**Risks of Recurrent Preterm Births by Clinical Subtype**

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SPECIFIC AIMS

Preterm birth is a serious public health concern associated with considerable morbidity and mortality and affecting nearly 10% of births.1 Though preterm birth has been largely declining in the United States in the last decade and a half,2 the US continues to have one of the highest rates of preterm birth of all developed countries.3 In order to better understand and predict preterm birth, a number of studies have sought to identify associated risk factors. One consistent finding is that mothers with a previous preterm birth have an elevated risk of subsequent preterm birth.4 We are interested in investigating this association with the added distinction of clinical subtype of preterm birth. Subtype is classified as either *indicated*, when risk to the mother and/or fetus requires delivery prior to 37 weeks gestation, or *spontaneous*, defined as otherwise spontaneous delivery before 37 weeks gestation not prompted by obstetric intervention. This distinction is crucial, as while the two types of birth may share some risk factors, they are conceptualized as qualitatively different processes. There are two primary gaps in the literature which this study seeks to address:

1. Primary aim – Explore the risk of subsequent preterm birth by clinical subtype to expand the limited available research in this area.

*Hypothesis 1 – The risk of both spontaneous and indicated preterm birth in the second pregnancy (P2) will be higher in individuals with a spontaneous preterm birth in their first pregnancy (P1).*

*Hypothesis 2 – The risk of both spontaneous and indicated preterm birth in P2 will be higher in individuals with an indicated preterm birth in P1.*

1. Secondary aim – Risk of recurrent preterm birth has been shown to differ by both race and interpregnancy interval.5,6 We will investigate whether these factors act as potential effect modifiers in the relationships assessed in aim 1.

*Hypothesis 3 – The risks of subsequent preterm birth as detailed in aim 1 are modified by race and interpregnancy interval.*

In order to better tailor public health approaches to reduce the rate of preterm birth, more information is needed to understand the specific risk factors associated with initial and multiple instances of preterm birth. Additionally, on a clinical level, more research on the aforementioned risk factors for subsequent preterm birth will allow health care providers to better monitor the care of subsequent births of individuals who have experienced an initial preterm birth.

RESEARCH STRATEGY

## Significance

The US continues to have one of the highest rates of preterm birth (birth before 37 weeks gestational age) of all developed countries.3  Preterm birth increases the risk of serious physical and cognitive adverse outcomes, including infant mortality. Previous research suggests that mothers who have had a previous preterm birth have an elevated risk of subsequent births also being preterm, though the mechanisms behind the risk remain somewhat unclear.4,6

Few studies have examined the associations between clinical subtypes (spontaneous or indicated) of recurrent preterm births. While the two subtypes share some risk factors, there are likely other factors that vary between spontaneous and indicated preterm births. Examining the associations between subtypes may lead to a better understanding of the risk factors for each subtype. In addition, knowing the relative risk of recurrent preterm birth by subtype can equip women and their providers with better knowledge of the risks faced in a subsequent pregnancy.

A small number of prior studies have examined associations between clinical subtypes of a first preterm birth and clinical subtypes of a second preterm birth, including three population-based retrospective cohort studies in Denmark, Missouri, and California using birth certificate data.6–8 The associations found in these studies are inconsistent. Although most studies found significant associations, one found no association between a first indicated preterm birth and a second spontaneous preterm birth.8 Additionally, the strength of these associations differed across studies. All studies found the strongest associations between births of the same subtype (e.g., first spontaneous preterm birth and second spontaneous preterm birth). However, some studies found the strongest association between recurrent spontaneous preterm births, while others found the strongest association between recurrent indicated preterm births.4,6–8 The studies also conflict in whether they found a significant difference in the overall risk of second preterm birth by subtype in the first. Some studies found no difference,7,8 while one found a higher risk of a second preterm birth if the first preterm birth was spontaneous.4

Additionally, risk of recurrent preterm birth differs by several factors, including race/ethnicity and interpregnancy interval.6 Investigators in one study stratified the subtype associations of recurrent preterm birth by race/ethnicity, but did not find statistically significant differences in the stratified associations.8  Our review uncovered no studies that presented results stratified by interpregnancy interval, although some did control for it in their analysis.6,8

By examining the associations of recurrent preterm births in Washington, we will expand the current knowledge in this area and help solidify a consensus regarding the strength of the associations by subtype. We will further stratify our analysis by race/ethnicity and also by interpregnancy interval in order to determine whether these differences persist by clinical subtype.

## Innovation

As described above, prior studies have used our approach, including three other population-based studies in Missouri, California, and Denmark.6–8  However, the available data on the risks of subsequent preterm birth by clinical subtype of the first preterm birth is limited and somewhat inconsistent.  In addition, only one of the prior studies examined how these risks are modified by race/ethnicity,8 and none of them examined modification by interpregnancy interval.

## Approach

We propose a retrospective cohort study of consecutive preterm births to examine the association between subtype of initial preterm birth (spontaneous or indicated) and risk of recurrent spontaneous or indicated preterm birth in the subsequent pregnancy.

### Data

Our study will leverage data abstracted from Washington State birth certificates and linked to Washington’s Comprehensive Hospital Abstract Reporting System (CHARS), a database of inpatient hospitalization records. Birth records representing nearly complete coverage of births in Washington between the years of 1987 and 2014 are linked longitudinally, enabling identification of sibling pairs.

### Exposures, Outcomes, and their Classification

In this study, we will examine two exposures, spontaneous and indicated preterm birth in the first pregnancy, and their associations with two outcomes, spontaneous and preterm birth in the second pregnancy. Preterm birth will be defined as a clinical estimate of gestational age of <37 weeks.

Our exposed cohorts will consist of women identified in the dataset with a history of two consecutive live singleton births, with the first birth being preterm (classified by subtype), from 2003-2014. Preterm births are defined as those before 37 weeks clinical gestational age. Data from these years use the 2003 version of the birth certificate which enables better classification of spontaneous vs. indicated preterm birth.

Additionally, we will acquire an unexposed cohort of women with a history of two consecutive live singleton births where the first birth was term, defined as birth between 37-42 weeks gestational age.. Each of these unexposed subjects will be matched on first birth year to women in our exposed cohort at a ratio of 4:1.

Determination of whether a preterm delivery is spontaneous or indicated has some uncertainty and the lack of specific designation on birth records will require us to make such judgement *post hoc* given what information is available. Several algorithms that attempt to do so have been described.8–10 We will adapt the method described by Klebanoff et al.10 This method is hierarchical in that once a condition is met for a particular birth, we assign a subtype and do not proceed to further steps in the algorithm. The method is as follows:

1. If premature rupture of membranes (PROM) was checked as onset of labor, the birth is classified as spontaneous.
2. If induction of labor was checked under characteristics of labor and delivery, the birth is classified as indicated.
3. If induction of labor was unchecked, but any onset of labor was checked (including PROM, precipitous labor, or prolonged labor) the birth is classified as spontaneous.
4. If induction of labor was unchecked, and the final route of delivery was marked either as vaginal (whether augmented, forceps, or vacuum) or as cesarean with a trial of labor, the birth is classified as spontaneous.

### Statistical analysis

We will employ a stratified analysis as our primary technique. We will calculate incidence rates of both spontaneous and indicated preterm birth in P2 in the three P1 exposure groups (term, spontaneous preterm, and indicated preterm). To test our hypotheses, we will compare the relative incidence risk of each combination of the outcomes and exposures, using those with a term first birth as the reference group.

### Potential Confounders and Effect Modifiers

Under our working definition of confounding - a variable that is associated with the exposure and outcome and not on the causal path - all known factors associated with preterm birth should be considered potential confounders. There are numerous potential risk factors and the list varies from source to source. We examine a selection of potential confounders: maternal age, race/ethnicity, BMI, tobacco use, a history of diabetes or hypertension, placenta previa, and infection.11–13

Subjects’ status regarding the potential confounders listed above can be classified from variables either present on the birth record or specific ICD codes in the CHARS database.

Each potential confounder will be evaluated for tangible confounding, indicated by a change in relative risk of 10% or more following adjustment, and adjusted for in the final relative risk estimate if found.

If the effect measures differ between strata of a potential confounder, the potential confounder may be in fact an effect modifier. Thus, though the process of evaluating potential confounders we also evaluate for effect modification. As discussed above, we suspect maternal race may be an effect modifier.  Additionally, though an overly short or long inter-pregnancy interval increases the risk of preterm delivery,14 this by definition does not meet our criteria of confounding because it cannot be associated with our exposure, preterm delivery in a women’s first pregnancy. However, we suspect it will be an effect modifier.

### Power/Sample Size Calculations

*Minimum Sample Required*

Table 1 provides the sample size analysis for our study given a two-sided alpha of .05 and power of 80%. As we are investigating more than one outcome, a range of expected risk ratios (RR) is provided based on the outcome with the smallest association in similar research. 8 For a 4:1 ratio of unexposed to exposed, in order to detect a minimum risk ratio of 1.15, we will need a sample of 4,120 exposed individuals in each exposed cohort. However, as one group of unexposed can serve as the reference category for both cohorts, sampling of unexposed individuals only needs be done once. Therefore, for the given minimum detectable RR and sampling ratio we will need a total sample of n = 24,270 (4,120 P1 spontaneous preterm + 4,120 P1 indicated preterm + 16,480 term/unexposed).

*Data Request*

As the 2003 Standard US Birth Certificate does not specify between subtypes of preterm birth, we will need to pull a sufficient number of all preterm births to ensure the specified number of cases are attained. A previous study has shown that estimates of the ratio of spontaneous to indicated preterm births amongst all preterm births typically range between 3:1 and 4:1,15 thus for this proposal we will adopt a conservative estimate of a ratio of 5:1. At that ratio in order to ensure 4,120 individuals with an indicated preterm birth at P1 and accounting for 10% missingness, we need to pull 27,467 individuals with a preterm birth at P1.



### Possible Limitations

Accurate classification of preterm birth subtype is, as discussed above, challenging with these data and though the use of a multivariate algorithm should improve our ascertainment, some degree of misclassification will persist. Fortunately, we have no reason to believe such misclassification will be differential, and we anticipate only a modest attenuation of risk estimates.

Limitations to our study due to data completeness and accuracy exist. For example, certain risk factors for preterm variables (e.g. alcohol use) are not present in this dataset and others (e.g. BMI) may suffer from a high degree of misclassification, raising the probability of residual confounding.

Additionally, though birth records should capture nearly every birth in Washington State, CHARS does not link to federal databases and so health records from those facilities, most notably VA hospitals, is absent.

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