A CASE CONTROL STUDY OF THE ASSOCIATION OF VAGINAL INFECTIONS WITH PRETERM LABOUR AND NEONATAL OUTCOME

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ABSTRACT

BACKGROUND
Prematurity accounts for 85% of neonatal mortality. The neonatal morbidity associated with preterm labour is also very high. About 40% of unexplained preterm labour is due to vaginal infections. Screening for genital infections especially in high risk pregnancies will decrease the incidence of preterm labour and associated neonatal mortality and morbidity.

MATERIALS AND METHODS
The study was a case control study conducted in the department of Obstetrics and Gynaecology Labour Ward in a tertiary level hospital in the government sector in South India. One hundred cases of spontaneous preterm labour with no identifiable cause were included as the cases. Equal number of cases of uncomplicated term pregnancies delivering in the labour ward was included in the control arm. This study focuses on the incidence of vaginal infections in preterm labour compared to their incidence in term pregnancies. It also aims to identify the most common organism isolated in pregnant women with preterm labour and to study the neonatal morbidity and mortality of preterm births which are associated with vaginal infections.

RESULTS
The incidence of infections was 28% in the study group where as it was 10% in the control group. The organisms isolated were group B streptococcus, E. coli and Klebsiella. Group B streptococci were isolated in 38.29% cases of spontaneous preterm labour and bacterial vaginosis in 28.57% of preterm deliveries. There were 5 cases of neonatal sepsis in the culture positive group whereas there was no case of neonatal sepsis in the culture negative group.

CONCLUSION
This study emphasizes that vaginal infection is a significant risk factor for unexplained preterm labour. Identification of high-risk women for preterm labour, antenatal screening for vaginal infections and the use of the appropriate prophylactic antibiotics will help to decrease the neonatal morbidity and mortality associated with prematurity.

KEYWORDS
Preterm Labour; Vaginal Infections; Group B Streptococcus; Bacterial Vaginosis.

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BACKGROUND
Preterm birth complications are the leading cause of death among children less than 5 years of age, responsible for approximately 1 million deaths in the world in 2015.¹ 85% of neonatal deaths occur in preterm babies.¹ Every year, an estimated 15 million babies are born preterm (before 37 completed weeks of gestation), and this number is rising.¹ Worldwide, the rate of preterm birth ranges from 5% to 18% of babies born. In India, out of 27 million babies born every year (2010 data), 3.5 million babies born are premature.²

In addition to its contribution to mortality, preterm birth accounts for half of the long term neurological morbidity in childhood such as increased risk of cerebral palsy, impaired learning, and visual disorders and an increased risk of chronic disease in adulthood.³ The economic cost of preterm birth is high in terms of neonatal intensive care and on-going health care and educational needs of the babies who were ‘born too soon.’

It is estimated that as much as 40% of preterm labour may be caused by intrauterine infection, majority of which may be of subclinical variety. The incidence of chorioamnionitis and preterm premature rupture of membranes is more in patients with positive cultures than women with negative cultures.⁴ They are also more likely to have neonates with complications.⁵ These are preventable causes and prompt recognition of infections and early institution of the appropriate treatment will help reduce the mortality and morbidity associated with preterm labour.

This study focuses on the incidence of vaginal infections in preterm labour compared to their incidence in term pregnancies. It also aims to identify the most common organism isolated in pregnant women with preterm labour. The study also aims to find the neonatal morbidity and
mortality of preterm births which are associated with vaginal infections.

**MATERIALS AND METHODS**

The study was a case control study conducted in the department of Obstetrics and Gynaecology Labour Ward in a tertiary level hospital in the government sector in South India. Ethical permission was obtained from the Institutional Review Board.

One hundred cases of spontaneous preterm labour with no identifiable cause were included as the cases. Cases were enrolled with consecutive sampling technique. Eligible cases were identified in the labour ward. Written Informed consent was obtained before enrolling in the study. Equal number of cases of uncomplicated term pregnancies delivering in the labour ward was included in the control arm.

**Inclusion Criteria**

Only cases of established preterm labour were included. Only cases of spontaneous preterm labour both with and without intact membranes were included in the study. Only preterm labour in which the cause was not identifiable was included in the study.

**Exclusion Criteria**

Pregnancies before 26 weeks and beyond 37 completed weeks; pregnant women with the last menstrual period not known, or pregnant women without an early ultrasound report (<24 weeks) available. Cases with any identifiable cause for preterm labour were excluded. Multiple pregnancies, placental abnormalities (abruption placenta and placenta praevia), hydramnios, malpresentations, uterine anomalies, any medical disorder complicating pregnancy including hypertension, diabetes, heart disease, anaemia at the time of admission were excluded. Cases with foetuses with congenital anomalies and intrauterine foetal deaths were also excluded from the study. Cases in which pregnancy was terminated preterm for any maternal or foetal indication was excluded from the study.

Gestational age assessment was done at the time of admission. In patients who had reliable dates, gestational age was calculated from their last menstrual period. In those without reliable dates, an early ultrasound (<24wks as recommended by WHO) was used to confirm the gestational age. Gestational age of 26 weeks was taken as the lower limit for viability taking into account the NICU facilities of the hospital. The booking status (booked or unbooked) of the patient was defined as at least 4 contacts with the antenatal care giver. Antibiotics (parenteral ampicillin 1 gm. intravenous twice a day) were started at admission itself for all cases of preterm labour. Steroids were also started for all cases of preterm labour between 28 weeks and 34 weeks. Cases were monitored for features of sepsis like fever, maternal tachycardia, uterine tenderness and foul smelling vaginal discharge.

An unstructured questionnaire was used to assess the demographic, obstetric and medical history of the patients. Detailed history was taken with respect to age, parity, socioeconomic status, residence, previous pregnancy outcomes. Presence of risk factors in the index pregnancy including genitourinary and respiratory infections, gestational diabetes, anaemia, hypertensive disorders, heart disease or any other medical disease, obstetric risks like hydramnios, multifetal gestation, malpresentation and uterine anomalies was also noted. The time of onset of pains and the rupture of membranes were also carefully noted. A thorough systemic and obstetric examination was done. An obstetric ultrasound was done for cervical length, liquor volume; estimated foetal weight, placental localisation and separation were done. Speculum examination was done to visualise cervix and vagina, identify any premature preterm rupture of membranes and to rule out cervical and vaginal infections. A vaginal smear was taken from the posterior fornix using sterile cotton tipped disposable swab in both the cases and controls. This specimen was immediately sent for culture and sensitivity. A sterile nonlubricated vaginal speculum was used. Midstream urine sample was sent for culture and sensitivity. The sterile swabs were cultured on sheep blood agar plates and read for haemolysis. The organism isolated was then identified. If a beta - haemolytic streptococci was identified further tests were done to confirm the group B strain. CAMP test was done. Grouping was also done with the group B specific sera to confirm the strain of organism. 10% KOH was added to identify the fishy odour. A wet mount preparation was made to detect the presence of clue cells. Amsel's criteria was used to identify Bacterial vaginosis and the Nugents score was used. Microbiological analysis and antimicrobial sensitivity testing of urine and high vaginal swab were done in the Department of Microbiology at our institute.

The babies are examined after delivery. Birth weights of the neonates were assessed using the electronic weighing scale. The Apgar score was assessed by the neonatologist and the data was collected from the Neonatal Intensive Care Unit (NICU) records. After delivery the gestational age was reconfirmed. The babies of both the study and control group were followed up till discharge from the hospital. Any neonatal morbidity in the form of sepsis, respiratory distress, Hyaline membrane disease (HMD) and Hyperbilirubinemia were recorded from the NICU records.

**Data analysis**

Data was entered in Microsoft Excel and analysed using open- source R. statistical software package version 3.02. Data was summarised as mean and percentage. Unpaired t-test was used to test the difference between the two groups. Chi-square test was used to analyse the difference in the proportion and p value was calculated.

**RESULTS**

100 cases of preterm labour of unexplained aetiology and equal number of uncomplicated term pregnancies were studied. The incidence of infections was 28% in the study group where as it was 10% in the control group. (p<0.001) (Figure 1).
There was 28% incidence of infection in the study population compared to 10% in the control population which was statistically significant.

The organisms isolated were group B streptococcus, E. coli and Klebsiella. Group B streptococci were isolated in 38.29% cases of spontaneous preterm labour without any identifiable risk factors. In 28.57% of preterm deliveries bacterial vaginosis was identified, no cases of term deliveries were associated with bacterial vaginosis. Bacterial vaginosis was significantly isolated from preterm labour cases, but no cases were found in term pregnancies (Table 1).

<table>
<thead>
<tr>
<th>Microorganism</th>
<th>Cases</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of Cases</td>
<td>%</td>
</tr>
<tr>
<td>E. coli</td>
<td>5</td>
<td>17.86%</td>
</tr>
<tr>
<td>Klebsiella</td>
<td>4</td>
<td>14.29%</td>
</tr>
<tr>
<td>Group B Streptococci</td>
<td>11</td>
<td>39.29%</td>
</tr>
<tr>
<td>Bacterial Vaginosis</td>
<td>8</td>
<td>28.57%</td>
</tr>
</tbody>
</table>

Table 1. Distribution of Microorganisms in Patients with Preterm Labour and Controls

In the infection positive group 70% of babies were less than 2kg. None of the babies in culture positive group weighed more than 2.5kg. In the culture negative group 63.25% of babies weighed more than 2.5kg (Table 2).

<table>
<thead>
<tr>
<th>Birth Weight</th>
<th>Culture Positive</th>
<th>Culture Negative</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of Cases</td>
<td>%</td>
</tr>
<tr>
<td>&lt;1.5kg</td>
<td>2</td>
<td>7.14%</td>
</tr>
<tr>
<td>1.5-2kg</td>
<td>17</td>
<td>60.7%</td>
</tr>
<tr>
<td>2-2.5kg</td>
<td>9</td>
<td>32.14%</td>
</tr>
<tr>
<td>&gt;2.5</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Table 2. Birth Weight of Foetuses in Culture Positive vs. Culture Negative Groups

DISCUSSION

Vaginal infection was identified in 28% of our preterm labour cases in this study. This is similar to the incidence noted by another Indian study by Yarlagadda S which noted vaginal infections in 33.62%. Different studies have noted varying rates of vaginal infection in preterm labour. A study done by Shannon FF et al reported an incidence of 8.29% and Samim A et al reported an incidence of 7.24% of women with vaginal infection in preterm labour. In the study done by Pradeep Raju S et al the incidence of vaginal infections was 58.06% in women with preterm labour which is higher than most studies. The variation may be due to high risk group of women being catered to, the difference in gestational age when screening was done in the different studies.

The vaginal flora has been studied extensively in different studies. Reagan et al demonstrated that Gardnerella vaginalis, bacteroides species, Escherichia coli, Klebsiella and Staph. aureus are significantly associated with preterm labor. In our study the group B streptococci was
the most common organism isolated. 39.29% cases had Group B streptococci. A Danish study in 2001 also concluded that GBS colonization was associated with preterm delivery. Variations of GBS identification in studies can be attributed to differences in the characteristics of the studied populations (such as age, parity, ethnic group, socioeconomic level and geographical location) and to the employed diagnostic methods to isolate group B streptococci. The high incidence of detection of GBS in our study may be attributed to the immediate transportation of the sample to the microbiology laboratory and to the highly sensitive medium of culture and the stringent conditions which were followed. Our study found an incidence of 28.57% for bacterial vaginosis in preterm labour. In a prospective study by Goyal et al it was found that bacterial vaginosis has a significant association with preterm labour and adverse pregnancy outcomes. Subtil D et al in their study of 102 patients also found that bacterial vaginosis is associated with preterm labour but does not appear to predict preterm birth. Carey et al concluded that an increase in E. coli or K. pneumoniae in the vagina is an independent risk factor for preterm birth.

The relationship between intermediate vaginal flora and adverse pregnancy outcomes has been highlighted in the literature. While the exact mechanism leading to preterm labour and adverse pregnancy outcomes is not known, inflammatory responses primarily due to IL1 and IL6 were reported to mediate the production of prostaglandins and cause preterm uterine contractions. GBS transmission in colonized mothers has been reported to be between 16-53% in studies. Neonatal disease develops in 1% to 22% in colonized neonates. Only 1-2% of infants of colonized women develop early-onset GBS disease in the first week of life.

We acknowledge a few limitations of our study. The rate of infections reported in our study represents the proportion of women infected during the onset of preterm labour pains. We have not studied the incidence of chlamydial infections in our study as it was outside the scope of the study. The strengths of our study is the heterogeneous population with respect to the socioeconomic characteristics and other demographic factors hence the rates of infections reported in the study can be generalized to pregnant women with diverse demographic characteristics. Also, the study emphasizes the high incidence of infections in the preterm group compared to the term group.

Guidelines from CDC and Canadian guidelines recommend universal screening for rectovaginal GBS colonization in pregnant women at 35-37 weeks of gestation and administration of prophylactic antibiotics during labour to all GBS positive women. These guidelines were easily adopted by the western population. But in the South Asian countries where infection is still the main contributor to preterm labour and the mortality and morbidity associated with prematurity is still very high, these guidelines are still not used in many centres. Practicing the screening guidelines in the high-risk obstetric population will help us in initiating prophylactic antibiotic therapy and thereby reduce neonatal morbidity.

CONCLUSION

This study emphasizes that vaginal infection is a significant risk factor for unexplained preterm labour. Though universal screening for vaginal infections is recommended, it may be cost effective and affordable to screen high risk pregnant women and symptomatic women for bacterial vaginosis and other vaginal infections. Patients in preterm labour with or without membranes should be provided group B streptococcus prophylaxis till delivery. Antenatal care in developing countries should focus on identification of high-risk women for preterm labour, antenatal screening for vaginal infections and the use of the correct prophylactic antibiotics during delivery to optimize the use of limited resources and to improve the quality of obstetric care.

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