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Effect of QUiPP prediction algorithm on treatment decisions in women with a previous preterm birth: a prospective cohort study

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Abstract

Objective

The QUiPP algorithm combines cervical length, quantitative fetal fibronectin (qfFN) and medical history to quantify risk of preterm birth. We assessed the utility of QUiPP to inform preterm birth prevention treatment decisions.

Design

A prospective cohort study with a subsequent impact assessment using the QUiPP risk of birth before 34 weeks gestation.

Setting

A UK tertiary referral hospital

Sample

119 women with previous spontaneous preterm birth (sPTB) or preterm premature rupture of membranes (PPROM) before 34 weeks gestation.

Methods

Cervical length and qfFN were measured at 19^{+0} - 23^{+0} weeks gestation. Clinical management was based on history and cervical length. After birth, clinicians were unblinded to qfFN results and QUiPP analysis was undertaken.

Main outcome measures

Predictive statistics of QUiPP algorithm using 10% risk of sPTB before 34^{+0} weeks as treatment threshold.

Results

Fifteen of 119 women (13%) had PPROM or sPTB before 34 weeks. Of these 53% (8/15) had QUiPP risk of sPTB before 34^{+0} weeks above 10%. Applying this treatment threshold in practice would have doubled our treatment rate (20% vs 42%). QUIPP threshold of 10% had positive likelihood ratio (LR) of 1.3 (95% CI 0.76-2.18), and negative LR of 0.8 (95% CI 0.45-1.40) for predicting sPTB before 34^{+0} weeks.

Conclusions

Use of the QUiPP algorithm in this population may lead to substantial increase in interventions without evidence that currently available treatment options are beneficial for this particular group.

Funding

Harris-Wellbeing Preterm Birth Research Centre.

Keywords

QUiPP; Preterm birth prevention treatment; Cervical length; Quantitative fetal fibronectin

Tweetable abstract

Independent study finds that the QUiPP algorithm could lead to substantial increases in treatment without evidence of benefit.

Introduction

In order to reduce the risk of preterm birth national guidelines often recommend targeted antenatal treatment based on obstetric history and a defined cervical length measurement, commonly <25mm.[1–3] However, cervical length screening alone does not detect all women who go on to have a preterm birth. Care et al have shown that in women with previous spontaneous preterm birth (sPTB) before 34 weeks or preterm premature rupture of membranes (PPROM) 9% of women will have another birth before 34 weeks gestation despite a cervical length >25mm at 20-25 weeks gestation.[4] There is, therefore, an urgent need to identify alternative methods in order to avoid these 'false negative' assessments, so that preterm birth prevention treatment can be considered.

The QUiPP application (App), developed by Shennan *et al.* is a way of quantifying a woman's risk of preterm birth and is a user-friendly algorithm, available free of charge on the internet and as a mobile application.[5] The current (October 2018) version of the App is based on 1803 asymptomatic women reviewed in preterm birth prevention clinics in London.[6] It can be applied from 18 weeks gestation onwards by inputting the following variables: obstetric history; history of cervical surgery; cervical length; quantitative fetal fibronectin (qfFN); current gestation; number of fetuses. The clinician is then presented with the probability of birth within one, two and four weeks, and prior to 30, 34 and 37 weeks gestation. There is currently no proposed protocol on how to use this information.

Preterm birth prevention clinics are becoming increasingly common in UK practice. As recently as 2012 the majority of preterm birth prevention clinics were researcher led, but a 2017 survey of UK practice[7] showed that the majority are now led by NHS clinicians. This survey showed that the QUiPP app was already being used to guide treatment decisions in 6% of UK hospitals (6/94).[7] This suggests an urgent need to assess and discuss the impact of this algorithm on preterm birth prevention treatment.

We therefore performed a prospective, blinded, analysis of the use of the QUiPP app in our preterm birth prevention clinic, to assess the potential impact on the management of women at high risk of preterm birth. This study aimed to involve patients in the study design to optimise participant engagegment with the study.

Method

Women with a singleton pregnancy and a history of sPTB or PPROM <34 weeks or late miscarriage (16^{+0}-23^{+6} weeks gestation) who attended our preterm birth prevention clinic were invited to take part in a biomarkers of preterm birth study. Participants were recruited from June 2015 until December 2017.

For the purposes of this paper we have combined the data collected at the 19^{+0}-23^{+0} weeks study visit for vaginal quantitative fetal fibronectin (qfFN), cervical length and past obstetric history. The qfFN swabs were processed by laboratory technicians, and both clinicians and participants were blinded to the qfFN result until all women in the study had given birth. Clinical management was based on cervical length, previous history and clinician and patient preference, as is normal practice in our clinic. Participants with a cervical length under the

3rd centile for their gestation[8] were offered preterm birth prevention treatment with vaginal progesterone, cervical cerclage or Arabin cervical pessary. Information was collected about initiation of preterm birth prevention treatment for the remainder of the pregnancy.

Women who had already received preterm birth prevention treatment prior to their study visit were not recruited. We felt that if treatment had already been initiated, it is unlikely that the 'negative' QUiPP risk assessment would have been sufficiently reassuring to prompt discontinuation of the preventative treatments.

All women were asymptomatic of preterm birth at the time of participation. Women were included even if they had had recent vaginal bleeding, as this has been shown to only have a small detrimental effect on the prediction of preterm birth by qfFN.[9] Participants were not recruited if they reported intercourse in the previous 48 hours, as this reduces the reliability of qfFN.[10] The speculum examination to obtain cervico vaginal fluid for qfFN analysis was performed prior to ultrasound and/or digital assessment of the cervix.

The qfFN swabs were analysed by the Rapid fFN® 10Q System (HOLOGIC, USA). Participant's obstetric history, cervical length and treatment decisions were entered onto our study database. Once the qfFN result was available these observations were then entered into the QUiPP application to obtain the participant's risk of birth prior to 34 weeks gestation. The study team corresponded with the QUiPP authors in order to apply the defintions of previous spontaneous miscarriage/PPROM/sPTB consistently with the original study. Pregnancies with PPROM that delivered spontaneously before 24^{+0} weeks gestation were classified as spontaneous miscarriage, and if they spontaneously laboured or developed

chorioamnionitis before 37^{+0} weeks gestation they were classified as sPTB. The PPROM label was applied to previous pregnancies that had PPROM before 37^{+0} week and with delivery after 37 weeks, or indicated delivery sooner for non-infectious indications.

After birth delivery two clinicians (AC and LG) reviewed the case notes and classified the pregnancies as either: PPROM or sPTB <34 weeks, birth ≥ 34 weeks, or iatrogenic preterm birth <34 weeks. Participants with iatrogenic preterm birth before 34 weeks were excluded from the analysis. For women who delivered elsewhere the participant and/or the delivering hospital were contacted to obtain the birth outcome details.

The primary outcome of PPROM or sPTB before 34^{+0} weeks gestation was chosen to reflect the gestational threshold used in QUIPP. In addition, the incidence of iatrogenic preterm birth rises significantly after 34 weeks in this high risk cohort. We chose to combine the outcome of spontaneous birth <34 weeks with PPROM < 34 weeks, as once the membranes are ruptured at early gestations any ongoing pregnancy remains vulnerable to serious complications including chorioamnionitis, cord prolapse and placental abruption.

In order to analyse the utility of the QUiPP app for the prediction of preterm birth in our cohort, it was necessary to apply a 'treatment threshold' to the QUiPP results. The initial publication describing the algorithm used a 'positive test' threshold of 10% for birth within the timeframe of interest.[11] We therefore started our analysis with a 'treatment threshold' of 10%, and assessed whether we could further optimise this threshold for the benefit of our population.

We considered the core outcome set for preterm birth.[12] We have reported on prelabour rupture of membranes and gestational age at birth. The remainder of the set is not relevant to this observational cohort study as these outcomes are not evaluated in the QUIPP app.

The prospective cohort study was funded as part of a charitable donation that founded the Harris-Wellbeing Preterm Birth Research Centre, University of Liverpool. This covered administrative costs, the quantitative fetal fibronectin tests, salary for AC, study support costs for AC and LG.

Patient involvement

The Harris-Wellbeing Preterm Birth Research Centre Patient and Public Involvement group were formed in 2015 and this group helped guide the research team on the practicalities of recruitment. This included discussing the qfFN testing process, and the blinding of the result with participants.

Results

The study population consisted of 123 women. There were four exclusions: two women were excluded because of intrauterine deaths at 20^{+4} and 30^{+0} weeks gestation; one woman was delivered for severe maternal disease at 31^{+4}; and one woman was induced for maternal anxiety at 33^{+6}. This gave a population of 119 women suitable for analysis. Birth outcome details were available for all participants. Table 1 shows their demographic details, and the cervical length and qfFN measurements.

Overall, 15 women (13%) had either spontaneous birth or PPROM before 34^{+0} weeks and 24 women (20%) received treatment because of short cervix, either at the study visit (7 women, 6%) or subsequently (17 women, 14%). Figure S1 details the preterm birth prevention treatment received and pregnancy outcomes for all participants.

If QUiPP treatment threshold had been set at 10%, then the treatment rate would have more than doubled to 42% (51/119). Figure 1 shows the QUiPP risk of preterm birth <34 weeks, and how a treatment threshold of 10% relates to the gestation of PPROM or birth. Forty three of 51 QUIPP positive women (84%) were still pregnant at 34 weeks (false positive rate). However 16 of these 43 women (37%) did receive preterm birth prevention treatment, as shown by the crosses (x) in Figure 1. If we were to assume that all women who were treated would have had a sPTB or PPROM $<34^{+0}$ weeks gestation then the false positive rate would be reduced to 53% (27/51). Twenty seven of the 51 QUiPP positive women (52%) had no preterm birth prevention treatment because their cervical length remained within normal range. Seven out of 68 QUIPP negative women (10%) had PPROM or sPTB <34 weeks (false negative rate). Table 2 shows the predictive statistics for QUIPP with a treatment threshold of 10%. Table S1 shows the adjusted predictive statistics for QUiPP with a treatment threshold of 10% if all women in the current study who received preterm birth prevention treatment had sPTB or PPROM $<34^{+0}$ weeks gestation.

In order to assess whether an alternative treatment threshold would have improved the utility of the QUiPP app we calculated the positive and negative likelihood ratios (LR + and LR-) for PPROM or sPTB <34 weeks over a range of clinically useful treatment thresholds. As shown in Figure 2 the best accuracy was achieved with an 8% threshold which gave a LR +ve

of 1.5 and LR -ve of 0.4. This would give a treatment rate of 55% (66/119), with a true positive rate of 80% (12/15), false positive rate of 81% (54/66) and false negative rate of 6% (3/53).

Our validation cohort had some dissimilarities to the QUiPP application development population which may explain the different performance of the algorithm. We limited our analysis to women with previous preterm birth; the QUiPP algorithm also includes women with previous cervical surgery as their only preterm birth risk factor. The algorithm is updated regularly by the team at Kings Health Partners and demographic data is not available for all participants used for version 2.0. [5] Compared to the initially published iteration of the QUiPP algorirthm our study participants: were slightly younger (mean age 30 years vs 33 years); had a higher rate of a cervical length under 25mm prior to 30 weeks gestation (20% vs 15%); and had a higher rate of white ethnic origin (96% vs 56%).[5]

The patient and public involvement group helped with the development of our participant information leaflet. They found the process of blinding of the fibronectin results to the participants and clinicians acceptable because the QUiPP algorithm was not yet in routine clinical practice. Patients have not yet been involved in the dissemination of results.

Discussion

Main Findings

In our high risk cohort, application of the QUiPP algorithm would have directed treatment to eight women (7% of the cohort) who were not treated using current care pathways and went on to have PPROM or sPTB < 34 weeks. This assumes application of the algorithm

between 19 and 23 weeks of gestation and a treatment threshold of QUiPP risk of PTB <34 weeks of >10%. However, our data suggest that this strategy may also lead to unnecessary treatment in a relatively high proportion of women. In our cohort the rate of treatment would be more than doubled if cervical length was replaced by QUIPP risk of preterm birth >10% as a trigger for treatment (20% vs 42%). Even with nearly half of women treated, 46% of women who had PPROM or sPTB <34 weeks would remain untreated. Changing the treatment threshold within clinically acceptable limits did little to improve this.

If we were to assume that the women treated in the current study would have all had a preterm birth $<34^{+0}$ weeks gestation without treatment then this does improve the predictive statistics of the QUiPP algorithm (Table S1). However the results are still within the confidence errors for our initial predictive statistics (Table 2), and still represent an increase in treatment of 27/119 women (23%).

The Harris patient and public involvement group welcomed this study and were very helpful in facilitating the practicalities of recruitement. There were no negative effects to this. Patients have not yet been involved in the analysis or interpretation of the results.

Strengths

This is the first study to analyse the application of the QUiPP algorithm on preterm birth prevention treatment decisions. The QUiPP app is already being adopted in clinical practice,[7] and so this is a timely assessment of the impact of this change.

Limitations

All women in this cohort received PTB prevention treatment based on cervical length, as is our standard clinical practice. This means that all women with a short cervix received treatment, and in doing so may have falsely reduced the predictive power of cervical length alone in predicting PPROM/sPTB. Conversely, clinicians and participants were blinded to the qfFN and so treatment was not offered to women with a normal CL and high QUiPP risk/qfFN, and their preterm birth risk was therefore not affected by treatment. This also means that direct comparison between predictive power of cervical length alone and QUiPP risk was not possible.

A second limitation is that the qfFN measurement was only performed on a single study visit for each participant. Using our current care pathway, 13% of participants received PTB prevention treatment because of short cervix detected at the subsequent visits. We are unable to assess the impact that QUiPP would have had on treatment rate if used later in the pregnancy.

The QUiPP algorithm has been developed using women based in and around London, UK. [6] Ultimately it is hoped that this tool can be modified for different populations and developed with additional predictors to improve its performance.

Interpretation

Use of the QUiPP algorithm in this population would increase our rate of treatment to 42% from 20%, and allow us to target 8/15 (53%) of women who went on to have PPROM or sPTB <34 weeks. It could be argued that a relatively high treatment rate is acceptable for high risk population in order to minimise the risk of severe complications of extreme

prematurity. The currently available preterm birth prevention treatments of cervical cerclage, Arabin pessary and vaginal progesterone are relatively well tolerated and have low complication rates. [13] Women who have had a previous preterm birth are often extremely motivated to achieve a term birth, and so there is the pressure to offer and accept treatments to prevent sPTB or PPROM recurrence. However, we do not currently have evidence for a preterm birth prevention treatment based on QUiPP risk of preterm birth.

A strength of the QUiPP algorithm is that it provides women and clinicians with a personalised risk of preterm birth. This can then be interpreted by the clinician, patient and family to make individual treatment decisions. On an individual level this is a goal of preterm birth prevention. In order to reach the goal and appropriately counsel a woman about her risk in a range of situations it would be ideal if a treatment threshold could be agreed, and then an intervention tested at that threshold for its ability to prevent preterm birth. Unfortunately the process of this analysis could be taking away the individualised nature of the risk scoring system.

Until such time when we have a better performing predictive tool for preterm birth, an alternative strategy is to offer prevention treatment to all women with a previous PPROM or sPTB. The American College of Obstetricians recommends weekly injections of 17 alpha-hydroxyprogesterone caproate to this group. [14] Vaginal admistration of natural progesterone could be an alternative strategy but the Cochrane review and OPPTIMUM study did not find evidence for reduction in PTB risk with this strategy. [15,16] It is hoped that soon to be published individual patient data analysis by the EPPPIC group will provide definitive evidence in this respect.[17]

Conclusion

The QUiPP algorithm is a novel tool in the field of preterm birth facilitating individualised prediction, and a welcome advance in personalised care. Our analysis suggests that the algorithm would more than double the preterm birth prevention treatment rate, and accordingly increase the number of women who receive treatment both appropriately and inappropriately. Future research should seek to refine individualised risk assessment and the utility of PTB prevention treatments based on it.

Disclosure of interests

LG, AC, AS and ZA received a grant from grant from the Wellbeing of Women charity to establish the Harris-Wellbeing Preterm Birth Research Centre, University of Liverpool, during the conduct of the study. BI, JI and DR have no relevant disclosures of interest. Completed disclosure of interest forms are available to view online as supporting information.

Contribution to authorship

ZA, AS and DR designed the cohort study. AC, LG, BP and JI performed the recruitment and data collection. LG and ZA performed the analysis and wrote the manuscript. All authors read and approved the manuscript.

Details of Ethics Approval

The study was approved by North West Research Ethics Committee- Liverpool Central, reference 11/NW/0720 on 4th November 2011.

Funding

The prospective cohort study was funded as part of a charitable donation that founded the Harris-Wellbeing Preterm Birth Research Centre, University of Liverpool. This covered administrative costs, the quantitative fetal fibronectin tests, salary for AC, study support costs for AC and LG. No additional funding was used.

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Figure legends

Figure 1

Gestational age at birth, or PPROM (which ever happened first) for 119 women and their QUiPP risk of birth <34 weeks calculated at 19^{+0} - 23^{+0} weeks gestation. Vertical dashed lines represent proposed treatment threshold (10%) and horizontal dashed lines represent 34^{+0} weeks gestation of event of birth or PPROM. Dots (●) represent participants who did not have preterm birth prevention treatment. Crosses (x) represent participants who did have preterm birth prevention treatment, either at the study visit or at a subsequent visit

Figure 2

Chart to show alteration in QUiPP likelihood ratio for prediction of PPROM or sPTB under 34 weeks by variation in QUiPP risk of birth under 34 weeks used as 'positive test' threshold

Figure S1

Diagram to show preterm birth prevention interventions and pregnancy outcomes for study participants

Table 1: **Demographic data, fetal fibronectin and cervical length data for our cohort.**

PPROM, preterm prelabour rupture of membranes. Results in brackets are percentages or standard deviation*.

			Value	
			(N=119)	
Age* (years)			30.1	(4.6)
Ethnicity	White		114	(95.8)
	Black		2	(1.7)
	Asian		0	(0)
	Not stated		3	(2.5)
Body mass index	<20 kg/m2		12	(10.1)
	20-24.9 kg/m2		46	(38.7)
	25-29.9 kg/m2		30	(25.2)
	≥30 kg/m2		30	(25.2)
	Unknown		1	(0.8)
Smoking	No		92	(77.3)
	Cigarettes/day			
		0-5	12	(10.1)
		6-10	10	(8.4)
		11-20	2	(1.7)
		>20	2	(1.7)
	Unknown		1	(0.8)
Risk factors	Previous			
		sPTB	87	(73.1)
		PPROM	5	(4.2)
		Late miscarriage	21	(17.6)
		sPTB and late miscarriage	6	(5.0)
Characteristic at 19+0-23+0 weeks gestation				
Quantitative fetal fibronectin (qfFN)		<10ng/ml	81	(68.1)
		10-19.9ng/ml	10	(8.4)
		20-49.9ng/ml	13	(10.9)
		50-99.9ng/ml	6	(5.0)
		100-199.9ng/ml	4	(3.4)
		≥200ng/ml	5	(4.2)
Cervical length		<15mm	1	(0.8)
		15-24.9mm	6	(5.0)
		≥25 mm	112	(94.1)

Table 2: Predictive Statistics for PPROM or sPTB<34 weeks using the QUiPP algorithm risk of birth under 34 weeks over 10% as the treatment threshold.

	sPTB or PPROM <34 weeks (n)	Birth after 34 weeks (n)
QUIPP >10%	8	43
QUIPP <10%	7	61

Parameter	Predictive statistics for PPROM or sPTB <34 weeks	95% Confidence Interval
Sensitivity	0.53	0.28-0.79
Specificity	0.59	0.49-0.68
PPV	0.16	0.06-0.26
NPV	0.90	0.82-0.97
LR +ve	1.29	0.76-2.18
LR-ve	0.80	0.45-1.40

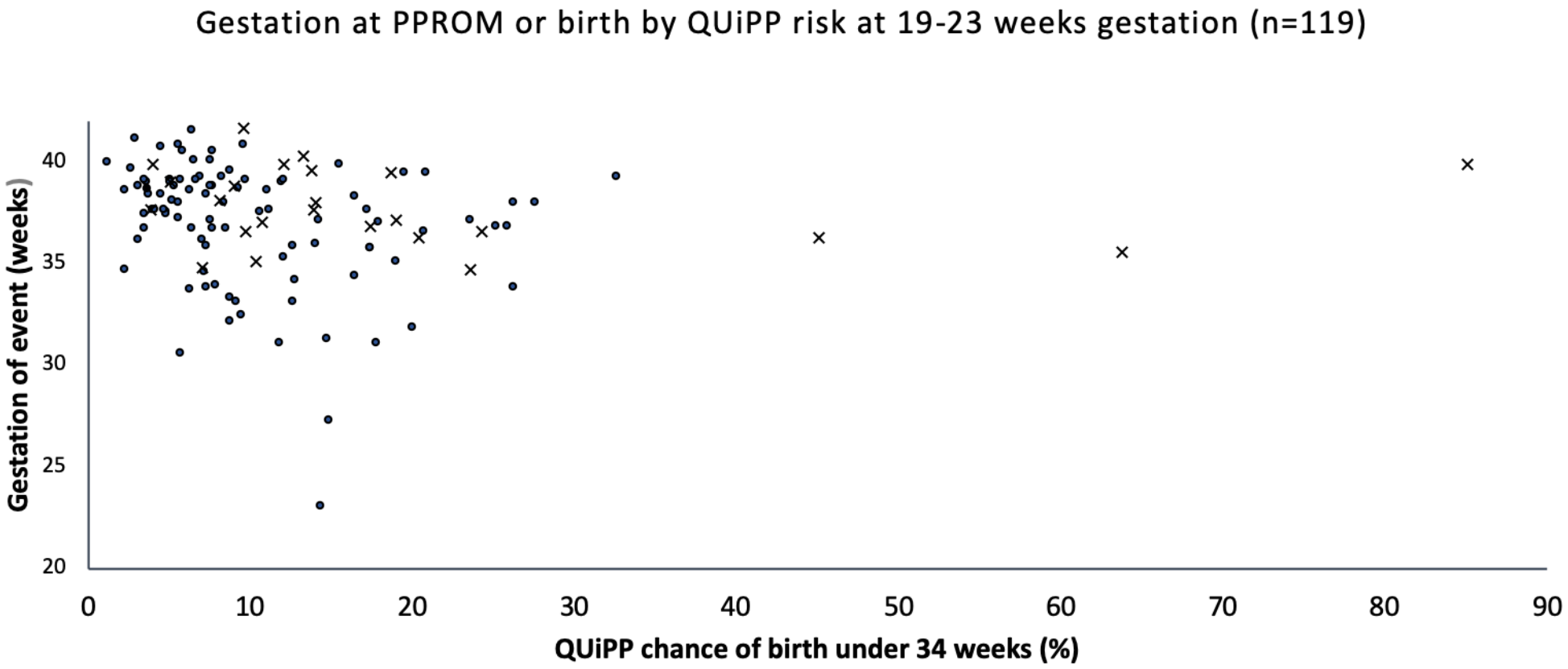

Figure 1: Gestational age at birth, or PPROM (which ever happened first) for 119 women and their QUiPP risk of birth <34 weeks calculated at 19^{+0} - 23^{+0} weeks gestation. Vertical dashed lines represent proposed treatment threshold (10%) and horizontal dashed lines represent 34^{+0} weeks gestation of event of birth or PPROM. Dots (●) represent participants who did not have preterm birth prevention treatment. Crosses (x) represent participants who did have preterm birth prevention treatment, either at the study visit or at a subsequent visit.