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QUiPP App Toolkit Group©

QUiPP Toolkit Evidence Summary

Version 2

Why do we need the QUiPP app?

In England and Wales, 7.9% of babies are born preterm. It is the leading cause for deaths under 5 years of age and survivors are at risk of major long-term morbidity(1)(2). The economic consequences are estimated at £2.95 billion per year (3).

The first opportunity to identify women at risk of preterm birth (PTB) is usually when they present with threatened preterm labour (TPTL) symptoms. This occurs in 9% of pregnancies but only 3-5% of women will deliver within 7 days (4)(5)(6). Current guidelines advise a treat-all policy for women presenting in TPTL before 30 weeks (7) and most women receive unnecessary treatments. Clinicians have a complex clinical dilemma where the need to prevent/ameliorate the consequences of PTB has to be balanced with fetal and maternal side-effects of interventions and their costs.

Why does the timing of preterm interventions matter?

Antenatal corticosteroids

Following Liggins' observations that lambs exposed to prenatal corticosteroids appeared viable at an earlier gestational age than expected (8), there were a series of clinical trials investigating the effects of antenatal corticosteroids on preterm birth outcomes (9) (10). Reviewed by *Crowley et al*. in 1990, the primary outcome of these trials was the incidence of neonatal respiratory distress syndrome (RDS). Administration of antenatal corticosteroids to women in preterm labour, with preterm prelabour rupture of membranes or prior to planned preterm delivery, was associated with a reduction in RDS rates of about 50% (typical odds ratio 0.49, 95% CI 041-0.60)(11). The Cochrane 2017 update including 30 studies confirmed the reduced risk of RDS (average RR 0.66 CI 0.56-0.77)(12).

Steroid administration also significantly reduces the occurrence of necrotising enterocolitis and intra-ventricular haemorrhages in preterm infants (11) (12). Fetal neuroprotection is thought to be mediated by corticosteroids vasoconstrictive effect on cerebral blood flow (13). Together with the impact on RDS, the reductions in neonatal morbidity are likely to reflect the significant reduction in perinatal death (average RR 0.72 CI 0.58-0.89)(12).

Although the health benefits of appropriate ACS are proven, reductions in RDS and intra-ventricular haemorrhage have only found to be significant if delivery occurs between 1 and 7 days from administration (12)(14)(Table 1). If treated outside the 7-day window, even with a single course, infants demonstrate lower birthweight (mean difference -147 g, 95% CI -291 to -2 g), head circumference, and length. More concerning still, the 2006 Cochrane Review described a worrying trend towards an increased risk of death for babies who received ACS and go on to deliver at full term (relative risk 3.25; 95% CI 0.99– 10.66).

Norman et al. (2017) confirmed that benefits from ACS are temporary, and do not exceed seven days (15). Importantly, they also reported that significant health-promoting effects were evident just hours after ACS administration. They observed (n = 4594) an immediate and rapid decline in composite mortality and severe neonatal morbidity at <12 hours, which plateaued at 18–36 hours [>50% relative risk (RR)]. Modelling predicted ACS, given just 6–12 hours before delivery, would have achieved a 51% reduction in infant mortality in the group who did not receive any steroids.

Targeting steroids administration appropriately is also a priority in light of increasing evidence of their harmful effects. These are offset by the benefits in preterm infants- but may be harder to justify in the majority who go on to deliver at term. The potential harmful effects of ACS are summarised in Table 1

Table 1 Effects of ACS

Fetal organ or system at risk of harm	Evidence summary	References
The hypothalamic-pituitary-adrenocortical (HPA) axis	Animal models suggest that steroids' effect on HPA-axis impairs regulation of growth, organ (including brain) development and immune function. The possibility that this impact may be transgenerational has been provided by increased ovulatory cycles in female guinea pig offspring exposed to steroids. In humans, cord blood studies have confirmed that corticosteroid treatment suppresses maternal and fetal cortisol and adrenocorticotropic hormone (ACTH). Studies suggest these hormones can take between seven days and eight weeks to return to normal levels.	(16). (17). (18) (19).
Fetal growth and Barker hypothesis	Animal studies and clinical trials have consistently demonstrated that corticosteroids impair fetal growth. Proposed mechanisms include glucocorticoid-induced alterations in placental nutrient transport and modulation of the insulin-like growth factor system, fundamental to fetal growth. A dose-dependent association has been observed between preterm infants' growth and corticosteroids use. In addition to the acute effect of fetal growth, there is growing awareness that the intra-uterine environment has repercussions for later life. In particular, it is hypothesised that placental insufficiency leads to an increased risk of cardiovascular disease and glucose intolerance/diabetes as adults.	(20) (21) (22) (23) (24) (25). (26) (27) (28). (29).
Fetal Brain	Rat models suggest that dexamethasone may interfere coping and learning in adverse situations via increased CRH levels in the amygdala Sheep studies suggest that delayed cerebral myelination may underlie impaired brain growth In humans repeated steroid doses are associated with a reduction in cerebral palsy, but increased rates of aggressive and hyperkinetic behaviour Behavioural assessments of the two groups of children were not significantly different but steroid-exposed children were twice as likely to be in the lower quartile of academic ability (p=0.01) (ARR 9.2% - 17.7% to 8.5%).	(25). (30) (31) (32). (33). (34).

A practical clinical consideration is the glucose dysregulation in diabetic mothers exposed to steroids- whilst this is transient, during steroid administration blood glucose needs to be monitored and managed with additional insulin infusions (35) for women with insulin-dependent diabetes. This requires an antenatal admission and its associated risks (e.g. VTE, infections) and there are significant resource implications as "sliding scales" require one-to-one midwifery care. In addition an observational study reported that 40% of women with diet-controlled diabetes required insulin for the first time after having received steroids for fetal lung maturity (36).

Tocolytic therapy

In the UK, tocolysis is advised for any women with symptoms of preterm labour between 24^{+0} and 33^{+6} weeks' gestation (7). Calcium channel blockers, prostaglandin-inhibitors and oxytocin-receptor antagonists are tocolytics which most consistently demonstrate reduction in RDS, neonatal mortality and delay of birth by up to 48 hours. and they are the most commonly offered to women in TPTL in the UK (37)(38) (39)(40)(7)(41).

However, use of tocolytics also carries risks of harm to fetus. In a placebo-controlled trial long-term follow-up of the children at 2 years, children of mothers who had received nifedipine maintenance therapy had higher rates of fine motor problems [22.2% versus 7.6%, OR 3.42 (95% CI: 1.29–9.14)] but a lower incidence of poor problem solving [21.1% versus 29.1%, OR = 0.27 (95% CI: 0.08– 0.95)](42).Concerns regarding fetal side effects have limited the use of prostaglandin inhibitors clinically. In a retrospective study of 114 preterm (< 30 weeks) deliveries, indomethacin, a non-selective PTGS inhibitor was found to significantly increase the incidence of premature closure of the ductus arteriosus, and fetal renal complications (43). In the TOCOX trial, Rofecoxib, a selective PTGS-2 inhibitor, was found to not only increase sPTB, but also significantly reduce fetal urine production [by 31% (95% CI 10–47%, P= 0.004)] causing oligohydramnios and impaired ductus arteriosus blood flow. There are also concerns regarding the use of Atosiban at extreme preterm gestations, when it appears to expedite delivery (44).(45)

Side effects from tocolytics occur in 13% of women(46). Usually the side effects of calcium-channel blockers are mild and self-limiting but include headache, rash, nausea and mild tachycardia. Their vasodilatation effect can also cause systemic hypotension which triggers a rebound increase in stroke volume and cardiac output which can lead to myocardial ischaemia. However the true incidence of maternal adverse events is difficult to determine as only a minority of trials report maternal outcomes (9/28 trials in *Conde-Aguedelo et al*. meta-analysis (47). Due to its uterine specificity, Atosiban is associated with fewer adverse maternal effects than either calcium-channel blockers or beta-mimetics. However they are still side effects which render women exposed to Atosiban were four times more likely (16% *versus* 4% RR 4.02, 95% CI 2.05 to 7.85) to discontinue their treatment, when compared to placebo (48). Prostaglandin inhibitors result in a range of side-effects due to the wide distribution of tissues in which prostaglandins are produced. Cyclo-oxygenase inhibition is known to interfere with gastric acid release and the mucosal barrier (49)and their inhibition of platelet aggregation is linked with increased rates of post-partum haemorrhage (50).

For situations where preterm birth appears truly imminent, tocolytics are relevant to ensure appropriate steroid delivery and timely in-utero transfer. Given the inadequate evidence regarding the short and long-term fetal and maternal harm of tocolytic drugs, their blanket use in TPTL cannot be justified.

In-utero transfer

As neonatology has advanced and subspecialised, there is an impetus to ensure babies have the opportunity to benefit from the relevant expertise as soon as they are born. Given geographic and funding pressures in the NHS, this requires significant numbers of transfers between neonatal facilities. The benefit of being born in a tertiary care centre has been proven to be most significant at early gestational ages.(51) The development of neonatal networks in the UK was primarily aimed at ensuring babies born less than 26 weeks receive the expertise of a level 3 (post intensive) neonatal unit. Despite this, the most recent UK national cohort (EpiCure 2) revealed that only 56.4% (1387/2640) of births between 22 and 26 weeks occurred in hospitals with a level 3 unit (52). Accurate identification of the women most at risk of preterm birth is key to prioritising who to transfer antenatally.

Accurate prediction is also key to prevention of unnecessary transfers for preterm labour. If based on symptoms alone more than 90% of women transferred for PTL will not deliver imminently, (6)(53) transferring everyone (as suggested by NICE) puts additional strain on an imperfect system and endangers successful transfer of those who most need it.

The emotional and financial burden of in-utero transfers upon the women and their families is beginning to be explored in the literature. Whilst women recognise the importance of in-utero transfer and find it acceptable (54) (55), the unplanned relocation to unfamiliar surroundings at al already stressful time in the pregnancy creates anxiety, shock and worry (54).

Magnesium sulphate

A systematic review of the evidence for magnesium sulphate as neuroprotection for preterm infants confirmed a 69% RR in cerebral palsy (3.9% *versus* 5.6% 95% CI, 0.55-0.88) and number needed to treat of 30 at < 28 weeks (56). Neuroprotection is also indicated by a decreased risk of MRI-detected cerebellar hemorrhages (57).These findings underpin UK guidance to offer magnesium sulphate to all women at risk of preterm birth before 30 week's gestation (7) and national efforts to improve compliance with this advice (58).

The timing of magnesium sulphate to maximise neuroprotection is also a subject of debate Pre-hypoxia regimens which have shown benefit range from 30 min to 24 hours prior to hypoxic episodes in term infants (59)(60). The dose the preterm fetus requires to reduce cerebral palsy Is not well established either. Clinical trials suggest that the median total dose should be more than 4 g to be effective but ranged from 4 and 49.8 g (56).

Magnesium sulphate does not appear to trigger any major maternal obstetric complication but it does confer around a 50% increased risk of hypotension and tachycardia. Respiratory depression and pulmonary oedema, need to be monitored for with magnesium infusions, as in pre-eclampsia. Side-effects (flushing, sweating, headache, dizziness, nausea or vomiting, soreness at injection site) are reported in 98% of women(56). Whilst all these side-effects are self-limiting they can contribute to treatment cessation, so optimal dosing to reduce maternal side-effects is likely to improve compliance with magnesium sulphate administration.

Magnesium sulphate is clearly a life-changing and safe treatment for early preterm babies. However given the uncertainties around its therapeutic window and optimal timing, preterm labour tests may have a role in preventing indiscriminate and excessive drug administration.

As well as physical harm, the above interventions are associated with anxiety (itself a risk factor for PTB (61)), financial burden for the women and family (62)(63)(54).

Why is the avoidance if excessive intervention important for healthcare services?

Threatened preterm labour is the most common reason for attending hospital before 37 weeks (64). The costs of bed days, blood tests, scans, and drugs exceed £1,000 per TPTL admission (64). Many women require in-utero transfer which is time-consuming and costly (approximately 340 mins of clinical time) (65).

Cost savings associated with introducing qualitative evaluation of cervico-vaginal fetal fibronectin are estimated at over 60% for admissions (64) and 90% for transfers (66). As outlined below, fetal fibronectin and QUiPP have the potential to magnify resource savings (67). QUiPP is free to all users and a cost-minimisation and cost-consequences analysis is being performed as part of the pilot EQUIPTT study which is due to be published in late 2020/2021 (data collection ended 12/2/2019, ISRCTN17846337).

What is the evidence for cervical length to predict preterm birth?

For women presenting with symptoms of preterm labour, cervical length measurement is only recommended for women beyond 30 weeks, based on the useful likelihood ratios of 13 studies reviewed (7). NICE admit that these recommendations are based on studies were of low-quality and that there are problems around thresholds. Their conclusion is that a 15mm cut-off has a moderately useful positive likelihood ratio (ranging from 4.23 to 20.0) compared to <25mm (2.83 to 19.5).

The largest prospective study to date is *Tsoi et al's* combined cohort of 510 women in TPTL with singleton pregnancies (68). It reported delivery within 7 days occurred in 42/95 (44.2% based on Table 2 not abstract) with a cervix < 15mm and only 0.7% of those with a cervix > 15mm delivered within 7 days. The AUC was 96% for delivery within seven days and the likelihood ratio was 8.61 (95% CI 7.04 to 8.96 (moderately useful)(7). Their logistic regression analysis found that cervical length was the only independent variable for birth within 7 days. A dramatic fall in event rates at CL > 15mm (30% delivery rate at CL 11-15mm compared to 0% at 16-20mm) support a distinct threshold (15mm) for intervention. In contrast, an 80.0% risk (of birth within 7 days) at CL < 5mm compared to 29.8% risk at 11-15mm supports the theory that biological continuous variables like cervical length are on a continuum. A binary threshold disregards this, as well as a woman's other risk factors and the gestation of presentation.

A meta-analysis of 28 studies (including those already mentioned: Palacio, Tsoi, Schmitz) reported a pooled PLR of 5.71 (3.77–8.65) and a NLR 0.51 (0.33–0.80) (69) suggesting that cervical length is a moderately useful test for sPTB prediction. However there is marked heterogeneity in performance between the studies. Study inclusion criteria (e.g. multiples, gestation/preterm labour definitions) may account for contrasting prevalence of imminent preterm birth, but it is likely that operator reproducibility of scanning is a factor, even where stated ultrasound methodology is sound. Defining a single threshold for intervention for all groups of women at all gestations is difficult based on these studies. The risk of sPTB changes across the range of cervical lengths and gestations: the challenge is how to transform this understanding into a useful clinical algorithm.

What is the evidence for fetal fibronectin to predict preterm birth?

Fetal fibronectin (fFN) is an epitope produced by fetal amniocytes and cytotrophoblast (70) and its function relates to its position in the extracellular matrix of the decidua basalis adjacent to the intervillous space.

Following Lockwood's seminal work on fFN, a number of prospective cohort studies were conducted in asymptomatic (with and without risk factors for PTB) well as symptomatic women (71)(72). In 1999 meta-analysis (27 studies) of the ability of fFN to predict preterm birth included 3613 women and reported overall sensitivity of predicting sPTB within 7 days of 76% (CI 57-96) and specificity of 88% (CI 81-96%) (73). Of the 11 studies in the symptomatic population, the combined sensitivity was higher (89% CI 80-97%) suggesting significant promise as tool for triaging TPTL.

Prospective cohorts of the use of quantitative fFN for women in TPTL suggest the predictive accuracy can be refined further by using more than one threshold (5)(74). In a prospective observational study of 300 singleton pregnancies using quantitative fFN testing for TPTL, the PPVs increased from 10.9 to 46.2% as the fFN threshold increased from 10- 500 ng/ml, with minimal impact on the NPV (98.5% at 10 ng/mL and 95.0% at 500 ng/mL thresholds) (5). The diagnostic ability of quantitative fFN as illustrated by receiving operator characteristic (ROC) curve was comparable at different thresholds, ranging from AUC 0.72-0.78), and as high as 0.82 (95% confidence interval 0.76-0.89) (75) and 0.85 (95% CI, 0.770-0.903) (76) in other studies.

Given the linear relationship between fFN and preterm birth (77) (78) a variable threshold better reflects individual patient circumstances and different treatment options (e.g. with-holding steroids *versus* commencing magnesium sulphate). A high PPV is desirable for confirming if intervention necessary and a high NPV for screening out condition altogether. The use of different thresholds may be influenced by the clinical details (e.g. gestation) and intervention under consideration (steroids, transfer, and discharge from hospital). Clinicians are used to varying their decision-making cross the risk range, as with in the management of blood pressure or interpretation of full blood counts. *Ridout et al 2016,* describe the more targeted approach this allows in the preterm labour setting, with the more costly or harmful intervention (e.g. steroids/IUT) saved for the most high risk groups (74).

Combining fFN and CL to predict preterm birth

A large multicentre study (n=455), used logistic regression to assess the relationship between Quantitative fetal fibronectin (qfFN) (with clinicians blinded to fFN value), cervical length and delivery within 7 days (79). Utilising qfFN appeared to add value across the risk range: for women in TPTL and a CL < 15mm, the risk of delivery within 7 days ranged from 5% in fFN < 10ng/mL, to 26% if 50-199, and 64% if fFN > 500. A high fFN (>500) was also able to identify a high-risk group (PTB 33%) with those with a long cervix (30-50mm) (Fisher's exact test p+0.01). The model with cervical length and quantitative fFN (AUC of 0.84 (95 CI 0.78- 0.89) was better than qualitative fFN and CL or quantitative fFN alone. Addition of cervical length (CL) further refines predictive ability of qfFN (79) and cost-effectiveness analysis of this approach has delivered approximately €848 euros savings per patient (80)(81).

Women in TPTL usually present out of hours but clinicians need to make important decisions quickly. The practical advantages of having two tests at their disposal are rarely described in the literature. Scanning equipment and expertise is limited in most parts of the UK and qfFN may be the only test that is practicable initially. Conversely there could be a contra-indication to fFN use (e.g. vaginal bleeding) or equipment failures/shortages. An appropriate triage strategy would allow both CL and qfFN for optimum prediction but acceptable prediction using one parameter alone.

The QUiPP App

Why was QUiPP app created?

There is a tension between the limitations of binary thresholds of predictive markers described above and the clinical need for simplicity. Seeking a solution to this problem our research group developed a tool to estimate the individual probability of preterm delivery using predictive modelling. Provision of a probability (% risk of delivery within certain timeframes) is meaningful and simple because it is more appropriate for a predictive test and widely understood. To facilitate usability and accessibility to this model it was converted into a freely available smartphone application:

Frequent consultation with the Guy's and St Thomas' Hospital Preterm Birth Patient and Public Involvement (PPI) group regarding the creation, aims and evaluation of QUiPP has also suggested that an app is a suitable tool to aid conversations with pregnant women. Indeed app use is high amongst this young and technologically-literate population with three-quarters of pregnant women using at least one pregnancy app (82) (83).

How does the QUiPP app work?

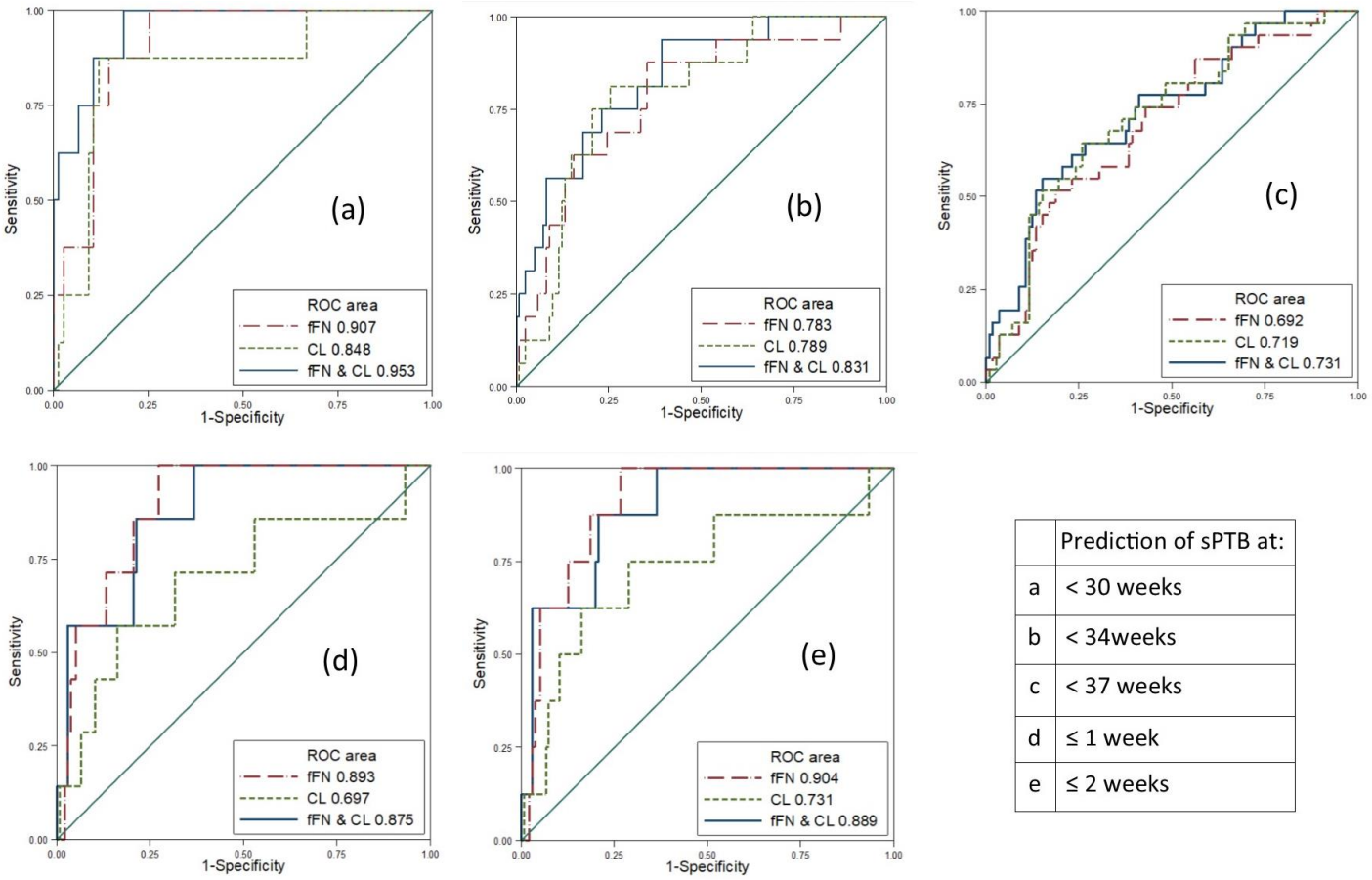
The six predictive models (three for asymptomatic women, three for symptomatic women - which is what is covered in this toolkit) of the QUiPP App were created using cervical length and fFN data, cervical length alone and fFN alone from symptomatic and asymptomatic datasets (84,85). Statistical analysis was performed with Stata software (86). Exclusions were made for: incomplete data; invalid visits (out of gestation range, inappropriate symptoms, invalid or missing test results, sexual intercourse within 24 hours) and major fetal abnormality. Women with twin pregnancies were included, using the first twin gestation at delivery, but triplets and higher order multiples were excluded due to inadequate numbers. Women whose labour was induced or who had caesarean section following preterm prelabour rupture of membranes (PPROM) were regarded as having had spontaneous preterm birth. Survival analysis with time-updated covariates was used to identify the principal predictors of premature delivery with premature onset of labour or PPROM. Six parametric structures for survival models were compared for each combination of predictors: exponential, Gompertz, log-logistic, Weibull, log-normal and gamma. The best models were then determined by reference to Akaike's Information Criterion (AIC) and Bayesian Information Criterion (BIC), where the lowest values are considered to have the best fit to the data). For each set of results, women were considered at risk of an event only from the time of the visit to the earliest of their next test, delivery or 37 weeks' gestation. Deliveries after 37 weeks' gestation or preceded by induction of labour or elective Caesarean section were regarded as censored at 37 weeks.

Quantitative fFN, cervical length (CL), gestational age at test and previous preterm delivery/PPROM/ and multiple pregnancy were considered as possible predictors. Late miscarriage was found to be a predictor in the asymptomatic algorithms only and cervical surgery was found to be a predictor in the symptomatic cohorts. Other potential predictors (body mass index, smoking, and ethnicity) were excluded as not significant in a multiple regression model.

The probabilities of delivery are estimated by survival analysis models using Lognormal (for symptomatic women) and loglogistic distributions (for asymptomatic women), adjusting for measured values of CL and fFN, and reported risk factors, conditional on the pregnancy having continued to the day of testing. Survival analysis accounts for fact that some iatrogenic women delivered preterm. Each variable was then investigated for non-linearity using fractional polynomials.

What is the evidence base for QUiPP?

The symptomatic prediction models were then tested by simple calibration which compared predicted and actual event rates, prior to a formal validation in the PETRA study (REC reference 14/LO/1988). In the qfFN group the ability of the algorithm to predict sPTB at less than 30 weeks' gestation had the highest balanced accuracy with a sensitivity of 90.0%, specificity of 90.8%, a positive likelihood ratio (LR+) of 9.83, a negative likelihood ratio (LR-) of 0.11, positive predictive value (PPV) of 27.3% and a negative predictive value (NPV) of 99.6%.(85) In order to directly compare predictive ability of the different combinations of predictors we compared area under the curve (AUC) in the validation set of women who had had both tests (Figure 1). For the qfFN group, the AUC for predicting sPTB at less than 30 weeks' indicates good prediction, at 0.96, with similarly large AUCs for predicting sPTB at less than 1 week and 2 weeks post-test.



	Prediction of sPTB at:
a	< 30 weeks
b	< 34weeks
c	< 37 weeks
d	≤ 1 week
e	≤ 2 weeks

Figure 1: *ROC curves showing ability of QUIPP app to predict spontaneous preterm birth (sPTB) at less than 30, 34 and 37 weeks' gestation and within 1 and 2 weeks of testing in the group of women with both fetal fibronectin (fFN) and cervical length (CL) in the validation set, based on qfFN alone, CL alone, or combination of both tests.*(85)

For the asymptomatic models the validation dataset was created from high-risk asymptomatic women enrolled in the EQUIPP and INSIGHT studies up to February 2019 where outcomes had been collected since creation of the prediction models using the training set in May 2017. This included 1400 visits and 904 women (none of whom were included in the validation set for the first QUiPP algorithms). AUCs for the qfFN, CL and qfFN/CL algorithms, based on all women in the dataset were produced. There were contrasts between the ethnicities and sPTB risk factors between the training and validation set which is an intended consequence of temporal validation method which aims to assess the generalizability of the predictive models in different populations (84). All algorithms demonstrated good accuracy with areas under the curve (AUC) between 0.75 and 0.90 for the use of qfFN and CL combined, between 0.68 and 0.90 for qfFN and between 0.71 and 0.87 for CL (84).

Bootstrapped confidence intervals were calculated for delivery within 4 weeks of test were narrow supporting the models' reliability and no significant difference between the three algorithms (qfFN 0.866 [0.784-0.927] cervical length 0.865 [0.720-0.919], fFN and cervical length [0.728-90.953]) Calibration for probability of delivery within 4 weeks (1095 observations for qfFN alone, 988 observations for CL alone and 694 for combined use of qfFN and CL) demonstrated no significant difference between the event rates and the predicted probabilities in any algorithm, confirming the QUiPP app's reliability at estimating risk of delivery within 4 weeks. Calibration of the qfFN algorithm demonstrated the app's ability to segregate women according to true risk; a low (<1%) risk on the QUiPP app is associated with an event rate of only 0.5%, while a high risk of delivery within 4 weeks (>10%) probability is associated with a 26% risk of delivery within 4 weeks, compared to a no information rate of 2.9%.(84)

EQUIPTT: The large cohort of women with TPTL symptoms recruited in the EQUIPTT trial has allowed extensive validation of the QUiPP app's predictive performance. Using qfFN combined with individual risk factors and gestation, the excellent ROC values for prediction of sPTB within 7, 14 and 28 days support the use of the tool to triage TPTL. Whilst thresholds for intervention may be altered to suit the clinical setting, a 5% risk of delivery within 7 days reliably distinguishes women most likely to need intervention both in ideal and in actual use.

In a survey of women's views, 92% found the QUiPP App provided understanding and reassurance, and 95% found the risk scores helpful (67). Qualitative findings from EQUIPTT suggest that clinicians using the app, largely felt QUiPP lowered their perception of risk, increased confidence in decision-making and reduced the tendency to over-treat.

How does QUiPP fit with NICE

For women in TPTL after 30 weeks' gestation, cervical length and fetal fibronectin are the only predictive tests recommended by NICE.(7)

We modelled the QUIPP app's ability to guide management relative to a "treat-all" strategy (NICE 2015) for women less than 30 weeks' gestation. If a 5% threshold of delivery within 7 days had been used to decide when to intervene, 89% of admissions could have been safely avoided compared to none with a treat-all strategy. No true cases would have been missed as no women delivered within 7 days who were given a risk less than 10% (67).

The EQUIPTT trial, once published, will provide a broad overview of actual UK practice of TPTL management. As was advised in the EQUIPTT protocol, the QUiPP App is a non-dogmatic tool to help clinicians. In rare cases where risk of delivery is less than 5%, clinicians are advised to follow their clinical acumen or the mother's symptoms if necessary, to outweigh low QUiPP scores. Through doing this we know women receive appropriate and timely treatments for their preterm infants. This judicious interpretation of quantitative fFN, with or without the QUiPP app by both women and clinicians in this trial creates the required evidence that in practice these tests are safe methods of identifying women most likely to benefit from preterm labour interventions.

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