

Periodontitis and Gestational Diabetes Mellitus: Exploring the Link in NHANES III

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Abstract

Objectives: The authors hypothesized that women with a history of gestational diabetes mellitus (GDM) during pregnancy would exhibit more severe periodontal disease than controls without a history of diabetes during pregnancy. **Methods:** Data from NHANES III provided information for 4,244 women ages 20-59. One hundred and thirteen had a history of GDM (GDM+), while 4,131 had no history of diabetes before or during their pregnancies (GDM-). Women were further classified by the presence or absence of diabetes mellitus (DM+ or DM-) at the time of their NHANES III examination. Periodontal disease (PD) was defined as one or more teeth with one or more sites with probing depth ≥ 4 mm, loss of attachment ≥ 2 mm, and bleeding on probing. **Results:** The PD prevalence among women who were GDM+DM- was 9.0% and 4.8% for those who were GDM-DM-. PD prevalence for women who were GDM+DM+ was 30.5% and 11.6% for GDM-DM+ subjects, respectively. A logistic regression model, controlling for age, calculus, smoking, and income estimated women who were GDM+DM+ were more likely to have periodontal disease than women who were GDM-DM- and women who were GDM-DM+. The GDM+DM- group also tended to be more likely to have PD than the GDM-DM- and GDM-DM+ groups. However, the odds ratios were not statistically significant. **Conclusions:** These results support the hypothesis that women with gestational diabetes mellitus (GDM) during pregnancy may be at greater risk for developing more severe periodontal disease than pregnant women without GDM.

Key Words: Gestational diabetes mellitus, diabetes mellitus, periodontal disease, NHANES III

Introduction

Gestational diabetes mellitus (GDM) occurs in approximately 5% of pregnant women with onset during pregnancy, and subsiding after parturition (1). Pregnant women who have never had diabetes before, but who have high blood glucose levels during pregnancy, are said to have GDM. Importantly, nearly 50% of women with GDM will eventually develop type 2 diabetes mellitus within 3-5 years post-partum. Moreover, acute and chronic neonatal morbidity as well as neonatal mortality have been described in neonates delivered by women with GDM and recent data have demonstrated an as-

sociation between GDM and an increased risk of spontaneous preterm birth (2,3).

Substantial evidence is available documenting that the extent and severity of periodontal disease is increased in patients with type 2 diabetes (4). In addition, data accruing from cross sectional and longitudinal studies support observations that the infection and inflammation associated with periodontal disease may have a negative impact on the period of gestation and on fetal growth leading to the birth of preterm, low birth weight infants (reviewed in 5). A recent case-control study supported an association between severe maternal

periodontal disease and spontaneous preterm birth at less than 32 weeks of gestation when compared to women with normal term births or women with early indicated preterm births at less than 32 weeks (6). There also is recent evidence that maternal periodontal disease not only increases the relative risk for preterm or spontaneous preterm births, but that periodontal disease progression during pregnancy is a predictor of the severe adverse outcome of very (<32 weeks) preterm birth. This finding is independent of traditional obstetric, periodontal and social risk factors (7).

Although there is a clear link between periodontal disease and diabetes, and accumulating evidence linking periodontal disease and negative pregnancy outcomes, there is limited published information on the relationship between diabetes, periodontal disease and pregnancy (combined effect). A study of 13 pregnant subjects with type 1 diabetes (onset prior to pregnancy) and 20 pregnant, non-diabetic controls, reported that pregnant subjects with diabetes had significantly higher plaque and gingival indices, and higher mean probing depths than the non-diabetic control subjects (8). These results supported the hypothesis that pregnant subjects with diabetes experienced greater periodontal inflammation and destruction than the pregnant controls without diabetes. However, there are no comparable published studies evaluating this relationship in subjects with GDM. The authors hypothesized that the preva-

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lence of periodontal disease in subjects with a history of GDM would be higher than in controls without a history of diabetes before, during, or after pregnancy. This study was designed to address this hypothesis through an analysis of data collected in the Third National Health and Nutrition Examination Survey (NHANES III) (9).

Methods

The authors of the study analyzed NHANES III data for women ages 20-59 who reported having had at least one pregnancy and a new diagnosis of diabetes while pregnant (GDM+). The analysis also included whether these women were positive (GDM+DM+) or negative (GDM+DM-) for type 2 diabetes (referred to as "diabetes" throughout the remainder of the Methods and Results sections) at the time of the NHANES III examination. Diabetes at the time of the examination (DM+) was based on their response when asked if a physician had ever told them they had diabetes other than at pregnancy, or having fasting plasma glucose levels greater than 126mg/dL to assess undiagnosed diabetes. The control subjects were women in the same age group without a history of GDM (GDM-), and with (GDM-DM+) or without (GDM-DM-) diabetes at the time of the NHANES III examination, based on the same diabetes diagnostic criteria as the women with GDM.

Additional study variables evaluated in this analysis included demographic data (age, race/ethnicity, and poverty income ratio), behavioral data (smoking history), systemic health data (pregnancy history and diabetes mellitus status), laboratory values (serum cotinine) and oral health data (probing pocket depths ≥ 4 mm, gingival bleeding, clinical attachment levels ≥ 2 mm, and presence of calculus). The oral health data collected in this survey were based on random half-mouth evaluation of two sites per tooth. The major exposure variable was a combination of history of gestational diabetes and diabetes status at the time of the NHANES III examination, and the outcome (dependent) variable was the presence of peri-

TABLE 1
Bivariable associations between selected characteristics and periodontitis (PD+) prevalence in U.S. adult women, ages 20 to 59, with pregnancy history, NHANES III

	Totals (wt'd%) N=4244	PD + (wt'd%) n=344	P-value
GDM history, diabetes status			<0.01
GDM-DM-	3982 (95.8)	303 (4.8)	
GDM-DM+	149 (2.6)	24 (11.6)	
GDM+DM-	88 (1.3)	11 (9.0)	
GDM+DM+	25 (0.3)	6 (30.5)	
Age			0.01
20-29	1159 (24.2)	55 (2.7)	
30-39	1426 (34.0)	129 (5.7)	
40-49	1014 (26.6)	96 (5.8)	
50-59	645 (15.2)	64 (6.5)	
Race/Ethnicity			<0.01
WA	1329 (71.0)	60 (4.1)	
AA	1406 (13.7)	155 (10.2)	
MA	1308 (6.2)	121 (8.2)	
Other	201 (9.1)	8 (3.5)	
Poverty Income Ratio			<0.01
<1.5X	1653 (24.5)	182 (9.4)	
1.5-2.5X	920 (24.2)	65 (5.5)	
2.6-3.9X	727 (25.8)	44 (3.5)	
>3.9X	601 (25.5)	16 (2.1)	
Calculus, sub-G			<0.01
0%	1607 (48.1)	20 (0.9)	
1%-20%	702 (17.6)	24 (3.0)	
$\geq 21\%$	1935 (34.3)	300 (12.2)	
Smoking, cotinine level			0.54
>10ng/mL	1128 (30.)	74 (4.6)	
≤ 10 ng/mL	3019 (69.8)	259 (5.3)	
Smoking, self-report			0.59
Never	2534 (52.2)	224 (5.0)	
Former	630 (18.7)	50 (6.1)	
Current	1080 (29.1)	70 (4.8)	

"Wt'd" = weighted percent; "PD+" = Number of people with periodontitis;
 "WA" = white Americans; "AA" = African Americans; "MA" = Mexican Americans
 Sub-G = subgingival calculus, percent of teeth with subgingival calculus

odontitis. Periodontitis was defined as the presence of one or more teeth with at least one site demonstrating probing pocket depth ≥ 4 mm, clinical attachment loss ≥ 2 mm and bleeding on probing. Statistical analyses included assessing bivariate associations and 3-way stratified associations of important covariates with periodontitis, and multivariable logistic regression modeling, adjusting for established risk factors using the statistical analysis program SUDAAN (10) to account for the complex survey sample design.

Results

There were 4,244 women eligible; 113 had a history of GDM (25 of whom

had diabetes at the time of examination; GDM+DM+), while 4,131 had no history of GDM (149 of whom had diabetes at the time of examination; GDM-DM+). The number of women meeting the periodontal disease definition were as follows: 6 with a history of GDM and diabetes (PD+ GDM+DM+; weighted prevalence of 30.5%); 11 with history of GDM and without diabetes (PD+ GDM-DM-; weighted prevalence of 9.0%); 24 without a history of GDM and had diabetes (PD+ GDM-DM+; weighted prevalence of 11.6%); and 303 without a history of GDM and no diabetes (PD+GDM-DM-; weighted prevalence of 4.8%) (Table 1). Among women with diabetes, mean duration was

96.6 months (95% confidence limits: 49.2, 144.1 months) for the GDM+DM+ group and 93.3 months (95% confidence limits: 61.8, 122.9 months) for the GDM-DM+ group. Mean levels of hemoglobin A1c were higher than current diabetes management targets for good glycemic control in both groups, 8.8 (95% confidence limits: 7.1, 10.5) for the GDM+DM+ group and 7.8 (95% confidence limits: 7.2, 8.4) for the GDM-DM+ group. While the mean values of HbA1c for the GDM+DM+ group and the GDM-DM+ differed, the difference in the values was not statistically significant, based on the overlap of the 95% confidence limits. Further, in our logistic regression models, the term for HbA1c was not statistically significant ($P=0.8$) and did not change the other parameter estimates in the models, therefore we did not to include it in the results reported in Table 2.

Bivariable associations for the prevalence of periodontitis among the covariates representing age, race/ethnicity and poverty income ratio in Table 1 revealed that (1) younger women had significantly less periodontitis than older women ($P=0.01$); (2) periodontitis prevalence differed significantly by race/ethnicity with African-American and Mexican-American women having greater prevalence than non-Hispanic White American and other women ($P<0.01$); and (3) women with income <1.5 times the poverty level had significantly more periodontitis than women of higher income levels (1.5 to >3.9 times the poverty level) ($P<0.01$). When evaluating two clinical/behavioral variables commonly associated with periodontitis, calculus and smoking, women with no subgingival calculus had significantly less periodontitis than women with subgingival calculus ($P<0.01$). However, there was no statistically significant association between smoking (determined by self-report or serum cotinine levels) and periodontitis in this population.

Crude bivariable analysis indicated that women with GDM history and diabetes (GDM+DM+) and women without GDM history, but

TABLE 2

Bivariable (crude) and multiple logistic regression model estimates for periodontitis associated with gestational diabetes history and diabetes status, age, subgingival calculus, smoking history, and poverty income ratio and in U.S. adult women, NHANES III

Independent variables	Odds ratios and 95% confidence intervals (in parentheses)				
	Crude	Model 1	Model 2	Model 3	Model 4A
GDM history and diabetes status					
GDM+DM+	8.7 (2.5, 29.8)	8.4 (2.3, 29.9)	8.7 (2.0, 37.9)	8.0 (1.9, 32.8)	8.0 (1.7, 37.2)
GDM+DM-	2.0 (0.6, 6.3)	2.4 (0.8, 7.9)	2.9 (0.8, 10.5)	2.9 (0.8, 11.0)	2.7 (0.7, 10.5)
GDM-DM+	2.6 (1.2, 5.6)	2.1 (1.0, 4.5)	1.3 (0.6, 2.9)	1.2 (0.5, 2.6)	1.2 (0.5, 2.7)
GDM-DM-	1.0 (referent)	1.0 (referent)	1.0 (referent)	1.0 (referent)	1.0 (referent)
Age at interview (yrs)		1.03 (1.01, 1.04)	1.02 (1.0, 1.03)	1.01 (1.0, 1.03)	1.02 (1.01, 1.04)
Subgingival calculus (% of teeth)			1.03 (1.03, 1.04)	1.04 (1.03, 1.04)	1.03 (1.02, 1.04)
Smoking history					
Never smoked				1.0 (referent)	1.0 (referent)
Former smoker				1.1 (0.7, 1.7)	1.1 (0.7, 1.9)
Current smoker				0.6 (0.4, 0.9)	0.6 (0.4, 0.9)
Poverty income ratio				0.8 (0.7, 0.9)	0.8 (0.7, 0.9)

Model 4B

Model 4C

with diabetes (GDM-DM+), were significantly more likely to have periodontal disease than those without GDM history and without diabetes (GDM-DM-; odds ratio=8.7; 95% CI: 2.5, 29.8 and odds ratio=2.6; 95% CI: 1.2, 5.6), respectively (Table 2). Women with GDM history and without diabetes (GDM+DM-) were approximately twice as likely to have periodontal disease (Table 2), however the association was not statistically significant ($P=0.2$). A series of multivariable logistic regression analyses, progressively controlling for additional, selected covariates having an established association with periodontal disease (age, presence of sub-gingival calculus, history of smoking, and income; Table 2, Models 1-4A) sustained the significant association of GDM and concomitant diabetes with periodontal disease ($OR_{\text{crude}}=8.7$; $OR_{\text{Model4A}}=8.0$), provided estimates that enhanced the association between GDM+DM- and periodontal disease ($OR_{\text{crude}}=2.0$; $OR_{\text{Model4A}}=2.7$), and attenuated the association for GDM-DM+ ($OR_{\text{crude}}=2.6$; $OR_{\text{Model4A}}=1.2$). The parameter estimates for race/ethnicity were not statistically significant in the multivariable models, hence we did not include race/ethnicity in the models shown in Table 2.

Models 4B and 4c in Table 2 are variations of Model 4A to conduct the analysis with different referent groups. Other than the referent group changing, the models are identical. Model 4B shows that the GDM+DM+ group and the GDM+DM- groups were 6.8 and 2.3 times more likely, respectively, to have periodontal disease than the GDM-DM+ group (referent), however the odds ratio for the GDM+DM- group was not statistically significant. Model 4C uses the group with GDM+DM- as the referent group. It estimates that the GDM+DM+ group is 3 times more likely and both the GDM-DM+ and GDM-DM- groups are less likely to have periodontal disease than the GDM+DM- group, however none of these point estimates are statistically significant as all of the 95% confidence intervals include 1.0.

Discussion

The results from the bivariate analyses demonstrated that the population selected for this study had characteristics similar to those expected in the general population relative to relationships between age, race/ethnicity, income, calculus presence, and the increased prevalence of periodontitis (11). The only variable with unexpected results was smoking, which generally has had a clear association with the prevalence and severity of periodontitis (12, 13). A plausible explanation for this variation in expected results is our inclusion of bleeding on probing as one of our criteria for defining periodontitis. Periodontitis patients who smoke generally have less bleeding on probing than patients with periodontitis who do not smoke. This is considered to be due to changes in peripheral vasculature and the inflammatory response within the periodontal tissues (12). Therefore, inclusion of this variable as a criterion for disease may have resulted in an underestimation of periodontitis in the subjects in this study who were current smokers.

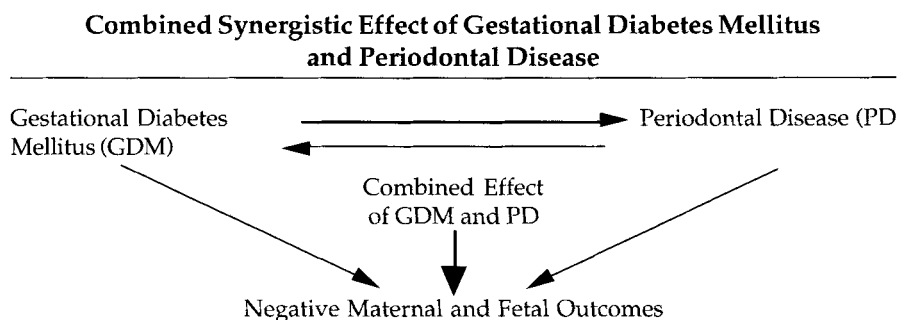
The results support the hypothesis that women with a history of GDM are more likely to have more severe periodontal disease than women with a history of pregnancies without GDM. The odds ratios estimated in the multivariable regression analyses suggest that GDM may lead to a stronger association with periodontal disease presence than diabetes in the absence of GDM history. However, the small sample size in some of the subgroups may have impeded our ability to estimate a statistically significant association in the GDM+DM- group and GDM-DM+ groups. The sample size also precluded testing more extensive multivariable logistic regression models. Nevertheless, our findings provide additional insights to explore that may extend evidence from previous studies documenting that the extent and severity of periodontal disease is increased in patients with type 2 diabetes mellitus (4). The potential significance of our findings relate not only to the oral health

status of women with a history of GDM, but also to overall maternal and fetal health. Periodontal disease and GDM can independently have a negative impact on both the mother and the fetus. Negative maternal outcomes associated with GDM include pre-eclampsia (hypertension), premature rupture of membranes and Caesarean section (14-16). There is also recent evidence to support an association between GDM and an increased risk of spontaneous preterm birth (17). In that cohort study, the risk of spontaneous preterm birth increased with increasing levels of pregnancy glycemia, even after adjusting for other perinatal complications such as age, race-ethnicity, preeclampsia-eclampsia-pregnancy-induced hypertension, chronic hypertension, polyhydramnios and birth weight for gestational age. While these results were inconsistent with three previous studies (18-20), they were consistent with a study by Yang *et al.* (3), in which 102 women with impaired glucose tolerance were at increased risk of preterm birth. Therefore, although the results are not unequivocal, women with GDM may be at greater risk for preterm birth than women without GDM.

The associations between periodontal infection, inflammation and pregnancy have been well documented. "Pregnancy gingivitis" characterized by erythema, edema, hyperplasia and increased bleeding, occurs in approximately 30-100% of pregnant women (21). Increased tissue edema may lead to increased pocket depths and subsequent increased tooth mobility (22). There are alterations in the subgingival microflora during pregnancy, with increases in anaerobic to aerobic ratios occurring in addition to *Bacteroides melaninogenicus* and *Prevotella intermedia* proportions (23). These increases may be related to hormonal alterations, specifically elevated levels of estradiol or progesterone.

The relationship between diabetes and periodontal disease has received considerable attention. In general, studies support the concept that uncontrolled diabetes, especially type 2

Figure 1



diabetes, will increase the severity and extent of periodontal destruction. Both type 1 diabetes and type 2 diabetes are major risk factors for the development of periodontal disease. Further, there is epidemiological and clinical evidence to support periodontal disease having an adverse effect on glycemic control in diabetes (4, 24).

An increase in the severity and extent of periodontal disease in pregnancy has been shown to be significantly associated with negative birthing outcomes, especially gestational age and fetal birth weight resulting in an increased incidence of preterm birth and delivery of low birth weight infants in women with periodontitis. There have been a series of clinical studies over the past 8-10 years that have explored the relationship between periodontal infection, inflammation and disease and preterm birth and low birth weight. The first case controlled study was published in 1996 (25) and showed an association between severe periodontal disease, preterm birth, and low birth weight with an odds ratio greater than 7. The most recent case-control study (6) showed an association between severe periodontitis and spontaneous preterm birth with an odds ratio of 3.5. A meta-analysis of 2 case-control studies and 3 prospective cohort studies published through August 2002 found pregnant women with periodontal disease had significantly greater risks for preterm birth and preterm low birth weight babies than women without periodontal disease (5). One published pilot randomized clinical trial reported a reduction in pre-term birth in women receiving periodontal scaling and root planing

compared to those receiving a dental prophylaxis only and to women in an untreated reference group drawn from the same population as the participants in the randomized clinical trial (26).

There is current evidence that both GDM and periodontitis can independently lead to negative birthing outcomes and that diabetes can increase the severity and extent of periodontitis. Our analysis of NHANES III data suggests that women who experience GDM during their pregnancy have more severe periodontal disease than women who have experienced a normal pregnancy without GDM. We hypothesize that the presence of both these diseases can result in a combined synergistic effect that exacerbates the negative impact of GDM on pregnant women and their children. (Figure 1). A logical and important next step is to assess the relationship between periodontal disease and GDM concurrently, i.e. following women at the time of their pregnancy, and to evaluate the impact of any effect of combined GDM and periodontitis on negative outcomes for the mother and fetus. Further prospective cohort studies are currently underway to address this hypothesis.

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