Screening to prevent spontaneous preterm birth: systematic reviews of accuracy and effectiveness literature with economic modelling

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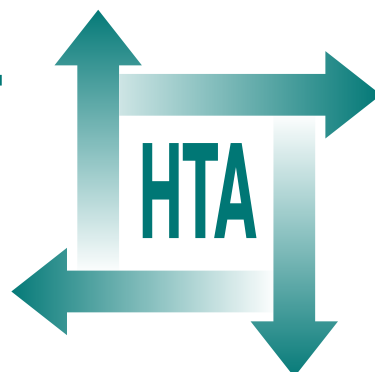 Epidemiology, University of Birmingham, UK

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Executive summary

Health Technology Assessment
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Executive summary

Background

A viable preterm birth is defined as any delivery of a pregnancy at less than 37 completed weeks (<259 days) and more than 23 completed weeks of gestation. It is a heterogeneous condition where 30–40% of all cases of preterm births are the result of elective delivery for a maternal or a fetal complication. The remaining 60–70% of preterm births occur spontaneously, and these are the focus of this report. Preterm birth complicates about 3% of pregnancies before 34 weeks' gestation and between 7 and 12% before 37 weeks' gestation. The former particularly has serious effects on mother, child and society, making preterm birth an important issue to public health worldwide. If women can be identified to be at high risk in early pregnancy, they can be targeted for more intensive antenatal surveillance and prophylactic interventions. When women present with symptoms of threatened preterm labour, if the likelihood of having a spontaneous preterm birth can be determined, interventions can be deployed to prevent or delay birth and to improve subsequent neonatal mortality/morbidity.

Objectives

The aim of this health technology assessment project was to identify combinations of tests and treatments that would predict and prevent spontaneous preterm birth. It completed three distinct pieces of work to contribute to this goal:

1. A series of systematic reviews of accuracy of tests for the prediction of spontaneous preterm birth in asymptomatic antenatal women in early pregnancy and in women symptomatic with threatened preterm labour in later pregnancy.
2. A series of systematic reviews of effectiveness of interventions with potential to reduce cases of spontaneous preterm birth in asymptomatic antenatal women in early pregnancy and to reduce spontaneous preterm birth and/or improve neonatal outcome in women with a viable pregnancy symptomatic of threatened preterm labour.

3. Health economic evaluation, including an economic model, of the combined effect of tests and treatments and their cost-effectiveness.

Methods

Protocols were developed for systematic reviews of test accuracy and effectiveness using standard review methods, including literature searches without language restrictions, study quality assessment and meta-analysis where appropriate. Two populations of interest were defined: asymptomatic antenatal women and women symptomatic with threatened preterm labour.

For test accuracy reviews, literature was identified from several sources (up to September 2005 inclusive), including databases: MEDLINE, EMBASE, DARE, Central, MEDION; contact with experts including the Cochrane Pregnancy and Childbirth Group; and checking of reference lists of review articles and papers that were eligible for the systematic reviews included in this report. Included were cohorts or case–control studies of any pregnant women where the index test was compared to the reference standard of spontaneous preterm birth and a 2×2 table could be calculated. Quality assessment was based on modified QUADAS criteria. Meta-analyses of likelihood ratios (LRs) were performed using random effects model. In general, the higher the LR+ (i.e. the likelihood ratio for a positive test) was above 1 the more accurate was the test in ruling in the condition while the lower the LR– (i.e. the likelihood ratio for a negative test) was below 1 the more accurate was the test in ruling out the condition.

Effectiveness reviews were identified (up to September 2005 inclusive) from a number of databases including the Cochrane Library (CENTRAL and Cochrane Pregnancy and Childbirth Group trials register), MEDLINE, EMBASE and reference lists of trial reports. Included were randomised or quasi-randomised controlled trials of the relevant intervention compared to placebo, no treatment or usual care in

any pregnant women that measured spontaneous preterm birth and neonatal complications as outcomes. Quality assessment was as described in the Cochrane Handbook. Meta-analyses were conducted in REVIEW MANAGER Software, using fixed effect models.

For the economic evaluation, the structure used a decision tree constructed in DATA TREEAGE software. 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 to test no one and treat no one. Inputs to the model were test accuracy and effectiveness systematic review results, test and intervention costs, cost of spontaneous preterm birth as an outcome and the prevalence of spontaneous preterm birth. The primary analysis used point estimates of key parameters of all tests and the most effective interventions. Extensive threshold, 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

For the 22 tests reviewed, the quality of studies and accuracy of tests was generally poor. Some tests were able to achieve high predictive value when positive, but at the expense of compromised low predictive value when negative. Only a few tests reached LR+ point estimates >5. In asymptomatic antenatal women these were ultrasonographic cervical length measurement and cervicovaginal fetal fibronectin screening for predicting spontaneous preterm birth before 34 weeks' gestation. In this group, tests with LR– point estimates <0.2 were detection of uterine contraction (by home uterine monitoring device) and amniotic fluid C-reactive protein measurement. In symptomatic women with threatened preterm labour tests with LR+ point estimate >5 were absence of fetal breathing movements, cervical length and funnelling, amniotic fluid interleukin-6 (IL-6), serum C-reactive protein (for predicting birth within 2–7 days of testing); and matrix metalloprotease-9, amniotic fluid interleukin-6, cervicovaginal fetal fibronectin and cervicovaginal human chorionic gonadotrophin (for predicting spontaneous preterm birth before 34 or 37 weeks' gestation). In this group, tests with LR– point estimate <0.2

were measurement of cervicovaginal interleukin-8, cervicovaginal human chorionic gonadotrophin, cervical length measurement, absence of fetal breathing movement, amniotic fluid interleukin-6, and serum C-reactive protein (for predicting birth within 2–7 days of testing); and cervicovaginal fetal fibronectin and amniotic fluid interleukin-6 (for predicting spontaneous preterm birth before 34 or 37 weeks' gestation).

Main findings of effectiveness review

The overall quality of many of the trials included in the 40 interventional topics reviewed was often poor or unclear because of poor reporting. However, a number of interventions did demonstrate some benefit towards preventing spontaneous preterm birth. Although antibiotic treatment was generally not beneficial, those used to treat bacterial vaginosis in women with intermediate flora did significantly reduce the incidence of spontaneous preterm birth. Smoking cessation programmes, progesterone, periodontal therapy and fish oil appeared promising as preventative interventions in asymptomatic women. Non-steroidal anti-inflammatory agents were found to be the most effective tocolytic agent in terms of reducing spontaneous preterm birth and prolongation of pregnancy in symptomatic women, although evidence to support their safety or a reduction in perinatal mortality and morbidity was less convincing. There was insufficient good-quality evidence to assess the use of tocolytic maintenance therapy. Antenatal corticosteroids were found to have a beneficial effect on the incidence of respiratory distress syndrome and the risk of intraventricular haemorrhage (28–34 weeks' gestation), but the effects of repeat courses were unclear because of insufficient data.

Main findings of economic evaluations

The cost of the tests for both asymptomatic and symptomatic women varied, ranging from £9.50 for venous blood tests like serum interleukin-6 to approximately £216 for an amniocentesis. Similarly the cost of the interventions for asymptomatic women varied, ranging from £1.08 for vitamin C to £1219 for cervical cerclage. In contrast, the cost of all interventions for symptomatic women was significant enough and varied little, ranging from £1645 for nitric oxide donors to £2555 for terbutaline; this was because the cost of hospitalisation was included in the estimate. The

best estimate of additional average cost associated with a case of spontaneous preterm birth was high, at approximately £15,688 for up to 34 weeks' gestation and £12,104 for up to 37 weeks' gestation.

Among women symptomatic of threatened preterm labour, there was insufficient evidence on which to base any firm conclusions for preventing spontaneous preterm birth at 34 weeks' gestation. The deterministic analysis suggested that hydration given to the positive cases tested with amniotic fluid interleukin-6 was the most cost-effective test–treatment combination. Indomethacin to all women without any initial testing was the most cost-effective option for preventing spontaneous preterm birth before 37 weeks' gestation among symptomatic women, delivering the greatest reduction in number of cases of spontaneous preterm birth and this result was produced in both the deterministic and probabilistic sensitivity analysis.

For a woman with symptoms of threatened preterm labour, the most cost-effective test and treatment combination for postponing delivery by at least 48 h, was shown to be the cervical length (15 mm) measurement test with treatment with indomethacin for all those testing positive. Other considered combinations, including treatments using atosiban and nifedipine, were however dominated by indomethacin. Separate data and a separate analysis showed the same test and treatment combination, cervical length (15 mm) measurement test with treatment for all those tested positive with indomethacin, was also the most cost-effective option for postponing delivery by at least 7 days after the test and treatment. These results did not take into account the potential side effects of indomethacin, nifedipine or atosiban on the fetus or mother.

For preventing preterm birth at 34 weeks' gestation among asymptomatic women, the most cost-effective option was to treat all with fish oils without the requirement for any preceding test. This finding was supported by the probabilistic sensitivity analysis but the effectiveness of fish oils requires further investigation because the underlying evidence was based on two relatively small trials. Antibiotic treatment for asymptomatic bacteriuria to all women without any initial testing was the most cost-effective option for preventing spontaneous preterm birth before 37 weeks' gestation among asymptomatic women, delivering the greatest reduction in number of cases of

spontaneous preterm birth but this result does not take into account the potential side effects of antibiotics or issues such as resistance if antibiotics were to be provided to all asymptomatic women.

The recommended option for the models in asymptomatic women was to provide treatment to all without a preceding test, but this was because of relatively poor information on inexpensive tests like mammary stimulation and previous history. These and other tests with negligible cost require further investigation. Treatments that require further investigation as a result of our analysis include hydration for symptomatic women, and fish oils, antibiotics for asymptomatic bacteriuria and periodontal therapy for asymptomatic women. Further research is also required for effective tests and treatments to reduce the risk of perinatal mortality as the result of spontaneous preterm birth.

Conclusions

An effective, affordable and safe intervention applied to all mothers without preceding testing is likely to be the most cost-effective approach to reducing spontaneous preterm births among asymptomatic antenatal women in early pregnancy for primary prevention. For secondary prevention among women symptomatic of threatened preterm labour in later pregnancy, a management strategy based on the results of testing is likely to be more cost-effective. It is premature to suggest implementation of a treat-all strategy of simple interventions such as fish oil for asymptomatic women. On the other hand, the case for a universal provision for high-quality ultrasound machine (e.g. for cervical length measurement and/or assessment for the absence of fetal breathing movement) in labour wards is stronger for predicting spontaneous preterm birth among women with a viable pregnancy who present with threatened preterm labour, in order to direct management (involving tocolysis and corticosteroids). Nevertheless, provision for round-the-clock trained personnel to perform such a scan in the interim is lacking. Additionally, the feasibility and acceptability to mothers and health providers of such strategies needs to be explored. Rigorous evaluation is needed of tests with minimal cost or invasiveness whose initial assessments suggest that they may have high levels of accuracy. Similarly, there is a need for high-quality, adequately powered randomised controlled trials to investigate whether interventions are indeed effective in reducing

(in asymptomatic women) and/or delaying (in symptomatic women with threatened preterm labour) spontaneous preterm birth. In future, an economic model should be developed which considers not just spontaneous preterm birth, but other related outcomes, particularly those relevant to the infant like perinatal death and shorter and longer-term outcomes amongst survivors. Such a modelling project should make provision for primary data collection on the safety of interventions and their associated costs.

Publication

NIHR Health Technology Assessment programme

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, from the public and consumer groups and from 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.

Second, 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.

Third, 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.

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