

Assessing the association between periodontitis and premature birth : A case control study

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Abstract

Background: Premature delivery is among the leading causes of perinatal mortality and morbidity in developed societies, which is an important obstetrics problem. Maternal periodontitis is a prevalent condition that has been suspected to be associated with adverse pregnancy outcomes such as premature birth. However, there are still conflicting results about this possible relationship, therefore this study was designed to test the association between maternal periodontitis and premature birth. This study also provides the information about a new screening tool recommended for use by nurses and midwives to screen for periodontal diseases during antenatal consultations in order to improve mothers' and children's health.

Methods: A case-control study was conducted at 12 health facilities in the Southern Province of Rwanda from February to August, 2018. A total of 555 women in the postpartum period were enrolled in the study. Cases and controls were enrolled in a ratio of 1:2; each enrolled case of preterm birth was followed by 2 control subjects that were next on the register and who delivered at term gestation. A total of 185 cases of preterm deliveries and 370 controls of term delivery were enrolled in the study. Multivariate regression analysis was used and the independent variables were hierarchically entered in three groups: The first group involved demographic variables that were put in the regression model as Step 1. The second group was made up of other potential factors that were placed in the regression model as the second step. Periodontitis was entered in the final regression step, as it was hypothesized to be a major predictor variable.

Results: A statistically significant association was found between periodontitis and premature birth. Women who had periodontitis had 6 times the odds of giving birth to premature birth infants compared to women who had no periodontitis ($p < 0.001$) (OR=6.360, 95% CI 3.9, 10.4).

Conclusion: The study results indicate that periodontitis is strongly associated with premature birth. Preventive solutions including the use of a periodontitis screening tool for nurses and midwives during antenatal care consultations, are highly recommended.

Background

Premature births are among the leading causes of perinatal mortality and morbidity globally [1]. In the United States, premature births and associated complications, such as immature lung development, reduced feeding ability and inferior weight gain, results in longer hospital stays and a higher cost of health care, and are responsible for up 70% of prenatal and infant mortality. Almost a quarter of prematurely born infants required hospitalization at least once during their first year, mostly associated with reduced birth weight [2].

Neonatal delivery before 37 weeks of gestation is the leading cause of low birth weight [3]. Premature birth is one of the major healthcare challenges and is associated with many potential consequences like lifelong disabilities and high health care costs [4]. Premature birth is the leading cause of neonatal

mortality in low-income countries [4]. Premature deliveries totalled approximately 12.9 million births worldwide, representing around 9.6% of all births, although there are clear regional discrepancies. Specifically, African nations reported a higher incidence of premature births (18%) followed by the United States (12-13%) and Europe (5-9%). According to a demographic health survey (DHS) 2014-2015 in Rwanda, the incidence of low birth weight deliveries was 6.3% [5], and according to the Rwanda Population Reference Bureau, premature birth complications are among the top ten causes of child mortality in Rwanda [6].

Studies have identified various risk factors related to premature birth and they are categorized as a) non-gynecological causes: socio-economic, malnutrition, early maternal age, short maternal stature, low maternal weight, low maternal heart volume, smoking, alcohol consumption, inadequate prenatal care, stress, genitourinary tract infections and malaria, b) gynecological causes: uterine malformations, uterine adhesions and pregnancy with intrauterine infection, c) obstetric causes: primiparity in both young and old mothers, short inter-conception interval, grand multiparity, previous premature births, previous stillbirth, multiple pregnancies, low insertion of the placenta and chorioamnionitis [7].

Although several risk factors are known, 25% of premature birth cases were of unknown etiology [8]. The recent review of Puertas et al (2018) documented evidence from several studies associating periodontitis with premature birth [8–12]. In 1996, Offenbacher and colleagues described this relationship between maternal periodontitis and premature delivery [13]. The study of Bobetsis et al (2020) argued that, based on biological plausibility, periodontitis can contribute to premature birth through bacteremia where toxins and their products derived from maternal periodontitis can reach the bloodstream and cause injury to the placenta unit and to the amniotic fluid, leading to chorio-amniotic infections, increasing risk premature birth [14]. It has also been reported that the dissemination of local inflammation throughout the body may contribute to preterm low birth weight [10]. Studies suggest that inflammation in periodontal tissues due to periodontitis increases secretion of different inflammatory cytokines, notably interleukin B (IL-1 β), interleukin IL-6, interleukin 8 (IL-8), interleukin 17 (IL-17), and tumor necrosis factors alpha (TNF- α) [8,10,15–18].

In Africa, some studies have associated poor periodontal status with premature birth and low birth weight deliveries. For example, a study done in Nigeria by Umoh and colleagues concluded that periodontal disease management reduced the prevalence of low birth weight deliveries [19]. The recent review conducted by Jajoo et al (2020), similarly indicated the need for periodontitis treatment for reducing the premature births. Although the studies highlighted the association between periodontal infection and the risk of premature birth, the literature search conducted did not find any research pointing to periodontal screening during pregnancy. Moreover, in most of African countries like Rwanda, nurses and midwives are on frontline of providing antenatal care consultation. Therefore, the current study aims to assess the association between periodontitis and premature birth with the long term goal of initiating the screening tool to be used by nurses and midwives for the screening of periodontitis during antenatal consultations.

Methods

Study design and setting

A case-control study was conducted to ascertain the predictability of periodontitis with premature birth. Participants were selected through hospital registers whereby research team would verify daily to see the cases for preterm deliveries and the controls would be the next 2 on the register. The sample was calculated using G-Power 3.1.9.6. The researcher used small effect size of 0.06, alpha of 0.05 and power of 0.95 with 10 predictors. The G-Power calculation gave the sample size of cases of 185 and since the ratio was 1:2, then the controls were 370 and the total sample size was 555. The study was conducted at 12 health facilities in the Southern Province of Rwanda from February to August 2018. The study was done in the Southern Province of Rwanda in 6 districts, including Kamonyi, Muhanga, Ruhango, Nyanza, Huye and Gisagara. Corresponding district hospitals and nearby health centers were selected for the study and one referral hospital in Huye.

Data sources and measurement

A structured clinical exam and standardized questionnaire were used to collect information regarding the presence of periodontal infection among pregnant women attending antenatal care clinics in the Southern Province of Rwanda. The study adopted the questionnaire from the WHO Oral Health Assessment Tool for Adults of 2013 [20] to the Rwandan context. The questionnaire was sent to experts for content validation. It was piloted to ensure that it captures all variables and ensured that the questions were clear to the respondents.

The questionnaire was piloted in Nyamata District Hospital in the Eastern Province to ensure cross-cultural validation, and to ensure that it captures all the information required and clarity of questions. After the pilot study, all the inputs from the participants were considered and questions that were not clear were corrected accordingly. The questionnaire was translated in Kinyarwanda using forward and backward translation whereby this questionnaire was translated in Kinyarwanda from English and it was again translated back to English by another translator to see if the meaning remains the same and the corrections were harmonized.

The questionnaire assessed the following variables: age of the respondent, education level, health and lifestyle behavior e.g. Smoking, socio-economic status, mother's weight, number of previous pregnancies, previous preterm and weight gain during pregnancy, illnesses during pregnancy and stress during pregnancy. The outcome variable was premature birth and other mentioned variables are independent variables.

Data collection procedures

A periodontal examination was performed on all women enrolled in the study. The study examiners used a calibrated William's periodontal probe to perform the periodontal clinical examination. Six examiners were calibrated by a qualified dentist on how to perform a periodontal examination to see that they all understood it in the same way, to avoid having false results or different findings between patients. The calibration process focused on probe design, gentle and constant force of probing and proper angulations. While no formal agreement analysis was conducted, the examiners were required to examine at least 2 patients and oral examination was conducted until all examiners were in agreement with each other and with the trainer. The calibration results were considered valid only when there was no discrepancy in results and when the results for 2 examiners were consistent. The examiners assessed bleeding on probing, probing depth and clinical attachment loss measured in mm at six different sites on each tooth (buccal-mesial, mid-buccal, buccal-distal, lingual-mesial, mid-lingual and lingual-distal). The mothers in the study group were asked about their dental care practices and their smoking habits. In addition, a full-mouth periodontal screening was done by the lead researcher with the calibrated dental therapists acting as research assistants. However, the research team were blind to the case and control.

The study subjects were examined at their bedsides by the researcher and calibrated research assistants using a periodontal probe, intraoral mirror and headlights. A gentle probing force was applied to guide the tip into the periodontal pocket until the resistance was felt. The pocket depth was measured using the gingival margin as a reference point.

Clinical attachment loss was measured as follows: when the gingival margin was at the cemento-enamel junction and there was no recession, then the CAL was equal to the pocket depth; when the gingival margin was apical to the cemento-enamel junction, CAL was equal to pocket depth plus gingival recession; when the gingival margin was on the anatomical crown in case of gingival overgrowth, CAL was equal to pocket depth minus gingival recession. CAL was not considered in some of the specific cases that were of non-periodontal cause. For example, when the gingival recession was of traumatic origin, dental caries extending in the cervical area of the tooth and in the cases of recession by malposition of the tooth [21].

The current study defined periodontitis as presence of pocket depth greater than 3 mm on either maxilla or mandible or both and presence of interdental clinical attachment loss (CAL) on either maxilla, mandible or both of 2mm or above and buccal or oral CAL of 3 mm or above [21].

Based on Jati et al (2016), gingival recession was defined as "apical migration of marginal gingiva and characterized by gradual displacement of gingiva away from the cemento-enamel junction that results in the root surface exposure to the oral environment" [22]. The research team completed the exams and questionnaires with study subjects until the required sample was reached.

The current study defined some of the variables as follows; physical trauma as a wound on the body that was caused by a sudden physical injury, for example, an accident. Violence as any behavior or action that intends to hurt someone, physical or verbal and stress during pregnancy as anything that causes emotional strain or tension to the pregnant women.

Participants and Inclusion/exclusion criteria

The inclusion criteria were postpartum mothers aged 18-35 who delivered singleton infants within 1 to 5 days before recruitment in all selected health facilities. Those women who delivered premature were recruited as cases and those who delivered at term were recruited as controls. Maternal registers were checked in order to determine who could be recruited as case or controls based on the above criteria. Mothers with twin infants, those with systemic conditions like uncontrolled diabetes, HIV infection and those without teeth in one or more sextants were excluded from the study. Women whose conditions could obviously lead to prematurity like abnormal placentation, eclampsia, uterine abnormalities, and other pregnancy complications that may easily lead to prematurity were also excluded from the study so that they do not bias the results. Other variables that were likely to cause prematurity were documented via the study questionnaire and were controlled during the multivariate analysis.

A total of 555 women in the post-partum period were enrolled in the study. Cases and controls were enrolled in a ratio of 1:2 and each enrolled case of premature birth was followed by 2 control cases delivered at term gestation that were next on the register. We used ratio of 1:2 in order to increase the study power and reduce data collection time as there were limited cases of premature birth. In total, there were 185 cases with preterm deliveries/ gestation age of 37 weeks and 370 controls with term delivery/ gestation age >37 weeks.

Data analysis

Descriptive statistics, including chi-square analysis was conducted as part of the background to the main hypothesis testing analysis using multiple logistic regression. The study regression model was built using a hierarchical approach, where the demographic (control) variables were entered first followed by the proposed risk factors. Hierarchical multivariate logistic regression analysis was used with the study variables being entered into the analysis using three groups: the demographic variables that were significant in the univariate analysis (age and employment status) were entered first in the regression model as step 1, followed by the second group in step 2, which included other known potential risk factors also identified as potential confounders in this study such as ever used tobacco, mother's weight, Inter-conception period, whether premature delivery was experienced before, whether stress was experienced before, malaria during pregnancy, urinary tract infection, physical trauma and violence during pregnancy. The third and final step of the regression analysis, added periodontitis to the model, as it was hypothesized as the study's main predictor variable.

The odds ratio was calculated with 95% confidence intervals and statistical significance was defined as $p < 0.05$.

Results

There were 555 women in their postpartum period that were screened and all questionnaires were filled in using a structured interview until the sample was accumulated. The participants were from 6 districts of the Southern Province of Rwanda and from 12 health facilities. The participants were distributed with respect to age, education level, employment status, socio-economic status. The mean age was 27.35 (SD=5.2) ranging from 18 to 35 years. Most participants (n=338, 60.9%) were in the age range of 26-35 years, 47.6% had primary education, 38.7% had secondary education, 7% had tertiary education and 6.7% had no formal education. The majority of the study participants (n=513, 92.4%) are from a rural setting, 63.2% are farmers and 55.5% are in category 3 of the “Ubudehe”/ socio-economic status as categorized by Rwanda national categories. **Table 1**

Table 1: Demographic characteristics of participants

Variables		Frequency (n)	Percent (%)
Age category	16-25	217	39.1
	26-35	338	60.9
Education level	No formal education	37	6.7
	Primary	264	47.6
	Secondary	215	38.7
	Tertiary	39	7
Residence	Urban	42	7.6
	Rural	513	92.4
		351	63.2
Employment status	Farmers		
	Employed	71	12.8
	Students	32	5.8
		101	18.2
	Not employed		
Economic status	Category 1	56	10.1
	Category 2	191	34.4
	Category 3	308	55.5

Regression analysis results: Factors associated with premature birth among pregnant women attending antenatal care clinics

To assess if there is a relationship between periodontitis and premature birth, characteristics were compared initially in a univariate fashion between the cases and controls. Results from the univariate regression analysis, suggest that 11 variables namely: employment status, ever used tobacco, periodontitis, mother’s weight, last pregnancy, malaria during pregnancy, urinary tract infection during pregnancy, previous premature delivery, stress and violence during pregnancy were all associated with premature birth and therefore eligible for the multivariate logistic regression analysis. Multivariate regression analysis was then performed and the variables were hierarchically grouped into three groups:

whereby demographic variable of employment status was put first in the regression model as step 1 and followed by other potential factors of ever used tobacco, mother's weight, last pregnancy, previous premature delivery, history of stress, presence of malaria or urinary tract infection during pregnancy, physical trauma during pregnancy and domestic violence during pregnancy. In the third step of the regression model, the researcher put periodontal diseases as it was hypothesized as a predictor variable.

After adjusting for the other variables in the model, the multiple logistic regression analysis revealed a strong independent association between periodontitis and premature birth, where periodontitis could lead to a six-fold higher risk of delivering premature infants compared to women who had no periodontitis ($p < 0.001$) (OR=6.360, 95% CI 3.9, 10.4). Other significant results from Table 2 suggest that low maternal weight, previous history of prematurity, exposure to violence during pregnancy and a shorter interconception period were also associated with pre-term birth.

Table 2: Multivariate logistic regression analysis of premature birth with possible risk factors (Final model)

Variables	Categories	Odds Ratio	p value	95% Confidence Interval
Periodontitis		6.360	$p < 0.001$	3.94-10.27
Employment status	Farmer	1		
	Employed	0.861	0.684	0.42 - 1.77
	Students	0.694	0.524	0.23 - 2.14
	Not employed	1.548	0.132	0.88 - 2.73
Tobacco use	Yes	3.394	0.165	0.60-19.07
Mother's weight in Kgs	51-75	1		
	30-50	3.207	0.001	1.64-6.28
	≥ 76	0.322	0.106	0.08-1.27
History of Malaria	Yes	1.521	0.106	0.91-2.53
History of Urinary Tract Infection	Yes	1.539	0.196	0.80-2.96
History of Respiratory Tract Infection	Yes	1.721	0.448	0.42-6.99
Other illness	Yes	0.741	0.764	0.11-5.23
History of premature delivery	Yes	10.596	$p < 0.001$	2.87-39.15
History of stress during pregnancy	Yes	0.809	0.758	0.21-3.11
History of Physical Trauma	Yes	0.511	0.307	0.14-1.85
History of Violence during pregnancy	Yes	5.382	0.009	1.51-19.15
Other causes of stress	Yes	1.652	0.457	0.44-6.20
	>24 months	1		
	12-24 Months	2.168	0.006	1.25-3.76

Discussion

Premature birth is a major healthcare challenge and is associated with many potential consequences such as lifelong disabilities and high healthcare costs [4]. Premature delivery, was defined in this study as any delivery within a period of less than 37 weeks, accounts for almost 15 million neonates born prematurely worldwide, mostly in low and middle-income countries [23]. Various risk factors have been identified related to the mother's premature birth. These maternal risk factors include age, weight, socio-economic status, smoking, multiple pregnancies, low prenatal care, nutrition, stress, genito-urinary tract infections, and malaria. In addition, some studies have reported on the possible relationship between periodontitis and premature birth.

Many studies have reported the association between maternal age and premature birth; both extreme ages either under 18 years or above 40 years are considered to be risk factors for premature birth [24–27]. Though the majority of the studies concluded that the older maternal age was associated with higher risk of premature birth, Ambrogio and colleagues in their study observed that both extreme ages that is, maternal age under 17 and advanced age over 40 were independent factors for premature birth (OR 2.97; 95%CI 1.24, 7.14 , $P < 0.005$) [24]. This was echoed by Florent and co-authors who also found that both advanced age and lower age were risk factors for premature birth [26].

On the other hand, Mumghamba in Tanzania compared mothers who had PTB infants and those with normal weight infants and reported that PLBW had a lower mean age [28]. Our study shows no association between maternal age and premature birth. In this study, most mothers were young, whereby the mean age was 27.35 (SD 5.2), ranging from 18 to 35 years This limited age range could be the reason why there was no statistical association between maternal age and premature birth in this study. Similarly, the study done in Uganda by Muwazi who also worked on a young population which also showed no association between age and premature birth [29].

Maternal weight has also been reported to be associated with premature birth, whereby in our study the logistic regression revealed that mothers with low weight had higher chances of premature deliveries as opposed to mother with normal weight whereas the odds of having a premature birth baby was 3.2 times for underweight compared to those with normal weight mothers ($p = 0.002$) (95% CI 1.64, 6.28). Our study findings were echoed by Zhen and colleagues, who revealed that neonates born to underweight mothers had higher chances of preterm delivery (RR 1.21, 95% CI 1.14, 1.25,) [30]. The other variables found to be associated with premature birth in this study included: the interval between last pregnancies and the current and previous premature birth

In this study, the presence or absence of periodontitis disease was a major predictor of preterm delivery. After controlling for other variables, the logistic regression analysis revealed a strong association between periodontitis and premature birth, where periodontitis could lead to a six-fold higher risk of giving birth to premature birth infants compared to women who had no periodontitis ($p < 0.001$) (OR=6.360, 95%

CI 3.9, 10.4). It is note worthy that our study results are different in comparison to other studies, for instance, the study done in Germany by Noack and colleagues who did not find any association between periodontitis and premature birth [31]. Similarly, Davenport in 2002, also in a case-control study, did not detect any association between periodontitis and premature birth [32] and also Mumghamba in Tanzania in 2017 did not find any evidence to support a link between periodontitis and premature birth [28].

However, our study findngs are in agreement with several other studies that have supported the association between periodontitis and premature birth. Offenbacher et al., 1996 reported for the first time that there was a possible relationship between maternal periodontitis and delivery of a preterm infant where they reported that periodontitis during pregnancy could lead to seven times more risk of premature birth [8]. Lopez and colleagues also assessed the risk of premature birth and low birth weight in women with periodontitis in the USA and found that pregnant women with periodontitis were at a high risk of giving birth to premature infants with low birth weight ($p=0.0004$; $RR=3.5$) [34]. Several other studies also confirmed the association [9,10,12,35–38]. A systematic review by Teshome in 2016 concluded there was an association between periodontitis and premature birth [33].

Also, in Africa, other studies have examined the link between premature birth and low birth weight deliveries and these were significantly associated with poor periodontal status; for example, a study done in Nigeria by Umoh and colleagues revealed that periodontal treatment was effective in preventing low birth weight deliveries [19]. In Uganda, Wandera and colleagues also found that mothers with periodontal problems and poor oral hygiene during pregnancy had a greater risk of premature birth as opposed to mothers who did not have periodontitis during pregnancy [39]. Lastly, Muwazi in Uganda in his cross-sectional study reported an association between gingival recession and premature birth [29].

Policy implications: The study results found associations between maternal periodontitis and the risk of preterm birth. There is a need to improve awareness of non-dental professionals working in antenatal care clinics especially nurses and midwives about periodontal diseases and to include periodontal screening in the antenatal care package for early detection and to proactively promote periodontal health during pregnancy.

Limitations of the study: The limitations of this study as applied to most of case control studies is recall bias for example some illnesses like UTI and other illnesses during pregnancy was based on mothers' self-report of symptoms and not on laboratory confirmation and therefore over-reporting was likely. Also only mothers who had live births were interviewed and their babies assessed for gestational age. The study did not address factors associated with preterm stillbirth. Some cases of incomplete or missing data especially on antenatal profile were encountered. Lastly, much as we did calibration of examiners there were still imprecisions of periodontal examination between examiners.

Conclusion

The study results suggest that periodontitis is associated with a six-fold increased risk of premature birth. Thus, preventive solutions such as having the development of a periodontitis screening tool for

nurses and midwives during antenatal care consultations is highly recommended.

Abbreviations

CAL: Clinical Attachment Loss

CI: Confidence Interval

DHS: Demographic Health Survey

IL-6: Interleukin-6

PD: Pocket Depth

SD: Standard Deviation

TNF- α : Tumor Necrosis Factor-alpha

TSAM: Training Support Access Model

WHO: World Health Organization

Declarations

Ethics approval and consent to participate: Permission to conduct the study was sought from the ethics committee of the University of Rwanda, College Medicine and Health Sciences and approval from study sites. Also permission from the Ministry of Health to conduct the study in the selected health facilities was sought and granted. Informed consent forms were given to the participants. Participants were informed of their right to withdraw at any time and that their participation was entirely voluntary. The participants were given the information sheet containing all the information about the study and was read to those who did not know how to read. After understanding the study's risks and benefits along with the details involved in the study, those who agreed were given the consent form to sign that they have voluntarily agreed to participate in the study. Information from the participants was kept confidential and used for study purposes.

Consent for publication: This manuscript contains no individual person's data in any form and consent for publication is not applicable for this section.

Availability of data and materials: The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Competing interests: All authors declared no competing interests.

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Authors' contributions: All authors made a significant contribution to the work reported that is; conception, study design, execution, acquisition of data, analysis and interpretation, have critically reviewed the article, have agreed on the journal to which the article will be submitted, gave approval of the final version to be submitted and agree to be accountable for all the content of the article.

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