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Placental inflammation and its relationship to cervicovaginal fetal fibronectin in preterm birth

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Short title: Placental inflammation and fFN in women who deliver preterm

Abstract

Objective

Late miscarriage and preterm birth are frequently thought to be associated with inflammation and infection, although in most cases the underlying cause of early delivery remains unknown. The

placenta is the organ that links mother and fetus during pregnancy, and postnatal examination may provide useful information about pathophysiology.

The relationship between placental pathological lesions and predictive markers of early delivery has not been explored. We sought to characterize preterm deliveries according to placental pathology and relate these to the performance of reliable predictive markers, fetal fibronectin and cervical length.

Study Design

This is a retrospective subanalysis from a larger prospective cohort study on sonographic cervical length, quantitative fetal fibronectin and risk of spontaneous preterm birth. Our cohort was comprised of high-risk asymptomatic women attending the Prematurity Surveillance Clinic at St Thomas' Hospital between 2002 and 2015, who went on to have a late miscarriage or preterm delivery (16 to 36⁺⁶ weeks') and who had available placental histology.

The placental pathology of these preterm deliveries was characterized according to the lesions identified, and categorized (according to the Redman classification) into inflammatory (e.g. chorioamnionitis) or non-inflammatory (histologically normal or vascular lesions indicating e.g. malperfusion).

We sought to relate placental findings to the performance of reliable predictive markers, in women who delivered early. Standard clinical cut offs for cervical length (< 25mm) and fetal fibronectin (>50 ng/mL) were used to identify the proportion of preterm births that were accurately predicted by the tests or who showed a false negative result, in relation to their placental histology findings. Binomial logistic regression was carried out to evaluate the

relationship between placental inflammation, quantitative fFN and cervical length as continuous variables.

Results

105 women who had a late miscarriage or preterm delivery (16-36⁺⁶ weeks') and available placenta pathology were identified. 66% (42/64) of those with inflammatory placental pathology had a positive fetal fibronectin swab result compared to 15% (6/41) of those with non-inflammatory placental pathology (chi-squared 25.9, 95% CI 31.5 to 65.6, $p<0.0001$).

A logistic regression model subanalysis of women in whom both CL and quantitative fFN results were available ($n=66$) revealed a highly statistically significant relationship with inflammatory placental lesions ($p=0.003$ and $p=0.001$ respectively). Placental inflammation was found to be associated with both increasing levels of fFN and a shortening cervix.

Conclusion

There is a significant association between a positive fetal fibronectin result and underlying inflammatory pathology of the placenta, even more so than the recognized relationship with short cervical length. Infective morbidity may be increased in women and neonates with positive fetal fibronectin who deliver preterm.

Keywords / phrases: preterm birth, fetal fibronectin, placental histology, inflammation, cervical length

Introduction

Preterm birth is the leading cause of perinatal and neonatal morbidity and mortality worldwide, accountable for 35% of neonatal deaths each year [1]. A phenomenon that is estimated to occur in 11.1% of all pregnancies, annually preterm birth (PTB) results in the deaths of more than one million children [2].

Despite increased understanding of risk factors and improved predictive markers of delivery, preterm birth (PTB) management strategies have made little impact on prevalence. The global rate

of PTB continues to rise. Traditionally perceived as a single condition, there is growing acceptance that PTB is a multifactorial syndrome, precipitated by a complex of aetiologies [3]. For best outcomes, focus must now be directed toward individualizing prediction and management. A more targeted approach, linking predictive tools to underlying aetiology would enable clinicians to personalise care planning and intervention, as well as rationalise unnecessary treatments and confidently reassure women and their partners.

Chorioamnionitis (intrauterine inflammation or infection detected in the placenta) is frequently implicated in spontaneous preterm birth, particularly in the early preterm period (<30weeks gestation) [4, 5, 6]. Not always obvious clinically, it can occur without symptoms and take hold within the decidua, invading the interface between the amnion and chorion, therefore reaching the amniotic cavity and fetus. Postnatal histological evaluation of the placenta can reveal important information about the underlying pathology, even when presentation is subclinical [7, 8].

Indicated preterm births are dominantly related to clinical conditions such as preeclampsia and fetal growth restriction, and placental lesions evidencing maternal malperfusion are more commonly seen in these cases, or those that are spontaneous but after 28 weeks [9, 10]. Examination of the placenta can therefore provide useful information about the aetiology underlying threatened preterm labour and delivery. What is missing is a test linking the underlying aetiology suggested by histopathological features from the placenta (which passes after the baby is born), with a predictive test that can be taken during the antenatal period. This information would be invaluable to the clinician; management may be altered for example tocolysis may be withheld in women thought to have subclinical infection.

Pathological lesions were categorized according to Redman's classification as signifying either vascular pathology relating to maternal malperfusion or intrauterine inflammation, each with important clinical applications [11, 12].

The accuracy of predictive markers was assessed; cervical length <25 mm was considered “short” and fFN > 50 ng/mL considered “positive”. If current biochemical and biophysical tests for PTB can be correlated with placental histopathology they could have potential for predicting preterm aetiology, as well as timing of delivery.

We compared placental histology from preterm births with the performance of current predictive tests, fetal fibronectin and cervical length.

Methods

This was a planned subanalysis of prospectively collected data from asymptomatic women at high-risk of preterm birth attending a single centre between 2002 and 2015. The Prematurity Surveillance Clinic at St Thomas’ Hospital sits within a major teaching hospital that serves the local population, but also receives nationwide referrals. Written informed consent was obtained from all participants prior to data being collected on a dedicated secure online database (ethical approval was obtained from the South East London Research Committee; REC no. 10/H0806/68).

Women were eligible to take part in the study if they were between 18⁺⁰ and 24⁺⁰ weeks of gestation, and were attending the St Thomas’ Prematurity Surveillance Clinic with one or more risk factors for preterm birth: previous preterm delivery (<37 weeks), previous late miscarriage (16 to 23⁺⁶ weeks), previous invasive cervical surgery or a congenital uterine abnormality.

All patients included in the study were managed in compliance with the preterm surveillance clinic (PSC) protocol for St Thomas’ Hospital. A combination of clinical history, serial transvaginal sonographic cervical length measurements and quantitative (Hologic Rapid fFN 10Q) cervicovaginal fluid (CVF) fetal fibronectin testing at two to four week intervals is used to screen women with risk factors for preterm birth. Those triaged as low risk are managed as outpatients and discharged at 24 weeks, whilst those who are asymptomatic but thought to be at increased risk of preterm birth due to CL < 25mm will receive ultrasound-indicated cervical cerclage. Progesterone and Arabin Pessary are not part of the usual clinical protocol, and would only have been given to patients as

part of a clinical trial. Based on a woman's risk of early delivery / symptoms they may be admitted to hospital for further observation and prophylactic intervention (e.g. antenatal corticosteroids). fFN testing is performed prior to ultrasound scan or digital examination using previously described methods, in line with manufacturer's guidelines from 18 weeks onwards [13]. For this cohort of patients the quantitative fFN was made available to the clinician, and a qualitative "positive" result was taken as qfFN >50 ng/mL. Women with blood stained CVF samples, sexual intercourse in the previous 24h, or suspected/confirmed rupture of membranes were excluded from the analysis, due to known interference with fFN measurement. The first test result after 22 weeks gestation was used (between 22 to 28 weeks' gestation) for analysis.

All women who delivered between 16-36⁺⁶ weeks' and had a placental pathology report available from our center, were included. Women with iatrogenic delivery were excluded.

Participant baseline demographics, obstetric history, risk factors for preterm delivery and birth outcome were collected. As per hospital policy, placental analysis was completed for all women for the following indications: perinatal loss due to miscarriage or still birth, unexpected admission to Neonatal Intensive Care Unit (NICU), requested by Fetal Medicine Unit following antenatal scan, Intrauterine Growth Restriction (IUGR), placental abruption or requested by a consultant (ie. preterm delivery <37weeks). Placental histology reports were routinely available as part of normal clinical care. Pathologists were blinded to clinical presentations, except gestation at delivery, and were all fully competent in both gross and microscopic placental evaluation. This study formed part of an institutional audit into the need for placental pathology.

Using Redman's classification, placental pathology was characterized according to histological lesions, signifying either inflammatory or vascular pathology, or indeed confirming a normal placenta [11, 12] The criteria for each category are summarised in Table 1.1.

The histological results were then sub-categorised as either inflammatory or non-inflammatory (vascular or normal pathology). Women were grouped based on fFN result (positive or negative)

and the absolute number and percentage of women with placentas in each histological category recorded. Pearson's independent chi square coefficient was calculated to determine whether results were statistically significant.

Using SPSS statistical software, a binomial logistic regression was carried out to determine if underlying infective placental pathology was related to CL and/or fFN.

Results

A total of 105 participants with early delivery <37 weeks, available placental histology and qualitative fFN results were identified. A sub-analysis of 66 women who had both cervical length measurement and a quantitative fFN was carried out.

Demographic and obstetric characteristics for study participants are described in Table 2. The mean gestational age at testing was 25^{+3} (range 22^{+1} to 27^{+5}) and the mean gestational age at delivery in this sample was 29^{+3} (range 25^{+1} to 33^{+5}). The majority of women had a live birth (87%, 91/105), of which 6% (6/105) went on to have a neonatal death. 10% (11/105) had a late miscarriage (16 to 23⁺⁶ weeks gestation) and 3% (3/105) a stillbirth. 63% (66/105) of women had a vaginal delivery. 19% (20/105) underwent cervical cerclage (history or ultrasound indicated) for prevention of preterm birth (neither progesterone nor Arabin Pessary was routinely prescribed within the clinic protocol at the time of study data collection; all women who developed a cervical length <25 mm were offered ultrasound indicated cervical cerclage, unless already in situ).

Out of the 105 participants who delivered early, 46% (48/105) women had a "positive" fFN (>50 ng/mL). The absolute number and percentage of placentas in each histological category is summarised in Table 3. In the majority (64%, 64/105), placental histopathology reported signs of inflammation.

The proportion of negative fFN tests in women with a normal placenta (14/18, 78%), or vascular (21/23, 91%) placental pathology was comparable (χ^2_1 1.3, $p=0.25$, 95% CI -12.0 to 40.0) (unlike in women who were found to have inflammatory placental histology at delivery (22/64, 34%)). As

fFN appears to perform similarly in these two categories, they were grouped together to form the comparison with the “inflammation” group in order, to test the hypothesis: positive fFN in a woman who delivers preterm has a significant correlation with inflammatory placental histology. Women who are “test negative” are more likely to show vascular changes, or have a normal placenta ($p < 0.0001$, 95% CI 31.7 to 65.7).

66% (42/64) of women with inflammatory placental pathology had a positive fFN swab result, compared to 15% (6/41) of those with non-inflammatory placental pathology. Pearson’s chi square coefficient ($p < 0.0001$, 95% CI 31.5 to 65.6), indicates that inflammatory placental histology is strongly associated with true positive fFN result.

A logistic regression model subanalysis of 66 women with quantitative fFN in whom CL was also available showed a statistically significant association with placental inflammation ($p = 0.003$; $p = 0.001$ respectively). The model explained 26% of the variance in placental histology and correctly identified 70% of the cases. When taking the two variables together fFN is more strongly associated with inflammatory histology - Wald Test 3.99 ($p = 0.046$) as compared with CL Wald Test 1.399 ($p = 0.237$). The results from the logistic regression are summarised in Table 3.

Comment

Recent advances in our understanding of biochemical and biophysical markers for sPTB have generated more accurate methods of risk prediction. Although previous work has related intrauterine infection to a short cervix [14, 15], this is the first study to report specifically on the strong relationship between fFN and placental inflammation. The high morbidity and mortality associated with maternal and neonatal infection justifies in-depth investigation into this area, as well as important implications resulting from the potential to predict aetiology. Patient triage driven by cause of preterm labour, rather than just risk of delivery would enable clinicians to target

management strategies, withhold inappropriate intervention and would likely facilitate improved outcomes for mother and baby.

fFN is a leading predictor of sPTB and is recommended in clinical practice for the identification of true preterm labour in those with symptoms [16], and as a screening tool for high-risk asymptomatic women. The predominant value of fFN is its high negative predictive value; a negative fFN can reclassify a high-risk patient back to background population risk of early delivery [17]. However the high negative predictive value is driven by low prevalence of the condition and most studies demonstrate modest sensitivity; the reason for false negative tests is not clear. This study suggests that the aetiology of preterm birth in women with negative tests is different, driven by vascular or other causes, rather than infective/inflammatory morbidity.

Failure of physiological transformation of the myometrial segment of the spiral arteries, decidual thrombosis and associated vascular lesions have been linked with sPTB as well as PPRM, PET, IUGR, spontaneous miscarriage and placental abruption [18]. Vascular lesions have been reported in the decidual vessels of 34% of women with sPTB, 35% of those with PPRM and only 12% of control women with term pregnancies [19]. The proposed mechanism linking vascular maltransformation and sPTB is uteroplacental ischaemia.

The majority of women with a true positive fFN result were found to have placental inflammation. Chorioamnionitis, either acute or subclinical/histological, is one of the most common antecedents of premature birth [1]. The incidence of intrauterine inflammation is inversely related to gestation age; it is implicated in the majority of extremely preterm births, and only 16% of preterm births at 34weeks [20, 21]. Other more chronic pathologies such as chronic villitis and intervillitis, which are caused by the TORCH infections and *Listeria*, or chronic deciduitis which is thought to reflect early gestational infection or persistent endometritis, also belong in this subset [5, 7].

Inflammation may be a trigger for PPRM and PTB, causing disturbance at the decidua-chorionic interface, threatening the integrity of the maternal-fetal boundary and as such leading to the

release of fFN into the cervicovaginal secretions, where it is picked up on testing. If maternal or fetal vascular pathology (or other, non-uterine, factors) is the underlying cause of early delivery, it may be reasonable to assume that this would not cause the same release of fFN, accounting for the 'false negative' tests in this group of preterm births.

Our study population includes only women who delivered preterm within our center; the majority of women (>90%) who are seen at the Preterm Surveillance Clinic go on to deliver at term [22], and therefore do not routinely have placental histology sent. We acknowledge that our cohort represents only high-risk patients, and was unable to capture placental histology for women who returned to deliver at their local hospital. We believe the sample is representative, even if not a systematic collection, as reasons to send placenta are principally related to gestation rather than signs of inflammatory pathology. The correlation between fFN result and placental histology was strong in this cohort ($p<0.0001$), however future studies with larger numbers may want to focus on the mechanism of fFN release in cases of inflammatory and vascular placental pathology, and link these to clinical interventions to reduce the burden of preterm delivery.

As noted, this population does not include subjects who delivered at term ie. women who had a true negative or false positive fFN result; this explains the high proportion of false negative fFN results. This study does not suggest the tests are poor in predicting delivery outcome. Indeed, there is a significant amount of evidence providing predictive statistics supporting clinical utility [13]. Fibronectin is now available as a quantitative test in Europe, where sensitivity and specificity can be improved by raising and lowering the threshold respectively. Further work needs to establish if the absolute level of fibronectin is related to level of inflammation, just as women under 10ng/mL are very low risk of preterm birth, and women over 200ng/mL are considerable higher. We had insufficient power to complete this analysis.

Many studies have shown a synergistic relationship between fFN and CL; a positive fFN increases the predictive value of CL [23, 24, 25, 26]. Our sub-analysis of the 66 women in whom both were

recorded supported this theory. Independently, placental histology was associated with shortening cervical length. This is similar to the results of other studies [14, 15]. However when taken together, an increasing quantitative fFN was significantly associated with inflammation, more than a shortening cervix.

Conclusion

We have shown a significant association between a true positive fFN result and inflammatory placental pathology. Indeed, this association is stronger than that already proven between cervical length and the placental inflammatory response. A false negative fFN swab test is more likely to correspond to non-inflammatory pathology; either normal histology or vascular lesions. Infective morbidity may be increased in women and neonates with positive fFN who deliver preterm.

Further work needs to establish if fFN has a previously unappreciated role, linking test result with neonatal infection risk, and for example could be used to guide the decision to administer antibiotics. If so, success of intervention may be related to quantitative fFN levels ie. underlying aetiology, and we must consider whether timing of intervention is critical and can be informed by such predictive biomarkers.

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Figure Caption

<i>Table 1: Criteria for categorising placental histology</i>		
<i>Inflammatory</i>	<i>Vascular</i>	<i>Normal</i>
Chorioamnionitis	Increased syncytial knots; increased villous fibrin deposition	No histological abnormalities seen
Funisitis	Chronic or marginal haematoma and abruptio placentae	
Deciduitis	Villitis of unknown aetiology	
Vasculitis	Fetal thrombotic vasculopathy	
Villitis; intervillitis	Decidual vasculopathy	

<i>Table 2: Demographic Characteristics of the Participants</i>	
<i>Characteristic</i>	<i>Number (%)</i>
Age (mean \pm sd)	32 \pm 3
Gestation age at testing – weeks ^{days} (mean \pm sd)	24 ³ \pm 3 ²
Gestational age at delivery – weeks ^{days} (mean \pm sd)	29 ³ \pm 5 ²
Cerclage Performed in Index Case	20 (19)

<i>Ethnicity</i>	
<i>White - British/European/Other</i>	34 (32)
<i>Black - African/AfroCaribbean/Other</i>	53 (51)
<i>Asian - Indian/Bangladeshi/Pakistani</i>	5 (5)
<i>Far East and South East Asian</i>	5 (5)
<i>Mixed</i>	4 (4)
<i>Unclassified and Other</i>	4 (4)
<i>Obstetric Risk Factor</i>	
<i>Previous preterm birth</i>	20 (19)
<i>Previous late miscarriage</i>	29 (28)
<i>Previous cervical surgery</i>	53 (51)
<i>Uterine Anomaly</i>	6 (6)
<i>Multiple pregnancy</i>	12 (11)
<i>Other Risk Factor</i>	
<i>Smoking</i>	
<i>Current</i>	8 (7)
<i>Ex-smoker</i>	8 (7)
<i>Never</i>	89 (85)
<i>Recurrent urinary tract infection</i>	6 (6)

Table 3: Logistic Regression Results for Placental Inflammation, Cervical Length and Fetal Fibronectin

	<i>CL</i>	<i>fFN</i>	<i>CL + fFN</i>
<i>Chi-Square Coefficient (p)</i>	9.61 (0.002)	9.61 (0.002)	13.8 (0.001)
<i>Wald Test (p)</i>	8.73 (0.003)	10.13 (0.001)	CL - 1.40 (0.237) fFN - 3.99 (0.046)
<i>Odds Ratio (95% CI)</i>	0.196 (0.066- 0.578)	0.114 (0.039- 0.463)	CL - 0.448 (0.118 - 1.70) fFN - 0.222 (0.051- 0.971)