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SHORT TITLE: QUIPP app triage

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Abstract

Objectives: To evaluate the impact of a treat-all policy (advocated by NICE) compared to the QUIPP app (predictive model combining history of spontaneous preterm birth gestation and

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quantitative fetal fibronectin) for women in threatened preterm labour at <30 weeks gestation.

Methods: We conducted a subanalysis of prospectively collected data of pregnant women presenting with symptoms of preterm labour from the EQUIPP (REC Ref. 10/H0806/68) and PETRA (REC Ref. 14/LO/1988) research database. Women between 24 and 34 weeks of gestation in suspected labour at a tertiary inner-city hospital (abdominal pain or tightenings) were identified. Each episode was retrospectively assigned a risk of birth within 7 days using the QUIPP app. A primary outcome of delivery within 7 days was used to model the accuracy of the QUIPP app compared with a treat-all policy..

Results: With a risk threshold of 5% (of delivery within 7 days) to treat, 9/9 women would have been correctly treated giving a sensitivity of 100% (one-sided 97.5% CI 0.664) and a negative predictive value PV of 100% (CI 98.9 to 100%). The positive predictive value was 30% (95% CI 4.3 to 49.1%) before 30 weeks and 20% (CI 11.9 to 54.3%) between 30 and 34 weeks. If this 5% threshold had been used to triage women between 24 and 29⁺⁶ weeks, 89% of admissions (168) could have been safely avoided compared to 0% with a treat-all strategy. No true cases would have been missed as none of the women who were given a risk less than 10% delivered within 7 days.

Conclusion: For women in threatened preterm labour, the QUIPP app can accurately guide management at risk thresholds of 1%, 5% and 10%, allowing outpatient management for the vast majority. A treat-all approach, would have protected none, exposed 188 mothers and babies to unnecessary hospitalisation and steroids, and increased the burden on networks

and transport services due to unnecessary *in-utero* transfers. Prediction should be used before 30 weeks to determine management until there is evidence that such high levels of unnecessary intervention do less harm than the rare false negatives.

Introduction

Women with symptoms of preterm labour have long posed a diagnostic challenge for clinicians concerned with balancing the risks of preterm birth with the reality that most women will not deliver imminently (2). Various prediction methods are available to direct interventions that delay or ameliorate the consequences of preterm birth (e.g. *in-utero* transfer, antenatal corticosteroids and tocolysis). However, recent UK guidance advises a treat-all policy prior to 30 weeks based on concern for women with false-negative tests, advocating the use of cervical length or fetal fibronectin (fFN) only after 30 weeks (1). Neither the actual harm of false negative tests nor the harms of over-treating the majority of women were evaluated.

Our research group has developed the QUIPP app, which improves prediction of preterm birth and simplifies the combining of continuous variables to better assess risk. It utilises quantitative fetal fibronectin (qfFN, a protein released into the vagina in high levels in preterm labour). This popular bedside test helps to triage threatened preterm labour with a negative predictive value (NPV) for qfFN at <10 ng/mL of 98.2%, and a positive PV (PPV) for delivery <34 weeks at a 200 ng/mL threshold of 37% (3). The performance reliability of the QUIPP app has been demonstrated by

comparison of expected and observed spontaneous preterm birth rates: ROC areas in the validation set differed from the training set by between -0.04 and +0.02 (3).

The aim of this study was to investigate the impact of using the QUIPP app relative to a treat-all strategy at 24-29⁺⁶ weeks. We modelled the effect of a treat-all strategy compared with a threshold for intervention/admission of 1%, 5% and 10% QUIPP risk (of delivery within 7 days) on a cohort of women who presented in threatened preterm labour between 2010 and 2015. We also compared the performance of QUIPP to triage threatened preterm labour before and after 30 weeks. Another implication of a treat-all strategy would be the loss of the useful long-term prediction that qfFN provides. Therefore we compared the QUIPP predicted risk within 7 days to the actual delivery rates before later clinically relevant gestations.

Method

This was a prospective observational secondary analysis of a population of women from the Evaluation of Fetal Fibronectin with a Quantitative Instrument for the Prediction of Preterm Birth (EQUIPP) (REC Ref. 10/H0806/68) and PETRA (REC Ref. 14/LO/1988) research database. We identified all first episodes of suspected labour (abdominal pain or tightenings), between 24 and 34 weeks, as assessed by the attending clinician. Women with a blood-stained swab or sexual intercourse within 24 hours were excluded from the study due to know interference with fFN quantification. Those with incomplete outcome data or significant additional diagnoses at presentation (ruptured membranes, pre-eclampsia) were also excluded.

The qFFN was obtained by a sterile speculum examination by an obstetrician as described elsewhere (4). Using the gestation, qFFN and previous preterm birth history, each episode was retrospectively assigned a risk of birth within seven days using the QUIPP app (Figure 1)

Statistical analysis was performed using Stata software Version 14.1 (StataCorp, College Station, Texas). Descriptive characteristics were calculated for baseline demographics. The 1%, 5% and 10% QUIPP thresholds for admission were used to establish sensitivity, specificity, positive predictive value, and negative predictive value for spontaneous delivery within 7 days (primary endpoint) and compared with a treat-all strategy. Exact 95% confidence intervals were calculated. The same predictive variables were calculated for the QUIPP app before and after 30 weeks gestation. Results of QUIPP risk prediction were also grouped into 5 prespecified incremental categories (<0.1%, 0.1-1%, 1-5%, 5-10% and >10%) and the corresponding spontaneous preterm birth <30 weeks' and <36 weeks' rates were calculated.

Results

There were a total of 536 eligible episodes of threatened preterm labour identified of which 181 were excluded due to additional symptoms or diagnoses relevant to decisions to intervene (e.g. pre-eclampsia) or unavailable outcomes (PETRA study ongoing). A total of 355 events were eligible for analysis. The baseline characteristics of this cohort are described in Table 1.

Table 2 compares a treat-all strategy for threatened preterm labour <30 weeks' (188 women) with the use of the QUIPP app at 1%, 5% and 10% risk of delivery within 7 days. With a risk threshold of 5% (of delivery within 7 days) to treat, 9/9 women were correctly treated giving a sensitivity of

100% (one-sided 97.5% CI 66.4 to 100%) and a negative predictive value PV of 100% (CI 98.9 to 100%). If this 5% threshold had been used to triage women between 24 and 29⁺⁶ weeks of gestation, 89% of admissions (168) could have been safely avoided compared to 0% with a treat-all strategy. No true cases would have been missed as none of the women who were given a risk less than 10% delivered within 7 days.

Table 3 shows actual delivery outcomes within 7 days, before 30 weeks and before 36 weeks (when antenatal corticosteroids relevant) for threatened preterm labour episodes ascribed different risk thresholds within 7 days.

Table 4 demonstrates similar utility of the app to guide admission/outpatient management at both 24-29⁺⁶ and 30-34 weeks'. There was a numerical trend suggesting better prediction at earlier gestations, with a positive predictive value (at a 5% risk threshold) of 30% (CI 4.3 to 48.1%) before 30 weeks and 20% (CI 11.9 to 54.3%) between 30 and 34 weeks of gestation.

Discussion

Main Findings

The QUIPP app can safely and accurately inform clinician decision-making for women in threatened preterm labour, allowing outpatient management for the vast majority. This holds whether 1%, 5% or 10% risk of delivery within 7 days is used as the threshold for admission. The QUIPP app therefore confers considerable advantage over NICE's recommended treat-all strategy, which allows no women to be managed as outpatients. Using the 5% threshold, nine times fewer women

would have received intervention, and all of the true cases would have been correctly identified to benefit from interventions.

The accuracy of quantitative fFN and the QUIPP app was similar before and after 30 weeks', which shows that these tests can be used safely at earlier gestations. The QUIPP app provides useful risk prediction for women later in pregnancy and at the time of threatened preterm labour. In this cohort it would be reasonable to manage as outpatients all women given <10% risk of delivery within 7 days as none were at imminent risk. However follow-up and pregnancy planning would differ considerably between the <1% risk and 5-10% risk groups given the different delivery rates <30 weeks. This advantage could be lost if all women were admitted and then discharged after a few days when labour did not ensue. The experience of an unnecessary admission could cause opportunities to intervene to be missed at a later, true presentation of preterm labour.

Strengths

Our study projects intervention thresholds onto a large prospectively-collected cohort of real women who experienced threatened preterm labour. It provides important new insight into the impact of these management strategies. Lacking such evidence, national guidelines have previously been based on a cost-utility analysis alone. The model presented by NICE also included some problematic assumptions such as costing for tocolytics only, no harm from unnecessary intervention and harm from all false-negatives.

Weaknesses

No test is perfect and we expect that a larger sample would have revealed false negatives. However the rate of delivery within seven days in our cohort is consistent with previous studies (3%) (5, 6)

and we do not anticipate that a larger sample size would have increased the false-negative rate beyond that which is acceptable for a diagnostic test. Further research is required to explore what a “false-negative” truly means. For example, whether in practice women who are sent home inappropriately experience adverse outcomes or do they rather re-present to be managed safely.

The data from a minority of women included in the study was used in developing the QUIPP model. So whilst this study provides useful insight into the properties of the app, a new and preferably external dataset is required for further validation of the app.

The model assumes that every clinician and patient accepts the findings of the app. Whilst QUIPP’s accuracy in prediction has been confirmed, its ability to influence practice and translate to improved clinical outcomes requires further research.

Implications

Preterm birth prediction which safely minimises interventions (e.g. steroids and *in-utero* transfer) reduces unnecessary risk to the mother and child and has significant cost benefits for service-providers. Whilst clinicians are familiar with steroid-induced glucose intolerance in mothers, fetal exposure to steroids has become the main concern. There is a reduction in birthweight in those women exposed to steroids who deliver more than 7 days after the first dose, compared to those receiving no treatment (mean difference -147 g, 95% CI -291.97 to -2.05 g). Infants exposed to steroids are at increased risk of neonatal hypoglycaemia (1.61 CI 1.38 to 1.87) and are more likely to be in the lower quartile of academic ability ($p=0.01$) (ARR 9.2% to 17.7% to 8.5%) (7). The latter finding is biologically plausible given decreased brain growth in infants exposed to antenatal corticosteroids in animal studies (8).

Appropriate antenatal *in-utero* transfer (as opposed to *ex-utero*) is essential to avoid the excessive neonatal morbidity and mortality associated with postnatal transport of preterm infants (9). In some units a treat-all policy for threatened preterm labour would dramatically increase the number of such transfers. NICE modelled for this potential effect by allowing £300 for ambulance costs. However, the clinical and financial impact of unnecessary *in-utero* transfers are likely to far exceed this estimate due to the stress and expense for the mother and her family (10) and the immediate clinical burden of transfer arrangements (11). Paradoxically, unwarranted antenatal transfers may increase the number of more dangerous postnatal transfers by impairing efficient management of neonatal cots (blocking cots reserved for babies that are not actually delivered preterm). With neonatal cots blocked, infants of women in true preterm labour can only be transferred postnatally.

In patient-centred care the appropriate weighting of these maternal and neonatal risks in relation to the risk of preterm birth cannot be acknowledged by a “blanket rule” to treat everyone in threatened preterm labour. Since the Montgomery ruling (March 2015) replaced the Bolam test in matters of consent, doctors are legally bound to make patients aware of any material risks involved in a treatment, as well as those of any reasonable alternatives (12). For many women, the rare false-negatives of the QUIPP app, which in themselves are not proven to cause harm, may be offset by reductions in proven risks and in the huge disruption which may be associated with over-intervention (e.g. transfer across the country).

In a women with symptoms of preterm labour less than 30 weeks of gestation, a treat-all approach would have protected none but exposed 89% of mothers and babies to unnecessary intervention.

The increased burden on networks and transport services due to unnecessary *in-utero* transfers has

indirect but major repercussions on other mothers/infants. Prediction with qfFN should be used before 30 weeks to determine management until there is evidence that such high levels of unnecessary intervention do less harm than the rare false negatives.

Authorship: HAW and AHS made significant contributions to the design, acquisition, analysis and manuscript preparation. JC made significant contributions to the acquisition of data and manuscript preparation. RMT made significant contributions to the analysis and manuscript preparation. PTS made significant contributions to the analysis and manuscript preparation. All authors had full access to all of the data (including statistical reports and tables) in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis.

Ethical approval: This study was a subanalysis of cases from the Evaluation of Fetal Fibronectin with a Quantitative Instrument for the Prediction of Preterm Birth (EQUIPP) (REC Ref. 10/H0806/68) and PETRA (REC Ref. 14/LO/1988) studies which were approved by the South East London Research Ethics Committee, and all local research governing bodies that were associated with participating centres.

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Transparency statement: Professor Andrew Shennan affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Data sharing statement: Anonymised patient level data and statistical code available from the corresponding author at Andrew.shennan@kcl.ac.uk

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Figure legend

Figure 1: QUIPP app risk scores

Symptomatic

Previous PPRM or Previous Preterm Birth $\leq 34+6$

Yes

No

Unknown

Gestation of test

23w

24w

25w

26w

27w

28w

29w

0d

1d

2d

3d

fFN result (ng/ml):

100

*Cervical length data currently not utilized for symptomatic patients

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Risk of sPTB:

< 30 weeks = 9.5%

< 34 weeks = 25.7%

< 37 weeks = 40.1%

Within 1 week = 1.7%

Within 2 weeks = 3.9%

Within 4 weeks = 9.5%

Table 1 Baseline characteristics of women in threatened preterm labour

Baseline Characteristics	N=355 (%)
Maternal age	30 yrs (16-46 yrs)
Singletons	350 (98.6%)
Ethnicity	
African / AfroCaribbean	137 (38.6%)
European	157 (44.2%)
Indian Subcontinent	19 (5.4%)
Other	42 (11.8%)
Previous PTB/late miscarriage	72 (20.3%)
Primigravida	102 (28.7%)

Table 2: Comparison of a treat-all strategy with the QUIPP app at 1%, 5% and 10% risk of delivery within 7 days

Parameter	Treat-all strategy	QUIPP app risk prediction of delivery within 7 days		
		1%	5%	10%
Sensitivity	100%	100%	100% (54.1 to 100%)	100%
Specificity	0%	83.5%	92.3% (87.4 to 95.7%)	95.0%
NPV	100%	100%	100% (97.8 to 100%)	100%
Sent home inappropriately	0	0	0	0
PPV	3% (6/188)	17%	30% (6/20) (11.9 to 54.3%)	40%
Pre-emptive hospital admissions	188	36	20	15
Negative screen (admissions avoided)	0%	81%	89.4%	86.7%

Table 3. Longer term prediction of QUIPP app for TPTL < 30 weeks

QUIPP risk of delivery within 7 days	Number of women triaged at this risk	Actual delivery within 7 days	Actual delivery <30 weeks	Actual delivery <30 weeks
<0.1%	96	0	1 (1%)	9 (9%)
0.1 -1%	56	0	2 (4%)	3 (5%)
1-5%	16	0	1 (6%)	5 (31%)
5-10%	5	0	2 (40%)	3 (60%)
>10%	15	6	7 (47%)	9 (71%)
Total	188	6	13	29

Table 4. QUIPP prediction before and after 30 weeks' gestation

Parameter	Threshold for admission: 5% QUIPP risk of delivery within 7 days	
	24-29+6 weeks	30-34 ⁺⁰ weeks
Sensitivity	100% (54.1 to 100%)	100% (29.2 to 100%)
Specificity	92.3% (87.4 to 95.7%)	92.7% (87.6 to 96.2%)
NPV	100% (97.8 to 100%)	100% (97.6 to 100%)
PPV	30% (11.9 to 54.3%)	20% (4.3 to 48.1%)
Pre-emptive admissions	20	(15)
Negative screen (admissions avoided)	89%	91%