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An Observational Study on the Role of Infection as a Maternal Risk Factor for Preterm Labour

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Abstract
Background: *Preterm delivery is one of the most challenging obstetric complication encountered in day to day practice Preterm delivery is the single greatest cause of perinatal mortality and morbidity worldwide*
Objective: *The aim of this study was to determine the role of infections as a maternal risk factor for preterm labour.*
Study Design: *It was a case control study in which 230 women who underwent preterm delivery were taken as cases and 230 women as control matching in age who underwent normal term delivery in our obstetric population. The study duration was 1 year from November 2012 to November 2013*
Results: *A total of 460 patients were studied. Women with history of maternal infections were significantly more in the case group (23.5%) than in the control group (9.6%). Women with vaginal infections were significantly more in the case group(9.1%) than the control group (1.3%). Discharge PV was observed more in the case group (26.5%) than the control group (10.4%) and the difference was significant also Mothers who had history of STD were significantly more in the case group (10%) than in the control group (2.2%) Women with UTI is significantly more in the case group(31.7%) than the control group(15.7%. Women with periodontal problems were significantly more in the case group (5.2%) than the control group (1.3%).*
Conclusion: *Maternal infection both systemic & local significantly contributed to produce the situation of pre-term labour.*
Keywords: *Preterm delivery, Periodontal infection, Vaginalinfection, Urinary tract infection.*

Introduction

Preterm delivery is defined as spontaneous expulsion of the products of conception after viability and before 37 completed weeks. Prematurity affects 1 in 10 births and 40-75% of neonatal deaths. The incidence of preterm delivery is rising worldwide because of increased frequency of multiple births due to artificial methods of reproduction, more working mothers, increased stress and medically induced prematurity. Despite decades of research much on the aetiology remains unknown and hence, the rate of premature births has not decreased and same data suggest that it is on the rise. Survival rates have increased and morbidity has decreased due to technologic advances in perinatal and neonatal medicine. Management of preterm delivery and care of preterm birth account for health care expenditures of over 3 billion per year.

The precise mechanisms by which human parturition is initiated spontaneously, either at term or preterm, are not well understood. It is established that microbial colonization and inflammation in the maternal genital tract is one cause of preterm birth and account for the majority of preterm births between 21 and 24 weeks. As gestation progresses to 33 weeks, however, the incidence of preterm birth due to infection drops below 10%. Thus, in the large majority of preterm births there is no known etiological agent. While the exact causes of preterm labor are not known, they may include behavioural, environmental, biological and psychosocial factors, medical conditions and genetics.

In under-resourced rural communities, infant mortality related to preterm and low birth rate birth exceeds that in urban communities, and is not solely attributed to limited access to secondary and tertiary care. The World Health Organization has recognized the “survival gap” between infants born in low and high resource settings: 90% of infants less than 28 weeks survive in high resource countries and 10% survive in low resource settings.

The cost associated with providing care for preterm infants, who may spend numerous months in hospital, has significant implications for the economy

Several factors have been identified that are associated with preterm birth. These include intrauterine inflammation/ infection, uterine over distension, uteroplacental ischemia /haemorrhage, and stress. Mothers exposed to high levels of psychological or social stresses are at increased risk of pre-term birth. Clinical depression, possibly due to its associated increase in smoking, alcohol and drug use also plays a role in increasing pre-term birth as mediated bythese behaviours. As the cause of labour still remains elusive, the exact cause of preterm birth is also uncertain. Approximately 30–35% of preterm births are indicated or iatrogenic due to medical orobstetric complications, 40–45% are related to spontaneous preterm labour, and 25–30% to preterm prelabour rupture of membranes (PPROM).

Materials and Methods

A case control study was conducted from November 1st 2012 to November 30th 2013 at Sree Avittom Thirunal Hospital, Medical College Thiruvananthapuram, Kerala. For the present study 230 case and controls were taken as sample size. For every preterm birth that occurred between gestational ages 24 -37 weeks while term babies were those whose delivery occurred at or beyond a gestation age of 37 but below 42 completed weeks. Gestational age was estimated by the patients’ last menstrual period (LMP). It was determined on the basis of whether menstruation was regular or by ultrasonography detecting gestational age of <20 weeks. Previous ultrasonogram should be showing normal fetal morphology. Consecutive cases satisfying the sample size and the succeeding normal delivery of each case is taken as control. All consecutive admissions screened and list of eligible made the units were selected.

Informed consent was taken for history taking, physical examination and relevant investigations in all patients of gestational age 28 -37 weeks in the reproductive age group of 18-35 years with preterm labour admitted in Obstetrics and Gynaecology department of SAT hospital was recruited for the study. An interview schedule with pre structured questions used to collect the relevant information.

First, the patients who fit the criteria was selected. A proper general physical examination including pulse rate, systemic examination, per abdomen, per speculum examination was done. A questionnaire prepared to assess the various maternal determinants of pre-term labour was used. Similarly the various causes and levels of maternal stress was assessed using a stress scale questionnaire by Kumar and Kumar. We intended to study the effect of maternal infections and its effect on pre-term labour and hence all women who had vaginal signs of infection – discharge per vaginum, itching, foul smelling discharge per vaginum where advised local treatment and high vaginal swab test; the reports of which we followed up from microbiology lab in our institute and women who had a positive culture were treated with antibiotics according to culture and sensitivity.

Antenatal History taken from mothers who underwent preterm delivery, the treatment given to them in labour room and the mode of delivery was noted. The babies who were admitted in in-born nursery were followed up. The babies who were left with their mothers were also examined every day till their discharge from hospital. Proper consent was taken before taking history from mother, before examining the baby.

No intervention was done in case of mothers who underwent preterm deliveries or for their babies other than the usual methods adopted in labour room procedures and neonatal ICU. The babies too received all the necessary treatments and no medical treatments were withheld for the sake of this study.

Collected data was entered in MS excel. Completeness was checked and analysis was done using statistical software SPSS version 20. Chi square test, Fischer‘s exact test and logistic regression used for finding the risk factors. Appropriate statistical tests were used to interpret the results and derive summary statistics the distribution of variables was looked into and appropriate statistical significance was undertaken.

Results

A total of 460 patients were studied of 460 patients 230 cases under the cases is between 24 - 37 weeks of gestation and 230 patients were taken as control are patients who delivered normally after 37 weeks but before 42 weeks.

Women with history of maternal infections were significantly more in the case group (23.5%) than in the control group (9.6%). It can be seen that more than 75 % of the study and control group had no history of maternal infections. But there was a significantly higher percentage of cases (23.5%) with h/o maternal infections in the ante-natal period than the controls (9.6%). The chi-square test showed a significant association between history of maternal infection and preterm labour.

Maternal infection significantly contributed to produce the situation of pre term labour and it was found that prevention of maternal infection significantly reduce the condition of pre term labour.

Table No 1: Distribution of Systemic Maternal Infections among the Patients during the Present Pregnancy

History of maternal infections	Case		Control		**Total**	
	N	**%**	**N**	**%**	**N**	**%**
Yes	54	23.5	22	9.6	76	16.5
No	176	76.5	208	90.4	384	83.5
Total	230	100	230	100	460	100

$\chi^2 = 16.140$ *df=1* $p<0.001$

Table No 2: Distribution of Local Infection among the Study Group:

Vaginal infections

Vaginal infections	Case		Control		**Total**	
	N	**%**	**N**	**%**	**N**	**%**
Yes	21	9.1	3	1.3	24	5.2
No	209	90.9	227	98.7	436	94.8
Total	230	100	230	100	460	100

$\chi^2 = 12.705$ *df=1* $p<0.001$

Table no 2 shows that 9.1% was having local infection which was detected by per speculum examination. When evidence of infection was found the same was taken up for microscopic slide examination and culture and sensitivity.

Women with vaginal infections were significantly more in the case group (9.1%) than the control group (1.3%). So it forms another reason for pre term labour.

Table No 3: Distribution of Discharge Per Vaginum among the Patients

Discharge PV	Case		Control		**Total**	
	N	**%**	**N**	**%**	**N**	**%**
Yes	61	26.5	24	10.4	85	18.5
No	169	73.5	206	89.6	375	81.5
Total	230	100	230	100	460	100

$\chi^2 = 19.757$ *df=1* $p<0.001$

Table no 3 showed the incidence of discharge per vaginum among the study and control group. Discharge PV was observed more in the case group (26.5%) than the control group (10.4%) and the difference was significant also. It is one of the significant maternal determinant ($p<0.001$)

Table No 4: Distribution of UTI among the Patients

UTI	Case		Control		**Total**	
	N	**%**	**N**	**%**	**N**	**%**
Yes	73	31.7	36	15.7	109	23.7
No	157	68.3	194	84.3	351	76.3
Total	230	100	230	100	460	100

$\chi^2 = 16.460$ *df=1* $p<0.001$

Women with UTI is significantly more in the case group(31.7%) than the control group(15.7%)

Table No 5: Distribution of Peri Odontal Infections among the Patients

Periodontal	Case		Control		**Total**	
	N	**%**	**N**	**%**	**N**	**%**
Present	12	5.2	3	1.3	15	3.3
Absent	218	94.8	227	98.7	445	96.7
Total	230	100	230	100	460	100

$\chi^2 = 5.582$ *df=1* $p=0.018$

The incidence of periodontal infections among both the study and control group is presented in the above table no. 5. Women with periodontal problems were significantly more in the case group (5.2%) than the control group (1.3%).So periodontal infection significantly contributed to produce the situation of pre-term labour and it was found that prevention of maternal periodontal infection significantly reduced the condition of pre-term labour. More than 95 % of the study and control group had no history of periodontal infections. Analysing the present data, there was association between periodontal infection and preterm labour and the patients with h/o periodontal infection in antenatal period had a higher incidence of pre-term labour.

Mothers who had history of STD were significantly more in the case group (10%) than in the control group (2.2%). It forms one of the maternal determinants of preterm labour. The chi

square test showed an association between history of STD's and pre-term labour. IT can be concluded that females with h/o STD were prone to pre-term labour.

Table No 6: Distribution of Study Subjects According to STD Status

	Case		Control		**Total**	
hoSTDs	**N**	**%**	**N**	**%**	**N**	**%**
Yes	23	10	5	2.2	28	6.1
No	207	90	225	97.8	432	93.9
Total	230	100	230	100	460	100

χ^2 =12.321df=1 p<0.001

Significant Risk Factors Derived on Univariate Analysis

	Case	Control	Total	χ^2	p	OR	95% CI of OR	
STDs	23(10%)	5(2.2%)	28(6.1%)	12.321	0.000	5.0	1.9	13.4
Maternal infections	54(23.5%)	22(9.6%)	76(16.5%)	16.14	0.000	2.9	1.7	5.0
Vaginalinfections	21(9.1%)	3(1.3%)	24(5.2%)	14.243	0.000	7.6	2.2	25.9
Discharge Per Vaginum	61(26.5%)	24(10.4%)	85(18.5%)	19.757	0.000	3.1	1.9	5.2
UTI	73(31.7%)	36(15.7%)	109(23.7%)	16.46	0.000	2.5	1.6	3.9
Periodontal Infections	12(5.2%)	3(1.3%)	15(3.3%)	5.582	0.018	4.2	1.2	15.0

A logistic regression was performed to ascertain the effects of independent variables which were found significant in the univariate analysis on the likelihood that participants will have preterm births. A test of full model against a constant only model was statistically significant indicating that the predictors as a set reliably distinguished between preterm and term births (Chi square= 419.7 p=.000). Nagelkerke's R^2 of 0.80 indicated a moderately strong relationship between prediction and grouping. Predication success overall was 90.7 % (90% for cases and 91.3% for controls). The inferential goodness-of-fit test is the Hosmer-Lemeshow test that yielded a Chi square of 4.824 and was insignificant (p>.05) suggesting the model was fit to the data well. In other words, the null hypothesis of a good model fit to data was tenable.

Variables	B	S.E.	Wald	df	P	OR	95% C.I.for OR	
							Lower	Upper
Vaginal infection	1.254	0.94	1.782	1	0.182	3.505	0.556	22.104
Maternal infections	1.021	0.541	3.563	1	0.059	2.777	0.962	8.019
Discharge Per Vaginum	0.527	0.541	0.951	1	0.329	1.695	0.587	4.89
UTI	0.562	0.459	1.499	1	0.221	1.754	0.713	4.313
Periodontal Infections	2.553	0.981	6.767	1	0.009	12.843	1.876	87.907

The Wald criterion, periodontal problems, history of maternal infections are the significant risk factors contributing to preterm deliveries. The present study showed that history of maternal systemic infection was a significant risk factors of preterm birth with odd's ratio of 2.73.

The study showed a significant finding that a woman with periodontal problems the risk is 11.8 times more as against a woman without the problems.

Comment

Infections and associated inflammation are important initiators of the preterm birth pathways. This is suggested by the repeated discovery of positive bacterial cultures from the placentas or membranes of a high proportion of patients with preterm birth[1].25% of all preterm births occur in mothers with bacterial colonization of the uterus[2].Other studies have shown that bacteria, which cause placental infection, are capable of

producing prostaglandins, which disrupts uterine quiescence, causing cervical softening and preterm birth[3]. In addition, vaginal infection and associated inflammation, causes an inflammatory response with cytokines, which cause a further increase in prostaglandin levels[4].Raised levels of neutrophils and a raised pH of more than 5, was shown to be significantly associated with preterm birth. There is an inverse relationship between neutrophilia and preterm birth, with the strength of the association increasing as the gestational age at delivery decreases[5]. Intrauterine infection is a partificial reproduction theraphyicularly important risk factor for adverse neuro-developmental outcomes after PPROM. The colonization of the placenta and membranes can arise directly from the genito-urinary tract with sexually transmitted infections or from haematogenous spread with systemic infections. In our study, mothers who had history of STD were significantly more in the case group (10%) than in the control group (2.2%)

In evaluating the risk of spontaneous preterm birth associated with genitourinary tract infections, Andrews et al, carried out a case control study in The Preterm Prediction Study[6].They found that women with Chlamydia trachomatis infection were more likely to have a short cervix less than 25mm, than uninfected controls (33% versus 17.9% respectively). They also noted that infection with C. trachomatis at 24 weeks gestation predisposed the mothers to a risk of preterm delivery 2 times and 3 times that of the uninfected controls at less than37 weeks' and less than 35 weeks' gestation respectively .Andrews etal also published a secondary analysis in 2006 on the relationship between mid-pregnancy genitourinary tract infection with Chlamydia and its association with subsequent preterm birth, refuting their primary results regarding an increased risk in Chlamydia infected mothers and preterm birth. Subsequent research in the area has resulted in conflicting results. It therefore remains uncertain if an association exists between sexually transmitted infections and preterm birth. The presence of bacterial vaginosis at 28 weeks' gestation is associated with an increased risk of spontaneous preterm birth[7].But contrary to this studies by Carey JC showed that treatment of women with bacterial vaginosis failed to prevent preterm birth[8]. Women with vaginal infections were significantly more in the case group(9.1%) than the control group (1.3%) in our study.

There is some indication that it is the relative load of bacteria, or the specific species of bacterium, rather than its presence per se, that predisposes to preterm birth.

Recent evidence suggests that infections remote from the fetal site may also be causative. Bacteria are capable of entering the uterine cavity by haematogenous spread. Periodontal disease, a chronic low-grade infection, has been repeatedly implicated in the causation ofpreterm birth. Oral and vaginal sites are comparable in their bacterial microbiology. Mothers with periodontitis and bacterial vaginosis also share similar social and socio demographic risk factors, suggesting a common pathophysiology [4].Low levels of infections and disturbances of the bacterial flora in the mouth have been shown to be enough to initiate preterm birth via the production of pro-inflammatory cytokines in the uterus Offenbacher and colleagues, in the OCAP (Oral Conditions and Pregnancy) study, investigated obstetric outcomes in women with periodontal disease. Their results illustrate a preterm birth incidence of 28.6% in women with moderate to severe periodontal disease compared to 11.2% among women with good oral health[9]. Several other studies report an inverse relationship between severe or generalized periodontal disease and decreasing gestational age at delivery, with an odds ratio of 4.45 for preterm delivery less than 37 weeks, increasing to an odds ratio of 7.07 for delivery before 32 weeks gestation[10].As regards antenatal treatment of periodontal disease, Offenbacher and colleagues carried out a randomized controlled trial, the Maternal Oral Therapy to Reduce Obstetric Risk (MOTOR) study, to evaluate the effect of non-surgical treatment of periodontal disease onpreterm birth rates. They found that treatment

of women with periodontal disease had minimal improved benefit on gestational age at delivery of less than 37, 35 or 32 weeks, 13.1% versus 11.5% in non-treated controls. This is in contrast to the recent Australian meta-analysis of 10 randomized trials by George et al 2011, which found that antenatal periodontal treatment significantly lowered preterm birth and low birth weight rates[11].Our study showed a significant finding that a woman with periodontal problems the risk is 11.8 times more as against a woman without the problems.

Conclusion

Given the mounting evidence and continued speculation regarding the effect of periodontal disease, maternal infections both systemic & local, and its treatment on preterm birth, every opportunity should be taken to advise mothers about the importance of good oral health preconceptually, prevention of periodontal disease and the opportunity for STD screening sought and treatment of systemic and local infections.

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