Authors' objectives
To address the question of how to best manage women in pre-term labour, a review of the scientific literature was undertaken on the following.

1. Appropriate criteria for diagnosing pre-term labour and the use of three biological markers: foetal fibronectin (fFN), endovaginal ultrasound (EVUSD) and salivary estriol.

2. The efficacy and effectiveness of tocolytics - pharmaceutical agents including beta-mimetics, calcium-channel blockers, magnesium sulfate, non-steroidal anti-inflammatory drugs (NSAIDs) and ethanol, that arrest pre-term labour symptoms.

3. The efficacy and effectiveness of antibiotics for treating covert infections that might have prompted pre-term labour.

4. The efficacy of home uterine activity monitoring.

Searching
The following databases were searched: MEDLINE, EMBASE, the Cochrane Library, Centre for Reviews and Dissemination (CRD) databases, International Pharmaceutical Abstracts, HEED, GenderWatch and Population Index. The MeSH terms used were limited by the subject heading 'premature labour'. A variety of study design terms were included in 'epidemiologic study characteristics' (exploded). Therapy search terms included 'biologic markers', 'antibiotics' and 'tocolytic agents'. The authors searched for the intersection of 'premature labour' and 'diagnosis', and also searched under 'costs and cost-benefit analysis'. The authors also performed an extensive search of the gray literature and reviewed article biographies.

Study selection
Study designs of evaluations included in the review
Included in the review were: efficacy studies in which health care is delivered under ideal settings, identified as randomised controlled trials (RCTs; double- and single-blinded); and effectiveness studies (non-RCTs, prospective and retrospective cohort studies, and case-control studies) in which health care is delivered under ordinary circumstances. Only RCTs were used for home uterine activity monitoring. Other information included meta-analyses, review articles for reference lists, and cost-effectiveness studies. Finally, sample sizes of 40 or more participants were required for inclusion. Only RCTs were included in the additional meta-analyses.

Specific interventions included in the review
Studies were included in the review if they evaluated biological markers (fFN greater than 50 ng/mL; EVUSD, length of cervix less than 30 mm; salivary estriol), tocolytics (beta-mimetics, calcium-channel blockers, magnesium sulphate, NSAIDs, other), antibiotics (ampicillin, erythromycin, clindamycin, indomethacin, amoxycillin, metronidazole, cefitoxime, pivampicillin, ampicillin-sulbactum, sulbactum sodium, ampicillin-clavulanate) and home uterine activity monitoring.

Reference standard test against which the new test was compared
No specific inclusion criteria relating to the reference standard were specified. Two studies of fFN compared the diagnostic accuracy of this biological marker with that of traditional clinical risk assessment based on cervical dilation, contraction frequency and vaginal bleeding.

Participants included in the review
Studies were selected for the review if they included pregnant women with signs and symptoms of pre-term labour.
Studies were excluded if all participants experienced pre-term premature rupture of membranes, medically indicated pre-term birth, or multiple gestation. Studies of fFN and EVUSD were excluded for asymptomatic women.

Outcomes assessed in the review
Studies had to measure pre-term birth, and were included if they examined at least one of three main categories of outcomes: birth, maternal morbidities and infant health.

How were decisions on the relevance of primary studies made?
Two reviewers independently rated the quality of each included article. Both reviewers' ratings (expressed in terms of a percentage score) for each article were tabulated.

Assessment of study quality
For each topic area of the literature reviewed (antibiotics, tocolytics, biological markers, home uterine activity monitoring), the validity assessment forms were designed to include appropriate questions with regard to most or all of the following categories: problem or question studied, sampling, measurement, internal validity, external validity, construct validity, statistical conclusions and justification for conclusions.

The quality or strength of the collective evidence on each topic was also summarised. This took into account the design quality of the individual studies and the efficacy or effectiveness of reported outcomes. Collective evidence ratings were: good (A), fair (B), poor(C), incomplete evidence (I), efficacy (1) and effectiveness (2). The overall evidence about harms for each topic was graded as either 'high' or 'low'. Two reviewers independently rated the quality of each included article. Both reviewers' ratings (expressed in terms of a percentage score) for each article were tabulated.

Data extraction
Two reviewers independently extracted data from the included articles. The reviewers were blinded to the authors’ names, the institution that produced the work and the journal name. Differences between the reviewers were reconciled by discussion. The data extraction forms varied between the topics, but all included: study design, description of the patient population (including maternal age, race and clinical inclusion/exclusion criteria), definition of pre-term labour, description of test, treatment of intervention, description of adjunct therapies, outcomes measured (e.g. prolongation of pregnancy, gestational age at delivery, rate of pre-term births, maternal morbidities, infant birth weight), and description of any secondary analyses performed.

Methods of synthesis
How were the studies combined?
The results of all the included studies were discussed in a narrative summary under the appropriate topic headings: antibiotics, tocolytics, biological markers and home uterine activity monitoring.

Where data were available, meta-analyses of RCTs were undertaken for tocolytics, adjunctive antibiotics and home uterine activity monitoring to determine the effects of each on: prolongation of pregnancy, estimated gestational age at delivery, and birth weight. Where possible, the continuous measures of the outcomes of interest were combined using mean differences. For all interventions and outcomes, the results were combined using a Bayes random-effects model as described by Hedges and Olkin (see Other Publications of Related Interest no.1).

For diagnostic studies, where possible, contingency tables describing the relationship between test results and an estimated gestational age of less than 37 completed weeks were constructed. These were used to calculate estimates of test sensitivity, specificity, positive predictive value, negative predictive value and likelihood ratios.

How were differences between studies investigated?
Important differences between the studies included in the comprehensive review were discussed in the narrative summary. Statistical heterogeneity between the studies included in the meta-analyses was determined using the chi-squared statistic.
Results of the review

A total of 84 studies met the review inclusion criteria. Seventeen studies evaluated biological markers (16 prospective cohort studies and 1 case-control study); 47 evaluated tocolytics (35 RCTs, 4 non-RCTs, 3 retrospective cohort studies and 2 prospective cohort studies); 16 evaluated antibiotics (15 RCTs and 1 observational study); and 4 evaluated home uterine activity monitoring.

Twenty-three trials of first-line tocolytics, 10 trials of maintenance tocolytics, 13 trials of adjunctive antibiotic treatment, and 3 trials of home uterine activity monitoring met the inclusion criteria for the meta-analyses.

The authors state that the quality of the literature is questionable in several respects. Their ability to draw conclusions was limited by the following five issues concerning research design and study execution: the definition of pre-term labour; the size of the trials; the confounding of the results because of the use of other interventions; the sole reliance on bivariate analysis; and the failure to analyse separately women with medically-indicated pre-term births and to compare results with those of the larger group of women with pre-term labour. These issues were discussed in detail in the review and formed the basis for the authors' recommendations for future research.

Biological markers.

Overall, there was strong evidence of the effectiveness of fFN and EVUSD as a diagnostic tool for assessing the risk of pre-term birth in women with symptoms of pre-term labour. Both tests were only moderately successful in predicting which women with a positive test would deliver before term, but they consistently exhibited strong negative predictive values, thereby identifying women at low risk of pre-term birth.

Tocolytics.

First-line tocolytic therapy: the studies of first-line tocolytic therapy provided mixed results. The meta-analyses suggested that all tocolytics, with the exception of ethanol, were effective in extending pregnancies at or beyond 36 to 38 weeks' gestation, compared with a no-treatment group. Beta-mimetics, calcium-channel blockers and magnesium sulfate nearly doubled the odds of term births, relative to control, with potentially small differences in effect sizes between classes (though data concerning relative efficacy were mixed).

Maintenance tocolytics: except for one small study, the efficacy studies showed no difference between treatment and control arms in managing women who had recently experienced an episode of pre-term labour; a meta-analysis confirmed these results.

Harms of tocolytics: beta-mimetics were graded as 'high' in terms of the probability of maternal risk, including serious cardiovascular harms, metabolic harms and psychologic harms. All other classes of tocolytic treatment were graded as 'low' in relation to maternal risk. All classes of tocolytics were graded as 'low' in relation to foetal or neonatal harms: evidence of short-term harms was inconsistent and evidence of longer term problems was insufficient.

Antibiotics.

The results of studies concerning therapy with antibiotics for treating occult in utero infections associated with pre-term labour were mixed. The meta-analysis showed the following: a marginally significant increase in the length of pregnancy of about 6 days; a marginally significant increase of about 0.60 of a week in gestational age resulting from antibiotic treatment; and a small increase in birth weight that was not statistically significant. The array of agents, routes of administration, and durations of therapy precluded any generalisations about the optional antibiotic regimen to achieve these benefits.

Home uterine activity monitoring.

Four RCTs were reviewed, one of which included but did not control for nursing support. Of the three RCTs which did control for nursing support as an element of the monitoring approach, none found a statistically-significant effect for home uterine activity monitoring. The meta-analysis confirmed this 'no-effect' conclusion in relation to gestational age at birth and birth weight.
Authors' conclusions

Based on the literature reviewed, two biological markers (fFN and EVUSD) were found to be quite useful in identifying women in pre-term labour who are at low risk of experiencing a pre-term birth. Although the evidence remains mixed, certain tocolytics (beta-mimetics, calcium-channel blockers, magnesium sulfate and NSAIDs) appear effective in prolonging pregnancy when used as first-line agents in arresting pre-term labour. However, beta-mimetics in comparison with other tocolytics seem to present a higher risk of maternal harms. Ethanol was not found to be an appropriate tocolytic agent. Tocolytics are not useful as maintenance interventions. Antibiotics for suspected genital tract infections may be useful. Home uterine activity monitoring was found to confer no maternal or foetal or neonatal benefits.

CRD commentary

This was a well-conducted and clearly reported review of the literature on the management of pre-term labour (it is further supplemented by a published review article, see Other Publications of Related Interest no.2). The review question was supported by appropriate inclusion and exclusion criteria, and the literature was searched extensively in order to identify all the relevant studies. Considerable details of the included studies were presented in tabular format and in the text of the review. Considering the comprehensive nature of the main body of the review, which included studies with various study designs and interventions, the narrative synthesis presented was appropriate. The additional meta-analyses of RCTs were also undertaken appropriately, with clearly stated statistical summary methods and approaches for investigating heterogeneity. The authors make several recommendations for future research, and their conclusions appear to follow from the evidence presented.

Implications of the review for practice and research

Practice: The authors did not make any clear recommendations for practice, but conclude, in relation to fFN and EVUSD, that 'the literature supports the notion that these tests can usefully supplement clinical judgement, especially in terms of identifying women who are not likely to experience a preterm birth'.

Research: Future research should address methodological issues, including explicit definitions of pre-term labour, clarity about cointerventions, and the separate analysis of women who have medically-indicated pre-term births. Other recommendations include the supplementation of dichotomous outcome measures with survival analysis (or related techniques). The authors specifically recommended survival analysis stratified by gestational age at enrolment as the analytical technique of choice. Further epidemiological research is recommended: biological mechanisms that result in birth before term; the incidence and prevalence of pre-term labour and the proportion that result in pre-term birth; modifiable risk factors for pre-term birth; and a better understanding of these basic facts in ethnic minorities. Further research in relation to to biological markers such as fFN and EVUSD, first-line tocolytics and antibiotics is also needed. The authors advised against any further research on maintenance tocolytics or home uterine activity monitoring.

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