The use of fetal fibronectin and cervical length measurements in the prediction of spontaneous preterm birth in women with an Arabin pessary in situ

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[1] ROC: Receive operator curve, Ffn: fetal fibronectin, CL: cervical length, sPTB: spontaneous preterm birth

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Abstract

Objectives

The ability to predict spontaneous PTB (sPTB) has improved greatly, allowing women at risk to be managed with prophylactic interventions such as cervical cerclage and the Arabin pessary. Cervicovaginal fetal fibronectin (fFN) concentration and ultrasound measurement of Cervical length (CL) are the two most established tools to predict sPTB. There is however limited data regarding the predictive value of qfFN and CL tests following insertion of an Arabin pessary. Our aim was therefore to determine the clinical use of qfFN and CL measurements to predict sPTB in women fitted with an Arabin pessary.

Study design

This study is a secondary analysis on the SUPPORT trial data. Data were prospectively collected from women attending high-risk preterm surveillance clinics in 3 London centres between July 2015 and April 2020. The matched control group was pregnant women attending the same high-risk preterm surveillance clinics who had not received an Arabin pessary. Receiver operating characteristic (ROC) curves for prediction of birth by 34 and by 37weeks' gestation were generated for qfFN and CL measurements combined for both study groups. A formal comparison of area under the curve before 34weeks' gestation (AUC <34 weeks) was made between the two study groups.

Results

At our primary endpoint of sPTB<34 weeks' gestation, qfFN was a good predictor of sPTB in cases with an Arabin pessary in situ (AUC, 0.79, 95% CI: 0.62-0.90) and no worse than the control group who did not have an Arabin pessary, (AUC 0.74, 95% CI: 0.48-0.96). CL had good prediction for sPTB<34 weeks' gestation in the control group (AUC 0.76, 95% CI:0.63-0.88) but was lower and non-significant in the Arabin pessary case group (AUC 0.60, 95% CI:0.43-0.76).

Conclusions

This study showed that cervicovaginal qfFN concentration is equally reliable in the prediction of sPTB in pregnant women at increased risk of sPTB with and without an Arabin pessary in situ, and significantly better than CL measurement alone for predicting delivery before 34 weeks. This commonly used test therefore has utility in predicting sPTB in pregnant women fitted with an Arabin pessary.

Keywords
Preterm birth, Cervical cerclage, Arabin pessary, fetal fibronectin, late miscarriage

Introduction

Preterm birth (PTB), defined as birth before 37 weeks' gestation, is estimated to occur in around 14-16 million pregnancies a year globally, with rates continuously rising and is associated with increased neonatal morbidity and mortality (1–3). The ability to predict spontaneous PTB (sPTB) has improved greatly, allowing women at risk to be appropriately managed with prophylactic interventions. In addition to identifying risk factors from women's medical history other methods to predict sPTB have been developed. Cervicovaginal fetal fibronectin (fFN) concentration and ultrasound measurement of Cervical length (CL) are the two most established tools to predict risk in women at increased risk of sPTB and in those with symptoms of threatened preterm labour (PTL) (4–7). High concentration of fFN (qfFN) and short CL measurement in asymptomatic high risk women are associated with increased risk of sPTB; combining the two gives the best prediction (8).

There are a number of prophylactic interventions that can be used to prevent sPTB in high risk women including cervical cerclage, progesterone and the insertion of an Arabin pessary (4). Cervical cerclage is an established surgical intervention to decrease the risk of sPTB (9). The Arabin pessary is a silicon ring that is inserted into the vagina to encompass the cervix and provide mechanical support (10). Predictive tests such as qfFN and CL can help to appropriately guide clinicians in selecting targeted intervention, as well as predicting gestational age at delivery (11).

There are however limited data regarding the predictive value of qfFN and CL tests following insertion of cerclage, and none related to prediction after insertion of an Arabin pessary (12). There are a number of reasons to suggest that qfFN and CL measurements could potentially be less predictive when used in women with an Arabin pessary in place. The Arabin pessary is known to increase vaginal discharge , and as qfFN is dependent on the swab taking up a fixed volume of fluid, dilutional errors could be present. Furthermore, optimal visualisation and correct measurement of the cervical length may be more difficult to achieve in women with an Arabin pessary in situ, potentially compromising the predictive value of CL measurements. It is important to note that even women who have had an intervention, such as a cervical cerclage or an Arabin pessary, can deliver preterm and continuous surveillance in these women may be valuable. Therefore, accurately predicting women at higher risk of sPTB after intervention can guide further management.

Our aim was to determine the clinical use of qfFN and CL measurements to predict sPTB in women fitted with an Arabin pessary.

Methods and Materials

This was a secondary analysis of prospectively collected data from 3 dedicated preterm birth prevention specialised services. Data were prospectively collected from women attending high-risk preterm surveillance clinics in 3 London centres (St Thomas', University College London Hospital NHS Foundation Trust (UCLH), West Middlesex University Hospital) between July 2015 and April 2020. All women were monitored according to the preterm surveillance service protocol, which included recurrent CL and qfFN measurements. Clinicians who were performing and measuring both CL and qfFN measurements were therefore unaware of this study taking place. Women who had a iatrogenic delivery intervention before 37 weeks were excluded, this included any delivery prior to 37 weeks due to a planned delivery in the absence of spontaneous preterm labour or preterm prelabour rupture of membrane. All cases were singleton pregnancies. Cases comprised all consecutive pregnant women fitted with an Arabin pessary who had at least one post-pessary qfFN measurement. All cases with no post-pessary qfFN were therefore excluded. Indication for the Arabin pessary was cervical <25mm and each woman was a participant in the Support trial (13). The matched control group was pregnant women attending the same high-risk preterm surveillance clinics who had not received an Arabin pessary and had at least one qfFN measurement. Controls were sequentially screened from the database and matched to the closest case by gestational age at delivery.

Demographic data and risk factors for sPTB were recorded, including previous sPTB, preterm prelabour rupture of membranes (PPROM) or late miscarriage/stillbirth as well as previous cervical surgery such as a large loop excision of the transformation zone (LLETZ) or cone biopsy procedure. Interventions and investigations during the pregnancy including qfFN and CL measurements were all recorded and analysed.

<u>Cervicovaginal fetal fibronectin and cervical length measurements</u>

Women who attend clinic undergo a speculum examination where a swab is inserted into the posterior fornix to collect a cervicovaginal fluid sample. This is then immediately analysed in

clinic to give a qfFn measurement. Following this, a transvaginal ultrasound scan is undertaken by trained clinicians to measure the length of the cervix. This is done by measuring the distance between the internal and external os three times, with the shortest measurement of these recorded.

Statistical Analysis

Descriptive statistics were used to ensure the case and control populations were evenly matched. Our predefined primary endpoint was birth before 34 weeks and secondary endpoint before 37 weeks. Receiver operating characteristic (ROC) curves for prediction of birth by 34 and by 37weeks' gestation were generated for qfFN and CL measurements combined for both study groups. A formal comparison of area under the curve before 34weeks' gestation (AUC <34 weeks) was made between the two study groups. The primary endpoint was delivery < 34 weeks' gestation. As repeated measurements from the same participants were analysed, clustered bootstrapping with bias correction was used. The prediction of sPTB <34 and <37 weeks by using qfFN alone was also compared to that of CL measurement alone. The DeLong method was used to compare ROC curves (14).

Ethics

This project was undertaken under the ethical approval for the SuPPoRT study, under REC ref. 15/LO/0485 and the Preterm Clinical Network (PCN) Database, under REC Ref. 16/ES/0093 (13,15) .

Results

Demographic

Between July 2015- April 2020 51 women received an Arabin pessary and had a qfFN test result. Of these, 8 women were excluded (no pregnancy outcome, n=3; iatrogenic labour before 37 weeks gestation, n=5). This left 43 cases for analysis. Thirty percent of women (n=13) had a sPTB, and 14% (n=6) delivered before 34 weeks' gestation. 43 controls were consecutively selected to the closest match by gestation age at delivery, all matches were within 4 days with 27 women (63%) being an exact match (same gestation). Demographic data of the Arabin pessary case and control study groups are described in Table 1.

Table 1: Characteristics and outcomes comparing Arabin pessary group with control.

Cervical surgery = LLETZ and cone biopsy; CS = Caesarean section; GA = gestational age in weeks NA = not available

	Pessary N=43	*Control N=43*
BMI, mean (STD)	25.2 (5.7)	28.9(6.2)
Ethnicity, n (%)		
- *European*	19 (44%)	13 (30%)
- *Black African/Caribbean*	18 (42%)	20 (47%)
- *Asian*	4 (9%)	3 (7%)
- *other*	2 (5%)	4 (9%)
Previous spontaneous SPTB <37 weeks, n (%)	16 (37%)	16 (37%)
Previous PPROM (<37 weeks), n (%)	13 (30%)	13 (30%)
Previous late miscarriage (16-23+6), n (%)	7 (16%)	25 (58%)
Previous cervical surgery, n (%)	18 (42%)	7 (16%)
Index pregnancy		
Antepartum comorbidity, n (%)	3 (7%)	11 (26%)
Labour augmented, n (%)	6 (14%)	10 (23%)
PPROM, n (%)	9 (%)	2 (5%)
GA at delivery, mean (STD)	36.9 (4.2)	37.0 (4.1)
Onset of Labour, n (%)		
- *Spontaneous*	28 (65%)	30 (70%)
- *Induced*	6 (14%)	11 (26%)
- *No labour*	7 (16%)	2 (5%)
- *N/A*	2 (5%)	0
Mode of Birth, n (%)		
- *Elective CS*	5 (12%)	2 (5%)
- *Spontaneous vaginal*	25 (58%)	24 (56%)
- *Emergency CS prior to labour*	2 (5%)	0
- *Instrumental vaginal*	4 (9%)	5(12%)
- *Emergency CS in labour*	6 (14%)	10 (23%)
- *NA*	0	1 (2%)
Pregnancy outcome, n (%)		
- *Live birth*	42 (98%)	41 (95%)
- *Still birth*	1 (2%)	1 (2%)
- *NA*	0	1 (2%)

Fetal fibronectin concentration

On average, each woman had 3.8 (mean) measurements per pregnancy (range 1-10) giving a total of 138 and 123 qfFN measurements available in the case and control groups respectively. At our primary endpoint of sPTB<34 weeks' gestation, qfFN was a good predictor of sPTB in cases with an Arabin pessary in situ (AUC, 0.79, 95% CI: 0.62-0.90), similar to the control group who did not have an Arabin pessary, (AUC 0.74, 95% CI: 0.48-0.96) (Figure 1). Formal statistical comparison between the case and control groups at 34 weeks' gestation showed no significant difference between the ROC areas (P=0.58).

Figure 1: Receiver operator curve for qfFN in Arabin Pessary and control groups to predict sPTB<34 weeks.

Results for sPTB<37 weeks' gestation were similar: for the Arabin pessary cases (AUC 0.69, 95% CI: 0.53-0.82) and the control group (AUC 0.60, 95% CI:0.46-0.79).

Cervical length

On average, each woman had 3.3 (mean) measurements per pregnancy (range 1-10) giving 153 and 124 CL measurements in the case and control groups respectively. The median CL in the Arabin pessary and control group were similar, 17.3 and 18.0 respectively

CL had good prediction for sPTB<34 weeks' gestation in the control group (AUC 0.76, 95% CI:0.63-0.88) but was lower and non-significant in the Arabin pessary case group (AUC 0.60, 95% CI:0.43-0.76) (Figure 2). Formal comparison between the case and control group ROC areas did not show a significant difference (p=0.0694), but this was borderline. For sPTB<37 weeks CL measurement did not give good prediction for either group, (Arabin pessary AUC: 0.57, 95% CI:0.42-0.73; Control AUC 0.59, 95% CI:0.44-0.74).

Figure 2: Receiver operator curve for sPTB<34 weeks using Cervical length measurements in cases with Arabin pessary and control group

When comparing the accuracy of qfFN and CL prediction of sPTB<34 weeks' gestation in the Arabin pessary cases, the p-value was 0.003, significantly favouring qfFN. All results are presented in Table 2.

Table 2
Accuracy of qfFN and CL measurements in the prediction of sPTB in Arabin pessary cases and control groups for delivery in <34 weeks.

	qfFN prediction		CL prediction	
Group	**ROC AUC, 95% CI**		**ROC AUC, 95% CI**	
Arabin Pessary cases sPTB<34 weeks	0.79*	**0.62-0.90**	0.60*	0.43-0.76
Control sPTB<34 weeks	0.74	0.48-0.96	0.76	**0.63-0.88**

*Significant difference between qfFn and CL ROC areas

Discussion

Principal findings

This study showed that cervicovaginal qfFN concentration is equally reliable in the prediction of sPTB in pregnant women at increased risk of sPTB with and without an Arabin pessary in situ, and significantly better than CL measurement alone for predicting delivery before 34 weeks. This commonly used test therefore has utility in predicting sPTB in pregnant women fitted with an Arabin pessary. CL measurements in women with an Arabin pessary were no better than chance at predicting sPTB, unlike the control group. These results do not support clinicians relying on CL to predict outcome following use of the Arabin Pessary; qfFN concentration may be a better way to guide management.

Findings in context

To our knowledge, this is the first study to assess cervical length and qfFN in women with an Arabin pessary. Currently, women fitted with an Arabin pessary are managed the same way as all other women attending the preterm surveillance clinic. qfFN and CL measurements are routinely undertaken in these clinics and used to predict sPTB and decide how to manage these women after intervention. However, due to the nature of the Arabin pessary, it is important to consider the accuracy and utility of these tests.

The Arabin pessary is known to increase vaginal discharge, more than three times to the control (16). This study shows, that despite high volumes of discharge there is no impact of this potential dilutional effect and therefore qfFN readings can be relied on in this context. In contrast, CL measurement in women with an Arabin pessary has a poor predictive value, significantly worse than that of control women who did not have an Arabin pessary. The difference in predictive performance between the two groups could be explained by the technical difficulty of visualising the cervix after insertion of the probe to take an accurate measurement of CL with an Arabin pessary in situ. Previous studies have shown the efficacy

of the use of fetal fibronectin in predicting spontaneous preterm birth in both asymptomatic and high risk symptomatic women (17). A retrospective observational study in 2019 assessed qfFN readings in women with emergency insertion of a cervical cerclage, it showed a significant difference in women who delivered preterm compared to those who did not (p=0.0048), confirming its role in predicting spontaneous preterm birth (18). A study by Zork et al in 2020 showed that qfFN measurements in women with a short CL (<10mm) were comparable to women with a longer CL (19). A number of reactive management options exist when risk of sPTB is high, such as antenatal corticosteroids for fetal lung maturation, Magnesium sulphate for fetal neuroprotection, hospital admission and in utero transfer (20).

Arabin pessary is relatively non-invasive compared to cervical cerclage and commonly used preventative therapy in Europe (21,22). Although it is not as widely established as cervical cerclage and progesterone pessary, the Arabin pessary is approved for use as a primary preventative therapy for PTB in Europe, USA and Australia.

Three randomised control trials have studied the efficacy of an Arabin pessary to prevent sPTB, and they show contradictory results (16,23,24). A recent systematic review and meta-analysis on the Arabin pessary concluded that it does not reduce the rate of sPTB in women with a short CL (25). It is thought that the success rate of the pessary increases with experience of the clinician inserting it, hence the range of results (26). The contradicting results highlight, that the Arabin pessary can fail, and women still have a risk of SPTB, it is therefore vital for there to be an accurate test to predict spontaneous preterm birth, to allow for reactive intervention.

<u>Study strengths and weaknesses</u>

According to our knowledge this study is the largest dataset evaluating qfFN concentration and CL in women with an Arabin pessary. Our study includes prospectively collected data on a dedicated PTB database in a research setting. Although, the sample size is small, we found a significant relationship and therefore show that the study is not underpowered. Future studies with a larger sample size can minimise possible publication bias . As there was wide variation in individual women, likely related to the difficulty in scanning following pessary insertion, we decided against taking a summary value for each women as it may hide the poor performance of individual scans. This allowed us to use all the data. We accepted that this may limit the overall performance of the test, but remained a valid way to compare the test with controls. We used bootstrapping to reduce the effect of individual women being over represented by multiple readings. We chose a control population with the same prevalence of outcome to limits confounders. The chosen population in both study and control group had a short CL, and so although this can affect prevalence due to the higher risk of preterm birth, the sensitivities and specificities of any predictive tests should not be affected. Since this is a prospective study, women and healthcare professionals were not blinded when originally collecting the data. However, no individual was aware of this study at the time of measurements. Furthermore, all participants in the study group who met the inclusion criteria were included and the matched control group was chosen in a systematic chronological way, to reduce risk of bias. Some differences in baseline characteristics existed in our control group, but none of these variables are known to influence the prediction of qfFN and CL. As the control group was matched by gestational age at delivery, these variations are unlikely to influence our results.

Conclusion and future research

Our findings suggest that the cervical vaginal qfFN concentration is an accurate test to predict sPTB in women with an Arabin pessary and can be used in clinical practice. However, CL measurement alone in these women should be used with caution as our data suggest this test is less accurate. Further research will establish the role of Arabin pessary in clinical practice, but in the meantime qfFN can be used to predict outcome in women fitted with it. However, caution in interpreting CL measurements following Arabin pessary insertion is recommended.

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Not applicable

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Supplementary figures

Figure 1: Scatter diagram of qfFN concentrations by transvaginal CL for both Arabin and control group