Project 3: Periodontal Disease and Preterm Birth

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Introduction

Periodontitis, also called gum disease, is a serious bacterial infection that destroys connective tissue and bone around teeth. Recent studies have indicated that periodontitis during pregnancy is associated with an increased risk of preterm birth, low birth weight, and preeclampsia, a serious hypertension condition that could develop during pregnancy.

Investigators speculate that the transport of bacteria from sites of periodontal infection into the placenta, fetal membranes, and amniotic cavity leads to these adverse outcomes (Srinivas 2012). The Obstetrics and Periodontal Therapy study, which evaluated the effect of nonsurgical periodontal treatment on preterm birth, failed to find a significant association between maternal periodontal treatment and preterm birth via a survival analysis model. (Michalowicz et al., 2006)

In this study, our group plans to re-analyze the original data in the Obstetrics and Periodontal Therapy. We hypothesize that nonsurgical periodontal treatment is associated with preterm birth when the baseline periodontal health is adjusted for.

Variables

Overall dataset contains 823 observations and 171 variables.

Primary Variable	Variable Label	Description
PID	Participant ID	
Clinic	Enrollment center	Four centers

Primary Variable	Variable Label	Description
Group	Randomized treatment assignment	T=Intervention;C=Control
Birth.outcome	Birth outcome	Elective abortion; Live birth; Lost to follow-up; Non-live birth
GA.at.outcome	Gestational age at end of pregnancy	days

Dataset also contains variables for baseline risk factors, periodontal therapy and health summary, dental care, obstetrical outcomes, risk factors for pregnancies, microbiological information, and immunological information. Since we are investigating the association between periodontal disease and preterm birth, we may also need to account for initial periodontal health. Therefore, we are also interested in the following variables meansured during baseline in the dataset.

Baseline Periodontal Summary	Variable Label
N.qualifying.teeth	Number of teeth meeting OPT
BL.GE	Whole mouth average gingival index
BL..BOP	Fraction of sites bleeding on probing
BL.PD.avg	Whole mouth average pocket depth at baseline
BL.CAL.avg	Whole mouth average clinical attachment level
BL.Calc.I	Whole mouth average calculus index
BL.Pl.I	Whole mouth average plaque index

In the dataset, there were 103 preterm births out of 814 (9 lost to followup and were censored at 37 weeks). Below are two table for Normal/Preterm birth stratified by treatment groups. Unfortunately, there does not appear to a treatment effect when compared between the groups.

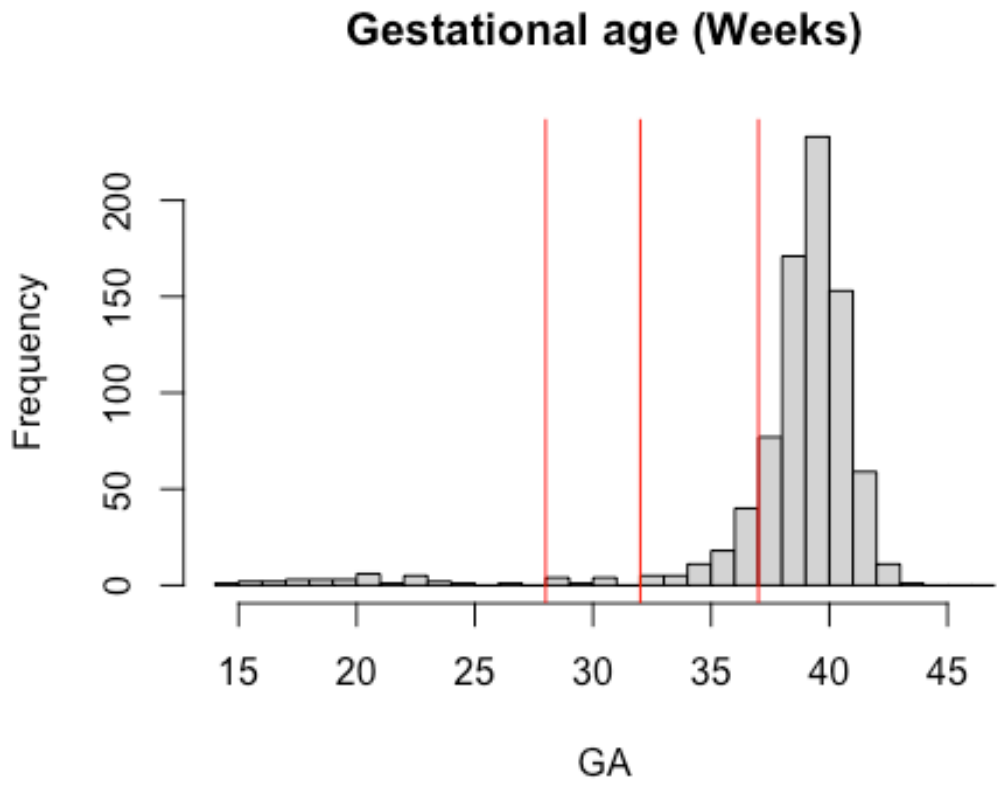
	NOT Extremely Preterm	Extremely Preterm
Control	393(48%)	17(2%)
Treatment	400(49%)	13(2%)

	NOT Very Preterm	Very Preterm
Control	387(47%)	23(3%)
Treatment	397(48%)	16(2%)

	Normal	Late Preterm
Control	353(43%)	57(7%)

	Normal	Late Preterm
Treatment	358(43%)	55(7%)

The figure below shows the distribution of gestational age in weeks. The red vertical lines indicates the 28th, 32nd, and 37th week so any births left of the red lines which indicate extreme preterm, very preterm, and moderate to late preterm respectively.



Lastly, gestation age and baseline periodontal summaries are summarized below.

	C / Mean	T / Mean	C / SD	T / SD
Gestational Age (Weeks)	38.26	38.45	4.25	3.81
Number of Teeth meeting OPT	14.36	15.16	6.69	6.79
Avg Gingival Index	1.42	1.45	0.40	0.44
% Bleeding on Probing	69.10	69.76	17.07	17.43
Avg Pocket Depth	2.84	2.90	0.53	0.59
Avg Clinical Attachment Level	1.37	1.45	0.66	0.71
Avg Calculus Index	1.13	1.15	0.62	0.62
Avg Plaque Index	1.23	1.24	0.48	0.50

Methods

For our proposed analyses, we first plan to replicate the results from the original study using a Cox Proportional hazards model while controlling for the four enrollment centers. We do not expect the results to be significant, rather, we would like to verify the lack of findings in the original study. Moreover, we are interested in the following regression model formula:

Late Preterm Birth ~ Group + Clinic

We are primarily interested in performing further exploratory analyses. We hypothesize that it may be important to adjust for baseline periodontal health. Thus, we plan to perform additional exploratory analyses using Firth's penalized logistic regression to handle rare events while adjusting for periodontal health at baseline. Furthermore, we will be estimating the treatment effect using doubly robust estimation. We may also be interested in adjusting for clinic sites in the logistic regression if we find a statistical significance. In addition, we would like to explore different categories of preterm birth (extremely preterm at 28 weeks, very preterm at 32 weeks, and late preterm at 37 weeks).

(1) Extremely Preterm Birth ~ Group + (Clinic + Baseline Periodontal Summaries)

(2) Very Preterm Birth ~ Group + (Clinic + Baseline Periodontal Summaries)

(3) Late Preterm Birth ~ Group + (Clinic + Baseline Periodontal Summaries)

Reference

Michalowicz BS, Hodges JS, DiAngelis AJ, Lupo VR, Novak MJ, Ferguson JE, Buchanan W, Bofill J, Papapanou PN, Mitchell DA, Matseoane S, Tschida PA; OPT Study. Treatment of periodontal disease and the risk of preterm birth. N Engl J Med. 2006 Nov 2;355(18):1885-94. doi: 10.1056/NEJMoa062249. PMID: 17079762.

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Appendix R Code

Setup

```
rm(list = ls())

library(tidyverse)
library(modelsummary)
library(logistf)

# Load data for preprocessing
df <- medicaldata::opt %>%
  mutate_if(is.factor,as.character)

# Create new preterm variables
df2 <- df %>%
  mutate(ExtremelyPreterm = ifelse(GA.at.outcome/7 < 28, 1,0),
         VeryPreterm = ifelse(GA.at.outcome/7 < 32, 1,0),
         LatePreterm = ifelse(GA.at.outcome/7 < 37, 1,0))

# Select variables of interest
df3 <- df2 %>%
  select(PID,Clinic,Group,Birth.outcome,GA.at.outcome,
         ExtremelyPreterm,VeryPreterm,LatePreterm,

N.qualifying.teeth,BL.GE,BL..BOP,BL.PD.avg,BL.CAL.avg,BL.Calc.I,BL.Pl.I)
```

Variable Description

```
tab = with(df3,table(Group,ExtremelyPreterm))
ptab = round(prop.table(tab),2)

ctab = matrix(paste0(tab,"(",100*ptab,"%)"),ncol = 2, nrow = 2)
colnames(ctab) <- c("NOT Extremely Preterm","Extremely Preterm")
rownames(ctab) <- c("Control","Treatment")

knitr::kable(ctab)

tab = with(df3,table(Group,VeryPreterm))
ptab = round(prop.table(tab),2)

ctab = matrix(paste0(tab,"(",100*ptab,"%)"),ncol = 2, nrow = 2)
colnames(ctab) <- c("NOT Very Preterm","Very Preterm")
rownames(ctab) <- c("Control","Treatment")

knitr::kable(ctab)

tab = with(df3,table(Group,LatePreterm))
ptab = round(prop.table(tab),2)
```

```r
ctab = matrix(paste0(tab,"(",100*ptab,"%)"),ncol = 2, nrow = 2)
colnames(ctab) <- c("Normal","Late Preterm")
rownames(ctab) <- c("Control","Treatment")

knitr::kable(ctab)

hist(df3$GA.at.outcome/7,breaks = 14:47,
     main = "Gestational age (Weeks)",
     xlab = "GA")
abline(v=28, col = "red")
abline(v=32, col = "red")
abline(v=37, col = "red")

dfoutput <- datasummary(
  GA.at.outcome/7 + N.qualifying.teeth + BL.GE + BL..BOP + BL.PD.avg +
BL.CAL.avg + BL.Calc.I + BL.Pl.I ~ Group*Mean + Group*SD,
  data = df3, output = "data.frame")

rownames(dfoutput) <- c("Gestational Age (Weeks)","Number of Teeth meeting
OPT","Avg Gingival Index","% Bleeding on Probing","Avg Pocket Depth","Avg
Clinical Attachment Level","Avg Calculus Index","Avg Plaque Index")

knitr::kable(dfoutput[,2:5])
```