Cervical Immunology 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 unite 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 Fαx 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 Stimulating 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

This is a hospital prospective observational cohort (non interventional study). Study was conducted in Liverpool Women’s Hospital from October 2007 until October 2009. One of the aims of this study was to estimate the parameters for sample size calculations in further studies, therefore there was no formal prior sample size calculation. The plane was to recruit 50 cases and 50 parous controls. Inclusion criteria for cases included being between 13-17 weeks gestation and certain gestational age confirmed by ultrasound with history of at least one unexplained previous birth between 20 and 32 completed weeks (preterm birth was not caused by preeclampsia, pregnancy induced hypertension, abruptio placenta, severe intrauterine growth retardation, intrauterine fetal death, haemophilia or any chronic systematic disease). Cases were excluded if they were primigravida, has a history of cervical cerclage, history of cervical weakness (need for elective cervical suture at or before 16 weeks gestation), uterine congenital anomalies, drug addiction, younger than 18 years old, planned for antenatal care or delivery elsewhere, history of chronic systematic disease requiring treatment during pregnancy, fetal congenital anomalies and fetal death.

Controls were recruited from the general antenatal clinic as pregnant women between 13-17 weeks and certain gestational age confirmed by ultrasound. Exclusion criteria for controls were the same as cases added to that any history of previous preterm birth (<37 weeks).

In the normal routine booking visit (12 – 18 weeks), all women with a history of previous preterm birth were assessed in the Preterm Labour Clinic. Routine investigations carried out following a booking ultrasound scan. At the end of this booking visit, women were informed about the study. Women who agree to take part were consented then had a cervical swab, Cytobrush swab of the external cervical os and 3D Trans-Vaginal Scan, Figure 1.

Control group had routine investigations done in the first visit (12 – 18 weeks). At the end of this booking visit, women were informed about this study and if agreed to participate, they were consented then had vaginal and cervical swabs and 3D ultrasound done as above.

Laboratory methods

Using sterile speculum cervix visualized and cytobrush used to collect cervical cells. A cytobrush is a fine cervical cytobrush (Cervix-brush, Rovers Medical Devices, Oss, Netherlands) gently rotated twice 360 degrees in the cervical canal. Tip of the brush is separated and pushed into the sample bottle, which is kept cold all the time. The sample then processed and
prepared for flow cytometry using different fluorescence labelled CD antigens, Table 1.

In flow cytometry Fluorescence-activated cell sorting (FACS) was used. Because of the differences in the size and granularity, different cervical cells are plotted in different gates. Since cervical epithelial cells are very large cells they are represented in the far end outside the scale of the forward scatter which is the X axis on the dot plot, while the difference in intensity of granularity between the types, different layers and function of these cells causes them to be distributed in relation to the side scatter on the Y axis, Figure 2.

FACS results are then analysed using WinMDI programme [35].

**Objective**

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 2.

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 3.

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 3. 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 placentaee 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.

The most common leukocytes present in both groups were macrophages. Leukocytes showed no difference between the 2 groups, Table 4.

**Hypothesis**

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.

While all previous studies used manual counting to quantify cervical leukocytes, this is the first study that utilized flow cytometry to characterise cervical leukocytes in pregnant women. This study has
characterised cervical leukocyte subpopulations in pregnant normal and high risk multiparous women. The most prevalent cervical leukocyte was the macrophage. Macrophages and the rest of the leukocyte types were fewer in high risk patients than in normal pregnant controls, but this difference did not reach statistical significance. This could be due to the sample size. Or this could be due to the collection of the cervical samples very early in pregnancy. The influx of leukocytes is expected later in pregnancy [40, 45], or at the time of cervical ripening prior to labour [43]. The reason for collecting the cervical samples very early in pregnancy was to have enough time to treat patients with infection, manifested as high leukocyte readings, since early treatment of ascending infections may reduce preterm labour and birth by preventing the development of a minor infection into intrauterine infection [46-49]. Future studies designed to investigate leukocyte populations of the cervix in high risk patients should be planned between 18+0 and 25+0 weeks since this is likely to provide better information about the premature preparation of the cervix for delivery.

The cytobrush technique was successfully used to collect cervical samples. There are two major concerns regarding the use of the cytobrush to study immunological cells in the intraepithelial layer of the cervix. The first is to confirm that there are minimal levels of blood contamination that would distort and invalidate analysis. The second is to know whether cells are derived from the lamina propria as well as the intraepithelial layer compartment [50]. Even with blood contamination, flow cytometry differentiates between cervical and blood leukocytes because each has different cell volume and complexity, therefore blood leukocytes are represented in a different gate than the one used for the cervical leukocytes. Regarding the second concern, during cervical sampling, dislodgement of ectocervical cells is unavoidable. However, few leukocytes reside within the superficial layers of the ectocervix and this would not affect the results [24, 26, 38, 40, 42].

The use of the flow cytometer technique to characterise cervical leukocytes proved successful in general and beneficial especially in resolving any concerns about blood contamination of the cervical samples. If the cervical samples are contaminated by blood, the technique of the FACS analysis differentiates blood cells and cervical leukocytes. Blood cells can be separated in to two main gates, one represents the red blood cells (erythrocytes) since they are agranular and in different sizes which direct the gate to be in the lower end of the Y axis and distributed over the X axis, while leukocytes originating from blood contamination are much smaller [50-52] and represented on the X axis far before cervical leukocytes which almost represented at the same level as blood leukocytes on the Y axis, this differentiation leads to the formation of 3 completely different gates one for the red blood cells, the other for leukocytes from blood contamination and the most important distinctive third is the gate of the cervical leukocytes, Figure 2.

Methods and Materials

35. Trotter J. WinMDI 2.9. 2.9 ed: Purdue University, USA 2000.
2004;8:87-95.

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 2.

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Discussion

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**Conclusion**

Cytobrush technique used successfully to collect cervical samples. Likewise, the use of flow cytometer technique to characterise cervical leukocytes proved successful in general and beneficial specially in resolving any concerns about blood contamination of the cervical samples. The most prevalent cervical leukocyte was macrophages.

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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35. Trotter J. WinMDI 2.9. 2.9 ed: Purdue University, USA 2000.
Illustrations

Illustration 1

Figure 1: Study flow chart
Illustration 2

Figure 2: Schematic representation of the FACâ€™s histogram and cervical gates
Illustration 3

Figure 3: Patient gestational age at delivery
Illustration 4

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 5

Table 2: Demographical proparties of the participants

<table>
<thead>
<tr>
<th></th>
<th>Patients N = 59</th>
<th>Controls N = 50</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age median (range)</td>
<td>31 (20-39)</td>
<td>29 (19-39)</td>
<td>0.366</td>
</tr>
<tr>
<td>Smoking %</td>
<td>23.08%</td>
<td>22%</td>
<td>0.904</td>
</tr>
<tr>
<td>parity median (range)</td>
<td>1 (1-6)</td>
<td>1 (1-3)</td>
<td>0.166</td>
</tr>
<tr>
<td>previous PTB median (range)</td>
<td>1 (1-6)</td>
<td>0 (0)</td>
<td>0.0001</td>
</tr>
<tr>
<td>gestational age median (range)</td>
<td>15 (13-16)</td>
<td>15 (13-16)</td>
<td>0.405</td>
</tr>
</tbody>
</table>
Illustration 6

Table 3: Distribution of participants in the study

<table>
<thead>
<tr>
<th>Participants</th>
<th>Delivered ≥34&lt;sup&gt;th&lt;/sup&gt; weeks N (%)</th>
<th>Delivered &lt;34&lt;sup&gt;th&lt;/sup&gt; weeks N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controls N=50</td>
<td>50 (100%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Patients N=39</td>
<td>22 (56.41%)</td>
<td>17 (43.59%)</td>
</tr>
</tbody>
</table>

Illustration 7

Table 4: Leukocytes results

<table>
<thead>
<tr>
<th>Cell count/10&lt;sup&gt;6&lt;/sup&gt; cells median (range)</th>
<th>PTB &lt;34&lt;sup&gt;th&lt;/sup&gt; N=17</th>
<th>Controls N=50</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Macrophages</td>
<td>14 (1-21)</td>
<td>16 (1-53)</td>
<td>0.16</td>
</tr>
<tr>
<td>Monocytes</td>
<td>0 (0-1)</td>
<td>0 (0-2)</td>
<td>0.81</td>
</tr>
<tr>
<td>B cells</td>
<td>0 (0)</td>
<td>0 (0-2)</td>
<td>0.41</td>
</tr>
<tr>
<td>T cells</td>
<td>0 (0-3)</td>
<td>0 (0-26)</td>
<td>0.98</td>
</tr>
<tr>
<td>Granulocytes</td>
<td>0 (0-23)</td>
<td>0 (0-54)</td>
<td>0.08</td>
</tr>
<tr>
<td>Dendritic cells</td>
<td>0 (0)</td>
<td>0 (0-21)</td>
<td>0.32</td>
</tr>
</tbody>
</table>
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