

The Additive Effects of Gestational Diabetes and
Periodontal Disease on the Risk for Adverse
Pregnancy Outcomes

by

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List of Abbreviations

AGE: Advanced glycation end-products

BoP: Bleeding on probing

CAL: Clinical attachment loss

CI: Confidence interval

Ig: Immunoglobulin

IL: Interleukin

MMP: Matrix metalloproteinase

NHANES: National Health and Nutrition Examination Survey

PD: Pocket depth

PGE: Prostaglandin

SE: Standard error

TNF: Tumor necrosis factor

Abstract

The Additive Effects of Gestational Diabetes and Periodontal Disease on Adverse Pregnancy Outcomes

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Co-Chairs: Sioban D. Harlow and George W. Taylor

This dissertation assesses the potential interaction between periodontal disease and gestational diabetes on the risk for adverse pregnancy outcomes. As chronic disease increases among women of reproductive age, understanding how chronic conditions manifest during pregnancy is of emerging public health importance. Gestational diabetes and periodontal disease are conditions associated with increased risks for adverse pregnancy outcomes. Poor glycemic control in persons with diabetes worsens periodontal disease while periodontal disease complicates glycemic control. Evidence suggests this inter-relationship between diabetes and periodontal disease extends to gestational diabetes. The independent effects of gestational diabetes and periodontal disease on adverse pregnancy outcomes have been studied but their joint effects have not.

Gestational diabetes and periodontal disease increase the risk for pre-eclampsia. Gestational diabetes increases the risk for fetal macrosomia while periodontal disease increases the risk for fetal growth restriction. These maternal and infant morbidities represent clinical indications for labor induction and cesarean delivery, procedures under significant scrutiny due to their rapid increase in prevalence over the past two decades.

The analyses in this dissertation are based on matched cohort data from the Oral Infection: Impact on Gestational Diabetes study conducted at the University of Kentucky Maternal-Fetal Medicine clinic. The cohort consisted of pregnant women with gestational diabetes who were matched to pregnant women without gestational diabetes. Analyses focus on infant birthweight, pre-eclampsia and the use of obstetric intervention. Based on this study population, women with both gestational diabetes and periodontal disease had the greatest risk for pre-eclampsia and obstetric intervention compared to women with only one condition or neither condition. However, periodontal disease did not yield additional risk for higher infant birthweight beyond the risk conferred by gestational diabetes. The external validity of these results is limited due to the high-risk population served by the clinic.

While gestational diabetes is a recognized clinical indication for high-risk pregnancies, periodontal disease can provide an additional high-risk marker. Clinical strategies that minimize the adverse impact of gestational diabetes and periodontal disease during pregnancy may reduce the prevalence of maternal morbidities and subsequent use of obstetric intervention.

Chapter 1

Introduction

As the prevalence of chronic disease increases throughout the population, the impact of chronic disease in women of reproductive age becomes of greater public health importance due to the potential risk of adverse outcomes for both the mother and infant. Diabetes (Kaaja 1995, Ros 1998, Catalano 1995) and periodontal disease (Barak 2007, Canakci 2007, Contreras 2006) are chronic conditions both associated with increased risk for adverse pregnancy outcomes. While periodontal disease has been decreasing in the population (Borell 2005), the prevalence of diabetes among women of reproductive age has increased (Fagot-Campagna 2000, Rosenbloom 1999). Since poor glycemic control in diabetes can further increase periodontal damage (Grossi 1997, Grossi 1998) and periodontal disease complicates glycemic control (Taylor 1996), the joint effects of these conditions during pregnancy may result in a synergistic increase in the risk for adverse pregnancy outcomes. Thus, the inter-relationship between these two chronic conditions during pregnancy represents an emerging public health concern.

Diabetes prevalence has continued to increase in the adult population, from 5.1 percent in 1988-1994 to 9.3 percent in 1999-2002. Increases in diabetes prevalence have been greater among minority populations (Harris 2001, Cowie 2006). The prevalence of type 2 diabetes was 9.9 percent for the 1999-2006 time period with rates greater in African American and Mexican American populations (Fryar 2010). As type 2 diabetes becomes more prevalent in the young adult population, it plays an increasingly important role as a chronic condition during pregnancy (Fagot-Campagna 2000, Rosenbloom 1999). Pregnancy can initiate an impaired glucose tolerance resulting in gestational diabetes mellitus. Gestational diabetes mellitus is characterized by increased insulin resistance during pregnancy. This increased resistance may result from hormonal factors, gene variants, or autoimmunity targeting pancreatic beta cells. The prevalence of gestational diabetes mellitus varies with the diagnostic criteria used and ranges between 2.9 percent and 8.8 percent in developed countries (Coustan 1995, Magee 1993). In the United States, gestational diabetes complicates approximately four percent of pregnancies (ADA 2006). Obesity is a common risk factor for gestational diabetes mellitus and its prevalence has increased over the past several years among younger women (Wild 2004). As with many other health conditions, minority women and women at lower socioeconomic levels are more likely to develop gestational diabetes mellitus (Narayan 2003, King 1998).

Gestational diabetes mellitus has health implications for both the mother and infant. The impaired glucose tolerance that results from insulin insensitivity

increases maternal blood pressure and places her at risk for pre-eclampsia (Kaaja 1995, Ros 1998). In addition, the insulin insensitivity may not subside after pregnancy, putting the woman at risk for type 2 diabetes (Kim 2002). Infants developing in this hyperglycemic environment are more likely to accrue a greater percentage of body fat and be placed in an extreme birthweight category (Catalano 1995). In addition, the resulting hyperglycemic state has been associated with an increased risk of childhood obesity and early onset of diabetes for the infant (Pettitt 1988). Glycemic control is important to reducing the risks to both the mother and infant that gestational diabetes mellitus confers. Insulin therapy has been effective at reducing the risk of pre-eclampsia in women with gestational diabetes (Alwan 2009) as well as the risk of severe perinatal complications including fetal macrosomia (Jacqueminet 2010). Oral antidiabetic agents have shown similar effectiveness as insulin therapy for the purpose of preventing pre-eclampsia but are currently not recommended as treatment until more studies have evaluated long-term impacts (Jacqueminet 2010). Oral antidiabetic agents have not shown effectiveness for reducing the risk of fetal macrosomia (Alwan 2009). One potentially negative impact of insulin therapy has been an increased likelihood of induced labor, although cesarean delivery rates were not found to have increased (Alwan 2009, Jacqueminet 2010).

The prevalence of periodontal disease among adults 18 years or older was 4.2 percent based on the 1999-2000 National Health and Nutrition Examination Survey (NHANES). NHANES used a similar partial mouth examination in both the 1999-2000 and 1988-1994 iterations of this survey ,

defining periodontal disease as at least three sites with clinical attachment loss of at least four millimeters and at least two sites with pocket depth of at least three millimeters. The 1999-2000 prevalence represented a decrease in periodontal disease from 7.3 percent in NHANES III, conducted between 1988 and 1994 (Borell 2005). This decrease may represent a cohort effect given increased attention to oral health by younger populations and changes in risk factors such as smoking during this time period. However, these national estimates of periodontal disease prevalence may be underestimated as much as 50 percent or greater due to the limitations of a partial mouth measurement (Eke 2010). The prevalence of periodontal disease was more common in socio-economically disadvantaged populations, socio-economically disadvantaged neighborhoods, and among certain demographic groups, notably African Americans and Mexican Americans (Borell 2005, Borell 2006).

In the 1999-2000 NHANES, the prevalence of periodontal disease among adult women was 2.7 percent for Whites, 2.5 percent for Mexican Americans, and 4.9 percent for African Americans (Borell 2005). In general the prevalence of periodontal disease in women was half that of the prevalence of periodontal disease in men. The prevalence of periodontal disease among adults between 18 and 34 years of age, particularly relevant when evaluating periodontal disease among pregnant women, was 1.5 percent among Whites, 1.2 percent among Mexican Americans, and 3.2 percent among African Americans (Borell 2005). Other risk factors for periodontal disease identified through NHANES include not

seeing a dentist recently, lack of dental insurance, cigarette smoking, and advanced age (Borell 2005).

Trials addressing treatment of periodontal disease during pregnancy with the goal of reducing adverse pregnancy outcomes have demonstrated mixed results with a meta-analysis resulting in an overall relative risk for preterm birth of 0.82 with a 95% confidence interval of 0.64 to 1.06 (Polyzos 2009). While not statistically significant based upon rigid standard application of p-value testing, the overall potential benefit may be underestimated as treatment may occur too late during pregnancy to have an impact for some women. The treatment itself leads to a temporary increase in bacterial products, and more than one treatment may be necessary. Studies have not addressed pre-conceptual treatment of periodontal disease (Xiong 2011).

Relationship between periodontal disease, glycemic control, and gestational diabetes mellitus.

Significant hormonal changes occur during pregnancy. These changes can trigger gestational diabetes mellitus, but can also increase sensitivity of the periodontium. An inflammatory relationship between periodontal disease and glycemic control has been proposed by Grossi and colleagues as demonstrated in Figure 1.1 (Grossi 1998) and recently updated (Lalla 2011). Under this model, the periodontal pathophysiologic proinflammatory processes and the release of endotoxins and cell membrane products from periodontal pathogens provide a mechanism by which insulin resistance may be initiated thus leading to increased

glycosylation of proteins. The host response to the periodontal pathogens may be more important than the level of bacterial challenge (Lalla 2006). Persons with diabetes are more likely to have exaggerated immune responses to periodontal pathogens (Salvi 2005). The secretion of proinflammatory factors to overall systemic inflammation may contribute to degradative processes damaging connective tissues. The increased glycosylation of proteins and the body's immune response to removal of these glycosylated materials feeds both the proinflammatory processes observed with diabetes as well as periodontal connective tissue degradation.

Infections of the periodontium have been associated with poor glycemic control (Taylor 1996). Likewise, treatment of periodontal disease has demonstrated improvements in glycemic control (Grossi 1997). Glycemic control is an important component of improving the health outcomes for mother and infant during the pregnancy of a woman with gestational diabetes mellitus. If periodontal disease complicates glycemic control, women with both comorbidities may be at an even greater risk of insulin insensitivity. Thus women with gestational diabetes mellitus and periodontal disease may be at an increased risk of delivering an extreme birthweight infant or developing pre-eclampsia than women with gestational diabetes mellitus alone. According to NHANES III, the prevalence of periodontal disease in women with gestational diabetes mellitus was 44.8 percent compared to 13.2 percent in nondiabetic pregnant women under a relaxed definition of periodontal disease (Xiong 2006). Under a more restrictive definition, it was found that among nondiabetic women with a history of

gestational diabetes mellitus the prevalence of periodontal disease was 9.0 percent and that among diabetic women with a history of gestational diabetes mellitus the prevalence of periodontal disease was 30.5 percent (Novak 2006).

Periodontal disease, inflammation, and the relationship to adverse pregnancy outcomes.

Periodontal infection can also elevate systemic inflammation markers. Periodontal disease has several pathogenic origins; *Actinobacillus actinomycetemcomitans*, *Streptococcus intermedius*, *Porphyromonous gingivalis*, *Prevotella intermedia*, and *Prevotella nigrescens* are just a few of the bacteria implicated in this destructive process. During the infectious process, gingival crevicular fluid is secreted as a response to pathogens in the mouth. This fluid consists of a large number of polymorphonuclear leukocytes, C3 and C4 complement, T cells, and B cells which have been recruited to fight the infectious process (Ebersole 2003). The result of this response to these pathogens includes systemic changes. Elevated antibody levels in the gingival crevice fluid correspond to elevated systemic levels of IgG in the individual (Ebersole 2003). During destructive periodontal disease, systemic levels of prostaglandins (PGE-2), interleukins (IL-1, IL-6, IL-8), and tumor necrosis factor alpha (TNF- α) are all elevated in the serum (Fujihashi 1994, Takahashi 1994).

Women have an increased susceptibility to the effect of periodontal infection during pregnancy. Progesterone hormones during pregnancy increase the vascular permeability of blood vessels which may increase the amount of

infectious material that can enter the bloodstream from the mouth (Amar 1994). Inflammatory markers elevated by periodontal disease are similar to elevated inflammatory markers found in women who have given birth to premature or low birthweight infants. Maternal serum markers of IL-6, IL-8, and TNF- α were all elevated in women who delivered premature or to a low birthweight infant (Hasegawa 2003). While the periodontal pathogens have not been found in the amnion, amniotic fluid levels of IL-6 and PGE-2 were both higher for premature births (Dortbudak 2004). Periodontal therapy during pregnancy has been demonstrated to reduce the levels of PGE-2 in the mother's serum (Yalcin 2002). Lastly, for women who failed to mount an effective response to certain periodontal pathogens, the corresponding fetal IgM response to periodontal pathogens measured in fetal cord samples was significantly elevated (Madianos 2001).

The hyperinflammatory process that results from periodontal disease may increase the risk of pre-eclampsia. Pre-eclampsia is the onset of hypertension and proteinuria after twenty weeks gestation in a previously normotensive, nonproteinuric pregnant woman. This positive relationship between periodontal disease and pre-eclampsia has been demonstrated in most (Barak 2007, Canakci 2007, Contreras 2006, Canakci 2004) but not all (Khader 2006) of the studies that have addressed it. Women with pre-eclampsia were more likely to have periodontal disease than women who did not have pre-eclampsia (Canakci 2004, Contreras 2006). Presence of periodontal pathogens has also been associated with an increased risk of pre-eclampsia (Contreras 2006). Placental

tissues of pre-eclamptic women were also more likely to test positive for periodontal pathogens than placental tissues of women who did not experience pre-eclampsia (Barak 2007). Inflammatory markers associated with the periodontal disease and infant health outcomes relationships were also elevated in women with pre-eclampsia compared to women without pre-eclampsia (Canakci 2007). In addition, it has been shown that if the periodontal status of the mother worsens during the course of the pregnancy, there is an even greater risk of developing pre-eclampsia (Boggess 2003). If both periodontal disease and gestational diabetes mellitus can independently increase the risk of pre-eclampsia, then in combination, these two risk factors may be associated with an even greater risk of pre-eclampsia.

Public health significance of adverse pregnancy outcomes

Adverse pregnancy outcomes include outcomes that are deleterious or potentially deleterious to the health of the mother or infant either during pregnancy, at the time of delivery, or in the postnatal period. Pre-eclampsia occurs in five percent to seven percent of all pregnancies and represents a potential increased risk for hemorrhage during pregnancy, seizures, and maternal mortality (Walker 2000). Pre-eclampsia, depending on its severity, may necessitate the early induction of labor or cesarean delivery to reduce these risks as the only cure for pre-eclampsia is delivery of the infant though risks can persist shortly after delivery (Lain 2002). Risk factors may vary based upon whether pre-eclampsia occurred early or late in pregnancy (Valensise 2008). In

addition to gestational diabetes and periodontal disease, increasing body mass index, advanced maternal age, first pregnancy are all associated with an increase in the risk of pre-eclampsia (Bodnar 2005, Duckitt 2005, Luo 2007) while smoking has been associated with a decreased risk (Conde-Agudelo 1999).

Commonly assessed adverse pregnancy outcomes for infants include prematurity and birthweight. While low birthweight and premature birth have received almost exclusive focus in the scientific literature, high birthweight infants also pose potential challenges during pregnancy. High birthweight infants, occurring in 7.6 percent of births in 2008 (Martin 2010), increase the likelihood of birth trauma (Vidarsdottir 2011, Zhang 2008). In response to suspected fetal macrosomia, the use of obstetric interventions such as cesarean section or early induction increase (Vidarsdottir 2011, Zhang 2008). In addition, high birthweight infants may have an increased risk for childhood obesity, and diabetes (Mehta 2011, Pettit 1988). Gestational diabetes and associated biomarkers of diabetes have been linked to increased risk of fetal macrosomia, even when insulin sensitivity falls below clinical thresholds for gestational diabetes. Periodontal disease has been assessed as a potential risk factor for low birthweight with mixed results (Marin 2005, Moliterno 2005, Moore 2004, Lunardelli 2005, Uppal 2010, Michalowicz 2006), but no relationship between periodontal disease and high infant birthweight has been assessed. Pre-pregnancy body mass index has been identified as a potential risk factor for delivery of a high birthweight infant (Kabali 2007, Rosenberg 2003), but its effect may be mediated by gestational

diabetes as increasing body mass index is associated with increasing maternal glucose levels (Torloni 2008, Kim 2010).

Suspected fetal macrosomia, fetal distress, and pre-eclampsia represent just a few of the potential clinical indications for obstetric intervention (ACOG 2009, Lagrew 2006, Barber 2011). As these two adverse outcomes are associated with gestational diabetes and periodontal disease, they may also indirectly lead to an increase in the use of obstetric intervention at delivery. Obstetric interventions such as cesarean sections and labor inductions have increased substantially in the past few decades. Cesarean deliveries occurred in 32.9 percent of births in 2009 representing a nearly 60 percent increase since 1996 (Hamilton 2010). The relationship between cesarean delivery and gestational diabetes varies by race with racial and ethnic minorities more likely to deliver by cesarean section compared to Whites based on a study of birth certificates in New York City but the differences in effect size do not support different thresholds for treatment of gestational diabetes to prevent cesarean delivery (Mocarski 2011). Labor induction occurred in 22.5 percent of births in 2006, more than double the rate from 1990 (Martin 2009). African American women were more likely to have late preterm induction of labor than non-Hispanic White women, while Hispanic women were less likely to have late preterm induction of labor compared to non-Hispanic White women (Murthy 2011). Indications for labor induction include but are not limited to pre-eclampsia, premature rupture of membranes, gestational diabetes, fetal conditions such as severe intrauterine growth restriction and congenital

anomalies, and need for post-term delivery (ACOG 2009, Gulmezoglu 2006, Joseph 2007, Spong 2011). Fetal macrosomia, however, is not a clinical indication for labor induction (Sanchez-Ramos 2002, ACOG 2009).

While both cesarean section and labor induction help to alleviate the risks posed by maternal morbidities such as pre-eclampsia and may prevent or alleviate infant morbidities such as fetal macrosomia, these procedures carry their own potential risks. Cesarean sections involve longer recovery times in the hospital, have greater risks of hospital-borne infections as a result of the surgery and recovery period, increase the risk of maternal mortality, and often lead to repeat cesarean sections for subsequent pregnancies (Smaill 2002, Hofmeyr 2001, Deneux-Tharaux 2006, Minkoff 2003, Hemminki 1996). Labor induction increases the likelihood of uterine rupture in the mother and has important implications for the infant as well (ACOG 2009). Early labor induction can result in a premature infant who may need substantial neonatal intensive care services and has a greater risk of infant mortality (Reddy 2009, Spong 2011).

While much of the controversy about use of obstetric interventions at delivery focuses on the electivity of such procedures, it is important to evaluate the impact of changes in the prevalence of risk factors that necessitate intervention on the growing trend of obstetric intervention. Understanding the full contribution of maternal risk factors to the need for obstetric intervention may provide useful information in this debate (Janakiraman 2010). If periodontal disease does increase the risk of adverse outcomes that are associated with clinically indicated induction and cesarean section, then periodontal disease may

have indirect effects of increasing the rate of cesarean section. Trends in the prevalence of periodontal disease among pregnant women should be taken into account when assessing trends in cesarean section and labor induction.

Potential for confounding in relationships between periodontal disease, gestational diabetes mellitus and adverse pregnancy outcomes.

Sociodemographic risk factors are also important to consider in relationships between periodontal disease, gestational diabetes and adverse pregnancy outcomes. Women with gestational diabetes mellitus are likely to be older than women without gestational diabetes mellitus. Likewise, hypertensive disorders are more likely to occur to women at older ages. Women of lower socioeconomic status are more likely to experience numerous chronic health conditions compared to higher socioeconomic status women (Narayan 2003, King 1998). Women at lower socioeconomic levels tend to have poorer maternal and infant health outcomes than women at higher socioeconomic levels (Gazmararian 1996). The effects of obesity, diabetes, and specifically maternal glucose levels on adverse pregnancy outcomes may also differ among persons of different races and/or ethnicities (Rosenberg 2005, Steinfeld 2000, Scholl 2002).

Smoking and tobacco use are important confounders in the relationship between periodontal disease, gestational diabetes, and adverse pregnancy outcomes. Smoking may interact with periodontal disease to increase the effect of periodontal disease beyond that conferred by periodontal disease alone as evidenced by previous studies on the relationship between periodontal infection

and systemic disease (Hyman 2002). Persons who use tobacco in its various forms are at an increased risk for periodontal disease (Albandar 2000). Tobacco use is also associated with an increased risk for low birthweight infants but a decreased risk for pre-eclampsia (Conde-Agudelo 1999, Floyd 1993). As a result, relationships between periodontal disease and either high birthweight infants or pre-eclampsia may be negatively confounded by the effect of tobacco use.

Obesity is another potential confounder to consider in the relationship between periodontal disease and high birthweight. Obese persons are more likely to have periodontal disease and gestational diabetes (Pischon 2007). Maternal obesity is associated with increased infant birthweight (Cnattingius 1998, Ovesen 2011). Similarly, obese women are more likely to experience pre-eclampsia (Cunningham 2002) and deliver by cesarean section (Ovesen 2011). While these relationships may suggest confounding, much of the effect of obesity may be mediated through gestational diabetes. Thus, adjusting for maternal obesity may over-control for much of the direct effect gestational diabetes may have on pregnancy outcomes. Every unit of body mass index is associated with an ever greater increased likelihood of developing gestational diabetes (Torloni 2009). Subclinical gestational diabetes is associated with increased risk of adverse outcomes such as greater infant birthweight (HAPO 2008). The population attributable fraction of gestational diabetes cases associated with obesity is estimated at 46 percent which means that nearly half of all cases of gestational diabetes could be prevented by reducing the pre-pregnancy weight of

overweight and obese women to normal weight ranges (Kim 2010). Thus it is unclear if obesity has an independent effect on adverse pregnancy outcomes other than its effect as mediated through gestational diabetes.

Nutritional intake (Ritchie 2003) and physical activity (Al-Zahrani 2005) can both influence periodontal disease and its progression, and the resulting poor oral health may lead to dietary changes to less healthy food choices (Al-Zahrani 2006, Enwonwu 2007). Nutritional intake (Rode 2007) and physical activity (Perkins) can affect weight gain and ultimately the birthweight of the infant.

In summary, the growing body of evidence demonstrating the inter-relationship of diabetes mellitus and periodontal disease appears to extend into pregnancy and the relationship between gestational diabetes and periodontal disease. However, it is unknown whether the combined effects of gestational diabetes and periodontal disease increase the risk of adverse pregnancy outcomes beyond the effects of either condition alone. This dissertation examined the relationship between periodontal disease and gestational diabetes mellitus by examining the impact of periodontal disease on the adverse pregnancy outcomes of high birthweight infants and pre-eclampsia – two conditions currently associated with gestational diabetes mellitus. In addition this research examined the indirect impact that periodontal disease may have on obstetric interventions associated with these adverse pregnancy outcomes.

Study Hypotheses

Most studies of the association between periodontal disease and maternal and infant health outcomes exclude women with gestational diabetes mellitus. However, periodontal disease and gestational diabetes mellitus may interact on inflammation and glycemic control to further enhance the risk of several maternal and infant health outcomes. Thus, the combined effect of the two conditions may be greater than either single condition alone, in which case, assessment of multiple inflammatory conditions during pregnancy and how they interact may provide greater understanding as to the role of inflammation in the development of adverse pregnancy outcomes. Figure 1.2 represents the theorized relationship between gestational diabetes and adverse pregnancy outcomes and their potential indirect effect on the need for obstetric intervention.

To evaluate the combined effect of periodontal disease and gestational diabetes on adverse pregnancy outcomes as a proxy for the continuous nature of the relationship between inflammation and adverse pregnancy outcomes, this dissertation assessed the relationship between periodontal disease and both infant and maternal health outcomes in women with gestational diabetes compared to women without gestational diabetes mellitus. These objectives include assessing the contributions of periodontal disease and gestational diabetes to the risk of delivering a high birthweight infant, to the risk of developing pre-eclampsia, and to the likelihood that a woman will use obstetric intervention at delivery.

Based on previous studies of the relationships between gestational diabetes, periodontal disease, and infant birthweight, I hypothesize that

periodontal disease increases the risk of delivering a high birthweight infant in women with gestational diabetes mellitus but does not increase the risk of delivering a high birthweight infant in women without gestational diabetes mellitus (Table 1.1).

Based on prior studies evaluating the relationships between gestational diabetes, periodontal disease and pre-eclampsia, I hypothesize that the risk of pre-eclampsia is higher in women with gestational diabetes compared to women without gestational diabetes, that the risk of pre-eclampsia is higher in women with periodontal disease compared to women without periodontal disease, and that the risk of pre-eclampsia is higher when both periodontal disease and gestational diabetes are present compared to either condition such that multiplicative interaction exists (Table 1.2).

I also hypothesize that women with periodontal disease are more likely to use obstetric interventions for delivery than women without periodontal disease, that women with gestational diabetes are more likely to use obstetric intervention compared to women without gestational diabetes, and that women with both conditions of periodontal disease and gestational diabetes are more likely to use obstetric intervention than women who have either condition alone such that multiplicative interaction exists.

In summary, through testing of these hypotheses, the relationship between gestational diabetes, periodontal disease, and how they may interact with one another to influence adverse pregnancy outcomes and associated use of obstetric interventions will become clearer. The potential combined effects of

these morbidities during pregnancy may help inform an underlying pathophysiological understanding of the inter-relatedness of these two conditions. Gestational diabetes is already viewed as a potential risk factor for adverse maternal and infant health outcomes while the role of periodontal disease still is disputed. However, if evidence for periodontal disease supports its risk factor status, periodontal disease would be a potentially modifiable risk factor whose treatment or alleviation may ultimately reduce adverse outcomes. Periodontal disease in to the presence of gestational diabetes may identify a subgroup of high risk pregnancies to which targeted interventions may be developed. Evaluations of the effect of these conditions on more distal outcomes such as the use of obstetric intervention, recognizes that the influence of chronic diseases during pregnancy have sequential impacts for mother and infant.

The methods for analyzing the effect of gestational diabetes, periodontal disease, and their interaction on the outcomes of infant birthweight, pre-eclampsia, and obstetric intervention are detailed in Chapter two. The results of the analyses specific to infant birthweight both as a categorical outcome and as a continuous outcome are illustrated in Chapter three. Chapter four contains the results of the analysis focusing on the maternal morbidity of pre-eclampsia, and Chapter five addresses the potential increased use of obstetric intervention as a result of gestational diabetes and periodontal disease. The results from each chapter of this dissertation are summarized in context with one another in Chapter six along with the public health implications of these results.

Figures and Tables

Figure 1.1: Original proposed model for 2-way relationship between periodontal disease and diabetes mellitus (Grossi 1998).

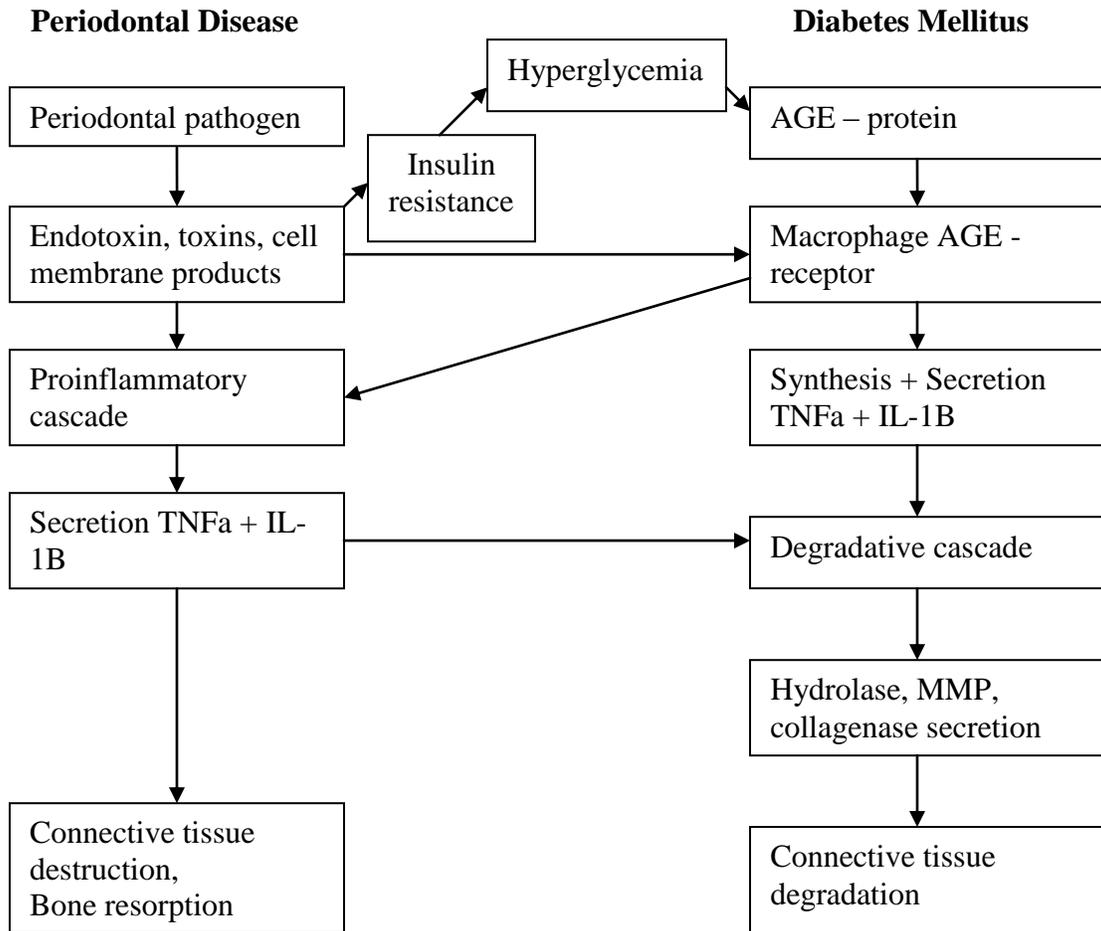


Figure 1.2: Conceptual diagram of the proposed hypotheses relating the interaction between periodontal disease and gestational diabetes mellitus on outcomes of interest.

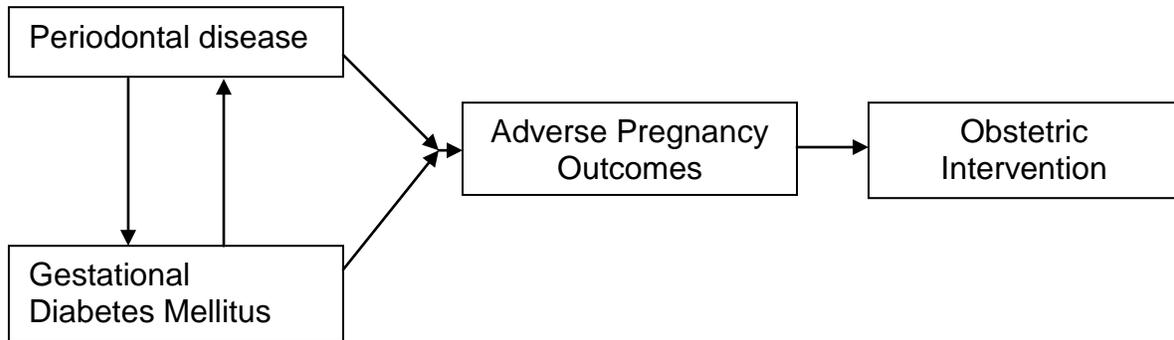


Table 1.1: Hypothesized increase in risk of delivering a high birthweight infant among women with and without gestational diabetes mellitus and periodontal disease.

Group	Periodontal Disease	Gestational Diabetes	Risk of High Birthweight Infant
A	(-)	(-)	Reference group
B	(+)	(-)	No increased risk
C	(-)	(+)	Increased risk associated with gestational diabetes
D	(+)	(+)	Increased risk associated with both periodontal disease and gestational diabetes

Table 1.2: Hypothesized increase in risk of pre-eclampsia among women with and without gestational diabetes mellitus and periodontal disease.

Group	Periodontal Disease	Gestational Diabetes	Risk of Pre-eclampsia
A	(-)	(-)	Reference group
B	(+)	(-)	Increased risk associated with periodontal disease
C	(-)	(+)	Increased risk associated with gestational diabetes
D	(+)	(+)	Increased risk associated with both gestational diabetes and periodontal disease

Table 1.3: Hypothesized increase in risk of the use of obstetric intervention among women with and without gestational diabetes mellitus and periodontal disease.

Group	Periodontal Disease	Gestational Diabetes	Risk of Using Obstetric Intervention
A	(-)	(-)	Reference group
B	(+)	(-)	Increased risk associated with periodontal disease
C	(-)	(+)	Increased risk associated with gestational diabetes
D	(+)	(+)	Increased risk associated with both gestational diabetes and periodontal disease

References

- (ACOG) American College of Obstetricians and Gynecologists. ACOG Practice Bulletin - Clinical management guidelines for obstetrician-gynecologists: Induction of labor. *Obstetrics & Gynecology*. 2009;114:386-397.
- (ADA) American Diabetic Association. Diagnosis and classification of diabetes mellitus. *Diabetes Care*. 2006;29S1:543-548.
- Albandar JM, Streckfus CF, Adesanya MR, Winn DM. Cigar, pipe, and cigarette smoking as risk factors for periodontal disease and tooth loss. *Journal of Periodontology*. 2000;71:1874-81.
- Alwan N, Tuffnell DJ, West J. Treatments for gestational diabetes. *Cochrane Database of Systematic Reviews*. 2009. Issue 3.
- Al-Zahrani MS. Increased intake of dairy products is related to lower periodontitis prevalence. *Journal of Periodontology*. 2006;77(2):289-94.
- Al-Zahrani MS, Borawski EA, Bissada NF. Increased physical activity reduces the prevalence of periodontitis. *Journal of Dentistry*. 2005;33(9):703-710.
- Amar S, Chung KM. Influence of hormonal variation on the periodontium in women. *Periodontology 2000*. 1994;6:79-87.
- Barak S, Oettinger-Barak O, Machtei EE, Sprecher H, Ohel G. Evidence of periopathogenic microorganisms in placentas of women with pre-eclampsia. *Journal of Periodontology*. 2007;78(4):670-6.
- Barber EL, Lundsberg LS, Belanger K, Pettker CM, Funai EF, Illuzzi JL. Indications contributing to the increasing cesarean delivery rate. *Obstetrics & Gynecology*. 2011;118(1):29-38.
- Bodnar LM, Ness RB, Harger GF, Roberts JM. Inflammation and triglycerides partially mediate the effect of prepregnancy body mass index on the risk of preeclampsia. *American Journal of Epidemiology*. 2005;162:1198-1206.
- Boggess KA, Lief S, Murtha AP, Moss K, Beck J, Offenbacher S. Maternal periodontal disease is associated with an increased risk for pre-eclampsia. *Obstetrics & Gynecology*. 2003;101(2):227-1.
- Borell LN, Burt BA, Warren RC, Neighbors HW. The role of individual and neighborhood social factors on periodontitis: the third National Health and Nutrition Examination Survey. *Journal of Periodontology*. 2006;77:444-53.

- Borrell LN, Burt BA, Taylor GW. Prevalence and trends in periodontitis in the USA: from the NHANES III to the NHANES, 1988 to 2000. *Journal of Dental Research*. 2005;84:924-30.
- Canakci V, Canakci F, Canakci H, Canakci E, Cicek Y, Ingec M, Ozgoz M, Demir T, Dilsiz A, Yagiz H. Periodontal disease as a risk factor for pre-eclampsia: a case control study. *Australia and New Zealand Journal of Obstetrics & Gynecology*. 2004;44(6):568-73.
- Canakci V, Canakci CF, Yildirim A, Ingec M, Eltas A, Erturk A. Periodontal disease increases the risk of severe pre-eclampsia among pregnant women. *Journal of Clinical Periodontology*. 2007;34(8):639-45.
- Catalano P, Drago NM, Amini SB. Factors affecting fetal growth and body composition. *American Journal of Obstetrics & Gynecology*. 1995;172:1459-63.
- Cnattingius S, Bergstrom R, Lipworth L, et al. Prepregnancy weight and the risk of adverse pregnancy outcomes. *New England Journal of Medicine*. 1998;338:147-52.
- Conde-Agudelo A, Althabe F, Belizan JM, et al. Cigarette smoking during pregnancy and risk of pre-eclampsia: a systematic review. *American Journal of Obstetrics & Gynecology*. 1999;181(4):1026-35.
- Contreras A, Herrera JA, Soto JE, Arce RM, Jaramillo A, Botero JE. Periodontal disease is associated with pre-eclampsia in pregnant women. *Journal of Periodontology*. 2006;77(2):182-8.
- Coustan, DR. Gestational diabetes. In: Diabetes in America. 2nd edition. National Institutes of Health, Baltimore, Maryland. 1995;703-717.
- Cowie CC, Rust KF, Byrd-Holt DD, et al. Prevalence of diabetes and impaired fasting glucose in adults in the US population: National Health and Nutrition Examination Survey 1999-2002. *Diabetes Care*. 2006;29:1263-8.
- Cunningham FG, Gant NF, Leveno KJ, et al. Hypertensive disorders in pregnancy. In: Cunningham FG, Gant NF, et al., eds. Williams Obstetrics. 21st edition. New York, NY: McGraw-Hill; 2001:567-618.
- Deneux-Tharoux C, Carmona E, Bouvier-Colle MH, Breart G. Postpartum maternal mortality and cesarean delivery. *Obstetrics & Gynecology*. 2006;108(3):541-48.
- Dortbudak O, Eberhardt R, Ulm M, Persson GR. Periodontal disease, a marker

- of risk in pregnancy for preterm birth. *Journal of Clinical Periodontology*. 2004;32:45-52.
- Duckitt K, Harrington D. Risk factors for pre-eclampsia at antenatal booking: systematic review for controlled studies. *British Medical Journal*. 2005;330(7491):565.ePub.
- Ebersole JL. Humoral immune responses in gingival crevice fluid: local and systemic implications. *Periodontology 2000*. 2003;31:135-66.
- Eke PI, Thornton-Evans GO, Wei L, Borgnakke WS, Dye BA. Accuracy of NHANES periodontal examination protocols. *Journal of Dental Research*. 2010;89(11):1208-13.
- Enwonwu CO, Ritchie CS. Nutrition and inflammatory markers. *Journal of the American Dental Association*. 2007;138(1):70-3.
- Fagot-Campagna A, Pettitt DJ, Engelgau MM, et al. Type 2 diabetes among North American children and adolescents: an epidemiologic review and a public health perspective. *Journal of Pediatrics*. 2000;136:664-72.
- Floyd RL, Rimer BK, Giovino GA, Mullen PD, Sullivan SE. A review of smoking in pregnancy: effects on pregnancy outcomes and cessation efforts. *Annual Review of Public Health*. 1993;14:379-411.
- Fryar CD, Hirsch R, Eberhardt MS, Yoon SS, Wright JD. Hypertension, high serum total cholesterol, and diabetes: racial and ethnic prevalence differences in US adults, 1999-2006. NCHS data brief, no 36. Hyattsville, MD: National Center for Health Statistics. 2010.
- Fujihashi K, McGhee JR, Yamamoto M, Beagley KW, Kiyono H. Cytokines networks and immunoglobulin synthesis in inflamed gingival tissues. *Molecular Pathogenesis of Periodontal Disease*. Washington DC, American Society of Microbiology. 1994:57-68.
- Grossi SG, Genco RJ. Periodontal disease and diabetes mellitus: a two-way relationship. *Annals of Periodontology*. 1998;3(1):51-61.
- Grossi SG, Skrepcinski FB, DeCaro T, Robertson DC, Ho AW, Dunford RG, Genco RJ. Treatment of periodontal disease in diabetics reduces glycosylated hemoglobin. *Journal of Periodontology*. 1997;68(8):713-19.
- Gulmezoglu AM, Crowther CA, Middleton P. Induction of labour for improving birth outcomes for women at or beyond term. *Cochrane Database of Systematic Reviews*. 2006. Issue 4.

- HAPO Study Cooperative Research Group. Hyperglycemia and adverse pregnancy outcomes. *New England Journal of Medicine*. 2008;358:1991-2002.
- Harris MI, Flegal KM, Cowie CC, et al. Prevalence of diabetes, impaired fasting glucose, and elevated HbA1c in US adolescents: the Third National Health and Nutrition Examination Survey. *Diabetes Care*. 2001;24:834-7.
- Hasegawa K, Furuichi Y, Shimotsu A, Nakamura M, Yoshinaga M, Kamitomo M, Hatae M, Maruyama I, Izumi Y. Associations between systemic status, periodontal status, serum cytokine levels, and delivery outcomes in pregnant women with a diagnosis of threatened premature labor. *Journal of Periodontology*. 2003;74:1764-70.
- Hemminki E, Merilainen J. Long-term effects of cesarean sections: ectopic pregnancies and placental problems. *American Journal of Obstetrics & Gynecology*. 1996;174:1569-74.
- Hofmeyr GJ, Hannah ME. Planned cesarean section for term breech delivery. *Cochrane Database of Systematic Reviews*. 2001;12:CD000166.
- Hyman JJ, Winn DM, Reid BC. The role of cigarette smoking in the association between periodontal disease and coronary heart disease. *Journal of Periodontology*. 2002;73:988-94.
- Jacqueminet S, Jannot-Lamotte MF. Therapeutic management of gestational diabetes. *Diabetes & Metabolism*. 2010;36:658-71.
- Joseph KS. Theory of obstetrics: an epidemiologic framework for justifying medically indicated early delivery. *BMC Pregnancy and Childbirth*. 2007;7:1-15.
- Kaaja R, Tikkanen M, Viinikka L, Ylikorkkala O. Serum lipoproteins, insulin and urinary excretion of prostanoid metabolites in normal and hypertensive pregnant women. *Obstetrics & Gynecology*. 1995;85:353-6.
- Kabali C, Werler MM. Prepregnancy body mass index, weight gain and the risk of delivering large babies among non-diabetic mothers. *International Journal of Gynaecology & Obstetrics*. 2007;97(2):100-104.
- Khader YS, Jibreal M, Al-Omiri M, Amarin Z. Lack of association between periodontal parameters and pre-eclampsia. *Journal of Periodontology*. 2006;77(10):1681-7.
- Kim C, Newton K, Knopp R. Gestational diabetes and the incidence of type 2 diabetes: a systematic review. *Diabetes Care*. 2002;25:1862-68.

- Kim SY, England L, Wilson HG, Bish C, Satten GA, Dietz P. Percentage of gestational diabetes mellitus attributable to overweight and obesity. *American Journal of Public Health*. 2010;100:1047-52.
- King H. Epidemiology of glucose intolerance and gestational diabetes in women of childbearing age. 1998. *Diabetes Care*. 21(S2):B9-B13.
- Lagrew DC, Bush MC, McKeown AM, Lagrew NG. Emergent (crash) cesarean delivery: indications and outcomes. *American Journal of Obstetrics & Gynecology*. 2006;194(6):1638-43.
- Lalla E, Papapanou PN. Diabetes mellitus and periodontitis: a tale of two common interrelated diseases. *Nature Reviews, Endocrinology*. 2011;7:738-48.
- Lalla E. Periodontal infection profiles in type 1 diabetes. *Journal of Clinical Periodontology*. 2006;33:855-62.
- Lain KY, Roberts JM. Contemporary concepts of the pathogenesis and management of preeclampsia. *JAMA*. 2002;287:3183-86.
- Lunardelli AN, Peres MA. Is there an association between periodontal disease, prematurity and low birth weight? A population-based study. *Journal of Clinical Periodontology*. 2005;32:938-46.
- Luo ZC, An N, Xu HR, Larante A, Audibert F, Fraser WD. The effects and mechanisms of primiparity on the risk of pre-eclampsia: a systematic review. 2007;21(S1):36-45.
- Madianos PN, Lieff S, Murtha AP, Boggess KA, Auten Jr RL, Beck JD, Offenbacher S. Maternal periodontal disease and prematurity. Part II: maternal infection and fetal exposure. *Annals of Periodontology*. 2001;6:175-82.
- Magee MS, Walden CE, Benedetti TJ, Knopp RH. Influence of diagnostic criteria on the incidence of gestational diabetes and perinatal morbidity. *JAMA*. 1993;269:609-15.
- Marin C, Segura-Egea JJ, Martinez-Sahuquillo A, Bullon P. Correlation between infant birth weight and mother's periodontal status. *Journal of Clinical Periodontology*. 2005;32:299-304.
- Martin JA, Hamilton BE, Sutton PD, Ventura SJ, Mathews TJ, Osterman MJK. Births: final data for 2008. National vital statistics reports; vol 59 no 1. Hyattsville, MD: National Center for Health Statistics. 2010.

- Martin JA, Hamilton BE, Sutton PD, Ventura SJ, Menacker F, Kirmeyer S, Mathews TJ. Births: final data for 2006. *National Vital Statistics Reports*. 2009;57:1-102.
- Mehta SH, Kruger M, Sokol RJ. Being too large for gestational age precedes childhood obesity in African Americans. *American Journal of Obstetrics & Gynecology*. 2011;204:265.e1-5.
- Minkoff H, Cervenak FA. Elective primary cesarean delivery. *New England Journal of Medicine*. 2003;348:946-50.
- Michalowicz BS, Hodges JS, DiAngelis, AJ, Lupo VR, Novak MJ, Ferguson JE, Buchanan W, Bofill J, Papapanou PN, Mitchell DA, Matseone S, Tschida PA. Treatment of periodontal disease and the risk of preterm birth. *New England Journal of Medicine*. 2006;355:1885-94.
- Moliterno LFM, Monteiro B, da Silva Figueredo CM, Fischer RG. Association between periodontitis and low birth weight: a case-control study. *Journal of Clinical Periodontology*. 2005;32:886-90.
- Moore S, Ide M, Coward PY, Randhawa M, Borkowska E, Baylis R, Wilson RF. A prospective study to investigate the relationship between periodontal disease and adverse pregnancy outcome. *British Dental Journal*. 2004;197:251-58.
- Murthy K, Holl JL, Lee TA, Grobman WA. National trends and racial differences in late preterm induction. *American Journal of Obstetrics & Gynecology*. 2011;205(5):458.e1-7.
- Narayan KM, Boyle JP, Thompson TJ, et al. Lifetime risk for diabetes mellitus in the United States. *JAMA*. 2003;290:1884-90.
- Novak KF, Taylor GW, Dawson Dr, Ferguson JE, Novak MJ. Periodontal disease and gestational diabetes mellitus: exploring the link in NHANES III. *Journal of Public Health Dentistry*. 2006;66(3):163-8.
- Ovesen P, Rasmussen S, Kesmodel U. Effect of prepregnancy maternal overweight and obesity on pregnancy outcome. *Obstetrics & Gynecology*. 2011;118:305-12.
- Perkins CC, Pivarnik JM, Paneth N, Stein AD. Physical activity and fetal growth during pregnancy. *Obstetrics & Gynecology*. 2007;109(1):81-7.
- Pettitt DJ, Aleck KA, Baird HR, Carraher MJ, Bennett PH, Knowler WC.

- Congenital susceptibility to NIDDM. Role of intrauterine environment. *Diabetes*. 1988;37:622-28.
- Pischon N, Heng N, Bernimoulin JP, Kleber BM, Willich SN, Pischon T. Obesity, inflammation, and periodontal disease. *Journal of Dental Research*. 2007;86(5):400-9.
- Polyzos NP, Polyzos IP, Mauri D, et al. Effect of periodontal disease treatment during pregnancy on preterm birth incidence: a meta-analysis of randomized trials. *American Journal of Obstetrics & Gynecology*. 2009;200:225-32.
- Reddy U, Ko CW, Raju TNK, Willinger M. Delivery indications at late pre-term gestations and infant mortality rates in the United States. *Pediatrics*. 2009;124:234-40.
- Ritchie CS, Kinane DF. Nutrition, inflammation, and periodontal disease. *Nutrition*. 2003;19(5):475-6.
- Rode 2007, Hegaard HK, Kjaergaard H, Moller LF, Tabor A, Ottesen B. Association between maternal weight gain and birth weight. *Obstetrics & Gynecology*. 2007;109(6):1309-15.
- Ros HS, Cnattingus S, Lipworth L. Comparison of risk factors for preeclampsia and gestational hypertension in a population-based cohort study. *American Journal of Epidemiology*. 1998;147:1062-70.
- Rosenberg TJ, Garbers S, Lipkind H, Chiasson MA. Maternal obesity and diabetes as risk factors for adverse pregnancy outcomes: differences among 4 racial/ethnic groups. *American Journal of Public Health*. 2005;95(9):1545-51.
- Rosenberg TJ, Garbers S, Chavkin W, Chiasson MA. Prepregnancy weight and adverse perinatal outcomes in an ethnically diverse population. *Obstetrics & Gynecology*. 2003;102:1022-27.
- Rosenbloom AL, Joe JR, Young RS, et al. Emerging epidemic of type 2 diabetes in youth. *Diabetes Care*. 1999;22:345-54.
- Salvi G, Kandylaki M, Troendle A, Persson GR, Lang NP. Experimental gingivitis in type 1 diabetics: a controlled clinical and microbiological study. *Journal of Clinical Periodontology*. 2005;32:310-16.
- Sanchez-Ramos L, Bernstein S, Kaunitz AM. Expectant management versus labor induction for suspected fetal macrosomia: a systematic review. *Obstetrics & Gynecology*. 2002;100:997-1002.

- Scholl TO, Chen X, Gaughan C, et al. Influence of maternal glucose level on ethnic differences in birth weight and pregnancy outcome. *American Journal of Epidemiology*. 2002;156:498-506.
- Smaill F, Hofmeyr GJ. Antibiotic prophylaxis for cesarean section. *Cochrane Database of Systematic Reviews*. 2002;3:CD000933.
- Spong CY, Mercer BM, D'Alton M, Kilpatrick S, Blackwell S, Saade G. Timing of indicated late-preterm and early-term birth. *Obstetrics & Gynecology*. 2011;118(2):323-33.
- Steinfeld JD, Valentine S, Lerer T, et al. Obesity-related complications of pregnancy vary by race. *Journal of Maternal & Fetal Medicine*. 2000;9:238-41.
- Takahashi K, Takashiba S, Nagai A, et al. Assessment of interleukin-6 in the pathogenesis of periodontal disease. *Journal of Periodontology*. 1994;65:147-53.
- Taylor GW, Burt BA, Becker MP, et al. Severe periodontitis and risk for poor glycemic control in subjects with non-insulin-dependent diabetes mellitus. *Journal of Periodontology*. 1996;67(suppl.):1085-1093.
- Torloni MR, Betran AP, Horta BL, Nakamura MU, Atallah AN, Moron AF, Valente O. Prepregnancy BMI and the risk of gestational diabetes: a systematic review of the literature with meta-analysis. *Obesity Reviews*. 2010;10:194-203
- Uppal A, Uppal S, Pinto A, Dutta M, Shrivatsa S, Dandolu V, Mupparapu M. The effectiveness of periodontal disease treatment during pregnancy in reducing the risk of experiencing preterm birth and low birth weight: a meta-analysis. *JADA*. 2010;141:1423-34.
- Valensise H, Vasapoll B, Gagliardi G, Novelli GP. Early and late preeclampsia: two different maternal hemodynamic states in the latent phase of the disease. *Hypertension*. 2008;52:873-80.
- Vidarsdottir H, Geirsson RT, Hardardottir H, Valdimarsdottir U, Dagbjartsson A. Obstetric and neonatal risks among extremely macrosomic babies and their mothers. *American Journal of Obstetrics & Gynecology*. 2011;204:423.e1-6.
- Walker JJ. Preeclampsia. *Lancet*. 2000;356:1260-65.
- Wild S, Roglic G, Green A, et al. Global prevalence of diabetes: estimates for

- the year 2000 and projections for 2030. *Diabetes Care*. 2004;27:1047-53.
- Xiong X, Buekens P, Goldenberg RL, Offenbacher S, Qian X. Optimal timing of periodontal disease treatment for prevention of adverse pregnancy outcomes: before or during pregnancy? *American Journal of Obstetrics & Gynecology*. 2011;205:111.e1-6.
- Xiong X, Buekens P, Vastardis S, Pridjian G. Periodontal disease and gestational diabetes mellitus. *American Journal of Obstetrics & Gynecology*. 2006;195(4):1086-9.
- Yalcin F, Basegmez C, Isik G, Berber L, Eskinazi E, Soydinc M, Issever H, Onan U. The effects of periodontal therapy on intracrevicular prostaglandin E2 concentrations and clinical parameters in pregnancy. *Journal of Periodontology*. 2002;73:173-77.
- Zhang X, Decker A, Platt RW, Kramer MS. How big is too big? The perinatal consequences of fetal macrosomia. *American Journal of Obstetrics & Gynecology*. 2008;198:517.e1-e6.

Chapter 2

Methods

Study design

These analyses draw upon data previously collected from the University of Kentucky, Oral Infection: Impact on Gestational Diabetes study. The primary design of that study was a prospective cohort study to assess the association between periodontal disease and gestational diabetes in pregnant women. However, follow-up information up to and including the delivery of the infant allows for treating the cases (pregnant women with gestational diabetes) and controls (women without gestational diabetes) as a matched cohort.

Source population

The University of Kentucky Maternal-Fetal Medicine Clinic located in Fayette County accounts for approximately 2,000 deliveries each year. Roughly 60 percent of these deliveries are to Caucasian women, 30 percent to Hispanic women, and 10 percent to African-American women. The overall prevalence of periodontal disease in pregnant women who utilize the clinic is roughly 33 percent using the case definition of four or more teeth with pocket depth of at

least four millimeters with bleeding on probing and clinical attachment loss of at least two millimeters. Previous studies in the clinic have reported higher rates of enrollment among Hispanic women.

Study population

The eventual final analysis will use data from 416 pregnant women recruited between September 2005 and September 2009. 208 women with gestational diabetes mellitus were expected to be recruited and matched by age within a five-year interval, race, and gestational week at enrollment within a two week interval to 208 women without gestational diabetes mellitus. However, the preliminary data used in these analyses focuses on 321 women who had been recruited at the time of analysis. Women with gestational diabetes mellitus were identified weekly through lab test results and recruited consecutively. Women without gestational diabetes were also identified weekly through lab test results and assessed for matching criteria to the women without gestational diabetes. Screening for gestational diabetes mellitus typically occurs between 24 and 32 weeks of pregnancy. For this study, the presence of gestational diabetes mellitus was assessed using universal screening of pregnant women entering the clinic with a two-step 50 gram glucose challenge test followed by a 100 gram oral glucose tolerance test and medical history. Controls without gestational diabetes mellitus who could be matched to already recruited women with gestational diabetes mellitus were then recruited to join the study. Pregnant women were included if they were at least 16 years of age and had at least 20 natural teeth at

the time of periodontal assessment. Women were excluded if they were unable to provide consent, unable to cooperate with the study, were placed at medical risk through participation, were under 16 years of age, or had a history of type 1 or type 2 diabetes prior to pregnancy.

Data Collection and Management

Medical staff with the University of Kentucky Bluegrass High Risk Maternal-Fetal Medicine Clinic spoke with patients about enrollment into the study. A medical research nurse contacted enrollees to arrange clinical visits. The research nurse extracted maternal and fetal data from medical records of participants. Oral examination was performed by Delta Dental Plan of Kentucky Clinical Research Center. Clinical periodontal disease measures were assessed at baseline (within one to two weeks of enrollment) and at 34 weeks gestation. No second measurement of periodontal disease was taken after delivery for women who gave birth prior to 34 weeks gestation.

Prior to data collection, an Access database was developed for entry of study data. This database was designed to prevent entry of erroneous information by setting valid data entry criteria. This database is password protected to permit only research staff access to obtained information. Dual data entry was implemented to identify erroneously entered data. Cleaned data was provided and maintained in a SAS data file.

Primary Outcomes – Infant birthweight, Pre-Eclampsia, Obstetric

Intervention

High infant birthweight was assessed as a continuous measure and categorically as infants with a birthweight greater than 4000 grams. A second categorical birthweight measure was defined as a function of gestational age to account for large infants born prematurely but not satisfying a 4000 gram threshold: Large for gestational age infants were defined as those infants who exceed the 90th percentile of weight expected at their gestational age compared to a standard United States birth population (Alexander 1996a). Growth curves for measuring weight appropriate for gestational age vary by race and gender and were also considered for analytic purposes (Alexander 1996b). In addition the measure of large-for-gestational age included suspected macrosomia that resulted in early induction.

Pre-eclampsia was defined using the case definition developed by the National High Blood Pressure Education Program Working Group as a systolic blood pressure of greater than or equal to 140mm Hg or a diastolic blood pressure of greater than or equal to 90mm Hg on two or more occasions after 20 weeks gestation for women with previously normal blood pressure. In addition, proteinuria must exceed 0.3g protein from a 24-hour urine sample (NHBPEPWP 2000). Pre-eclampsia outcome status was based upon information obtained from clinic visits.

When potential birth trauma is expected, a cesarean section is more likely to be performed than a vaginal birth. When cesarean sections are performed in

one pregnancy they are more likely to also be performed in subsequent pregnancies (Simpson 2005). Thus it is important to distinguish between elective procedures and clinically indicated procedures in assessment of methods of delivery. While there are two primary modes of delivery, cesarean section and vaginal delivery, these can be further subclassified as planned or not planned, with or without complications, and by whether a previous delivery was done by cesarean section (Viswanathan 2006). Women with non-elective cesarean sections, cesarean sections performed for maternal or fetal complications, and unplanned induction of delivery have been previously combined to measure whether women needed obstetric intervention while women with other deliveries were grouped as women who did not need obstetric intervention. Under this definition for premature births only, a tertiary referral center found 14.8 percent of preterm births to have been in need of mandated obstetric intervention (Fronterhouse 2001). Medically necessary indications were assessed through the evaluation of individual medical records by clinical research staff. For this analysis, obstetric intervention will be evaluated as the use of obstetric intervention rather than the need for obstetric intervention as a review of the dataset yielded that every use of obstetric intervention had a valid clinical indication supporting its use. In addition to any use of obstetric intervention (either labor induction or cesarean delivery), the specific interventions of cesarean delivery and labor induction were modeled separately to determine whether differences in obstetric intervention is driven by one procedure or the other.

Primary Exposures – Periodontal Disease and Gestational Diabetes

Periodontal disease status was assessed through a full mouth periodontal assessment within one to two weeks of gestational diabetes mellitus assessment and again at 34 weeks gestation or immediately after pregnancy when it occurred prior to 34 weeks gestation. The periodontal disease assessment included measures of pocket depth, clinical attachment loss, gingival inflammation, and bleeding upon probing. The proportion of sites with each clinical indicator provides a summary measure for classification of periodontal disease. Algorithms exist to further classify periodontal disease by severity status (Page 2007). Progression of periodontal status, independent of the dichotomous periodontal status, has been associated with birthweight differences. Periodontal disease was defined as four or more teeth with at least one probing depth of at least four millimeters, clinical attachment loss of at least two millimeters, and bleeding on probing. To evaluate the potential impact of periodontal disease severity, different case definitions of periodontal disease were substituted into models to assess whether they changed the risk estimate. The differing case definitions for periodontal disease when assessing adverse pregnancy outcomes is a common criticism of studies the relationship as findings seem dependent based upon the case definition used (Manau 2008). Assessing the impact of different case definitions for evaluating severity will facilitate comparison with other studies and the role of case definition in assessing results.

Gestational diabetes was evaluated as a dichotomous variable, and based upon the results of glucose tolerance screening. Women whose screening test

values exceeded the thresholds for the two-step 50 gram glucose challenge test and 100 gram oral glucose tolerance tests were considered to have gestational diabetes. I used a dichotomous variable for gestational diabetes and did not take advantage of the linear glucose tolerance screening value.

Potential Confounding Variables

Confounding has been an important consideration in the relationship between periodontal disease and systemic diseases due to the commonality of risk factors between periodontal disease and systemic diseases. Many studies relating periodontal disease to systemic diseases have not fully addressed potential confounders or effect modifiers and when considered, studies have yielded heterogeneous results (Hyman 2006). For instance, in a study of periodontal disease and cardiovascular disease, a positive association was found among smokers but not among nonsmokers (Hyman 2002). Thus the effect of periodontal disease on adverse pregnancy outcomes may also be heterogeneous across subgroups.

A medical history was conducted to assess the presence of any confounding medical conditions such as heart disease, kidney disease, past illicit drug and alcohol use, and presence of vaginal infection. Heart disease and kidney disease may share common mechanisms of disease as pre-eclampsia (Bellamy 2007, Hladunewich 2007). If heart disease were already present, the underlying mechanism may contribute to pre-eclampsia. Exclusion of women with pre-existing heart disease would help to reduce this variation in potential

causes of pre-eclampsia. Proteinuria as part of the case definition of pre-eclampsia may arise from pre-existing kidney disease which predisposes the woman to develop pre-eclampsia. Thus, kidney disease provides another source of variation that can contribute to pre-eclampsia that should be controlled for in the analysis. Drug and alcohol use are associated with fetal growth restriction and birth defects that may contribute to clinically indicated obstetric interventions (Young 1992, Jaddoe 2007). Vaginal infections are associated with adverse pregnancy outcomes independent of associations between periodontal disease and adverse pregnancy outcomes (Oittinen 2005). The medical chart abstraction identified women with heart disease, kidney disease, and vaginal infection.

Demographic information such as race (Caucasian, Black, Asian), Hispanic ethnicity, and maternal age were recorded as part of the medical history. Smoking was assessed through an interviewer-administered health history conducted by a medical research nurse. Tobacco use was measured by the self-reported use of cigarettes, chewing tobacco, snuff, cigars, and pipe tobacco. Current and past tobacco use, duration of tobacco use, and frequency of tobacco use were all assessed. As women in this study rarely used forms of tobacco other than cigarettes and never used non-cigarette tobacco products without also using cigarette, we used cigarette smoking status as a proxy for their total tobacco use status.

Height and weight measurements were taken at both the enrollment visit and update visit. Maternal obesity was calculated as the pre-pregnancy body mass index based upon these height and weight measurements. Obesity was

defined as a body mass index of 30 or higher based upon Centers for Disease Control and Prevention classifications. In the preliminary data, the majority of enrolled women lacked information on pre-pregnancy weight and thus pre-pregnancy obesity was not assessed. Nutritional intake was not assessed with the exception of identifying women on special diets.

Overall analytic approach and statistical analyses

In each analysis, periodontal disease was assessed as a dichotomous exposure as was gestational diabetes. In regression models, a multiplicative interaction term was included to determine whether statistically significant interaction existed between these two conditions. In a second model, periodontal disease and gestational diabetes status were combined into a four level categorical variable containing each potential combination of the dichotomous exposure categories: periodontal disease with gestational diabetes, periodontal disease only, gestational diabetes only, and neither periodontal disease nor gestational diabetes. For the four level exposure analysis, the group with neither periodontal disease nor gestational diabetes served as the reference group. Subsequent analyses considered the effect of periodontal disease by severity level, in accordance with the differing case definitions, to assess dose-response relationships (Page 2007). Through these multiple methods of assessment, the analysis explored the different mechanisms by which the exposures of gestational diabetes and periodontal disease may impact the outcomes of interest.

Analyses were performed at two levels, one that accounts for the matched pairs and one that treats the matched pairs as unmatched. In the matched pair analysis, McNemar's test and conditional regression techniques were used to assess the associations between the periodontal disease and gestational diabetes exposure groups and the outcomes of interest. The matched analysis provided better estimation of regression coefficients but at the cost of precision around those estimates. Matching in observational cohort studies does not entirely guarantee that efficiency is gained as the matching will alter the covariate distributions of unmatched, potentially important, confounding variables (Rothman 1998). The matched analysis was performed in SAS[®] version 9.2 for Windows (SAS 2011) using PROC PHREG (Alexander 2007). This command procedure used matched pairs in the analysis where the outcome of interest was different between the pregnant women with gestational diabetes and the pregnant women without gestational diabetes (Walker 1982, Walker 1981). Thus, in order to be used, this procedure requires an adequate number of outcome events amongst both cases and controls. If there are too few outcome events, then PROC GENMOD can be used to estimate the point estimates of the parameters. However, the confidence intervals provided by PROC GENMOD are anti-conservative or narrower than expected (Alexander 2007). Corrections to the confidence intervals can be performed. However, some of these corrections may still result in anti-conservative confidence intervals or overly conservative estimates (Alexander 2007, Cummings 2003).

The unmatched analysis uses chi square tests and Fischer exact tests when cell sample sizes are small to evaluate the differences in categorical risk factors and outcomes between exposure groups. For continuous outcomes and risk factors, t-tests were used to evaluate the between exposure group differences. Unconditional regression modeling techniques were used to estimate the adjusted risk of adverse pregnancy outcomes as unmatched analyses can still yield unbiased risk ratio estimates in matched cohort studies (Rothman 1998). Both the unmatched linear and logistic regression analyses were performed in PROC GENMOD in SAS 9.2. The unmatched analyses provide greater precision at the potential cost of accuracy of the regression coefficients. In both analytic approaches (matched and unmatched), categorical approaches require adequate cell sizes to produce reliable estimates. The majority of analyses of the preliminary data focus on using the unmatched analytic approaches due to the limited number of outcome events in the partial population.

Statistical analyses specific to infant birthweight

Birthweight was evaluated as a continuous outcome and used to measure the difference in the mean birthweight among the periodontal disease and gestational diabetes mellitus exposure groups. However, the effects of periodontal disease may not be entirely linear as periodontal disease may lead to reductions in infant birthweight in women with periodontal disease, but may also

increase the occurrence high birthweight infants in women with gestational diabetes.

To account for the potential nonlinear association between exposure categories and birthweight, birthweight was also defined categorically. As a categorical measure, analysis focused on the comparison of the proportion of live births that result in high birthweight or large-for-gestational age among the periodontal disease and gestational diabetes exposure groups. Bivariate analyses using Chi-square tests for categorical measures and t-tests for continuous measures were used to identify potential confounders in the relationship between periodontal disease and high birthweight and large-for-gestational age infants. Multivariable analyses were used to test the relationship between periodontal disease, gestational diabetes mellitus and adverse pregnancy outcomes by controlling for multiple confounding variables. Methods of multivariable analysis varied with the continuous/categorical classification of birthweight. For birthweight treated as a continuous outcome in an unmatched analysis, the multivariable linear regression model is depicted in Figure A1. For the categorical comparison of birthweight in terms of high birthweight and large-for-gestational age, the multivariable logistic regression models used in the matched analysis can be found in Figure A2 while the multivariable logistic regression models used for the unmatched analysis can be found in Figure A3. The estimated power of the test to find a significant difference between exposure groups in the prevalence of high birthweight infants at the 0.05 alpha level can be found in Table B1.

Statistical analyses specific to pre-eclampsia

Pre-eclampsia was defined in this study as a dichotomous outcome. The proportion of births that result in pre-eclampsia can be measured among the periodontal disease and gestational diabetes mellitus exposure groups and compared using Chi-square tests in the unmatched analysis. As with measures of birthweight, bivariate analytic approaches (t-tests for continuous measures, chi-square tests for categorical measures) were used to assess potential and expected confounders. For the multivariable logistic regression model performed to assess the association between periodontal disease and gestational diabetes exposure and pre-eclampsia in the unmatched analysis, the regression equation is shown in Figure A4. For the multivariable conditional logistic regression model performed to assess the association between the exposure variables of gestational diabetes and periodontal disease and the outcome of pre-eclampsia in the matched analysis, the regression equation is found in Figure A5. The estimated power of this test, dependent on the prevalence of pre-eclampsia in the exposure groups can be found in Table B3.

Statistical analyses specific to obstetric intervention

The analysis of obstetric intervention using preliminary data focused on the unmatched analysis although in the complete data set there should be adequate numbers of outcomes in the exposure group categories due to the overall high prevalence of obstetric intervention. For the unmatched analysis, the prevalence

of obstetric intervention was compared across exposure groups of periodontal disease and gestational diabetes with Chi-square tests for categorical measures and t-tests for continuous measures. In the multivariable logistic regression model using the unmatched approach, the relationship between the exposures of periodontal disease and gestational diabetes and the outcome of obstetric intervention was evaluated as depicted in the regression equation in Figure A6. For the multivariable conditional logistic regression model that uses the matched data, the regression equation to test the relationship between the exposures of gestational diabetes and periodontal disease and the outcome of obstetric intervention can be found in Figure A7. Similar multivariable regression modeling equations were performed separately for the component outcomes of labor induction and cesarean section delivery. These separate models for labor induction and cesarean delivery were used to determine the contributions of each mode of delivery to the observed association with overall obstetric intervention. For cesarean delivery, separate models with and without women with a previous cesarean delivery were modeled due to the high likelihood that women with a previous cesarean delivery will have subsequent cesarean deliveries. The estimated power, dependent on the prevalence of obstetric intervention, to test for differences in obstetric intervention prevalence rates between exposure groups can be found in Table B5.

While these analyses intend to take advantage of the study design, the preliminary sample size can result in an inability to take full advantage of the design. Modifications to these analytic approaches are detailed in the following

chapters to address the impact of sample size in this preliminary analysis. Additional limitations for each of the different analyses are discussed in each subsequent chapter and summarized in Chapter six.

References

- Alexander GR, Himes J, Kaufman R, Mor J, Kogan M. A United States national reference for fetal growth. *Obstetrics & Gynecology*. 1996;87:163-8.
- Alexander GR, Allen MC. Conceptualization, measurement, and use of gestational age. I. Clinical and Public Health Practice. *Journal of Perinatology*. 1996;16(1):53-9.
- Alexander MT, Kufera JA. Butting heads on matched cohort analysis using SAS software. *Statistics and Data Analysis*. 2007:1-11.
- Bellamy L, Casas JP, Hingorani Ad, et al. Pre-eclampsia and risk of cardiovascular disease and cancer in later life: systematic review and meta-analysis. *British Medical Journal*. 2007;335(7627):974.
- Cummings P, McKnight B, Greenland S. Matched cohort methods for injury research. *Epidemiologic Reviews*. 2003;25:43-50.
- Fronterhouse W, Christensen FC, Rayburn LA, et al. Mandated preterm delivery: its prevalence and impact at a tertiary referral center. *Journal of Maternal and Fetal Medicine*. 2001;10(3):162-5.
- HAPO Study Cooperative Research Group. Hyperglycemia and adverse pregnancy outcomes. *New England Journal of Medicine*. 2008;358:1991-2002.
- Hladunewich M, Karumanchi SA, Lafayette R. Pathophysiology of the clinical manifestations of pre-eclampsia. *Clinical Journal of the American Society of Nephrology*. 2007;2:543-549.
- Hyman J. The importance of assessing confounding and effect modification in research involving periodontal disease and systemic diseases. *Journal of Clinical Periodontology*. 2006;33:105-9.
- Hyman JJ, Winn DM, Reid BC. The role of cigarette smoking in the association between periodontal disease and coronary heart disease. *Journal of Periodontology*. 2002;73:988-94.
- Jaddoe VW, Bakker R, Hofman A, et al. Moderate alcohol consumption during pregnancy and the risk of low birth weight and preterm birth. The generation R study. *Annals of Epidemiology*. 2007;17(10):834-40.
- Jeffcoat MK, Geurs NC, Reddy MS, Cliver SP, Goldenberg RL, Hauth JC. Periodontal infection and preterm birth: results of a prospective study. *Journal of the American Dental Association*. 2001;132:875-80.

- Manau C, Echeverria A, Agueda A, Guerrero A, Echeverria JJ. Periodontal disease definition may determine the association between periodontitis and pregnancy outcomes. *Journal of Clinical Periodontology*. 2008;35:385-97.
- National High Blood Pressure Education Program Working Group on High Pressure in Pregnancy (2000). Report of the National High Blood Pressure Education Program Working Group on High Blood Pressure in Pregnancy. *American Journal of Obstetrics & Gynecology*. 2000;183:S1-22.
- Nicholson W, Bolen S, Witkop CT, Neale D, Wilson L, Bass E. Benefits and risks of oral diabetes agents compared with insulin in women with gestational diabetes: a systematic review. *Obstetrics & Gynecology*. 2009;113:193-205.
- Oittinen J, Kurki T, Kekki M, et al. Periodontal disease and bacterial vaginosis increase the risk for adverse pregnancy outcome. *Infectious Diseases in Obstetrics and Gynecology*. 2005;13(4):213-216.
- Page RC, Eke PI. Case definitions for use in population-based surveillance of periodontitis. *Journal of Periodontology*. 2007;78(7S):1387-99.
- Polyzos NP, Polyzos IP, Zavos A, et al. Obstetric outcomes after treatment of periodontal disease during pregnancy: systematic review and meta-analysis. *British Medical Journal*. 2011;341:c7017.
- Rothman KJ, Greenland S. Matching. *Modern Epidemiology*, 2nd edition. 1998. Lippincott, Williams & Wilkins, Philadelphia, PA.
- SAS Institute. SAS[®] 9.2 for Windows. 2011. SAS Institute Inc., Cary, North Carolina.
- Simpson KR, Thorman KE. Obstetric “conveniences”: elective induction of labor, cesarean birth on demand and other potentially unnecessary interventions. *Journal of Perinatology and Neonatal Nursing*. 2005;19(2):134-44.
- Virally M, Laloi-Michelin M. Methods for the screening and diagnosis of gestational diabetes mellitus between 24 and 28 weeks of pregnancy. *Diabetes & Metabolism*. 2010;36:549-65.
- Viswanathan M, Visco AG, Hartmann K, et al. Cesarean delivery on maternal

- request. Evidence report/technology assessment No. 133. AHRQ Publication No. 6-E009. Rockville, MD. Agency for Healthcare Research and Quality. March 2006.
- Walker AM, Hunter JR, Watkins RN, Jick H, Danford A, Alhadeff L, Rothman K. Vasectomy and non-fatal myocardial infarction. *Lancet*. 1981;13-15.
- Walker AM. Efficient assessment of confounder effects in matched follow-up studies. *Applied Statistics*. 1982;31(3):293-7.
- Ylostalo PV, Knuuttila ML. Confounding and effect modification: possible explanation for variation in the results on the association between oral and systemic diseases. *Journal of Clinical Periodontology*. 2006;33:104-8.
- Young SL, Vosper HJ, Phillips SA. Cocaine: its effects on maternal and child health. *Pharmacotherapy*. 1992;12(1):2-17.

Chapter 3

Fetal Macrosomia

Introduction

Fetal macrosomia, often synonymous with large-for-gestational age and high birthweight, occurred in 7.6 percent of live births in the United States in 2008 (Martin 2010). The prevalence of fetal macrosomia was highest in non-Hispanic White infants at 9.5 percent compared to 7.2 percent in Hispanic infants and 4.1 percent in African American infants using the 4,000 gram threshold definition of fetal macrosomia (Martin 2010). Fetal macrosomia is more common among infants born to women with pre-existing diabetes (Persson 2011) or pregnancy-induced gestational diabetes (Ehrlich 2011, HAPO 2008). Fetal macrosomia is associated with increased risk for birth trauma events such as shoulder dystocia (Zhang 2008, Vidarsdottir 2011). In addition, fetal macrosomia is associated with an increased likelihood of emergency cesarean delivery (Zhang 2008, Vidarsdottir 2011), or early induction to prevent the maternal complications posed by having a high birthweight infant (Vidarsdottir 2011). Fetal macrosomia may also have long-term impacts such as greater likelihood of childhood obesity

(Mehta 2011) and increased likelihood of early onset diabetes for the infant (Pettit 1988).

One of the risk factors most often associated with high infant birthweight is gestational diabetes (HAPO 2008, Ehrlich 2011, Mocarski 2011). Insulin resistance increases the risk for fetal macrosomia at both clinical and subclinical levels with no clear minimum or maximum threshold for increasing risk (HAPO 2008, Ehrlich 2011). Inflammatory markers are correlated across all levels of maternal glucose levels which may ultimately impact infant birthweight (Lowe 2010). Ethnic differences have been reported in the association between gestational diabetes and infant birthweight, with African American women typically demonstrating greater risks, but these differences are not large enough to suggest differing thresholds for treatment or diagnosis (Mocarski 2011).

While gestational diabetes has demonstrated relationships with high birthweight infants, periodontal disease associations with high birthweight have not been previously assessed. Periodontal disease has been linked to an increased risk for delivery of a low birthweight infant, particularly of a preterm low birthweight infant (Lopez 2002, Marin 2005, Moliterno 2005, Moreu 2005). Studies evaluating the relationship between periodontal disease and birthweight specifically have demonstrated mixed results (Marin 2005, Moliterno 2005, Moore 2004, Lunardelli 2005) with randomized controlled trials and meta-analyses (Uppal 2010, Michalowicz 2006) less likely to demonstrate significant associations. Thus it is unclear whether periodontal disease truly affects

birthweight, and if so, whether it affects birthweight directly or as a side effect of its impact on prematurity.

Gestational diabetes and periodontal disease may be of greater importance together rather than as individual risk factors for high or low infant birthweight. The destructive processes of periodontal disease may contribute to factors that increase the severity of gestational diabetes, and the glycated proteins and inflammation from gestational diabetes may generate feedback to enhance the destructive impact of periodontal disease (Grossi 1998, Lalla 2011). Periodontal disease has been linked to complications with glycemic control in persons with diabetes (Taylor 1996). Periodontal disease has also been shown to be greater in prevalence among women with gestational diabetes (Xiong 2006). Thus periodontal disease may enhance the effects of gestational diabetes even though periodontal disease itself may have a limited impact on infant birthweight.

Factors that contribute to either reduction or increase in infant birthweight should be considered important as potential confounding variables regardless of the hypothesized direction of effect of the primary variables of interest. Infant growth curves demonstrate the relationship between gestational age and infant birthweight (Alexander 1996). Thus gestational age is a very strong predictor of infant birthweight. Both smoking and illicit drug use have been linked to reduced infant birthweight which may confound associations of other potential risk factors with infant birthweight (Floyd 1993, Higgins 2002, Bailey 2011). Birthweight distributions also vary by race (Martin 2010). Pre-pregnancy body mass index

has been linked to fetal macrosomia (Kabali 2007, Rosenberg 2003, Ovesen 2011), but gestational diabetes and associated insulin insensitivity may mediate the effect of body mass index on infant birthweight because increasing body mass index is associated with increasing risk for gestational diabetes (Torloni 2008, Kim 2010, Ovesen 2011). Therefore it is unclear whether body mass index truly exhibits an independent effect on infant birthweight beyond that mediated through gestational diabetes. Thus controlling for body mass index may be inappropriate in analyses when trying to estimate the direct effect of gestational diabetes. This study aims to address possible biological synergism by examining whether the impact of gestational diabetes on infant birthweight is greater in the presence of periodontal disease than when gestational diabetes is present without periodontal disease.

Methods

This analysis used preliminary data collected for the University of Kentucky, Oral Infection: Impact on Gestational Diabetes study. Between September 2005 and September 2009, 321 pregnant women were recruited consecutively based upon the presence or absence of gestational diabetes mellitus. Pregnant women were included if they were at least 16 years of age and had at least 20 natural teeth at the time of periodontal assessment. Women were excluded if they were unable to provide consent, unable to cooperate with the study, were placed at medical risk through participation, were under 16 years of age, or had a history of type 1 or type 2 diabetes prior to pregnancy.

Gestational diabetes mellitus was identified through universal screening with a two-step diagnostic test, a 50 gram glucose challenge test followed by a 100 gram oral glucose tolerance test, performed for all pregnant women who visited the University of Kentucky Bluegrass High Risk Maternal-Fetal Medicine Clinic. Women identified with gestational diabetes were then matched to a pregnant woman without gestational diabetes based upon age within a five-year interval, race, and gestational week at enrollment within a two week interval. Both women with and without gestational diabetes were followed from the time of enrollment through delivery and then compared.

A total of 162 potential cases were identified. Figure 3.1 describes the process of determining eligibility for this analysis. Nine cases, women with gestational diabetes, and six controls, women without gestational diabetes, were excluded for the lack of a match. One matched pair was removed for a pre-existing health condition, eight matched pairs were removed for multiple gestation, and an additional 41 matched pairs were excluded due to a lack of periodontal disease examination information. An additional eight matched pairs were removed for extremely high birthweight, extremely low birthweight, or missing birthweight information. The extremely high and low birthweight values were not only excluded due to their potential as data recording errors, but also for their potential as overly influential data points since they fell out of the range of the typical birthweight distribution. Thus, for this analysis, 95 matched cases and controls with complete periodontal disease examination information and adequate birthweight information were evaluated to assess the relationship

between gestational diabetes, periodontal disease, and their potential interaction with infant birthweight.

Infant birthweight was recorded in grams at the time of delivery and abstracted during the chart reviews by the medical research nurse. In addition to a continuous measure of infant birthweight in grams, infant birthweight was also categorized into low birthweight (below 2,500 grams), expected birthweight (2,500 to 4,000 grams), and high birthweight (over 4,000 grams) according to standard definitions (Alexander 1996). Gestational diabetes was evaluated as a dichotomous variable based upon the screening results that led to selection into the study as a case or control . Oral examination was performed by Delta Dental Plan of Kentucky Clinical Research Center. Clinical periodontal disease measures were assessed at baseline (within one to two weeks of enrollment). The periodontal disease assessment included a full mouth examination that captured measures of pocket depth, clinical attachment loss, gingival inflammation, and bleeding upon probing at six sites per tooth. The proportion of sites with each clinical indicator provides a summary measure for classification of periodontal disease. Periodontal disease was defined as four or more teeth with bleeding on probing, pocket depth of at least four millimeters and clinical attachment loss of at least two millimeters for analysis unless otherwise specified. Third molars were excluded from the periodontal disease status classification.

A medical research nurse contacted enrollees to arrange clinical visits. The research nurse extracted maternal and fetal data from medical records of

participants. Demographic information including race (Caucasian, Black, Asian), Hispanic ethnicity, and maternal age were recorded as part of the medical history. Tobacco use was measured by self-reported use of cigarettes, chewing tobacco, snuff, cigars, and pipe tobacco. Tobacco use as a confounding variable was limited to cigarette use (current smoker, former smoker, and never smoker) as other forms of tobacco use were rare and always occurred in conjunction with cigarette smoking. A medical history was conducted to dichotomously assess the presence or absence of any confounding medical conditions such as heart disease, kidney disease, past illicit drug and alcohol use, and presence of vaginal infection. Height and weight measurements were taken at both the enrollment visit and update visit. Pre-pregnancy weight was not available for the majority of study participants. Nutritional intake was not assessed with the exception of identifying women on special diets.

Cross-tabulations of each variable by case-control status were assessed to identify potential confounding variables using chi-square and Fischer exact tests depending upon cell sample size. However, the limited sample size from the preliminary dataset resulted in small cell sizes inappropriate for further regression analytics. Therefore no multivariable logistic regression analyses were performed based on the categorical definition of high birthweight. Bivariate analyses using the continuous measure of infant birthweight to assess influence of potential confounding variables were evaluated through t-tests. An unmatched analysis using linear regression with the continuous outcome measure of infant birthweight was performed in SAS version 9.2 using PROC GENMOD. Bell-

shaped curves for normally distributed data have been observed for birthweight (Persson 2011).

Results

The mean infant birthweight among study participants was 3,407g (SE: 33g), and its relationship with gestational diabetes and periodontal disease are illustrated in Table 3.1. The mean birthweight was higher among women with gestational diabetes (3,449g, SE: 48g) compared to women without gestational diabetes (3,366g, SE 45g) but not at a significant level ($p=0.2084$). The mean infant birthweight was not different ($p=0.8745$) in women with periodontal disease (3,412g, SE: 50g) compared to women without periodontal disease (3,401g, SE: 43g). Women with both gestational diabetes and periodontal disease had nonstatistically significant ($p=0.33$) higher infant birthweight (3,445g, SE: 64g) compared to women without either gestational diabetes or periodontal disease (3,360g, SE: 59g). The birthweight distributions across all four categories of the two combined conditions were similar in shape and appearance to each other (Figure 3.2).

In examining the potential for confounding from other risk factors that can influence infant birthweight, we identified potential associations of gestational diabetes with maternal age, smoking status, and estimated gestational age at delivery. Women with gestational diabetes were older despite matching on maternal age, delivered infants at greater gestational age, and were more likely

to be a current or former smoker compared to women without gestational diabetes (Table 3.2).

Potential associations were identified between the risk factor of periodontal disease and other risk factors associated with infant birthweight. Women with periodontal disease were more likely to be current smokers, be of Hispanic ethnicity, be of greater maternal age, and have infants at an earlier gestational age (Table 3.3).

The association between gestational diabetes and potential confounding variables on the continuous outcome of birthweight are displayed in Table 3.4. Women who had never smoked had a lower mean infant birthweight compared to women who were current smokers which was contrary to expectation ($p=0.0605$). Women with a history of illicit drug use also had a lower mean infant birthweight compared to women without a history of illicit drug use ($p=0.0444$). Hispanic women had a nonstatistically significant lower mean infant birthweight compared to White women ($p=0.1820$). The mean birthweight was also higher among infants born at term compared to infants born prematurely ($p < 0.0001$).

The associations between periodontal disease and potential confounding variables are demonstrated below in Table 3.5. Infant birthweight did not vary substantially between women with periodontal disease and women without periodontal disease by any of the potential confounding variables evaluated.

The relationship between periodontal disease case definition, gestational diabetes and the continuous outcome of infant birthweight is presented in Table 3.6. Among women with periodontal disease, women with gestational diabetes

consistently had higher mean infant birthweight than women without gestational diabetes. When the measurement of periodontal disease was changed from lower severity levels to higher severity levels, we observed only minor changes in the difference in birthweight between women with and without gestational diabetes. Among women without periodontal disease, infant birthweight did not differ between women with gestational diabetes and women without gestational diabetes for low severity case definitions. The difference increased modestly with severity but without any substantial trend corresponding with periodontal disease severity.

In single risk factor regression models (Table 3.7), birthweight was a significantly associated with estimated gestational age. History of illicit drug use had a borderline nonsignificant relationship with infant birthweight. Periodontal disease ($p=0.8758$) and gestational diabetes ($p=0.2113$) failed to achieve statistical significance either on their own or with a multiplicative interaction term ($p=0.8697$), or when periodontal disease and gestational diabetes were modeled as a categorical combination variable. The potential confounding variables, identified through the literature or analysis, that can contribute to infant birthweight differences and to the two conditions of periodontal disease and gestational diabetes were examined in the multivariable linear regression model presented in Table 3.8.

Potential multicollinearity was present for smoking status and history of illicit drug use. When placed into the model together, each of the variables weakened the effect of the other variable with a tolerance of 0.6. When the

model included only one of these two variables, the tolerance rose to 0.9. Tolerance is the inverse of a measure, ranging between 0 and 1, that describes how much variance of a regression coefficient is caused by colinearity. Therefore, a higher value of tolerance corresponds to less colinearity. Given its low prevalence relative to smoking, illicit drug use was dropped from the model. After adjusting for gestational age, gestational diabetes was significantly associated with higher infant birthweight ($p=0.0234$). However, no other potential confounding variable when added to a bivariate model resulted in statistical significance for effects of periodontal disease or gestational diabetes (Table 3.8) including when current and former smokers were combined into an ever smoker category ($p=0.3084$)

In the multivariable model (Table 3.9), gestational diabetes remained associated with an increased infant birthweight. Periodontal disease was not associated with increased infant birthweight. The multiplicative interaction term between gestational diabetes and periodontal disease was nonsignificant despite both terms suggesting positive relationships with infant birthweight ($p=0.4104$).

In the multivariable model with the categorical combination of gestational diabetes and periodontal disease (Table 3.10), the highest increase in infant birthweight was among women with both gestational diabetes and periodontal disease followed by women with gestational diabetes alone and then periodontal disease alone. Compared to women without either gestational diabetes or periodontal disease, the women with at least one or both of these risk factors

demonstrated a statistically significant increase in infant birthweight after adjusting for gestational age, smoking status, and maternal race.

Gestational age was highly predictive, with birthweight increasing as gestational age increased ($p < 0.0001$). Current smoking status was associated with lower infant birthweight, but was not significant in this model ($p=0.4297$).

Discussion

Maternal periodontal disease does not appear to be associated with infant birthweight or modify the relationship between gestational diabetes and birthweight. Gestational diabetes was associated with higher birthweight, but did not appear to have a stronger association in the presence of periodontal disease, even after adjusting for smoking, maternal age, race, ethnicity, and gestational age at delivery. However, the power to detect a multiplicative interaction in the multivariable model was limited due to the preliminary sample size. This study supports a pathophysiologic process whereby gestational diabetes can influence birthweight but where periodontal disease either does not influence infant birthweight, or represents a small influence relative to that of gestational diabetes. Only the effect of clinical gestational diabetes was evaluated, not its severity. Gestational diabetes measured on a continuous scale, both clinically and subclinically has been associated with adverse pregnancy outcomes including increasing likelihood of fetal macrosomia (HAPO 2008). Some risk misclassification may occur when using a dichotomous measure for gestational

diabetes exposure. Continuous measures would be preferred due to these demonstrated relationships in future studies.

The effect of gestational diabetes should be interpreted not as the true effect of gestational diabetes but as the effect of gestational diabetes under current standard treatment of care. Insulin therapy has demonstrated success in preventing adverse pregnancy outcomes associated with gestational diabetes and may weaken observed associations between gestational diabetes and fetal macrosomia (Alwan 2011, Jacqueminet 2010, Landon 2009).

No studies have previously addressed whether treatment of periodontal disease can prevent fetal macrosomia, and the reported effects of periodontal disease treatment on other adverse pregnancy outcomes reported in studies have been mixed for both infant health outcomes (Uppal 2010, Michalowicz 2006) and maternal health outcomes (Newnham 2009, Michalowicz 2006, Offenbacher 2009).

Multiple studies have assessed the effects of periodontal disease and gestational diabetes alone on infant birthweight. Gestational diabetes, both clinically and subclinically, has demonstrated relationships with higher birthweight infants (HAPO 2008). Studies of periodontal disease have produced mixed results with studies often showing lower birthweight infants more common among women with periodontal disease (Marin 2005, Moliterno 2005, Moore 2004, Lunardelli 2005). Given the proposed relationship between periodontal disease and gestational diabetes, it was unclear as to the potential synergistic or oppositional effects of the combined conditions on infant birthweight. While the

direction of impact on birthweight was similar for gestational diabetes and periodontal disease, the magnitude of impact for gestational diabetes was higher than that of periodontal disease and the magnitude for gestational diabetes alone was not noticeably different from gestational diabetes in combination with periodontal disease. The birthweight distributions across all four categories of the two combined conditions were similar in shape and appearance to each other. This finding does not lend support to the notion that periodontal disease may be having direct impacts on the tails of the birthweight distribution. The severity of the case definition for periodontal disease did not appear to impact the relationship of infant birthweight, providing more evidence that periodontal disease is not related to infant birthweight.

The results of this study only represent the defined population served by the University of Kentucky Maternal-Fetal Medicine practice and may not be fully generalizable to larger populations or to geographic-based populations in the same network area as the clinic. This clinic serves a greater proportion of women with Hispanic ethnicity than the overall population, important because the birth rate among the Hispanic population is highest in the United States (Hamilton 2010). It should also be noted that the analyses were only preliminary, and these results may change when a full dataset is available. However, the matched analyses do not guarantee gains in efficiency beyond that obtained from having an increased sample size (Rothman 1998).

In summary, we found gestational diabetes as an important predictor of high infant birthweight and no effect of periodontal disease on infant birthweight

regardless of gestational diabetes status. The results of this study are important for management of patients with gestational diabetes, when fetal macrosomia is suspected. Periodontal disease does not appear to represent an increased risk of fetal macrosomia and thus would likely perform poorly as a risk marker to induce delivery or perform a cesarean section to prevent fetal macrosomia from complicating the delivery. Likewise, periodontal disease treatment would likely have little impact on women with gestational diabetes for the purpose of preventing fetal macrosomia. However, because periodontal disease was not associated adversely with infant birthweight does not mean that periodontal disease should not be considered a risk marker when other maternal morbidities are present.

Figures and Tables

Figure 3.1: Population flow diagram for selection of cases and controls used in the preliminary analysis of gestational diabetes, periodontal disease and infant birthweight.

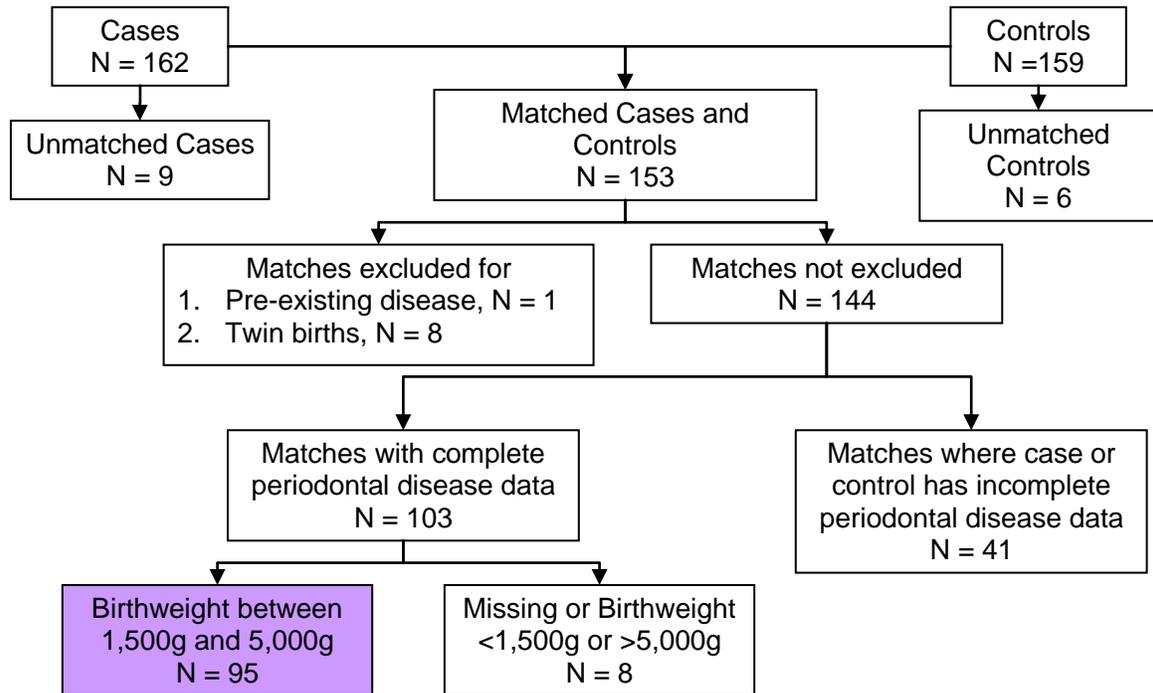


Figure 3.2: Distribution of Infant Birthweight by Gestational Diabetes Status and Periodontal Disease Status

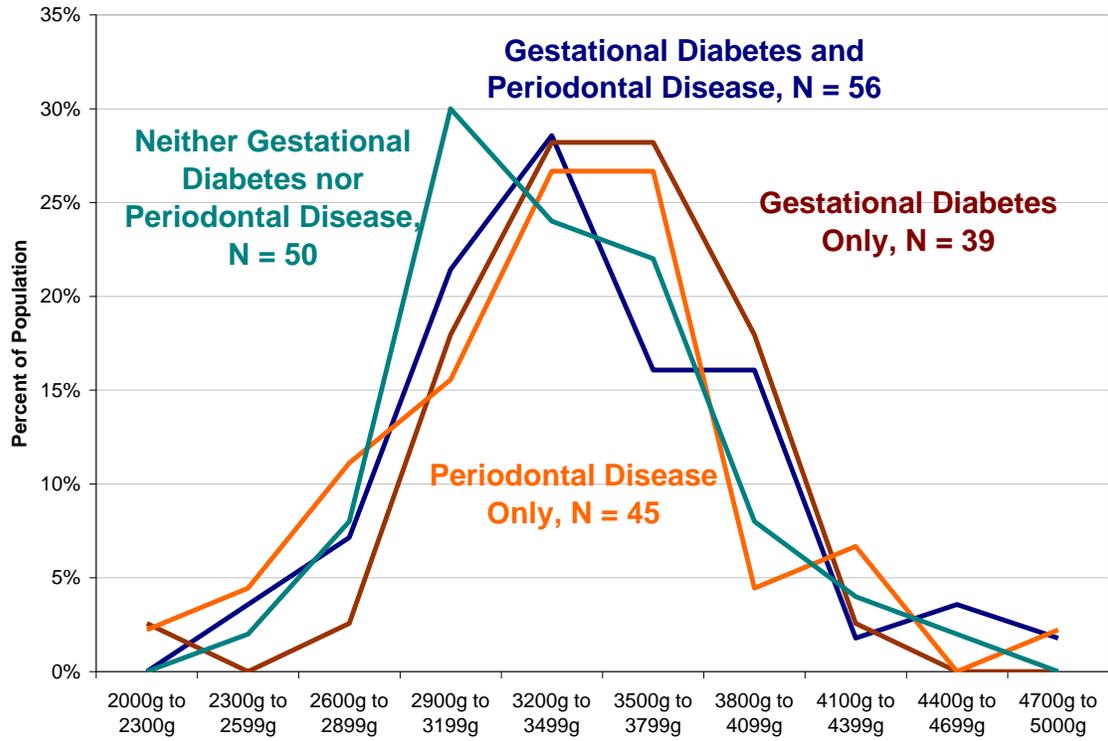


Table 3.1: Mean infant birthweight (grams) and standard error among study participants by gestational diabetes and periodontal disease status

Independent variable	N	Mean	Standard Error	P-value
Gestational diabetes				
Yes	95	3,449	48	0.2084
No	95	3,366	45	
Periodontal disease				
Yes	101	3,412	50	0.8745
No	89	3,402	43	
Gestational diabetes, periodontal disease combination				
Both gestational diabetes and periodontal disease	56	3,445	64	0.3300
Gestational diabetes only	39	3,455	61	
Periodontal disease only	45	3,372	78	
Neither gestational diabetes nor periodontal disease	50	3,360	59	
Total	190	3,407	33	

Table 3.2: Prevalence and association of potential confounding variables among pregnant women with and without gestational diabetes for evaluating the relationship between gestational diabetes and infant birthweight.

Variable	Total		Gestational Diabetes		No Gestational Diabetes		p-value
	N	%	N	%	N	%	
Smoking Status							
Current Smoker	19	10.0%	13	13.7%	6	6.3%	0.0684
Previous Smoker	37	19.5%	22	23.2%	15	15.8%	
Never Smoker	134	70.5%	60	63.2%	74	77.9%	
Race/Ethnicity							
Caucasian	68	35.8%	34	35.8%	34	35.8%	1.0000
Black	20	10.5%	10	10.5%	10	10.5%	
Hispanic	84	44.2%	42	44.2%	42	44.2%	
Asian	18	9.5%	9	9.5%	9	9.5%	
Estimated Gestational Age							
< 37 weeks	13	6.8%	6	6.3%	7	7.4%	0.7738
37 to 41 weeks	177	93.2%	89	93.7%	88	92.6%	
History of Drug Use							
Yes	13	7.0%	6	6.5%	7	7.6%	0.7582
No	172	93.0%	87	93.5%	85	92.4%	
Birthweight							
>= 4000 grams	17	8.9%	7	7.4%	10	10.5%	0.6621
>= 2500g and < 4000 grams	168	88.4%	86	90.5%	82	86.3%	
< 2500 grams	5	2.6%	2	2.1%	3	3.2%	
Periodontal disease							
Yes	101	53.2%	56	58.9%	45	47.4%	0.1098
No	89	46.8%	39	41.1%	50	52.6%	
Variable	N	Mean±SE	N	Mean±SE	N	Mean±SE	p-value
Mean Maternal Age (years)	190	29.0±0.4	95	29.4±0.6	95	28.6±0.5	0.2976
Mean Gestational Age (weeks)	190	38.6±0.1	95	38.4±0.1	95	38.7±0.2	0.0790
Mean Birthweight (grams)	190	3,407±33	95	3,449±45	95	3,366±48	0.2084

Table 3.3: Prevalence and association of potential confounding variables among pregnant women with and without periodontal disease for evaluating the relationship between periodontal disease and infant birthweight.

Variable	Total		Periodontal Disease		No Periodontal Disease		p-value
	N	%	N	%	N	%	
Smoking Status							
Current Smoker	19	10.0%	13	12.9%	6	6.7%	0.0641
Previous Smoker	37	19.5%	14	13.9%	23	25.8%	
Never Smoker	134	70.5%	74	73.3%	60	67.4%	
Race/Ethnicity							
Caucasian	68	35.8%	33	32.7%	35	39.3%	0.1596
Black	20	10.5%	9	8.9%	11	12.4%	
Hispanic	84	44.2%	52	51.5%	32	36.0%	
Asian	18	9.5%	7	6.9%	11	12.4%	
Estimated Gestational Age							
Less than 37 weeks	13	6.8%	8	7.9%	5	5.6%	0.5304
37 to 41 weeks	177	93.2%	93	92.1%	84	94.4%	
History of Drug Use							
Yes	13	7.0%	7	7.2%	6	6.8%	0.9157
No	172	93.0%	90	92.8%	82	93.2%	
Birthweight							
More than 4000 grams	17	8.9%	11	10.9%	6	6.7%	0.5679
>= 2500 and < 4000 grams	168	88.4%	87	86.1%	81	91.0%	
Less than 2500 grams	5	2.6%	3	3.0%	2	2.2%	
Gestational diabetes							
Yes	95	50.0%	56	55.4%	39	43.8%	0.1098
No	95	50.0%	45	44.6%	50	56.2%	
Variable	N	Mean±SE	N	Mean±SE	N	Mean±SE	p-value
Mean Maternal Age (years)	190	29.0±0.4	101	29.9±0.5	89	28.0±0.6	0.0163
Mean Gestational Age (weeks)	190	38.6±0.1	101	38.4±0.1	89	38.8±0.2	0.0267
Mean Birthweight (grams)	190	3,407±33	101	3,412±50	89	3,402±43	0.8745

Table 3.4: Mean infant birthweight (grams) and standard error of women with and without gestational diabetes, stratified by potential risk factor or confounding variable.

Variable	Total			Gestational Diabetes			No Gestational Diabetes		
	N	Mean	SE	N	Mean	SE	N	Mean	SE
Smoking Status									
Current Smoker	19	3,216	129	13	3,200	121	6	3,250	336
Previous Smoker	37	3,432	72	22	3,474	77	15	3,371	139
Never Smoker	134	3,428	38	60	3,494	59	74	3,374	50
Race/Ethnicity									
Caucasian	68	3,451	57	34	3,402	85	34	3,501	77
Black	20	3,381	130	10	3,369	166	10	3,393	210
Hispanic	84	3,354	46	42	3,469	63	42	3,239	64
Asian	18	3,519	88	9	3,622	77	9	3,416	157
Estimated Gestational Age									
< 37 weeks	13	2,919	146	6	3,093	266	7	2,770	143
37 to 41 weeks	177	3,443	32	89	3,473	44	88	3,413	47
History of Drug Use									
Yes	13	3,153	130	6	3,187	217	7	3,125	169
No	172	3,418	35	87	3,461	46	85	3,374	51
Periodontal disease									
Yes	101	3,412	50	56	3,445	64	45	3,372	78
No	89	3,402	43	39	3,455	61	50	3,360	59
Total	190	3,407	33	95	3,449	45	95	3,366	48

Table 3.5: Mean infant birthweight (grams) and standard error of women with and without periodontal disease, stratified by potential risk factor or confounding variable.

Variable	Total			Periodontal Disease			No Periodontal Disease		
	N	Mean	SE	N	Mean	SE	N	Mean	SE
Smoking Status									
Current Smoker	19	3,216	129	13	3,302	166	6	3,028	192
Previous Smoker	37	3,432	72	14	3,439	158	23	3,428	68
Never Smoker	134	3,428	38	74	3,427	54	60	3,429	53
Race/Ethnicity									
Caucasian	68	3,451	57	33	3,436	92	35	3,466	70
Black	20	3,381	130	9	3,605	181	11	3,197	172
Hispanic	84	3,354	46	52	3,347	66	32	3,365	59
Asian	18	3,519	88	7	3,534	176	11	3,510	99
Estimated Gestational Age									
< 37 weeks	13	2,919	146	8	2,973	223	5	2,832	152
37 to 41 weeks	177	3,443	32	93	3,450	49	84	3,436	42
History of Drug Use									
Yes	13	3,153	130	7	3,071	163	6	3,250	217
No	172	3,418	35	90	3,423	53	82	3,412	44
Gestational diabetes									
Yes	95	3,449	45	56	3,445	64	39	3,455	61
No	95	3,366	48	45	3,372	78	50	3,360	59
Total	190	3,407	33	101	3,412	50	89	3,402	43

Table 3.6: Mean infant birthweight and standard error by combination of gestational diabetes and periodontal disease, dependent upon periodontal disease case definition

Periodontal Disease Status	Periodontal Disease Definition	"Gestational Diabetes"			"No Gestational Diabetes"		
		N	Mean Birthweight	SE	N	Mean Birthweight	SE
Yes	>=2 Teeth with PD >= 4mm, CAL >= 2mm, BoP	69	3,483	55	56	3,368	69
	>=3 Teeth with PD >= 4mm, CAL >= 2mm, BoP	64	3,481	59	51	3,373	73
	>=4 Teeth with PD >= 4mm, CAL >= 2mm, BoP	56	3,445	64	45	3,372	78
	>=2 Teeth with PD >= 5mm, CAL >= 2mm, BoP	62	3,467	59	54	3,379	71
	>=3 Teeth with PD >= 5mm, CAL >= 2mm, BoP	55	3,452	65	49	3,384	75
	>=4 Teeth with PD >= 5mm, CAL >= 2mm, BoP	48	3,453	72	41	3,382	85
No	>=2 Teeth with PD >= 4mm, CAL >= 2mm, BoP	26	3,359	73	39	3,362	63
	>=3 Teeth with PD >= 4mm, CAL >= 2mm, BoP	31	3,383	66	44	3,357	62
	>=4 Teeth with PD >= 4mm, CAL >= 2mm, BoP	39	3,455	61	50	3,360	59
	>=2 Teeth with PD >= 5mm, CAL >= 2mm, BoP	33	3,415	68	41	3,349	62
	>=3 Teeth with PD >= 5mm, CAL >= 2mm, BoP	40	3,445	60	46	3,346	60
	>=4 Teeth with PD >= 5mm, CAL >= 2mm, BoP	47	3,445	55	54	3,353	56

Table 3.7: Unadjusted associations between predictor variables and birthweight (grams) with gestational diabetes and periodontal disease measured separately and in combination

Variable	Beta estimate	95% Confidence Interval	P-value
Maternal Age (per year)	1.16	(-10.35, 12.68)	0.8111
Gestational Age (per week)	128.80	(86.34, 171.24)	0.0001
Smoking Status			
Current smoker	-211.84	(-429.76, 6.09)	0.3108
Previous smoker	4.23	(-160.87, 169.33)	
Never smoker	<i>Reference</i>	<i>Reference</i>	
History of drug use	-264.11	(-519.72, -8.50)	0.0615
Race/Ethnicity			
Caucasian	<i>Reference</i>	<i>Reference</i>	0.1830
Black	-70.71	(-293.49, 152.08)	
Hispanic	-97.53	(-240.40, 45.34)	
Asian	67.71	(-164.44, 299.86)	
Periodontal disease	10.00	(-119.99, 140.00)	0.8758
Gestational diabetes	83.36	(-46.96, 213.67)	0.2113
Combined Periodontal Disease and Gestational Diabetes			
Gestational Diabetes and Periodontal Disease	84.44	(-90.63, 259.50)	0.6345
Gestational Diabetes Only	94.87	(-97.41, 287.16)	
Periodontal Disease Only	11.32	(-172.90, 195.55)	
Neither Gestational Diabetes nor Periodontal Disease	<i>Reference</i>	<i>Reference</i>	

Table 3.8: Unadjusted associations and bivariate adjusted associations between gestational diabetes and infant birthweight (grams) and between periodontal disease and infant birthweight

Adjustment Variable	Gestational Diabetes			Periodontal Disease		
	Beta estimate	95% Confidence Interval	P-value	Beta estimate	95% Confidence Interval	P-value
Unadjusted	83.36	(-46.96, 213.67)	0.2113	10.00	(-119.99, 140.00)	0.8758
Adjusted for...						
Maternal Age	82.84	(-48.21, 213.89)	0.2211	7.94	(-120.74, 136.62)	0.8359
Gestational Age	132.04	(18.26, 245.83)	0.0234	72.74	(-48.83, 194.30)	0.2188
Smoking	101.55	(-28.20, 231.31)	0.1464	24.63	(-106.86, 156.11)	0.7136
History of Drug Use	85.21	(-45.39, 215.81)	0.2029	-2.00	(-133.28, 129.28)	0.9756
Race/Ethnicity	83.36	(-48.05, 214.77)	0.2113	27.43	(-104.19, 159.04)	0.6635
Gestational Diabetes		<i>Not Applicable</i>		0.61	(-130.15, 131.36)	0.9925
Periodontal Disease	83.29	(-48.25, 214.83)	0.2168		<i>Not Applicable</i>	

Table 3.9: Multivariate model for the association between gestational diabetes, periodontal disease and infant birthweight (grams) with multiplicative interaction term.

Predictor Variable	Beta estimate	95% Confidence Interval	P-value
Gestational Age (per week)	134.62	(90.78, 178.46)	<0.0001
Smoking Status			
Current smoker	-200.40	(-429.63, 28.82)	0.4297
Previous smoker	-23.69	(-190.59, 143.20)	
Never smoker	<i>Reference</i>	<i>Reference</i>	
Race/Ethnicity			
Caucasian	<i>Reference</i>	<i>Reference</i>	0.2479
Black	-43.60	(-271.99, 184.79)	
Hispanic	-155.46	(-309.01, -1.91)	
Asian	-43.91	(-281.37, 193.54)	
Periodontal disease	135.73	(-35.84, 307.30)	0.1102
Gestational diabetes	191.91	(17.93, 365.88)	0.0181
GDM * Periodontal Disease	-101.06	(-341.81, 139.68)	0.4104

Table 3.10: Multivariable model for the association between gestational diabetes, periodontal disease and infant birthweight (grams) with periodontal disease and gestational diabetes in combined strata.

Predictor Variable	Beta estimate	95% Confidence Interval	P-value
Gestational Age (per week)	134.62	(90.78, 178.46)	<0.0001
Smoking			
Current smoker	-200.40	(-429.63, 28.82)	0.4297
Previous smoker	-23.69	(-190.59, 143.20)	
Never smoker	<i>Reference</i>	<i>Reference</i>	
Race/Ethnicity			0.2479
Caucasian	<i>Reference</i>	<i>Reference</i>	
Black	-43.60	(-271.99, 184.79)	
Hispanic	-155.46	(-309.01, -1.91)	
Asian	-43.91	(-281.37, 193.54)	
Combined Periodontal Disease and Gestational Diabetes			
Gestational Diabetes and Periodontal Disease	226.57	(65.74, 387.41)	0.0309
Gestational Diabetes Only	191.91	(17.93, 365.88)	
Periodontal Disease Only	135.73	(-35.84, 307.30)	
Neither Gestational Diabetes nor Periodontal Disease	<i>Reference</i>	<i>Reference</i>	

References

- Alexander GR, Himes J, Kaufman R, Mor J, Kogan M. A United States national reference for fetal growth. *Obstetrics & Gynecology*. 1996;87:163-8.
- Alwan N, Tuffnell DJ, West J. Treatments for gestational diabetes. *Cochrane Database of Systematic Reviews*. 2009. Issue 3.
- Bailey BA, McCook JG, Hodge A, McGrady L. Infant birth outcomes among substance using women: why quitting smoking during pregnancy is just as important as quitting illicit drug use. *Maternal & Child Health Journal*. 2011;15:ePub.
- Ehrlich SF, Crites YM, Hedderson MM, Darbinian JA, Ferrara A. The risk for large for gestational age across increasing categories of pregnancy glycemia. *American Journal of Obstetrics & Gynecology*. 2011;204:240.e1-6.
- Floyd RL, Rimer BK, Giovino GA, Mullen PD, Sullivan SE. A review of smoking in pregnancy: effects on pregnancy outcomes and cessation efforts. *Annual Review of Public Health*. 1993;14:379-411.
- Grossi SG, Genco RJ. Periodontal disease and diabetes mellitus: a two-way relationship. *Annals of Periodontology*. 1998;3(1):51-61.
- Hamilton BE, Martin JA, Ventura SJ. Births: Preliminary data for 2009 [online]. National vital statistics reports; vol 59 no 3. National Center for Health Statistics. 2010.
- HAPO Study Cooperative Research Group. Hyperglycemia and adverse pregnancy outcomes. *New England Journal of Medicine*. 2008;358:1991-2002.
- Higgins S. Smoking in pregnancy. *Current Opinion in Obstetrics & Gynecology*. 2002;14:145-51.
- Jacqueminet S, Jannot-Lamotte MF. Therapeutic management of gestational diabetes. *Diabetes & Metabolism*. 2010;36:658-71.
- Kabali C, Werler MM. Prepregnancy body mass index, weight gain and the risk of delivering large babies among non-diabetic mothers. *International Journal of Gynaecology & Obstetrics*. 2007;97(2):100-104.
- Kim SY, England L, Wilson HG, Bish C, Satten GA, Dietz P. Percentage of gestational diabetes mellitus attributable to overweight and obesity. *American Journal of Public Health*. 2010;100:1047-52.

- Lalla E, Papapanou PN. Diabetes mellitus and periodontitis: a tale of two common interrelated diseases. *Nature Reviews, Endocrinology*. 2011;7:738-48.
- Landon MB, Spong CY, Thorn E, Carpenter MW, Ramin SM, Casey B, Wapner RJ, Varner MW, Rouse DJ, Thorp JM, Sciscione A, Catalano P, Harper M, Saade G, Lain KY, Sorokin Y, Peaceman AM, Tolosa JE, Anderson GB. A multicenter, randomized trial of treatment for mild gestational diabetes. *New England Journal of Medicine*. 2009;361:1339-48.
- Lopez NJ, Smith PC, Gutierrez J. Higher risk of preterm birth and low birth weight in women with periodontal disease. *Journal of Dental Research*. 2002;81(1):58-63.
- Lowe LP, Metzger BE, Lowe WL, Dyer AR, McDade TW, McIntyre D. Inflammatory mediators and glucose in pregnancy: results from a subset of the hyperglycemia and adverse pregnancy outcome (HAPO) study. *Journal of Clinical Endocrinology & Metabolism*. 2010;95:5427-34.
- Lunardelli AN, Peres MA. Is there an association between periodontal disease, prematurity and low birth weight? A population-based study. *Journal of Clinical Periodontology*. 2005;32:938-46.
- Marin C, Segura-Egea JJ, Martinez-Sahuquillo A, Bullon P. Correlation between infant birth weight and mother's periodontal status. *Journal of Clinical Periodontology*. 2005;32:299-304.
- Martin JA, Hamilton BE, Sutton PD, Ventura SJ, Mathews TJ, Osterman MJK. Births: final data for 2008. National vital statistics reports; vol 59 no 1. Hyattsville, MD: National Center for Health Statistics. 2010.
- Mehta SH, Kruger M, Sokol RJ. Being too large for gestational age precedes childhood obesity in African Americans. *American Journal of Obstetrics & Gynecology*. 2011;204:265.e1-5.
- Michalowicz BS, Hodges JS, DiAngelis, AJ, Lupo VR, Novak MJ, Ferguson JE, Buchanan W, Bofill J, Papapanou PN, Mitchell DA, Matseone S, Tschida PA. Treatment of periodontal disease and the risk of preterm birth. *New England Journal of Medicine*. 2006;355:1885-94.
- Mocarski M, Savitz DA. Ethnic differences in the association between gestational diabetes and pregnancy outcome. *Maternal & Child Health Journal*. 2011;15:ePub.
- Molitero LFM, Monteiro B, da Silva Figueredo CM, Fischer RG. Association

- between periodontitis and low birth weight: a case-control study. *Journal of Clinical Periodontology*. 2005;32:886-90.
- Moore S, Ide M, Coward PY, Randhawa M, Borkowska E, Baylis R, Wilson RF. A prospective study to investigate the relationship between periodontal disease and adverse pregnancy outcome. *British Dental Journal*. 2004;197:251-58.
- Moreu G, Tellez L, Gonzalez-Jaranay M. Relationship between maternal periodontal disease and low-birth-weight pre-term infants. *Journal of Clinical Periodontology*. 2005;32:622-27.
- Newnham JP, Newnham IA, Ball CM, Wright M, Pennell CE, Swain J, Doherty DA. Treatment of periodontal disease during pregnancy: a randomized controlled trial. *Obstetrics & Gynecology*. 2009;114(6):1239-48.
- Offenbacher S, Beck JD, Jared HL, Mauriello S, Mendoza M, Couper LC, Stewart DD, Murtha AP, Cochran DL, Dudley DJ, Reddy MS, Geurs NC, Hauth JC. Effects of periodontal therapy on rate of preterm delivery: a randomized controlled trial. *Obstetrics and Gynecology*. 2009;114:551-59.
- Ovesen P, Rasmussen S, Kesmodel U. Effect of prepregnancy maternal overweight and obesity on pregnancy outcome. *Obstetrics & Gynecology*. 2011;118:305-12.
- Persson M, Pasupathy D, Hanson U, Norman M. Birth size distribution in 3,705 infants born to mothers with type 1 diabetes. *Diabetes Care*. 2011;34:1145-49.
- Pettitt DJ, Aleck KA, Baird HR, Carraher MJ, Bennett PH, Knowler WC. Congenital susceptibility to NIDDM. Role of intrauterine environment. *Diabetes*. 1988;37:622-28.
- Rosenberg TJ, Garbers S, Chavkin W, Chiasson MA. Prepregnancy weight and adverse perinatal outcomes in an ethnically diverse population. *Obstetrics & Gynecology*. 2003;102:1022-27.
- Rothman KJ, Greenland S. Matching. *Modern Epidemiology*, 2nd edition. 1998. Lippincott, Williams & Wilkins, Philadelphia, PA.
- Taylor GW, Burt BA, Becker MP, et al. Severe periodontitis and risk for poor glycemic control in subjects with non-insulin-dependent diabetes mellitus. *Journal of Periodontology*. 1996;67(suppl.):1085-1093.
- Torloni MR, Betran AP, Horta BL, Nakamura MU, Atallah AN, Moron AF, Valente

- O. Prepregnancy BMI and the risk of gestational diabetes: a systematic review of the literature with meta-analysis. *Obesity Reviews*. 2010;10:194-203.
- Uppal A, Uppal S, Pinto A, Dutta M, Shrivatsa S, Dandolu V, Mupparapu M. The effectiveness of periodontal disease treatment during pregnancy in reducing the risk of experiencing preterm birth and low birth weight: a meta-analysis. *JADA*. 2010;141:1423-34.
- Vidarsdottir H, Geirsson RT, Hardardottir H, Valdimarsdottir U, Dagbjartsson A. Obstetric and neonatal risks among extremely macrosomic babies and their mothers. *American Journal of Obstetrics & Gynecology*. 2011;204:423.e1-6.
- Xiong X, Buekens P, Vastardis S, Pridjian G. Periodontal disease and gestational diabetes mellitus. *American Journal of Obstetrics & Gynecology*. 2006;195(4):1086-9.
- Zhang X, Decker A, Platt RW, Kramer MS. How big is too big? The perinatal consequences of fetal macrosomia. *American Journal of Obstetrics & Gynecology*. 2008;198:517.e1-e6.

Chapter 4

Pre-Eclampsia

Introduction

Pre-eclampsia occurs in five percent to seven percent of pregnancies and can contribute to several maternal complications that include increased risk of hemorrhage, seizures, and maternal mortality (Walker 2000). Pre-eclampsia only resolves after delivery of the infant (Lain 2002). Early induction of labor in severe cases may be required which may then result in iatrogenic prematurity of the infant (Lain 2002). Pregnant women with chronic conditions such as heart disease and kidney disease are at increased risk of pre-eclampsia and may share common underlying pathophysiology (Bellamy 2007, Hladunewich 2007). Primiparous women are more likely to develop pre-eclampsia (Luo 2007) as are women over 40 years of age (Duckitt 2005). When pre-eclampsia is differentiated as to the timing of its detection, early onset pre-eclampsia is typically associated with placental factors while late onset pre-eclampsia is typically associated with maternal factors (Valensise 2008). Smoking has been shown to reduce the risk of pre-eclampsia (Conde-Agudelo 1999), but is not recommended due its contribution to other adverse outcomes such as birth

defects and fetal growth restriction (Higgins 2002). Pre-eclampsia is more common in African American women than White or Hispanic women (Brown 2007).

Gestational diabetes contributes to the risk of pre-eclampsia and pregnancy-induced hypertensive disorders (Bryson 2003). Gestational diabetes and pre-eclampsia share common risk factors and may ultimately share an underlying pathophysiology (Ros 1998). Others have found a relationship between induced hypertensive disorders but not with pre-eclampsia (Caruso 1999). Markers of inflammation are elevated in women with gestational diabetes (Barden 2004) and markers of inflammation increase with maternal glucose level even in women who do not meet clinical definitions of diabetes (Lowe 2010). These inflammatory markers and increased blood lipids that may present during gestational diabetes mediate the influence of pre-pregnancy body mass index on the risk of pre-eclampsia (Bodnar 2005). Insulin resistance has been linked as a contributor to pregnancy-induced hypertension (Hauth 2011). Pathophysiologic relationships between gestational diabetes and endothelial damage have also been demonstrated (Anastasiou 1998, Paradisi 2002). Insulin therapy has demonstrated results in reducing the risk of pre-eclampsia (Alwan 2009). Oral antidiabetic agents have demonstrated effectiveness at reducing the risk of pre-eclampsia but are currently not recommended as an alternative treatment (Jacqueminet 2010).

Periodontal disease has also demonstrated a relationship with pre-eclampsia (Cota 2006, Contreras 2006, Boggess 2003, Canakci 2004, Canakci

2007), although not universally (Khader 2006). The strength of this relationship has been demonstrated to increase with severity as well as with progression of periodontal disease through the course of pregnancy (Boggess 2003). Inflammatory markers found in serum and gingival crevicular fluid were significantly higher among women with pre-eclampsia (Canakci 2007). The relationship between pre-eclampsia and periodontal disease was found among women with high levels of C-reactive protein but not among women with low levels of C-reactive protein. (Ruma 2008). In women with high levels of 8-isoprostane, a marker of oxidative stress, there was no relationship between pre-eclampsia and periodontal disease (Horton 2009). Randomized controlled trials evaluating the effectiveness of periodontal disease treatment in pregnant women have found no significant reduction in the risk of developing pre-eclampsia (Newnham 2009, Michalowicz 2006, Offenbacher 2009).

Recent studies examining a relationship between both gestational diabetes and periodontal disease suggest a possible synergistic relationship between the two conditions. A mechanism has been proposed by which diabetes contributes to inflammation while also increasing the severity of periodontal disease and by which periodontal disease contributes to inflammation while also increasing the severity of diabetes (Grossi 1998). Because of the potential implications of these two comorbid conditions, gestational diabetes and pre-eclampsia, sharing similar underlying pathophysiological relationships with pre-eclampsia, this study is designed to provide information about the extent to which these two conditions may have biologically synergistic effects. We have

found no other study that assessed whether additive effects of these two conditions exist, such that the risk of pre-eclampsia is greater when both conditions are present compared to when only one condition or neither condition are present.

Methods

This study used preliminary data collected for the University of Kentucky, Oral Infection: Impact on Gestational Diabetes study, a prospective matched cohort study. 321 pregnant women were recruited consecutively between September 2005 and September 2009 based upon the presence or absence of gestational diabetes mellitus. Pregnant women were included if they were at least 16 years of age and had at least 20 natural teeth at the time of periodontal assessment. Women were excluded if they were unable to provide consent, unable to cooperate with the study, were placed at medical risk through participation, were under 16 years of age, or had a history of type 1 or type 2 diabetes prior to pregnancy.

Gestational diabetes mellitus was identified through universal screening with a two step diagnostic test, a 50 gram glucose challenge test followed by a 100 gram oral glucose tolerance test, performed for all pregnant women who visited the University of Kentucky Bluegrass High Risk Maternal-Fetal Medicine Clinic. Women identified with gestational diabetes were then matched to a pregnant woman without gestational diabetes by age within a five-year interval, race, and gestational week at enrollment within a two week interval. Nine cases

and six controls were excluded for the lack of a match. One matched pair was removed for pre-existing health condition, and an additional 42 matched pairs were excluded due to a lack of periodontal examination information. After exclusions, 110 matched cases and controls with complete periodontal disease examination information were used for this analysis.

Pre-eclampsia was assessed during clinic visits and defined as a dichotomous outcome using the National High Blood Pressure Education Program Working Group criteria of a systolic blood pressure of greater than or equal to 140mm Hg or a diastolic blood pressure of greater than or equal to 90mm Hg on two or more occasions after 20 weeks gestation for women with previously normal blood pressure. In addition, proteinuria must exceed 0.3g protein from a 24-hour urine sample (NHBPEPWP 2000).

Clinical periodontal disease measures were assessed at baseline (within one to two weeks of enrollment) using a full mouth examination. Oral examination was performed by Delta Dental Plan of Kentucky Clinical Research Center. A medical research nurse contacted enrollees to arrange clinical visits. The periodontal disease assessment included measures of pocket depth, clinical attachment loss, gingival inflammation, and bleeding upon probing. The proportion of sites with each clinical indicator provides a summary measure for classification of periodontal disease. Periodontal disease was defined as bleeding on probing, pocket depth of at least four millimeters and clinical attachment loss of at least two millimeters at four or more teeth, excluding third molars, for analysis unless otherwise specified.

The research nurse extracted maternal and fetal data from medical records of participants. Demographic information such as race (Caucasian, Black, Asian), Hispanic ethnicity, and maternal age were recorded as part of the medical history. Smoking was assessed through an interviewer-administered health history conducted by a medical research nurse. Tobacco use was measured by self-reported use of cigarettes, chewing tobacco, snuff, cigars, and pipe tobacco. Tobacco use in the analysis was limited to cigarette smoking status (current smoker, former smoker, never smoker) as other forms of tobacco use were rare and did not exist in the absence of cigarette smoking. A medical history and pregnancy history were conducted to assess the presence of any confounding medical conditions such as heart disease, kidney disease, past pregnancy experiences, and presence of vaginal infection, all treated as dichotomous exposure variables. Height and weight measurements were taken at both the enrollment visit and update visit, but pre-pregnancy body mass index was not available for the majority of study participants. Nutritional intake was not assessed with the exception of identifying women on special diets.

I performed bivariate analysis of categorical variables to assess associations between predictors, potential confounders, and outcomes using chi-square and Fischer exact tests depending upon cell sample size. T-tests were used to assess associations with continuous variables. Because a matched analysis ultimately is limited to matched pairs with discordant outcomes, the low frequency of discordance where pre-eclampsia was present in the absence of gestational diabetes and periodontal disease led to unreliable confidence limits.

Therefore, an unmatched analysis using multivariate logistic regression was performed in SAS version 9.2 due to the preliminary sample size that did not meet the assumptions for matched longitudinal approaches (Alexander 2007).

Results

While periodontal disease was more common among women with gestational diabetes compared to women without gestational diabetes, it was not statistically significantly higher across several periodontal case definitions in unadjusted analyses. Table 4.1 details how the prevalence of periodontal disease varies across gestational diabetes exposure groups by severity of the periodontal disease case definition.

Using the definition of four or more teeth with at least four millimeters of pocket depth, two millimeters of clinical attachment loss and bleeding upon probing, periodontal disease was found among 56.4% of study participants, among 60.0% of women with gestational diabetes and among 52.7% of women without gestational diabetes ($p=0.2768$). The prevalence of pre-eclampsia was 6.4% among all study participants, 8.2% among women with gestational diabetes and 4.6% among women without gestational diabetes ($p=0.2693$). Pre-eclampsia was present in 9.7% of women with periodontal disease and 2.1% of women without periodontal disease ($p=0.0155$). Women with both gestational diabetes and periodontal disease had the highest prevalence of pre-eclampsia at 12.1% compared to a prevalence of 6.9% in women with periodontal disease alone, a prevalence of 2.3% in women with gestational diabetes alone, and a

prevalence of 1.9% in women with neither condition ($p=0.0125$). The number of cases of pre-eclampsia and prevalence of pre-eclampsia stratified by both gestational diabetes and periodontal disease status can be found in Table 4.2.

Maternal demographic data, pregnancy data, and medical history about potential confounding characteristics and their associations with gestational diabetes, periodontal disease, and pre-eclampsia can be found in Table 4.3 and 4.4. Current and former smokers and higher maternal age were more common among women with gestational diabetes. Hypertension and/or pre-eclampsia were more common among women with gestational diabetes. In each instance differences were not statistically significant. (Table 4.3).

Women with periodontal disease were more likely to be current smokers, to be of Hispanic ethnicity, and to have higher maternal age compared to women without periodontal disease. While hypertension was not associated with periodontal disease, the prevalence of pre-eclampsia was significantly higher in women with periodontal disease compared to women without periodontal disease (Table 4.4).

None of the potential confounding variables demonstrated statistically significant associations with the outcome of pre-eclampsia (Table 4.5) although when current and former smokers were combined into an ever smoker category, this demonstrated borderline increased risk. No Asian women in this study developed pre-eclampsia, and were combined with the lowest prevalent racial group, Whites, in subsequent unadjusted and adjusted analyses.

In unadjusted analysis, pregnant women with periodontal disease were five times more likely to develop pre-eclampsia than women without periodontal disease. Women with a previous pregnancy had nonstatistically significant reduced risks of pre-eclampsia while women who had nonstatistically significant increased risks of pre-eclampsia. When ever smokers were evaluated in the multivariable model, I found no statistical significance as well. Gestational diabetes was associated with an increased risk of pre-eclampsia but not at a statistically significant level (Table 4.6)

Variables with literature-supported associations with pre-eclampsia or with statistically relevant associations were considered for multivariable logistic regression. These included maternal race and ethnicity, smoking status, maternal age, and whether the woman had a previous pregnancy. After adjusting for race, ethnicity, and smoking status, risks for pre-eclampsia were elevated among women with gestational diabetes and periodontal disease with periodontal disease contributing far greater risk than gestational diabetes (Table 4.7). However the multiplicative interaction term was non-significant ($p=0.6831$) which suggests only an additive relationship between the two conditions on the outcome of pre-eclampsia.

When periodontal disease and gestational diabetes mellitus were modeled as a combined variable no elevation in risk was observed among women with gestational diabetes alone. The magnitude of the relationship increased among women with periodontal disease alone, and was greatest among women with

both periodontal disease and gestational diabetes (Table 4.8). However, the wide confidence intervals limit the interpretability of the observed magnitudes.

To assess the impact of the periodontal case definition, multiple case definitions at differing severity levels of periodontal disease were assessed in the multivariable model. Under more severe case definitions for periodontal disease, the association between periodontal disease and pre-eclampsia became stronger (Table 4.9).

Discussion

The presence of periodontal disease during pregnancy was associated with an increased risk of pre-eclampsia. In the presence of gestational diabetes, the magnitude of the relationship between periodontal disease and pre-eclampsia was even stronger suggesting at least an additive effect of these two conditions on the development of pre-eclampsia. This relationship was demonstrated independent of the effects of maternal age, race, and smoking status. Gestational diabetes failed to demonstrate a significant relationship with pre-eclampsia after risk adjustment in the multivariable model. The failure to demonstrate an association between gestational diabetes and pre-eclampsia after risk adjustment may result in part from women with gestational diabetes undergoing standard treatment of care for gestational diabetes as insulin therapy and oral antidiabetic agents have both demonstrated reduced risks for pre-eclampsia (Alwan 2009, Jacqueminet 2010). No multiplicative interaction was found, possibly the result of inadequate power to test for that interaction since the

results reflect preliminary data rather than the full expected data. However it can be assumed that if two factors are independently associated with an outcome that an interaction that is either additive or multiplicative exists (Greenland 1998a).

While studies have examined the effects of gestational diabetes and periodontal disease on the occurrence of pre-eclampsia, they have not assessed their combined effects. The proposed mechanisms of relationships between periodontal disease and gestational diabetes suggest an increasing severity of each condition in the presence of the other. Here we have demonstrated that this increased severity may manifest in a greater likelihood of pre-eclampsia. This study only evaluated gestational diabetes as a dichotomous measure while its potential impact on pre-eclampsia may potentially be better evaluated as a continuous measure (HAPO 2008). This paper could not address whether the combined conditions and the related inflammation function as a continuous increase in risk throughout the distribution within the population of interest or whether a threshold value is achieved after which additional inflammatory conditions no longer contribute additional risk of developing pre-eclampsia.

The proposed pathophysiologic mechanism linking periodontal disease and gestational diabetes to pre-eclampsia often includes inflammatory processes (Bardon 2004, Lowe 2010, Hauth 2011, Canakci 2007, Ruma 2008). However, the inflammation may only be a marker of other processes that cause endothelial damage to blood vessels such as oxidative stress (Noris 2005). This study may contribute to understanding how the underlying pathophysiological processes for

gestational diabetes and periodontal disease interact to contribute to this adverse outcome.

A limitation of the measure of pre-eclampsia in this study is that it was not differentiated into early or late onset pre-eclampsia as maternal factors are more likely to be related to late onset pre-eclampsia (Valensise 2008). If the increased prevalence of disease represents early onset pre-eclampsia, it may implicate the placental response to periodontal pathogens that have been found in placental tissues. If the increased prevalence of pre-eclampsia occurs as late-onset pre-eclampsia, greater emphasis may be needed on maternal inflammatory responses to gestational diabetes and periodontal disease. Also, severity of pre-eclampsia was not assessed. These results may simply demonstrate an epiphenomenon that periodontal disease and gestational diabetes become worse in the presence of another underlying factor that is the actual cause of pre-eclampsia. However, even if these conditions are not causal in their relationship with pre-eclampsia, they may represent risk markers for identifying high risk pregnancies.

The results of this study only represent the defined population served by the University of Kentucky Maternal-Fetal Medicine practice and may not be fully generalizable to other populations. This clinic serves a greater proportion of women with Hispanic ethnicity than the overall population. Also, these results represent only a preliminary analysis before full recruitment had been completed. A final analysis would likely incorporate the matched design using Cox regression on matched pairs with discordant outcomes to improve efficiency

(Alexander 2007, Greenland 1998b). The current unmatched analysis, because it occurs in an observational cohort study as opposed to a case-control study, does not yield biased point estimates but there is no guarantee the matching will truly improve efficiency when a final dataset is used (Rothman 1998). Residual confounding may exist. While residual confounding is not unique to periodontal disease and systemic disease outcome relationships, computer model simulations for incomplete control of confounders in the periodontal disease and systemic disease relationships can yield spurious positive relationships (Ylostalo 2006).

Despite the observed combined association between periodontal disease and gestational diabetes on the outcome of pre-eclampsia, studies of treatment for periodontal disease will have to assess whether treatment would impact this combined likelihood. Periodontal therapy aimed at ameliorating the level of inflammation from disease during pregnancy has demonstrated mixed results around the ability to reduce the risk of pre-eclampsia, with no randomized controlled trials yet demonstrating a significant reduction (Michalowicz 2006, Offenbacher 2009, Newnham 2009). However, no studies have assessed whether periodontal disease treatments prior to pregnancy reduce the risk of pre-eclampsia or whether the timing or intensity of periodontal treatment during pregnancy matters in the prevention of pre-eclampsia (Xiong 2011). Intensive treatment with insulin has been associated with a reduced risk for pre-eclampsia (Alwan 2009). For women with both conditions present, gestational diabetes therapies may ultimately have greater impacts for women with gestational

diabetes alone if the underlying mechanism is biological synergism between the two conditions.

Pre-eclampsia is a potentially preventable condition, poses additional health risks to pregnant women and their infants, and is an indication for obstetric intervention. Further research is needed to address potential relationships between periodontal disease and gestational diabetes, to assess the modifiable impact from treating these conditions before and during pregnancy, and to evaluate relationships with other co-morbid conditions in the development of pre-eclampsia.

Figures and Tables

Figure 4.1: Population flow diagram for the selection of cases and controls used in the unmatched preliminary analysis of gestational diabetes, periodontal disease, and the potential interaction with pre-eclampsia.

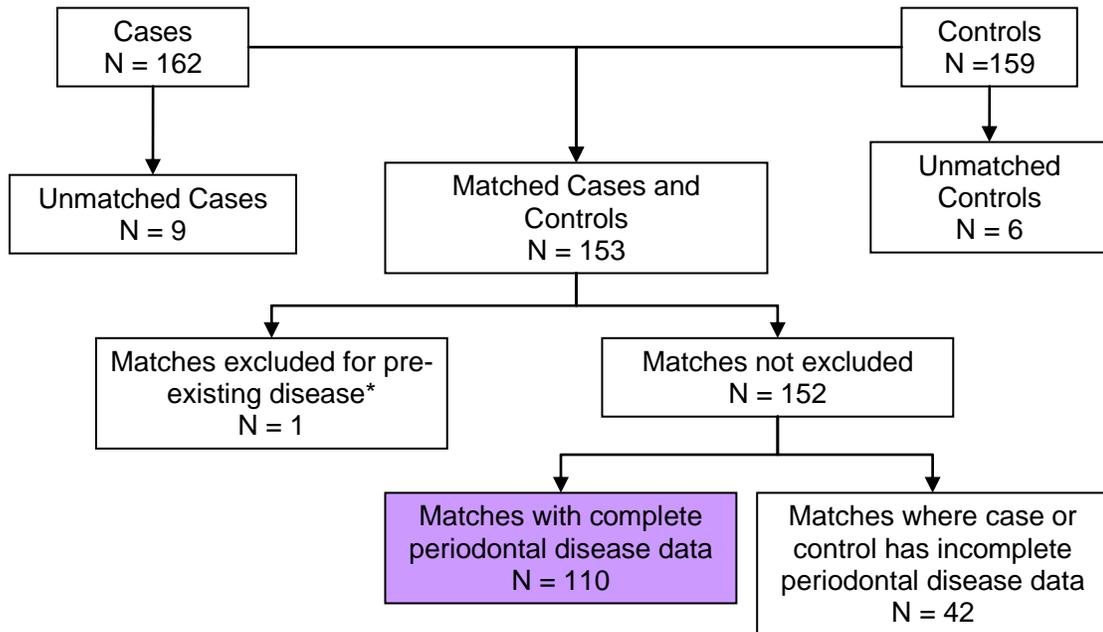


Table 4.1: Prevalence of periodontal disease among pregnant women with and without gestational diabetes by periodontal disease case definition

Periodontal Disease Case Definition	Gestational Diabetes (N=110)		No Gestational Diabetes (N=110)		P-value
	N	%	N	%	
>=2 Teeth with PD >= 4mm, CAL >= 2mm, BoP	80	72.7%	70	63.6%	0.1478
>=3 Teeth with PD >= 4mm, CAL >= 2mm, BoP	74	67.3%	64	58.2%	0.1632
>=4 Teeth with PD >= 4mm, CAL >= 2mm, BoP	66	60.0%	58	52.7%	0.2768
>=2 Teeth with PD >= 5mm, CAL >= 2mm, BoP	72	65.5%	68	61.8%	0.5751
>=3 Teeth with PD >= 5mm, CAL >= 2mm, BoP	64	58.2%	62	56.4%	0.7852
>=4 Teeth with PD >= 5mm, CAL >= 2mm, BoP	57	51.8%	54	49.1%	0.6858

Table 4.2: Prevalence of pre-eclampsia by periodontal disease status (≥ 4 teeth with at least 4mm pocket depth, 2mm clinical attachment loss and bleeding upon probing) among women with and without gestational diabetes

Gestational Diabetes	Periodontal Disease	N	Number with Pre-eclampsia	Percent with Pre-eclampsia	P-value
Gestational diabetes	Periodontal disease	66	8	12.1%	0.0125
	No periodontal disease	44	1	2.3%	
	Total	110	9	8.2%	
No gestational diabetes	Periodontal disease	58	4	6.9%	
	No periodontal disease	52	1	1.9%	
	Total	110	5	4.6%	
Total	Total	220	14	6.4%	

Table 4.3: Prevalence and association of potential confounding variables among pregnant women with and without gestational diabetes for evaluating the relationship between gestational diabetes and pre-eclampsia

Variable	Gestational Diabetes (N=110)		No Gestational Diabetes (N=110)		P-value
	N	%	N	%	
Previous Pregnancy	73	66.4%	81	73.6%	0.5751
Race/Ethnicity					
White	41	37.3%	41	37.3%	1.0000
Black	12	10.9%	12	10.9%	
Hispanic	49	44.5%	49	44.5%	
Asian	8	7.3%	8	7.3%	
Smoking Status					
Current smoker	13	11.9%	9	8.2%	0.1072
Former smoker	27	24.8%	17	15.5%	
Never smoker	69	63.3%	84	76.4%	
Outcomes					
Hypertension	9	8.2%	6	5.6%	0.4548
Pre-eclampsia	9	8.3%	5	4.7%	0.2848
Hypertension or pre-eclampsia	17	15.5%	10	9.3%	0.1729
Variable	Mean	SE	Mean	SE	P-value
Mean age(years)	29.4	0.5	28.4	0.5	0.1634

Table 4.4: Prevalence and association of potential confounding variables among pregnant women with and without periodontal disease for evaluating the relationship between periodontal disease and pre-eclampsia

Variable	Periodontal Disease (N = 124)		No Periodontal Disease (N = 96)		P-value
	N	%	N	%	
Previous Pregnancy	97	80.2%	57	61.3%	0.0023
Race/Ethnicity					
White	42	33.9%	40	41.7%	0.1247
Black	13	10.5%	11	11.5%	
Hispanic	63	50.8%	35	36.5%	
Asian	6	4.8%	10	10.4%	
Smoking Status					
Current smoker	16	13.0%	6	6.3%	0.0615
Former smoker	19	15.4%	25	26.0%	
Never smoker	88	71.5%	65	67.7%	
Outcomes					
Hypertension	8	6.6%	7	7.4%	0.8152
Pre-eclampsia	12	10.1%	2	2.1%	0.0190
Hypertension or pre-eclampsia	19	15.6%	8	8.4%	0.1133
Variable	Mean	SE	Mean	SE	P-value
Mean age(years)	29.7	0.5	27.9	0.6	0.0177

Table 4.5: Prevalence of pre-eclampsia by potential confounding variables

Variable	Number of Study	Number with	Prevalence of
	Participants	Pre-eclampsia	Pre-eclampsia
	N	N	%
Previous Pregnancy			
One or more	149	8	5.4%
None	59	6	10.2%
Race/Ethnicity			
White	80	5	6.3%
Black	22	3	9.1%
Hispanic	96	7	7.3%
Asian	16	0	0.0%
Smoking Status			
Current smoker	22	2	9.1%
Former smoker	42	5	11.9%
Never smoker	149	7	4.7%
Maternal Age			
16 to 24 years	46	4	8.7%
25 to 34 years	133	8	6.0%
35 years and above	35	2	5.7%

Table 4.6: Unadjusted odds ratio and 95% confidence interval for the association between gestational diabetes, periodontal disease, and potential confounding variables with pre-eclampsia

Variable	Odds Ratio	95% Confidence Interval	P-value
Previous Pregnancy (Yes vs. No)	0.50	0.17 – 1.51	0.2203
Maternal Age (per 1 year)	0.97	0.88 – 1.08	0.5802
Race/Ethnicity			
White, Asian	0.85	0.26 – 2.78	0.9732
Black	1.27	0.25 – 6.59	
Hispanic	<i>Reference</i>	<i>Reference</i>	
Smoking Status			
Current smoker	2.03	0.39 – 10.46	0.0481
Former smoker	2.74	0.82 – 9.13	
Never smoker	<i>Reference</i>	<i>Reference</i>	
Periodontal disease, Gestational Diabetes			
Periodontal disease	5.22	1.14 – 23.90	0.0127
Gestational diabetes	1.84	0.60 – 5.67	0.2909
Periodontal disease, Gestational Diabetes - Combined			
Both Gestational Diabetes and Periodontal Disease	7.14	0.86 – 59.12	0.1344
Periodontal Disease Only	3.92	0.42 – 36.32	
Gestational Diabetes Only	1.16	0.07 – 19.15	
Neither Gestational Diabetes nor Periodontal Disease	<i>Reference</i>	<i>Reference</i>	

Table 4.7: Adjusted odds ratio and 95% confidence interval for the association between gestational diabetes, periodontal disease and pre-eclampsia with gestational diabetes and periodontal disease modeled separately

Variable	Adjusted Odds Ratio	95% Confidence Interval	P-value
Previous Pregnancy (Yes vs. No)	0.30	0.08 – 1.14	0.0773
Maternal Age (per 1 year)	0.97	0.86 – 1.09	0.5908
Race/Ethnicity			
White, Asian	1.00	Reference	0.3728
Black	2.31	0.35 – 15.19	
Hispanic	2.87	0.60 – 13.70	
Smoking Status			
Current smoker	3.26	0.39 – 27.22	0.0496
Former smoker	7.44	1.49 – 37.13	
Never smoker	1.00	Reference	
Periodontal disease, Gestational Diabetes			
Periodontal disease	10.38	1.82 – 59.10	0.0084
Gestational diabetes	1.32	0.40 – 4.37	0.6544

Table 4.8: Adjusted odds ratio and 95% confidence interval for the association between gestational diabetes, periodontal disease and pre-eclampsia with gestational diabetes and periodontal disease modeled as a combined variable

Variable	Adjusted Odds Ratio	95% Confidence Interval	P-value
Previous Pregnancy (Yes vs. No)	0.30	0.08 – 1.15	0.0784
Maternal Age (per 1 year)	0.97	0.86 – 1.09	0.5949
Race/Ethnicity			
White	1.00	Reference	0.3597
Black	2.38	0.36 – 15.79	
Hispanic	2.94	0.61 – 14.19	
Smoking Status			
Current smoker	3.24	0.39 – 27.16	0.0481
Former smoker	7.50	1.51 – 37.34	
Never smoker	1.00	Reference	
Periodontal disease, Gestational Diabetes			
Both Gestational Diabetes and Periodontal Disease	10.78	1.12 – 104.25	0.0562
Periodontal Disease Only	7.42	0.66 – 83.05	
Gestational Diabetes Only	0.81	0.05 – 14.44	
Neither Gestational Diabetes nor Periodontal Disease	1.00	Reference	

Table 4.9: Adjusted odds ratio and 95% confidence interval for the association between periodontal disease and pre-eclampsia by periodontal disease case definition

Periodontal Disease Definition	*Adjusted Odds Ratio	95% Confidence Interval	P-value
>=2 Teeth with PD >= 4mm, CAL >= 2mm, BoP	5.20	0.94 – 28.78	0.0590
>=3 Teeth with PD >= 4mm, CAL >= 2mm, BoP	8.38	1.43 – 49.02	0.0183
>=4 Teeth with PD >= 4mm, CAL >= 2mm, BoP	10.38	1.82 – 59.10	0.0084
>=2 Teeth with PD >= 5mm, CAL >= 2mm, BoP	6.86	1.21 – 38.80	0.0293
>=3 Teeth with PD >= 5mm, CAL >= 2mm, BoP	10.42	1.83 – 59.36	0.0083
>=4 Teeth with PD >= 5mm, CAL >= 2mm, BoP	12.31	2.24 – 67.71	0.0039

*Adjusted for maternal age, smoking status, gestational diabetes, previous pregnancy

References

- Alexander MT, Kufera JA. Butting heads on matched cohort analysis using SAS software. *Statistics and Data Analysis*. 2007;1-11.
- Alwan N, Tuffnell DJ, West J. Treatments for gestational diabetes. *Cochrane Database of Systematic Reviews*. 2009. Issue 3.
- Anastasiou E, Lekakis JP, Alevizaki M, Papamichael CM, Megas J, Souvatzoglou A, Stamatelopoulos SF. Impaired endothelium-dependent vasodilation in women with previous gestational diabetes. *Diabetes Care*. 1998;21:2111-5.
- Barden A, Singh R, Walters BN, Ritchie J, Roberman B, Beilin LJ. Factors predisposing to pre-eclampsia in women with gestational diabetes. *Journal of Hypertension*. 2004;22:2371-8.
- Bellamy L, Casas JP, Hingorani Ad, et al. Pre-eclampsia and risk of cardiovascular disease and cancer in later life: systematic review and meta-analysis. *British Medical Journal*. 2007;335(7627):974.
- Bodnar LM, Ness RB, Harger GF, Roberts JM. Inflammation and triglycerides partially mediate the effect of prepregnancy body mass index on the risk of preeclampsia. *American Journal of Epidemiology*. 2005;162:1198-1206.
- Boggess KA, Lief S, Murtha AP, Moss K, Beck J, Offenbacher S. Maternal periodontal disease is associated with an increased risk for pre-eclampsia. *Obstetrics & Gynecology*. 2003;101(2):227-1.
- Brown HL, Chireau MV, Jallah Y, Howard D. The "Hispanic" paradox: an investigation of racial disparity in pregnancy outcomes at a tertiary care medical center. *American Journal of Obstetrics & Gynecology*. 2007;197:197.e1-e9.
- Bryson CL, Ioannou GN, Rulyak SJ, Critchlow C. Association between gestational diabetes and pregnancy-induced hypertension. *American Journal of Epidemiology*. 2003;158:1148-53.
- Canakci V, Canakci F, Canakci H, Canakci E, Cicek Y, Ingec M, Ozgoz M, Demir T, Dilsiz A, Yagiz H. Periodontal disease as a risk factor for pre-eclampsia: a case control study. *Australia and New Zealand Journal of Obstetrics & Gynecology*. 2004;44(6):568-73.
- Canakci V, Canakci CF, Yildirim A, Ingec M, Eltas A, Erturk A. Periodontal disease increases the risk of severe pre-eclampsia among pregnant women. *Journal of Clinical Periodontology*. 2007;34(8):639-45.

- Caruso A, Ferrazzani S, DeCarolis S, Succhese A, Lansone A, DeSantis L, Paradisi G. Gestational hypertension but no pre-eclampsia is associated with insulin resistance syndrome characteristics. *Human Reproduction*. 1999;14:219-23.
- Conde-Agudelo A, Althabe F, Belizan JM, et al. Cigarette smoking during pregnancy and risk of pre-eclampsia: a systematic review. *American Journal of Obstetrics & Gynecology*. 1999;181(4):1026-35.
- Contreras A, Herrera JA, Soto JE, Arce RM, Jaramillo A, Botero JE. Periodontal disease is associated with pre-eclampsia in pregnant women. *Journal of Periodontology*. 2006;77(2):182-8.
- Cota LO, Guimaraes AN, Costa JE, Lorentz TC, Costa FO. Association between maternal periodontitis and an increased risk of pre-eclampsia. *Journal of Periodontology*. 2006;12:2063-9.
- Duckitt K, Harrington D. Risk factors for pre-eclampsia at antenatal booking: systematic review for controlled studies. *British Medical Journal*. 2005;330(7491):565.ePub.
- Greenland S, Rothman KJ. Concepts of Interaction. *Modern Epidemiology*, 2nd edition. 1998. Lippincott Williams & Wilkins. Philadelphia, PA.
- Greenland S, Rothman KJ. Applications of Stratified Analysis Methods. *Modern Epidemiology*, 2nd edition. 1998. Lippincott Williams & Wilkins. Philadelphia, PA.
- Grossi SG, Genco RJ. Periodontal disease and diabetes mellitus: a two-way relationship. *Annals of Periodontology*. 1998;3(1):51-61.
- HAPO Study Cooperative Research Group. Hyperglycemia and adverse pregnancy outcomes. *New England Journal of Medicine*. 2008;358:1991-2002.
- Hauth JC, Clifton RG, Roberts JM, Myatt L, Spong CY, Leveno KJ, Varner MW, Wapner RJ, Thorp JM, Mercer BM, Peaceman AM, Ramin SM, Carpenter MW, Samuels P, Sciscione A, Tolosa JE, Saade G, Sorokin Y, Anderson GD. Maternal insulin resistance and preeclampsia. *American Journal of Obstetrics & Gynecology*. 2011;204:327.e1-6.
- Higgins S. Smoking in pregnancy. *Current Opinion in Obstetrics & Gynecology*. 2002;14:145-51.
- Hladunewich M, Karumanchi SA, Lafayette R. Pathophysiology of the clinical

- manifestations of pre-eclampsia. *Clinical Journal of the American Society of Nephrology*. 2007;2:543-549.
- Horton AL, Boggess KA, Moss KL, Beck J, Offenbacher S. Periodontal disease, oxidative stress, and risk for pre-eclampsia. *Journal of Periodontology*. 2010;81:199-204.
- Jacqueminet S, Jannot-Lamotte MF. Therapeutic management of gestational diabetes. *Diabetes & Metabolism*. 2010;36:658-71.
- Khader YS, Jibreal M, Al-Omiri M, Amarin Z. Lack of association between periodontal parameters and pre-eclampsia. *Journal of Periodontology*. 2006;77(10):1681-7.
- Lain KY, Roberts JM. Contemporary concepts of the pathogenesis and management of preeclampsia. *JAMA*. 2002;287:3183-86.
- Lowe LP, Metzger BE, Lowe WL, Dyer AR, McDade TW, McIntyre HD. Inflammatory mediators and glucose in pregnancy: results from a subset of the hyperglycemia and adverse pregnancy outcomes (HAPO) study. *Journal of Clinical Endocrinology & Metabolism*. 2010;95:5427-34.
- Luo ZC, An N, Xu HR, Larante A, Audibert F, Fraser WD. The effects and mechanisms of primiparity on the risk of pre-eclampsia: a systematic review. 2007;21(S1):36-45.
- Michalowicz BS, Hodges JS, DiAngelis, AJ, Lupo VR, Novak MJ, Ferguson JE, Buchanan W, Bofill J, Papapanou PN, Mitchell DA, Matseone S, Tschida PA. Treatment of periodontal disease and the risk of preterm birth. *New England Journal of Medicine*. 2006;355:1885-94.
- National High Blood Pressure Education Program Working Group on High Blood Pressure in Pregnancy (2000). Report of the National High Blood Pressure Education Program Working Group on High Blood Pressure in Pregnancy. *American Journal of Obstetrics & Gynecology*. 2000;183:S1-22.
- Newnham JP, Newnham IA, Ball CM, Wright M, Pennell CE, Swain J, Doherty DA. Treatment of periodontal disease during pregnancy: a randomized controlled trial. *Obstetrics & Gynecology*. 2009;114(6):1239-48.
- Noris M, Perico N, Remuzzi G. Mechanisms of disease: pre-eclampsia. *Nature*. 2005;1(2):98-114.
- Offenbacher S, Beck JD, Jared HL, Mauriello S, Mendoza M, Couper LC,

- Stewart DD, Murtha AP, Cochran DL, Dudley DJ, Reddy MS, Geurs NC, Hauth JC. Effects of periodontal therapy on rate of preterm delivery: a randomized controlled trial. *Obstetrics and Gynecology*. 2009;114:551-59.
- Paradisi G, Biaggi A, Ferrazzani S, DeCarolis S, Caruso A. Abnormal carbohydrate metabolism during pregnancy. *Diabetes Care*. 2002;25:560-4.
- Ros HS, Cnattingus S, Lipworth L. Comparison of risk factors for preeclampsia and gestational hypertension in a population-based cohort study. *American Journal of Epidemiology*. 1998;147:1062-70.
- Rothman KJ, Greenland S. Matching. *Modern Epidemiology*, 2nd edition. 1998. Lippincott, Williams & Wilkins, Philadelphia, PA.
- Ruma M, Boggess K, Moss K, Jared H, Murtha A, Beck J, Offenbacher S. Maternal periodontal disease, systemic inflammation, and risk for preeclampsia. *American Journal of Obstetrics & Gynecology*. 2008;389:e1-e5.
- Valensise H, Vasapoll B, Gagliardi G, Novelli GP. Early and late preeclampsia: two different maternal hemodynamic states in the latent phase of the disease. *Hypertension*. 2008;52:873-80.
- Walker JJ. Preeclampsia. *Lancet*. 2000;356:1260-65.
- Xiong X, Buekens P, Goldenberg RL, Offenbacher S, Qian X. Optimal timing of periodontal disease treatment for prevention of adverse pregnancy outcomes: before or during pregnancy? *American Journal of Obstetrics & Gynecology*. 2011;205:111.e1-6.
- Ylostalo PV, Knuuttila ML. Confounding and effect modification: possible explanation for variation in the results on the association between oral and systemic diseases. *Journal of Clinical Periodontology*. 2006;33:104-8.

Chapter 5

Obstetric Intervention

Introduction

Obstetric intervention during pregnancy has increased significantly over the past 20 years. Between 1996 and 2009, the prevalence of cesarean section increased nearly 60 percent with the 2009 cesarean delivery rate at 32.9 percent (Hamilton 2010). This increase is notably important since a cesarean section during one pregnancy often results in repeat cesarean sections in subsequent pregnancies (Flamm 1997). Meanwhile, the prevalence of labor induction to initiate labor has more than doubled from 1990 to 2006 in the United States with a 2006 prevalence rate of 22.5 percent (Martin 2009). The prevalence of labor induction is important to cesarean delivery rates because failed induction is a clinical indication for the need for cesarean section and may contribute to a substantial portion of the cesarean delivery rate (Ehrenthal 2010, Seyb 1999). Increased use of obstetric intervention is partially the result of increases in the prevalence of maternal morbidities for which obstetric intervention is clinically indicated (Barber 2011). However, the increases in cesarean delivery and labor induction have also been associated with increased elective use of these

procedures for potential convenience of the mother as well as the physician (Gonen 2002, Simpson 2005, Gossman 2006). Increases in obstetric intervention have been associated with subjective use of the procedures rather than objective use of the procedures (Barber 2011). This subjective use may reflect increasing obstetric interventions as a response to marginal clinical indications to avert potential litigation (Yang 2009).

Clinical indications for cesarean section include fetal distress, multiple gestation, suspected uterine rupture, suspected fetal macrosomia (Lagrew 2006, Barber 2011). While cesarean delivery is indicated in some pregnancies as a means to reduce the risk of adverse outcomes, the procedure also carries notable risks to both the mother and infant. Potential complications of cesarean delivery include post-surgical infections, increased hemorrhaging (Smaill 2002, Hofmeyr 2001), and increased risks for maternal mortality although this risk has decreased over time (Deneux-Tharaux 2006, Minkoff 2003). In addition to the risks during the current pregnancy, cesarean delivery can adversely impact future pregnancies by increasing the risk for uterine rupture and placental abnormalities (Hemminki 1996).

Indications for labor induction include pre-eclampsia, intrauterine growth restriction, multiple gestation, severity of gestational diabetes, congenital anomalies and post-term delivery (Spong 2011, Joseph 2007, ACOG 2009, Gulmezoglu 2006) but not fetal macrosomia (Sanchez-Ramos 2002, ACOG 2009). Some risk factors affect multiple clinical indications. For instance, gestational diabetes is associated with increased risk for pre-eclampsia (HAPO

2008), and insulin therapy treatment for gestational diabetes is associated with an increased likelihood of labor induction (Alwan 2009, Jacqueminet 2010). Smoking has been associated with a decreased risk of pre-eclampsia (Conde-Agudelo 1999), but with an increased risk for fetal growth restriction and congenital anomalies (Higgins 2002). Periodontal disease, while still controversial as a risk factor for adverse pregnancy outcomes, has shown mixed associations with low infant birthweight (Marin 2005, Moliterno 2005, Moore 2004, Lunardelli 2005) and pre-eclampsia (Cota 2006, Contreras 2006, Boggess 2003, Canakci 2007, Khader 2006). Even though labor induction is used to prevent maternal and infant complications, risks accompany use of labor induction. Labor induction is associated with an increased risk for uterine rupture in the mother. Labor induction may also have adverse consequences for the infant with iatrogenic prematurity of notable concern due to increased infant mortality and neonatal morbidities such as respiratory distress that may result from preterm inductions (Reddy 2009, Spong 2011).

As clinical indications for obstetric intervention directly increase prevalence of obstetric intervention, the underlying conditions that contribute to risk for clinical indications likely further increases prevalence of obstetric intervention through these clinical indications. Thus, if the goal of reducing the prevalence of these interventions is to ultimately succeed, attention should be paid to these underlying conditions in addition to the electivity of such procedures. Gestational diabetes is a condition that has been linked to pregnancy-induced hypertension, pre-eclampsia, and fetal macrosomia –

potential indications for obstetric intervention. Periodontal disease has been linked to pre-eclampsia as well and thus may also indirectly contribute to the prevalence of obstetric intervention. As demonstrated in Chapter 3, the increased likelihood of pre-eclampsia when both gestational diabetes and periodontal disease are present together may further increase the need for obstetric intervention. The goal of this study is to determine whether a relationship exists between periodontal, gestational diabetes and obstetric intervention and whether the magnitude of this relationship is greater when both conditions are present than when either condition is present alone or neither condition is present.

Methods

This study used preliminary data from the University of Kentucky, Oral Infection: Impact on Gestational Diabetes study, a prospective matched cohort study. 321 pregnant women were recruited consecutively between September 2005 and September 2009 based upon the presence or absence of gestational diabetes mellitus. Gestational diabetes mellitus was identified through universal screening with a two-step glucose tolerance test, 50 gram glucose challenge test followed by a 100 gram oral glucose tolerance test, performed for all pregnant women who visited the University of Kentucky Bluegrass High Risk Maternal-Fetal Medicine Clinic. Women identified with gestational diabetes were then matched to a pregnant woman without gestational diabetes based upon by age within a five-year interval, race, and gestational week at enrollment within a two week

interval. Preliminary data were used for this analysis. Nine cases and six controls were excluded for the lack of a match. One matched pair was removed for pre-existing health condition, and an additional eight matched pairs were excluded for multiple gestation. Periodontal examination results were not available for 41 matched pairs. For this analysis, 103 matched cases and controls with complete periodontal disease examination information.

Pregnant women were included if they were at least 16 years of age and had at least 20 natural teeth at the time of periodontal assessment. Women were excluded if they were unable to provide consent, unable to cooperate with the study, were placed at medical risk through participation, were under 16 years of age, or had a history of type 1 or type 2 diabetes prior to pregnancy.

Mode of obstetric intervention was obtained via chart review conducted by a clinical research nurse. Separate variables were created for labor induction and for cesarean delivery. These variables were combined as a single dichotomous outcome of obstetric intervention if either a cesarean delivery was performed or labor induction was used to initiate labor. The research nurse extracted other maternal and fetal data from medical records of participants.

A full mouth oral examination was performed by Delta Dental Plan of Kentucky Clinical Research Center. Clinical periodontal disease measures were assessed at baseline (within one to two weeks of enrollment). A medical research nurse contacted enrollees to arrange clinical visits. The periodontal disease assessment included measures of pocket depth, clinical attachment loss, gingival inflammation, and bleeding upon probing. The proportion of sites with

each clinical indicator provides a summary measure for classification of periodontal disease. Periodontal disease was defined as four or more teeth with bleeding on probing, pocket depth of at least four millimeters and clinical attachment loss of at least two millimeters for analysis unless otherwise specified. Third molars were excluded in the periodontal disease case definition.

Demographic information such as race (Caucasian, Black, Asian), Hispanic ethnicity, and maternal age were recorded as part of the medical history. Smoking was assessed through an interviewer-administered health history conducted by a medical research nurse. Tobacco use was measured by self-reported use of cigarettes, chewing tobacco, snuff, cigars, and pipe tobacco. The preliminary analysis only uses cigarette smoking status (current, former, and never smokers) as tobacco use outside of cigarette use was rare and always in combination with cigarette use. A medical history was conducted to assess the presence of any confounding medical conditions, measured as dichotomous variables, such as heart disease, kidney disease, past illicit drug and alcohol use, and presence of vaginal infection. Height and weight measurements were taken at both the enrollment visit and update visit. However, in the preliminary data, weight and calculated BMI were missing for most study participants. Nutritional intake was not assessed with the exception of identifying women on special diets.

Bivariate analysis was performed on potential confounding categorical variables by using chi-square and Fischer exact tests depending upon cell sample size. For continuous variables, associations between exposure variables

across exposure and outcome groups were assessed using t-tests. An unmatched multivariate logistic regression analysis of the observational cohort was performed in SAS version 9.2.

Results

In total, 82 of the 206 women delivered by cesarean section (39.8%) while 59 women had labor induction performed (28.6%). Overall, 123 of the 206 women (59.7%) had either labor induction performed or delivered by cesarean section. All 37 women with a prior cesarean section had a repeat cesarean section at the time of delivery. In the 169 women without a prior history of cesarean section, 45 women (26.6%) delivered by cesarean section, 58 women (34.3%) had labor induction performed, for a total of 86 women (50.9%) having at least one method of obstetric intervention.

Women with gestational diabetes had a higher prevalence of previous cesarean section than women without gestational diabetes ($p=0.0183$) even though the proportion with a previous pregnancy did not differ ($p=1.000$). Women with gestational diabetes were more likely to be current or former smokers with some evidence suggesting women with gestational diabetes were older than women without gestational diabetes. The unadjusted prevalence of obstetric intervention was higher in women with gestational diabetes compared to women without gestational diabetes. This increased prevalence of obstetric intervention was statistically significant for cesarean deliveries. The unadjusted

prevalence of labor induction was higher in women with gestational diabetes as well but did not reach statistical significance (Table 5.1).

Among pregnant women with periodontal disease, there was a greater prevalence of prior pregnancy ($p=0.0068$) but not prior cesarean section ($p=0.4282$). Hispanic women were more likely to be classified as having periodontal disease compared to women of other races and ethnicities though this was not statistically significant. Women with periodontal disease were also more likely to be current smokers compared to women without periodontal disease. The frequency of labor induction and cesarean delivery were both higher in women with periodontal disease than in women without periodontal disease, as was the prevalence of any obstetric intervention, but none of these measures were significantly different (Table 5.2). Prevalence of illicit drug use did not differ between women with and without gestational diabetes or women with and without periodontal disease.

When comparing the prevalence of obstetric intervention by the potential confounding variables (Table 5.3), the prevalence of any obstetric intervention was found to be higher among pregnant women who smoked compared to former smokers and never smokers. I observed no difference in the prevalence of obstetric intervention by race, maternal age or previous pregnancy status. When evaluating the two different obstetric interventions as separate entities, the prevalence of cesarean section was higher among women with gestational diabetes. Cesarean section was also more common among former smokers and current smokers compared to never smokers. The prevalence of labor induction

varied by race and ethnicity and was also higher among women of greater maternal age. Labor induction itself was not strongly associated with either gestational diabetes or periodontal disease even though the prevalence of this intervention was higher in both women with gestational diabetes and women with periodontal disease.

The unadjusted analysis (Table 5.4) showed a 2.6 fold increase in the risk of obstetric intervention among women with gestational diabetes compared to women without gestational diabetes. Women with periodontal disease were 1.5 times more likely to have obstetric intervention than women without periodontal disease although confidence intervals included one. None of the potential confounding variables demonstrated strong relationships with the risk of having obstetric intervention. However, when current and former smokers were combined into ever smokers, I found borderline nonstatistical significance for increased risk ($p=0.0541$)

After adjusting for the potential confounding variables, the odds associated with gestational diabetes was slightly attenuated but odds for periodontal disease did not change (Table 5.5). The interaction term between periodontal disease and gestational diabetes testing for multiplicative interaction was not significant ($p = 0.5998$). Although nonsignificant, women who were current and former smokers were both more likely to deliver using obstetric intervention, but women without a history of illicit drug use were less likely to deliver using obstetric intervention. When current and former smokers were combined, again I found borderline statistical nonsignificance for increased risk of

obstetric intervention ($p=0.0512$). Previous pregnancies and maternal age exhibited no increase in the likelihood of delivery via obstetric intervention. Hispanic women appeared to be less likely to deliver via obstetric intervention compared to Caucasian women while Asian women were more likely to deliver obstetric intervention. However, the difference in likelihood of having obstetric intervention was not statistically significant between racial and ethnic groups.

When periodontal disease and gestational diabetes were modeled as a combined variable, the greatest likelihood of having obstetric intervention was among women with both gestational diabetes and periodontal disease. This likelihood was roughly twice as high among women with both conditions compared to either group of women with only one of the conditions present. Both women with only periodontal disease and only gestational diabetes had a greater likelihood of obstetric intervention compared to women without either condition (Table 5.6).

The separate adjusted models for cesarean section delivery and labor induction are presented in Table 5.7. For cesarean section, the risk of obstetric intervention varied significantly by the combined gestational diabetes and periodontal disease status with the greatest risk occurring among women with both gestational diabetes and periodontal disease and the lowest risk occurring among women without either condition. The risk of having labor induction did not vary by the combined gestational diabetes and periodontal disease status. The odds for labor induction were similar in women with gestational diabetes alone, periodontal disease alone, and with the two conditions together. Minor

differences in the risk of cesarean section by race were observed, but the risk for labor induction had notable differences by race. Black women and Asian women both had notably higher risks of labor induction while Hispanic women demonstrated lower risks of labor induction relative to Caucasian women.

The impact of the periodontal disease case definition on the relationship with obstetric intervention is demonstrated in Table 5.6. The odds of having obstetric intervention were relatively consistent across the varying case definitions regardless of severity level. Five of the six case definitions demonstrated statistically significant associations between periodontal disease and obstetric intervention after adjusting for smoking status, history of illicit drug use, previous pregnancy, maternal age, maternal race and ethnicity, and gestational diabetes exposure status.

Given the high likelihood of a cesarean section after previous cesarean deliveries, matched pairs that involve a woman with a previous cesarean delivery were removed (Table 5.9). After removal, the association between gestational diabetes and obstetric intervention and the association between periodontal disease and obstetric intervention both weakened, and the combined periodontal disease and gestational diabetes measure was no longer significantly associated with any obstetric intervention. Results were similar for cesarean section and labor induction examined separately (Table 5.10). In this same adjusted model, I also found a borderline nonstatistically significant association between ever smokers and cesarean delivery (Odds ratio: 3.10, 95% confidence interval: 0.85-11.35).

Discussion

Given the importance in differentiating elective and non-elective sources of variation in the use of obstetric intervention, the focus of this study on a potential non-elective source may help to explain a portion of the increased use of such procedures. Obstetric intervention was more prevalent in both women with gestational diabetes and women with periodontal disease compared to their counterparts without gestational diabetes or without periodontal disease, respectively. Women with both conditions present appeared to have an even greater likelihood of obstetric intervention suggesting some interaction between these conditions and obstetric intervention. However, after adjustment for potential confounding and removal of women with a previous cesarean delivery, the relationship between gestational diabetes, periodontal disease and obstetric intervention weakened. The results suggest that this interaction between gestational diabetes and periodontal disease is more likely to result in a cesarean section rather than labor induction although both interventions were higher in women with gestational diabetes and women with periodontal disease. Again, after removal of women with a previous cesarean delivery, the relationships between gestational diabetes and periodontal disease with each obstetric outcome weakened.

Gestational diabetes was more likely to be associated with obstetric intervention than was periodontal disease. This finding may reflect that gestational diabetes is currently used as a clinical indicator to stratify

pregnancies as high risk pregnancies that may require obstetric intervention (ACOG 2009). While having weaker associations than gestational diabetes, periodontal disease still had elevated associations with obstetric intervention. Should periodontal disease become a clinical indication for high risk pregnancies and associated intervention, there may be stronger associations between periodontal disease and obstetric intervention in future studies due to changes in physician practice patterns.

The increased likelihood of obstetric intervention in women with gestational diabetes and women with periodontal disease may reflect the increased likelihood of developing risk factors during pregnancy that indicate obstetric intervention. Both gestational diabetes and periodontal disease have been associated with an increased risk for pre-eclampsia (Kaaja 1995, Ros 1998) which is a clinical indication for obstetric intervention (ACOG 2009). Gestational diabetes has been associated with fetal macrosomia (Catalano 1995) and the associated need for cesarean deliveries for large infants when suspected fetal macrosomia may lead to complications during delivery (Vidarsdottir 2011, Zhang 2008).

The increasing prevalence of the use of obstetric interventions, both cesarean section and labor induction, may partially reflect the increasing prevalence of diabetes and periodontal disease among younger women and their increased prevalence during child-bearing years (Fagot-Campagna 2000, Rosenbloom 1999). It is important to distinguish between medically necessary

obstetric interventions and elective obstetric interventions as the potential overuse of obstetric intervention is controversial (Flamm 1997, Moleti 2009).

While treatment regimens for gestational diabetes have demonstrated effectiveness in reducing the risk of developing maternal morbidities such as pre-eclampsia and infant morbidities such as fetal macrosomia (Alwan 2009, Jacqueminet 2010), data on effectiveness of treatment for periodontal disease are mixed (Newnham 2009, Michalowicz 2006, Offenbacher 2009, Uppal 2010). Ultimately, treatments for gestational diabetes may have an influence on obstetric intervention while treatments for periodontal disease may not influence obstetric intervention. Yet, insulin therapy has not been associated with decreases in cesarean section, but has been associated with increased risk for labor induction (Jacqueminet 2010). However, periodontal treatments during pregnancy have only been assessed and not interventions aimed at alleviating the impact of periodontal disease prior to pregnancy (Xiong 2011).

While significant associations were observed between gestational diabetes, periodontal disease and obstetric intervention, there was limited power to detect these associations. Thus, some of the elevated but nonsignificant associations may become statistically significant when the full sample size is included. The high repeat cesarean delivery rate further complicated the sample size and power of the study by leading to removal of roughly one-third of the observations. We also evaluated gestational diabetes as a dichotomous variable and did not account for its potential linear relationship with obstetric intervention by using a continuous variable.

Gestational diabetes has previously demonstrated associations with clinical indications that may necessitate obstetric intervention. In this study, gestational diabetes was associated with an increased likelihood of labor induction. However, periodontal disease did not further increase the likelihood of labor induction. Neither gestational diabetes nor periodontal disease exhibited strong associations with cesarean delivery, except when both conditions were present together. These observed associations may reflect that periodontal disease and gestational diabetes contribute both toward an indirect effect of increased risk of cesarean delivery, or that periodontal disease is a risk marker for more severe disease than a dichotomous measure of gestational diabetes represents. Periodontal disease may also increase the risk of developing clinical indications for obstetric interventions, but the increased risk may represent only marginal complications that do not require any additional need for intervention.

In summary, further research is needed to determine the potential causal role that periodontal disease may contribute to increased obstetric intervention use in women with gestational diabetes or whether this relationship is simply an epiphenomenon of the severity of other underlying conditions.

Figures and Tables

Figure 5.1: Population flow diagram for selection of cases and controls used in the preliminary analysis of gestational diabetes, periodontal disease and obstetric intervention.

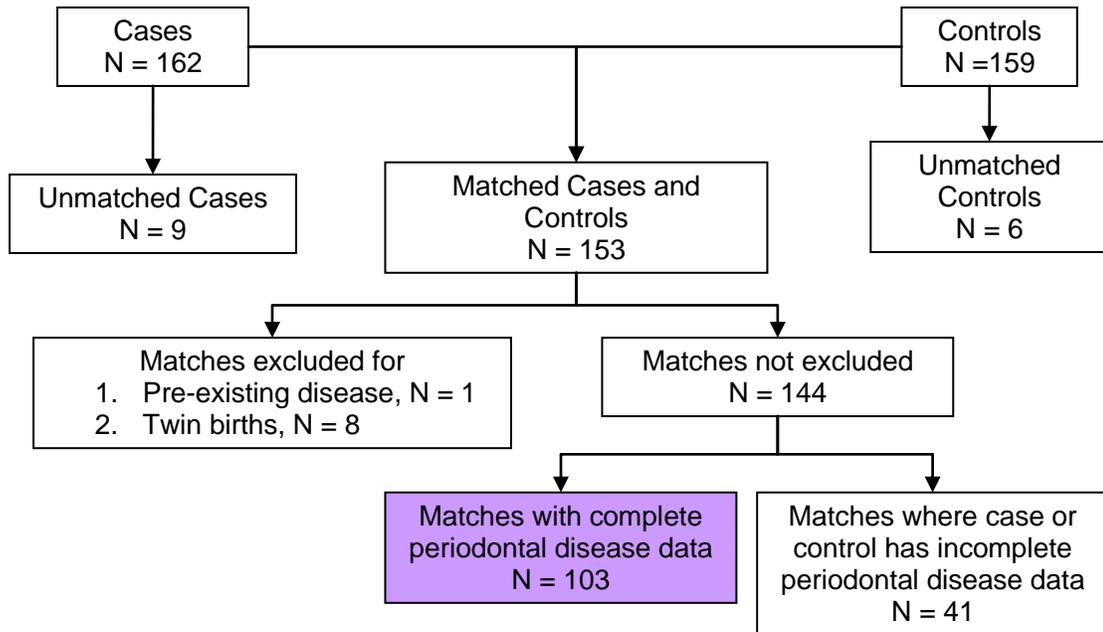


Table 5.1: Prevalence and association of potential confounding variables among pregnant women with and without gestational diabetes for evaluating the relationship between gestational diabetes and obstetric intervention

Variable	Gestational Diabetes (N=103)		No Gestational Diabetes (N=103)		P-value
	N	%	N	%	
Previous Pregnancy	74	71.8%	74	71.8%	1.0000
Previous Cesarean section	25	24.3%	12	11.7%	0.0183
Race/Ethnicity					
White	38	36.9%	38	36.9%	1.0000
Black	12	11.7%	12	11.7%	
Hispanic	45	43.7%	45	43.7%	
Asian	8	7.8%	8	7.8%	
Smoking Status					
Current smoker	13	12.8%	8	7.8%	0.0460
Former smoker	26	25.5%	15	14.6%	
Never smoker	63	63.4%	80	77.7%	
History of Drug Use	6	5.9%	8	8.0%	0.5663
Outcomes					
Labor Induction	34	33.0%	25	24.3%	0.1654
Cesarean section	53	51.5%	29	28.2%	0.0006
Labor induction or Cesarean section	73	70.9%	50	48.5%	0.0011
Variable	Mean	SE	Mean	SE	P-value
Mean age(years)	29.46	0.58	28.30	0.50	0.1329

Table 5.2: Prevalence and association of potential confounding variables among pregnant women with and without periodontal disease for evaluating the relationship between periodontal disease and obstetric intervention

Variable	Periodontal Disease (N = 116)		No Periodontal Disease (N = 90)		P-value
	N	%	N	%	
Previous Pregnancy	92	79.3%	56	62.2%	0.0068
Previous Cesarean section	23	19.8%	14	15.6%	0.4282
Race/Ethnicity					
White	40	34.5%	36	40.0%	0.2063
Black	13	11.2%	11	12.2%	
Hispanic	57	49.1%	33	36.7%	
Asian	6	5.2%	10	11.1%	
History of drug use	8	7.1%	6	6.7%	0.9116
Smoking Status					
Current smoker	15	13.0%	6	6.7%	0.1018
Former smoker	18	15.7%	23	25.6%	
Never smoker	82	71.3%	61	67.8%	
Outcomes					
Labor induction	36	31.0%	23	25.6%	0.3883
Cesarean section	50	43.1%	32	35.6%	0.2723
Labor induction or Cesarean section	74	63.8%	49	54.4%	0.1748
Variable	Mean	SE	Mean	SE	P-value
Mean age(years)	29.67	0.48	27.86	0.61	0.0192

Table 5.3: Prevalence of any obstetric intervention, Cesarean section, and labor induction by potential confounding variable, gestational diabetes status, periodontal disease status

Variable	Number of Study Participants	Obstetric Intervention N(%)	Cesarean Section N(%)	Labor Induction N(%)
Previous Pregnancy				
Yes	148	88 (59.5)	58 (39.2)	41 (27.7)
No	58	35 (60.3)	24 (41.4)	18 (31.0)
Previous Cesarean section				
Yes	37	**37 (100.0)	**37 (100.0)	**1 (2.7)
No	169	86 (50.9)	45 (26.6)	58 (34.3)
Race/Ethnicity				
White	76	48 (63.2)	31 (40.8)	*20 (26.3)
Black	24	15 (62.5)	11 (45.8)	8 (33.3)
Hispanic	90	49 (54.4)	35 (38.9)	22 (24.4)
Asian	16	11 (68.8)	5 (31.3)	9 (56.3)
History of drug use				
Yes	14	7 (50.0)	6 (42.9)	*1 (7.1)
No	192	112 (58.3)	74 (39.6)	56 (30.0)
Smoking Status				
Current smoker	21	*16 (76.2)	**10 (47.6)	7 (33.3)
Former smoker	41	28 (68.3)	23 (56.1)	7 (17.1)
Never smoker	143	78 (54.6)	48 (33.6)	44 (30.8)
Age category				
16 – 24 years	58	34 (58.6)	29 (50.0)	*10 (17.2)
25 – 34 years	115	68 (59.1)	43 (37.4)	36 (31.3)
35 or more years	33	21 (63.6)	10 (30.3)	13 (39.4)
Gestational Diabetes				
Yes	103	**73 (70.9)	**53 (51.5)	34 (33.0)
No	103	50 (48.5)	29 (28.2)	25 (24.3)
Periodontal Disease				
Yes	116	74 (63.8)	50 (43.1)	36 (31.0)
No	90	49 (54.4)	32 (35.6)	23 (25.6)

* p < 0.10

** p < 0.05

Table 5.4: Unadjusted odds ratio and 95% confidence interval for the association between gestational diabetes, periodontal disease and obstetric intervention with gestational diabetes and periodontal disease modeled separately

Variable	Unadjusted Odds Ratio	95% Confidence Interval	P-value
Previous Pregnancy (Yes vs. No)	0.96	0.52 – 1.79	0.9074
Maternal Age (per 1 year)	1.01	0.96 – 1.07	0.6250
Race/Ethnicity			
White	<i>Reference</i>	<i>Reference</i>	0.56800872
Black	0.97	0.38 – 2.51	
Hispanic	0.70	0.37 – 1.30	
Asian	1.28	0.40 – 4.07	
History of drug use	0.67	0.23 – 1.99	0.4699
Smoking Status			
Current smoker	2.67	0.93 – 7.67	0.0802
Former smoker	1.80	0.86 – 3.75	
Never smoker	<i>Reference</i>	<i>Reference</i>	
Periodontal disease, Gestational Diabetes			
Periodontal disease	1.47	0.84 – 2.59	0.1756
Gestational diabetes	2.58	1.45 – 4.58	0.0012

Table 5.5: Adjusted odds ratio and 95% confidence interval for the association between gestational diabetes, periodontal disease and obstetric intervention with gestational diabetes and periodontal disease modeled separately

Variable	Adjusted Odds Ratio	95% Confidence Interval	P-value
Previous Pregnancy (Yes vs. No)	1.01	0.50 – 2.05	0.9797
Maternal Age (per 1 year)	0.97	0.91 – 1.04	0.3827
Race/Ethnicity			
White	<i>Reference</i>	<i>Reference</i>	0.4036
Black	0.90	0.30 – 2.72	
Hispanic	0.67	0.32 – 1.42	
Asian	1.88	0.54 – 6.58	
History of drug use	0.18	0.03 – 1.05	0.0563
Smoking Status			
Current smoker	5.40	1.00 – 29.1	0.0889
Former smoker	1.89	0.81 – 4.44	
Never smoker	<i>Reference</i>	<i>Reference</i>	
Periodontal disease, Gestational Diabetes			
Periodontal disease	1.57	0.83 – 2.98	0.1656
Gestational diabetes	2.20	1.19 – 4.05	0.0118

Table 5.6: Adjusted odds ratio and 95% confidence interval for the association between gestational diabetes, periodontal disease and obstetric intervention with gestational diabetes and periodontal disease modeled as a combined variable

Variable	Adjusted Odds Ratio	95% Confidence Interval	P-value
Previous Pregnancy (Yes vs. No)	1.02	0.50 – 2.07	0.9635
Maternal Age (per 1 year)	0.97	0.91 – 1.03	0.3679
Race/Ethnicity			
White	<i>Reference</i>	<i>Reference</i>	0.3923
Black	0.93	0.31 – 2.82	
Hispanic	0.67	0.32 – 1.42	
Asian	1.91	0.55 – 6.68	
History of drug use	0.17	0.03 – 1.01	0.0509
Smoking Status			
Current smoker	5.47	1.02 – 29.4	0.0836
Former smoker	1.91	0.55 – 6.68	
Never smoker	<i>Reference</i>	<i>Reference</i>	
Periodontal disease, Gestational Diabetes			
Both Gestational Diabetes and Periodontal Disease	3.46	1.45 – 8.26	0.0329
Periodontal Disease Only	1.36	0.59 – 3.14	
Gestational Diabetes Only	1.84	0.74 – 4.53	
Neither Gestational Diabetes nor Periodontal Disease	<i>Reference</i>	<i>Reference</i>	

Table 5.7: Adjusted odds ratio and 95% confidence interval for the association between gestational diabetes, periodontal disease and both cesarean section and labor induction with gestational diabetes and periodontal disease modeled as a combined variable

Variable	Cesarean Section		Labor Induction	
	Adjusted Odds Ratio	95% Confidence Interval	Adjusted Odds Ratio	95% Confidence Interval
Previous Pregnancy (Yes vs. No)	1.05	0.51 – 2.16	0.74	0.34 – 1.61
Maternal Age (per 1 year)	0.92	0.86 – 0.98	1.04	0.97 – 1.11
Race/Ethnicity				
White	<i>Reference</i>	<i>Reference</i>	<i>Reference</i>	<i>Reference</i>
Black	1.00	0.34 – 2.94	1.93	0.62 – 6.03
Hispanic	1.00	0.46 – 2.17	0.67	0.29 – 1.53
Asian	1.37	0.37 – 5.03	2.53	0.76 – 8.49
History of drug use	0.78	0.18 – 3.30	0.07	0.01 – 0.74
Smoking Status				
Current smoker	1.48	0.43 – 5.11	2.34	0.61 – 8.94
Former smoker	2.74	1.18 – 6.35	0.42	0.16 – 1.12
Never smoker	<i>Reference</i>	<i>Reference</i>	<i>Reference</i>	<i>Reference</i>
Periodontal disease, Gestational Diabetes				
Both Gestational Diabetes and Periodontal Disease	4.93	1.98 – 12.29	1.67	0.64 – 4.36
Periodontal Disease Only	1.58	0.61 – 4.04	1.33	0.50 – 3.52
Gestational Diabetes Only	2.60	1.00 – 6.77	1.43	0.51 – 4.01
Neither Gestational Diabetes nor Periodontal Disease	<i>Reference</i>	<i>Reference</i>	<i>Reference</i>	<i>Reference</i>

Table 5.8: Adjusted odds ratio and 95% confidence interval for the association between periodontal disease and obstetric intervention by periodontal disease case definition

Periodontal Disease Case Definition	Adjusted Odds Ratio	95% Confidence Interval	P-value
>=2 Teeth with PD >= 4mm, CAL >= 2mm, BoP	2.35	1.17 – 4.72	0.0169
>=3 Teeth with PD >= 4mm, CAL >= 2mm, BoP	2.91	1.46 – 5.80	0.0024
>=4 Teeth with PD >= 4mm, CAL >= 2mm, BoP	1.57	0.83 – 2.98	0.1656
>=2 Teeth with PD >= 5mm, CAL >= 2mm, BoP	2.32	1.16 – 4.62	0.0168
>=3 Teeth with PD >= 5mm, CAL >= 2mm, BoP	2.85	1.47 – 5.53	0.0019
>=4 Teeth with PD >= 5mm, CAL >= 2mm, BoP	2.59	1.34 – 4.98	0.0044

*Adjusted for maternal age, smoking status, gestational diabetes, previous pregnancy

Table 5.9: Adjusted odds ratio and 95% confidence interval for the association between gestational diabetes, periodontal disease and obstetric intervention with gestational diabetes and periodontal disease modeled as a combined variable, previous cesarean removed.

Variable	Adjusted Odds Ratio	95% Confidence Interval	P-value
Previous Pregnancy (Yes vs. No)	0.46	0.19 – 1.10	0.0793
Maternal Age (per 1 year)	0.97	0.90 – 1.06	0.5324
Race/Ethnicity			
White	<i>Reference</i>	<i>Reference</i>	0.4371
Black	0.87	0.22 – 3.34	
Hispanic	0.70	0.26 – 1.89	
Asian	2.26	0.54 – 9.49	
History of drug use	0.16	0.02 – 1.26	0.0811
Smoking Status			
Current smoker	5.67	1.00 – 32.20	0.1452
Former smoker	1.23	0.41 – 3.68	
Never smoker	<i>Reference</i>	<i>Reference</i>	
Periodontal disease, Gestational Diabetes			
Both Gestational Diabetes and Periodontal Disease	2.56	0.89 – 7.38	0.1847
Periodontal Disease Only	0.93	0.32 – 2.74	
Gestational Diabetes Only	1.11	0.35 – 3.54	
Neither Gestational Diabetes nor Periodontal Disease	<i>Reference</i>	<i>Reference</i>	

Table 5.10: Adjusted odds ratio and 95% confidence interval for the association between gestational diabetes, periodontal disease and both cesarean section and any obstetric intervention, matched pairs including women with prior cesarean delivery were excluded

Variable	Cesarean Section		Labor Induction	
	Adjusted Odds Ratio	95% Confidence Interval	Adjusted Odds Ratio	95% Confidence Interval
Previous Pregnancy (Yes vs. No)	**0.26	0.10 – 0.71	0.92	0.35 – 2.38
Maternal Age (per 1 year)	**0.88	0.79 – 0.98	1.04	0.95 – 1.14
Race/Ethnicity				
White	<i>Reference</i>	<i>Reference</i>	<i>Reference</i>	<i>Reference</i>
Black	0.68	0.12 – 3.85	2.37	0.56 – 9.99
Hispanic	1.77	0.46 – 6.89	0.63	0.22 – 1.84
Asian	4.31	0.68 – 27.45	2.16	0.52 – 8.96
History of drug use	0.53	0.05 – 5.37	**0.07	0.01 – 0.99
Smoking Status				
Current smoker	2.46	0.41 – 14.86	*3.24	0.64 – 16.42
Former smoker	3.38	0.85 – 13.37	0.43	0.12 – 1.50
Never smoker	<i>Reference</i>	<i>Reference</i>	<i>Reference</i>	<i>Reference</i>
Periodontal disease, Gestational Diabetes				
Both Gestational Diabetes and Periodontal Disease	*4.21	1.17 – 15.14	2.83	0.89 – 9.05
Periodontal Disease Only	1.35	0.34 – 5.47	1.46	0.43 – 4.97
Gestational Diabetes Only	0.81	0.19 – 3.51	2.53	0.69 – 9.30
Neither Gestational Diabetes nor Periodontal Disease	<i>Reference</i>	<i>Reference</i>	<i>Reference</i>	<i>Reference</i>

* p < 0.10

** p < 0.05

References

- (ACOG) The American College of Obstetricians and Gynecologists. Induction of Labor. ACOG Practice Bulletin No. 107. *Obstetrics & Gynecology*. 2009;114:386-97.
- Alwan N, Tuffnell DJ, West J. Treatments for gestational diabetes. *Cochrane Database of Systematic Reviews*. 2009. Issue 3
- Barber EL, Lundsberg LS, Belanger K, Pettker CM, Funai EF, Illuzzi JL. Indications contributing to the increasing cesarean delivery rate. *Obstetrics & Gynecology*. 2011;118(1):29-38.
- Boggess KA, Lief S, Murtha AP, Moss K, Beck J, Offenbacher S. Maternal periodontal disease is associated with an increased risk for pre-eclampsia. *Obstetrics & Gynecology*. 2003;101(2):227-1.
- Canakci V, Canakci CF, Yildirim A, Ingec M, Eltas A, Erturk A. Periodontal disease increases the risk of severe pre-eclampsia among pregnant women. *Journal of Clinical Periodontology*. 2007;34(8):639-45.
- Catalano P, Drago NM, Amini SB. Factors affecting fetal growth and body composition. *American Journal of Obstetrics & Gynecology*. 1995;172:1459-63.
- Conde-Agudelo A, Althabe F, Belizan JM, et al. Cigarette smoking during pregnancy and risk of pre-eclampsia: a systematic review. *American Journal of Obstetrics & Gynecology*. 1999;181(4):1026-35.
- Contreras A, Herrera JA, Soto JE, Arce RM, Jaramillo A, Botero JE. Periodontal disease is associated with pre-eclampsia in pregnant women. *Journal of Periodontology*. 2006;77(2):182-8.
- Cota LO, Guimaraes AN, Costa JE, Lorentz TC, Costa FO. Association between maternal periodontitis and an increased risk of pre-eclampsia. *Journal of Periodontology*. 2006;12:2063-9.
- Deneux-Tharaux C, Carmona E, Bouvier-Colle MH, Breart G. Postpartum maternal mortality and cesarean delivery. *Obstetrics & Gynecology*. 2006;108(3):541-48.
- Ehrenthal DB, Jiang X, Strobino DM. Labor induction and the risk of a cesarean delivery among nulliparous women at term. *Obstetrics & Gynecology*. 2010;116(1):35-42.
- Fagot-Campagna A, Pettitt DJ, Engelgau MM, et al. Type 2 diabetes among

- North American children and adolescents: an epidemiologic review and a public health perspective. *Journal of Pediatrics*. 2000;136:664-72.
- Flamm BL. Once a cesarean, always a controversy. *Obstetrics & Gynecology*. 1997;90:312-15.
- Gonen R, Tamir A, Degani S. Obstetricians' opinions regarding patient choice in cesarean delivery. *Obstetrics & Gynecology*. 2002;99:577-80.
- Gossman GL, Joesch JM, Tanfer K. Trends in maternal request cesarean delivery from 1991-2004. *Obstetrics & Gynecology*. 2006;108:1506-16.
- Gulmezoglu AM, Crowther CA, Middleton P. Induction of labour for improving birth outcomes for women at or beyond term. *Cochrane Database of Systematic Reviews*. 2006. Issue 4.
- Hamilton BE, Martin JA, Ventura SJ. Births: Preliminary data for 2009 [online]. National vital statistics reports; vol 59 no 3. National Center for Health Statistics. 2010.
- HAPO Study Cooperative Research Group. Hyperglycemia and adverse pregnancy outcomes. *New England Journal of Medicine*. 2008;358:1991-2002.
- Higgins S. Smoking in pregnancy. *Current Opinion in Obstetrics & Gynecology*. 2002;14:145-51.
- Jacqueminet S, Jannot-Lamotte MF. Therapeutic management of gestational diabetes. *Diabetes & Metabolism*. 2010;36:658-71.
- Joseph KS. Theory of obstetrics: an epidemiologic framework for justifying medically indicated early delivery. *BMC Pregnancy and Childbirth*. 2007;7:1-15.
- Kaaja R, Tikkanen M, Viinikka L, Ylikorkkala O. Serum lipoproteins, insulin and urinary excretion of prostanoid metabolites in normal and hypertensive pregnant women. *Obstetrics & Gynecology*. 1995;85:353-6.
- Khader YS, Jibreal M, Al-Omiri M, Amarin Z. Lack of association between periodontal parameters and pre-eclampsia. *Journal of Periodontology*. 2006;77(10):1681-7.
- Hemminki E, Merilainen J. Long-term effects of cesarean sections: ectopic pregnancies and placental problems. *American Journal of Obstetrics & Gynecology*. 1996;174:1569-74.

- Hofmeyr GJ, Hannah ME. Planned cesarean section for term breech delivery. *Cochrane Database of Systematic Reviews*. 2001;12:CD000166.
- Lagrew DC, Bush MC, McKeown AM, Lagrew NG. Emergent (crash) cesarean delivery: indications and outcomes. *American Journal of Obstetrics & Gynecology*. 2006;194(6):1638-43.
- Lunardelli AN, Peres MA. Is there an association between periodontal disease, prematurity and low birth weight? A population-based study. *Journal of Clinical Periodontology*. 2005;32:938-46.
- Marin C, Segura-Egea JJ, Martinez-Sahuquillo A, Bullon P. Correlation between infant birth weight and mother's periodontal status. *Journal of Clinical Periodontology*. 2005;32:299-304.
- Martin JA, Hamilton BE, Sutton PD, Ventura SJ, Menacker F, Kirmeyer S, Mathews TJ. Births: final data for 2006. *National Vital Statistics Reports*. 2009;57:1-102.
- Michalowicz BS, Hodges JS, DiAngelis, AJ, Lupo VR, Novak MJ, Ferguson JE, Buchanan W, Bofill J, Papapanou PN, Mitchell DA, Matseone S, Tschida PA. Treatment of periodontal disease and the risk of preterm birth. *New England Journal of Medicine*. 2006;355:1885-94.
- Minkoff H, Cervenak FA. Elective primary cesarean delivery. *New England Journal of Medicine*. 2003;348:946-50.
- Moleti CA. Trends and controversies in labor induction. *American Journal of Maternal/Child Nursing*. 2009;34(1):40-47.
- Molitero LFM, Monteiro B, da Silva Figueredo CM, Fischer RG. Association between periodontitis and low birth weight: a case-control study. *Journal of Clinical Periodontology*. 2005;32:886-90.
- Moore S, Ide M, Coward PY, Randhawa M, Borkowska E, Baylis R, Wilson RF. A prospective study to investigate the relationship between periodontal disease and adverse pregnancy outcome. *British Dental Journal*. 2004;197:251-58.
- Newnham JP, Newnham IA, Ball CM, Wright M, Pennell CE, Swain J, Doherty DA. Treatment of periodontal disease during pregnancy: a randomized controlled trial. *Obstetrics & Gynecology*. 2009;114(6):1239-48.
- Offenbacher S, Beck JD, Jared HL, Mauriello S, Mendoza M, Couper LC, Stewart DD, Murtha AP, Cochran DL, Dudley DJ, Reddy MS, Geurs NC, Hauth JC. Effects of periodontal therapy on rate of preterm delivery: a

- randomized controlled trial. *Obstetrics and Gynecology*. 2009;114:551-59.
- Reddy U, Ko CW, Raju TNK, Willinger M. Delivery indications at late pre-term gestations and infant mortality rates in the United States. *Pediatrics*. 2009;124:234-40.
- Ros HS, Cnattingus S, Lipworth L. Comparison of risk factors for preeclampsia and gestational hypertension in a population-based cohort study. *American Journal of Epidemiology*. 1998;147:1062-70.
- Rosenbloom AL, Joe JR, Young RS, et al. Emerging epidemic of type 2 diabetes in youth. *Diabetes Care*. 1999;22:345-54.
- Sanchez-Ramos L, Bernstein S, Kaunitz AM. Expectant management versus labor induction for suspected fetal macrosomia: a systematic review. *Obstetrics & Gynecology*. 2002;100:997-1002.
- Seyb ST, Berka RJ, Socol ML, Dooley SL. Risk of cesarean delivery with elective induction of labor at term in nulliparous women. *Obstetrics & Gynecology*. 1999;94:600-7.
- Simpson KR, Thorman KE. Obstetric "conveniences": elective induction of labor, cesarean birth on demand, and other potentially unnecessary interventions. *Journal of Perinatal and Neonatal Nursing*. 2005;19:134-44.
- Smaill F, Hofmeyr GJ. Antibiotic prophylaxis for cesarean section. *Cochrane Database of Systematic Reviews*. 2002;3:CD000933.
- Spong CY, Mercer BM, D'Alton M, Kilpatrick S, Blackwell S, Saade G. Timing of indicated late-preterm and early-term birth. *Obstetrics & Gynecology*. 2011;118(2):323-33.
- Uppal A, Uppal S, Pinto A, Dutta M, Shrivatsa S, Dandolu V, Mupparapu M. The effectiveness of periodontal disease treatment during pregnancy in reducing the risk of experiencing preterm birth and low birth weight: a meta-analysis. *JADA*. 2010;141:1423-34.
- Vidarsdottir H, Geirsson RT, Hardardottir H, Valdimarsdottir U, Dagbjartsson A. Obstetric and neonatal risks among extremely macrosomic babies and their mothers. *American Journal of Obstetrics & Gynecology*. 2011;204:423.e1-6.
- Virally M, Laloi-Michelin M. Methods for the screening and diagnosis of

- gestational diabetes mellitus between 24 and 28 weeks of pregnancy. *Diabetes & Metabolism*. 2010;36:549-65.
- Xiong X, Buekens P, Goldenberg RL, Offenbacher S, Qian X. Optimal timing of periodontal disease treatment for prevention of adverse pregnancy outcomes: before or during pregnancy? *American Journal of Obstetrics & Gynecology*. 2011;205:111.e1-6.
- Yang YT, Mello MM, Subramanian SV, Studdert DM. Relationship between malpractice litigation pressure and rates of cesarean section and vaginal birth after cesarean section. *Medical Care*. 2009;47:234-42.
- Zhang X, Decker A, Platt RW, Kramer MS. How big is too big? The perinatal consequences of fetal macrosomia. *American Journal of Obstetrics & Gynecology*. 2008;198:517.e1-e6.

Chapter 6

Summary

While gestational diabetes and periodontal disease are thought to contribute to adverse maternal and infant health outcomes independently, studies have not previously addressed their potential combined interaction. Examination of this potential additive relationship in this dissertation yielded mixed results. Pre-eclampsia was more prevalent in pregnant women with both gestational diabetes and periodontal disease compared to either condition alone. In addition, both conditions demonstrated positive associations with pre-eclampsia relative to the absence of both conditions. Because both conditions are positively associated with pre-eclampsia, additive or multiplicative interaction should be present as long as each condition alone does not achieve a maximum threshold for risk (Greenland 1998). The test for multiplicative interaction was not significant, suggesting additive interaction is present between gestational diabetes and periodontal disease for the outcome of pre-eclampsia.

A similar relationship existed between gestational diabetes, periodontal disease and obstetric intervention as that observed with pre-eclampsia. This finding may reflect the additive relationship between these two conditions

observed with pre-eclampsia as pre-eclampsia is a clinical indication for obstetric intervention (ACOG 2009). The greatest risk for obstetric intervention occurred in women with both gestational diabetes and periodontal disease. Women with gestational diabetes alone or periodontal disease alone both had increased risk of obstetric intervention relative to women without either condition. As with pre-eclampsia, the multiplicative interaction was not statistically significant, suggesting that the effects of gestational diabetes and periodontal disease are additive for the outcome of obstetric intervention. When obstetric intervention was broken into component parts of cesarean delivery and labor induction, the risk for each intervention was greatest when both conditions were present. For all these relationships, the risk was greater for gestational diabetes than for periodontal disease. However, gestational diabetes is an established clinical indication for intervention (ACOG 2009) while periodontal disease is not. Thus, the greater risk for obstetric intervention observed for gestational diabetes may reflect both biological significance and clinical decision-making.

While additive effects between gestational diabetes and periodontal disease were observed for the outcomes of pre-eclampsia and obstetric intervention, they were not observed for infant birthweight measured on a continuous scale. Gestational diabetes, as expected, was associated with increased infant birthweight. Infant birthweight was not increased when both gestational diabetes and periodontal disease were present compared to gestational diabetes alone. Periodontal disease was associated with a small increase in infant birthweight, but this was not statistically significant. Neither an

additive or multiplicative interaction appears to exist between gestational diabetes and periodontal disease for infant birthweight. Also, the increased infant birthweight observed among women with periodontal disease is contrary to previous studies that found a relationship between periodontal disease and low birthweight infants (Marin 2005, Moliterno 2005, Moore 2004, Lunardelli 2005).

For each outcome assessed in this dissertation, the periodontal disease case definition was examined to determine the extent to which the severity influenced the magnitude the relationship. For pre-eclampsia, as the case definition for periodontal disease became more severe, the magnitude of the association between periodontal disease and pre-eclampsia also became stronger. This finding provides additional evidence in support of periodontal disease as a potential causal factor for pre-eclampsia. Regardless of severity level, each case definition for periodontal disease maintained a two-fold increase in the risk for obstetric intervention. This constant risk may suggest that a minimum level of periodontal disease is needed to confer an additional risk for obstetric intervention, but this risk does not increase beyond a two-fold threshold. Severity of periodontal case definition did not impact the relationship between periodontal disease and infant birthweight.

The observation that periodontal disease and gestational diabetes may have additive effects for adverse pregnancy outcomes provides an opportunity to risk stratify pregnant women who may benefit from therapeutic interventions. Temporality is a strength of this study in that both periodontal disease and gestational diabetes were identified prior to the occurrence of the outcomes.

Gestational diabetes is a recognized risk factor for adverse pregnancy outcomes while periodontal disease is controversial as a causal risk factor. Periodontal disease, even if not a causal risk factor, may provide a risk marker for stratification purposes that may improve obstetric intervention use when other clinical indications provide marginal evidence. The additive nature of the relationship between gestational diabetes and periodontal disease suggests treatments for each condition may have greater effectiveness in reducing risk for adverse pregnancy outcomes when both conditions are present by preventing feedback loops that further facilitate the underlying pathophysiological processes. Periodontal therapy during pregnancy has demonstrated mixed results on its effect on adverse pregnancy outcomes with clinical trials typically demonstrating little effectiveness (Newnham 2009, Michalowicz 2006, Offenbacher 2009, Uppal 2010). Thus, potential for periodontal therapy as an effective prevention tool for adverse pregnancy outcomes may be limited. However, the effectiveness of periodontal therapy prior to pregnancy to reduce adverse pregnancy outcomes has not been evaluated. The intensity of periodontal therapy has also not been evaluated in these studies aimed at reducing adverse pregnancy outcomes (Xiong 2011). The additive effects observed in this dissertation suggests potential opportunities for biologic synergism when other infectious-related contributors to inflammation exist during pregnancy. Further research is needed to assess contributions from these multiple sources of systemic disease on the risk for adverse pregnancy outcomes.

Routine dental examination has the potential to identify undiagnosed or early stages of diabetes as a substantial majority of the adult population routinely visits the dentist for care (CDC 2008) and a simple method of combined patient self-reported risk factors with periodontal assessment can identify diabetes (Borrell 2007). Thus, dental providers have opportunities to impact diabetes in the population in the preconceptual period. In addition to educating dental providers about identification of diabetes, education of medical providers about the oral health – systemic health relationship provides opportunities to identify oral health problems and refer the persons for treatment. In North Carolina, a study of internists and endocrinologists found that 88 percent recommend these physicians should learn about the oral health – systemic health connection, but also significant variability in the self-efficacy of these physicians to provide oral health screening (Owens 2011). A study of obstetrician knowledge about oral health – systemic health issues in pregnancy found that only 22 percent looked in the patient’s mouth at initial prenatal care screening with 48 percent of that group only looking when a problem was specifically mentioned by the patient (Wilder 2007). Greater educational efforts are necessary to translate oral health screening into routine prenatal care practice. However, studies have not addressed the cost-effectiveness of either universal or targeted screening. In addition, the issues surrounding the effectiveness of periodontal therapy on adverse pregnancy outcomes need resolved to support a rationale for routine screening. Currently, screening of women with high risk of adverse outcomes may provide further opportunities to risk-stratify pregnancies.

This education of medical providers may also have importance internationally where gestational diabetes, periodontal disease, or adverse pregnancy outcomes are more prevalent. In Brazil, a study assessing obstetrician knowledge of periodontal disease and adverse pregnancy outcomes found that 80 percent were aware of these associations and 94 percent accurately reported that periodontal disease was a condition more severe than gingivitis (Rocha 2008). However, a study in Jordan found that while 54 percent of obstetricians thought that teeth and gums could impact a pregnancy, only 32 percent advised women planning a pregnancy to include periodontal evaluation in prenatal care (Al-Habashneh 2008).

While much of this study has focused on the prevalence and treatment of gestational diabetes and periodontal disease during pregnancy, primary prevention opportunities exist for both conditions. Programs aimed to prevent uptake of smoking behaviors and tobacco cessation strategies to aid people currently smoking could ultimately decrease incident periodontal disease in the preconceptional period. Programs aimed at improved nutritional intake, increased physical activity, and reducing obesity in the general population could reduce both the prevalence of gestational diabetes and periodontal disease. For instance, soda intake is associated with increased risk for type 2 diabetes (Nettleton 2009) and periodontal disease (Heller 2001). Thus school policies that remove soda from vending machines are an opportunity to alter nutritional behaviors in childhood and adolescence that affect both gestational diabetes and periodontal disease and ultimately, adverse pregnancy outcomes. Thus, many

opportunities exist prior to pregnancy for primary care prevention of the risk factors that lead to diabetes and periodontal disease.

Study strengths and limitations

While the study population was chosen for its high prevalence of gestational diabetes and periodontal disease, the population served by the University of Kentucky Maternal-Fetal Medicine clinic may not be fully generalizable to larger populations or to geographic-based populations in the same network area as the clinic. The population at the University of Kentucky Maternal and Fetal Medicine clinic has a notably larger minority population than the overall United States population, particularly a larger Hispanic population. The matched design reduces confounding by maternal age and maternal race and ethnicity in the study design stage.

Despite controlling for confounding in multivariable analysis, residual confounding may persist as the measures of operationalized confounders may not represent the full effect of the confounding variable. While residual confounding is not unique to periodontal disease and systemic disease outcome relationships, computer model simulations for incomplete control of confounders in the periodontal disease and systemic disease relationships can yield spurious positive relationships (Ylostalo 2006). Residual confounding from matching variables was addressed by including these variables in multivariable models. However, measurement of the full effect of the matched variables by themselves is not possible in a matched design.

The sample used for analysis was only half of the expected study population. This limited the power of the study and the ability to use more robust analysis that could take advantage of the matching in the study design. In the analysis of pre-eclampsia, the limited sample size manifested in an inadequate occurrence of outcome events in the pregnant women without gestational diabetes. In the analysis of infant birthweight, the preliminary sample size limited the analysis to linear regression models as categorical analysis could not be performed due to small cell sizes. To account for these limitations, matching was broken as is allowed in matched cohort analyses (Rothman 1998). While this allowed for estimation of the point estimates in the relationships, this also led to wider confidence intervals and as a result a less efficient study design than was initially intended. Preliminary sample sizes also may not have adequate power to sufficiently test the nature of the interaction between periodontal disease and gestational diabetes mellitus on the outcomes of interest. If both periodontal disease and gestational diabetes mellitus are associated with the outcome, an interaction would exist. However, one would not be able to determine whether that interaction is on an additive or multiplicative scale. Also, interactions between these exposures may exist mathematically but not biologically.

Given that the preliminary data were missing for a substantial number of women, I compared women excluded from the analysis to those who remained (Table 6.1). Most pregnant women not included in the analysis were missing information on both the outcomes and predictors. Only the obstetric intervention outcome demonstrated statistically significant differences between included

women and excluded women. It is unclear whether this difference reflects a true difference between included and excluded women or whether this difference reflects that data from all study data sources had not been fully recorded in the excluded population as most other data elements were missing.

A potential challenge of evaluating clinical measures of disease as opposed to underlying biomarkers is that the clinical measure of disease requires achieving a minimum threshold for the case definition. These clinical thresholds may not capture when subclinically relevant risk factors can also contribute to disease outcomes. Thus a clinical threshold may misclassify a person's true risk of disease. This risk factor misclassification is particularly important when the exposure to outcome relationship follows a continuous scale or toxicity S-shaped curve before achieving the clinical threshold of the disease outcome of interest. Evaluating conditions with similar underlying pathophysiology may provide knowledge as to the potential relationships between underlying diseases and whether a single condition alone can maximize the risk of disease or whether the risk of disease is on a continuous scale that is not fully addressed when assessing single risk factor to disease outcome relationships. Subclinical disease is important when assessing relationships between gestational diabetes and adverse pregnancy outcomes because subclinical maternal glucose levels have been associated with increased infant birthweight and pre-eclampsia (HAPO 2008). Thus observations that a clinical defined condition was not associated with an outcome of interest, does not necessarily mean that the underlying pathophysiology contributing to a subclinical mechanism is not

contributing to disease. Also, it should be noted that the two-step glucose tolerance test used in this study may not be an ideal means of classifying gestational diabetes on a dichotomous scale as one-step 75 gram glucose tolerance tests with measurements each hour from 0 to 2 hours may provide a better classification of gestational diabetes status (Virally 2010). However, it is unclear whether either test truly provides a better measure of gestation diabetes status. If the 75 gram test were better, then there may be some misclassification of gestational diabetes exposure status resulting in risk estimates for gestational diabetes closer to the null. Periodontal disease, much like gestational diabetes, has different degrees of severity as a clinically defined condition. In this dissertation, different clinical periodontal disease case definitions were tested to assess severity and its impact on the magnitude of observed associations. However, the extent to which subclinical periodontal disease may contribute to adverse pregnancy outcomes is unknown. Clinically relevant severe periodontal disease has been associated with stronger severity of premature birth (Jeffcoat 2001), so it might be reasonable to assume that subclinical periodontal disease may be capable of contributing some level of effect toward adverse pregnancy outcomes.

Treatment of conditions during pregnancy may also impact the risk estimates observed in this study. Even though we are interested in the effect of gestational diabetes, we are actually evaluating the effect of gestational diabetes under standard of care treatment protocols. The assumption is that all women in this study were treated with the same standard of care for gestational diabetes

since evidence suggest that treatment may alleviate the effects of gestational diabetes (Nicholson 2009) and to deny treatment would be unethical. Because periodontal disease treatment is less likely to be treated in a clinical setting, the risk estimates for periodontal disease may ultimately be more reflective of the condition itself rather than the condition under standard treatment. Since most randomized trials of periodontal disease treatment show small to no effects on adverse outcomes, women who were treated for periodontal disease may not ultimately have their adverse outcomes prevented through treatment (Polyzos 2011). On the other hand, women who were being treated for periodontal disease before pregnancy may receive a benefit from treatment as it is unknown whether pre-conceptual treatment of periodontal disease reduces the risk of adverse outcomes.

Another important consideration and limitation in the interpretation of parameter estimates specifically for obstetric intervention is the response clinically by a physician to act upon the presence of a maternal morbidity such as gestational diabetes while not acting upon the presence of periodontal disease. Because of the historical evidence supporting gestational diabetes and its associated maternal morbidities as clinical indications for obstetric intervention, clinicians may be more likely to request that an intervention be performed. For periodontal disease, the evidence supporting its impact on adverse pregnancy outcomes is newer and controversial. Thus, clinicians may not act as aggressively in terms of requesting an obstetric intervention when periodontal

disease is present compared to when other maternal morbidities such as gestational diabetes are present.

These limitations are all important to consider when interpreting the results. Power to detect differences was smaller using the preliminary data than the estimated power from the expected sample size. Confidence intervals as a result were wider than expected, even around statistically significant contributors to the adverse outcomes. The dichotomous classification of the primary exposures of gestational diabetes and periodontal disease may not capture the full effect of their relationship with the adverse outcomes relative to if these exposures were measured on a linear or ordinal scale. Treatment of these conditions and their influence on clinical decision-making confer additional challenges to the interpretability of the parameters.

Future research

While these analyses demonstrated the potential for synergism between periodontal disease and gestational diabetes, additional research on this synergism should aim to address gestational diabetes on a continuous scale. This continuous assessment of gestational diabetes can further the knowledge of this interaction, or it could identify gestational diabetes as the source of the epiphenomenon between periodontal disease and adverse pregnancy outcomes. Studies focusing on different treatment strategies for periodontal disease for the purpose of preventing adverse pregnancy outcomes are also needed. These treatment studies should address preconceptual and

interconceptual treatment, timing of treatment, and intensity of treatment. To effectively translate knowledge into practice, education of medical providers about oral-systemic health issues is needed. Studies about the awareness of oral-systemic relationships are needed for pre-eclampsia, as this has not been included in previous studies assessing physician knowledge. Studies are also needed to assess the impact of screening high-risk women for oral health issues with the goal of targeted interventions where appropriate. Should high risk screening strategies prove useful, then universal screening for oral disease in pregnancy should be considered. These future research opportunities can further pathophysiological understanding and applied public health practice to prevent adverse pregnancy outcomes.

Figures and Tables

Table 6.1: Comparison of pregnant women who were included in the analyses and the women who were universally excluded from the analyses.

Variable	Women included in analyses		Women excluded from analyses		p-value
	N	%	N	%	
Birthweight					
>= 4000 grams	17	8.9	4	9.8	0.7635
>= 2500g and < 4000 grams	168	88.4	34	82.9	
< 2500 grams	5	2.7	3	7.3	
Pre-eclampsia					
Yes	14	6.4	2	1.8	0.1009
No	206	93.6	107	98.2	
Obstetric intervention					
Yes	123	55.9	19	17.4	< 0.0001
No	97	44.1	90	82.6	
Smoking status					
Current smoker	22	10.0	2	9.1	0.3363
Previous smoker	44	20.0	7	31.8	
Never smoker	153	70.0	13	59.1	
Race/Ethnicity					
Caucasian	82	37.3	10	29.4	0.5338
Black	24	10.9	7	20.6	
Hispanic	102	46.4	12	35.3	
Asian	16	7.3	5	14.7	
History of drug use					
Yes	14	9.1	2	9.1	0.6501
No	200	90.9	20	81.9	
Previous pregnancy					
Yes	152	69.1	19	86.4	0.1383
No	68	30.9	3	13.6	
Gestational diabetes					
Yes	110	50.0	52	51.5	0.8113
No	110	50.0	49	48.5	
Periodontal disease					
Yes	124	56.4	12	54.5	1.0000
No	96	43.6	10	45.5	
Variable	N	Mean±SE	N	Mean±SE	p-value
Mean maternal age (years)	220	29.0 (0.4)	6	31.6 (2.8)	0.2610
Mean gestational age (weeks)	220	38.5 (0.1)	6	38.8 (0.3)	0.6251
Mean birthweight (grams)	217	3,395 (31)	41	3,473 (180)	0.6882

References

- (ACOG) The American College of Obstetricians and Gynecologists. Induction of Labor. ACOG Practice Bulletin No. 107. *Obsetrics & Gynecology*. 2009;114:386-97.
- Al-Habashneh R, Aljundi SH, Alwaeli HA. Survey of medical doctors' attitudes and knowledge of the association between oral health and pregnancy outcomes. *International Journal of Dental Hygiene*. 2008;6:214-20.
- Borell LN, Kunzel C, Lamster I, Lalla E. Diabetes in the dental office: using NHANES III to estimate the probability of undiagnosed disease. *Journal of Periodontal Research*. 2007;42:559-65.
- (CDC) Centers for Disease Control and Prevention. Behavioral risk factor surveillance system survey data. 2008. US Department of Health and Human Services, Centers for Disease Control and Prevention, Atlanta, GA.
- Greenland S, Rothman KJ. Concepts of Interaction. *Modern Epidemiology*, 2nd edition. 1998. Lippincott Williams & Wilkins. Philadelphia, PA.
- HAPO Study Cooperative Research Group. Hyperglycemia and adverse pregnancy outcomes. *New England Journal of Medicine*. 2008;358:1991-2002.
- Heller KE, Burt BA, Eklund SA. Sugared soda consumption and dental caries in the United States. *Journal of Dental Research*. 2001;80(10):1949-53.
- Jeffcoat MK, Geurs NC, Reddy MS, Cliver SP, Goldenberg RL, Hauth JC. Periodontal infection and preterm birth: results of a prospective study. *Journal of the American Dental Association*. 2001;132:875-80.
- Lunardelli AN, Peres MA. Is there an association between periodontal disease, prematurity and low birth weight? A population-based study. *Journal of Clinical Periodontology*. 2005;32:938-46.
- Marin C, Segura-Egea JJ, Martinez-Sahuquillo A, Bullon P. Correlation between infant birth weight and mother's periodontal status. *Journal of Clinical Periodontology*. 2005;32:299-304.
- Michalowicz BS, Hodges JS, DiAngelis, AJ, Lupo VR, Novak MJ, Ferguson JE, Buchanan W, Bofill J, Papapanou PN, Mitchell DA, Matseone S, Tschida PA. Treatment of periodontal disease and the risk of preterm birth. *New England Journal of Medicine*. 2006;355:1885-94.

- Moliterno LFM, Monteiro B, da Silva Figueredo CM, Fischer RG. Association between periodontitis and low birth weight: a case-control study. *Journal of Clinical Periodontology*. 2005;32:886-90.
- Moore S, Ide M, Coward PY, Randhawa M, Borkowska E, Baylis R, Wilson RF. A prospective study to investigate the relationship between periodontal disease and adverse pregnancy outcome. *British Dental Journal*. 2004;197:251-58.
- Nettleton JA, Lutsey PL, Wang Y, Lima JA, Michos ED, Jacobs DR. Diet soda intake and risk of incident metabolic syndrome and type 2 diabetes in the Multi-Ethnic Study of Atherosclerosis (MESA). *Diabetes Care*. 2009;32(4):688-94.
- Newnham JP, Newnham IA, Ball CM, Wright M, Pennell CE, Swain J, Doherty DA. Treatment of periodontal disease during pregnancy: a randomized controlled trial. *Obstetrics & Gynecology*. 2009;114(6):1239-48.
- Nicholson W, Bolen S, Witkop CT, Neale D, Wilson L, Bass E. Benefits and risks of oral diabetes agents compared with insulin in women with gestational diabetes: a systematic review. *Obstetrics & Gynecology*. 2009;113:193-205.
- Offenbacher S, Beck JD, Jared HL, Mauriello S, Mendoza M, Couper LC, Stewart DD, Murtha AP, Cochran DL, Dudley DJ, Reddy MS, Geurs NC, Hauth JC. Effects of periodontal therapy on rate of preterm delivery: a randomized controlled trial. *Obstetrics and Gynecology*. 2009;114:551-59.
- Owens JB, Wilder RS, Southerland JH, Buse JB, Malone RM. North Carolina internists' and endocrinologists' knowledge, opinions, and behaviors regarding periodontal disease and diabetes: need and opportunity for interprofessional education. *Journal of Dental Education*. 2011;75(3):329-38.
- Polyzos NP, Polyzos IP, Zavos A, et al. Obstetric outcomes after treatment of periodontal disease during pregnancy: systematic review and meta-analysis. *British Medical Journal*. 2011;341:c7017.
- Rocha JM, Chaves VR, Urbanetz AA, Baldissera RS, Rosing CK. Obstetricians' knowledge of periodontal disease as a potential risk factor for preterm delivery and low birth weight. *Brazilian Oral Research*. 2011;25(3):248-54.
- Rothman KJ, Greenland S. Matching. *Modern Epidemiology*, 2nd edition. 1998. Lippincott, Williams & Wilkins, Philadelphia, PA.

- Uppal A, Uppal S, Pinto A, Dutta M, Shrivatsa S, Dandolu V, Mupparapu M. The effectiveness of periodontal disease treatment during pregnancy in reducing the risk of experiencing preterm birth and low birth weight: a meta-analysis. *JADA*. 2010;141:1423-34.
- Wilder R, Robinson C, Jared HL, Lieff S, Boggess K. Obstetricians' knowledge and practice behaviors concerning periodontal health and preterm delivery and low birth weight. *Journal of Dental Hygiene*. 2007;81(4):1-15.
- Xiong X, Buekens P, Goldenberg RL, Offenbacher S, Qian X. Optimal timing of periodontal disease treatment for prevention of adverse pregnancy outcomes: before or during pregnancy? *American Journal of Obstetrics & Gynecology*. 2011;205:111.e1-6.
- Ylostalo PV, Knuutila ML. Confounding and effect modification: possible explanation for variation in the results on the association between oral and systemic diseases. *Journal of Clinical Periodontology*. 2006;33:104-8.

Appendices

Appendix A: Regression Equations

Figure A1: Multivariable linear regression model for infant birthweight measured as a continuous outcome of gestational diabetes and periodontal disease

$$BW = \beta_0 + \beta_1(\text{PD,GDM}) + \beta_2(\text{PD}) + \beta_3(\text{GDM}) + \gamma_1(\text{C}_1) + \dots + \gamma_x(\text{C}_x)$$

BW = Infant birthweight

PD,GDM = Dummy variable representing mothers with both periodontal disease and gestational diabetes mellitus.

PD = Dummy variable representing mothers with periodontal disease but not gestational diabetes mellitus.

GDM = Dummy variable representing mothers with gestational diabetes mellitus but not periodontal disease.

C = Confounding variable

β_0 = Intercept

β_1 = The difference in the birthweight between mothers with periodontal disease and gestational diabetes and mothers with neither periodontal disease nor gestational diabetes mellitus, adjusted for all other variables.

β_2 = The difference in the birthweight between mothers with periodontal disease but without gestational diabetes and mothers with neither periodontal disease nor gestational diabetes mellitus, adjusted for all other variables.

β_3 = The difference in the birthweight between mothers with gestational diabetes but without periodontal disease and mothers with neither periodontal disease nor gestational diabetes mellitus, adjusted for all other variables.

γ = The difference in infant birthweight associated with the presence of the confounding variable represented, adjusted for all other variables.

Figure A2: Multivariable conditional logistic regression for infant birthweight measured as a categorical outcome in a matched analysis

$$\text{Log [Odds Ratio(HBW)]} = \beta_1(\text{PD,GDM}) + \beta_2(\text{PD}) + \beta_3(\text{GDM}) + \gamma_1(\text{C}_1) + \dots + \gamma_x(\text{C}_x) + \alpha_1 + \alpha_2 M_1 + \dots + \alpha_{208} M_{207}$$

HBW = High birthweight

PD,GDM = Dummy variable representing mothers with both periodontal disease and gestational diabetes mellitus.

PD = Dummy variable representing mothers with periodontal disease but not gestational diabetes mellitus.

GDM = Dummy variable representing mothers with gestational diabetes mellitus but not periodontal disease.

C = Confounding variable

β_1 = The difference in the stratum-adjusted log odds ratio of having a large-for-gestational age infant between mothers with periodontal disease and gestational diabetes and mothers with neither periodontal disease nor gestational diabetes mellitus.

β_2 = The difference in the stratum-adjusted log odds ratio of having a large-for-gestational age infant between mothers with periodontal disease but without gestational diabetes and mothers with neither periodontal disease nor gestational diabetes mellitus, adjusted for all other variables.

β_3 = The difference in the stratum-adjusted log odds ratio of having a large-for-gestational age infant between mothers with gestational diabetes but without periodontal disease and mothers with neither periodontal disease nor gestational diabetes mellitus, adjusted for all other variables.

γ = The difference in the stratum-adjusted log odds ratio of having a large-for-gestational age infant associated with the presence of the confounding variable represented, adjusted for all other variables

α = Nuisance parameters

M = Matched pair

Figure A3: Multivariable logistic regression for infant birthweight as a function of gestational age measured as a categorical outcome in an unmatched analysis

$$\text{Log}[\text{Odds Ratio(LGA)}] = \beta_0 + \beta_1(\text{PD,GDM}) + \beta_2(\text{PD}) + \beta_3(\text{GDM}) + \gamma_1(\text{C}_1) + \dots + \gamma_x(\text{C}_x)$$

LGA = Large for gestational age

PD,GDM = Dummy variable representing mothers with both periodontal disease and gestational diabetes mellitus.

PD = Dummy variable representing mothers with periodontal disease but not gestational diabetes mellitus.

GDM = Dummy variable representing mothers with gestational diabetes mellitus but not periodontal disease

C = Confounding variable

β_0 = Baseline risk of delivering a high birthweight infant.

β_1 = The difference in the log odds ratio of having a large-for-gestational age infant between mothers with periodontal disease and gestational diabetes and mothers with neither periodontal disease nor gestational diabetes mellitus.

β_2 = The difference in the log odds ratio of having a large-for-gestational age infant between mothers with periodontal disease but without gestational diabetes and mothers with neither periodontal disease nor gestational diabetes mellitus, adjusted for all other variables.

β_3 = The difference in the stratum-adjusted log odds ratio of having a large-for-gestational age infant between mothers with gestational diabetes but without periodontal disease and mothers with neither periodontal disease nor gestational diabetes mellitus, adjusted for all other variables.

γ = The difference in the log odds ratio of having a large-for-gestational age infant associated with the presence of the confounding variable represented, adjusted for all other variables.

Figure A4: Multivariable conditional logistic regression for pre-eclampsia in a matched analysis

$$\text{Log}[\text{Odds Ratio}(\text{PE})] = \beta_1(\text{PD,GDM}) + \beta_2(\text{PD}) + \beta_3(\text{GDM}) + \gamma_1(\text{C}_1) + \dots + \gamma_x(\text{C}_x) + \alpha_1 + \alpha_2 M_1 + \dots + \alpha_{208} M_{207}$$

PE = Pre-eclampsia binary outcome variable

PD,GDM = Dummy variable representing mothers with both periodontal disease and gestational diabetes mellitus.

PD = Dummy variable representing mothers with periodontal disease but not gestational diabetes mellitus.

GDM = Dummy variable representing mothers with gestational diabetes mellitus but not periodontal disease

C = Confounding variable

β_1 = The difference in the stratum-adjusted log odds ratio of developing pre-eclampsia between mothers with periodontal disease and gestational diabetes and mothers with neither periodontal disease nor gestational diabetes mellitus, adjusted for all other variables.

β_2 = The difference in the stratum-adjusted log odds ratio of developing pre-eclampsia between mothers with periodontal disease but without gestational diabetes and mothers with neither periodontal disease nor gestational diabetes mellitus, adjusted for all other variables.

β_3 = The difference in the stratum-adjusted log odds ratio of developing pre-eclampsia between mothers with gestational diabetes but without periodontal disease and mothers with neither periodontal disease nor gestational diabetes mellitus, adjusted for all other variables.

γ = The difference in the stratum-adjusted log odds ratio of developing pre-eclampsia associated with the presence of the confounding variable represented, adjusted for all other variables.

α = Nuisance parameters

M = Matched pair

Figure A5: Multivariable logistic regression for pre-eclampsia as a categorical outcome in an unmatched analysis

$$\text{Log}[\text{Odds Ratio(PE)}] = \beta_0 + \beta_1(\text{PD,GDM}) + \beta_2(\text{PD}) + \beta_3(\text{GDM}) + \gamma_1(\text{C}_1) + \dots + \gamma_x(\text{C}_x)$$

PE = Pre-eclampsia binary outcome variable

PD,GDM = Dummy variable representing mothers with both periodontal disease and gestational diabetes mellitus.

PD = Dummy variable representing mothers with periodontal disease but not gestational diabetes mellitus.

GDM = Dummy variable representing mothers with gestational diabetes mellitus but not periodontal disease

C = Confounding variable

β_0 = Baseline risk of developing pre-eclampsia

β_1 = The difference in the log odds ratio of developing pre-eclampsia between mothers with periodontal disease and gestational diabetes and mothers with neither periodontal disease nor gestational diabetes mellitus, adjusted for all other variables.

β_2 = The difference in the log odds ratio of developing pre-eclampsia between mothers with periodontal disease but without gestational diabetes and mothers with neither periodontal disease nor gestational diabetes mellitus, adjusted for all other variables.

β_3 = The difference in the log odds ratio of developing pre-eclampsia between mothers with gestational diabetes but without periodontal disease and mothers with neither periodontal disease nor gestational diabetes mellitus, adjusted for all other variables.

γ = The difference in the log odds ratio of developing pre-eclampsia associated with the presence of the confounding variable represented, adjusted for all other variables.

Figure A6: Multivariable conditional logistic regression for obstetric intervention in a matched analysis

$$\text{Log}[\text{Odds Ratio(OI)}] = \beta_1(\text{PD,GDM}) + \beta_2(\text{PD}) + \beta_3(\text{GDM}) + \gamma_1(\text{C}_1) + \dots + \gamma_x(\text{C}_x) + \alpha_1 + \alpha_2\text{M}_1 + \dots + \alpha_{208}\text{M}_{207}$$

OI = Obstetric Intervention

PD,GDM = Dummy variable representing mothers with both periodontal disease and gestational diabetes mellitus.

PD = Dummy variable representing mothers with periodontal disease but not gestational diabetes mellitus.

GDM = Dummy variable representing mothers with gestational diabetes mellitus but not periodontal disease.

C = Confounding variable

β_1 = The difference in the stratum-adjusted log odds ratio of using obstetric intervention between mothers with periodontal disease and gestational diabetes and mothers with neither periodontal disease nor gestational diabetes mellitus, adjusted for all other variables.

β_2 = The difference in the stratum-adjusted log odds ratio of using obstetric intervention between mothers with periodontal disease but without gestational diabetes and mothers with neither periodontal disease nor gestational diabetes mellitus, adjusted for all other variables.

β_3 = The difference in the stratum-adjusted log odds ratio of using obstetric intervention between mothers with gestational diabetes but without periodontal disease and mothers with neither periodontal disease nor gestational diabetes mellitus, adjusted for all other variables.

γ = The difference in the stratum-adjusted log odds ratio of the use of obstetric intervention associated with the presence of the confounding variable represented, adjusted for all other variables.

α = Nuisance parameters.

M = Matched pair

Figure A7: Multivariable logistic regression for obstetric intervention as a categorical outcome in an unmatched analysis

$$\text{Log}[\text{Odds Ratio(OI)}] = \beta_0 + \beta_1(\text{PD,GDM}) + \beta_2(\text{PD}) + \beta_3(\text{GDM}) + \gamma_1(\text{C}_1) + \dots + \gamma_x(\text{C}_x)$$

OI = Obstetric Intervention

PD,GDM = Dummy variable representing mothers with both periodontal disease and gestational diabetes mellitus.

PD = Dummy variable representing mothers with periodontal disease but not gestational diabetes mellitus.

GDM = Dummy variable representing mothers with gestational diabetes mellitus but not periodontal disease.

C = Confounding variable

β_0 = The baseline risk of using obstetric intervention

β_1 = The difference in the log odds ratio of using obstetric intervention between mothers with periodontal disease and gestational diabetes and mothers with neither periodontal disease nor gestational diabetes mellitus, adjusted for all other variables.

β_2 = The difference in the log odds ratio of using obstetric intervention between mothers with periodontal disease but without gestational diabetes and mothers with neither periodontal disease nor gestational diabetes mellitus, adjusted for all other variables.

β_3 = The difference in the log odds ratio of using obstetric intervention between mothers with gestational diabetes but without periodontal disease and mothers with neither periodontal disease nor gestational diabetes mellitus, adjusted for all other variables.

γ = The difference in the log odds ratio of the use of obstetric intervention associated with the presence of the confounding variable represented, adjusted for all other variables.

Appendix B: Power Calculations

In the following power calculations, the prevalence of periodontal disease was estimated at 57 percent using a case definition of four or more teeth with at least four millimeters pocket depth, two millimeters clinical attachment loss, and bleeding upon probing. The prevalence estimate of gestational diabetes was artificially set at 50 percent due to the matched study design. Thus power estimates for periodontal disease and gestational diabetes should be relatively similar. I calculated the power to detect a difference in proportions, if one exists, between two groups of unequal size in an unmatched analysis using a one-sided test (Figure B1). The power to detect an interaction was based upon the comparison with the two smallest exposure groups (Figure B2). Each power calculation was based upon the following formula for differences in proportions between unequal size populations (Fleiss 1981):

Figure B1: Power calculation for associations between periodontal disease and outcomes of interest:

$$N_1 = [z_{\alpha/2} \sqrt{[(r+1)p\bar{p}q\bar{q}] + z_{\beta} \sqrt{(rp_1q_1+p_2q_2)}]^2 / rd^2$$

$$\text{where } p_1+q_1=1, p_2+q_2=1, p\bar{p}+q\bar{q}=1, p\bar{p}=(p_1+rp_2) / r+1, n_2=r*n_1$$

$$a=0.05, z_{\alpha/2} = 1.96$$

$$b=0.80, z_{\beta} = 1.6$$

$$r = n_2/n_1 = 133/233 = 0.57$$

p_1 = prevalence of outcome in the population with periodontal disease

p_2 = prevalence of outcome in the population without periodontal disease

$$d = p_1-p_2$$

Figure B2: Power calculation for associations of outcomes of interest with the interaction term for gestational diabetes and periodontal disease:

$$N_1 = [z_{\alpha/2} \sqrt{[(r+1)p_{\text{bar}}q_{\text{bar}}] + z_{\beta} \sqrt{(rp_1q_1+p_2q_2)}}]^2 / rd^2$$

$$\text{where } p_1+q_1=1, p_2+q_2=1, p_{\text{bar}}+q_{\text{bar}}=1, p_{\text{bar}}=(p_1+rp_2) / r+1, n_2=r*n_1$$

$$a=0.05, z_{\alpha/2} = 1.96$$

$$b=0.80, z_{\beta} = 1.6$$

$$r = n_2/n_1 = 108/75 = 1.33$$

p_1 = prevalence of outcome in the population with periodontal disease but without gestational diabetes mellitus

p_2 = prevalence of outcome in the population with neither gestational diabetes mellitus nor periodontal disease

$$d = p_1-p_2$$

Outcome 1: High Birthweight

The prevalence of high birthweight is estimated at five percent in the population without periodontal disease. Table B1 shows the power to detect a difference between exposure groups if a difference exists at different levels of high birthweight prevalence. Table B2 shows the power to detect the interaction of periodontal disease and gestational diabetes on birthweight:

Table B1: Power estimates for the ability to detect an association between periodontal disease and the delivery of a high birthweight infant.

Prevalence of outcome among exposed (periodontal disease)	Prevalence of outcome among unexposed (no periodontal disease)	Difference in prevalence between exposed and unexposed	*Power (1- β)
0.08	0.05	0.03	33%
0.10	0.05	0.05	60%
0.12	0.05	0.07	81%
0.14	0.05	0.09	93%

*Calculated for sample size of unequal groups with N=233 exposed, 183 unexposed

Table B2: Power estimates for the ability to detect an interaction between periodontal disease and the delivery of a high birthweight infant.

Prevalence of outcome among exposed (gestational diabetes -, periodontal disease +)	Prevalence of outcome among unexposed (gestational diabetes -, Periodontal disease -)	Difference in prevalence between exposed and unexposed	*Power (1- α)
0.08	0.05	0.03	21%
0.10	0.05	0.05	37%
0.12	0.05	0.07	53%
0.14	0.05	0.09	67%

*Calculated for sample size of unequal groups with N=75 exposed, 108 unexposed

Outcome 2: Pre-eclampsia

The prevalence of pre-eclampsia is estimated at four percent in the population without periodontal disease. Table B3 shows the power to detect a difference if it exists at different levels of pre-eclampsia prevalence. Table B4 shows the power to detect an interaction between periodontal disease and gestational diabetes on pre-eclampsia:

Table B3: Power estimates for the ability to detect an association between periodontal disease and the presence of pre-eclampsia

Prevalence of outcome among exposed (periodontal disease)	Prevalence of outcome among unexposed (no periodontal disease)	Difference in prevalence between exposed and unexposed	*Power (1- α)
0.07	0.04	0.03	36%
0.09	0.04	0.05	65%
0.11	0.04	0.07	85%
0.13	0.04	0.09	95%

*Calculated for sample size of unequal groups with N=233 exposed, 183 unexposed

Table B4: Power estimates for the ability to detect an interaction between periodontal disease and the presence of pre-eclampsia

Prevalence of outcome among exposed (gestational diabetes -, periodontal disease +)	Prevalence of outcome among unexposed (gestational diabetes -, Periodontal disease -)	Difference in prevalence between exposed and unexposed	*Power (1- α)
0.07	0.04	0.03	24%
0.09	0.04	0.05	41%
0.11	0.04	0.07	57%
0.13	0.04	0.09	71%

*Calculated for sample size of unequal groups with N=75 exposed, 108 unexposed

Outcome 3: Obstetric Intervention

The prevalence of obstetric intervention is estimated at fourteen percent in the population without periodontal disease. Table B5 shows the power to detect a difference if it exists in the prevalence of obstetric intervention. Table B6 shows the power to detect an interaction between periodontal disease and gestational diabetes on the need for obstetric intervention:

Table B5: Power estimates for the ability to detect an association between periodontal disease and the need for obstetric intervention

Prevalence of outcome among exposed (periodontal disease)	Prevalence of outcome among unexposed (no periodontal disease)	Difference in prevalence between exposed and unexposed	*Power (1- α)
0.17	0.14	0.03	20%
0.19	0.14	0.05	38%
0.21	0.14	0.07	58%
0.23	0.14	0.09	75%

*Calculated for sample size of unequal groups with N=233 exposed, 183 unexposed

Table B6: Power estimates for the ability to detect an interaction between periodontal disease and the need for obstetric intervention

Prevalence of outcome among exposed (gestational diabetes -, periodontal disease +)	Prevalence of outcome among unexposed (gestational diabetes -, Periodontal disease -)	Difference in prevalence between exposed and unexposed	*Power (1- α)
0.17	0.14	0.03	14%
0.19	0.14	0.05	23%
0.21	0.14	0.07	35%
0.23	0.14	0.09	47%

*Calculated for sample size of unequal groups with N=75 exposed, 108 unexposed

References

Fleiss JL. Chapter 3. Statistical Methods for Rates and Proportions, 2nd ed. 1981. John Wiley & Sons, New York.