Cervical Anatomy in Women at Risk of Preterm Labour

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Background

Preterm birth, defined as birth occurring after the gestational age of viability (23 weeks, 500 grams weight) and before 37 completed weeks (259 days) of pregnancy, is one of the most important problems in medicine today. Preterm birth is the single largest cause of mortality and morbidity for newborns. It accounts for 5% to 11% of births in the world but is responsible for 28% of all deaths within 28 days of birth and 50% of childhood neurological disabilities [1, 2]. Other important adverse outcomes of preterm birth include respiratory distress syndrome, intraventricular haemorrhage, leukomalacia, necrotizing enterocolitis and prolonged hospitalisation [2]. Survivors can experience life-long complications including cerebral palsy, blindness and deafness [1, 2].

Psychologically, giving birth to a preterm infant is considered to be a stressful event for parents. Many studies have shown that mothers of these infants experience increased levels of stress in the neonatal period compared with mothers of term infants, and they are more likely to suffer from depression and anxiety at the time of hospital discharge [3]. There is also increased depressive symptoms among fathers of preterm infants during the neonatal intensive care unit stay [4]. It is assumed that increased parenting stress could interfere with the parent-child relationship during early childhood and consequently increase the risk for later behavioural problems [3, 5].

The direct and indirect costs of prematurity can be immense [2]. The lifetime costs per preterm birth (baby's birth weight less than 2500 grams) have been estimated at £511,614 [1, 6].

The incidence of preterm deliveries in developed countries is 6% to 9%, currently it is 7% in the UK affecting 21,000 babies each year in England. Preterm premature rupture of the membranes and spontaneous preterm labour accounts for approximately 80% of preterm deliveries; the remaining 20% are planned deliveries for maternal or fetal reasons (for example, eclampsia) [7].

In the last 20 years it has become clear that infection is an important cause of preterm labour and delivery leading to more than 50% of the all preterm deliveries world-wide [1, 8-14]. Infection has been recognised as an important and frequent mechanism of disease in preterm birth with a firm link to prematurity. The evidence that implicate infection as a cause of preterm labour and birth includes:

- Administration of microbial products to pregnant animals results in preterm birth.
- Systematic maternal infection, for example, pyelonephritis, pneumonia or even Dental caries are associated with preterm labour.
- Subclinical intrauterine infections usually trigger preterm birth.
- Treatment of asymptomatic bacteriuria prevents preterm labour.
- Clinical infection is increased in the infant and the mother after preterm birth.
  - 10-15% of amniotic fluid cultures from preterm labour patients are positive for microorganisms.
  - Antibiotic treatment of intrauterine infections can prevent prematurity in experimental models of chorioamnionitis [15].

Since infection is frequently difficult to confirm, we often refer to women with positive amniotic culture, histological evidence of chorioamnionitis or elevated cytokines in the amniotic fluid as having a subclinical infection. In this context, the organisms involved may not be necessarily pathogenic; a change in vaginal flora may be enough to trigger the sequence of events leading to a preterm birth [1, 2, 8, 11, 14, 16-18].

The most common pathway for pathogens to cause preterm labour is the ascending route [2, 14]: several mechanisms contribute to this pathway. Pathogens produce proteolytic enzymes including different types of mucinases, sialidases, peptidase and protease. The presence of bacterial sialidases facilitates the attachment of bacteria to cervical mucus and the breakdown of mucin, while bacterial mucinases assist ascent into uterine tissues [2, 12, 19]. Other enzymes may act directly on cervical collagen leading to premature shortening and ripening cervix while also weakening the fetal membranes leading to preterm premature rupture of the membranes [2, 12, 19].

Microorganisms stimulate maternal monocytes and macrophages resulting in the production of phospholipase A₂. This is an enzyme that liberates arachidonic acid from the phospholipids of the membranes leading to the synthesis of prostaglandins.
E2 and F2α by the placental membranes: prostaglandins are potent stimulator of uterine contractions [14, 20-27]. Similarly, protease toxins activate the decidua and fetal membranes to produce Cytokines such as Tumour Necrosis Factor (TNF), Interleukin (IL1α, IL1β, IL6, IL8), and Granulocyte-Macrophage Colony Stimulation Factor (GM-CSF) [9, 12, 14, 20-22, 25-27]. The activation of a local inflammatory reaction leads to prostaglandin synthesis and release which subsequently stimulate uterine contractions [28-30]. Moreover, in infected foetuses, there is an increase in both fetal hypothalamic and placental production of corticotrophin releasing hormone leading to increase in fetal corticotrophin secretion, which in turn increases fetal adrenal cortisol production leading to increased production of prostaglandins [20, 25, 28]. When the fetus is infected, there is a high increase in the production of cytokines and marked decrease in the delivery time with a high chance of direct fetal tissue damage (e.g. fetal brain or lung) [2, 14, 19, 20, 24, 25, 31].

During pregnancy the primary function of the uterine cervix is to remain closed in order to retain the baby within the uterus until fetal maturity and birth. A secondary function of the cervix is to prevent infection ascending from the vagina into the uterus. Prior to normal delivery at term, cervix shortens, softens and ripens (becomes more distensible), to facilitate cervical dilatation by myometrial contractions during labour. The cervix consists mainly of connective tissue, principally, collagen fibres in a proteoglycan ground substance. The interaction between these two substances gives the cervix its unique characteristics, where the collagen fibres resist pulling forces and the ground substance resists compressive forces [32]. Various methods have been used to try and detect cervical changes that predict preterm labour. These include manual vaginal examination, transabdominal ultrasound, and transvaginal ultrasound [29, 33]. Of these modalities, measurements of cervical length using transvaginal ultrasound scanning appear to have the highest sensitivity, whereas transabdominal scanning was not predictive [29, 30]. There is however, no clear cut gestation at which the test should be performed or what cervical length provides the best cut-off for a diagnostic test [29, 33].

Rationale

We have analysed observational data on 106 women with a past history of preterm labour and birth [34] in order to test the hypothesis that women with a past history of preterm labour and birth have a more marked inflammatory response in the cervical mucus. Strikingly, we found that in a subsequent pregnancy, women with a low macrophage count (<5% of cervical epithelial cells expressing CD14 antigen) before 20 weeks gestation were more likely to have recurrent preterm birth compared with women who had normal cervical macrophage count (Odds Ratio 4.9, 95%CI 1.5 to 18.7; P 0.0037). This prompted us to develop a new model for ascending infection, that ascending infection occurs in the presence of a defective cervical barrier.

Objective

To investigate to what extent a defective cervical barrier is a contributory factor to recurrent preterm labour.

Hypothesis

Patients at high risk of preterm labour will have lower number of cervical leukocytes in general and macrophages specifically. The lower the number of macrophages the less vascular the cervix would be, which would result in low readings on power Doppler indices.

Methods and Materials

This is a hospital prospective observational cohort (non interventional study). Study was conducted in Liverpool Women's Hospital from October 2007 until October 2009. Methods were explained in a previous publication (Cervical Immunology in Women at Risk of Preterm Labour).

3D ultrasound methods

After collecting the cervical sample from the participants 3D ultrasound with power Doppler examination carried out using Voluson i machine with LOGIQ 9 transvaginal transducer, using Preset default and Gain 5. For Power Doppler settings were Quality low and PRF 0.6, while 3D ultrasound settings are Static, Max angle and Quality low.

Figure 1. Ultrasound results were analysed using 4D view programme.

Primary descriptive analysis used aiming to estimate the parameters for sample size calculations in further hypothesis testing studies. Standard parametric and nonparametric testing used to compare the results
between high risk group and controls. Conventional level of statistical significance (P<0.05) used.

Results

89 participants were recruited, 50 controls and 39 patients. Demographically both groups were similar. The difference in the history of previous preterm birth was statistically significant but this is expected since patients were defined as having history of previous preterm birth while, this is an exclusion criteria in the controls, Table 1.

Of the 39 patients 22 delivered after 34+0 completed weeks and 17 delivered before 34+0 weeks. Of those delivered preterm, three delivered before 20+0 completed weeks, one before 24+0 completed weeks and thirteen before 28+0 completed weeks, Figure 2.

Only one patient underwent caesarean section (for history of previous caesarean section). Another patient developed pregnancy induced hypertension and on admission she complained of abdominal pain. She delivered within 4 hours of admission at 26+3 weeks gestation.

Three babies delivered before 20+0 weeks died within 30 minutes of delivery. One baby delivered before 24+0 weeks was admitted to the NICU, but unfortunately developed infection and died at the age of 2 weeks. The rest of the patient’s babies were admitted to the NICU and later discharged in good condition.

All controls delivered after 34+0 completed weeks of the pregnancy, Table 2. Six controls underwent caesarean section. Three of those controls had a history of previous caesarean section. The other three had caesarean sections for antepartum haemorrhage, one for abruptio placentae and two for placenta praevia. Two sets of twins delivered vaginally. One at 36+4 weeks, the other at 37+2 weeks.

Of all babies delivered to controls, three babies were admitted to the NICU for meconium ingestion and discharged later in good condition.

For the rest of the results, patients who delivered after completed 34+0 weeks of gestation were excluded from the analysis.

Ultrasound results showed a statistically significant association between decrease in cervical length and preterm labour. On the other hand, a decrease in cervical volume was not associated with preterm labour, Table 3.

Settings for the ultrasound examination found to be different from the agreed settings in two patients. Added to that, artifacts affected two other examinations. Consequently, power Doppler data were also affected. Those four patients were excluded from the analysis. For the controls, settings of the ultrasound examination found to be different from the agreed settings in thirteen controls. In the other hand, artifacts did not affect any of the controls examinations. Those thirteen controls were excluded from the analysis.

An increase in vascular index and vascular flow index were associated with preterm labour. The flow index did not show any significant difference between the two groups, Table 4.

Discussion

Twin pregnancies were included in this study because there were plans to perform a separate analysis for twin pregnancies. This analysis would have been used as a pilot for a future large study of twin pregnancies. However, recruiting twin pregnancies proved difficult. It is recognised that the recruitment of twin pregnancies in this study is inappropriate because twin pregnancies are more prone to preterm labour than singleton pregnancy [36-38]. This will be taken into consideration in designing further studies.

The mucosal surface of the female genital tract serves as a potential site of entry for a variety of bacterial and viral pathogens [24, 26, 38-41]. Most infections are confined to the lower genital tract. Consequently, a higher level of immunological activity is associated with this region [24, 38, 40-42].

In the cervix, leukocytes are sparse prior to the onset of labour [14, 40, 43]. There is increasing evidence that the process of cervical dilatation resembles an inflammatory response [40, 43]. Leucocytes migrate into cervical stroma and mucus during labour reaching a density 2–3-fold higher than that found in late pregnancy [7, 43, 44]. This stromal infiltrate is composed principally of neutrophils and macrophages [43]. In contrast, others reported an increase in macrophage and neutrophil numbers in cervical stroma during late pregnancy, but no further changes during labour [40, 45]. This discrepancy may relate to differences in cervical ripening at the time of the sample collection, but no clinical information on the state of the cervix was provided in any studies. This means that the identification of leukocyte phenotypes at the mucosal surface of the endocervix is integral to understanding the pathogenesis of genital infection and the role of protective immunity.

Traditional methods to evaluate the cervix in...
pregnancy are limited and unsatisfactory. Attempts to screen women efficiently with risk-scoring systems or digital examination of the cervix, the standard method, suffers from large variation among examiners, and have revealed low sensitivities and low predictive values [53-55]. Vaginal ultrasonography produces good images and is well accepted by patients. There are no apparent risks associated with the examination [53-56]. In contrast, transvaginal ultrasonography is a reproducible method of examination during pregnancy. The length of the cervix is directly correlated with the duration of pregnancy: the shorter the cervix, the greater the likelihood of preterm delivery. This is mainly because uterine contractions, whether perceived by the woman or not, shorten the cervix [53-60].

3D ultrasound was first developed at Duke University in 1987 by Olaf von Ramm and Stephen Smith [61]. It was available for clinical research in the beginning then for clinical use in 1992. In 3D ultrasound scanning, instead of sound waves being sent straight down and reflected back, they are sent at different angels. The returning echoes processed by computer program which reconstruct three dimensional volume image, but no movement is shown [61, 62]. 3D ultrasonography has the potential to provide more accurate volume measurements than conventional 2D ultrasound [56-58, 61, 63]. 3D imaging combined with power Doppler became available for clinical use in 1995 and provided the potential to quantify power Doppler signals in a whole organ [56-59, 63, 64].

Results of this study showed a significant association between cervical length and preterm labour, but not the cervical volume. This could be due to the sample size or due to the difficulty of estimating cervical volume. Since one of the methodological difficulties when estimating cervical volume and vascularity using 3D ultrasound is defining landmarks when drawing the contours of the cervix [53, 56-59, 64-66]. The delineation between the cervix and the lower uterine segment is particularly difficult, especially early in pregnancy and at mid-gestation when the lower uterine segment is thick and the cervix often curved. It may also be difficult to clearly separate the cervix from the surrounding vaginal tissue [53, 56-59, 64, 66].

Our hypothesis was that patients at high risk will have lower numbers of macrophages, and in turn less vascular cervix which would be seen as low readings on the power Doppler indices, but against our hypothesis, results of this study showed a significant inverse association between both vascular index and vascular flow index and preterm labour. On the other hand, flow index also increased in preterm labour patients than controls but this is not statistically significant. This means there is an increase in the vascularity of the cervix in preterm labour patients. This result could be due to the small sample size or the difficulty in defining the landmarks when drawing the contours of the cervix which in turn affects the calculation of power Doppler indices. The last possible explanation is a premature remodeling of cervical architecture and this may include an element of preconceptional hypervascularity since all these women have previous history of preterm labour. The cervix of a patient who has had a previous history of preterm labour may have permanent changes to her cervix [40, 67-69]. Part of the ripening process is cytokine stimulation of an influx of macrophages and neutrophils which in turn not only produce more cytokines but also induce angiogenic activity with the result of newly formed microvessels which will allow more influx of the macrophages and neutrophils [67, 69]. Newly formed microvessels resolve soon after delivery but a small fraction remains as part of the normal structure of the cervix. In the next pregnancy these microvessels are represented as hypervascularity of the cervix [40, 67-71]. Accordingly, a preconceptional ultrasound with power Doppler is needed to confirm or refute the presence of this phenomenon.

Conclusion

There was a significant association between cervical length and preterm labour, but not the cervical volume. There is a real requirement for more research on cervical leukocyte population at reasonable time in pregnancy. Adding the 3D ultrasound element and power Doppler at the same time will provide volatile information about the cervical morphology.

References

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Three dimensional imaging system USA. 1987.
Illustrations

Illustration 1

Figure 1: Picture of the 3D ultrasound with power Doppler examination results on the ultrasound machine
Illustration 2

Figure 2: Patient gestational age at delivery
Illustration 3

Table 1: used CD antigens based on leukocyte types

<table>
<thead>
<tr>
<th>Leukocyte Type</th>
<th>CD antigen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Granulocytes</td>
<td>CD66b (specific), CD49d, CD16</td>
</tr>
<tr>
<td>Lymphocytes</td>
<td></td>
</tr>
<tr>
<td>T cells</td>
<td>CD3 (specific)</td>
</tr>
<tr>
<td>B cells</td>
<td>CD19 (specific)</td>
</tr>
<tr>
<td>NK cells</td>
<td>CD16, CD49d</td>
</tr>
<tr>
<td>Dendritic cells</td>
<td>CD1a (specific), CD49d</td>
</tr>
<tr>
<td>Monocytes</td>
<td>CD14, CD163, CD49d</td>
</tr>
<tr>
<td>Macrophages</td>
<td>CD14, CD163</td>
</tr>
</tbody>
</table>
Illustration 4

Table 2: Distribution of participants in the study

<table>
<thead>
<tr>
<th>Participants</th>
<th>Delivered $\geq 34^{\circ}$ weeks</th>
<th>Delivered $\lt 34^{\circ}$ weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controls</td>
<td>50 (100%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>N=50</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients</td>
<td>22 (56.41%)</td>
<td>17 (43.59%)</td>
</tr>
<tr>
<td>N=39</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Illustration 5

Table 3: 3D ultrasound results

<table>
<thead>
<tr>
<th>Cervix mean (SD)</th>
<th>PTB &lt;34+0 N= 17</th>
<th>Controls N= 50</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Length (mm)</td>
<td>41.3 (5.2)</td>
<td>44.4 (7.8)</td>
<td>0.04</td>
</tr>
<tr>
<td>Volume (cm³)</td>
<td>30.4 (8.9)</td>
<td>33.1 (14.7)</td>
<td>0.25</td>
</tr>
</tbody>
</table>
Illustration 6

Table 4: 3D ultrasound with power Doppler results

<table>
<thead>
<tr>
<th>Doppler indices median (SD)</th>
<th>PTB &lt;34+0 N= 13</th>
<th>Controls N= 37</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vascular Index (%)</td>
<td>31.3 (8.7)</td>
<td>15.5 (9.6)</td>
<td>0.0006</td>
</tr>
<tr>
<td>Flow Index (unit)</td>
<td>36.1 (2.6)</td>
<td>35.2 (2.9)</td>
<td>0.61</td>
</tr>
<tr>
<td>Vascular Flow Index (unit)</td>
<td>12 (3.5)</td>
<td>5.3 (3.7)</td>
<td>0.0009</td>
</tr>
</tbody>
</table>
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