Maternal Periodontal Status and Risk of Adverse Pregnancy Outcomes A Case Control Study on Indian Mothers

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Abstract: Objective: This study was conducted to - a) Determine the association, if any between maternal periodontal infection and Preterm Birth low birth weight (PLBW) in Indian population b) Evaluate the correlation ,if any, between the severity of maternal periodontal infection and the birth weight of the neonate. Methods: This Case control study was conducted on 100 mothers. Cases (n=50) were mothers who delivered preterm low birth weight infants (PLBW). Controls were mothers with normal pregnancy outcomes. Periodontal status of the mothers and PGE_2 level in the GCF was recorded postpartum. . Multivariate regression models were fitted controlling for common covariates. Results: Multivariate logistic regression models controlling for other risk factors and covariates, demonstrated that maternal localized moderate periodontitis is significantly associated with preterm low birth weight, with an adjusted odds ratio of 3.16 PLBW cases. GCF–PGE_2 level provided further evidence for the association and there was negative correlation between the GCF-PGE_2 level and birth weight of the infant. Conclusion: The data support the notion that maternal periodontitis is independently associated with preterm low birth weight in Indian population. [Smitha K et al NJIRM 2013; 4(2) : 82-90]

Key words; low birth weight; periodontal disease/adverse effects; preterm birth, PGE_2, risk factors

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Introduction: Preterm and low birth weight (PLBW) infants are a major challenge for maternal and perinatal care worldwide and a leading cause of neonatal morbidity and mortality, and yet, it is an unmet challenge. Children born prematurely with low birth weight have higher rates of learning disabilities, cerebral palsy, sensory deficits and respiratory illnesses compared to children born at term, and often these negative effects extend to later life, resulting in a corresponding increase in the expenditure on their family and on society towards their health and education. Advanced perinatal care and specific interventions have led to significant improvement in outcome for preterm infants. But in a developing country like India, these improved facilities are not available to all and these facilities involve significant financial burden on the immediate family and society. Experts suggest that a continued decline in low birth weight requires a shift in emphasis from tertiary intervention to prevention.

According to UNICEF, the incidence of PLBW neonates is 30% in India which accounts for almost 40 percent of the global burden and accounts for 15% of all neonatal deaths.[1] The cause of babies being born too small and too soon is unknown in almost 50% of preterm births, in spite of considering all the known obstetric risk factor.[2] The role of ascending vaginal infection and systemic infections as a risk factor is receiving increasing attention.[3-5] Bacteria associated with the infection activate immunological responses, leading to the production and release of cytokines, including interleukin-1 (IL-1), IL-6, tumour necrosis factor-a (TNF-α) and prostaglandins. These inflammatory mediators or endotoxins from the bacteria itself, may shorten gestational age, if they reach the foeto-placental unit.[6] It is plausible that micro-organisms may gain direct access to the amniotic fluid and fetus in several ways: a)ascending *via* the vagina into the choriodecidual sac during pregnancy,b) *via* the endometrial wall which may be chronically infected prior to pregnancy, or c)alternatively through a haematogenous route.[7-9] Hypothesis that infection remote from the fetal placental unit may influence PLBW has led to an increased awareness of the potential role of chronic bacterial infections elsewhere in the body.

Periodontal disease is associated with a chronic Gram-negative infection of the periodontal tissues which results in local elevation of pro-inflammatory prostaglandins and cytokines [10] and

an increase in the systemic levels of some of these inflammatory mediators.[11] There is evidence of an association between periodontal disease and a variety of systemic conditions like cardiovascular disease, diabetes mellitus, and respiratory disease.[12] The study that evaluated the relationship between the levels of PGE_2 and TNF-α in the GCF and in the amniotic fluid in pregnant women with periodontal disease concluded that there is a positive relationship between PGE_2 levels in the crevicular fluid and those in the amniotic fluid.[13] The detection of oral pathogens in amniotic fluids by PCR tests suggests a possible haematogenous spread of these infections.[14] In the pioneering study by Offenbacher and colleagues in 1996,[15] the authors suggested that maternal periodontal disease could lead to a seven fold increased risk of delivery of a PLBW infant. Several subsequent studies have found a relationship between preterm birth and periodontal disease, indicating that the severe, generalized infection of the periodontium is a possible risk factor for PLBW. [5-6].[16-20] However, others have found no such evidence.[21-23]

Because of the controversies raised, we are reporting this Case–Control study, which was conducted to test the hypothesis that a) Periodontal infection of the mother as evidenced in clinical examinations and as assessed by PGE_2 levels in GCF, can be an independent risk factor for PTLB in Indian mothers, and that b) Severity of maternal periodontitis negatively correlates with the infant birth weight. If the association is proved, in a developing country like India, treating the periodontal disease would offer a simple low cost intervention that could help promote positive pregnancy outcome.

Materials and Methods: A matched Case- control study with a selection ratio of one was conducted on 100 mothers (50 in each group) from Bangalore and surrounding area, who delivered their babies at Vanivilas Hospital, Bangalore, India between Jan 1999 and July1999. After obtaining the approval from the institutional ethical committee and informed written consent of the subjects, cases and controls were selected from among 1098 mothers who delivered their babies at the hospital. Out of 1089 neonates delivered during the study period, 292 neonates were preterm low birth weight neonates (incidence of 27%) and 62 fitted the selection criteria. Out of these 62 neonates, 7 neonates died after the birth and 12 mothers refused to participate in the study.

Cases, defined as those mothers between the age group of 19and 30 years, who delivered a neonate, whose birth weight was less than 2500gm and gestational period <37 weeks either due to spontaneous preterm labour or premature rupture of membrane (PROM) were selected.

Controls were Age (with in 1 Year, i.e. $\pm$ I year), gravida and parity matched mothers with normal pregnancy outcome(birth weight>2500gm and born after 38 weeks, were selected from among the mothers who delivered their babies , within 24 hours before or after the delivery of the case mothers, randomly by computer selection (by MF)

Data regarding the personal and medical history of the mother, gender and birth weight of the neonate, date of delivery, mother`s age at delivery, maternal weight gain, blood group , haemoglobin level, ultrasound scanning and relevant medical history of the subject and immediate family, gestational period, onset of prenatal care, previous pregnancy history regarding number of pregnancies , number of term pregnancies, number of abortions and medical histories pertaining to the exclusion criteria, were obtained from hospital records by daily scrutiny and confirmed later by personal interview with the mothers. An infection history including genitourinary tract infection for the present pregnancy was recorded including the medication for the infection. Mothers with diabetes, asthma, heart disease, glomerulonephritis and hyperthyroidism or those currently on antibiotics were excluded from the study. Mothers with the habit of tobacco smoking, tobacco chewing and alcohol consumption were excluded. Mothers with early onset prenatal care (prior to 20 weeks of gestational age) and greater than six prenatal visits were only considered for the study. Subjects with intrauterine growth retardation, fetal death, fetal abnormalities, twin delivery, placenta abruption,

placenta previa, uterine fibroids, Rh factor iso-immunity were excluded from the study.

Socio economic status was classified according to father`s occupation as follows:
ClassI(Professionals),Class II (intermediate),ClassIII(skilled worker), class IV (Partly skilled worker), classv(unskilled).[24]

Periodontal status of the subjects was examined within 48 hours of delivery. The same calibrated dental clinician (SK) carried out the periodontal examination and collection of Gingival crevicular fluid (GCF) for biochemical evaluation and was blind to the case or control status of the subjects. The examination took place in the maternity ward, with the subject made to sit erect at the bedside, under artificial light. Oral hygiene Index, (simplified) [25] was recorded. Bleeding on Probing (BOP) was recorded dichotomously as present or absent and expressed as percentage of sites that bled on probing. Probing depth (PD), clinical attachment level (CAL) using CEJ as reference was recorded at six sites/tooth, on all the teeth, except third molar using UNC-15 probe Sites with CAL≥3mm was considered as periodontally diseased sites.CAL was operationalised at 3mm threshold and expressed dichotomously as extent and severity (Extent and severity index).[26]

GCF was collected from all the 100 mothers for PGE_2 estimation, before probing, using micro capillary tubes (Sigma chemicals) using a method as described in a previous study [27]and stored immediately at -70`c till the analysis. The $PGE_2$ level in gingival crevicular fluid was quantified by enzyme-linked immunosorbent assay using a commercial kit (Oxford Biochemicals) as per the manufacturer`s instruction.

Data analysis: Periodontal disease status was first defined using full mean clinical attachment levels (mean CAL) for each subject, pooling to form group means. The periodontal status was also operationalised as extent of attachment level (greater than or equal to 3 mm respectively). These are referred to as Extent N scores, Where N= CAL threshold. Disease severity S is expressed as the mean loss of attachment in excess of 3mm or more sites. [26]
Student `t` test was used to test the mean differences between the groups. Relationships between all exposure and outcome variables were explored with bivariate analysis. Chi square test was used to test the association. Fisher exact probability test was used to find the proportion between two groups with respect to a particular characteristic for2x2 contingency table, when the cell frequency is very small.

This continuous variable was dichotomized at 20% ,meaning that subject with attachment loss of 3+mm affecting less than 20% of their sites are more like to be in the control group .This cut off was chosen as this was roughly 3 standard deviations above the value for control mothers. Finally a logistic regression model was developed with Case Vs control status as outcome and Extent 3:20 being the periodontal status exposure interest.

The relationship between periodontal status, control variables and other risk factors preterm low birth were tested in the logistic regression model. After the final effects model was established, interaction effects were allowed to enter the model in a stepwise fashion.

The correlation between GCF level of PGE_2 and birth weight of the neonate, and gestational period was tested by Pearsson correlation test and the correlation coefficient was calculated.

Results: The demographic and other characteristics of cases and controls, Table .1 The mean maternal age, parity and gravidae for cases was not significantly different from controls as it was matched during the selection of the cases and controls. None of the study subjects used tobacco or alcohol.

The mean maternal weight gain of case mothers was not statistically different from that of the case mothers. The mean maternal weight of case mothers was 56.22 kg±15.8kg and that of control

mothers was 55.76±14.39 kg. However, the difference was not statistically different (P>0.05).
The level of prenatal care of the case mothers was not statistically significant from that of the controls with most mothers seeking prenatal care prior to 20 weeks of gestation. The number of case mothers who suffered from genito-urinary tract infection were more when compared to control mothers, (30%Vs20%) , This was statistically significant at P<0.05 .As both case and control mothers were derived from the same socioeconomic strata, (group IV and v), socioeconomic status was not significantly different.

Table-1: Demographics and description of Cases and Controls

Variable	PLBW, Case n=50	NBW Control n=50
Age in years	22.52±2.7	22.44±2.38
Mean Birth Weight in gms	2032±246.56	2875±140.78
Genito Urinary tract infection during this pregnacy		
YES NO	19(38%) 31(62%)	10(20%) 40(80%)
	t=-2.003 df=98, **P<0.05***	
Gravida		
1 2 3	19(38%) 15(30%) 16(32%)	19(38%) 15(30%) 16(32%)

P value in bold indicates significant difference

Table 2 shows the case –control comparisons for periodontal disease indicators. The mean probing depth (PD) of cases mother set was highly significant, with case mothers having mean PD/ site of 2.70±0.22mm/site Vs 2.48±0.17 mm/site in controls (P<0.001). The case mothers had mean CAL of 2.20-+0.17mm/site. By comparison Controls had a mean CAL of 2.02±0.133mm/site. The difference was highly significant at P<0.001, with case mothers having more mean CAL, compared to controls .Even the Extent and severity of periodontal disease (Extent3 scores, and Severity 3 scores)demonstrated a consistent trend with cases having more severe, involving more number of sites than controls which was highly significant (P<0.001) . However, the percentage of sites which bled on probing and Oral hygiene index in cases was not statistically different from that of controls (P>0.05) Higher mean GCF PGE_2 level was observed in case mothers compared to controls which was statistically significant(P<0.001) , with case mothers having mean GCF PGE_2 level of 84.15±24.94 ng/ml. By comparison control mothers had mean GCF PGE_2 level of 45.73±13.08 ng/ml (Table3)

Table-2: Periodontal disease indicators

Variable	All PLBW Case n=50 Mean±SD	All NBW Control n=50 Mean±SD
Probing Depth In mm/site	2.70±0.22	2.48±0.18
	t= 5.591,df=98,	**P<0.001**
M CAL	2.20±0.17	2.02±0.33
	t= 6.061,df=98,	**P<0.001**
Extent N Scores (Proportion of Sites)		
Extent 3	29.18±9.71	17.89±6.85
	t= 6.714,df=98, **P < 0.001**	
Severity N scores		
Severity3	3.29±0.29	3.14±0.2020
	t= -.953,df=98, **P <0.01**	
BOP	32.25± 7.77	30.33± 6.39
	t= -1.348,df=98, P>0.05	
OHI	2,1894±0.5276	2.0948± 0.3670
	t= -1.043,df=98, P>0.05	

P value in bold indicates significant difference

Table-3: Periodontal disease indicator- Comparision of PGE_2 level in GCF

Group	Mean	Std dev	Mean difference	P-Value
Case	84.15	24.94	38.420	**<0.001***
Control	45.73	13.08		

The logistic model (Table 4, Fig- 1) was developed using following variables- E: 20 of CAL, age, genitourinary tract infection, maternal weight gain, gravidae which are known to affect relationship between risk factors and PLBW. None of the above mentioned variables appear to influence PLBW

except periodontal disease as indicated by Extent: 20 scores, which increased the risk by 3 fold at P< 0.0001, which was highly significant .Although gravidae was not significantly associated in the model, the odds of being in PLBW group increased with the number of pregnancies.

TABLE-4: Multivariate logistic regression model for PLBW using cases and controls

Variable	Regression Coefficient	SE	Wald	DF	Significance	Odds ratio
ESI 3:20	1.1535	0.2486	21.5319	1	**P<0.0001***	3.1693
Age	0.0052	0.1420	0.0019	1	P>0.05	0.9948
Gravida						
1	-0.1704	0.4270	0.1592	1	P>0.05	0.8432
2	0.1243	0.3680	0.1140	1	P>0.05	1.1323
G.U.T infection	0.2581	0.2809	0.8442	1	P>0.05	1.2944
Maternal weight	-0.0215	0.0492	0.1906	1	P>0.05	0.9788

*Highly significant

Fig-1: Multivariate Logistic Regression Model for PLBW

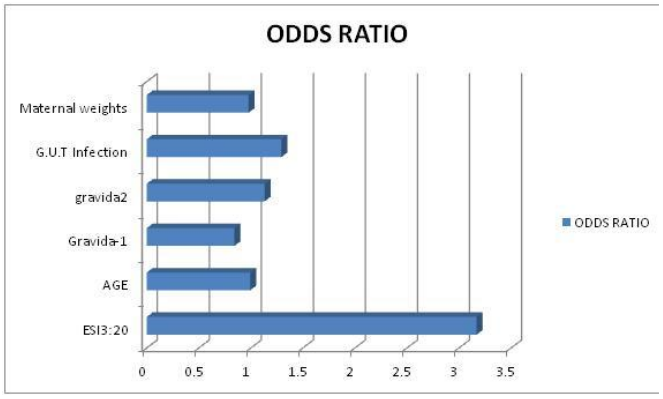


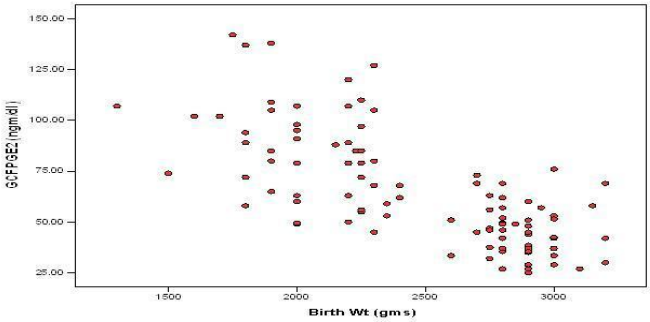
Table -5: Correlation between GCF PGE_2 level and birth weight of the neonate

Group	r	P-Value
Case	-0.331	**0.019***
Control	-0.116	0.423
Case & Control	-0.716	**<0.001***

* significant correlation

We observed a negative correlation (r =-0.331) between GCF PGE2 and birth weight in cases and this correlation was found to be statistically significant (P<0.05). (Table5). In controls, weak negative correlation (r=-0.116) was found between GCF PGE2 and birth weight of the neonate and this correlation was not statistically significant (P>0.05) (Table-5).Considering cases and controls together, we find that there is a strong negative correlation (r =-0.716) and the correlation is found to be statistically significant at P<0.001 (Table-5) (Fig 2).

Fig2: Correlation between maternal GCF PGE_2 level and Birth weight of the neonate



Discussion: This Case control study on Indian mothers illustrates a strong association between periodontal disease and PLBW, even after controlling for multiple risk factors. Multivariate logistic regression analysis controlling for other risk factors and co-variates demonstrated that localized ,moderate periodontitis ,which is defined dichotomously as 3+mmCAL in 20% of the sites was significantly associated with PLBW, with an adjusted odd ratio of 3.17 (P<0.001). Further, GCF PGE2 level, which serves as a static assessment of ongoing disease, showed significantly higher level

in PLBW mothers when compared to control mothers, which significantly correlated negatively with the birth weight of the neonate.

The following major criterion were considered while designing this study- to ensure 1) That controls were true representatives by avoiding selection bias , and 2) That all potential confounders were measured. To minimize confounding of the primary association due to age, parity, gravida, cases and controls were matched using these variables. The exposure to the established risk factors for PLBW such as inadequacy of prenatal care, poor maternal weight gain, tobacco smoking, genitourinary tract infection, were established by daily scrutanisation of the hospital records and further confirmed by personal interview and structured questionnaire. The hospital records show that pregnant mothers, both in control and case group, who had genitourinary tract infection, had been treated by metranidazole. However, study by Carey et al,[28] has not found any reduction in the incidence of PLBW in mothers who have been treated for genitourinary tract infection.

The study population belonged to the same ethnicity, and was drawn from the same pool of community, who belonged to the same lower socioeconomic strata (group1V and group V), with almost same education level and similar oral hygiene practices and awareness. Hence, there was no influence of ethnicity and socio-economic status on the pregnancy outcome of the study subjects of this study, unlike in several studies which have considered their influence.[22,29]

The prevalence of tobacco smoking and alcohol use, the two traditional risk factors for PLBW is very rare in South Indian mothers. However, tobacco will be used as an ingredient of pan chewing. Consequently, during personal interview particular attention was paid to this aspect and mothers with these habits were excluded from the study.

Periodontal examination conducted at a point of time is a measure of past periodontal experience of an individual and cannot determine whether the diseased sites were in active state during the pregnancy. Hence, additionally, levels of a biochemical marker of ongoing disease- PGE2 level in GCF samples was assessed from the cases and control mothers. Biochemical analysis of GCF showed that Case mothers had significantly higher GCF PGE2 level than control mothers with case mothers having mean GCF PGE2 level of 84.15+24.94 ng/ml Vs 45.73+13.08 in NBW mothers . This result is consistent with earlier case control study reported by Offenbacher et al.[16] In the present study, GCF PGE2 level correlated inversely with the birth weight of the of the neonates which was highly significant in the present study.

Earlier case-control studies available in the literature have provided inconsistent data on the issue of periodontitis and PLBW. In a study of 124 predominantly white women with substantially higher prevalence and severity of periodontitis, Offenbacher et al[15] reported statistically significant differences in mean attachment loss between women who gave birth to preterm and/or LBW infants compared with term delivery controls (3.10 vs. 2.80 mm).In contrast, in a case-control study of 164 black women by Mitchell-Lewis et al [21] failed to detect any differences in clinical periodontal conditions between women who had delivered preterm, LBW infants and control women. Similarly, a large case-control study[22] of an ethnically mixed population in the United Kingdom, also failed to detect differences in periodontal status between the cases and control. However, it is important to emphasize that none of the latter two studies included assessments of CAL, but solely analyzed periodontal data on gingival inflammation and probing depth. An advantage of the study design of the present study was the complete and comprehensive nature of the periodontal examination. Six surfaces on all teeth present, with the exception of the third molars, were examined in all women. So it is unlikely that periodontal disease levels were underestimated, as might have been the case in studies [22,30] that failed to identify an association between preterm low birth weight and periodontal disease, where a

less comprehensive examination was used to ascertain periodontal disease levels. On the other hand, several cohort studies have revealed a positive association between the severity of periodontal disease and the incidence of PTB. In a study of 639 pregnant women in Chile, Lopez et al [19] reported that the incidence of delivery of a PLBW infant increased from 2.5% in periodontally healthy women to8.6% in women with periodontal disease. Jeffcoat et al [17] studied prospectively a sample of 1313 primarily black pregnant women and reported an adjusted odd ratio (OR) of 4.4 for preterm delivery and generalized periodontitis. This odd ratio increased to 5.3 for delivery before 36 weeks of gestation, and to 7.1 for delivery before the 32nd week.

There are several potential explanations for the inconsistencies in the literature regarding the association between periodontal disease and adverse pregnancy outcomes. Firstly, criteria used to define periodontal disease in the literature and the timing of this assessment in relation to period of pregnancy is inconsistent. Secondly, periodontal disease is more common in economically disadvantaged populations, the same women who are at increased risk for adverse pregnancy outcomes. The studies[15,17-20,31,32,34-37] that have consistently demonstrated an association between periodontal disease and variety of pregnancy outcomes have been on economically weaker section, so are the results of our study, which had both cases and controls belonging to lower socioeconomic group and most of them were from rural areas surrounding Bangalore. However, studies which demonstrated negative association belonged to largely urban populations .[22,30,38,39] Thirdly , As noted by Hujoel et al ,[40] failure to control adequately for potential confounding factors may be the reason for inconsistency between the results in different studies. And finally, the definition of adverse pregnancy outcomes. For example, the use of composite outcomes that include preterm low birth weight (PLBW)[22,41], preterm labor, and premature membrane rupture may confound study results.[42,43]

The present study indicates that localized moderate periodontitis of mother is significantly associated with PLBW with adjusted odds ratio of 3.17. Furthermore, the results of interventional studies [17,18,44] were also contradictory. Michalowicz et al [44] showed that the non-surgical treatment of periodontitis in pregnant women did not alter the rate of preterm birth (PB), whereas the studies of Jeffcoat et al [17] and Lopez et al [18] showed that periodontal treatment reduced PB and/or LBW rates. A recent meta-analysis [45] suggested that periodontal treatments could influence pregnancy outcomes in patient subgroups (women without a history of PB) with mild periodontitis. However, the specifics of periodontal treatment modalities, such as the period of treatment, as well as treatment efficiency may influence the results.

Early results from intervention trial on Indian women [46,47] have shown that basic periodontal therapy significantly reduces the incidence of PTB and LBW. The results reported in our study provide additional evidence regarding the question as to whether periodontal infection, in terms of early localized periodontitis of the women during pregnancy, has an association with PLBW. These data highlight the importance of the information related to periodontal risk in the context of pregnancy for prenatal health programs in India
However, association in a small case control study does not imply causation, and it seems important to consider the possibility that there is some underlying mechanism causing both periodontal disease and adverse pregnancy outcome.

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