased following pre-eclampsia and pre-eclampsia accounts for an estimated one-fifth of antenatal admissions, two-thirds of referrals to day-care assessment units and one-quarter of obstetric admissions to intensive care units.(1)

The causes of pre-eclampsia are not clearly known and many theories have been suggested. It is thought that the placenta plays a key role in pre-eclampsia as a placenta must be present for pre-eclampsia to occur. Factors that appear to have a role in the development of pre-eclampsia include the anatomy and physiology of the placenta itself, the maternal immune response, genetic predisposition, maternal vascular disease and diet. There are no known detectable risk factors or disease markers for pre-eclampsia that are consistently present in the first half of pregnancy for women who will go on to develop pre-eclampsia and consistently absent in those who do not develop pre-eclampsia.(1)

3. All the cost-effective primary prevention interventions should have been implemented as far as practicable.

The HTA report included a systematic review of preventive interventions for pre-eclampsia (1) and evaluated the following interventions:

- Ambulatory v conventional methods for monitoring blood pressure
- Antihypertensives
- Anti-oxidants (vitamin C, vitamin E, selenium, lycopene, red palm oil)
- Antiplatelet agents
- Balanced protein/energy intake
- Bed rest in women with high blood pressure
- Calcium supplementation
- Diuretics
- Energy and protein restriction
- Exercise
- Garlic
- Isocaloric balanced protein supplementation
- Magnesium supplementation
- Marine oil and other prostaglandin precursor supplements
- Nitric oxide
- Nutritional advice
- Progesterone
- Reduced salt intake
- Rest in women with normal blood pressure

These were based on Cochrane reviews that were updated to 2004, 2005 or 2006 depending on the review. Four interventions were found to reduce the risk of pre-eclampsia with statistically significant results.

I. Anti-oxidants (RR 0.61 (95%CI 0.50-0.75) but the next update of the Cochrane review included two new large trials which meant that the overall estimate of effectiveness of anti-oxidants to prevent pre-eclampsia was no

longer statistically significant. The current version of the Cochrane review from 2008 also shows no significant difference (RR 0.73 (95%CI 0.51-1.06).

II. Antiplatelets (RR 0.81 (95%CI 0.75-0.88). This systematic review did not evaluate the full potential side effects of anti-platelet agents on pregnancy, for example on bleeding events. The latest version from 2009 continues to show a statistically significant difference to prevent pre-eclampsia (RR 0.83 (95%CI 0.77-0.89). There was no significant difference in intraventricular haemorrhage rates but a possibility of a higher rate of gross and fine motor problems in treated women compared to controls. The Cochrane review conclusion includes the following “Starting aspirin before 12 weeks or using higher doses, or both, cannot be recommended for clinical practice until more information is available about safety”(2)

III. Calcium supplementation (RR 0.48 (95%CI 0.33-0.69). Much of this evidence was based on trials in women who lived in areas of the world where they were likely to have low dietary calcium, unlike the UK where dietary calcium is usually adequate. The subgroup analysis by dietary calcium availability demonstrated this effect (adequate calcium diet RR 0.62 (95%CI 0.32-1.20), low calcium diet RR 0.36 (95%CI 0.18-0.70)). The 2010 version of the Cochrane review shows the same subgroup results so dietary calcium is unlikely to be a useful primary prevention intervention for the UK.

IV. Rest in women with normal blood pressure (RR0.05 (95%CI 0.00-0.83). This was based on a single trial with 32 women so results should be viewed with caution. The latest update (2010) found no additional evidence on pre-eclampsia.

The evidence suggests that there are no suitable primary prevention interventions currently available that could be used in a UK population.

The HTA report developed an exploratory model to evaluate the cost effectiveness of different strategies such as test then treat women with positive test results or treat all without testing first (1). Section 5 below lists the tests that were evaluated. The HTA report found that none of the tests evaluated were sufficiently accurate to suggest routine use in clinical practice. The most likely cost-effective approach to reducing pre-eclampsia was found to be the provision of an effective, affordable and safe intervention such as applied to all mothers without prior testing to assess levels of risk. Anti-platelet agents may be one possibility but, as mentioned above, their safety has not been fully assessed for use in pregnancy.

4. If the carriers of a mutation are identified as a result of screening the natural history of people with this status should be understood, including the psychological implications.

No genetic mutations were identified to be consistently associated with the development of pre-eclampsia.

The Test

5. There should be a simple, safe, precise and validated screening test.

The aim of screening should be to identify pregnant women in the first trimester who are at risk of developing pre-eclampsia later in pregnancy and to offer interventions to reduce this risk.

The HTA report included a systematic review of predictive tests (1) that evaluated the following tests:

- Body Mass Index
- Alphafoetoprotein
- Fibronectin (cellular and total)
- Foetal DNA
- Human chorionic gonadotrophin
- Oestriol
- Serum uric acid
- Urinary calcium excretion and calcium/creatinine ratio
- Total proteinuria
- Total albuminuria and microalbuminuria and microalbumin/creatinine ratio
- Kallikreinuria
- SDS-Page proteinuria
- Doppler indices (any/unilateral notching, bilateral notching, other ratios, pulsatility index, resistance index, combinations of flow velocity waveforms)

All of the tests were relatively safe but their sensitivities and specificities were relatively low, so that no test was identified that would be useful for the prediction of pre-eclampsia. The best test found was kallikreinuria with a sensitivity of 83% (95%CI 52 – 98) and specificity of 98% (95%CI 98 – 100) but this was based on one study only.

Tests that have been evaluated in other systematic reviews more recently than the HTA report include the following:
I. Mean arterial pressure and blood pressure (3). For readings in the second trimester of pregnancy, the AUC results were systolic blood pressure 0.68 (95%CI 0.64-0.72), diastolic blood pressure 0.66 (95%CI 0.59-0.72) and mean arterial pressure 0.76 (95%CI 0.70-0.82) in women at low risk of pre-eclampsia. Findings for the first trimester showed a similar pattern.

II. Soluble fms-like tyrosine kinase receptor (sFlt-1) and Placental growth factor (4). This review used a vote-counting approach to integration of results but concluded that the evidence was insufficient to recommend either marker for screening.

III. Combination of biochemical and ultrasonographic markers (5). The biochemical markers included placental protein 13 (PP13), pregnancy-associated plasma protein A (PAPP-A), a disintegrin and metalloprotease-12 (ADAM12), HCG, AFP, PIGF, homocysteine, activin A and inhibin A. The

ultrasonic markers included uterine artery notch, bilateral notches, Pulsatility Index and Resistance Index. Combinations could be one or more biochemical markers with one or more ultrasonographic markers. In low risk women the sensitivities varied between 7.8% and 100% and specificities between 80% and 100%. No combination had excellent sensitivity and specificity. The nearest was PIGF, PAPP-A and Pulsatility Index, MAP and maternal factors which had a sensitivity of 93.1% and specificity of 95% for early pre-eclampsia.

This suggests that there is no simple, safe, precise and validated screening test for the prediction of pre-eclampsia that would be useful for general UK population screening in the first or second trimesters of pregnancy.

6. The distribution of test values in the target population should be known and a suitable cut-off level defined and agreed.

See above.

7. The test should be acceptable to the population.

Acceptability of the tests was not explored in the HTA report (1).

8. There should be an agreed policy on the further diagnostic investigation of individuals with a positive test result and on the choices available to those individuals.

See above

9. If the test is for mutations the criteria used to select the subset of mutations to be covered by screening, if all possible mutations are not being tested, should be clearly set out.

There is no suitable genetic mutation test available at the moment.

The Treatment

10. There should be an effective treatment or intervention for patients identified through early detection, with evidence of early treatment leading to better outcomes than late treatment.

The HTA report assessed treatments to prevent pre-eclampsia and these have been summarised above (see section 3). In the absence of preventive treatments, clinical management during pregnancy is by regular testing for pre-eclampsia through blood pressure and urine monitoring then treatment of those who develop the condition.

The main management strategy in the presence of established pre-eclampsia is the early delivery of the baby (and the placenta). This is not usually a problem if the pre-eclampsia develops late in pregnancy. If it develops early then a difficult choice is made between delivering the baby and protecting the mother. Treatments that can be used to delay the need for delivery include

administration of magnesium sulphate, antihypertensives and bed rest. The evidence for bed rest in women with high blood pressure does not suggest that it is an effective treatment (see above).

11. There should be agreed evidence based policies covering which individuals should be offered treatment and the appropriate treatment to be offered.

In the UK, guidance on pre-eclampsia detection and treatment is based on the National Institute for Health and Clinical Excellence (NICE) guideline (6) from 2008 (CG62). NICE recommend that blood pressure and proteniuria should be assessed at each antenatal visit. Women should also be assessed for risk of preeclampsia using a range of maternal risk factors. Women identified as at risk should then be followed up with more frequent surveillance. For prediction of preeclampsia, this guideline is based on a smaller systematic review with fewer included studies than the HTA report (1) but has the same conclusion that there are none of the predictive tests have satisfactory sensitivity and specificity and are not recommended. The recommended approach is a pragmatic guide for clinicians' assessment of individual women. There is very little on the management of pre-eclampsia in this guideline and its evidence base is a little unclear. A new NICE guideline on hypertensive disorders during pregnancy was published in August 2010. This covers management of pre-eclampsia and refers back to CG62 (6) for risk factors.

12. Clinical management of the condition and patient outcomes should be optimised in all health care providers prior to participation in a screening programme.

The aims of the NICE guidelines are to optimise management. No published audits of the NICE guideline on antenatal care were available that would give information on whether clinical management is currently optimised within the NHS.

The Screening Programme

Pre-eclampsia is an important health problem so if a screening programme could be developed this would be of considerable benefit in detecting women likely to develop pre-eclampsia. Given the lack of an appropriate predictive test and preventive treatment with a suitably safe profile, the development of a screening programme for pre-eclampsia in the UK is not currently recommended. Considerable further work is required to understand the underlying processes that cause pre-eclampsia, from which more accurate predictive tests could be developed. Audits of current practice, based on the NICE guideline, and assessment of its outcomes is required to establish whether current clinical practice has been optimised.

References

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