Rapid fetal fibronectin testing to predict preterm birth in women with symptoms of premature labour: a systematic review and cost analysis

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Scientific summary

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Background

Premature birth is defined as birth before 37 completed weeks' gestation. In the UK, spontaneous preterm birth (PTB) occurs in 7–12% of pregnancies before 37 weeks' gestation and in about 4% of pregnancies before completion of 34 weeks' gestation. PTB accounts for 60–80% of neonatal mortalities and 75% of morbidities in most developed countries. PTB can cause severe morbidities such as bronchopulmonary dysplasia, respiratory distress syndrome, necrotising enterocolitis, intraventricular haemorrhage, retrolental fibroplasia, sepsis and long-term cognitive difficulties. These morbidities also impose sociological, psychological and financial burdens on the parents or the carers.

The timely use of antenatal corticosteroids can significantly reduce neonatal morbidity and mortality. In addition, tocolytic agents can be used to delay labour temporarily. In order to effectively administer these therapies and to plan necessary arrangements for delivery, it is important to determine the chances of having PTB at an early stage after the appearance of symptoms. Not all women showing symptoms of preterm labour will go on to deliver before 37 weeks' gestation; hence, overcautious management may result in unnecessary hospitalisations, unnecessary interventions and wastage of resources; there is, therefore, a need for improved assessment.

Fetal fibronectin (fFN) is an extracellular matrix glycoprotein produced by amniocytes and by cytotrophoblast and can be found in cervicovaginal secretions. The detection of an increase in levels of fFN in cervicovaginal secretions between 22 and 37 weeks' gestation can be considered as an indicator of PTB. Hence, inclusion of fFN testing in the diagnostic workup may help to predict which women displaying the symptoms of preterm labour will actually have a preterm delivery. This assessment focuses on rapid fFN testing because it represents a more practical approach as the results are available within 30 minutes unlike the enzyme-linked immunosorbent assay which delivers results only after 4–48 hours.

Addition of fFN testing to the diagnostic workup of women with suspected preterm labour may help to identify those women who do not require active management, and thus avoid unnecessary interventions, hospitalisations and associated costs. Hence, a systematic review was conducted which aimed to assess the impact on NHS resource use of including fetal fibronectin testing in the diagnostic workup and to inform possible changes in maternal management policy.

Objectives

1. To assess the clinical effectiveness and accuracy of the fFN test (commercial rapid test kit) in predicting PTB in symptomatic women.
2. To assess, from an NHS perspective, the cost-effectiveness of the use of fibronectin (rapid fFN testing) in the assessment of women with symptoms of threatened preterm labour, in comparison with no testing (current usual care).

Methods

A systematic review of clinical effectiveness, test accuracy and cost-effectiveness was undertaken using standard review methods, including literature searches without language and publication restrictions. Inclusion screening was done by two reviewers independently and was based on predefined inclusion

criteria; any discrepancies were resolved by consensus. The population of interest was defined as pregnant women with singleton or twin gestations who presented with symptoms of PTB before 37 weeks' gestation. The data extraction and quality assessment were done by one reviewer, using a piloted data extraction sheet, and checked by the second reviewer.

Searches for effectiveness studies used randomised controlled trial (RCT) and systematic reviews filters. Searches for test accuracy studies were based on an update of previous review Honest *et al.* [Honest H, Forbes CA, Duree KH, Norman G, Duffy SB, Tsourapas A, *et al.* Screening to prevent spontaneous preterm birth: systematic reviews of accuracy and effectiveness literature with economic modelling. *Health Technol Assess* 2009;**13**(43)] and were limited by date from 2000 to September 2011, but did not include methodological terms for test accuracy studies. We searched 14 databases including: MEDLINE, MEDLINE In-Process & Other Non-Indexed Citations and Daily Update, EMBASE, Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials, Database of Abstracts of Reviews of Effects, Health Technology Assessment Database and the Cumulative Index to Nursing and Allied Health Literature.

Randomised controlled trials in which participants were assigned to fFN testing plus usual care or usual care only (no fFN test results) were eligible for inclusion. Quality assessment was done using Cochrane tool for assessing risk of bias. Where three or more studies reported the same outcome, a random-effects model was used to generate pooled estimates of risk ratio, with 95% confidence intervals (CIs), for dichotomous outcomes and weighted mean difference, with 95% CIs, for continuous outcomes. Test accuracy studies, published since the previous systematic review, wherein the participants were tested with fFN and the reference standard was occurrence of PTB before 37 weeks' gestation, before 34 weeks' gestation or within 7–10 days of testing, were also included [Honest H, Forbes CA, Duree KH, Norman G, Duffy SB, Tsourapas A, *et al.* Screening to prevent spontaneous preterm birth: systematic reviews of accuracy and effectiveness literature with economic modelling. *Health Technol Assess* 2009;**13**(43)]. We included only studies from which we could extract the accuracy data (2×2 tables) for the above-mentioned reference standards (preterm delivery at various gestational ages and times from testing). The quality of the new studies was assessed using a modified version of QUADAS-2 [Solarino G, Piazzolla A, Mori CM, Moretti L, Patella S, Notarnicola A. Alumina-on-alumina total hip replacement for femoral neck fracture in healthy patients. *BMC Musculoskelet Disord* 2011;**12**(32)]. Numbers of true-positive, false-negative (FN), false-positive and true-negative test results, as well as sensitivity and specificity values, with 95% CIs, were extracted or calculated for each study and reference standard outcome reported. Pooled estimates of test performance were calculated by combining data extracted from studies included in this assessment with individual study results and data taken from the previous Health Technology Assessment (HTA) report [Honest H, Forbes CA, Duree KH, Norman G, Duffy SB, Tsourapas A, *et al.* Screening to prevent spontaneous preterm birth: systematic reviews of accuracy and effectiveness literature with economic modelling. *Health Technol Assess* 2009;**13**(43)]. Separate summary receiver operating characteristic (SROC) curves were calculated to summarise test accuracy data for each reference standard outcome. SROC modelling used the bivariate approach. Sensitivity analyses and subgroup analyses were performed to assess the effect of population and study characteristics on test accuracy.

The health economic analysis was intended to model the cost-effectiveness of fFN testing compared with usual care based on clinical signs and symptoms. However, the clinical evidence was most consistent with there being no difference in pregnancy outcome between these two strategies. There was an indication of a possible effect of fFN testing on admission rate, which led to the pragmatic decision to drop the effectiveness component of the model and focus on the cost consequences. This resulted in a very simple decision tree. The outcome measure was therefore incremental costs. The analysis included symptomatic women and the time horizon included hospital admission for observation, but not the delivery itself, since the fFN testing was assumed not to impact on this. A main structural assumption of the model was that, compared with usual care, fFN testing will not lead to any additional adverse events or worse pregnancy outcomes. This is justified by the evidence of no difference from the trials included

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in the systematic review and an assumption that the place of testing in the care pathway in practice was similar to that in the only UK trial, by Dutta and Norman [Dutta D, Norman JE. Pilot study into the efficacy of foetal fibronectin testing in minimising hospital admissions in women presenting with symptoms of preterm labour: a randomised controlled trial of obstetric and neonatal outcomes. *Arch Gynecol Obstet* 2011;**284**:559–65].

As there was only one UK-based trial among the studies included in the systematic review, it was decided to use results from this study as inputs for the base-case analysis [Dutta D, Norman JE. Pilot study into the efficacy of foetal fibronectin testing in minimising hospital admissions in women presenting with symptoms of preterm labour: a randomised controlled trial of obstetric and neonatal outcomes. *Arch Gynecol Obstet* 2011;**284**:559–65]. Model parameters that were not available from this study were gathered from other written sources or from expert opinion. Inputs from other studies were considered in sensitivity analyses. Additional analyses further included varying the price range of the test, a scenario assuming that not all patients need testing, and probabilistic sensitivity analysis.

Results

The literature searches of the bibliographic databases identified 1294 references. After initial screening of titles and abstracts, 112 full papers were ordered. Twenty-two publications of 20 studies were included in the review; five of the included studies (seven publications) were RCTs assessing the clinical effectiveness of fFN testing and 15 were diagnostic test accuracy (DTA) studies.

We included five RCTs, of which only four were full published articles; the remaining one was an abstract. Overall, for all the domains across all the included studies, the majority of studies were rated 'unclear' risk of bias. Lowe *et al.* was the only study which was rated as at low risk of bias for the majority of the key domains [Lowe MP, Zimmerman B, Hansen W. Prospective randomized controlled trial of fetal fibronectin on preterm labor management in a tertiary care center. *Am J Obstet Gynecol* 2004;**190**:358–62]. The results of clinical effectiveness studies (RCTs) were summarised by outcome measure (e.g. incidence of PTB, incidence of hospital admissions, and administration of treatment). Individual study results were summarised in text and tables and, where appropriate, were illustrated using forest plots. However, none of these outcomes showed a significant difference between groups. None of the included studies reported any adverse events. The only significant result was reported by Plaut *et al.* and derived from a subgroup analysis of women with negative fFN test observed for >6 hours; this showed a significant reduction in the length of hospital stay where the test result was known to clinicians. The hospital stay was shortened by 40%, from 37.8 hours to 22.7 hours ($p = 0.04$) [Plaut MM, Smith W, Kennedy K, Nageotte M, DeCastro E, Steinke R, *et al.* Fetal fibronectin: the impact of a rapid test on the treatment of women with preterm labor symptoms. *Am J Obstet Gynecol* 2003;**188**:1588–95]. All the included studies were of poor quality and likely to be underpowered.

We also included 15 newly identified DTAs from our update searches and 39 DTAs from the previous HTA review [Honest H, Forbes CA, Duree KH, Norman G, Duffy SB, Tsourapas A, *et al.* Screening to prevent spontaneous preterm birth: systematic reviews of accuracy and effectiveness literature with economic modelling. *Health Technol Assess* 2009;**13**(43)]. A modified version of QUADAS-2 was used to assess the quality of 15 new studies in this report. The main risk of bias for these studies related to the 'patient selection' domain of our modified version of QUADAS-2; only three studies reported prospective, consecutive recruitment of participants [Diaz J, Chedraui P, Hidalgo L, Medina M. The clinical utility of fetal fibronectin in the prediction of pre-term birth in a low socio-economic setting hospital in Ecuador. *J Matern Fetal Neonatal Med* 2009;**22**:89–93; Asakura H, Fukami T, Kurashina R, Tateyama N, Doi D, Takeshita T. Significance of cervical gland area in predicting preterm birth for patients with threatened preterm delivery: comparison with cervical length and fetal fibronectin. *Gynecol Obstet Invest* 2009;**68**:1–8;

Tsoi E, Akmal S, Geerts L, Jeffery B, Nicolaides KH. Sonographic measurement of cervical length and fetal fibronectin testing in threatened preterm labor. *Ultrasound Obstet Gynecol* 2006;**27**:368–72]. Missing data were found in one study and hence was judged to be at 'high risk' of bias for QUADAS-2 domain 'flow and timing' [Skoll A, St Louis P, Amiri N, Delisle M-F, Lalji S. The evaluation of the fetal fibronectin test for prediction of preterm delivery in symptomatic patients. *J Obstet Gynaecol Can* 2006;**28**:206–13]. The accuracy of fFN testing to predict preterm delivery within 7–10 days testing was reported by 10 studies from our up-date searches and data from 17 studies were taken from previous HTA report appendices. The overall sensitivity and specificity estimates were 76.7% and 82.7%, respectively. Accuracy data for PTB before 34 weeks' gestation were reported by 19 studies (11 new and eight from the previous HTA report). The overall sensitivity and specificity estimates were 69.1% and 84.4%, respectively. Accuracy data for PTB before 37 weeks' gestation were reported by 39 studies (eight new and 31 from the previous systematic review). The overall sensitivity and specificity estimates were 60.8% and 85.3%, respectively. Estimates of the test performance were similar across all the subgroup and sensitivity analyses.

The base-case cost analysis resulted in a cost of £599.53 for usual care (no fFN-testing) compared with £575.65 for usual care plus fFN-testing, which indicates that fFN-testing saves £23.88 compared with usual care. This was based on the findings by Dutta and Norman that patients who are tested for fFN have a slightly lower chance of admission, which then offsets the costs of testing all patients [Dutta D, Norman JE. Pilot study into the efficacy of foetal fibronectin testing in minimising hospital admissions in women presenting with symptoms of preterm labour: a randomised controlled trial of obstetric and neonatal outcomes. *Arch Gynecol Obstet* 2011;**284**:559–65]. Probabilistic sensitivity analysis gave an incremental cost (saving) of –£25.58 with a 2.5th and 97.5th percentile of –£304.96 and £240.06, respectively, indicating substantial uncertainty. Sensitivity analyses showed that the admission rate had by far the largest impact on the final results. This is expected, since all other costs and incidences included in the model are admission-driven. For the base-case analysis, the price at which fFN testing is cost-neutral lies at around £45.

Conclusion

The results of our systematic review suggest that fFN testing has a moderate accuracy for predicting PTB (with 7–10 days of testing, < 34 weeks' gestation, or < 37 weeks' gestation) and may be most sensitive for predicting PTB within 7–10 days of testing. The main potential role of fFN testing is likely to be to reduce health-care resource usage by identifying women who do not require active intervention (i.e. by ruling out likely PTB). The sensitivity estimates for fFN would suggest that, alone, the test would be unlikely to be adequate for this purpose. However, because in practice clinical decision-making is multifactorial, FN results on fFN may not translate into an increase in adverse outcomes for mothers and neonates. The trials included in this review suggested that adverse outcomes do not increase as a result of including fFN in the diagnostic workup, where treatment decisions remain at the discretion of clinicians. There was also some, very limited, evidence that including fFN in the diagnostic workup may reduce resource use (e.g. maternal hospitalisation). It should be noted that the studies identified by our review do not provide information on the effect of fFN testing on clinical decision-making.

Although the base-case analysis shows a modest cost difference in favour of fFN-testing, the conclusion of the cost analysis is largely dependent on whether or not fFN-testing indeed reduces hospital admission. This depends on precisely the place of fFN testing in the care pathway (i.e. essentially the weight placed on the fFN test results in conjunction with or as opposed to other information such as signs, symptoms and physical examination). When fFN testing reduces admissions testing will be very likely to save costs. When it does not, there obviously is only a very limited possibility that fFN testing will save costs; given the assumption that testing will not impact on the delivery and subsequent events.

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