Influence of maternal periodontitis on adverse pregnancy outcome: An observational study

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ABSTRACT

Background: Adverse pregnancy outcome is due to deviation from the normal physiological and immunological process. There is conflicting evidence in support of maternal periodontitis as a risk factor for preterm low birth weight (PTLBW). Thus, the aim of the present study is to evaluate the correlation between PTLBW and periodontitis in postpartum mothers based on clinical and microbiological parameters.

Materials and Methods: An observational retrospective study was conducted. A total of 103 women with singleton births were included in the study, which was divided into two groups, i.e., Group I-PTLBW and Group II-normal term normal birth weight (NTNBW). Clinical parameters such as oral hygiene index simplified, gingival bleeding index (BOP %), periodontal probing depth (PPD) and clinical attachment loss (CAL) were recorded on the next day of postpartum. Two samples from each group, i.e., placental extract and the subgingival plaque were collected and transported to the laboratory in an anaerobic medium for microbiological analysis. The statistical analysis was performed using an unpaired t-test and Wilcoxon Mann–Whitney U-test. The P < 0.001 was considered statistically significant.

Results: PTLBW group showed significantly higher amounts of periodontal destruction in terms of clinical parameters. The pathogens were also in higher quantities in the PTLBW group compared to the NTNBW group.

Conclusion: Periodontitis is related to PTLBW in pregnant women of the studied population. Maternal oral hygiene status delivering PTLBW babies are compromised compared to mothers delivering NTNBW babies. Hence, periodontitis during pregnancy phase is an important health concern for the growing fetus.

Key Words: Low birth weight, Parvimonas micra, periodontitis, premature birth, Veillonella

INTRODUCTION

Periodontitis is a polymicrobial infection in which complex interaction takes place between host immune response and tooth-associated microbial plaque. Apart from causing the connective tissue breakdown, periodontitis also influences systemic health. There is established evidence that suggests the role of periodontitis as a contributing etiologic factor for certain chronic inflammatory conditions such as diabetes mellitus, cardiovascular disease,
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and hypertension. With the increasing literature evidence along with confirmative mechanisms between periodontitis and other systemic diseases, the quest for the relationship between periodontitis and PTLBW has also gained importance.

According to the World Health Organization, preterm birth is defined as babies that are born alive before the completion of 37 weeks (259 days) of gestation period. This was further classified as extremely preterm (<28 weeks), very preterm (28–32 weeks), and moderate to late preterm (32–37 weeks). Low birth weight is a condition where the babies are <2500 g at the time of birth. In 2012, the WHO for the first time published an estimate of preterm birth around the globe and stated it as a true health problem. According to the WHO, the causes of preterm birth are idiopathic (45%–50%), preterm membrane rupture (30%), and rest are medically indicated deliveries.[3]

Offenbacher was the first person to highlight the link between periodontitis and preterm low birth weight (PTLBW).[4] It was hypothesized that the resultant immune-inflammatory response due to the Th1/Th2 cell ratio was the cause of PTLBW. Since then, several studies have been performed to elucidate the link between periodontitis and PTLBW.[5‑7] This leads to the evidence stating that the increased levels of progesterone and estrogen during pregnancy causes an increase in vascular permeability leading to low‑grade bacteremia. Further, it has been hypothesized that in the presence of periodontal disease, oral microorganisms disseminate hematogenously to target the placenta, amniotic membrane, and fetus leading to adverse pregnancy outcomes.

To the best of our knowledge, there is no conclusive evidence as to which oral microbiota causes PTLBW. Hence, the objective was to find the relationship between periodontitis and PTLBW along with trying to access the causative pathogenic bacteria responsible for the same.

MATERIALS AND METHODS

This observational study was conducted on the parturition women in the in‑patient department of obstetrics and gynecology with the institutional ethical committee clearance. A total of 392 women aged between 18 and 35 years were screened for their eligibility for enrolment into the study. Thorough case history and obstetric history were recorded. Case history included subject address, socioeconomic status, oral hygiene measures, and maintenance and adverse oral habits (smoking or alcohol). The case history was recorded at the time of the periodontal examination. Obstetric history comprised of two parts: demographic data and actual birth-date of delivery, weight at birth, and gestational age. Data were obtained from the subject’s obstetric records during periodontal examination on the next day of delivery. Obstetric exclusion criteria were multiple births (twins, triplets), maternal systemic disease and genitourinary tract infections. A total of 103 subjects were taken into the study which was meeting the required sample size according to the G power software analysis with a study power of 90%. Written informed consent was obtained for confirmation of the willingness of the participants for the study protocol.

Inclusion and exclusion criteria

Singleton normal vaginal delivery participants were included in the study, satisfying either the PTLBW criteria (gestation period <37 weeks and birth weight of baby <2.5 kg) or the normal term normal birth weight (NTNBW) criteria (gestation period ≥37 weeks and birth weight of baby ≥2.5 kg).[8] Subjects were considered to be having periodontitis if they fulfilled the case definition according to the AAP/EFP workshop for classification of periodontal and peri-implant diseases.[9]

Subjects having systemic problems such as gestational diabetes, hypertension, cardiovascular disorders, anemia, or any other chronic inflammatory conditions that can alter the course of periodontitis were excluded from the study. Patients having cesarean sections or any history of preeclampsia were also excluded from the study. Patients with a history of any past dental treatment within the past 6 months of delivery were also not considered for the study.

Clinical parameter assessment

Clinical parameters were taken on the next day of postpartum, which included oral hygiene index-simplified (OHI-s by Greene and Vermillion 1964), gingival bleeding index (GBI by Ainamoand Bay 1975), clinical attachment loss (CAL), probing pocket depth (PPD). A subject was considered to be having periodontitis if a minimum of 2 nonadjacent teeth showed detectable interproximal or buccal clinical attachment loss (CAL) of ≥3 mm with PPD >3 mm on the same tooth.[9] All the parameters were recorded under artificial light by a single
calibrated examiner using a dental mirror and UNC-15 periodontal probe (Hu-Freidy, CP-15 #PCPUNC156) for the standardization of readings.

Microbiological sampling procedure
Two samples, one each from the placenta and dental plaque, were collected from each subject, accounted for a total of 206 microbiological samples. Immediately after delivery, the placental sample was collected in completely aseptic conditions into dark-colored glass vials containing Robertson’s cooked meat broth medium by experienced para-medical staff. Briefly, the placental sample was collected from margins at 6 o’clock position and the umbilical cord at the placental junction, according to the procedure mentioned by Langston et al.[10] The next day, the dental plaque sample was collected using the paper point method. The dental plaque sample was obtained from the deepest pocket by introducing two 30 number sterile standardized paper points for 20 s only after achieving proper isolation using cotton. Paper points were discarded if they were contaminated with saliva or gingival crevicular fluid. Paper points were then immediately transferred into separate glass vials containing Robertson’s cooked meat broth medium (anaerobic medium).

The collected vials were then transported to the microbiology laboratory immediately where they were stored at −20°C till further microbiological analysis.

Microbiological analysis
Placental and plaque samples were processed within 24 h of collection. One loopful of placental, as well as plaque sample, was inoculated on blood agar supplemented with Haemin (5 µg/ml) and Vitamin K (10 µg/ml). Culture plates were then incubated in anaerobic conditions for 5 days at 37°C in McIntosh anaerobic jar. The chemical indicator used for this purpose was “chemical methylene blue” strips. It is deep blue in the presence of oxygen but becomes colorless when all oxygen is consumed, thus confirming anaerobic conditions in the jar. After 5 days of incubation at 37°C, the anaerobic jar was unlocked. The plates were examined for the morphology of the bacterial colonies. After the colony identification, the microorganisms were gram-stained. Slides were sequentially stained with crystal violet, iodine, then de-stained with alcohol and counter-stained with safranin. Stained slides were then blot-dried and examined under light microscope at ×100 using an oil immersion lens. All anaerobes were identified based on the guidelines specified by Koneman et al.[11] After identification, data were recorded and sent to the statistician for the frequency distribution of bacteria (%) isolated in placental and plaque samples of both the study groups (Group I and Group II).

Statistical analysis
After obtaining the values, data were entered into an excel sheet and statistical package Statistical package for social sciences (SPSS) version 4.0, Chicago, Illinois, USA. was used for analysis. The values were presented in number, arithmetic means, standard deviation, and frequency distribution (%) for the Group I and Group II. The mean values were compared using a non-parametric Mann–Whitney U-test. The $P < 0.001$ was considered statistically significant.

RESULTS

Analysis of the data obtained from the 103 subjects who were examined gave the following results. Table 1 shows the comparative evaluation of the mean value of age, gestational period, weight of the baby, OHIs, BOP percentage, and the number of periodontally involved teeth (with CAL ≥3 mm and PPD >3 mm) between PTLBW (Group I) and NTNBW (Group II). The mean age of Group I was 25.80 ± 5.28 whereas Group II was 26.21 ± 3.43 revealing no statistically significant difference ($P = 0.641$). The mean weeks of pregnancy and weight of babies in PTLBW (Group I) were 33.19 ± 2.70 and 1.09 ± 0.44 respectively whereas, in NTNBW (Group II), it was 39.47 ± 1.02 and 2.87 ± 0.31, respectively. Statistically, there was a significant intergroup difference when the gestational age and weight of babies were compared ($P < 0.001$).

Comparison of mean OHI-s, % of bleeding on probing and number of teeth (CAL ≥3 mm and PPD >3 mm) revealed a statistically significant difference ($P < 0.001$). The mean of oral hygiene index–simplified for the Group I (3.53 ± 1.24) was significantly higher than that of Group II (1.62 ± 0.72). The mean BOP percentage was 59.2 ± 9.91 in Group I and 50.21 ± 19.31 in Group II ($P < 0.001$). The mean number of teeth (with CAL ≥3 mm and PPD >3 mm) was 9.58 ± 4.36 in Group I, whereas in Group II it was 1.30 ± 1.78.

Culture-based identification of bacteria was based on colony morphology on agar plates, gram staining, and biochemical tests [Figure 1]. Gram-positive bacteria
stained blue-purple and Gram-negative bacteria stained red [Figure 2]. The frequency distribution (%) of bacteria isolated in Group I (PTLBW) and Group II (NTNBW) based on culture-based identification is shown in Table 2. Microbiological analyses of placental and plaque samples from the Group I revealed more anaerobic bacteria compared to Group II. *Parvimonas micra*, *Fusobacterium* species, Group B *Streptococcus* and *Veillonella* were present in Group I but absent in Group II suggesting the potential role of these bacteria in PTLBW.

**DISCUSSION**

Pregnancy is a dynamic sequence of physiological processes in which various inflammatory signals, triggers the normal course of parturition. Pregnancy-induced immunological modification in the maternal host can be modified by an external stimulus like periodontal infections. Although periodontitis may be only one aspect among many other risk factors in preterm deliveries, its relative importance cannot be neglected. The pathogenic mechanism that has been hypothesized by Bobetsis *et al.* in 2006 causing PTLBW as a consequence of the periodontal disease is the translocation of bacteria or their by-products such as lipopolysaccharides to the foetoplacental unit which indeed triggers the release of mediators and pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-1), IL-6, and PGE₂ thus initiating preterm delivery.

Table 1: Comparative evaluation of various demographic and clinical parameters between preterm low birth weight (Group I) and normal term normal birth weight (Group II) using the Mann-Whitney U-test

| Category                  | Group    | n  | Mean±SD   | P     |
|---------------------------|----------|----|-----------|-------|
| Age (years)               | Group I  | 50 | 25.80±5.28| 0.641 |
|                           | Group II | 53 | 26.21±3.43|       |
| Gestational period (weeks) | Group I  | 50 | 33.19±2.70| <0.001*|
|                           | Group II | 53 | 39.47±1.02|       |
| Weight of the baby (kg)   | Group I  | 50 | 1.90±0.44 | <0.001*|
|                           | Group II | 53 | 2.87±0.31 |       |
| OHI-S                     | Group I  | 50 | 3.53±1.24 | <0.001*|
|                           | Group II | 53 | 1.62±0.72 |       |
| BOP %                     | Group I  | 50 | 59.2±9.91 | <0.001*|
|                           | Group II | 53 | 50.21±19.31|      |
| Number of teeth (CAL ≥3 mm and PD >3 mm) | Group I | 50 | 9.58±4.36 | <0.001*|
|                           | Group II | 53 | 1.30±1.78 |       |

*Statistically significant at P<0.001. OHI-s: Oral hygiene index simplified, BOP%: The percentage of sites with bleeding on probing, CAL: Clinical attachment loss, PD: Probing depth, n: Number of subjects, SD: Standard deviation

Table 2: Frequency distribution (%) of bacteria isolated in the placental extract and dental plaque samples of preterm low birth weight group (group I) and normal term normal birth weight group (group II) based on culture-based identification

| Bacteria isolated (percentage of bacteria) | Group I | Group II |
|-------------------------------------------|---------|----------|
|                                           | Placental extract | Dental plaque | Placental extract | Dental plaque |
| *Bacteroides* spp.                        | 16       | 28       | 66           | 13.2          |
| *Dialister pneumosintes*                  | 00       | 8        | 00           | 00            |
| *Fusobacterium* nucleatum                 | 22       | 18       | 00           | 00            |
| *Parvimonas* micra                        | 52       | 28       | 00           | 24.6          |
| Group B *Streptococcus*                   | 4        | 2        | 00           | 00            |
| *Veillonella*                             | 6        | 16       | 00           | 22.6          |
| Not specified/No growth                   | 00       | 00       | 34           | 39.6          |
The present study was performed to find the possible relation between periodontitis and PTLBW along with finding the causative etiologic oral pathogen. Initially, 392 women who gave birth between March 2018 and September 2018 were assessed. Twenty-nine subjects delivered twins, 90 subjects who had caesarian deliveries and 5 dropped out for personal reasons. Furthermore, 110 subjects who were not examined within 2 days of postpartum, 35 subjects who delivered preterm normal weight babies and 20 delivered full-term low birth weight babies were also excluded which might act as a confounder. Finally, the present study included 103 subjects that were assessed as Group I (PTLBW) and Group II (NTNBW).

The mean age of the women in the present study (Group I) was about 25 years which was similar to Offenbacher’s study\(^4\) in which was 22 years. Among the controls (Group II), there was also similar age distribution. Although age <18 years and more than 35 years are known risk factors for preterm labor, no subject belonged to this age group in our study.

The mean gestational age at delivery in Group I was 33.19 ± 2.70 weeks and 39.47 ± 1.02 weeks in Group II. Goefpert \(\text{et al.}\)\(^{12}\) reported that severe periodontal disease had a significant association with spontaneous preterm birth at <32 weeks of gestation which was not similar to the present study. This can be due to moderate periodontitis subjects which showed a gestation age of more than 32 years. Thus indicating that the severity of periodontal disease may directly affects the duration of labor and cause early preterm delivery.

The OHI-s of the present study showed a statistically significant difference between Group I and Group II. Although the NTNBW group showed fair oral hygiene, the PTLBW group also showed poor hygiene. This can be related to low socioeconomic status, educational and financial status in the studied population. The results were in accordance with a study conducted by Dasanayake.\(^{13}\)

In the present study, significant differences were found in bleeding sites between both the PTLBW and NTNBW groups. The increased level of circulating progesterone during pregnancy indeed causes dilation of the gingival capillaries, increased permeability, and gingival exudates that may elucidate increased bleeding tendency. Along with these changes, the response of different subgingival microflora toward gingival tissue also acts as a contributing factor. Our result was in agreement with the study done by Zadeh-Modarres \(\text{et al.}\),\(^{14}\) Dempsey \(\text{et al.}\)\(^{15}\) and Dasanayake.\(^{13}\)

The periodontal examination was carried out within 2 days’ postdelivery, coinciding with a study conducted by Offenbacher \(\text{et al.}\)\(^4\) in which examination was carried out within 3 days of postpartum. This was done to make sure that our examination depict the same previous prepartum disease condition and ensures the samples (plaque and placental) were collected before their discharge from the hospital.

Two kinds of mechanisms, i.e., direct and indirect mechanisms have been established in the recent literature evidence of Elano Figuero, in 2020.\(^{16}\) This result was based on a systemic review of 24 studies. The direct mechanism was based on the theory of microbiological component invading the fetal placental unit while the indirect mechanism was based on the theory that inflammatory component entering the fetal placental circulation.

\(P. \text{micra}\) is part of the normal commensal flora of gingival crevice. Therefore 24.6% of the dental plaque sample of NTNBW (group II) showed \(P. \text{micra}\). On comparing plaque samples of both the groups, the PTLBW group showed more \(P. \text{micra}\) (28%) than the NTNBW group. This may be due to the presence of other anaerobic bacteria like \(Fusobacterium \text{nucleatum}\) and Group B \(\text{Streptococcus}\) in plaque samples of the PTLBW group which were not isolated in the NTNBW group. It has been shown that \(P. \text{micra}\) coaggregates with \(F. \text{nucleatum}\) and acts synergistically with other facultative and anaerobic bacteria during its growth and virulence factors production.\(^{17}\) The results of the present study were in accordance with Nonnanmecher 2004, who reported a higher count of \(P. \text{micra}\) in subgingival plaque samples from periodontitis patients.

The present study showed significantly increased amounts of anaerobic bacteria in the placental extracts such as \(P. \text{micra}\) (52%), \(F. \text{nucleatum}\) (22%) and Group B \(\text{Streptococcus}\) (4%) compared to plaque samples which showed \(P. \text{micra}\) (28%), \(F. \text{nucleatum}\) (18%) and Group B \(\text{Streptococcus}\) (2%) in PTLBW subjects. This may indicate their role in translocating the placental barrier membrane and leading to PTLBW. According to a study
performed by Waghmare2013, which included 40 chronic periodontitis subjects with PTLBW. *P. gingivalis* (37%), *Micromonas micra* (22.5%), and *P. intermedia* (15%) were isolated from the samples of placental extracts.[18] The results of this study coincided with the presence of *Micromonas micra*. In another study performed by Sahrmann 2015, *Fusobacterium* was one of the abundant species which was found in the current study.[19]

*P. micra* binds to human plasminogen and once bound, plasminogen activators of bacterial (streptokinase) and human (urokinase) origin activate plasminogen to plasmin. Activated plasmin on the bacterial surface interacts with the extracellular matrix and has significantly greater tissue penetrating ability. Lafaurie et al. 2007, stated that *P. micra* was the most frequently identified periodontopathogen in peripheral blood.[20] As the capability of neutralizing bacterial challenge in the bloodstream varies among individuals, this may represent a risk factor for translocation and intrauterine infection leading to PTLBW. Mikamo et al. has shown that *P. micra* strains isolated from amniotic fluid of preterm rupture of membrane demonstrated elastase activity.[21] Hence, it can be hypothesized that virulence factor of *P. micra* such as chymotrypsin-like proteases, gelatinases and collagenases production along with its hemolytic activity may directly or in conjugation with other anaerobic bacteria contribute to bacterial penetration into the placenta leading to adverse pregnancy outcomes. Furthermore, various intracellular signaling pathways are induced by *P. micra* cell wall[22] including PKA, ERK2, JNK, and p38 leading to increased production of pro-inflammatory cytokines, placental inflammation/damage, and possibly contributing to the indirect mechanism of PTLBW.

Another possible relationship that led to the intrauterine infection could be through the bacterial receptor and endothelium ligand interactions. The bacterial adhesion of *F. nucleatum*, FadA which binds to endothelial cadherin is the plausible explanation for the intrauterine infection that led to a rise in inflammatory mediators. The pro-inflammatory mediators especially PGE2 cause premature rupture of the membrane leading to PTLBW. *Veillonella* as well as *Streptococcus* are a well-recognized oral commensal species. In the present study, *Veillonella* (6%) and Group B *Streptococcus* (4%) were present in the placental samples of the PTLBW group. Fardini et al. indicated the potential significance of commensal oral species translocating to the murine placenta and leading to intrauterine infection.[23] Our results also indicated the presence of commensal oral species in intrauterine infection.

The strength of the study lies in the fact that microbiological analysis was performed, which is linked to the direct mechanism of causing intrauterine infection. These proposed bacteria were also not a part of vaginal microflora that adds on weightage for considering *F. nucleatum*, *P. micra*, and *Veillonella* as the causative pathogens.

One interesting finding that warrants future research is the presence of a significantly higher amount of *Bacteroid* spp. in NTNBW subjects that might play a protective role.

Limitations of the study include the lack of identification of pro-inflammatory cytokines such as PGE2, IL-6, IL-8, and TNF-α, which form the part of the indirect mechanism linking periodontitis to PTLBW, and also lack of advanced microbial analysis such as enzyme-based immunosorbent assay and polymerase chain reaction.

**CONCLUSION**

Within the limitations of the present study, it can be strongly suggested that *P. micra*, *F. nucleatum* and *Veillonella* are associated with PTLBW. Further multi-centered longitudinal study with larger sample sizes are required to strengthen the present study. Also advanced microbiological and inflammatory biomarkers from GCF are advocated for future research.

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**Conflicts of interest**

The authors of this manuscript declare that they have no conflicts of interest, real or perceived, financial or non-financial in this article.

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