

## Obstetrics and Periodontal Therapy

### Dataset Introduction

#### **Abstract**

Maternal periodontal disease has been linked in observational studies to preterm birth ( $\leq 37$  weeks) and low birth weight ( $\leq 2500$  g) outcomes. The Obstetrics and Periodontal Therapy study was a multi-center randomized trial evaluating the effect of nonsurgical periodontal treatment intervention on preterm birth, comparing outcomes of women treated before 21 weeks gestation (treatment) to those treated after delivery (control). 823 participants enrolled at 4 centers underwent stratified randomization, resulting in 413 women assigned to the treatment group and 410 to control. Regardless of assignment, all participants were 13-16 weeks pregnant at time of randomization (baseline/visit 1) and went on to attend monthly follow-up visits defined as visits 2, 3, 4, and 5 corresponding to gestational age ranges of 17-20, 21-24, 25-28, and 29-32 weeks. The treatment group received periodontal treatment, oral hygiene instruction, and tooth polishing at their follow-ups, while those assigned to control underwent only brief oral exams. Data collection occurred at visits 1 (baseline), 3, and 5. The primary outcome of interest is gestational age at end of pregnancy. Additional outcomes include birthweight, clinical measures of periodontal disease, and various microbiological and immunological outcomes.

Statistical analyses were carried out on an intent-to-treat basis. Gestational age can be thought of as “time until end of pregnancy,” for which certain survival analysis methods would be appropriate. The study used a log-rank test stratified by center to compare time until end of pregnancy for treatment and control groups. A semiparametric proportional hazards model was also used for this purpose, incorporating maternal risk factors as predictors. For the study’s main analyses, gestational age was censored at 37 weeks (259 days) because the interest was in extending pregnancies that would otherwise end pre-term, not extending pregnancies generally. Though not used in the study itself, logistic regression is another method that could be applied: for example, to gestational age, dichotomized as “preterm” or “not preterm” according to a gestational age cutoff, or to birthweight dichotomized as “low” or “high” at the 2500 g or other cutoff (2500 g would be in keeping with the World Health Organization’s definition for low birth weight). Changes in clinical measures of periodontal disease from baseline to visits 3 or 5 could be analyzed using mixed effects linear models. The dataset also features a number of baseline characteristics, which could be compared in treatment and control groups via t-tests, Wilcoxon rank sum tests, Fisher’s exact tests or Pearson’s chi-square tests, as appropriate, to confirm the effectiveness of randomization.

The nonsurgical periodontal treatment involving scaling and root planing induced significant improvements in periodontal health. The study did not however find a significant relation between periodontal treatment and preterm birth risk. The results of this study were published in 2006 by Michalowicz et al., “Treatment of periodontal disease and the risk of preterm birth”, in *The New England Journal of Medicine*. The Obstetrics and Periodontal Therapy Dataset contains the data used in this study.

#### **Background**



Preterm birth, defined as delivery before 37 weeks of gestation, is a growing problem. In some cases, preterm birth can lead to infant death; in others, its consequences may include neurodevelopmental disabilities, cognitive impairment, and/or respiratory disorders in the child. Many risk factors for preterm birth have already been identified, including maternal age, drug use, and diabetes. However, such factors are exhibited in only about half of preterm birth mothers, highlighting a need to expand our understanding of what contributes to preterm birth risk.

Several observational studies have suggested an association between maternal periodontal disease and preterm birth. Periodontal disease is an inflammatory condition characterized by the destruction of tissue and/or bone around the teeth. A major component of periodontal disease is oral colonization by gram-negative bacteria; systemic release of cytokines and/or lipopolysaccharides from these bacteria may impact fetal condition. Inoculation of the periodontal pathogen *P. gingivalis* into pregnant animals does have a dose-dependent effect on birth weight and preterm birth signaling, but no such causal link has been shown in humans, only some associations. Though not definitive, the possibility of a significant relationship raises the question of whether treatment of maternal periodontal disease can decrease preterm birth risk.

### **Study Objective**

The objective of this randomized controlled trial was to determine whether treatment of maternal periodontal disease can reduce risk of preterm birth and low birth weight.

### **Study Design**

Randomized controlled clinical trial

### **Participants & Variables**

Patients were enrolled at 4 centers: the University of Kentucky (KY), the Hennepin County Medical Center (MN), the University of Mississippi Medical Center (MS), and Harlem Hospital (NY). All participants were 16 years of age or older with at least 20 teeth, were 13-16 weeks pregnant with a single fetus, and were diagnosed with periodontal disease at baseline. Diagnosis of periodontal disease was defined based on pocket depth, clinical attachment loss, and bleeding on probing: (1) At least 4 teeth with probing depth  $\geq 4$  mm and clinical attachment loss  $\geq 2$  mm, and (2) Bleeding on probing at  $\geq 35\%$  of all sites. All 823 randomized participants received nonsurgical periodontal treatment, but the timing of intervention was randomized to either before 21 weeks gestation (413 assigned to treatment), or after delivery (410 assigned to control). Randomization was performed separately within each center, and subsequent analyses were performed on an intent-to-treat basis. All participants attended monthly follow-up visits until delivery. At these visits, the treatment group received periodontal therapy, oral hygiene instruction, and tooth polishing, and the control group received brief oral exams. Developments in dental health and other risk factors (including medication use, serum measures, and adverse experiences) from baseline were recorded at visits 3 and 5 (21-24 and 29-32 weeks gestation, respectively). Notably, there is quite a lot of missing data. Some may have resulted from missed visits, others from human error, or other practical issues. Entries for microbiological and immunological outcomes, for example, may have been left blank due to a melted sample, lost mail, or instrument malfunction. Ultimately



however, the nature of the missing data cannot be known with specificity, and most of the dataset's blanks are referred to as generally "missing."

The primary obstetrical outcome was gestational age at end of pregnancy. Secondary outcomes included birthweight and Apgar scores, The primary and secondary obstetrical outcomes are recorded in columns 69-77. Previously known risk factors for preterm birth are included in the dataset. Risk factors assessed at baseline (including age, race, and history of previous births) are recorded in columns 4-28, with additional factors (including medications or conditions that may have been used or developed during pregnancy) summarized in columns 78-100.

Because dental health of participants may vary beyond periodontal disease status, essential dental care (EDC) was provided to all participants on an individualized basis. Variables 33-36 provide details on the EDC actually provided.

The dataset also includes a number of microbiological and immunological outcomes, recorded in columns 104-171. The measures were obtained at scheduled data collection visits 1 (baseline), 3, and 5 (defined above). The study focused on 7 periodontal bacteria: *A. actinomycetemcomitans*, *C. rectus*, *F. nucleatum*, *P. gingivalis*, *P. intermedia*, *T. denticola*, and *T. forsythus*. A number of these are associated with adverse obstetrical outcomes; in particular, *A. actinomycetemcomitans*, *C. rectus*, *P. gingivalis*, and *T. denticola* have been linked with preterm birth, and *F. nucleatum* with low birth weight. The counts of antibodies to these bacteria were recorded as well. Levels of biomarkers for preterm birth including prostaglandin E<sub>2</sub> (PGE<sub>2</sub>), tumor necrosis factor alpha (TNF $\alpha$ ), gelatinase (MMP9), and interleukins-1 $\beta$ , -6, and -8 were obtained using ELISA methods. Endotoxin activity was analyzed using the Charles River Endosafe system.

N = 823 participants

171 variables

### Citation(s)

#### Primary paper:

Michalowicz BS, Hodges JS, DiAngelis AJ, Lupo VR, Novak MJ, Ferguson JE, Buchanan W, Bofill J, Papapanou PN, Mitchell DA, Matseoane S, Tschida PA. "Treatment of periodontal disease and the risk of preterm birth." *New England Journal of Medicine*. 2006 Nov 2. 355 (18): 1885-94.

#### Secondary papers:

Michalowicz BS, DiAngelis AJ, Novak MJ, Buchanan W, Papapanou PN, Mitchell DA, Curran AE, Lupo VR, Ferguson JE, Bofill J, Matseoane S, Deinard AS Jr, Rogers TB. "Examining the safety of dental treatment in pregnant women." *J Am Dent Assoc*. 2008 Jun. 139(6): 685-95.

Novak MJ, Novak KF, Hodges JS, Kirakodu S, Govindaswami M, Diangelis A, Buchanan W, Papapanou PN, Michalowicz BS. "Periodontal bacterial profiles in pregnant women: response to treatment and associations with birth outcomes in the obstetrics and periodontal therapy (OPT) study." *J Periodontol*. 2008 Oct. 79 (10): 1870-9.



Kirakodu SS, Govindaswami M, Novak MJ, Ebersole JL, Novak KF. "Optimizing qPCR for the Quantification of Periodontal Pathogens in a Complex Plaque Biofilm." *Open Dent J.* 2008. 2: 49-55.

Michalowicz BS, Hodges JS, Novak MJ, Buchanan W, DiAngelis AJ, Papapanou PN, Mitchell DA, Ferguson JE, Lupo VR, Bofill J, Matseoane S. "Change in Periodontitis during Pregnancy and Risk of Preterm Birth and Low Birthweight." *J Clin Periodontol.* 2009. 36 (4): 308-314.

Ebersole JL, Novak MJ, Michalowicz BS, Hodges JS, Steffen MJ, Ferguson JE, Diangelis A, Buchanan W, Mitchell DA, Papapanou PN. "Systemic Immune Responses in Pregnancy and Periodontitis: Relationship to Pregnancy Outcomes in the Obstetrics and Periodontal Therapy (OPT) Study." *J Periodontol.* 2009. 80 (6): 953-60.

Michalowicz BS Novak MJ, Hodges JS, DiAngelis A, Buchanan W, Papapanou PN, Mitchell DA, Ferguson II JE, Lupo V, Bofill J, Matseoane S, Steffen M, Ebersole JL. "Serum Inflammatory Mediators in Pregnancy: Changes Following Periodontal Treatment and Association with Pregnancy Outcomes." *J Periodontol.* 2009. 80 (11): 1731-41.

Ebersole JL, Stevens J, Steffen MJ, Dawson III D, Novak MJ. "Systemic endotoxin levels in chronic indolent periodontal infections." *J Periodont.* 2010. 45: 1-7.

