A prognostic model, including quantitative fetal fibronectin, to predict preterm labour: the QUIDS meta-analysis and prospective cohort study

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Scientific summary

The QUIDS meta-analysis and prospective cohort study

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Scientific summary

Background

Preterm birth (before 37 weeks) occurs in 7.1% of pregnancies in the UK (> 50,000 deliveries per annum) and the majority of preterm births are the result of spontaneous preterm labour. Preterm birth remains the leading cause of neonatal morbidity and mortality, but timely interventions in women with preterm labour can improve neonatal outcome.

Establishing a diagnosis of preterm labour is challenging, and false-positive diagnoses are common. Such diagnostic uncertainty means that a large proportion of women with symptoms of preterm labour are treated unnecessarily to ensure that treatment is given to the few women who do actually deliver preterm. Unnecessary interventions result in both a substantial economic burden to health services and potential adverse maternal and neonatal events.

Diagnostic tests for preterm labour are available and used in many units in the UK. The most commonly used type of diagnostic test in the UK is for fetal fibronectin. This is available in the UK as a bedside test: Rapid fFN® (Hologic, Inc., Marlborough, MA, USA). Fetal fibronectin is a biochemical marker of preterm labour that can be measured in samples of cervicovaginal secretions collected at a speculum examination.

The aim of the Quantitative fetal fibronectin to improve decision-making in women with symptoms of preterm birth (QUIDS) study was to determine the best way in the NHS to use fetal fibronectin testing for the prediction of preterm birth in women with symptoms of preterm labour.

Objectives

The primary aim of the QUIDS study was to create a validated prognostic model for preterm birth within 7 days in women presenting with signs and symptoms of preterm labour.

The principal objectives were to:

- determine the decisional needs of pregnant women with signs and symptoms of preterm labour, their partners and their caregivers (QUIDS qualitative substudy)
- perform a meta-analysis of individual participant data from existing efficacy studies of quantitative fetal fibronectin to develop prognostic models using quantitative fetal fibronectin and other clinical characteristics (QUIDS individual participant data meta-analysis) and to explore the potential cost-effectiveness of these models
- externally validate and, if necessary, refine (update) the QUIDS prognostic models using data collected in a prospective cohort study of women presenting with symptoms suggestive of preterm labour in UK hospitals (QUIDS prospective cohort study)
- perform an economic evaluation of the QUIDS prognostic model, comparing it to other strategies for prediction of preterm birth, and explore the potential economic implications of using different thresholds of risk (percentage chance of birth within 7 days) predicted by the model to guide management decisions (QUIDS economic evaluation)
- assess the acceptability of the QUIDS prognostic model to women and clinicians, and explore the effect of fetal fibronectin testing on maternal anxiety (QUIDS acceptability).

Methods

In the QUIDS qualitative substudy we used semistructured interviews and focus groups to explore the decisional requirements and experiences of women, their partners and clinicians. Participants were purposively sampled to cover a range of personal and professional experiences of preterm labour and birth. Data were collected between January and May 2016 via semistructured interviews – in focus groups, one-to-one sessions in a hospital setting or over the telephone – using semistructured topic guides. Data were analysed independently by three researchers using a framework approach.

The target population for the QUIDS study was pregnant women attending hospital with signs and symptoms of preterm labour. The primary end point, consistent with the findings of the QUIDS qualitative substudy, was the binary outcome of whether or not spontaneous preterm birth occurred within 7 days of quantitative fetal fibronectin test.

An individual participant data meta-analysis was performed for model development. We included prospective cohort studies or trials of women with signs and symptoms of preterm labour that included quantitative fetal fibronectin results determined by the Rapid fFN 10Q analyser system (Hologic, Inc.) and pregnancy outcome data. We excluded studies in which fetal fibronectin concentration was measured by enzyme-linked immunosorbent assay and studies in which individual participant data were not available for meta-analysis. A literature search was completed and ongoing cohort studies of quantitative fetal fibronectin were identified using search terms for quantitative and preterm birth. Six studies fulfilled the eligibility criteria and five investigators agreed to provide data. Study quality was assessed. A prespecified set of factors thought to influence the probability of spontaneous preterm birth was considered for inclusion as predictors in the prognostic model.

For prognostic model development, a logistic regression modelling framework was used to develop the models using a one-stage approach. Backwards selection procedure was used to decide which of the candidate predictor variables should be included in the final prediction model. Multiple imputation using chained equations was used to impute missing predictors.

The apparent performance of the models created was assessed (area under the receiver operating characteristics curve, calibration and fit). Internal validation was undertaken using a non-parametric bootstrap resampling technique to adjust for overfitting. The potential clinical value of the prognostic model was evaluated using decision curve analysis.

Models were externally validated in a prospective cohort study in 26 consultant-led obstetric units in the UK, which included women with signs and symptoms of preterm labour at 22^{+0}–34^{+6} weeks' gestation in whom admission, transfer or treatment for preterm labour was being considered. Women with signs and symptoms of preterm labour were identified on presentation to obstetric services. Baseline demographics were collected on participants. Samples for fetal fibronectin analysis were taken at speculum examination as per manufacturer's instructions. Data were collected on paper-based case report forms and inputted into a web-based electronic database by research staff. All other data were collected from the participant records and recorded in the study database.

We aimed for a sample size of 3000 participants to obtain ≈ 100 events of preterm birth within 7 days of testing, based on guidance recommending a minimum of ≈ 100 events and ≈ 100 non-events for prognostic model validation. Model validation was performed using similar methods to those used for model development. When multiple tests (quantitative fetal fibronectin) were performed, the first recorded quantitative fetal fibronectin result was used in the model.

During the prospective cohort study, data were collected on resource use associated with women presenting with signs and symptoms of preterm labour. This resource use data were combined with the prognostic model performance data derived from the cohort study and used to estimate the cost and

health outcomes associated with a decision to treat at alternative thresholds of probability of spontaneous preterm birth within 7 days. The economic evaluation was undertaken from the perspective of the UK NHS and Personal Social Services. The base-case economic evaluation used a decision-analytic model to assess the costs and health outcomes associated with the QUIDS prognostic model compared with qualitative fetal fibronectin over (1) a 7-day time period, in line with the primary study outcome (birth at 7 days), and (2) over a lifetime horizon to account for relevant morbidities associated directly with not receiving treatment (corticosteroids and magnesium sulphate) for preterm labour.

Acceptability of fetal fibronectin testing was evaluated using purposive sampling of 30 women and 30 clinicians from a subset of trusts ($n = 14$).

Results

The QUIDS qualitative substudy supported the primary end point of the prognostic model being birth within 7 days. It also supported the prognostic model being made available through an electronic format, thus being available for use by clinicians in conjunction with women and their partners.

Six studies fulfilled the eligibility criteria for the QUIDS individual participant data meta-analysis, and five investigators agreed to provide data. Data were provided for two large cohort studies performed in mainland Europe [Alleviation of Pregnancy Outcome by Suspending of Tocolysis in Early Labour – 1 (APOSTEL-1) and European Fibronectin Study (EUFIS)], a UK multicentre cohort study [Evaluation of Fetal Fibronectin with a Quantitative Instrument for the Prediction of Preterm Birth (EQUIPP)] and two smaller UK studies [Quantitative fetal Fibronectin, Cervical length and Actim Partus for the prediction of Preterm birth in Symptomatic women (QFCAPS) and University College Hospital/ Whittington (UCLH/Whit)]. In total there were 139 events of spontaneous preterm birth within 7 days of fetal fibronectin testing among 1783 women with signs and symptoms of preterm labour (overall outcome proportion 7.8%). There was a higher rate of spontaneous preterm birth within 7 days in the APOSTEL-1 and EUFIS studies than in the UK studies.

The QUIDS prognostic model included quantitative fetal fibronectin, smoking, ethnicity, nulliparity and multiple pregnancy. After applying a uniform shrinkage factor of 0.92 to adjust for overfitting, on internal validation the model showed an area under the receiver operating characteristics of 0.90 (95% confidence interval 0.87 to 0.93). An alternative model without predictor selection was developed for comparison and had near-identical performance. Other models developed included cervical length measurement and these also had similar model performance. Net benefit analysis suggested that there was little added clinical value from inclusion of cervical length measurement. Economic analyses indicated that the quantitative fetal fibronectin prognostic model was likely to be cost-effective compared with qualitative fetal fibronectin and at a $\geq 2\%$ risk threshold of birth within 7 days.

The QUIDS model was validated in a cohort of 2837 women with 83 events of spontaneous preterm birth within 7 days (event rate 2.93%). On external validation it had an area under the curve of 0.89 (95% confidence interval 0.84 to 0.93), a calibration slope of 1.22 and a Nagelkerke R^2 of 0.34. The lifetime economic analysis found that the quantitative fetal fibronectin prognostic model was optimal at a threshold of $\geq 2\%$ probability of spontaneous preterm birth within 7 days for admission to hospital and treatment and that it improved outcomes (additional 0.008 quality-adjusted life-year gain) with an additional cost of £40 per patient to the NHS compared with using qualitative fetal fibronectin alone. This resulted in an incremental cost-effectiveness ratio of £5000 per quality-adjusted life-year, which is highly cost-effective given the recommended National Institute for Health and Care Excellence threshold of £20,000 per quality-adjusted life-year.

In a qualitative study, fetal fibronectin testing was acceptable to women and clinicians and the QUIDS prognostic model was likely to be well received.

Conclusions

We have used rigorous methodology to create the QUIDS prognostic model for prediction of spontaneous preterm birth within 7 days. It includes quantitative fetal fibronectin and clinical risk factors and can be used to inform a decision support tool to help guide management decisions for women with threatened preterm labour. It is highly cost-effective, can be readily implemented and is likely to bring immediate benefits to women, their babies and health services through reducing unnecessary treatment and reducing costs to the NHS in both the short term (7 days post birth) and the long term. The prognostic model will be embedded in electronic maternity records and a mobile telephone application, enabling ongoing data collection for further refinement and validation of the model.

Study registration

This study is registered as PROSPERO CRD42015027590 and ISRCTN41598423.

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