Periodontal diseases and adverse pregnancy outcomes: is there a relation?

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Abstract: Periodontal disease (PD) is one of the most common chronic disorders of infectious origin known in humans. Maternal periodontal disease is a chronic oral infection with local and systemic inflammatory responses and may be associated with adverse pregnancy outcomes. **Objective:** To evaluate whether or not periodontal disease (PD) in pregnancy is associated with adverse pregnancy outcomes, and to find the possible pathogenesis of these adverse outcomes if present. **Patients and methods:** 300 pregnant women were assessed for periodontal status by the criteria commonly used in epidemiological studies, probing depth (PD) and clinical attachment level (CAL). Women were then classified according to periodontal status in to two patient groups (145 pregnant women with periodontitis) and control group (155 pregnant women without periodontitis). For all participants C-reactive protein (CRP) assay was performed, follow up of all participants until delivery was done to evaluate obstetric complications associated with each group. **Results:** PD is associated significantly with adverse pregnancy outcomes as preeclampsia, gestational diabetes, preterm labor, low birth weight, and prelabor rupture of membranes ($p<0.05$). The mean $\pm$ SD levels of CRP was 75.8% higher among patient group compared to control group and the difference was statistically significant (mean $\pm$ SD 2.55 $\pm$0.25 vs. 1.45 $\pm$ 0.22). **Conclusions:** This study supports the hypothesis of an association between periodontal disease and adverse pregnancy outcomes. The study also suggests that CRP in periodontitis may mediate the effect of periodontitis on pregnancy outcomes.
[Ahmed A. M. Nasr, Faisal Ali Mustafa, Mahammad G. Nasr, Abd El-Naser Abd El-Gaber Ali, Hossam Alktatny. **Periodontal diseases and adverse pregnancy outcomes: is there a relation?** *J Am Sci* 2012;8(9):737-744]. (ISSN: 1545-1003). http://www.jofamericanscience.org. 101

Key words: periodontal disease, adverse pregnancy outcomes, CRP.

1. Introduction:

Periodontal disease (PD) is one of the most common chronic disorders of infectious origin known in humans, with a reported prevalence varying between 10 and 90% in adults, depending on diagnostic criteria(1).

Periodontal disease refers to an inflammatory condition of the soft tissues surrounding the teeth (i.e., gingivitis) and the destruction of the supporting structures of the teeth, including the periodontal ligament, bone, cementum and soft tissues (i.e. periodontitis) (2).

There is increasing evidence suggesting that periodontal disease is associated with an increased risk of systemic diseases such as cardiovascular diseases, respiratory diseases, diabetes mellitus and osteoporosis (1).

Maternal periodontal disease is a chronic oral infection with local and systemic inflammatory responses and may be associated with adverse pregnancy outcomes (3, 4).

Periodontitis is caused by gram-negative anaerobic bacteria that induce local and systemic elevations of pro inflammatory mediators (5).

Several studies have suggested that periodontitis during pregnancy could be associated with adverse pregnancy outcomes such as preterm birth, low birth weight, gestational diabetes mellitus, premature rupture of membrane, and preeclampsia, but their methods are heterogeneous and their results are inconsistent (6 - 12).

On the other hand, some studies showed a modest association between PD and adverse pregnancy outcomes (13), or no association at all (14, 15).

Studies suggesting an association between periodontal diseases and adverse pregnancy outcomes attribute this action to the presence of some inflammatory mediators that mediate this effect (16).

Destructive periodontal diseases are associated with increase in C-reactive protein (CRP) (16, 17).

CRP is an acute-phase reactant synthesized by the liver in response to the inflammatory cytokines, interleukin (IL)-6, IL-1, and tumor necrosis factor-alpha. Circulating CRP levels are a marker of systemic inflammation and are associated with periodontal disease. CRP could amplify the inflammatory response through complement activation, tissue damage, and induction of inflammatory cytokines and may mediate the relationship between periodontitis and adverse pregnancy outcomes (16).

In spite of medical improvements and public health interventions in order to reduce

pregnancy complications, a large proportion still has no known etiology, and, consequently, the identification of their risk factors seems important for the development of specific strategies for reducing their occurrence (8, 12).

2. Aim of the study: The purpose of this study is to evaluate whether periodontal diseases is associated with increased risk of certain pregnancy complications or not, and the possible pathogenesis for these complications.

3. Patients and Methods

Study design: This is a contemporary cohort study that evaluates the relationship between PD and some adverse pregnancy outcome as preterm birth, low birth weight, prelabor rupture of membranes, preeclampsia, and gestational diabetes.

Study Population: 300 pregnant women attending the prenatal outpatient clinic at Al-azhar university hospital in Assiut and voluntarily agreed to participate in the study after signing an informed consent form during the period 2010-2011 were included in this study.

Inclusion criteria: Maternal age 18 to 42 years old, gestational age ≤ 32 weeks at recruitment, singleton pregnancy and absence of chronic pre gestational conditions that may affect pregnancy outcomes as pre gestational diabetes and chronic hypertension.

Exclusion criteria: Maternal age below 18 or above 42 years, women with multiple pregnancy due to greater risk of preterm and/or low birth-weigh, uterine or cervical anomalies (cervical incompetence, prior cervical surgery), a previous history of preterm, any chronic pre gestational conditions that may affect pregnancy outcomes as pre gestational diabetes and chronic hypertension.

Each participant was subjected to all of the following:

A) Assessment of periodontal status: a single periodontal examination on the day of a scheduled prenatal visit was carried out once during pregnancy before 32 weeks of gestation by the same periodontist and an assistant who provided technical support and who filled the data collection forms. Periodontal status was assessed by the criteria commonly used in epidemiological studies, probing depth (PD) and clinical attachment level (CAL), (18, 19).

Probing depth (PD): measured as the distance (in millimeters) from the gingival margin to the bottom of the pocket (18)

Clinical attachment level (CAL): measured as the distance (in millimeters) from the cemento-enamel junction of the tooth to the bottom of the pocket (19).

Diagnosis of periodontities depended on: the presence of 4 or more teeth showing at least one site with 4 mm of PD and clinical attachment loss at the same site, with bleeding on probing (BOP) (12).

Study populations were then classified according to their periodontal status in to two groups:

Group I (patient group): consists of 145 patients with periodontities.

Group II (control group): consists of 155 patients without periodontities.

Pregnant women were then referred directly to the prenatal outpatient clinic to receive additional information and sign the informed consent form immediately afterwards.

B) ***Detailed history*** with fulfilling off a questionnaire for collecting socio-demographic, habit and gestational variables.

C) ***General, abdominal and local examination.***

D) ***Abdominal ultrasound:*** to confirm gestational age, estimate fetal weight, diagnose IUGR, and for evaluation of other parameters as amniotic fluid and placenta.

E) ***Routine pregnancy investigations:*** CBC, Rh typing, urine analysis for protinuria and glucosuria, screening for gestational diabetes between 24 –30 weeks of gestation or later based on the American College of Obstetricians and Gynecologists' recommendation (17) by performing a standard 1-hour 50-g oral glucose challenge test (GCT) If the GCT is positive, they then underwent a confirmatory test.

F) **C-** ***reactive protein assay:*** CRP is an acute-phase reactant; its levels are considered as a marker of systemic inflammation and are associated with periodontal disease (17). Each participant provided a blood sample at the initial study visit or shortly thereafter. Plasma samples were stored in EDTA, refrigerated for several hours, and then transported on ice to the laboratory, where they were centrifuged, aliquotted, and frozen in liquid nitrogen until the time of analysis. Plasma samples were thawed and assayed using clinically validated immunoturbidimetric assays on an analyzer with reagents and calibrators. One laboratory technician who was blinded to the participants' periodontal condition and pregnancy outcome performed all assays.

Diagnosis of gestational diabetes depended on: a 3h, 100-gm oral glucose tolerance test (OGTT)

after a 10- 12-h overnight fast for those patients with positive screening by GCT (level greater than 135 mg/dl). Women whose glucose levels exceed two or more threshold values on the OGTT are diagnosed as having GDM (20).

Diagnosis of preeclampsia depended on: maternal systolic blood pressure ≥ 140mm Hg or diastolic pressure ≥ 90mm Hg with proteinuria (0.3 g/24 h).

Diagnosis of preterm labor (PTL) is defined as: labor occurring after 28 weeks and before 37 weeks of gestation (21).

Low birth weight (LBW) is defined as: birth weight below 2500 gm (21).

Prelabor rupture of membranes (PROM) is defined as: rupture of membranes occurring before the onset of labor, diagnosed clinically, by increased vaginal pH and decreased amount of amniotic fluid confirmed by ultrasound scan (22).

Statistical Analysis

When each case was finished, with information on delivery and perinatal outcomes available, the form was checked for completeness and correctness. Then the information was entered to feed a computer database specifically prepared for this study.

Differences between periodontitis cases and controls were compared using two sample *t* tests or Wilcoxon rank-sum test for continuous variables and Fisher's exact test for categorical variables.

To evaluate the association between CRP and periodontitis, we performed multivariate linear regression analysis with adjusting for factors known to affect CRP levels, including age, pre-pregnancy BMI, completed college education, and gestational age at blood collection.

4. Results:

300 pregnant women were included in this study. They were evaluated and followed until delivery. Among these, 145 pregnant women had PD (patient group) and 155 pregnant women had been classified as without PD (control group), what represents a 48.3% prevalence of exposure. In general, all pregnant women presented similar socio-demographic characteristics and habits in both groups. Likewise, the groups did not present significant differences regarding the number of prenatal visits, time of odontologists visiting, frequency of tooth brushing, systemic antibiotic use in pregnancy or mode of delivery.

Table (1) shows the demographic, social and clinical characteristics of the study groups, there was no significant difference between both groups (p>0.05).

Figure (1) shows mean ± SD levels of C-reactive protein (CRP) of patients (with periodontities) and control (without periodontities), there was strong positive association between CRP and periodontities as the level of CRP in patient group was significantly higher than that of the control group (p <0.05).

Table 1: Demographic, social and clinical characteristics of the study groups

Maternal Characteristics	(Group l) (n=145)	(Group ll) (n=155)
Gestational age at recruitment(wks)*	30.8±4.7	30.8±3.8
Maternal age (yrs)*	28.2±5.6	27.4±5.9
BMI *	23±5.1	23.5±5
Parity		
Primipara	29 (20%)	38 (24.5%)
Multipara	116 (80%)	117(75.5%)
Marital status		
Married	100(68.97%)	105(67.7%)
Divorced	20 (13.79%)	23 (14.8%)
Widow	25 (17.24%)	27 (17.4%)
Educational level		
Secondary school	40 (27.6%)	40 (25.8%)
University	15 (10.4%)	15 (9.7%)
Last visit for dental cleaning		
Within 6 months	30(20.7%)	35(22.6%)
6–12 months	30 (20.7%)	33 (21.3%)
2 years	40 (27.7%)	44 (28.4%)
>2 years	25 (17.2%)	27 (17.4%)
Never	20 (13.7%)	16 (10.3%)
Brushing teeth		
≥2 times per day	30 (20.7%)	33 (21.3%)
Once per day	35 (24.1%)	40 (25.8%)
A few times /week	80 (55.17%)	82 (52.9%)
Antibiotic use in pregnancy	30 (20.7%)	33 (21.3%)
Mode of delivery		
Vaginal delivery	101 (69.7%)	105(67.7%)
Cesarean section	44 (30.3%)	50(32.25)

Values are given as (number.%)
*Values are given as mean ± SD
p value between groups > 0.05

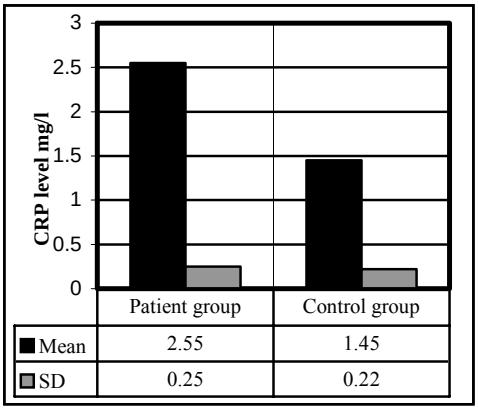


Figure 1: CRP levels in patint and control groups (p <0.05).

Table (2) and **figure (2)** show pregnancy complications according to periodontal status. The incidence of obstetric complications (preeclampsia, gestation diabetes, preterm labor, low birth weight and prelabor rupture of membranes) was higher in patient group than that of control group and the difference between both groups was statistically significant (p <0.05).

Table 2: Pregnancy complications according to periodontal status

Obstetric complications		Periodontal status		*P* value
		With PD (n=145)	Without PD (n=155)	
GDM	Yes	18 (12.4%)	10 (6.5%)	**
	No	127(87.6%)	145(93.5%)	
PE	Yes	16(11.1)	8 (5.2%)	*
	No	129(88.9%)	147 (94.8)	
PTL	Yes	17 (11.7%)	9 (5.8%)	**
	No	128 (88.3%)	146(94.2%)	
LBW	Yes	18 (12.4%)	10 (6.5%)	**
	No	127(87.6%)	145(93.5%)	
PROM	Yes	34 (23.5%)	14 (9.1%)	***
	No	111(76.5%)	141(90.9%)	

Values are given as (number. %)

*** p < 0.05 ** p < 0.01 *** p < 0.001**

GDM= gestational diabetes mellitus.

PE= preeclampsia

PTL= preterm labor. LBW= low birth weight

PROM= prelabor rupture of membrane

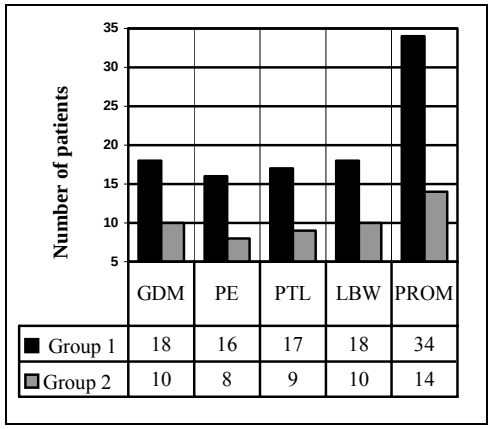


Figure (2): Pregnancy complications according to periodontal status

Table (3) and **figure (3)** show the risk of periodontal disease in occurrence of obstetric complications, periodontal disease approximately double the risk of development of obstetric complications that assessed in this study (RR= 2.16; 95%CI). As regard to individual obstetric complications it was found that periodontities increases the relative risk (RR) of GDM, PE, PTL, LBW and PROM by 1.9, 2.1, 2, 1.9, 2.58 (95% CI) respectively.

Table 3: the relative risk of periodontal disease in occurrence of obstetric complications.

Obstetric complications	Periodontal status		Relative risk (95% CI)
	With PD (n=145)	Without PD (n=155)	
GDM	18 (12.4%)	10 (6.5%)	**1.9**
PE	16(11.1)	8 (5.2%)	**2.1**
PTL	17 (11.7%)	9 (5.8%)	**2**
LBW	18 (12.4%)	10 (6.5%)	**1.9**
PROM	34 (23.5%)	14 (9.1%)	**2.58**
Total	103/145 (71%)	51/155 (32.9)	**2.16**

Values are given as (number. %)

GDM= gestational diabetes mellitus

PE= preeclampsia

PTL= preterm labor

LBW= low birth weight

PROM= prelabor rupture of membrane

Figure (3): Risk of development of obstetric complications with periodontitis

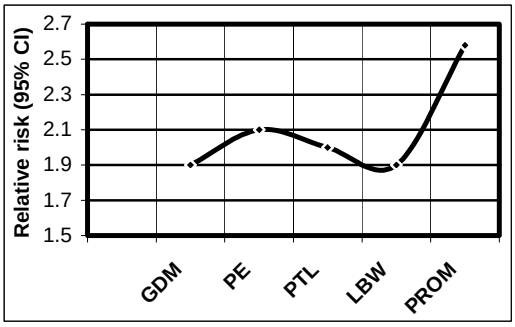
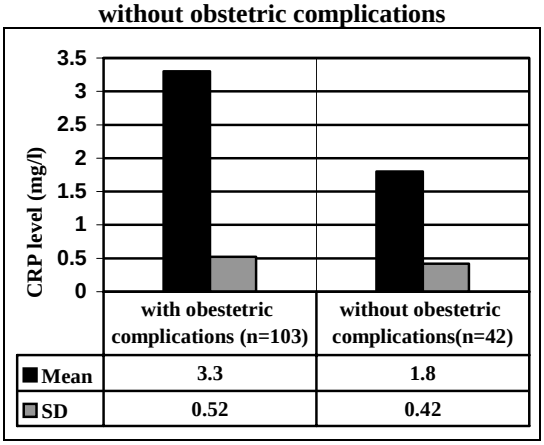


Figure (4) shows comparisons between CRP (mean ± SD) levels in patient with periodontities according to the presence or absence of obstetric complications. It was found that (mean ± SD) levels of CRP in patients with obstetric complications and periodontities is significantly higher than those with periodontities only without obstetric complications (3.8±0.52 Vs 1.8 ± 0.42) (*p* <0.01).

Figure (4): CRP levels in patient group with and without obstetric complications



***p* value between groups <0.01**

5. Discussion:

Periodontal disease refers to an inflammatory condition of the soft tissues surrounding the teeth (i.e., gingivitis) and the destruction of the supporting structures of the teeth, including the periodontal ligament, bone, cementum and soft tissues (i.e.periodontitis) (2). There is increasing evidence suggesting that periodontal disease is associated with an increased risk of systemic diseases such as cardiovascular diseases, respiratory diseases, diabetes mellitus and osteoporosis (1).

The relation between periodontal diseases and pregnancy complications is a matter of controversy and has been investigated during the last decade to evaluate the actual association with different obstetric complications. Periodontal disease (PD) has been suggested to be associated with preterm, low birth weight (PTB/LBW), and small for gestational age neonates (SGA) with higher risk of perinatal and neonatal mortalities, development of health problems during childhood (neurological, respiratory, gastrointestinal and cardiovascular), and risk of diseases during adulthood (12, 23).

This study was conducted to evaluate the relation of periodontal disease with the adverse pregnancy outcomes and to highlights the possible pathogenesis for this adverse pregnancy outcomes.

In this study we found that the prevalence of periodontal disease among pregnant female in the study population was 48.3%. We found also that 71% of patients with periodontitis were associated significantly with adverse pregnancy outcomes ($p<0.05$) and the presence of periodontal disease among pregnant women double the risk of developing pregnancy complication (RR 2.16, 95% CI) suggesting a strong positive association between PD and adverse pregnancy outcomes.

In the current study we found that the incidence of GDM was significantly higher in patient group compared to control group (12.4% vs. 6.5%) also we found that maternal periodontitis is associated with increased risk of developing GDM (RR= 1.9, 95% CI). This result is in accordance with (20 , 24), however on contrary to our results Dasanayke *et al.* (25) found an increase of GDM in women with clinical periodontal disease compared to women without periodontal disease but this increase did not reach statistical significance.

In this study the incidence of preeclampsia was significantly higher in patient group compared to control group (11.1% vs. 5.2%) this result is in accordance with (26-29) also we found that maternal periodontitis nearly double the risk of developing PE (RR= 2.1, 95% CI),

In the present study the incidence of preterm labor and low birth weight were significantly higher in patient group compared to control group (11.7 vs. 5.8% and 12.4% vs. 6.5% for PTL and LBW respectively), also we found that maternal periodontitis double the risk of developing PTL (RR= 2, 95% CI) and increase the risk of LBW (RR 1.9, 95% CI). This result is comparable to Dolapo *et al.* (11) and Ismail *et al.* (30) who found that periodontities increase the risk of preterm low birth weight almost 4 times. However on contrary to our results Marianna *et al.* (12) found no association between periodontitis and PTL and Cathy *et al.* (26) found a significant association between generalized periodontitis and induced

preterm birth for preeclampsia but not for spontaneous PTL.

In this study the incidence of prelabor rupture of membranes was significantly higher in patient group compared to control group (23.5% vs. 9.1%) this result is in accordance with Marianna *et al.* (12). Also we found that maternal periodontitis increased the risk of developing PROM by more than 2.5 times (RR= 2.58, 95% CI).

In this study, we found that the mean ± SD level of CRP was 75.8% higher among patient group compared to control group and the difference was statistically significant (2.55 ± 0.52 vs. 1.45 ± 0.22). This result is comparable to Waranuch *et al.* (31) who found 65% higher CRP levels among pregnant women with periodontitis compared to periodontally healthy women.

Moreover when we measure the mean ± SD level of CRP among patient group we found that periodontitis with adverse pregnancy outcomes was 94.4% higher compared to patients with periodontitis but not associated with adverse pregnancy outcomes and the difference was statistically significant (3.5 ± 0.52 vs. 1.8 ± 0.42).

In the present study we measured CRP in a single blood sample, which is reasonable as there is little seasonal or diurnal variation in CRP levels (32). In addition, most participants in the study had CRP levels below 10 mg/l, the standard threshold associated with acute-phase effects, reducing the possibility that CRP levels were raised as a result of acute infections or trauma (33).

The association between PD and the adverse outcomes of pregnancy that were found in this study are consistent with those in other studies (20, 21, 24, 28, 30-35). However they differ from outcomes of a study carried out by many investigators (12, 25, 26) which either used a partial periodontal evaluation that does not include important periodontal clinical parameters, such as CAL, or used different criteria for diagnosis. We observed a difference between the conclusions of the studies due to distinct definitions of periodontitis (2).

One of the goals of this study is to find an explanation to the pathogenesis by which periodontal disease affects pregnancy outcome. Our study suggests the presence of local and systemic inflammatory reaction associated with periodontitis, as evidenced by elevated levels of CRP. Maternal infections, acts as a reservoir of gram-negative anaerobic microorganisms results in a state of transient bacteremia. Viable bacteria and bacterial products (e.g., lipopolysaccharide) from the sub gingival plaque and pro-inflammatory cytokines (tumor necrosis factor -α, IL-1β, IL-6, IL-8, prostaglandin E2 and C-reactive protein) from the inflamed periodontal tissues can enter the circulation and trigger a maternal systemic inflammatory response amplified by CRP leads to complement activation, tissue damage, and induction of inflammatory cytokines that mediate the relationship between periodontitis and some adverse pregnancy outcomes as preeclampsia, PTL, LBW and PROM (29, 31).

The pathogenesis for GDM may be explained by the same mechanism mentioned before. The pro-inflammatory cytokines from the inflamed periodontal tissues trigger a maternal systemic inflammatory response. Pregnancy itself is a stressful state with increased inflammatory activity and increased insulin resistance (20). It is known that pancreatic β-cell destruction can result from the pro-inflammatory imbalance created by sustained elevation of cytokines. It is well accepted that infection results in a state of insulin resistance. Therefore, maternal chronic periodontal disease could induce a sustained systemic inflammatory response that may result in a state of insulin resistance. Such an infection-induced insulin resistance could exacerbate the preexisting pregnancy-induced insulin resistance and may cause impaired glucose tolerance and the manifestation of GDM (20, 36-38).

6. Conclusions:

This study supports the hypothesis of an association between periodontal disease and adverse pregnancy outcomes. The study also suggests that periodontitis associated with increased plasma CRP levels may mediate the association of periodontitis with adverse pregnancy outcomes.

7. Recommendations:

Careful periodontal diagnosis and treatment should be a routine practice during antenatal care visits. Oral health programs should be conducted in populations with high incidence of PD, eliminating it completely, to reduce the proportion of these adverse pregnancy outcomes. Further prospective studies are needed to examine whether periodontal disease is really a causal risk factor for these pregnancy complications or not.

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8/15/2012