INTERPREGNANCY INTERVAL, PRETERM BIRTH, & OTHER ADVERSE PREGNANCY OUTCOMES: HOW DOES PREVIOUS PREGNANCY OUTCOMES AFFECT INTERPREGNANCY INTERVALS?

By

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ABSTRACT

Introduction: Preterm birth (PTB), gestational age of < 37 weeks, is a leading cause of infant mortality across the globe. There are multiple risk factors associated with PTB but one approach to reducing PTB risk is birth spacing of 24 months or more between pregnancies. The interval between pregnancies is known as interpregnancy intervals (IPI). An IPI of less than 24 months increases the risk for preterm births. Few studies have studied the factors associated with short, appropriate, or optimal IPI. Furthermore, recent studies suggest that previous pregnancy outcomes may be related to IPI and the optimal IPI may be shorter following an early pregnancy loss than for a previous livebirth. The purpose of this study is to 1) examine the gaps in knowledge for IPIs, 2) assess the determinants of short IPIs, and 3) determine the optimal IPI window for different previous pregnancy outcomes.

Methods: We first conducted a systematic review of the literature to evaluate gaps in knowledge gaps about IPI and pregnancy outcomes. We also analyzed the INTERBIO-21st Fetal and Neonatal Study data to study IPI determinants and estimate optimal IPI based on previous pregnancy outcomes. The INTERBIO-21st studies allowed for the evaluation of IPI in an multinational setting due to the standardized methods of measurement of gestational age. To identify potential determinants of IPIs, we used descriptive statistics and bivariate analysis. We identified optimal IPIs using restricted cubic spline regression across months for women with different previous pregnancy

outcomes. We used Poisson regression with robust standard errors to evaluate the associations of selected interpregnancy windows to the risk of preterm birth.

Results: Previous pregnancy history was a major predictor of short IPI. The selected IPIs for women with a previous preterm and term birth were not associated with preterm birth. However, an IPI of less than nine months was protective against the risk of preterm birth when the previous pregnancy resulted in an early pregnancy loss.

INDEX WORDS: Interpregnancy interval, preterm birth, obstetric history, pregnancy, family planning

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Project Narrative

Preterm birth (PTB), defined as gestation less than 37 weeks, is a leading cause of neonatal morbidity and mortality worldwide. PTB is a pregnancy outcome that may result from multiple underlying conditions. They include maternal or fetal medical conditions that may require early induction of labor or a cesarean section. Other preterm births occur spontaneously, and their primary cause often is unclear. Few strategies are available to reduce the risk of PTB. One potentially actionable factor associated with PTB is pregnancy spacing. A key element of pregnancy spacing is considering how the time between pregnancies, or the interpregnancy interval, is related the risk of preterm birth. Previous studies have shown that short interpregnancy interval (IPI), defined as less than 18 weeks is associated with an increased risk for PTB. Alternatively, IPI of 18 to 24 months have been associated with lower risk of preterm births. Those findings have led professional organizations such as the American Congress of Obstetrics and Gynecology to recommend a pregnancy interval of at least 18 to 24 months to reduce the risk of PTB. This period of 18 to 24 months can also be described as the optimal interpregnancy interval with the objective of reducing the risk of preterm births. The biological basis of an optimal IPI is not fully understood. Current recommendations are based on data of a previous livebirth and there is some evidence that risks for PTB associated with short IPI may vary by the type of previous pregnancy outcomes. Some recent studies suggest that the optimal IPI following an early pregnancy loss may be shorter than for a previous livebirth term outcome. Our study focuses on identifying approaches to categorize interpregnancy interval and the role that previous

pregnancy outcome may have in defining the optimal interpregnancy interval, with the optimal IPI being the period of lowest risk for a preterm birth.

Statement of the Problem

Overview of Preterm Birth

Preterm birth (PTB), defined as a birth following less than 37 weeks of gestation, is a leading cause of neonatal morbidity and mortality worldwide. Globally, each year, approximately 15 million infants are born preterm, or about 11% of all deliveries(1). Preterm births account for about 35% of neonatal mortality worldwide(1). The burden of PTB is not uniformly shared across the globe, for example, PTB mortality accounts for close to 28% of all deaths in children aged under 5 years in North America and in Western Europe compared to approximately 13% in sub-Saharan Africa and 25.5% in South Asia(1).

Pathways to Preterm Birth

PTB is not a unique condition but a multifaceted phenotype with significant etiologic heterogeneity. For some, the etiology may be known, such as PTBs resulting from early induction of pregnancy as a result of diverse maternal and fetal medical fetal medical conditions but most PTBs are spontaneous.

Parturition, or spontaneous labor, occurs in four stages: quiescence, activation, stimulation, and involution(2). Phase 0, quiescence takes up 95% of the time during human pregnancy. During this stage, rarely there are contractions, which is primarily due to the lack of gap junctions in the pregnant myometrium being inhibited by progesterone and other related hormones(2). Phase 1 is when labor begins, with the number of gap junctions increasing due to an

increased expression of contraction-associated proteins(2). Uterine stretch occurs, resulting from fetal growth or activation of the fetal HPA axis. Phase 2, stimulation, involves a biological cascade of events which leads to common pathway of spontaneous labor, characterized by uterine contractions, cervical ripening, and fetal membrane activation(2). The Phase 3, involution, involves placental separation and uterine contraction ending with birth(2). Both spontaneous preterm and full-term births share this common pathway of partition. Spontaneous preterm labor is likely the result of external stimuli that cause the parturition pathway to activate(2). PPROM is the rupture of the membranes prior the beginning of labor and can occur in both preterm and full-term birth (3,4). During pregnancy, the fetal membranes serve as a barrier preventing infection, as well as other functions, such as maintaining amniotic fluid. Fetal membranes rest on collagen, which provides the structural strength for the membranes(3). When the membranes have ruptured, the mother and her fetus are at increased risk of infection and other complications. Medically indicated, or non-spontaneous PTB, also leads to PTB(2). Medically indicated PTB occurs when labor is initiated by medical intervention because of pregnancy complications that can affect the life and well-being of the mother and/or the fetus(2). Well established medical indications for early elective delivery include preeclampsia, uncontrolled hypertension, fetal growth restriction, PPROM, and others(2,5).

Causes and Risk Factors for Preterm Birth

There is extensive research focused on understanding the biologic causes, medical conditions, and epidemiologic risk factors that increase the risk of PTB. While the understanding of risk factors for preterm birth has progressed, known risk factors only explain approximately a third of PTB (6). Biologic factors that put women are at high risk for PTB include prior PTB, preterm labor, PPROM. Other factors include cervical insufficiency, uterine overdistention, or having reproductive organ abnormalities such as short cervix(2,7). Medical conditions that increase the risk for PTB include urinary tract and sexually transmitted infections, vaginal

infections or bleeding, inflammation of the fetal membranes, and developmental abnormalities of the fetus. Maternal weight, specifically pre-pregnancy underweight or obese body mass index and low or excessive gestational weight gain, also place a woman at increased risk for delivering preterm (2,7). Pregnancy specific medical conditions include gestational diabetes mellitus, preeclampsia and eclampsia, uteroplacental thrombosis, fetal abruption, placenta previa, and rupture of the uterus (2,7).

Sociodemographic risk factors for PTB include low educational attainment, maternal age, being unmarried, and lifestyle factors such as smoking, alcohol consumption, and illicit drug use, as well as psychosocial stress, and unintended pregnancy(2). Women less than 18-year-old are at increased risk for delivering preterm, as well as women older than 35 years. The factors associated with each age group may be different. For instance, women older than 35 years are more likely to have medical conditions, including hypertension and diabetes that may cause complications that may pose a greater risk for a medically indicated PTB while younger individuals may be more likely to experience lifestyle factors and stress (2,7).

Health Conditions Related to Preterm Birth

Infants born preterm are predisposed to numerous health conditions in the neonatal period that can lead to significant life-long disabilities (2). Complications arise from underdeveloped organ systems and immature regulatory systems that can result in respiratory distress syndrome, bleeding, and may lead to neurodevelopmental problems (2). Infants born preterm also have difficulty digesting food and are more likely to develop long term gastrointestinal problems(2). Relative to infants born at term, preterm infants are more prone to infections, including pneumonia or sepsis and more than 65% of infants born premature have at least one infection during hospitalization (2). After the initial discharge, late preterm infants also have a high rate of hospital admission, mostly due to infection (8).

The health impact of PTB is not limited to early life, infants born preterm are at an increased risk of suffering long-term health issues ranging from cardiovascular disease, hearing loss, and visual abnormalities (9,10). One of the underlying reasons for the increased risk among preterm infants is due to being born during a critical period of organ development, preventing optimal development (10). This severity of the stunting in development increases inversely with the gestational age of the infant. Those born closest to the beginning of this period of organ development (28 weeks) face the highest risk of death or disabilities.

While all cases of PTB may not be preventable given current knowledge, there are several potential actions that may reduce the risk of PTB. One potential is through family planning incorporating interpregnancy intervals (IPI) – defined as the time between the end of the previous pregnancy and the beginning of the current pregnancy. Currently the World Health Organization (WHO) identifies a short IPI as less than two years for livebirth pregnancy outcomes, and less than 6 months for women that experienced a loss(11). It should be noted that the use of 24 months to define a short IPI is not universally agreed upon, with many studies using less than 18 months as the cut-off(12). These recommendations were developed from previous studies which were limited in the way they investigated the relationship between IPI and PTB. These recommendations also conflict with some studies which claim that the short IPI cut off is less than twelve weeks, and ignore the role of long IPIs on the risk of PTB. Ignoring the risk from long IPIs could be placing women planning to become pregnant into higher risk groups than intended. The recommendations and the literature do not fully consider previous pregnancy history among live births as well, leaving a gap in the literature on the potential relationship between optimal IPI and previous pregnancy outcomes.

Overview of Interpregnancy Interval

The recognition of short IPI as a risk factor for adverse pregnancy outcomes has been evolving in the literature since the 1970's. A driver to measure IPI has been the improved methods to measure gestational age, such as use of ultrasound fetal measurements before 20 weeks of gestation. The introduction of ultrasound to estimate gestational age has significantly improved the precision of the estimate compared the traditional methods of maternal report of last menstrual period (LMP). IPI is a modifiable factor to reduce adverse pregnancy outcomes, such as PTB (13–16). An IPI of less than 6 months, has been associated with an increased risk of PTB, low birth weight, and small-for-gestational age. (16,17). It should be highlighted that what period constitutes a short IPI is debated, with multiple studies providing contradictory definitions of short IPI.

Long IPI, generally defined as an IPI longer than 60 months, has also been associated with an increased risk of PTB (18). The concern of having a too short or too long of an IPI is based on the "J-shaped" relationship of IPI and risk of PTB from short to long IPI (18). The risk of a PTB does not decrease and flatten to a baseline after a certain period of time, but rather falls and then rises. That observation is from studies on IPI based on a previous term birth. The J-shape risk curve raised the question of what the optimal window is when the risk for an adverse pregnancy outcome is the lowest and how wide that period is. Identifying an optimal window would allow for the

appropriate modification of maternal preconception behaviors that may result in an effective approach to reduce PTB.

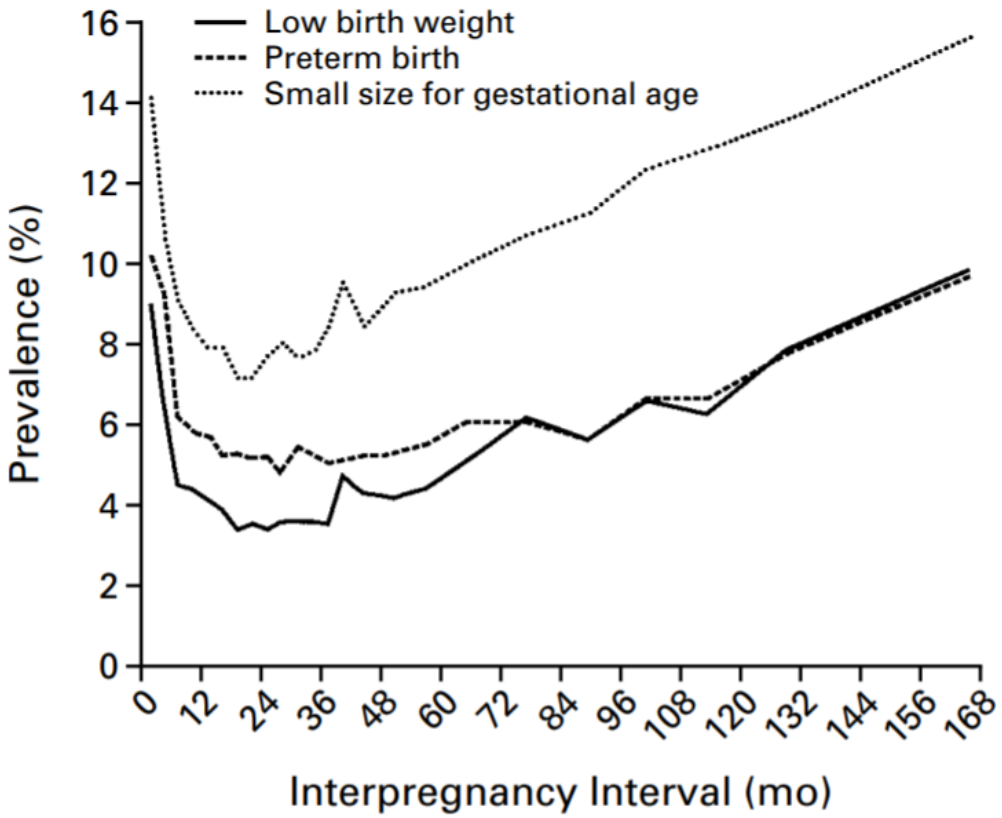


Figure 1. Prevalence of adverse perinatal outcomes according to interpregnancy interval among 173,205 singleton infants born alive in Utah from 1989 to 1996.

As seen in Figure 1, taken from Zhu et al. 1997, the risk of a PTB does not decrease and flatten to a baseline after a certain period of time, but rather falls and then rises (20). That observation is from studies on IPI based on a previous term birth. The J-shape risk curve raised the question of what the optimal IPI window is, defined as the time period when the risk for an adverse pregnancy outcome is the lowest. Another question is how wide that period is. Identifying an optimal window would allow for the appropriate modification maternal preconception behaviors that may result in an effective approach to reduce PTB.

Beyond PTB, studies have found associations between shorter and longer IPIs for outcomes such as small-for-gestational-age, low birth weight, and infant mortality (21) and shown in Figure 1. Studies have also found associations between short IPI and maternal severe morbidity and mortality (22). Moreover, the outcome of the previous pregnancy may also be relevant. Sundermann found that following a miscarriage, (pregnancy loss before 20 weeks), an IPI of less than three months was associated with the lowest risk for a subsequent miscarriage (23). That study raised the question of the impact that the previous pregnancy may have on what the optimal IPI is.

Biological Basis of Short Interpregnancy Interval Effects

One possible explanation in the literature about adverse outcomes from short interpregnancy intervals is the possibility of maternal nutritional depletion syndrome (24). This hypothesis proposes that a closely spaced pregnancies worsen the maternal nutritional status because of the limited recovery time after the stress of the previous pregnancy and subsequent post-partum breastfeeding. This impaired maternal nutritional status then increases the risk of adverse perinatal outcomes(25). These associations have not been consistently found which may be due to the differences in methods used to measure IPI, categorization of IPI, and the populations included. Moreover, this theory may not explain the optimal IPI following a miscarriage.

Methods to Estimate and Categorize Interpregnancy Interval

Early studies on IPI were inconsistent in selecting the number and length of the interval categories to be used in their analysis. Some used combinations of three- and six-month intervals, others included one two categories, but most used six months intervals. The larger amount of variance came from how studies handled the extreme ends of the intervals, particularly IPIs greater than 24 months. An example is Atreya et al. that its upper most category was greater or

equal to 60 months while DeFranco et al. used greater than 18 months(26,27). The intervals chosen as the reference interval varied considerably as well. These inconsistency makes it difficult to compare the results from various studies due to the lack of commonality in interpregnancy intervals. This variation becomes dramatically less frequent after the publication of Conde-Agudelo's seminal study in 2004. He used six-month intervals lengths for below 24 months and defined the reference period as 18 to 23 months. The other intervals were "24 to 59" months, "60 and greater" months(28).

This categorization has become the de facto standard, except for a few studies that did not follow this framework.

Interpregnancy Interval Measurement

IPI has been investigated since the 1970's, with studies looking at adverse pregnancy outcomes such as PTB. Measurement of IPI requires knowing the date when the previous pregnancy ended and the date for the beginning of the current pregnancy. While date of birth is a

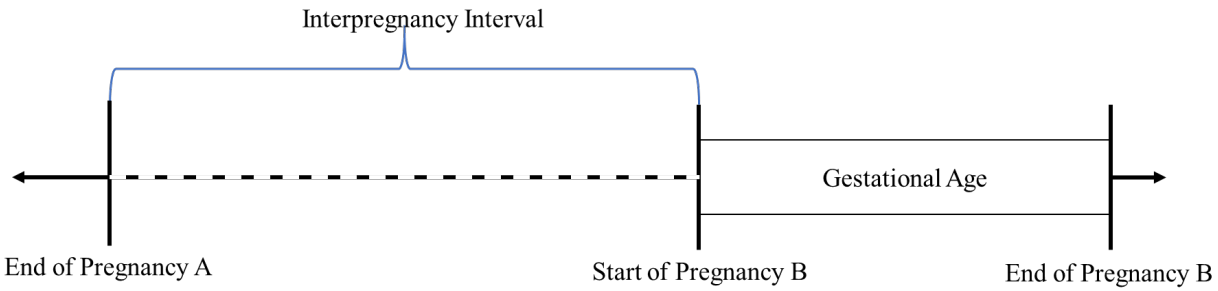


Figure 2. Interpregnancy interval definition

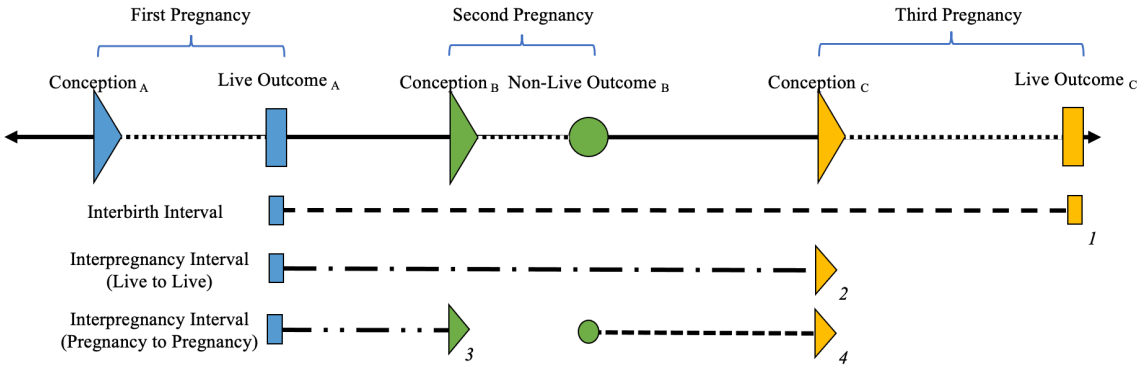
date that reliably can be obtained from maternal history, estimating the start of the current pregnancy is based on the birth date of the current pregnancy and the estimated gestational age of the liveborn which often is estimated based on maternal report of LMP, but preferably using ultrasound sound based obstetric estimates for more accurate estimations. This was mainly due to

three factors: endpoints used to define IPI, estimation of the beginning of a pregnancy, and the number and length of interval categories used for IPI.

The selection of the endpoint and estimation of the start of a pregnancy are critically important to defining IPI. Figure 2 visually represents the current standard measurement of IPI, with the end of pregnancy A as the beginning of the interval, and the start of pregnancy B as the end. In order to derive the start of pregnancy B, typically the gestational age of the infant– or gestational age of the fetus at time of termination – is subtracted from the date the pregnancy ended. In Figure 2 above this would be the following:

(""Date of End of Pregnancy B" – "Gestational Age of B") – "" Date of End of Pregnancy A" = Interpregnancy Interval (in days)"

The resulting IPI is generally converted into months. The subtraction of the gestational age allows for a more consistent IPI measurement that is not affected by the health of the subsequent pregnancy.



Line 1: Interbirth interval is defined as the time between two live outcomes, Live Outcome $_C$ – Live Outcome $_A$.
Line 2: Interpregnancy interval as defined as the time between two pregnancies with live outcomes, Conception $_C$ – Live Outcome $_A$.
Line 3: Interpregnancy interval is defined as the time between two consecutive pregnancies, Conception $_B$ – Live Outcome $_A$.
Line 4: Interpregnancy interval is defined as the time between two consecutive pregnancies, Conception $_C$ – Non-Live Outcome $_B$.

Figure 3. Comparison of interbirth, live-to-live IPI, and true interpregnancy intervals

The measurement of IPI is highly sensitive to the start and endpoints used to define the boundaries of the interval. Early literature, limited by the data available, relied on measuring the time between to births to create an interbirth interval (IBI), sometimes called an inter-delivery interval. In Figure 3, the IBI is represented in line 1, with the interval beginning with the live outcome of the first pregnancy and terminating with the live outcome of the third. A major weakness of IBI is that it can overestimate or underestimate the time between pregnancies because it does not consider variances in gestational age. The IBI shown in Figure 3 demonstrates the issue of overestimation clearly with the inclusion of the second pregnancy in the interval. The reliance of this sort of interval persist to modern papers.

The estimation of the start of a pregnancy is done by taking the subsequent pregnancy's end date and subtracting the gestational age. The precision of the IPI estimate will depend on the method use to estimate gestational age. Early studies used the last menstrual period (LMP) which is known have about a two week (29). The introduction of ultrasound in early pregnancy has improved the precision of gestational age estimate to about a week (29,30). As ultrasound technology measurements were developed, and it was shown to have greater accuracy than LMP, best obstetrical estimate became the gold standard for gestational age estimation. While using LMP was a method that hold obstetric tradition, its measurements have wide variations in estimates. Deputy et al. found that estimates derived from LMP alone has an error of about two weeks compared to ultrasound estimates that were able to narrow that error to within a week(29). In recent years, the use of standardized ultrasound technology in obstetrical offices, prior to 20 weeks' gestation has added accuracy to the estimating gestational age from the date of the subsequent birth has proven accurate measurement of the start date of a pregnancy. Newer technics such as Crown-to-Rump measurements have provided more precise methods of determining gestational age and have a higher degree of consistency and repeatability. The use of

ultrasound methods, rather than LMP, has allowed for greater uniformity and certainty in the accuracy of the start of pregnancies and the estimation of gestational age (30).

Impact of measurement error in estimating IPI and the optimal IPI period

There is a major need to examine how differences in measuring IPI impact the optimal IPI period, defined as the period with the lowest rate of the adverse pregnancy outcome(18). Precise measurement of IPI requires accurate estimation of date of conception, using best obstetrical estimate (31).There is also a need to examine IPI distribution in diverse populations and different geographical areas to determine if optimal IPI is similar or different. Moreover, there is a dearth of data on optimal IPI when the previous pregnancy outcome is not a livebirth. There is a need to address these issues as recommendations for optimal IPI are developed and reviewed.

Estimating Interpregnancy Intervals based on previous pregnancy outcome

The current optimal IPI estimates, based mainly on a previous live birth, introduce two potential sources of bias. The first source comes from selection bias, as women pregnancies resulting in early pregnancy losses may be fundamentally different those resulting in live births. One example of the fundamental differences between pregnancies which terminate in an early pregnancy loss compared to live births is the high frequency of chromosome abnormalities (32). Women with previous pregnancy loss, termination, or stillbirth potentially may have a different optimal IPI (17,33). There is a need to study optimal IPI based on previous pregnancy history. A second source of potential bias comes from the overestimation of the interval length due to the way non-live births are accounted. Some studies have considered a birth interval to be any time span between two live births, regardless of pregnancy history between those events. This could result in the actual intervals to be assumed longer than may be the case.

The issue of interval length is important due to the nature of the question being asked, what is an optimal interval. The imprecise, non-uniform nature of the current literature presents a potential issue due to the assumption that the intervals are measured in a manner that allows for comparison. This problem exists for defining short and long IPIs, whether this is being done implicitly or explicitly.

Pathways of Interpregnancy Intervals and Preterm Birth

The reasons for the association between a short interval between pregnancies and adverse perinatal outcomes are unclear. A plausible explanation is the maternal nutritional depletion hypothesis, which states that a close succession of pregnancies and periods of lactation worsen the mother's nutritional status because there is not adequate time for the mother to recover from the physiological stresses of the preceding pregnancy before she is subjected to the growth restriction, PTB, and low birth weight (25,34). Some investigators have attributed the higher risk of poor pregnancy outcomes to several factors associated with having short intervals, such as socioeconomic status, unstable lifestyles, failure to use health care services or inadequate use of such services, unplanned pregnancies, and other behavioral or psychological determinants. However, the fact that birth spacing effects are not strongly attenuated when socioeconomic and maternal characteristics are controlled for suggests that the effects are not associated with these confounding factors.

Some hypotheses have also been proposed to explain the relationship between long intervals and adverse perinatal outcomes. Zhu et al. have hypothesized that, after delivery, a woman's physiologic reproductive capacities gradually decline, becoming similar to those of primigravid women (ie, "the physiological regression hypothesis") (35). This hypothesis is supported by the observation that perinatal outcomes for infants conceived after an excessively long interpregnancy interval are similar to outcomes of infants born to primigravid women.

Another possibility is that unmeasured factors, such as sexually transmitted infections or maternal illnesses, may cause both adverse fertility and pregnancy outcomes (35,36). These factors could differ for women in developed and developing countries. Finally, residual confounding may still be an explanation for at least part of the reported associations.

The exact mechanism by which having a short IPI leads to adverse perinatal outcomes is not entirely understood, but it has been shown that short IPI increases the risk of uterine rupture in women attempting vaginal birth after cesarean, premature rupture of membranes, endometritis, third trimester bleeding, placenta previa, placental abruption, maternal death, and anemia (37–39). One potential explanation in the literature that may lead to these adverse outcomes is the possibility of maternal nutritional depletion syndrome. This hypothesis proposes that a closely spaced pregnancies worsen the maternal nutritional status because of the limited recovery time after the stress of the first pregnancy and subsequent post-partum breastfeeding. This impaired maternal nutritional status then increases the risk of adverse perinatal outcomes (25).

An excessively short or long IPI may subsequently lead to an increased risk of PTB though the other risk factors for PTB. Regardless, reduction and prevention of excessively short and long IPIs is a potentially achievable intervention to reduce the PTB especially in high-risk groups.

Current Standards of Interpregnacy Intervals

The most recent literature has moved towards standardization of the interpregnancy intervals used and reference group as developed by Conde-Agudelo et al. Following their study, subsequent studies cited their paper for justification but that changed in the most recent studies have not cited any reference – implying a common knowledge and understanding – or cited newer published papers uses the Conde-Agudelo intervals without citing – implying a common knowledge and understanding. In recently published studies, the use of LMP is nearly non-

existent, only included as a backup measurement in the absence of ultrasound gestational age data.

Consecutive live-to-live births have become standard baseline for optimal IPI, focusing on the 1st and 2nd pregnancies, to the point that studies do not specify live-to-live births outside of their methods sections. These changes improved the ability for researchers to better estimate the relationship between IPI and PTB and have allowed for results to be comparable across studies. Based on recent studies, organizations such as the WHO have developed recommendations for avoiding short IPIs derived from this research, less than 2 years in the case of the WHO (11, 36). However, the movement towards these standards has created an environment where the methods used have progressed. The conditions that required the use of predefined intervals and live-to-live birth intervals are no longer present, and the literature should adapt new standards as it did with its move from LMP to ultrasound estimates.

Limitations predefined interpregnancy intervals

The use of predefined interpregnancy intervals rather than treating IPI as a continuous, or near continuous, variable is a major limitation in the literature. The initial reason for doing so was the limited data available for use for analysis, although many studies with sufficient sample sizes continued to conduct categorical analysis based on established intervals. Seems that following the seminal publication by Conde-Agudelo with suggested categories, many studies have followed this approach using predefined intervals without offering a rational for their use, particularly in recently reported studies (include a couple of references as examples). Much of the literature has defaulted on the 18-23-month interval, as originally used by Conde-Agudelo, as the reference interval for IPI comparisons. The reported reason for choosing "18-23" months was due to that interval having the lowest rate of perinatal death, following the work of Zhu et al (17, 19) rather

than preterm births or other adverse pregnancy outcome. Moreover, those studies do not present an analysis of IPI associated risk as a continuous variable.

Jansa et al. examined IPI as a continuous variable in a study conducted in Ljubljana, Slovenia between 2004 and 2012, This study restricted sampling to consecutive deliveries where the first pregnancy ended in a live term birth. This study found that the period of lowest risk for preterm births in their population was 15 months, with a window of 10 to 20 months (41). This study suggested that the optimal IPI interval in their population was different to that estimated by Conde-Agudelo using a categorical analysis. This study also suggest that optimal intervals may vary by the selected pregnancy outcome. The optimal window observed by Jansa does not align with the specific categories aligned by Conde-Agudelo et al. For instance, the 10-month window observed by Jansa does not align with the previous 6-month intervals. This differences raise the question that preset gestational categories may hide the optimal pregnancy interval obtained from a month to month estimates. Recent studies still utilize this interval, such as in the study by Gupta et al. which may be bias the conclusions regarding the optimum, short, or long IPI (17). The treatment of IPI as continuous or near continuous would allow for a more accurate estimation of the relationship of IPI and PTB and other adverse pregnancy outcomes (19).

Considering the previous pregnancy outcome is an important factor, as shown by the increased risk of recurrence given a previous preterm outcome. The focus on live-to-live consecutive birth intervals for IPI was probably due to the lack of data available for other pregnancy outcomes. Some studies have examined IPI distribution for previous still births and terminations, however these have been vastly outnumbered by the live-to-live intervals (14). Studies which have investigated IPI and adverse pregnancy outcomes amoung women with terminations immediately previous have found that shorter IPIs were protective, highlighting the issue with presenting short IPI as universally negative (15,33,42). Treating live-to-live intervals as the standard narrows the perspective of IPI as it has been presented in the literature. Studies

will discuss live-to-live IPI intervals as simply IPI intervals, only addressing the use of live-to-live births in the methods section. This could result in the assumption that live-to-live intervals are the norm and can be applied universally, rather than taking into account obstetric history when formulating IPI recommendations. The discussion around IPI should include pregnancy history and be explicit in the kind of interval being investigated, whether it is for a previous term livebirth, preterm livebirth, early pregnancy loss, or stillbirth.

Many previous studies mainly utilized data from birth records due to the lack of other viable alternatives. The advantages to these records were the large size of the datasets, and in more recent years, the ability to sibling match which improved the quality of data. The limitations of birth records include underreported terminations, stillbirths, and early pregnancy losses. More recent studies have used consecutive live birth intervals for IPI measurement; however, these studies assume that the records being utilize record a complete pregnancy history, Additionally, these records globally tend to be limited in geographic and socio-economic scale, generally focusing on single developed countries. However, there are studies based on recruited birth cohorts conducted in middle-income and low-income countries that have included or focused on more diverse societies, such as Conde-Agudelo et al.'s Latin America study(18). The lack of comparisons between countries of varying cultures and economic realities relies on the assumption that none of these factors potentially affect the relationship between IPI and PTB.

Pregnancy History

Defining the type of IPI being studied based on pregnancy history could potentially yield a greater understanding in how IPI affects the risk of PTB. If previous pregnancy history alters the relationship of IPI and PTB, the optimal IPI would differ. Conzuelo-Rodriguez et al. identified the methods of handling IPI measurement start and end points, with the five categories definitions being the time between (22):

1. Two consecutive live births
2. Two pregnancies with an outcome of either a livebirth or stillbirth
3. Two pregnancies with an outcome of either a livebirth or miscarriage
4. Two pregnancies with an outcome of either a livebirth or abortion
5. Two pregnancies with any of the previous outcomes

They found that associations between short IPI, defined as less than 18 months, and birth outcomes differed depending on whether miscarriage was included or excluded. They found that the association between short IPI and PTB was not affected. However, they found that predictors and risk factors such as age and intention of pregnancy was associated with short IPI. Conzuelo-Rodriguez et al. showed that the choice in IPI start, and endpoints could potentially affect the associations found for outcomes and risk factors (22).

Conzuelo-Rodriguez et al. does not fully investigate how IPI is affected by these different measurement methods, in addition to using predefined short intervals, less than 12 and less than 18 months, in line with previous studies. The data set used, the National Study Family Growth solely relied on the recall of mothers for the start and does not use best obstetric estimate (22). While their study did consider pregnancy outcomes other than livebirths, they did not sufficiently distinguish the intervals from the consecutive live-to-live birth interval. Allowing for either end of the interval to consist of a different pregnancy outcome will yield more accurate IPIs, but a fair number of live-to-live will be captured in each definition. This could potentially bias the results towards the consecutive live-to-live birth intervals, as women with them could be fundamentally different than women with non-live birth outcomes at either point. All these factors could be contributing to the lack of an associated risk from short IPI found in their analysis for PTB when comparing their different IPI definitions.

The importance for clearly defining the start- and endpoints of an IPI can be seen in studies such as Regan el al. study, which showed a potential association between previous pregnancy outcomes and differences in the optimal IPI. They found that, with women with a previous stillbirth with an IPI of less than 12 months were not associated with an increased risk of adverse pregnancy outcomes. Schummers et al. found that women with an IPI of less than six months more likely to have a history of stillbirth, neonatal death, preterm delivery, or spontaneous abortion (43). Regan et al. found that women with a previous still birth with an IPI of less than 12 months were not associated with an increased risk of adverse pregnancy outcomes (44).

In summary, there is a need for studies examining IPI in diverse in populations from different geographic areas, race and ethnicity that use methods of ultrasound measurements to establish gestational age using best obstetrical estimate. This approach would considering interpregnancy interval as a continuous variable and considering different previous pregnancy outcomes would provide a stronger basis to develop public health recommendations that are specific to the specific previous obstetric history.

Risk Factors for Short and/or Long Interpregnancy Intervals

The research into the risk factors of IPI has produced inconsistent associations, mainly due to the differences in the methods of measuring and categorizing IPI as stated above. The biological factors which have been found to be associated with short IPIs have been pre-pregnancy body mass index (BMI), parity, uterine rupture(among women with a prior caesarean delivery), preeclampsia, eclampsia, maternal infection, hemorrhage, hypertension, PPROM, anemia, and maternal death (45–48). Though it should be noted that near all these factors have been found to not be associated with short IPI (18,49,50). The biological factors which are

associated with long IPI are perineal laceration, pre-eclampsia, eclampsia, maternal death, parity, and third trimester bleeding.

Demographic risk factors associated with short IPI include are maternal age, marital status, educational status, and maternal race (51,52). Interestingly, advance maternal age has been shown to attenuate the risk of PTB for short IPI (53). Potentially, educational attainment is acting as a proxy for sexual education and access to sexual health care in pregnancy prevention products. However, this is potentially contradicted by studies such as Condo-Agudelo et al. found that mother's education did not correlate to IPI (18). All of these factors, however, have been found to not be associated in other studies (18,54).

Maternal race is a sensitive topic that has many implicit and explicit factors that contribute to stress from systemic racism and access to care which can vary from culture to culture(52,55). Non-white race has been found to be associated with having shorter interpregnancy intervals compared to whites. Khoshnood et al. focused on Puerto Rican, Indigenous, African American, Mexican, and White pregnant women in the United States, and found that non-White women were more likely to have an IPI of less than six (6) months (52). It should be noted that the association between an adverse pregnancy outcome and an IPI of less than six months was found to be statistically significant across all racial/ethnicity groups (52).

Studies that have had access to clinical data that included measures of chronic conditions and morbidities have elected to not include them in their models due to a concern of introducing bias (48). The source of this potential bias, according to Haight et al., was the length of time of the IPI. These factors were also extended to smoking during pregnancy, birthweight, infant sex, and cesarean delivery (48). The current understanding in the literature of what factors potentially affect the relationship between IPI and PTB are not completely understood, with much of the

literature presenting conflicting information. In our meta-analysis of IPI should offer additional data to identify potential factors are associated with IPI and PTB.

CHAPTER 2: INTERPREGNANCY INTERVAL AND ADVERSE PREGNANCY AND MATERNAL OUTCOMES: SYSTEMATIC REVIEW AND META-ANALYSIS

Introduction

Globally, low birth weight (LBW), premature births (PTB), small-for-gestational age (SGA), account for approximately 14.6%, 11%, and 27% of all births (56–58). These outcomes have been linked to higher risk of infant mortality, complications, and developmental disabilities later in life. These outcomes are potentially preventable, with one suggested method being family planning, specifically encouraging women to achieve adequate interpregnancy intervals (IPI). The WHO recommends that women avoid an IPI of less than 24 months in order to minimize the risk of preterm birth and other adverse pregnancy outcomes. While the WHO defines an IPI of less than two years as short, other studies have defined used different cutoffs to establish short IPI. The intervals used to define short IPI have ranged from less than 6 months to less than 24 months, with varying levels of association being found to with increased risk of adverse perinatal outcomes, such as PTB, SGA, LBW. These differences in definitions for short IPI differences in interpregnancy measurement, lack of consideration of previous pregnancy history, and categorization of interpregnancy intervals for analysis. Due to previous studies relying on These limitations have produced inconsistent results in the literature, with different researchers and organizations developing varying recommendations for what IPI's to avoid. Proper measurement of IPI is required to establish recommendations which reflect reality.

Determining the effectiveness of a short IPI length is relevant to public health due to the potential for utilizing family planning to reduce the risk of adverse pregnancy outcomes from inadequate IPI. There are currently recommendations for avoiding short interpregnancy intervals, though they are not consistent between organizations and focus on avoiding short IPIs. Ignoring

the risk of long IPIs could be placing women planning pregnancies into a higher risk group and needs to be addressed but will not be the focus of this study. The recommendations developed by the World Health Organization (WHO) recommends waiting to get pregnant at least two years after a live birth, and six months after an abortion (11). These recommendations consider at least some aspects of the outcome of the previous pregnancy but make no mention of the potential risk of long IPIs – assuming they are present – for either case. Furthermore, these recommendations are based on studies which relied on IPIs between live deliveries, which could be overestimating the true IPI length. The American College of Obstetrics and Gynecology has a strong recommendation that women avoid an IPI of less than 6 months, and a weak recommendation of avoiding less than 18 months. Theses recommendations makes no mention of the previous pregnancy outcomes, or of the potential risk of long IPIs. The reliance on studies which focused on IPIs bracketed by live deliveries could be hiding the true interpregnancy interval, and current recommendations are do not account for the J-shaped relationship between IPI and adverse outcomes.

This meta-analysis seeks to test whether the WHO recommendations, avoidance of an IPI < 24 months, adequately move women to a lower risk group overall, and within different previous outcomes, using pooled data from previously published studies.

Methods

Search strategy and selection criteria

We conducted our systematic review and meta-analysis in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis guidelines. We searched for articles which included interpregnancy intervals and birth or maternal outcomes using PubMed, EMBASE, Scopus, Cochrane, and Web of Science database. Only papers from January 1st, 1980, to February 23, 2021, were included.

Studies were eligible for inclusion if they measured infant outcomes by interpregnancy intervals. Interpregnancy interval was defined as the time from the end of one pregnancy and the start of the next pregnancy. Terms such as birth spacing and birth interval were included to ensure that studies using different terminology but measuring IPI describing were captured. Infant outcomes included: preterm birth, defined as a gestational age of less than 37 weeks; low birth weight, defined as a birth weight of less than 2500 gram. Studies were excluded if: review or commentary piece; did not measure IPI or the specified outcomes; measured birth to birth intervals; or was an animal study. Two reviewers independently screened and reviewed titles and abstracts and performed full-text reviews for content of identified abstracts. A third reviewer resolved any conflicts in the review decisions.

Study screening and selection

Study screening and selection of articles was done in two phases, (1) reviewing of titles and abstracts, and (2) reviewing of full studies for content. During the first phase, titles and abstracts were evaluated for inclusion based on whether they meet the inclusion criteria. During the second phase, studies will be evaluated on content of the paper and whether frequencies of outcomes by IPI were included. During both phases two independent readers evaluated search results for selection based on the stated inclusion/exclusion criteria.

Study Quality Assessment

Assessment of methodological quality of each study was carried out by 2 of the authors working independently. Differences of opinion were resolved through discussion.

Data Extraction and Analysis

For each accepted study, at least two reviewers independently extracted details of articles, including: lead author and year published, geographic setting, time period of study, method of estimating gestational age, study design, data source, sample size, study outcomes, outcome of

previous pregnancy, measurement of IPI, and effect estimates, and adjustment variables included in the model.

Risk of bias independently assessed for included studies by at least two reviewers using the Risk of Bias in Non-randomized Studies - of Exposures (ROBINES-E). The ROBINS-E tool assesses seven (7) domains of bias: confounding, selection of participants into the study, classification of exposures, departures from intended exposures, missing data, measurement of outcomes and selection of the reported result. Within each of these domains, 'signaling questions' are asked to aid the user in making judgements. Lastly, judgements within each domain are summarized into an overall risk of bias assessment for each study. Each reader evaluated each metric independently, with differences of opinion were resolved through discussion and the input of a third reader.

Using raw frequency data, we synthesized the data collected from all included studies, using author-defined categories of IPI. When the reporting of the data allowed, we did comparisons of studies based on the WHO recommendations of <2 and >=2 years, studies which are not able to produce both intervals were excluded from analysis. The main sub-group analysis of interest was on previous pregnancy outcome. To further explore the origin of heterogeneity, additional sub-group analyses were done on to check for any potential biases based on decade of publication, study design, data source, gestational age estimation method, study quality, and region. Risk ratios were calculated for women with an IPI of <2 and >= 2 years. We pooled the results from the individual studies using a random-effects model was used to control for potential differences across studies.

To quantify statistical heterogeneity of study results, we report the I^2 statistic, estimated as $I^2 = 100\%(Q–df)/Q$, where Q is Cochrane's heterogeneity statistic and df represents the degrees of freedom. I^2 indicates the percentage of total variation across studies due to true variation. To detect publication and location biases, we explored asymmetry in funnel plots. This

was examined visually, and the degree of asymmetry was measured using the Egger unweighted regression asymmetry test, with P<.10 indicating significant asymmetry. Analysis was done in R version 3.6.1 using the "metafor" (59).

Potential Conflict of Interest

None of the authors have a potential conflict of interest to report.

Ethics and dissemination

Ethical approval is not required for this systematic review and meta-analysis as only a secondary analysis of data already available in scientific databases will be conducted. The results of this review will be submitted for peer-reviewed publication and will be presented at relevant conferences.

Results

The search returned 3809 articles for review, of which 170 met criteria for full-text review. Overall, 32 articles met all inclusion criteria after data review. A summary of all the studies reviewed can be found in the appendix. Case-control studies were excluded from inclusion in the analysis due to the small numbers found in the review, with the rest of the articles included for review being cohort and cross-sectional studies. Two studies had different definitions for preterm birth and were not able to be included for analysis. The included studies had seventy-nine different interval lengths reported, with the found intervals included in Table 1 below. Efforts to pool the data for analysis were complicated by overlapping IPI categories used by studies which did not align with the specified WHO recommended intervals.

Table 1. Reported interpregnancy intervals

0 to 11	12 to 14	18 to 23	24 to Inf	37 to 59	6 to Inf	97 to Inf
0 to 12	12 to 17	18 to 24	25 to 36	4 to 6	60 to 119	
0 to 17	12 to 18	18 to 36	25 to 48	42 to 47	60 to 95	
0 to 2	12 to 23	18 to 50	25 to Inf	48 to 59	60 to Inf	
0 to 23	12 to 36	18 to 59	26 to 51	48 to Inf	61 to Inf	
0 to 24	12 to Inf	18 to Inf	26 to Inf	49 to 60	7 to 12	
0 to 3	120 to Inf	19 to 24	3 to 5	49 to 72	7 to 24	
0 to 5	13 to 18	19 to Inf	30 to 35	49 to Inf	7 to 9	
0 to 6	13 to 24	21 to 23	36 to 41	52 to 103	7 to Inf	
0 to 8	13 to 25	24 to 29	36 to 47	6 to 11	73 to 96	
1 to 5	13 to Inf	24 to 35	36 to 59	6 to 12	9 to 11	
10 to 12	15 to 17	24 to 36	36 to Inf	6 to 17	9 to Inf	
104 to Inf	18 to 20	24 to 59	37 to 48	6 to 8	96 to 136	

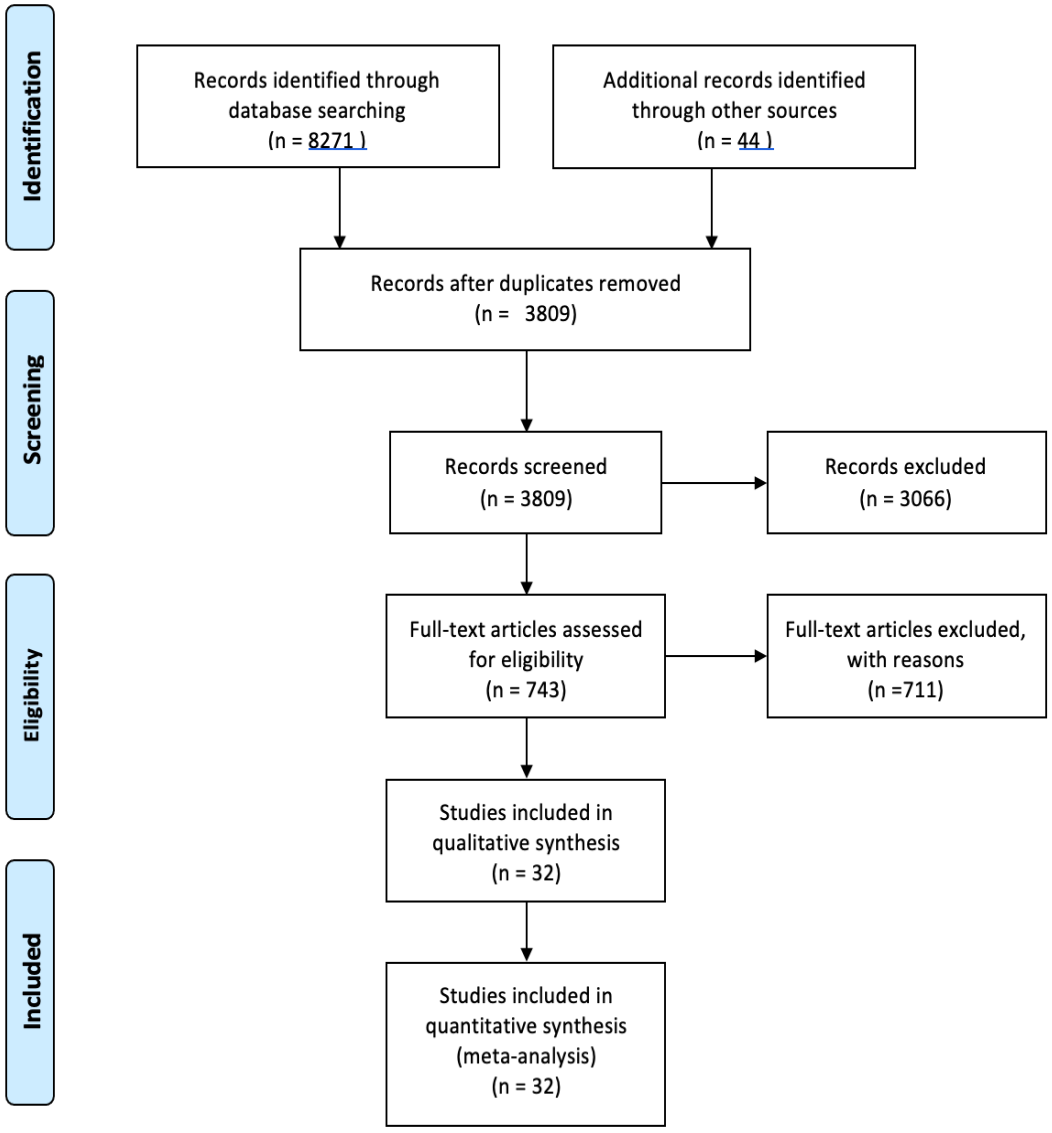


Figure 4. Prisma flow chart of study screening and selection

Studies in the WHO analysis, 14 (41%) were conducted in the United States and Canada. The remaining 20 studies were conducted in countries from Latin America (16 countries), Asia (3 countries), Africa (1), Europe (5 countries), and Australia.

The characteristics and main findings of the cohort and cross-sectional studies included in the systematic review are presented in Table 2. The sample size in the cohort or cross-sectional

studies ranged from 106 to 9,782,029. For the analysis utilizing the WHO intervals, 28 studies provided data on PTB, 21 on LBW, and 13 on SGA.

Overall, among the studies that provided data on preterm birth, 21 reported an association with short intervals, 6 association with long intervals, and 6 found no association. Regarding studies that reported data on LBW, 13 found an association with short intervals, 8 an association with long intervals, and 6 found no association. Among the studies that provided data on SGA, 8 reported an association with short intervals, 3 reported an association with long intervals, and 3 found no association. The definition of a short IPI ranged from 3 months to 2 years, long IPI ranged from 18 months to 5 years, and the most common reference interval was 18 to 23 months.

Preterm Birth Studies

WHO

Overall, women with an IPI of less than two years were not found to be at a statistically significant risk of having a preterm birth compared to women with an IPI of two or more years. The overall between-study heterogeneity was high ($I^2 = 98.7\%$). When testing across the subgroups for previous pregnancy outcomes, studies where women with a previous non-live birth were not found to have a statistically significant difference in risk between the two IPIs. Studies with any previous outcome and previous non-live outcome were not found to have a statistically significant difference in risk between the two IPIs. Only in studies where the beginning of the interval was defined using a previous live delivery did was there was a statistically significant, with a found association 5% reduction of risk for preterm birth for women with an IPI of less than two years compared to women with an IPI of two years or greater.

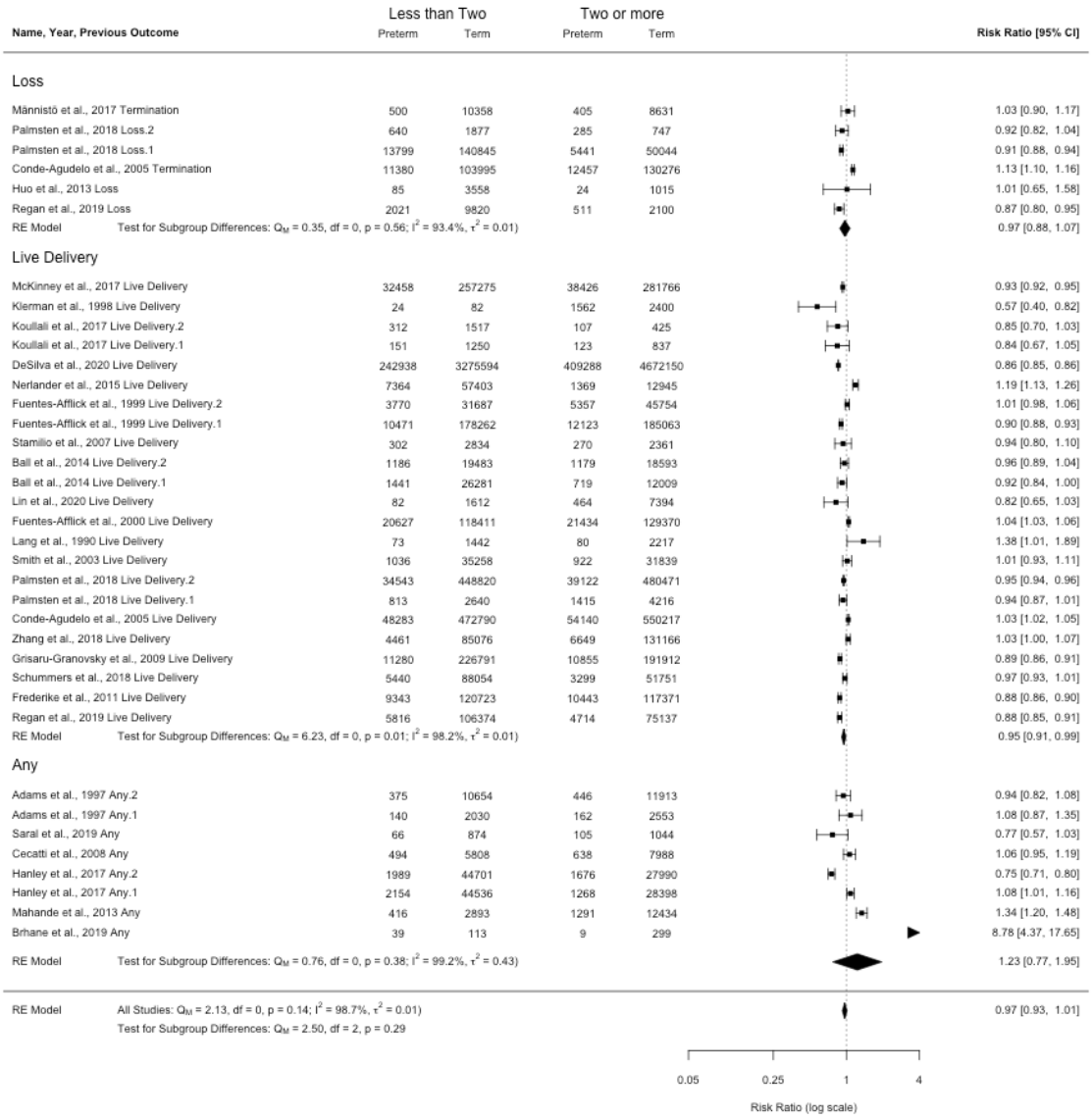


Figure 5. Forest plot of the risk ratio of preterm birth by previous outcome subgroup

Low Birth Weight Studies

Overall, women with an IPI of less than two years were .82 (CI .82, .95, p=.00) times the risk of having a low birthweight infant compared to women with an IPI of two or more years. The overall between-study heterogeneity was high (I^2 = 99.9%). When testing across the subgroups

for previous pregnancy outcomes, studies where women with a previous non-live birth were not found to have a statistically significant difference in risk between the two IPIs. Studies where women with any previous outcome were used to defined IPI, women with an IPI of less than two years had no statistically significant difference in the risk for low birth weight. In studies with the beginning of the interval was defined using a previous live delivery, women with an IPI of less than two years had .85(.77, .94, p=0.04) times the risk for low birth weight.

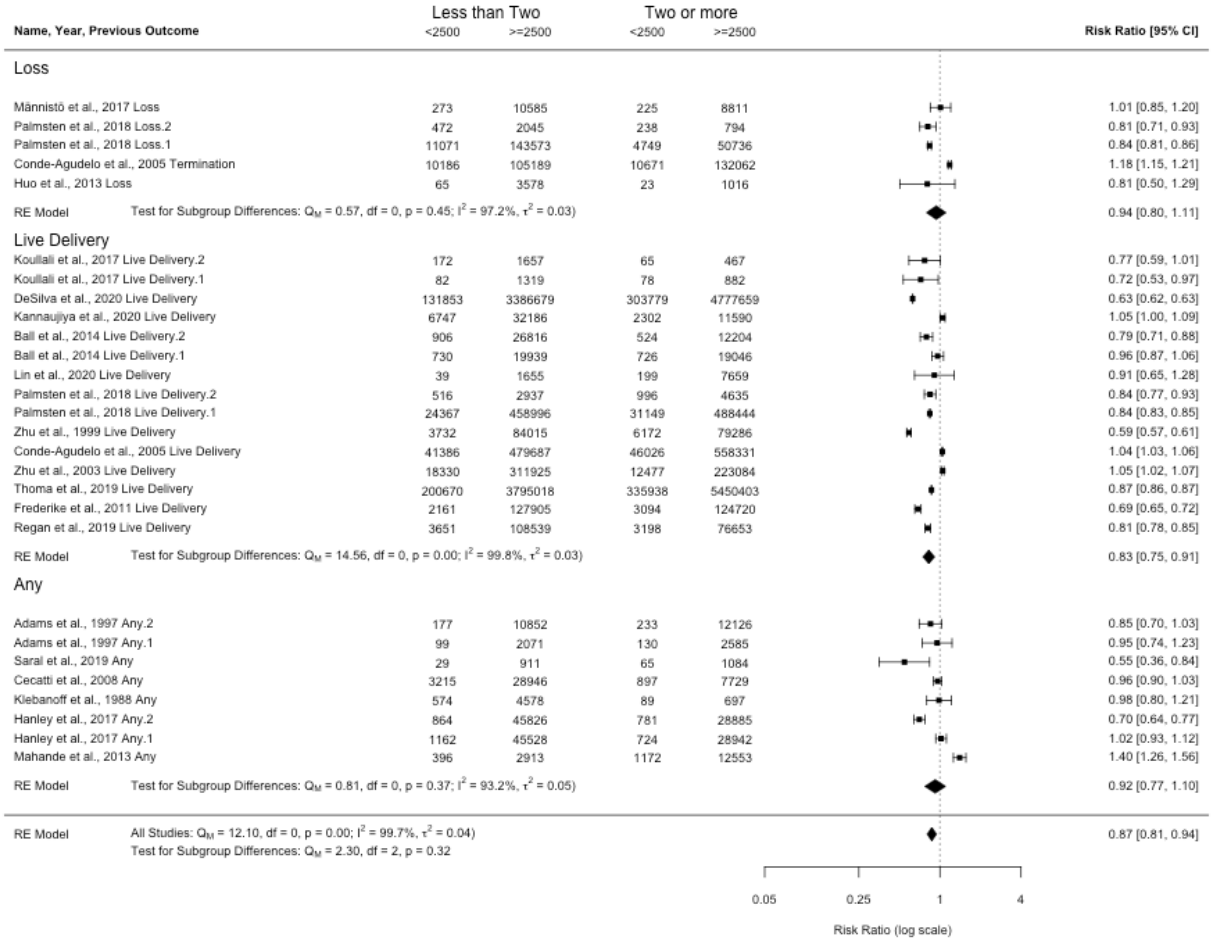


Figure 6. Forest plot of risk ratios for low birth weight and interpregnancy interval

Small for Gestational Age Studies

Overall, women with an IPI of less than two years were did not have a statistically significant risk of the risk of having an infant that is small for gestational age compared to women with an IPI of two or more years. The overall between to study heterogeneity was high (I^2 = 98.8%). When testing across the subgroups for previous pregnancy outcomes, studies where women with a previous non to live birth, women with an IPI of less than two years had .87(.75, 1.00, p=0.05) times the risk of having an SGA infant. Studies where women with any previous outcome was used to defined IPI, women with an IPI of less than two years had no statistically significant difference in the risk for SGA. In studies with the beginning of the interval was defined using a previous live delivery, no statistically significant difference in risk was found for women with an IPI of less than two years compared to women with an IPI of two years or greater.

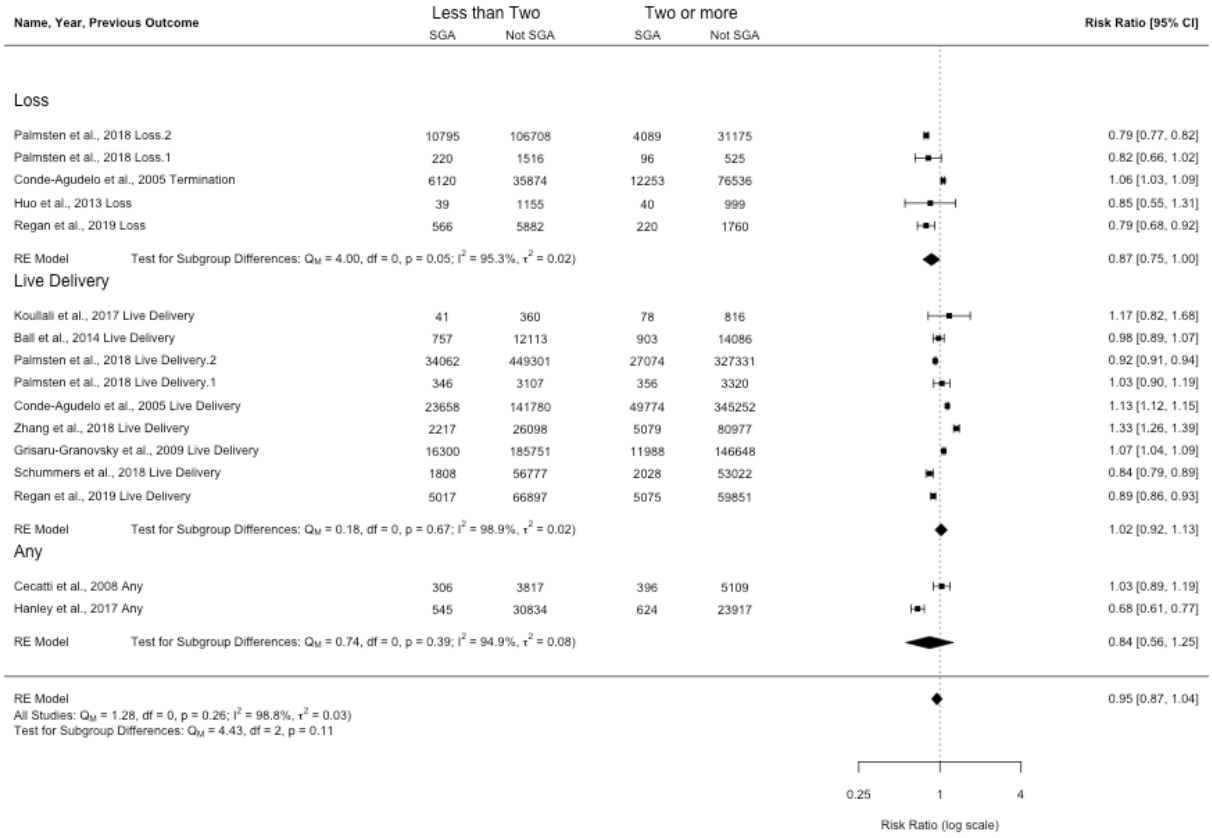


Figure 7. Forest plot of risk ratios for small for gestational age and interpregnancy interval

Funnel Plot Analysis

No evidence of publication bias was present either visually or via statistical testing for all outcomes and analyses.

Discussion

After pooling reported intervals in the included studies, we found that association between adverse pregnancy outcomes and an IPI of less than two years was the associated are potentially sensitive to the previous pregnancy outcome used to define the beginning of IPI. When looking at the risk for an adverse outcome in a total population, an IPI of less than two

years is associated with a decreased risk of LBW, however no statistically significant difference in risk for PTB and SGA. However, the high level of heterogeneity present in the data required that we investigate whether there are potential differences in the subgroups creating noise and hiding the true effect. The primary subgroup of concern was the previous pregnancy outcome, however IPI definition, gestational age estimation, and year were also analyzed. Testing for differences in the subgroups, we did not find a statistically significant difference, however, it should be noted that subgroups did yield differences in found associations in PTB, LBW and SGA. The failure to find differences in the subgroups may be largely due to the large estimates due the high levels of heterogeneity which persisted in many of the subgroups, as well as the concentration of RRs near and around the null.

The subgroup analysis for the WHO intervals found that an IPI of less than two years was protective in studies which defined IPI beginning with a live delivery, with a 5% reduction in risk of preterm birth and 17% reduction in risk for LBW. This association was not found with studies utilizing previous pregnancies which ended in non-live or any outcomes not having a statistically significant difference. An IPI of more than two years with studies using previous loss, was found to be potentially associated with SGA, a 13% reduction in risk. This association was not found in studies with a live delivery or any outcome as the index pregnancy did not find an association with an IPI of less than two years and SGA. These differences in associations suggest that the selection of the index pregnancy potentially affects the found associations between IPI and adverse pregnancy outcomes.

The results of this meta-analysis for the WHO intervals does not directly contradict the WHO recommendations for women to avoid an IPI of less than two years. However, the reduction in risk is not as large as previous studies suggest, though the potential reason for this difference in findings could be due to the exclusion of studies which utilize birth-to-birth intervals, or inter-delivery intervals, which could have been overestimating the effect of IPIs.

Limitations

One of the major limitations of this study will be due to the inclusion of only full text published articles. The inclusion of data from unpublished sources could be potential useful but may introduce bias that is unwanted and complicates analysis without sufficient benefit. Unpublished analyses may include undeveloped versions of published studies, resulting in double counting of results. Unpublished studies may also be of lower methodological quality than published studies. The exclusion of case-control studies could bias our results. The high level of heterogeneity in the data reduces the ability for us to interpret the effect size of the found associations.

Strengths

The strengths of our systematic review and meta-analysis include the broad search criteria utilizing multiple databases, with no restrictions on language. Excluding studies which measured inter-delivery interval, even when reported as IPI, ensuring that we avoided studies which were excessively overestimating the IPI. This allowed for a large and high-quality selection of studies which could be used for the pooled analysis. The use of pooled intervals allowed for the comparison of studies which otherwise may not have been possible due to the differences in interval categories.

Conclusion

Using two different analyses, we were able to show how the outcome of the index pregnancy affects the found associations between a specified IPI and an adverse outcome. The WHO recommendations of avoiding an IPI of less than two years appears to be protective against PTB, LBW, and SGA. The association between PTB and LBW remains true in studies which specify a previous live delivery; however, this recommendation is not protective when looking at studies which do not specify the previous outcome or non-live outcome. Interestingly, only

studies with a non-live index pregnancy were found to be associated between an IPI of less than two years and SGA. PTB and LBW having the same associations within subgroups may be due to the tendency for preterm infants to also be born with a low birth weight. When looking at IPI using the intervals popularized by Conde-Agudelo et al. the optimal IPI for reducing the risk of PTB and LBW overall appears to be 12 to 23 months, and 6 to 59 months for reducing the risk for an infant born SGA. The associated optimal intervals by outcome differ however when taking into consideration outcome of the index pregnancy, indicating that the optimal IPI may differ. Identifying this optimal IPI is important for informing women, clinicians, and policy makers and requires more studies to specifically analyze.

The high levels of heterogeneity present in the analysis were not explained by region, year, or IPI measurement. This heterogeneity has been seen in past meta-analysis, but the underlying cause of the heterogeneity is unclear. It should be noted that the subgroup of interest with the least amount of heterogeneity was the non-live outcome studies. This maybe in part due to the more consistent capturing of the true IPI, whereas studies relying on defining IPI between two live deliveries may be overestimating the true length of the interval. Evidence of this potential source of bias can be seen in the analysis for studies with a previous live birth further stratified by whether IPI was measuring using consecutive pregnancies compared to two deliveries. Reliance on IPI measured using the traditional delivery to delivery minus gestational age seems to be introducing bias in the analysis, however this still does not account for the high levels of heterogeneity present in our meta-analysis.

The use of the 18 to 23 as a reference interval does not introduce biases, but the potential optimum does change according to the outcome of the index pregnancy. These changes in associations should be considered when creating recommendations for optimal IPI. Further research needs to be done to consider the various preterm phenotypes which could affect the found associations between IPI and previous outcomes in the index pregnancy. The

recommendations proposed by the WHO, when applied to studies reporting consecutive pregnancies for IPIs, do not show adequate protection against adverse pregnancy outcomes. While the lack of a statistically significant difference may indicate that their association between IPI and adverse pregnancy outcomes is a non-issue, the reality is that the women could be being shifted to a higher risk group than necessary by following the recommendations. Our analysis using the CA intervals shows that the risk of adverse pregnancy outcomes is "J-shaped" for IPI intervals where the index pregnancy was a live birth, meaning that there is a short and long IPI interval of elevated risk.

The findings of our meta-analysis highlight the need for clinicians and policy makers to incorporate the obstetric history of women into their recommendations, particularly with IPI. The mechanisms for how IPI affects the risk of adverse pregnancy outcomes are still unclear, and future studies will need to further explore how the outcome of the index pregnancy affects the optimal IPI for the subsequent pregnancy. Capturing this relationship will be critical for improving the general understanding of IPI and lead to more effective recommendations.

Table 2. Summary of selected studies

LEAD AUTHOR	YEAR	STATE / PROVINCE, COUNTRY	STUDY DESIGN	GESTATIONAL AGE ESTIMATION METHOD	REPORTED IPI INTERVALS (MONTHS UNLESS OTHERSWISE SPECIFIED)	OUTCOME OF PREVIOUS PREGNANCY	STATED REFERENCE	REPORTED HEALTH OUTCOMES
REGAN ET AL. (60)	2019	Western Australia	Cohort study	Not Reported	<6, 6 to 11, 12 to 17, 18 to 23, 24 to 59, >=60	Live Birth	18 to 23 months	preterm birth, SGA, low birthweight
DE WEGER ET AL. (53)	2011	Netherlands	Cohort study	LMP or Best Obstetric Estimate	<6, 6 to 11, 12 to 17, 18 to 23, >=24	Live Birth	18 to 23 months	preterm birth, SGA, low birthweight
REGAN ET AL. (44)	2019	Norway, Finland, Australia	Cohort study		<6, 6 to 11, 12 to 23, 24 to 59, >59	Still birth	24 to 59 months	stillbirth, preterm birth, and SGA birth
SCHUMMERS ET AL.(61)	2018	British Columbia, Canada	Cohort study	Best Obstetric Estimate	<6, 6 to 11, 12 to 17, 18 to 23, >=24	Live Birth	18 to 23 months	SGA, Spontaneous PTB, Indicated PTB, Maternal Mortality or

								Morbidity, and Adverse Fetal and Infant composite
BRHANE ET AL.(62)	2019	Tigray Region, Northern Ethiopia	Cohort study	LMP	0 to 24, 24 to 36	Any	24 to 36 months	PTB
MAHANDE ET AL. (63)	2013	Northern Tanzania, Australia	Cohort study	LMP	<24, 24 to 36, 37 to 59, >=60	live birth or fetal death at >=28 weeks	24 to 36 months	PTB, LBW, perinatal death
HUO ET AL. (64)	2013	Beijing, Chengdu, Shanghai	Cohort study	LMP	<6, 6 to 12, 12 to 18, 18 to 24, >=24	Mifepristone to induced abortion	18 to 24 months	SGA, LBW, PTB
GRISARU-GRANOVSKY ET AL. (65)	2009	Israel	Cohort study	Not Reported	<6, 6 to 11, 12 to 23, 24 to 59, >=60	Live Birth	12 to 23 months	preterm delivery, very preterm birth, small for gestational age (SGA), very SGA (VSGA), early neonatal death and major

								congenital malformations
ZHANG ET AL.(66)	2018	Guangzhou, China	Cohort study	Not Reported	<6, 6 to 11, 12 to 17, 18 to 23, 24 to 29, 30 to 35, 36 to 59, 60 to 119, >=120	Live	24 to 29 months	PTB, moderate to late PTB, extremely to very PTB, SGA and LGA
ZHU ET AL.(67)	2003	Michigan, USA	Cohort study	LMP	<6, 6 to 11, 12 to 17, 18 to 23, 24 to 59, 60 to 95, 96 to 136	Live	18 to 23 months	LBW
CONDE-AGUDELO ET AL. (68)	2005	Montevideo, Uruguay	Cohort study	LMP, amended by ultrasonography in 1/4 of women	0 to 2, 3 to 5, 6 to 11, 12 to 17, 18 to 23, 24 to 59, >=60	Abortion	18 to 23 months	preeclampsia, eclampsia, LBW, very LBW, PTB, very PTB, SGA, fetal death, early

								neonatal death
CONDE-AGUDELO ET AL. (18)	2005	Montevideo, Uruguay	Cohort study	LMP, amended by ultrasonography in 1/4 of women	<6, 6 to 11, 12 to 17, 18 to 23, 24 to 59, >=60	Ended after 19 weeks of gestation	18 to 23 months	LBW, very LBW, PTB, very PTB, SGA, fetal death, early neonatal death
ZHU ET AL.(20)	1999	Utah, USA	Cohort study	LMP	0 to 5, 6 to 11, 12 to 17, 18 to 23, 24 to 59, 60 to 119, >=120	Any pregnancy	18 to 23 months	LBW, PTB, SGA, only raw data for LBW
PALMSTEN ET AL.(69)	2018	Massachusetts and Michigan, USA	Cohort study	Not Reported	<12, 12 to 23, 24 to 59, and 60	Live	12 to 23 months	preterm birth and low birth weight, SGA
MÄNNISTÖ ET AL.(33)	2017	Oulu, Finland	Cohort study	Best Obstetric Estimate	0 to 5, 6 to 11, 12 to 17, 18 to 23, 24 or greater	Terminated Pregnancy	18 to 23 months	Preterm birth, low birth weight <2500 grams, and SGA

HANLEY ET AL. (70)	2017	British Columbia, Canada	Cohort study	Not Reported	0–5, 6–11, 12–17, 18–23, 24–59, and 60 months or greater	Any	18 to 23 months	Preterm birth, SGA, And LBW
SMITH ET AL. (55)	2003	Scotland, United Kingdom	Cohort study	estimates of gestational age in the United Kingdom incorporated ultrasound measurements taken in the first half of pregnancy.	1 to 5, 6 to 11, 12 to 17, 18 to 23, 24 to 59	Live Birth	18 to 23 months	birth weight <5th centile, preterm delivery, perinatal death: fetal abnormality or rhesus, unexplained stillbirth, all other still births, all other neonatal deaths
LANG ET AL.(71)	1990	Boston, Massachusetts, USA	Cohort study	Not Reported	<=3, >3 to 6, >6 to 12 (7 to 12), >12 to 18 (13 to 18), >18 to 24 (19 to 24), >24 to 36 (25 to 36), >36 to 48 (37 to	Prior Full-term Birth	25 to 36 months	premature birth, full termbirth

					48), and >48 (>=49)			
FUENTES TO AFFLICK ET AL.(72)	2000	USA	Cohort study	Not Reported	<6, 6 to 11, 12 to 17, 18 to 59, >=60	previous premature or SGA infant	18 to 59 months	Very premature and moderately premature
LIN ET AL.(73)	2020	China	Cohort study	LMP or Best Obstetric Estimate	<12, 12–23, 24–59 ,60–119, and ≥120	Any pregnancy	12 to 23 months	LBW, LGA, SGA, Macrosomia, Preterm delivery and other maternal characteristics
BALL ET AL.(74)	2014	Perth, Western Australia	Cohort study	Best Obstetric Estimate	0 to 5, 6 to 11, 12 to 17, 18 to 23, 24 to 59, 60 to 119, or >120	Any pregnancy	18 to 23 months	Preterm birth, small for gestational age, low birth weight

STAMILIO ET AL. (75)	2007	Northeastern United States	Cohort study	Not Reported	<6, 6 to 11, 12 to 27, 18 to 59, 60 or more	Any pregnancy	18 to 59 months	Uterine rupture, composite morbidity, blood transfusion
FUENTES-AFFLICK ET AL.	1999	California	Cohort study	Best Obstetric Estimate	<6, 6 to 11, 12 to 17, 18 to 23, 24 to 29, 30 to 35, 36 to 47, 48 to 59, >60	Any pregnancy	18 to 23 months	Preterm birth
KLEBANOFF ET AL.(54)	1988	Norway	Cohort study	Last menstrual period	<3, 3 to 5.9, 6 to 8.9, 9 to 11.9, 12 to 14.9, 15 to 17.9, 18 to 20.9, 21 to 23.9, >24	Any pregnancy	Not stated	Birthweight, intrauterine growth retardation
NERLANDER ET AL.(76)	2015	United States	Cohort study	Not Reported	<3, 3–5, 6–11, 12–17, 18–23,24–36, and >36	Live Birth	18 to 23 months	Preterm birth
DESILVA ET AL.(45)	2020	United States	Cohort study	Best Obstetric Estimate	<6 months, 6 to 11, 12 to 17, 18 to 23, 24 to 59, >60	Live Birth	18 to 23 months	Severe maternal morbitity (maternal transfusion, ICU admission, uterine rupture, perineal laceration)

CECATTI ET AL.(77)	2008	Brazil	Cohort study	Not Reported	<6, 6–11, 12–17,18–23, 24–59 and >59	Any pregnancy	18 to 23 months	C to section rate, PROM, hypertension, maternal bleeding, maternal infection, stay > 7 days after delivery, stillbirth, neonatal death, LBW, preterm birth, small for gestational age.
KOULLALI ET AL. (78)	2017	Netherlands	Cohort study	Not Reported	0 to 5, 6 to 12, 12 to 17, 18 to 23, 25 to 59, >60	Any pregnancy	18 to 23 months	Preterm birth, low birth weight, small for gestational age
SARAL ET AL. (79)	2019	Turkey	Cohort study	Not Reported	< 2 years, 2 years	Any pregnancy	2 years	Preterm birth, stillbirth, low birth weight

KLERMAN ET AL.(34)	1998	Birmingham, Alabama, USA	Cohort study	Last menstrual period and at least 1 ultrasound	<13, 13 to 25, 26 to 51, 52 to 103, 104 weeks	Any pregnancy	Not stated	Preterm delivery, intrauterine growth retardation
MCKINNEY ET AL.(16)	2017	Ohio, USA	Cohort study	Not Reported	0 to 6, 6 to 12, 12 to 24, 24 to 60, >60	Any pregnancy	12 to 24 months	Infant mortality
ADAMS ET AL. (81)	1997	Georgia, USA	Cohort study	Best Obstetric Estimate	0 to 2, 3 to 5, 6 to 8, 9 to 11, 12 to 17, 18 to 23, 24 to 35, 36 to 47, >48	Live Birth	24 to 35 months	Birth weight, length of gestation, adequacy of fetal growth

CHAPTER 3: INTRODUCTION TO THE INTRBIO-21ST PROJECT AND METHODOLOGY

Specific Aims of the Dissertation

To address the gaps in knowledge in the literature for the relationship between interpregnancy intervals (IPI) and preterm birth, our study seeks to implement three elements into our analysis(22):

Aim 1: Examine the gaps in knowledge on IPI risk factors for diverse pregnancy outcomes.

Aim 2: Examine determinants of interpregnancy intervals in the INTERBIO-21st multicultural study.

AIM 3: Estimate the optimal interpregnancy interval (IPI) based on the outcome of the previous pregnancy for previous early pregnancy loss and for diverse preterm births phenotypes.

Our approach in addressing these three AIMS will incorporate three elements in the analysis:

1) Treat IPI as a discrete variable by month
2) Address how previous pregnancy outcome and other factors impact the optimal IPI
3) Improving accuracy of IPI using ultrasound measures in early pregnancy to estimate gestational age.

By incorporating these elements, we will be able to fill gaps in the current literature, as well as improve the understanding of IPI's effect on the risk of PTB of both policy makers and mothers.

Our study will be utilizing data from the INTERBIO-21st study, a multi-center cohort and case control study conducted during 2011-2014 in six countries and seven sites. Case and controls were selected based on gestational age or potential IUGR/SGA, for the purpose of this study, we

will be focusing on the gestational age cases(82). The use of case-control studies has been used before in research focusing on IPI, such as Gupta et al. investigation between IPI and stillbirth(17). The use of a case-control study is not ideal but will allow for rare events such as IUGR to be investigated. Additionally, the use of the INTERBIO-21st dataset provides advantages that are not present in the typical certificate-based datasets used by current literature. The first advantage is the uniform methods of recruitment, and the methods used for data collection, allowing for a high degree of confidence of the quality and consistency of the data. Second, the collection from multiple countries allows for an international perspective which is lacking from the current literature. Third, the start and end points of the IPI calculations are based on ultrasound measurements in gestation with a strong quality control approach.

The current literature does not address these concerns about IPI granularity, pregnancy history, and international populations. The INTERBIO-21stdataset, covered below, will allow for our study to potentially better address these concerns.

Foundations of INTERBIO-21st

The INTERBIO-21st project builds upon the International Fetal and Newborn Growth Consortium for the 21st Century (INTERGROWTH-21st) Project, which was a large, multicenter, population-based, research initiative, coordinated by the University of Oxford and being carried out by a multidisciplinary network of more than 400 healthcare professionals and scientists from 35 institutions in 21 countries worldwide. The project, involving nearly 70,000 mothers and babies, was established to assess human growth, neurodevelopment and associated behaviors from early pregnancy to 2 years of age under healthy conditions and various sub-optimal conditions (e.g. maternal infections, malnutrition and pregnancy complications) and other risk factors for adverse outcomes.

INTERGROWTH-21st's overall mission was guided by a comprehensive series of conceptual papers, systematic reviews, epidemiological studies and evidence-based tools for providing continuity of clinical care. The insights gained supported the project's guiding principle: namely that the main negative perinatal outcomes—fetal death, preterm birth and fetal growth restriction (FGR)—are complex, inter-related syndromes that require targeted interventions focused on etiological factors.

To facilitated INTERGROWTH-21st's mission, the study was designed to all for the creation and development of new "prescriptive" standards describing optimal fetal and preterm neonatal and postnatal growth, and the related health risk. In order to achieve this, the project was comprised of three studies, 1) the Newborn Cross-Sectional Study (NCSS), 2) the Fetal Growth Longitudinal Study (FGLS), and 3) the Preterm Postnatal Follow-up Study. All these studies were highly detailed and standardized collection and recording of maternal characteristics and anthropometry, pregnancy complications, exposures to pollutants, fetal growth, neonatal characteristics, and perinatal outcomes. Below in Figure 8, the recruited subgroups for the FGLS and PPFS are shown and will be further expanded upon.

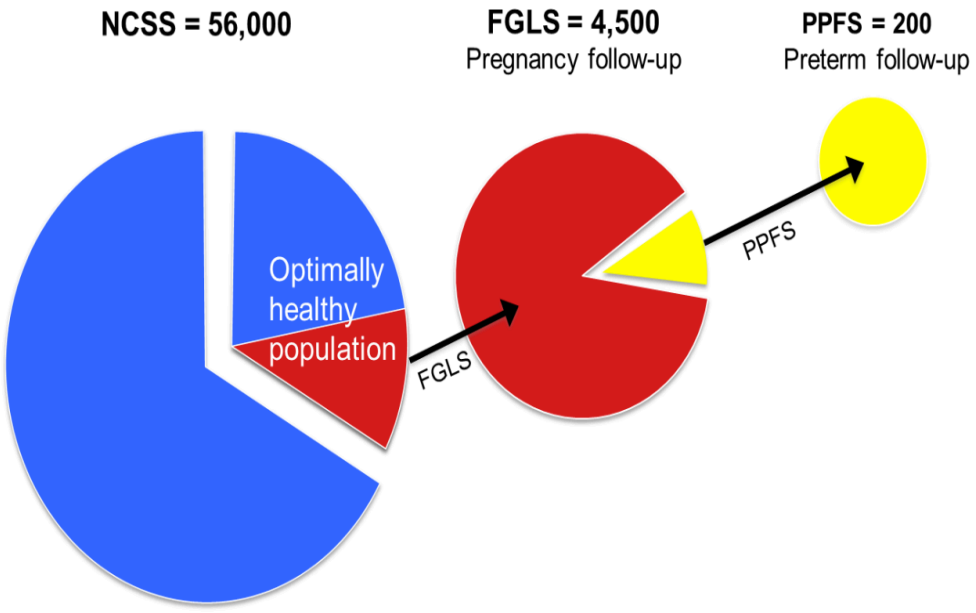


Figure 8. The three intergrowth-21st cohorts

Phase I of the INTERGROWTH-21st Project, conducted between 2008 and 2015, consisted of nine complementary studies designed to describe optimal human growth and neurodevelopment, based conceptually on the World Health Organization (WHO) prescriptive approach(83). Across eight urban areas worldwide, which were geographically delimited to ensure the study was population-based, the study enrolled a large cohort of healthy pregnant women before 14^{+0} weeks' gestation(84). The specific aim was to monitor their babies prospectively until 2 years of age to generate international standards for: estimating gestational age in early and late pregnancy; monitoring symphysis-fundal height and maternal weight gain; measuring fetal size and estimated fetal weight with ultrasound to monitor fetal growth; and assessing newborn size for gestational age, newborn body composition and the postnatal growth of preterm infants. Up to 2 years of age, children included in this cohort remained healthy with adequate growth and motor development, supporting its appropriateness for the construction of international standards(85).

The NCSS study involved all deliveries captured over a 12-month timespan from all study sites, with recruitment occurring at the first trimester visit for women screened at $<14^{+0}$ weeks from the start of their pregnancy, determined using crown-to-rump length gestational age dating. The purpose of the study was to establish a study population from which optimally healthy women were selected to develop newborn and fetal growth standards. Optimally healthy in this context meaning, non-smokers, with a normal pregnancy history, and without health problems likely to influence fetal growth or indicate a risk for pregnancy-related pathological conditions. In addition, women had to come from areas with no socio-economic constraints on growth, low morbidity and perinatal mortality, and adequate nutritional status. The goal being to create a population from which the standards could be developed for an internationally representative cohort of healthy women to serve as the reference for optimal fetal and newborn growth.

The FGLS study was comprised of women recruited from the optimally healthy subset of women from the NCSS study. Ultrasound and clinical assessments of fetal growth every five weeks for the duration of the pregnancy were done, with a maximum number of follow-ups at six.

The PPFS study selected women preterm deliveries, greater than 26^{+0} and less than 37^{+0} weeks, within the FGLS study. Infants were followed for the first eight months of life using the same protocol as the WHO Child Growth Study. The follow-up period of 8 months was chosen so that all infants could be followed to the "ideal" gestational age plus 3 months of "true" postnatal life for even infants born 27-30 weeks of gestation. Newborns from the FGLS and the PPFS studies had follow-ups at 1 and 2 years to evaluate health, nutrition, and development. By limiting the study to optimally healthy women, the goal of the study was to develop the Preterm Postnatal Growth Standards which could be globally applicable.

In all studies, the same protocols were followed for collection of anthropometric measurements.

INTERBIO-21st

Phase II of the INTERGROWTH-21st Project (The INTERBIO-21st Study) aims to improve the functional classification of previously evaluated, preterm birth and FGR syndromes through a better understanding of how environmental exposures, clinical conditions and nutrition influence patterns of human growth from conception to childhood. Additionally, women answered questions regarding obstetric history, end date of last pregnancy, and details related to the outcome of the previous pregnancy(85). The goal of INTERBIO-21st was to capturing exposures to a variety of potentially disadvantageous intrauterine environments (including poor nutrition, pregnancy complications and infections) in geographically diverse populations worldwide. The explicit inclusion of women who were less than optimally healthy is a key differentiator of the recruited populations of INTERGROWTH-21st and INTERBIO-21st.

The INTERBIO-21st Study was conducted between February 2012 and June 2018 at seven sites: Pelotas (Brazil), Kilifi (Kenya), Nairobi (Kenya), Karachi (Pakistan), Soweto (South Africa), Mae Sot (Thailand) and Oxford (UK), of which two (Kilifi and Mae Sot) were rural and the others urban. The sites in Pelotas, Nairobi and Oxford also participated in Phase I of the INTERGROWTH-21st Project.

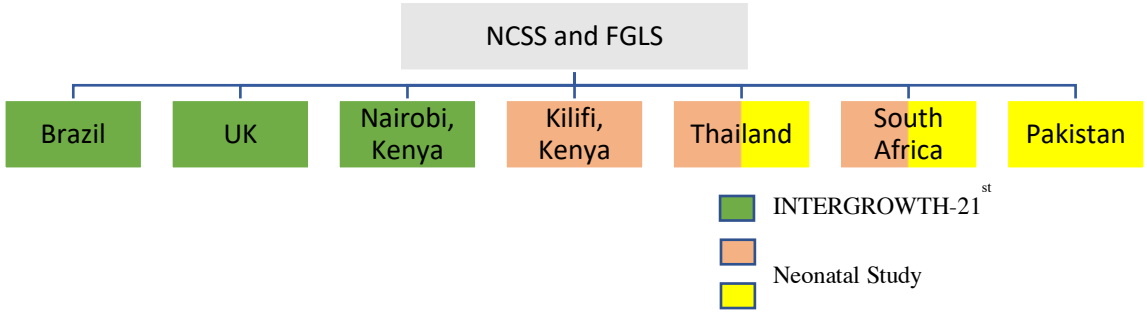


Figure 9. Interbio-21st study sites and participation

The two parts of the INTERBIO-21st Study are the Fetal and the Neonatal study, a cohort and case-control study respectively. The goals for this study are to use the two studies to test how pregnancy history affects the relationship between IPI and PTB.

INTERBIO-21st Fetal Cohort

The goal of the INTERBIO-21st Fetal Study was to provide detailed phenotypic information based on fetal growth patterns and biological samples to investigate maternal/fetal nutritional status and maternal/placental/fetal biomarkers. Included healthy pregnancies, as well as those complicated by a range of factors, including in resource-poor settings, HIV, malaria, malnutrition, and anemia. Sites included in the study were Pelotas, Brazil; Oxford, UK; Nairobi, Kenya; Mae Sot, Thailand; Soweto, South Africa; and Karachi, Pakistan.

Collected and stored maternal blood, maternal feces and cord blood/placental samples from pregnancies in three INTERGROWTH-21st centers (n=500 per center) and was supplemented by samples from high-risk populations monitored using the same protocols in centers in resource-poor settings (n=500 per center). All centers collected maternal blood, maternal feces, and cord blood and placental samples.

Women from the site population were recruited during antenatal care prior to 14^{+0} weeks of gestation. TO be included in the study, women had to be at least 18 years of age, and the pregnancy had to be conceived naturally. Women with a BMI over 35 were excluded from recruitment due to their weight being a barrier to accurate ultrasound scans.

The Fetal Study had a total population of 5,301 women before exclusions were applied. Inclusion and exclusion criteria for our analysis was established as the following and shown in Figure 10 below: women had to have

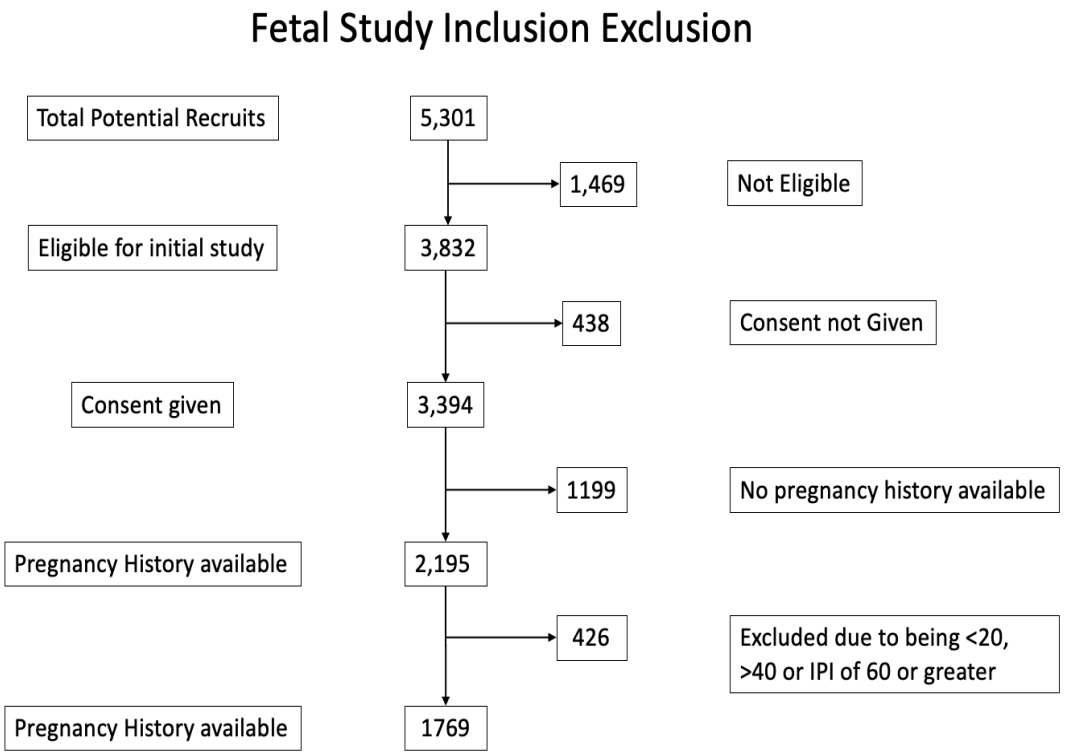


Figure 10. Fetal study inclusion exclusion flow chart

one at least one prior pregnancy, a month and year of end of the immediately previous pregnancy, given consent to be included in analysis, be of at least 20 years of age, be no older than 40 years of age, and have an IPI of less than 60 months. After all exclusions were applied, 1769 women were eligible for analysis.

INTERBIO-21st Newborn Case-Control Study

The goal of the INTERBIO-21st Neonatal Study was to provide detailed newborn phenotypic information (including accurate gestational age at birth and neonatal morbidity) and

biological samples for case-control studies of maternal/fetal nutritional and maternal/placental/fetal biomarkers. Included healthy pregnancies, as well as those complicated by a range of factors, including in resource-poor settings, HIV, malaria, malnutrition, and anemia. Sites included in the study were Pelotas, Brazil; Oxford, UK; Nairobi, Kenya; Mae Sot, Thailand; Soweto, and Kilifi, Kenya. South Africa was initially included in the study, however due to insufficient numbers of recruits with given consent, the site has been excluded from the Newborn Study.

The process for selecting cases and controls, illustrated below in Figure 11, was designed to select cases for SGA and PTB infants. Infants were initially screened based on gestational age at the time of recruitment into the study, with gestational age confirmed using CRL or head circumference (HC). Infants with a gestational age at birth of 42^{+0} or older were excluded from selection. An infant below a gestational age at birth of 38^{+0} were considered preterm, this cutoff was selected due to the associated morbidities the week after 37^{+0}, and selected as a case for preterm birth. An infant was selected as a SGA case with the infant was not preterm, according to the study definition, and small-for-gestational age. All other infants were selected as potential controls if the birth immediately followed a recruited case.

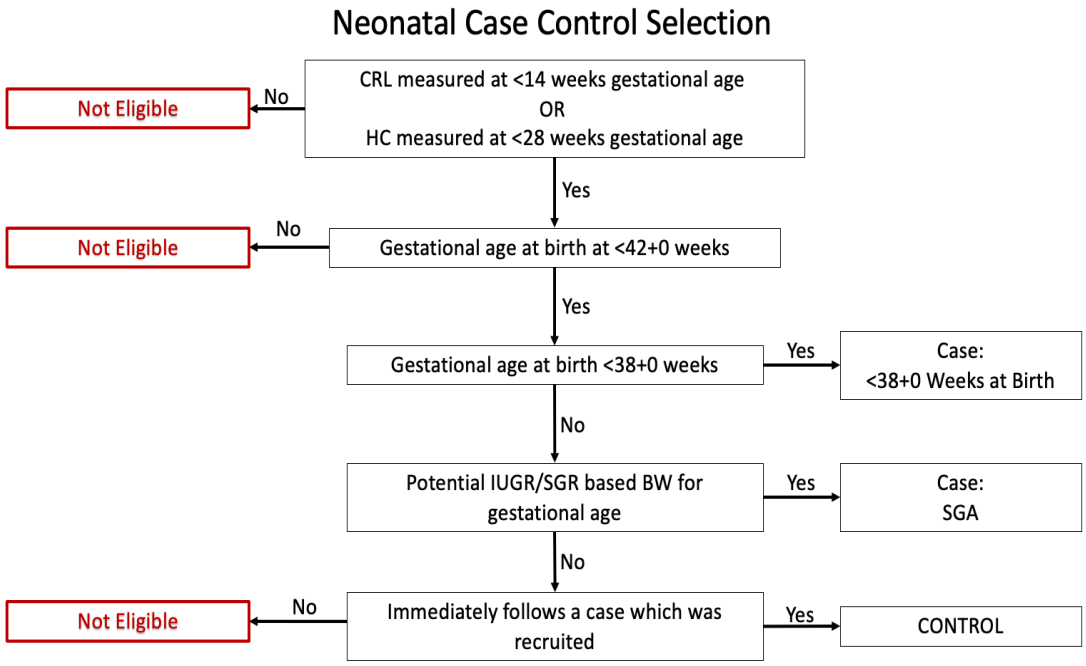


Figure 11. Neonatal study case-control selection flow chart

Due to the over sampling of SGA in the population, down-weighting is required for analysis. Down-weighting is calculated as the proportion of all infants in the control pool who were included in the detailed study.

Set	Infants born <38^{+0} weeks' gestation	Infants born IUGR/SGA	Description	Number of births at study site	Number to be included in the case-control study
A	Yes	No	Non-IUGR/SGA infants born <38^{+0} weeks	A	A (all)
B	No	Yes	IUGR/SGA infants born ≥38^{+0} weeks	B	B (all)
C	Yes	Yes	IUGR/SGA infants born <38^{+0} weeks	C	C (all)
D	No	No	Non-IUGR/SGA infants born ≥38^{+0} weeks	D	Sample = A+B+C

Figure 12. Neonatal study case and control classification

The inclusion and exclusion criteria for the analysis of the Newborn study was at least one previous pregnancy, year and month date recorded for end of immediately previous pregnancy,

were at least 20 years of age and at most 40 years of age at time of recruitment and did not have an IPI of 60 months or greater. The purpose of these selection criteria was to limit the potential confounders for preterm birth and IPI. Excluding very young and advanced age women from our sample, we have reduced the potential noise. After applying inclusion and exclusion criteria, 1721 women were eligible for analysis.

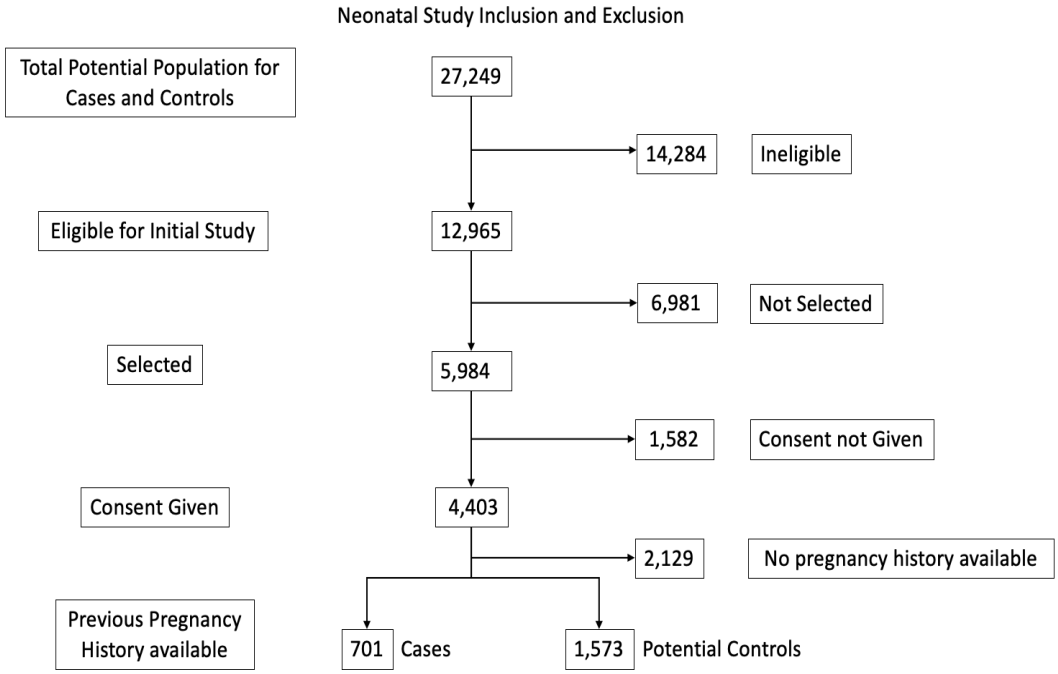


Figure 13. Neonatal study inclusion and exclusion flow chart

Gestational age estimation by ultrasound

The accurate measurement of gestational age is greatly important to the ability of a researcher to investigate the potential relationships between birth outcomes and IPI. The INTERBIO-21st study utilized the rigorous and standardized methods developed for the INTERGROWTH-21st project. The centralized processing and monitoring of data allowed for the feasible comparison across countries with a high level of confidence in the accuracy and consistency of the hospital data. The method of gestational age measurement in the INTERBIO-

21st study relied on the use of crown-rump length (CRL) measurements and was supplemented with head circumference (HC) measurements.

CRL measurements were taken <14+0 weeks' gestation in a mid-sagittal view of the horizontal fetus in a neutral position, with an angle of insonation as close as possible to 90°. The image could not fill less than 30% of the monitor screen. The calipers were placed on the outer borders of the head and rump, and gestational age was estimated using the INTERGROWTH-21st standards for pregnancy dating.(82,86)

Head measurements were taken <24+0 weeks' gestation in an axial view at the level of the thalami, with an angle of insonation as close as possible to 90° using the same ultrasound machine at each site (Philips HD-9, Philips Ultrasound, USA with curvilinear abdominal transducers C5-2, C6-3, V7-3). The head had to be oval in shape, symmetrical, centrally positioned, filling at least 30% of the monitor. The midline echo (representing the falx cerebri) had to be broken anteriorly, at one-third of its length, by the cavum septum pellucidum. The thalami had to be located symmetrically on either side of the midline. The head circumference was measured using the ellipse facility on the outer border of the skull, and gestational age was estimated using the INTERGROWTH-21st standards for late pregnancy dating (82,86).

The ultra-sonographers at each site were selected based on their technical expertise, motivation, reliability, and ability to speak the local language(s). Through rigorous training they gained theoretical knowledge and familiarity with the study protocol, operations manual, data collection and quality control measures. Centralized hands-on training and initial standardization were also conducted, and the Oxford-based Ultrasound Quality Control regularly carried out site-specific standardization to ensure proper use of the ultrasound equipment, calibration, and adherence to the protocol. Quality control was maintained throughout the study by taking a random

10% sample of all ultrasound images and assessing their quality using a validated scoring system. (82,86)

INTERBIO-21st Interpregnancy

The INTERBIO-21st study collected information from mothers on previous obstetric history, and importantly the end date of the previous pregnancy and outcome. This provides us the unique opportunity to measure IPI utilizing maternal recall rather than relying on birth records linked to mothers. Using maternal recall affords our study with multiple advantages over previous studies which relied on maternal and infant records for establishing IPI. One of the primary concerns for measuring IPI is the risk of overestimating the length of IPI due to a lack of records on non-live pregnancy outcomes which may occur between live deliveries. Many countries do not have adequate systems in place to record pregnancy losses, and even developed countries, such as the United States, lack the infrastructure to capture non-live pregnancy outcomes. This leaves researchers with a database which reports inter-delivery intervals, unless the population is limited to women with only two births. Even then the assumption is that the women selected only have had one prior pregnancy.

Utilizing the INTERBIO-21st study will allow for further exploration of IPI and adverse pregnancy outcomes and allow for the inclusion of accurate previous pregnancy history which does not rely solely on birth records. Furthermore, the use of a true international cohort and case-control study which used the same which utilizes standardized methods for recruitment of pregnant women, measurement, and recording of information on maternal, fetal, and infant characteristics. The current literature does not address these concerns about IPI granularity, pregnancy history, and international populations. The INTERBIO-21st dataset will allow for our study to potentially better address these concerns. The limitations in our study design are borne from the structure and design of the data, however the advantages of the dataset allow for our study to address the concerns.

CHAPTER 4: DETERMINANTS OF SHORT AND LONG INTERPREGNANCY INTERVALS IN THE INTERBIO-21ST PROJECT[1]

Introduction

Interpregnancy intervals (IPI), the time between the end of one pregnancy and the start of the subsequent pregnancy. Studies have shown that short IPIs have been identified as a risk indicator for adverse pregnancy outcomes, however few studies have explored determinants of short IPIs. Most studies which focused on the relationship between adverse pregnancy outcomes and short IPIs adjust for confounding using risk indicators for that have been linked to the adverse outcomes with the assumption that the same risk indicators are tied to short IPIs. The issue with this assumption is that the factors which contribute to short IPI may not directly affect adverse pregnancy outcomes. Studies which have considered short IPI as a primary outcome have focus on developed countries and relied on maternal and birth records for estimating IPI. Potentially these studies over-estimate the length of IPI in their populations, as non-live outcomes, such as miscarriage, fetal loss, and terminations, tend to be underreported.

No studies have considered how obstetric history affects the likelihood of short IPI, and only included women with a previous live birth. In addition, these studies have relied on maternal and infant records to establish the IPI, which can potentially overestimate the IPI. This has left a hole in the literature on the potential determinants of short IPI in an international setting, looking across previous pregnancy outcomes. This study's objective is to use the INTERBIO-21st Fetal Study to evaluate what potential determinants exist in an international cohort, and to evaluate whether determinants are different for previous obstetric experiences.

Materials and Methods

Study Population

The women included in this study came from the INTERBIO-21st Fetal cohort, due to its rigorous data collection methods, extremely accurate gestational age estimation methods, and international representation. The main aim of the INTERGROWTH-21st was to improve the functional classification of the previously evaluated preterm birth and FGR syndromes. Women were recruited into the study within the first fourteen weeks of their pregnancy, and had maternal, fetal, and infant characteristics and history recorded by trained clinicians. The initial study included 3394 women, of which 2370 had a at least the month and year recorded for the end date of the prior pregnancy. After exclusions on age and maximum IPI were apply, 1787 women were available for the analysis. The study included women from six countries and was conducted from February 2012 and June 2018. The study population was limited to women of 20 to 40 years of age and had at least one previous pregnancy.

Outcome Variable

The outcome variable was IPI, defined as the period from the end of the previous pregnancy to the start of the current pregnancy. The start date of the current pregnancy was derived by subtracting the gestational age from the date of delivery from the index pregnancy, in order to derive the conception date. IPI was then calculated by subtracting the end date of the previous pregnancy from the date of conception of the index pregnancy, measured in days. The calculated days were then converted into weeks by dividing by 7, and then converted into months by dividing by 4.345. The first month after end of the previous pregnancy was recorded as "0." There were 91 women, 5% of total sample, with missing the day which the previous pregnancy ended were assigned the 15th as the date, due to the mean day in the sample being the 15th. An IPI was considered short if it was shorter than 18 months. This cutoff was chosen due to the "18 to

23” month intervals common use as a reference period. We restricted analysis to women with an IPI of less than 60 months, to limit the potential noise from women with an extremely long IPI. Short IPI was defined as an IPI of less than 18 months, using previous literature as the basis for our cutoff.

Explanatory Variables

Previous pregnancy outcome was defined as the outcome of the immediately previous pregnancy as reported by the mother. The possible previous outcomes were previous term, previous preterm, or previous loss. Occupation was recoded as encompass white-collar, blue-collar, and student/housework/other. White-collar was defined as employment as a manager, professional, technical person, clerical support, and service or sales. Blue-collar was defined as employment in skilled and non-skilled labor. Education was categorized into three groups, less than high school, high school, and professional/university. Marital status was dichotomized into not married or not cohabitating vs married or cohabitating. Occupational status was categorized as student/houseworker/other, blue-, and white-collar workers. Pre-pregnancy BMI was categorized into four categories underweight (below 18.5), normal (18.5 to 24.9), overweight (25 to 29.9), and obese (30 or above). Other explanatory variables were site location (six sites), maternal age (20 to 24, 25 to 29, 30 to 34, and 35 to 40), maternal age at previous pregnancy (less than 20 to 24, 25 to 29, 30 to 34, and 35 to 40), any tobacco use during pregnancy, any alcohol use during pregnancy, gravida, parity, any previous terminations, any previous miscarriages, any previous still births, any morbidities before current pregnancy, any morbidities before or during current pregnancy, and any pregnancy related complications.

Statistics

Data preparation and analysis was carried out in R (version 1.4.1717) and STATA/IC version 16.1, with 1787 women included in the final analysis for women 20 to 40 years of age

and restricted to an IPI of less than 60 months. Mean IPIs were compared with the identified potential risk indicators using Kruskal-Wallis one way analysis of variance. Distributions were compared using Wilcoxon rank sum test and Pearson's Chi-squared test, when appropriate. Multivariate analysis was conducted using a Poisson regression with robust standard errors and a stepwise forward selection model with the cut-off of $p < 0.2$ for addition to the model and terms with a p-value >= 0.5. A stratified analysis using stepwise forward model was conducted on previous pregnancy outcome to evaluate whether the identified determinants of short IPI in the overall population, using the same p-value cut-offs for inclusion and exclusion.

Results

Sample Characteristics

Of the 1,787 mothers included in the analysis, 796 women (44.5%) had an IPI of less than 18 months. The median IPI in the overall dataset was 21 months, with a mean IPI of 22.53 months. The mean maternal age of the study population was 30.1, with a median age of 30.

Mean IPI by Maternal Characteristics

The mean IPI by maternal characteristic is shown in Table 3 below. Women in from Oxford, UK, had the shortest mean IPI (19.4 months) and women from Pelotas, Brazil, had the longest IPI on average (27.8 months). Women is a previous term birth had longer mean IPI, followed by previous preterm, and women with a previous loss being the shortest. Women who were 20 to 29 years of age had a shorter mean IPI compared to women 30 to 40 years of age at the time of their most recent pregnancy. Women younger than 29 years of age during their previous pregnancy had a longer mean IPI compared to women who were 30 to 40 at the time of their previous pregnancy. Women who were not married or cohabitating had shorter mean IPI than married or cohabitating women. Mean IPI decreased with higher levels of educational attainment. Mean IPI decreased with higher gravida. Women with any previous stillbirths had

lower mean IPIs. Women with any pregnancy complication during their most recent pregnancy had shorter mean IPIs.

Potential risk factors which did not have significantly different mean IPIs were pre-pregnancy BMI, occupational status, tobacco use, alcohol use, mode of delivery, women with any previous morbidities during previous pregnancy, and women with any previous morbidities before or during current pregnancy.

Characteristics associated with short IPI

Women with a short IPI compared with women with a non-short IPI were more likely to be younger during their most recent pregnancy, older during their previous pregnancy, not married or cohabitating, have at least a high school education, more than more previous pregnancy, lower parity, any previous terminations, previous miscarriage, any previous still births, and had any pregnancy related complications during their most recent pregnancy.

Table 4 shows the results of the multivariate analysis for the full model and the forward stepwise model, as well as sub-group analyses for women with previous term, preterm, and non-live outcomes, with the cut-off of $p < 0.2$ for addition to the model and terms with a p-value >= 0.5. Cut-offs were selected based on previous literature and intended to be conservative values for inclusion into the model.

The stepwise model for the overall population excluded marital status, education, occupation, tobacco use, alcohol use, gravida, parity, mode of delivery of most recent infant, the score for morbidly during or before current pregnancy, and pregnancy related complications during most recent pregnancy. The stepwise model showed that women with an IPI of less than 18 months, compared to women with an IPI of 18 to 59 months, with either a preterm birth or non-live outcome during the pregnancy immediately before, younger at current pregnancy, older at the time of previous pregnancy, had a previous termination, higher number of miscarriages, a previous

stillbirth, and no previous morbidities had an increased risk of having a short IPI. The analysis also found that compared to women in Mae Sot, Thailand, women in Karachi, Pakistan, Pelotas, Brazil, and Oxford, UK had higher risk of having a short IPI.

The stratified stepwise analysis was done on previous pregnancy outcomes, previous term, previous preterm, and previous non-live. The stepwise model for the previous term birth subgroup found that women who were younger during their current pregnancy, older during their previous pregnancy, had a white-collar job, a previous termination, previous miscarriage, previous still birth, and did not have a morbidity before the recruited pregnancy had higher risk of having a short IPI. Women with a previous preterm birth who were younger during their current pregnancy, older during their previous pregnancy normal weight, had three previous pregnancies, a previous termination, and did not have a morbidity before the recruited pregnancy had higher risk of having a short IP. Women with a previous non-live birth who did not use alcohol use during pregnancy, no previous terminations, and had one previous miscarriage had higher risk of having a short IPI.

Discussion

This study showed that after adjustment, women with a short IPI compared to women with a non-short IPI had higher risk to be younger during the latest pregnancy, older during their previous pregnancy, immediately previous pregnancy ending in either a preterm birth or a loss, experienced a previous termination, experienced a previous miscarriage, experienced a previous stillbirth, and had a morbidity before the latest pregnancy. No social factors were found to be associated with short IPI after adjustment. What these various risk indicators suggest is that two primary areas serve as determinants for short IPI in the INTERBIO-21st Fetal cohort study, obstetric history and health, and maternal age.

The risk indicators which fall under the category of obstetric history and health are previous pregnancy outcome, previous terminations, previous miscarriages, previous stillbirths, and having a pre-existing morbidity. higher gravida, lower parity, experienced a previous termination, experienced a previous miscarriage, experienced a previous stillbirth, and had a pregnancy complication during their most recent pregnancy.

The population used in this study came from an international-based cohort with high quality data measurement, collection, and monitoring methods, attributing to a high level of internal validity in the study. The population was restricted to women 20 to 40 years of age, in order to narrow the population to reduce potential selection bias for women at the extreme ends of child-bearing age due to unlikeliness of intended or adequate family planning practices of women outside our specified range. Further the study population used for analysis was restricted to an IPI of less than 60 months in order to limit the potential bias from women with excessively long IPIs. No restrictions were placed on previous pregnancy history, as we wanted to capture women with varying obstetric history. This study benefits from the use of maternal recall for identifying end date of previous pregnancy, with secondary supplementation from hospital records, rather than solely relying on maternal and infant hospital records. This minimizes the risk of overestimating the length of the IPI, which is common for studies utilizing maternal and infant hospital records. Additionally, the use of maternal recall allows for the accurate recording of previous pregnancy outcomes, allowing for a study which includes not only previous live births, but also previous pregnancies with non-live outcomes. The use of risk ratios is appropriate, the prevalence of short IPI was above 10%, however this makes direct comparison of results to other studies difficult due to the common use odds ratios in the literature.

Limitations of this study are that these findings may not be generalizable to women outside these study sites, and that our populations may not be representative of the local populations. Potential for recall bias exist in our study, though the use of maternal records to help

verify the recorded information alleviates some of this concern. We were unable to adequately capture family planning practices or pregnancy intention, which can contribute greatly to behaviors which lead to short IPI. A major limitation of this study was that we did not have information on breastfeeding practices between pregnancies, or contraceptive use. These would have allowed for proxy measuring of fecundity and pregnancy intention, respectively, and would have been important risk indicators for short IPI. The definition we have set for short IPI overly inclusive, as the cutoff we have selected may not capture the true short IPI, however the use of less than 18 months has been commonly used as a cut-off and been shown to be associated with higher rates of preterm births. However, it is still important that we identify potential risk indicators using a cut-off that has been often used in the literature for a preliminary analysis.

After adjustment, this study showed that risk indicators with the risk indicators for short IPI were linked to maternal age and obstetric history. Maternal age followed the expected pattern for short IPI, with younger women at the time of the recruited pregnancy and women who were older at the previous pregnancy having shorter IPIs. One explanation for this difference in mean IPIs and found associations is the timing for when women are planning for their ideal family size. The shorter IPIs found in women above 30 years of age during their previous pregnancy potentially suggest that these women are trying to quickly achieve their ideal family size before they are limited by biology. This is potentially problematic, as not only is short IPI associated with increased risk of adverse pregnancy outcomes, but additionally these women are at an elevated risk for adverse pregnancy outcomes compared to women younger than 30 years.

Previous pregnancy outcomes and obstetric history were found to an impact on the risk of short IPI, with shorter length of gestation time for the previous pregnancy being associated with increased risk. The reason for this is unclear, as it has been common belief that women with adverse pregnancy outcomes should wait longer between pregnancies. The underlying logic to this was that woman with an adverse pregnancy outcome were more likely to suffer from

maternal depletion syndrome, necessitating the need for these women to wait longer to recuperate. If this theory is true, then potentially these women are exposing themselves to elevated risk for adverse pregnancy outcomes in the subsequent pregnancy. However, the definition of short IPI we have utilized is based on studies which utilized live were developed without differentiating between live outcomes and did not include previous non-love outcome pregnancies. Due to this concern, and the large disparity in mean IPIs between women with previous term, preterm, and non-live outcomes, we decided to conduct a sensitivity analysis to determine whether the risk indicators identified in the overall population were maintained after adjustment. We found that the models selected with stepwise forward selection were similar for women with a previous term or preterm birth, with only onset of labor not being included in the model for previous preterm. Onset of labor was not significant in the previous term model, with no difference being found between induced labor and spontaneous labor.

Women with a previous term birth who were younger during the recruited pregnancy, older during the previous pregnancy, were unemployed, had a previous termination, a previous miscarriage, and did not have a morbidity before pregnancy. Women in this stratum closely followed the found associations and model selection of the overall population, with the previous term stratified model including occupation and gravida. White-collar workers compared to unemployed women had lower risk of having a short IPI, while gravida had no statistically significant effect. The models for women with a previous preterm birth and previous term birth were nearly identical in included terms, with the model for the previous preterm stratum only not including onset of labor in the model. The general directions of effect are similar for the two strata, though differences in statical significance are present. In the previous preterm stratum, women with a normal BMI, a gravida of three or more, were found to be statistically at higher risk of a short IPI whereas women with a previous term birth saw no statistically significant effect in these terms.

The final strata of women with a previous non-live outcome had location, BMI, alcohol use during pregnancy, previous terminations, and one previous miscarriage included in the final model. Of those included terms, it was found that women who did not use alcohol during their pregnancy, did not have any previous terminations, and had one previous miscarriage had higher risk of experiencing a short IPI. The effect of previous terminations in this stratum were inversed in comparison to the previous term and preterm strata. This suggest that women in this stratum experienced a previous non-live outcome due to issues related to biological viability of the fetus, rather than voluntary termination of the fetus. It should be noted that 98% of women in this group did not have any prior live births. We were unable to measure intention of pregnancy directly in this study, however the patterns for previous terminations and miscarriages in this stratum potentially suggest that women with a previous non-live outcome are intentionally becoming pregnant within the short IPI period we have identified.

In all models we looked at the potential association of short IPI and country location of site, with Mae Sot, Thailand used as the reference site. In the unadjusted model, Pakistan, Kenya, and Oxford had a higher risk for short IPI compared to Thailand.

Future research needs to evaluate the potential differences between younger and older women, particularly for women with a previous live outcome. Research needs to also consider intention of pregnancy, as this may contribute greatly to the risk of short IPI, though it is unclear whether this may change with previous pregnancy outcomes. The potential differences we found between our strata suggest that the experience and outcomes of previous pregnancies greatly affects the risk of having a short IPI, but it is unclear whether that is due to pregnancy intention or other potential explanations.

Short IPIs are considered a risk indicator for adverse pregnancy outcomes, and in our study, we identified that past obstetric experience and maternal age were a large predictor for

short IPIs. It is unclear the degree to which unplanned pregnancies attributed to short IPIs in this study, as it was not explicitly measured. For clinicians seeking to identify patients that are at higher risk of short IPI, maternal age and obstetric history need to be taken into consideration.

Table 3. Mean and median IPI by maternal characteristics

Variable	*Number*	*Mean*	*SD*	*95% Confidence Interval*		*Kruskal-Wallis*
City, Country						<0.001
Karachi, Pakistan	356	20.8	15.4	19	22.5	
Mae Sot, Thailand	272	27.2	15.4	25.3	29.1	
Nairobi, Kenya	304	23.5	14.9	21.8	25.3	
Oxford, UK	398	19.4	15	17.8	20.9	
Pelotas, Brazil	100	27.8	17	24.4	31.3	
Soweto, South Africa	357	22	17.4	20	23.9	
Previous Pregnancy Outcome						<0.001
Term	1274	25	15.8	24	25.9	
Preterm	217	21	15.6	18.8	23.2	
Loss	296	13.2	13.6	11.6	15	
Maternal Age at Previous Pregnancy Group 10-year Intervals						<0.001
Under 24	471	24.4	16.4	22.8	26	
25 to 29	642	24.3	16.3	22/9	26	
30 to 34	526	21	15.3	19.6	22.4	
35 to 40	148	14.5	12	12.4	16.6	
Maternal Age Group 10-year Intervals						<0.001
20 to 24	543	21.3	15.8	19.9	22.7	
25 to 29	241	19.4	14.4	17.4	21.3	
30 to 34	671	24	15.9	22.7	25.2	
35 to 40	332	24	17	22.1	25.9	
Pre-pregnancy BMI						0.3684
Normal	823	22.5	16	21.4	23.7	
Underweight	84	23.5	14.5	20.2	26.8	
Overweight	596	21.8	15.8	20.5	23.2	

Obese	269	23.9	16.8	21.7	26	
Marital Status						0.04364
Not Married/Cohabiting	240	21.2	17.5	18.9	23.6	
Married/Cohabiting	1547	22.7	15.7	21.9	23.6	
Highest Education Attained						<0.001
Less than Highschool	245	27.5	16	25.4	29.6	
Highschool	548	22.6	16.8	21.2	24.1	
Professional or University	993	21.3	15.3	20.2	22.3	
Missing	1	22		-	-	
Occupational Status						0.5199
Student/Housework/Other	887	22.7	16.3	21.6	23.9	
Blue-Collar	169	23.9	17.1	21.2	26.7	
White-Collar	731	22	15.3	20.8	23.1	
Tobacco Use During Pregnancy						0.3629
No Tobacco Use	1658	22.3	15.8	21.5	23.1	
Tobacco Use	129	25.3	17.8	22.1	28.6	
Alcohol Use During Pregnancy						0.3629
No Alcohol Use	1736	22.4	15.9	21.7	23.2	
Alcohol Use	51	25.7	19.5	20.1	31.3	
Gravida						<0.001
1	767	24.1	15.2	23	25.3	
2	488	22.5	16.5	20.8	23.9	
3 or more	532	20.3	16.2	18.9	21.9	
Parity						<0.001
0	289	12.8	13.2	11.1	14.5	
1	938	23.6	15.5	22.5	24.6	
2	357	25.7	16.1	24	27.5	
3 or more	202	26	16.6	23.6	28.4	
Missing	1	38		-	-	

Number of Previous Terminations						0.002
None	1645	22.9	15.9	22	23.7	
Any	142	18.8	16	16	21.7	
Any Previous Miscarriages						<0.001
None	1029	27.8	15	26.8	28.7	
Any	758	15.4	14.5	14.3	16.5	
Any Previous Stillbirths						0.001
None	1693	22.8	16	22	23.6	
Any	94	17.5	14.4	14.4	20.6	
Mode of Delivery						0.4519
Vaginal or Other	116	22.2	15.7	21.2	23.2	
Caesarean	671	23.1	16.5	21.7	24.4	
Any Morbidities Before Current Pregnancy						0.5122
0	1115	22.4	16	21.4	23.4	
1	671	22.8	15.9	21.5	24.1	
Missing	1	12		-	-	
Any Morbidities Before and During Current Pregnancy						0.303
0	1099	22.3	16.1	21.3	23.3	
1	677	23	15.8	21.7	24.2	
Missing	11	23.9	15.8	14.1	33.8	
Any Pregnancy Related Complications of Current Pregnancy						0.03954
0	1277	23	16	22.1	23.9	
1	495	21.3	15.8	19.8	22.8	
Missing	15	23.9	17.1	14.8	33.1	

Table 4. Maternal characteristics by short vs non-short IPI

Variable	***N***	***0 to 17***, *N = 796*[1]	***18 to 59***, *N = 991*[1]	***p-value***[2]
City, Country	1,787			<0.001
Karachi, Pakistan		183 (51%)	173 (49%)	
Mae Sot, Thailand		83 (31%)	189 (69%)	
Nairobi, Kenya		122 (40%)	182 (60%)	
Oxford, UK		202 (51%)	196 (49%)	
Pelotas, Brazil		30 (30%)	70 (70%)	
Soweto, South Africa		176 (49%)	181 (51%)	
Previous Pregnancy Outcome	1,787			<0.001
Term		471 (37%)	803 (63%)	
Preterm		114 (53%)	103 (47%)	
Loss		211 (71%)	85 (29%)	
Maternal Age Group 10-year Intervals	1,787			<0.001
20 to 24		115 (48%)	126 (52%)	
25 to 29		285 (52%)	258 (48%)	
30 to 34		399 (59%)	272 (41%)	
35 to 40		192 (58%)	140 (42%)	
Previous Pregnancy Maternal Age Group 10-year Intervals	1,787			<0.001
24 or less		282 (60%)	189 (40%)	
25 to 29		381 (59%)	261 (41%)	
30 to 34		275 (52%)	251 (48%)	
35 to 40		53 (36%)	95 (64%)	
Pre-pregnancy BMI	1,787			0.11
Normal		381 (45%)	457 (55%)	
Underweight		28 (33%)	56 (67%)	
Overweight		275 (46%)	321 (54%)	
Obese		112 (42%)	157 (58%)	
Marital Status	1,787			0.025
Not Married/Cohabiting		123 (51%)	117 (49%)	
Married/Cohabiting		673 (44%)	874 (56%)	
Highest Education Attained	1,786			<0.001
Less than Highschool		79 (32%)	166 (68%)	
Highschool		253 (46%)	295 (54%)	
Professional or University		464 (47%)	529 (53%)	
Missing		0	1	
Occupational Status	1,787			0.7

Student/Housework/Other		401 (45%)	486 (55%)	
Blue-Collar		71 (42%)	98 (58%)	
White-Collar		324 (44%)	407 (56%)	
Tobacco Use During Pregnancy	1,787			0.3
No Tobacco Use		744 (45%)	914 (55%)	
Tobacco Use		52 (40%)	77 (60%)	
Alcohol Use During Pregnancy	1,787			0.3
No Alcohol Use		777 (45%)	959 (55%)	
Alcohol Use		19 (37%)	32 (63%)	
Gravida	1,778			<0.001
1		299 (38%)	483 (62%)	
2		229 (47%)	262 (53%)	
3 or more		262 (52%)	243 (48%)	
Missing		6	3	
Parity	1,786			<0.001
0		210 (73%)	79 (27%)	
1		377 (40%)	561 (60%)	
2		137 (38%)	220 (62%)	
3 or more		72 (36%)	130 (64%)	
Missing		0	1	
Number of Previous Terminations	1,787			<0.001
None		714 (43%)	931 (57%)	
Any		82 (58%)	60 (42%)	
Number of Previous Miscarriages	1,787			<0.001
0		303 (29%)	726 (71%)	
1		302 (63%)	179 (37%)	
2		134 (70%)	58 (30%)	
3 or more		57 (67%)	28 (33%)	
Any Previous Stillbirths	1,787	60 (64%)	34 (36%)	<0.001
Mode of Delivery	1,787			0.5
Vaginal or Other		491 (44%)	625 (56%)	
Caesarean		305 (45%)	366 (55%)	
Onset of Labour	1,787			0.2
Missing		4 (40%)	6 (60%)	
Induced		135 (50%)	135 (50%)	
No labour		192 (43%)	258 (57%)	
Spontaneous		465 (44%)	592 (56%)	
Any Morbidities Before Current Pregnancy	1,786			0.3
None		506 (45%)	609 (55%)	

Any		289 (43%)	382 (57%)	
Missing		1	0	
Any Morbidities Before and During Current Pregnancy	1,776			0.6
None		496 (45%)	603 (55%)	
Any		296 (44%)	381 (56%)	
Missing		4	7	
Any Pregnancy Related Complications of Current Pregnancy	1,772			0.04
None		550 (43%)	727 (57%)	
Any		240 (48%)	255 (52%)	
Missing		6	9	

[1] *Mean (Range); n (%)*

[2] *Wilcoxon rank sum test; Pearson's Chi-squared test; Fisher's exact test*

Table 5. Full and Stepwise Logistic Regressions

	Unadjusted Model		*Stepwise Model*		*Previous Term Model*		*Previous Preterm Model*		*Previous Loss Model*	
	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI
Previous Pregnancy Outcome										
Term	1	[1,1]								
Preterm	1.431*	[1.011,2.026]	1.386	[0.984,1.953]						
Loss	0.188	[0.0138,2.557]	2.362***	[1.658,3.366]						
City, Country										
Karachi, Pakistan	2.535**	[1.405,4.574]	2.566***	[1.708,3.853]	2.282***	[1.427,3.650]	0.873	[0.128,5.961]	2.836	[0.686,11.72]
Mae Sot, Thailand	1	[1,1]	1	[1,1]	1	[1,1]	1	[1,1]	1	[1,1]
Nairobi, Kenya	1.909*	[1.014,3.596]	1.730*	[1.129,2.649]	2.509**	[1.437,4.379]	0.0824*	[0.00687,0.988]	2.009	[0.507,7.962]
Oxford, UK	2.681***	[1.507,4.769]	2.668***	[1.788,3.981]	3.242***	[1.985,5.296]	0.313	[0.0432,2.270]	3.634	[0.828,15.95]
Pelotas, Brazil	1.141	[0.575,2.262]	1.012	[0.564,1.817]	0.84	[0.389,1.817]	0.566	[0.0585,5.466]	0.796	[0.174,3.651]
Soweto, South Africa	1.464	[0.786,2.728]	1.502	[0.999,2.259]	2.039**	[1.256,3.309]	0.318	[0.0457,2.207]	0.58	[0.167,2.014]
Maternal Age Group 10-year Intervals										
20 to 24	3.640***	[2.320,5.711]	3.619***	[2.325,5.634]	3.758***	[2.144,6.586]	8.290**	[2.243,30.64]		
25 to 29	1	[1,1]								
30 to 34	0.177***	[0.120,0.262]	0.177***	[0.120,0.261]	0.180***	[0.113,0.289]	0.388*	[0.188,0.798]	0.629	[0.315,1.254]
35 to 40	0.0454***	[0.0252,0.0817]	0.0454***	[0.0254,0.0811]	0.0429***	[0.0218,0.0845]				
Previous Pregnancy Maternal Age Group 10-year Intervals										

24 or under	1	[1,1]										
25 to 29	4.530***	[2.962,6.927]	4.146***	[2.738,6.280]	4.821***	[2.832,8.207]						
30 to 34	23.97***	[13.40,42.90]	21.64***	[12.26,38.19]	27.09***	[13.38,54.84]						
35 to 40	107.4***	[49.08,235.0]	96.85***	[44.86,209.1]	129.2***	[51.70,322.7]						
Pre-pregnancy BMI												
Normal	1	[1,1]										
Underweight	0.713	[0.411,1.238]									0.294	[0.0597,1.452]
Overweight	0.856	[0.657,1.115]					2.291*	[1.122,4.678]				
Obese	0.669*	[0.471,0.951]	0.708*	[0.516,0.972]	0.705	[0.481,1.033]						
Marital Status												
Not Married/Cohabiting	1	[1,1]										
Married/Cohabiting	1.036	[0.655,1.639]										
Highest Education Attained												
Less than Highschool	1	[1,1]										
Highschool	1.029	[0.802,1.320]										
Professional or University	1.035	[0.798,1.342]										
	1	[1,1]										
Occupational Status												
Student/Housework/Other	1	[1,1]										
Blue-Collar	0.917	[0.608,1.384]										
White-Collar	0.792	[0.577,1.088]			0.657*	[0.454,0.950]	1.769	[0.751,4.165]				
Tobacco Use During Pregnancy												

No Tobacco Use	1	[1,1]								
Tobacco Use	1.228	[0.749,2.014]								
Alcohol Use During Pregnancy										
No Alcohol Use	1	[1,1]								
Alcohol Use	0.658	[0.320,1.352]							0.118*	[0.0221,0.629]
Gravida										
1	1	[1,1]								
2	1.089	[0.734,1.614]								
3 or more	1.49	[0.820,2.707]					2.347	[0.998,5.521]		
Parity										
0	1	[1,1]								
1	0.0659*	[0.00466,0.933]								
2	0.0505*	[0.00334,0.763]								
3 or more	0.0391*	[0.00244,0.625]								
Any Previous Terminations										
None	1	[1,1]								
Any	1.328***	[1.127,1.565]	1.305***	[1.132,1.505]	1.600***	[1.315,1.947]	1.672**	[1.162,2.404]	0.681*	[0.506,0.915]
Any Previous Miscarriages										
None	1	[1,1]								
Any	1.909***	[1.626,2.240]	1.860***	[1.649,2.098]	1.813***	[1.532,2.145]	1.315*	[1.010,1.712]	1.203*	[1.023,1.416]
Any Preious Stillbirths										

None	1	[1,1]								
Any	3.751***	[2.176,6.464]	3.346***	[1.974,5.672]	2.843**	[1.484,5.445]	3.525**	[1.378,9.022]	11.36***	[4.441,29.04]
Mode of Delivery										
Vaginal or Other	1	[1,1]								
Caesarean	0.879	[0.613,1.261]								
Onset of Labour										
Induced	1	[1,1]								
No labour	0.807	[0.570,1.142]	0.802	[0.581,1.107]	0.731	[0.489,1.094]				
Spontaneous	1.039	[0.696,1.551]								
Any Morbidities Before Current Pregnancy										
None	1	[1,1]								
Any	0.720*	[0.554,0.936]	0.701**	[0.549,0.894]	0.725*	[0.540,0.972]	0.432*	[0.206,0.906]		
Any Morbidities Before and During Current Pregnancy										
None	1	[1,1]								
Any	0.945	[0.735,1.215]					0.562	[0.268,1.177]		
Any Pregnancy Related Complications of Current Pregnancy										
None	1	[1,1]								
Any	0.948	[0.720,1.247]								
Observations	1762		1762		1264		216		282	
F										

df_m	35	17	17	18	12
df_r					
Exponentiated coefficients; 95% confidence intervals in brackets					
* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$					

CHAPTER 5: IDENTIFYING THE OPTIMAL INTERPREGNANCY INTERVAL BASED ON PREVIOUS PREGNANCY HISTORY

Introduction

Interpregnancy interval, the period between the end of one pregnancy and the start of the next, has been shown to have a "J-shaped" relationship with PTB (87). Due to this relationship, studies have sought to identify the optimal IPI period where the lowest risk of preterm birth (PTB) exist. Studies conducted by Zhu et al. and Conde-Agudelo et al. utilizing and popularized the use of 6-month intervals, with longer IPIs combined after 23 months, to explore this relationship (18,20). Studies using these intervals have found various associations depending on their populations, however reliance on these intervals has led to an overreliance on categorization to capture the non-linear relationship between IPI and PTB.

The purpose of utilizing the interval categories was to capture the shape of the curve in a manner which was easily interpretable, as to be able to identify an optimum. The issue is that the categories chosen where not based on medical reason nor were they given justification for the 6-month intervals. A further limitation of the literature has been the overreliance on maternal and infant records to define IPI, as well as the limited work to approach IPI with consideration to previous pregnancy history.

The optimal IPI could potentially differ by previous pregnancy outcome, with current research suggesting that women with previous live vs non-live outcomes have distinctly different optimal pregnancy outcomes. Studies which have investigated the relationship between IPI and adverse pregnancy outcomes for women with previous terminations and losses have found that women IPIs ranging from 3 to 9 months were less likely to have an adverse pregnancy outcome (15,33,42). This deviates from the found associations for women with previous live births, which have found shorter IPIs, ranging from 12 to 24 months, were more likely to have an adverse pregnancy outcome (18). These differences in the

associated protective IPIs suggest that the outcome of the immediately previous pregnancy influences the relationship between IPI and adverse pregnancy outcomes. This potential relationship is shown in Figure 14 below, with previous pregnancy outcome being shown as a modifier.

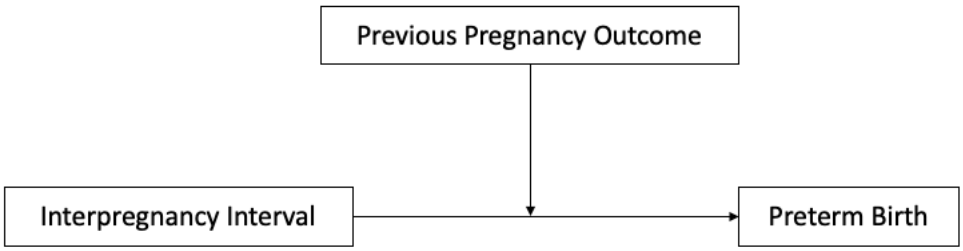


Figure 14. Interpregnancy interval and preterm birth DAG

Methods

Study Population

We conducted an international cohort study to evaluate the associations between IPI and preterm using INTERBIO-21st Fetal and Neonatal studies. The INTERBIO-21st Study was conducted between February 2012 and June 2018 at seven sites: Pelotas (Brazil), Kilifi (Kenya), Nairobi (Kenya), Karachi (Pakistan), Soweto (South Africa), Mae Sot (Thailand) and Oxford (UK), of which two (Kilifi and Mae Sot) were rural and the others urban. The sites in Pelotas, Nairobi and Oxford also participated in Phase I of the INTERGROWTH-21st Project. The two parts of the INTERBIO-21st Study are the Fetal and the Neonatal study, a cohort and case-control study respectively. The INTERBIO-21st Fetal and Neonatal studies were selected, due to its rigorous data collection methods, extremely accurate gestational age estimation methods, and international representation. The main aim of the original study was to improve the functional classification of the previously evaluated preterm birth and FGR syndromes. Women were recruited into the study within the first fourteen weeks of their pregnancy, and had maternal, fetal, and infant characteristics and history recorded by trained clinicians. The study population was limited to women of 20 to 40 years of age and had at least one previous pregnancy for this analysis. Women with

either a spontaneous or non-spontaneous preterm delivery were included in the analysis. The initial Fetal study included 3394 women, of which 2370 had a recorded date for a prior pregnancy. After exclusions on age and maximum IPI were apply, 1769 women were available for the analysis. The study included women from six countries and was conducted from February 2012 and June 2018. The Newborn study initially included 4150 women who had been selected and given consent for use of their information, of which 1769. After applying exclusion criteria, 1721 women were available for analysis.

Outcome Variable

Preterm birth was the outcome of interest for this study and was defined as an infant born before 37 weeks of gestation.

Assessment of Interpregnancy Interval

IPI was defined as the period from the end of the immediately previous pregnancy to the start of the current pregnancy. The start date of the current pregnancy was derived by subtracting the gestational age from the date of delivery from the index pregnancy, in order to derive the conception date. Gestational age was estimated using the standardized ultrasound dating procedures developed in the INTERGROWTH-21st Project (81,82,86). To derive IPI, we subtracted the end date of the previous pregnancy from the date of conception of the index pregnancy, measured in days. The calculated days were then converted into weeks by dividing by 7, and then converted into months by dividing by 4.345. The first month after end of the previous pregnancy was recorded as "0." Women with missing the day which the previous pregnancy ended were assigned the 15th as the date, due to the mean day in the sample being the 15th. An IPI was considered short if it was shorter than 18 months. This cutoff was chosen due to the "18 to 23" month intervals common use as a reference period. We restricted analysis to women with an IPI of less than 60 months, to limit the potential noise from women with an extremely long IPI. Short IPI was defined as an IPI of less than 18 months, using previous literature as the basis for our cutoff.

Explanatory Variables

Previous pregnancy outcome was defined as the outcome of the immediately previous pregnancy as reported by the mother. The possible previous outcomes were previous term, previous preterm, or previous loss. Occupation was recoded as encompass white-collar, blue-collar, and student/housework/other. Education was categorized into three groups, less than high school, high school, and professional/university. Marital status was dichotomized into not married or not cohabitating vs married or cohabitating. Occupational status was categorized as student/houseworker/other, blue-, and white-collar workers. Other explanatory variables were site location (six sites), maternal age (20-to-29 vs 30-to-40), maternal age at previous pregnancy (less than 29 vs 30-to-40), pre-pregnancy BMI (categorized in four groups), any tobacco use during pregnancy, any alcohol use during pregnancy, gravida, parity, any previous terminations, number of previous miscarriages, any previous still births, any morbidities before current pregnancy, any morbidities before or during current pregnancy, and any pregnancy related complications.

Statistical analysis

To evaluate the associations between IPI and preterm birth, we conducted a Poisson regression with robust variance, due to the prevalence of preterm birth greater than 10% and recommendations made by the INTERBIO-21st protocol (84). The reference IPI used was 12 to 24 months, based on the interval identified in a study by Conde-Agudelo et al. as having the lowest odds of preterm birth, for all previous outcomes (18). IPI was first compared using 12 to 24 as the reference period compared to all IPI outside the reference, and if no statistical significance was found then IPI was evaluated using short (0-to-11), medium(12-to-24), and long (25-to-59).

If no statistically significant effect was found, then optimal IPI categories were selected using an unadjusted restricted cubic spline was conducted to determine the overall shape and location of the curve. Cut-offs for the optimal IPI interval were created by setting the upper and lower limits based on a 1%-

point increase from the lowest point of the curve or 5% increase from the lowest point, using which ever created the narrower interval. Using previous literature, cutoffs were adjusted when appropriate if the interval selected was deemed too restrictive. The number of knots selected for the restricted cubic splines was based on the lowest Akaike information criterion (AIC).

Data preparation and analysis was carried out in R (version 1.4.1717) and STATA/IC version 16.1, with 1787 women included in the final analysis for women 20 to 40 years of age and restricted to an IPI of less than 60.

Results

Sample Characteristics

Of the 1,787 mothers included in the analysis from the Fetal Study, 796 women (44.5%) had an IPI of less than 18 months. The median IPI in the overall dataset was 21 months, with a mean IPI of 22.53 months. The mean maternal age of the study population was 30.1, with a median age of 30.

Of the 1,716 women included in the analysis from the Neonatal Study, 666 women (37.7%) had an IPI of less than 18 months. The mean IPI of the Neonatal study overall was 24.74 months. The mean age of the sample was 29.5 years at the time of delivery, and 26.96 years at the time of the end of their previous pregnancy.

12-to-23 IPI interval

The analysis was done for women in the Fetal and Neonatal studies separately, and stratified on previous pregnancy outcome, using 12-to-23 months as the reference period. For women in the Fetal study, IPI was only found to have a statistically significant effect on preterm birth among women with a previous preterm birth. Among women with a previous preterm birth, women with an IPI of 24-to-59 months had 1.193 times the rate of preterm birth compared to women with an IPI of 12-to-23 months in the full model. This association was not seen in the crude analysis. In the previous term birth population,

country of origin, and having any pregnancy complications was associated with higher RRs of preterm birth. In the previous preterm population, women from Brazil, obese, did not use tobacco during pregnancy, never had a previous still birth, had no morbidities before the recruited pregnancy, and did not have a pregnancy complication had lower RRs. For women with a previous early pregnancy loss, women with a pregnancy complication had a higher RR for preterm birth.

The associations and trends between IPI and PTB differed for the Neonatal study, compared to the Fetal study. Women from the previous term population had an inverted "J-shape" with an IPI of 24-to-59 months having .66 times the rate of PTB compared to women with an IPI of 12 to 24 months. This association was reinforced with all IPIs outside of the 12-to-24-month window being found to have .706 times the rate of PTB. Women with a previous preterm birth did not have any IPI categories which were statistically significant, however there was an observed downward trend for increasing categories of IPI. Women with a previous early pregnancy loss did not have any IPI categories associated with PTB, though there was also an inverted "J-shaped" curved observed in the reported RRs.

Spline Curves

Unadjusted restricted cubic splines were done for each of the strata of immediate previous pregnancy outcomes: term birth, preterm birth, and early pregnancy loss. The lowest point of the curves for each of the curves was 15 months for previous term, 12 months for previous preterm, and 0 months for previous early pregnancy loss. The IPI window for the previous term strata was set using the 5% increase rule, resulting in a window of 12-to-19 months. The IPI window selected for women with a previous preterm was 8 to 18 months, set using the 1%-point increase cutoff. Women with previous early pregnancy loss saw the lowest probability for preterm birth at 0 months, and both the 1%-point and 5% increase cutoffs yielded and IPI window of 0-to-3 months. Due to the steep incline of the curve and limited numbers of women with an IPI of 0-to-3 months, this window was deemed too restrictive. To address this, we utilized the previous literature for establishing a window of 0-to-9 months, due to this

falling between previously found associations of less than 6 and less than 12 months for women with previous terminations(33,42).

Newly Selected IPI Window Analysis

The crude analysis did not find that the new IPI windows for the previous term and preterm strata were not found to be statistically significant for women in the Fetal study. The 0-to-9 month interval in the crude analysis was found to be associated with .596 times the rate of preterm birth. After adjustment, the selected IPI windows in all strata are not statistically significant. The observed direction of effects of the selected intervals indicated a protective effect.

The associations and directions found in the Neonatal study did not follow those found in the Fetal study for women with a previous term birth. Women in the previous preterm and early pregnancy loss groups observed similar direction of effect and effect sizes in the adjusted models, though these effects were not statistically significant. Women with a previous term birth had a statistically significant effect, with women less than 10 months and greater than 18 months had .665 and .763 times the rate of preterm birth compared to women with an IPI of 8 to 18 months.

Discussion

The goal of this study was to investigate how the relationship between IPI and PTB was potentially modified by previous pregnancy outcome, shifting the optimal IPI for minimizing the risk of PTB. We found that the use of a universal interval did not yield useful optimal IPIs and had different directions of effect for women of differing previous pregnancy histories. The use of spline curves allowed for a novel method of evaluating the underlying shape of the risk curve by strata and implement objective parameters for selecting a new potential optimal IPI window. The largest differences were seen between women with a previous early pregnancy loss and women with previous live birth outcome, with women with previous early pregnancy loss requiring an IPI window that occurred much sooner after the end of the previous pregnancy.

We observed differences in the curves developed using the restricted cubic splines, particularly in the previous early pregnancy loss group compared to the previous term group. The lowest observed points of the spline curves suggest that potentially there is a relationship between the length of gestation of the previous pregnancy and the optimal IPI. When we applied our rules for selecting a window around the IPI, we did not see statistically significant effects in both the previous term and preterm group, but the direction of effects suggested a potentially protective effect. Women in the previous early pregnancy loss with an IPI of less than 10 months had .596 times the rate of PTB compared to women with an IPI of 10 or more months in crude analysis. This effect was no long present once we added potential confounders into the model. One of the main contributors for a lack of statical significance could be due to the either incorrect window selection or due to the inadequate numbers in our study population. Evidence that the window selection method we utilized were inadequate was most evident in the previous early pregnancy loss group, where the selection method yielded a window of 0-to-3 months. This window was too restrictive and required that we expand the window to 0-to-9 months to see a statistically significant effect due to small numbers. A future study needs to consider study designs which allow for large enough sample sizes and improve upon IPI window selection.

This study reinforced previous finding on the effect of previous preterm births on the risk of subsequent preterm birth, with the women with a previous preterm birth seeing over triple the rate of preterm births compared to women with a previous term birth. Additionally, women with an early pregnancy loss experienced over double the rate of preterm births compared to women with a previous term birth. For families planning to expand their families, this is an element to take into consideration but not an actionable item. Thus, it is necessary for policy makers and clinicians to be able to provide information that is actionable and appropriate to the families according to their circumstances, needs, and wants.

The strengths of this study were that is implemented a novel method of approaching identification of the optimal IPI window utilizing spline curves, utilized a diverse and international cohort of women

who were recruited and followed in a uniform and systematic method, incorporated maternal recall of previous pregnancies, and included a large representation of women from developing countries, which are typically underrepresenting in the literature. Previous studies have replied on the use of predetermined IPI categories, with a reference period identified by Zhu et al, with the assumption that the chosen intervals adequately captured with the true shape of the curve. The flaw to continuing this method is that this assumption has not been proven, and ultimately the use of the intervals is done because these studies are searching for an optimal IPI. Our own data showed that using pre-existing IPIs, the 18-to-23-month period had the lowest rates of PTB – placing the theoretical lowest point of the curve at ~20.5 months.

One of the elements of our study that was of interest were the shapes of the curves for the different previous pregnancy outcomes. Women with an immediately previous term birth, Figure 15 below, exhibited a similar shape to the curves produced previous in the literature, however women with a immediately previous loss, Figure 17 below, exhibited significantly different curve. The lack of a 'J-shaped" curve is interesting and indicates that there is a fundamental difference between women with an immediately previous live vs non-live birth. Furthermore, the flatness of the curve in Figure 17 below from ~20 months raise concerns. It is unclear whether the flatness of the curve comes from a small sample size, or represents the true level of risk present in the population.

The lack of a found association between IPI and preterm birth in our adjusted models and in the crude analysis for women with previous term and preterm births does not indicate that there is no real connection, but rather may be due to the limited size of our sample. This is shown in that the crude analysis for women with previous early pregnancy loss found that an IPI of less than 10 months was protective against the risk of preterm birth. The spline curves also reinforced what previous studies had identified with a "J-shaped" relationship between IPI and preterm birth. The traditional argument of maternal depletion has been used to explain the potential reason why short IPIs higher risk of preterm births had, however this explanation does not help explain why women with a previous early pregnancy loss do not suffer from short IPIs, but rather benefit, and why the "J-shaped" relationship exist at all.

Some studies conjecture that maternal age was the driving force behind the upward inflection in risk for preterm birth for women with long IPIs, however this has been shown to not be the significant driver of higher PTB rates among IPIs(53,89). Potential explanation of why optimal IPI may exist is that a woman's readiness for pregnancy may differ depending on the level of depletion of reserves of nutrients from the previous pregnancy, with depletion being proportional to the length of gestation of the previous pregnancy. However, the readiness for pregnancy is not sustainable indefinitely, and the body must return to a normal state. This would account for the elevated risk of preterm birth in both the short and long periods of IPI, as well as account for the trend of the leftward shift of optimal IPIs for shorter gestational lengths of previous pregnancies. Future studies need to investigate whether nutritional levels differ for women with different IPIs and previous pregnancy outcomes.

Current recommendations from the WHO have identified an IPI of less than two years as harmful for women with a previous live birth and to avoid an IPI of less than 6 months for women with a termination or loss. These recommendations are potentially problematic, as this study shows that an IPI of less than 9 months is protective for women with a previous early pregnancy loss, meaning that these recommendations are pushing women into higher periods of risk unnecessarily. While this study was not able to statistically prove the selected windows for the women with previous term or preterm births, the lowest points of the spline curves were below the 24 months WHO minimum. This suggest that the WHO's recommendation is potentially shifting women into a higher risk group than is necessary, and this is supported by the work of Conde-Agudelo et al., who found in their seminal study found that short IPIs of 12 to 23 months had to lowest rates of preterm birth(18). These recommendations were created with the intent of avoiding short IPI, ignoring the risk of longer IPIs, and thus assume that selecting a short IPI cut-off that is above the found minimums is safe due to uniform risk after their defined short IPI. Future recommendations need to consider the role long IPIs have in the risk of preterm birth.

This study has shown that new methods of approaching IPI may be necessary, rather than relying on 6-month intervals, as previously developed by Zhu et al. and popularized by Conde-Agudelo et al(18,20).

The use of 6-month intervals was done due to the uncertainty regarding optimal IPI, and the "18 to 23" month interval was chosen as reference due to its low rate of preterm birth. The issue that developed from this method was that future studies continued to utilize these intervals without consideration as to whether these intervals accurately captured the true shape of the risk curve. In the case of this study, we found that for women with a previous early pregnancy loss that 6-month window did not adequately capture the optimal IPI window. We hope that future studies take into consideration the shape of the IPI curve and the role of pregnancy history on optimal IPI.

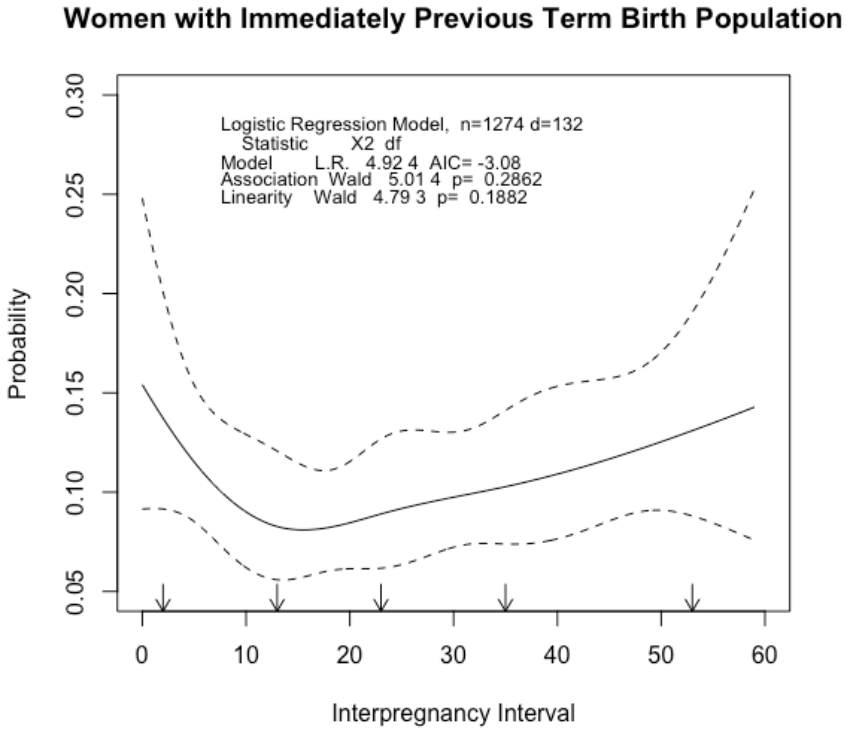


Figure 15. Restricted cubic spline of the probability of preterm birth by IPI - immediately previous term birth

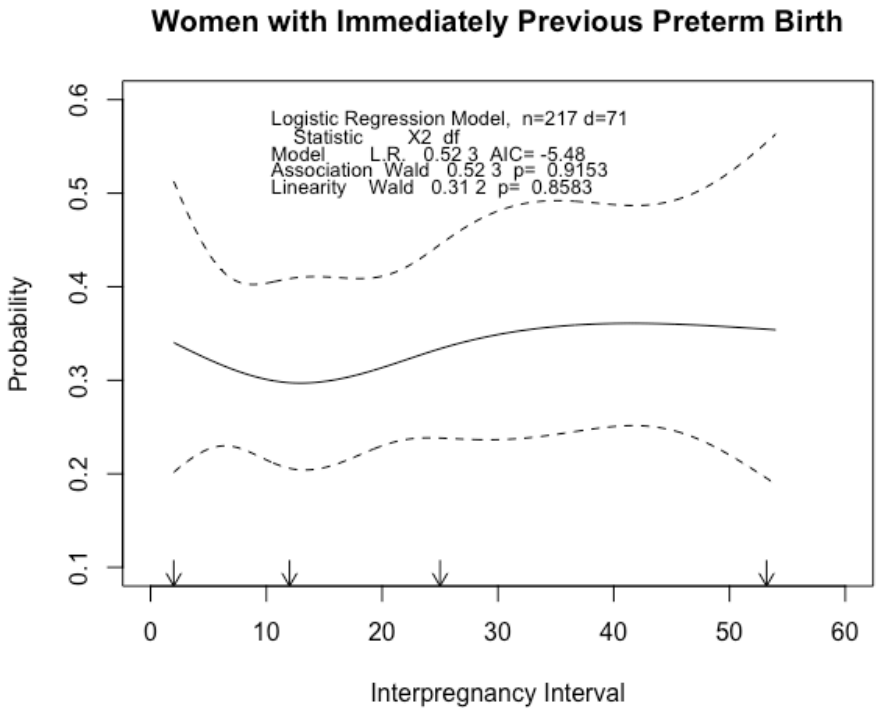


Figure 16. Restricted Cubic Spline of The Probability Of Preterm Birth By IPI - Immediately Previous Preterm Birth

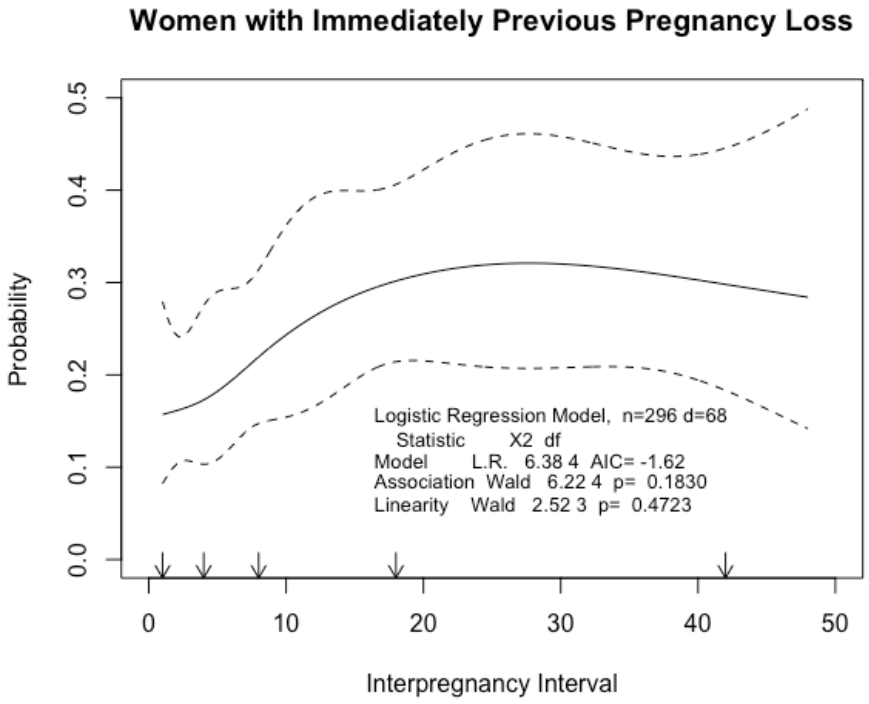


Figure 17. Restricted Cubic Spline of The Probability Of Preterm Birth By IPI - Immediately Previous Early Pregnancy Loss

Table 6. Distributions Of Maternal Characteristics of the Fetal Study

Variable	N	Full-term Birth, N = 1,516[1]	Preterm Birth, N = 271[1]	p-value[2]
Interpregnancy Interval	1,787	23 (16)	22 (16)	0.6
Conde-Agudelo Intervals	1,787			0.7
0 to 5		247 (83%)	51 (17%)	
6 to 11		207 (83%)	41 (17%)	
12 to 17		215 (86%)	35 (14%)	
18 to 23		206 (87%)	31 (13%)	
24 to 59		641 (85%)	113 (15%)	
WHO Intervals	1,787			0.9
More than 2 Years		641 (85%)	113 (15%)	
Less than 2 Years		875 (85%)	158 (15%)	
Standard IPI	1,787			0.4
0 to 11		454 (83%)	92 (17%)	
12 to 24		448 (86%)	72 (14%)	
25 to 59		614 (85%)	107 (15%)	
City, Country	1,787			<0.001
Karachi, Pakistan		276 (78%)	80 (22%)	
Mae Sot, Thailand		255 (94%)	17 (6.2%)	
Nairobi, Kenya		282 (93%)	22 (7.2%)	
Oxford, UK		356 (89%)	42 (11%)	
Pelotas, Brazil		90 (90%)	10 (10%)	
Soweto, South Africa		257 (72%)	100 (28%)	

Previous Pregnancy Outcome	1,787			<0.001
Term		1,142 (90%)	132 (10%)	
Preterm		146 (67%)	71 (33%)	
Loss		228 (77%)	68 (23%)	
Maternal Age	1,787	30.1 (4.7)	29.8 (4.5)	0.2
Age at Previous Pregnancy	1,707	27.6 (4.7)	27.4 (4.4)	0.3
Missing		75	5	
Maternal Age Group 10-year Intervals	1,787			0.11
20 to 29		653 (83%)	131 (17%)	
30 to 40		863 (86%)	140 (14%)	
Maternal Age Group 5-year Intervals	1,787			0.016
25 to 29		440 (81%)	103 (19%)	
20 to 24		213 (88%)	28 (12%)	
30 to 34		573 (85%)	98 (15%)	
35 to 40		290 (87%)	42 (13%)	
Previous Pregnancy Maternal Age Group 10-year Intervals	1,787			0.13
29 or less		933 (84%)	180 (16%)	
30 to 40		583 (86%)	91 (14%)	

Previous Pregnancy Maternal Age Group 5-year Intervals	1,787			0.3
24 or less		401 (85%)	70 (15%)	
25 to 29		532 (83%)	110 (17%)	
30 to 34		452 (86%)	74 (14%)	
35 to 40		131 (89%)	17 (11%)	
Pre-pregnancy BMI	1,787			0.061
Normal		726 (87%)	112 (13%)	
Underweight		75 (89%)	9 (11%)	
Overweight		497 (83%)	99 (17%)	
Obese		218 (81%)	51 (19%)	
Marital Status	1,787			<0.001
Not Married/Cohabiting		174 (72%)	66 (28%)	
Married/Cohabiting		1,342 (87%)	205 (13%)	
Highest Education Attained	1,786			<0.001
Less than Highschool		225 (92%)	20 (8.2%)	
Highschool		433 (79%)	115 (21%)	
Professional or University		857 (86%)	136 (14%)	
Missing			1	0
Occupational Status	1,787			<0.001
Student/Housework/Other		724 (82%)	163 (18%)	
Blue-Collar		137 (81%)	32 (19%)	
White-Collar		655 (90%)	76 (10%)	

Tobacco Use During Pregnancy	1,787				0.032
No Tobacco Use		1,415 (85%)	243 (15%)		
Tobacco Use		101 (78%)	28 (22%)		
Alcohol Use During Pregnancy	1,787				0.004
No Alcohol Use		1,480 (85%)	256 (15%)		
Alcohol Use		36 (71%)	15 (29%)		
Gravida	1,778				<0.001
1		703 (90%)	79 (10%)		
2		408 (83%)	83 (17%)		
3 or more		402 (80%)	103 (20%)		
Missing			3	6	
Parity	1,786				<0.001
0		224 (78%)	65 (22%)		
1		828 (88%)	110 (12%)		
2		297 (83%)	60 (17%)		
3 or more		167 (83%)	35 (17%)		
Missing			0	1	
Number of Previous Terminations	1,787				0.069
None		1,403 (85%)	242 (15%)		
Any		113 (80%)	29 (20%)		
Number of Previous Miscarriages	1,787				<0.001
0		904 (88%)	125 (12%)		

1		406 (84%)	75 (16%)	
2		148 (77%)	44 (23%)	
3 or more		58 (68%)	27 (32%)	
Any Previous **Stillbirths**	1,787	67 (71%)	27 (29%)	<0.001
Mode of Delivery	1,787			0.002
Vaginal or Other		970 (87%)	146 (13%)	
Caesarean		546 (81%)	125 (19%)	
Onset of Labour	1,787			<0.001
		0 (0%)	10 (100%)	
Induced		230 (85%)	40 (15%)	
No labour		366 (81%)	84 (19%)	
Spontaneous		920 (87%)	137 (13%)	
Any Morbidities Before Current Pregnancy	1,786			<0.001
0		971 (87%)	144 (13%)	
1		545 (81%)	126 (19%)	
Missing			0	1
Any Morbidities Before and During Current Pregnancy	1,776			0.013
0		956 (87%)	143 (13%)	
1		560 (83%)	117 (17%)	

Missing			0	11	
Any Pregnancy Related Complications of Current Pregnancy	1,772				<0.001
	0	1,141 (89%)	136 (11%)		
	1	375 (76%)	120 (24%)		
Missing			0	15	
[1] Mean (SD); n (%)					
[2] Wilcoxon rank sum test; Pearson's Chi-squared test; Fisher's exact test					

Table 7. Distributions of maternal characteristics in neonatal study

Variable	**N**	**Full-term Birth**, N = 1,341[1]	**Preterm Birth**, N = 380[1]	**p-value**[2]
Interpregnancy Interval	1,721	25 (16)	23 (16)	0.021
Conde-Agudelo Intervals	1,721			0.001
0 to 5		150 (71%)	60 (29%)	
6 to 11		185 (78%)	53 (22%)	
12 to 17		168 (77%)	50 (23%)	
18 to 23		152 (71%)	62 (29%)	
24 to 59		686 (82%)	155 (18%)	
WHO Intervals	1,721			<0.001
More than 2 Years		686 (82%)	155 (18%)	
Less than 2 Years		655 (74%)	225 (26%)	
Standard IPI	1,721			0.008

0 to 11		335 (75%)		113 (25%)	
12 to 24		353 (75%)		116 (25%)	
25 to 59		653 (81%)		151 (19%)	
City, Country	1,721				
Kilifi, Kenya		244 (81%)		57 (19%)	
Mae Sot, Thailand		287 (88%)		41 (12%)	
Nairobi, Kenya		237 (72%)		94 (28%)	
Oxford, UK		456 (78%)		129 (22%)	
Pelotas, Brazil		112 (65%)		59 (35%)	
Soweto, South Africa		5 (100%)		0 (0%)	
Previous Pregnancy Outcome	1,721				<0.001
Term		1,103 (82%)		236 (18%)	
Preterm		95 (52%)		89 (48%)	
Loss		143 (72%)		55 (28%)	
Maternal Age	1,721	29.6 (5.2)		29.4 (5.2)	0.6
Age at Previous Pregnancy	1,512	27.0 (5.3)		26.8 (5.3)	0.5
Missing			186	23	
Maternal Age Group 10-year Intervals	1,721				0.5
20 to 29		645 (77%)		190 (23%)	
30 to 40		696 (79%)		190 (21%)	
Maternal Age Group 5-year Intervals	1,721				>0.9
25 to 29		380 (78%)		110 (22%)	
20 to 24		265 (77%)		80 (23%)	

30 to 34		418 (78%)	116 (22%)	
35 to 40		278 (79%)	74 (21%)	
Previous Pregnancy Maternal Age Group 10-year Intervals	1,721			>0.9
29 or less		871 (78%)	246 (22%)	
30 to 40		470 (78%)	134 (22%)	
Previous Pregnancy Maternal Age Group 5-year Intervals	1,721			>0.9
24 or less		466 (78%)	135 (22%)	
25 to 29		405 (78%)	111 (22%)	
30 to 34		357 (78%)	102 (22%)	
35 to 40		113 (78%)	32 (22%)	
Pre-pregnancy BMI	1,696			0.7
Normal		669 (79%)	181 (21%)	
Underweight		74 (80%)	18 (20%)	
Overweight		361 (77%)	110 (23%)	
Obese		218 (77%)	65 (23%)	
Missing		19	6	
Marital Status	1,721			0.027
Not Married/Cohabiting		58 (68%)	27 (32%)	
Married/Cohabiting		1,283 (78%)	353 (22%)	
Highest Education Attained	1,720			0.2
Less than Highschool		429 (80%)	105 (20%)	
Highschool		348 (75%)	113 (25%)	

Professional or University		564 (78%)		161 (22%)	
Missing			0	1	
Occupational Status	1,720				0.14
Student/Housework/Other		618 (77%)		186 (23%)	
Blue-Collar		185 (83%)		38 (17%)	
White-Collar		537 (77%)		156 (23%)	
Missing			1	0	
Tobacco Use During Pregnancy	1,721				0.14
No Tobacco Use		1,201 (78%)		330 (22%)	
Tobacco Use		140 (74%)		50 (26%)	
Alcohol Use During Pregnancy	1,719				0.2
No Alcohol Use		1,320 (78%)		370 (22%)	
Alcohol Use		20 (69%)		9 (31%)	
Missing			1	1	
Gravida	1,718				0.075
1		588 (79%)		153 (21%)	
2		376 (79%)		97 (21%)	
3 or more		375 (74%)		129 (26%)	
Missing			2	1	
Parity	1,721				<0.001
0		136 (72%)		52 (28%)	
1		657 (79%)		175 (21%)	
2		332 (83%)		67 (17%)	
3 or more		216 (72%)		86 (28%)	

Number of Previous Terminations	1,721			0.2
None		1,256 (78%)	349 (22%)	
Any		85 (73%)	31 (27%)	
Number of Previous Miscarriages	1,721			0.034
0		918 (79%)	241 (21%)	
1		318 (76%)	100 (24%)	
2		82 (77%)	24 (23%)	
3 or more		23 (61%)	15 (39%)	
Any Previous Stillbirths	1,721	55 (66%)	28 (34%)	0.009
Mode of Delivery	1,721			<0.001
Vaginal or Other		937 (81%)	214 (19%)	
Caesarean		404 (71%)	166 (29%)	
Onset of Labour	1,721			0.014
Induced		213 (78%)	59 (22%)	
No labour		326 (73%)	120 (27%)	
Spontaneous		802 (80%)	201 (20%)	
Any Morbidities Before Current Pregnancy	1,721			0.065
0		877 (79%)	229 (21%)	
1		464 (75%)	151 (25%)	
Any Morbidities Before and During Current Pregnancy	1,721			0.009
0		864 (80%)	217 (20%)	
1		477 (75%)	163 (25%)	

Any Pregnancy Related Complications of Current Pregnancy	1,721			<0.001
	0	974 (88%)	129 (12%)	
	1	367 (59%)	251 (41%)	
[1] Mean (SD); n (%)				
[2] Wilcoxon rank sum test; Pearson's Chi-squared test				

Table 8. Fetal study population, Poisson regression of interpregnancy intervals and preterm birth by previous pregnancy outcome

	Term				Preterm			
	Crude		Full		Crude		Full	
Preterm Birth								
IPI (Months)								
0 to 11	1.236	[0.776,1.969]	0.915	[0.573,1.462]	1.315	[0.760,2.276]	1.058	[0.600,1.865]
12 to 23	1	[1,1]	1	[1,1]	1	[1,1]	1	[1,1]
24 to 59	1.089	[0.723,1.642]	0.973	[0.634,1.493]	1.494	[0.888,2.514]	1.913*	[1.075,3.404]
City, Country								
Karachi, Pakistan			5.380**	[1.936,14.95]			0.846	[0.263,2.716]
Mae Sot, Thailand			1	[1,1]			1	[1,1]
Nairobi, Kenya			2.711	[0.809,9.083]			0.81	[0.141,4.660]
Oxford, UK			1.734	[0.589,5.102]			0.876	[0.256,3.002]
Pelotas, Brazil			4.331*	[1.413,13.27]			0.000000361***	[9.00e-08,0.00000145]
			6.977***	[2.432,20.02]			0.957	[0.265,3.464]
Maternal Age Group 10-year Intervals								
20 to 29			1	[1,1]			1	[1,1]
30 to 40			1.041	[0.664,1.633]			0.585	[0.315,1.086]
Previous Pregnancy Maternal Age Group 10-year Intervals								
29 or less			1	[1,1]			1	[1,1]
30 to 40			0.825	[0.520,1.307]			1.267	[0.701,2.291]

Pre-pregnancy BMI				
Normal	1	[1,1]	1	[1,1]
Underweight	1.666	[0.758,3.660]	0.579	[0.118,2.839]
Overweight	1.094	[0.731,1.638]	0.663	[0.418,1.050]
Obese	1.151	[0.722,1.834]	0.437*	[0.222,0.860]
Marital Status				
Not Married/Cohabiting	1	[1,1]	1	[1,1]
Married/Cohabiting	1.668	[0.948,2.936]	0.973	[0.471,2.009]
Highest Education Attained				
Less than Highschool	1	[1,1]	1	[1,1]
Highschool	1.154	[0.534,2.495]	1.421	[0.511,3.951]
Professional or University	0.897	[0.389,2.067]	1.532	[0.514,4.566]
Student/Housework/Other	1	[1,1]	1	[1,1]
Occupational Status				
Blue-Collar	1.262	[0.751,2.119]	0.792	[0.433,1.446]
White-Collar	0.888	[0.530,1.490]	0.945	[0.524,1.704]
Tobacco Use During Pregnancy				
No Tobacco Use	1	[1,1]	1	[1,1]
Tobacco Use	1.127	[0.592,2.144]	2.407*	[1.211,4.785]

Alcohol Use During Pregnancy				
No Alcohol Use	1	[1,1]	1	[1,1]
Alcohol Use	0.905	[0.358,2.290]	0.62	[0.165,2.330]
Gravida				
1	1	[1,1]	1	[1,1]
2	1.475	[0.749,2.904]	1.938	[0.944,3.977]
3 or more	1.755	[0.654,4.707]	1.925	[0.521,7.109]
Parity				
0				
1	1	[1,1]	1	[1,1]
2	1.02	[0.588,1.770]	0.738	[0.368,1.481]
3 or more	1.339	[0.619,2.899]	0.848	[0.257,2.793]
Number of Previous Terminations				
None	1	[1,1]	1	[1,1]
Any	1.123	[0.567,2.224]	0.773	[0.386,1.546]
Number of Previous Miscarriages				
0	1	[1,1]	1	[1,1]
1	1.087	[0.618,1.911]	0.776	[0.423,1.425]
2	1.047	[0.450,2.437]	0.948	[0.266,3.376]

3 or more		1.006	[0.390,2.598]	1.603	[0.480,5.350]
Any Previous **Stillbirths**					
None		1	[1,1]	1	[1,1]
Any		0.651	[0.303,1.400]	1.976**	[1.217,3.208]
Mode of Delivery					
Vaginal or Other		1	[1,1]	1	[1,1]
Caesarean		1.498	[0.912,2.462]	1.118	[0.630,1.985]
Onset of Labour					
Induced		1	[1,1]	1	[1,1]
No labour		1	[0.499,2.002]	0.733	[0.342,1.572]
Spontaneous		1.587	[0.872,2.890]	0.805	[0.412,1.572]
Any Morbidities Before Current Pregnancy					
None		1	[1,1]	1	[1,1]
Any		1.168	[0.802,1.703]	1.504	[0.982,2.303]
	1264				
Any Morbidities Before and During Current Pregnancy					
None	2	1	[1,1]	1	[1,1]
Any		1.109	[0.767,1.605]	1.153	[0.777,1.711]

Any Pregnancy Related Complications of Current Pregnancy					
None	1	[1,1]		1	[1,1]
Any	2.014***	[1.383,2.932]		2.100**	[1.330,3.316]
Observations	1264		216	216	
df_m					
df_r	34		2	34	
Exponentiated coefficients; 95% confidence intervals in brackets					
* p < 0.05, ** p < 0.01, *** p < 0.001					
* p < 0.05, ** p < 0.01, *** p < 0.001					

Table 9. Fetal study population, Poisson regression of interpregnancy intervals and preterm birth by previous pregnancy outcome

	Early Pregnancy Loss			
	Crude		Full	
Preterm Birth				
IPI (Months)				
0 to 11	0.731	[0.416,1.282]	1.026	[0.552,1.909]
12 to 23	1	[1,1]	1	[1,1]
24 to 59	1.096	[0.569,2.110]	1.136	[0.553,2.333]
City, Country				
Karachi, Pakistan			1.98	[0.494,7.932]
Mae Sot, Thailand			1	[1,1]
Nairobi, Kenya			2.61	[0.534,12.76]
Oxford, UK			0.737	[0.129,4.206]
Pelotas, Brazil			0.394	[0.0332,4.668]
			3.888	[0.913,16.55]
Maternal Age Group 10-year Intervals				
20 to 29			1	[1,1]
30 to 40			0.787	[0.328,1.888]
Previous Pregnancy Maternal Age Group				
10-year Intervals				
29 or less			1	[1,1]
30 to 40			1.137	[0.415,3.117]
Pre-pregnancy BMI				
Normal			1	[1,1]
Underweight			0.866	[0.163,4.602]
Overweight			1.524	[0.816,2.846]
Obese			1.676	[0.836,3.361]
Marital Status				
Not Married/Cohabiting			1	[1,1]
Married/Cohabiting			0.908	[0.491,1.682]
Highest Education Attained				

Less than Highschool	1	[1,1]
Highschool	0.484	[0.133,1.760]
Professional or University	0.546	[0.152,1.957]
Student/Housework/Other	1	[1,1]
Occupational Status		
Blue-Collar	1.292	[0.594,2.812]
White-Collar	0.774	[0.412,1.453]
Tobacco Use During Pregnancy		
No Tobacco Use	1	[1,1]
Tobacco Use	1.498	[0.639,3.512]
Alcohol Use During Pregnancy		
No Alcohol Use	1	[1,1]
Alcohol Use	1.549	[0.684,3.506]
Gravida		
1	1	[1,1]
2	1.085	[0.0986,11.93]
3 or more	4.51	[0.101,201.2]
Parity		
0	1	[1,1]
1	0.00000306***	[9.73e-08,0.0000962]
2	15.49	[0.0929,2582.7]
3 or more	0.000000562***	[2.07e-09,0.000153]
Number of Previous Terminations		
None	1	[1,1]
Any	0.762	[0.0517,11.23]
Number of Previous Miscarriages		
0	1	[1,1]
1	0.887	[0.0511,15.39]
2	0.579	[0.00425,78.83]
3 or more	0.256	[0.000441,148.0]

Any Previous **Stillbirths**			
None		1	[1,1]
Any		226336.5***	[2389.0,21443794.0]
Mode of Delivery			
Vaginal or Other		1	[1,1]
Caesarean		0.744	[0.416,1.332]
Onset of Labour			
Induced		1	[1,1]
No labour		2.052	[0.869,4.845]
Spontaneous		1.132	[0.537,2.388]
Any Morbidities Before Current Pregnancy			
None		1	[1,1]
Any		1.044	[0.612,1.781]
Any Morbidities Before and During Current Pregnancy			
None		1	[1,1]
Any		0.956	[0.549,1.664]
Any Pregnancy Related Complications of Current Pregnancy			
None		1	[1,1]
Any		1.761*	[1.026,3.024]
Observations	282	282	
df_m			
df_r	2	35	
Exponentiated coefficients; 95% confidence intervals in brackets			
* p < 0.05, ** p < 0.01, *** p < 0.001			

Table 10. Neonatal study population, poisson regression by previous pregnancy outcome (term and preterm)

Preterm Birth	Term				Preterm			
	Crude		Full		Crude		Full	
IPI (Months)								
0 to 11	0.809	[0.590,1.109]	0.652*	[0.469,0.906]	1.21	[0.819,1.787]	1.016	[0.694,1.486]
12 to 23	1	[1,1]	1	[1,1]	1	[1,1]	1	[1,1]
24 to 59	0.666**	[0.512,0.865]	0.690**	[0.538,0.887]	0.853	[0.568,1.281]	0.852	[0.570,1.273]
City, Country								
Kilifi, Kenya			1.731*	[1.069,2.804]			1.409	[0.681,2.916]
Mae Sot, Thailand			1	[1,1]			1	[1,1]
Nairobi, Kenya			3.994***	[2.328,6.853]			2.094*	[1.108,3.956]
Oxford, UK			2.074**	[1.246,3.451]			1.479	[0.809,2.705]
Pelotas, Brazil			2.219**	[1.372,3.588]			1.037	[0.512,2.100]

Maternal Age Group 10-year Intervals				
20 to 29	1	[1,1]	1	[1,1]
30 to 40	0.887	[0.644,1.223]	0.792	[0.453,1.384]
Previous Pregnancy Maternal Age Group 10-year Intervals				
29 or less	1	[1,1]	1	[1,1]
30 to 40	1.11	[0.807,1.527]	1.142	[0.628,2.074]
Pre-pregnancy BMI				
Normal	1	[1,1]	1	[1,1]
Underweight	1.194	[0.691,2.063]	1.403	[0.669,2.946]
Overweight	1.006	[0.774,1.308]	1.015	[0.684,1.505]
Obese	0.829	[0.622,1.104]	0.520**	[0.318,0.850]

Marital Status				
Not Married/Cohabiting	1	[1,1]	1	[1,1]
Married/Cohabiting	0.659	[0.411,1.055]	1.003	[0.425,2.368]
Highest Education Attained				
Less than Highschool	1	[1,1]	1	[1,1]
Highschool	0.721	[0.508,1.025]	1.305	[0.702,2.428]
Professional or University	0.591*	[0.373,0.937]	1.094	[0.477,2.507]
Student/Housework/Other				
Occupational Status	1	[1,1]	1	[1,1]
Blue-Collar	0.640*	[0.423,0.967]	1.008	[0.585,1.736]
White-Collar	0.961	[0.719,1.284]	0.989	[0.611,1.600]

Tobacco Use During Pregnancy				
No Tobacco Use	1	[1,1]	1	[1,1]
Tobacco Use	0.894	[0.629,1.271]	0.898	[0.535,1.505]
Alcohol Use During Pregnancy				
No Alcohol Use	1	[1,1]	1	[1,1]
Alcohol Use	1.452	[0.802,2.629]	9.47e-08***	[1.55e-08,0.000000579]
Gravida				
1	1	[1,1]	1	[1,1]
2	0.983	[0.634,1.524]	1.186	[0.646,2.177]
3 or more	0.734	[0.372,1.449]	0.897	[0.364,2.207]
Parity				
0				

1	1	[1,1]	1	[1,1]
2	0.891	[0.574,1.383]	0.994	[0.553,1.787]
3 or more	1.787	[0.976,3.272]	1.807	[0.752,4.342]
Number of Previous Terminations				
None	1	[1,1]	1	[1,1]
Any	0.688	[0.376,1.259]	1.407	[0.864,2.290]
Number of Previous Miscarriages				
0	1	[1,1]	1	[1,1]
1	1.358	[0.943,1.954]	1.072	[0.641,1.793]
2	1.032	[0.589,1.808]	1.027	[0.359,2.943]
3 or more	1.347	[0.650,2.791]	1.757	[0.627,4.926]
Any Previous Stillbirths				
None	1	[1,1]	1	[1,1]

Any	1.045	[0.655,1.667]	0.862	[0.545,1.364]
Mode of Delivery				
Vaginal or Other	1	[1,1]	1	[1,1]
Caesarean	2.364***	[1.710,3.268]	1.112	[0.641,1.928]
Onset of Labour				
Induced	1	[1,1]	1	[1,1]
No labour	0.545**	[0.360,0.825]	1.872	[0.877,3.995]
Spontaneous	1.241	[0.863,1.786]	2.363*	[1.133,4.929]
Any Morbidities Before Current Pregnancy				
None	1	[1,1]	1	[1,1]
Any	0.994	[0.769,1.285]	0.946	[0.658,1.360]

Any Morbidities Before and During Current Pregnancy						
None		1	[1,1]		1	[1,1]
Any		1.192	[0.921,1.541]		0.993	[0.708,1.393]
Any Pregnancy Related Complications of Current Pregnancy						
None		1	[1,1]		1	[1,1]
Any		3.992***	[3.029,5.260]		2.015***	[1.352,3.004]
Observations		1316		184	183	
df_m	1335					
df_r		33		2	33	
Exponentiated coefficients; 95% confidence intervals in brackets	2					

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

Table 11. Neonatal study population, poisson regression, interpregnancy interval and preterm birth by previous pregnancy outcome (loss)

	Loss			
Preterm Birth	Crude		Full	
IPI (Months)				
0 to 11	0.787	[0.467,1.326]	0.656	[0.389,1.106]
12 to 23	1	[1,1]	1	[1,1]
24 to 59	0.865	[0.451,1.661]	0.6	[0.319,1.131]
City, Country				
Kilifi, Kenya			0.418	[0.127,1.372]
Mae Sot, Thailand			1	[1,1]
Nairobi, Kenya			1.369	[0.338,5.537]
Oxford, UK			0.627	[0.187,2.099]
Pelotas, Brazil			1.221	[0.339,4.400]
Maternal Age Group 10-year Intervals				
20 to 29			1	[1,1]
30 to 40			1.297	[0.596,2.823]
Previous Pregnancy Maternal Age Group 10-year Intervals				
29 or less			1	[1,1]

30 to 40		0.452	[0.188,1.085]
Pre-pregnancy BMI			
Normal		1	[1,1]
Underweight	0.350*		[0.131,0.939]
Overweight	0.460*		[0.247,0.856]
Obese		1.095	[0.596,2.012]
Marital Status			
Not Married/Cohabiting		1	[1,1]
Married/Cohabiting		0.641	[0.289,1.423]
Highest Education Attained			
Less than Highschool		1	[1,1]
Highschool		0.848	[0.297,2.421]
Professional or University		1.057	[0.274,4.080]
Student/Housework/Other			
Occupational Status		1	[1,1]
Blue-Collar		0.669	[0.288,1.555]
White-Collar		0.862	[0.471,1.579]
Tobacco Use During Pregnancy			

No Tobacco Use		1	[1,1]
Tobacco Use		0.867	[0.325,2.312]
Alcohol Use During Pregnancy			
No Alcohol Use		1	[1,1]
Alcohol Use	4.368**		[1.704,11.20]
Gravida			
1		1	[1,1]
2		0.753	[0.230,2.468]
3 or more		0.817	[0.258,2.584]
Parity			
0		1	[1,1]
1	0.000000153***		[1.84e-08,0.00000127]
2	0.00000168***		[7.46e-08,0.0000378]
3 or more		2.353	[0.229,24.16]
Number of Previous Terminations			
None		1	[1,1]
Any		1.243	[0.366,4.221]
Number of Previous Miscarriages			

0		1	[1,1]
1		0.787	[0.216,2.863]
2		1.188	[0.168,8.391]
3 or more		5.112	[0.706,37.02]
Any Previous Stillbirths			
None		1	[1,1]
Any	0.000000175***		[2.26e-08,0.00000135]
Mode of Delivery			
Vaginal or Other		1	[1,1]
Caesarean	0.409*		[0.173,0.969]
Onset of Labour			
Induced		1	[1,1]
No labour	3.080*		[1.093,8.679]
Spontaneous	2.106*		[1.027,4.321]
Any Morbidities Before Current Pregnancy			
None		1	[1,1]
Any		0.776	[0.429,1.402]

Any Morbidities Before and During Current Pregnancy				
None			1	[1,1]
Any			1.22	[0.728,2.044]
Any Pregnancy Related Complications of Current Pregnancy				
None			1	[1,1]
Any		3.645***		[2.034,6.535]
Observations	198		190	
F				
df_m	2		34	
df_r				
Exponentiated coefficients; 95% confidence intervals in brackets				
* p < 0.05, ** p < 0.01, *** p < 0.001				

Table 12. Fetal study, new IPI intervals and preterm birth for women with a previous term birth

	Crude	95% CI	Full	95% CI
Preterm Birth				
IPI (Months)				

0 to 11	1.699	[0.929,3.105]	1.231	[0.664,2.282]
12 to 19	1	[1,1]	1	[1,1]
20 to 59	1.581	[0.913,2.738]	1.454	[0.818,2.584]
City, Country				
Karachi, Pakistan			1	[1,1]
Mae Sot, Thailand			0.179***	[0.0645,0.495]
Nairobi, Kenya			0.499	[0.230,1.085]
Oxford, UK			0.322***	[0.172,0.606]
Pelotas, Brazil			0.76	[0.350,1.652]
			1.269	[0.720,2.237]
Maternal Age Group 10-year Intervals				
20 to 29				
30 to 40			1	[1,1]
			0.985	[0.629,1.540]
Previous Pregnancy Maternal Age Group 10-year Intervals				
29 or less				
30 to 40			1	[1,1]
			0.874	[0.551,1.384]
Pre-pregnancy BMI				
Normal				
Underweight			1	[1,1]
Overweight			1.643	[0.755,3.573]
Obese			1.086	[0.725,1.628]
			1.131	[0.714,1.793]

Marital Status		
Not Married/Cohabiting		
Married/Cohabiting	1	[1,1]
	1.665	[0.951,2.916]
Highest Education Attained		
Less than Highschool		
Highschool	1	[1,1]
Professional or University	1.159	[0.537,2.500]
Student/Housework/Other	0.906	[0.392,2.092]
Occupational Status		
Blue-Collar	1	[1,1]
White-Collar	1.243	[0.744,2.076]
	0.88	[0.527,1.470]
Tobacco Use During Pregnancy		
No Tobacco Use		
Tobacco Use	1	[1,1]
	1.123	[0.590,2.137]
Alcohol Use During Pregnancy		
No Alcohol Use		
Alcohol Use	1	[1,1]
	0.893	[0.352,2.264]
Gravida		
1		
2	1	[1,1]

3 or more	1.492	[0.759,2.935]
	1.758	[0.657,4.703]
Parity		
0		
1	1	[1,1]
2	1.005	[0.579,1.745]
3 or more	1.327	[0.615,2.862]
Number of Previous Terminations		
None	1	[1,1]
Any	1.165	[0.587,2.315]
Number of Previous Miscarriages		
0	1	[1,1]
1	1.098	[0.629,1.914]
2	1.07	[0.462,2.481]
3 or more	1.035	[0.403,2.660]
Any Previous **Stillbirths**		
None	1	[1,1]
Any	0.672	[0.314,1.440]
Mode of Delivery		
Vaginal or Other	1	[1,1]
Caesarean	1.482	[0.907,2.421]

Onset of Labour		
Induced	1	[1,1]
No labour	1.007	[0.506,2.004]
Spontaneous	1.597	[0.881,2.896]
Any Morbidities Before Current Pregnancy		
None	1	[1,1]
Any	1.138	[0.779,1.663]
Any Morbidities Before and During Current Pregnancy		
None	1	[1,1]
Any	1.111	[0.769,1.605]
Any Pregnancy Related Complications of Current Pregnancy		
None	1	[1,1]
Any	2.005***	[1.379,2.917]
Observations	1264	1264
df_m		
df_r	2	34
Exponentiated coefficients; 95% confidence intervals in brackets		
* p < 0.05, ** p < 0.01, *** p < 0.001		

Table 13. Fetal study, Poisson regression of new interpregnancy intervals and preterm birth, previous preterm birth

Preterm Birth	Crude	95% CI	Full	95% CI
IPI (Months)				

0 to 7	1.185	[0.685,2.050]	0.857	[0.485,1.514]
8 to 18	1	[1,1]	1	[1,1]
19 to 59	1.194	[0.759,1.878]	1.458	[0.892,2.385]
City, Country			1	[1,1]
Karachi, Pakistan			1.009	[0.322,3.158]
Mae Sot, Thailand			0.958	[0.206,4.464]
Nairobi, Kenya			0.953	[0.497,1.827]
Oxford, UK			0.00000134** *	[0.000000462,0.00000390]
Pelotas, Brazil			1.099	[0.511,2.363]
Maternal Age Group 10-year Intervals				
20 to 29			1	[1,1]
30 to 40			0.651	[0.358,1.186]
Previous Pregnancy Maternal Age Group 10-year Intervals				
29 or less			1	[1,1]
30 to 40			1.219	[0.671,2.214]
Pre-pregnancy BMI				
Normal			1	[1,1]
Underweight			0.59	[0.125,2.779]
Overweight			0.614*	[0.387,0.975]
Obese			0.451*	[0.223,0.914]

Marital Status			
Not Married/Cohabiting		1	[1,1]
Married/Cohabiting		0.962	[0.468,1.976]
Highest Education Attained			
Less than Highschool		1	[1,1]
Highschool		1.483	[0.524,4.201]
Professional or University		1.593	[0.521,4.874]
Student/Housework/Other			
Occupational Status		1	[1,1]
Blue-Collar		0.773	[0.413,1.444]
White-Collar		0.882	[0.482,1.616]
Tobacco Use During Pregnancy			
No Tobacco Use		1	[1,1]
Tobacco Use	2.535**		[1.270,5.058]
Alcohol Use During Pregnancy			
No Alcohol Use		1	[1,1]
Alcohol Use		0.612	[0.169,2.217]
Gravida			
1		1	[1,1]
2		1.774	[0.878,3.586]
3 or more		1.623	[0.484,5.438]

Parity			
1		1	[1,1]
2		0.808	[0.414,1.577]
3 or more		0.906	[0.303,2.710]
Number of Previous Terminations			
None		1	[1,1]
Any		0.701	[0.348,1.411]
Number of Previous Miscarriages			
0		1	[1,1]
1		0.802	[0.432,1.487]
2		1.123	[0.362,3.483]
3 or more		1.77	[0.561,5.587]
Any Previous **Stillbirths**			
None		1	[1,1]
Any	1.899*		[1.165,3.097]
Mode of Delivery			
Vaginal or Other		1	[1,1]
Caesarean		1.046	[0.578,1.894]
Onset of Labour			
Induced		1	[1,1]
No labour		0.723	[0.331,1.580]

Spontaneous			0.802	[0.402,1.598]
Any Morbidities Before Current Pregnancy				
None			1	[1,1]
Any		1.606*		[1.057,2.441]
Any Morbidities Before and During Current Pregnancy				
None			1	[1,1]
Any			1.071	[0.728,1.577]
Any Pregnancy Related Complications of Current Pregnancy				
None			1	[1,1]
Any		2.052**		[1.282,3.284]
Observations	216		216	
df_m				
df_r	2		34	
Exponentiated coefficients; 95% confidence intervals in brackets				
* p < 0.05, ** p < 0.01, *** p < 0.001				

Table 14. Fetal study, Poisson regression of new interpregnancy intervals and preterm birth, previous early pregnancy loss

Preterm Birth	Crude	95% CI	Full	95% CI
IPI (Months)				
0 to 9	1	[1,1]	1	[1,1]
10 to 59	0.596*	[0.372,0.955]	0.78	[0.449,1.354]
City, Country			1	[1,1]

Karachi, Pakistan	0.48	[0.125,1.849]
Mae Sot, Thailand	1.271	[0.407,3.965]
Nairobi, Kenya	0.374	[0.117,1.191]
Oxford, UK	0.189	[0.0329,1.080]
Pelotas, Brazil	1.737	[0.617,4.892]
Maternal Age Group 10-year Intervals		
20 to 29	1	[1,1]
30 to 40	0.759	[0.313,1.838]
Previous Pregnancy Maternal Age Group 10-year Intervals		
29 or less	1	[1,1]
30 to 40	1.188	[0.428,3.297]
Pre-pregnancy BMI		
Normal	1	[1,1]
Underweight	0.826	[0.155,4.392]
Overweight	1.505	[0.814,2.781]
Obese	1.635	[0.820,3.260]
Marital Status		
Not Married/Cohabiting	1	[1,1]
Married/Cohabiting	0.884	[0.474,1.647]
Highest Education Attained		
Less than Highschool	1	[1,1]

Highschool	0.501	[0.143,1.759]
Professional or University	0.554	[0.163,1.886]
Student/Housework/Other		
Occupational Status	1	[1,1]
Blue-Collar	1.308	[0.606,2.824]
White-Collar	0.765	[0.401,1.460]
Tobacco Use During Pregnancy		
No Tobacco Use	1	[1,1]
Tobacco Use	1.443	[0.605,3.442]
Alcohol Use During Pregnancy		
No Alcohol Use	1	[1,1]
Alcohol Use	1.529	[0.666,3.510]
Gravida		
1	1	[1,1]
2	1.142	[0.102,12.74]
3 or more	5.224	[0.113,242.3]
Parity		
0	1	[1,1]
1	0.00000275***	[9.46e-08,0.0000797]
2	12.94	[0.0762,2196.8]
3 or more	0.000000462***	[1.49e-09,0.000143]

Number of Previous Terminations		
None	1	[1,1]
Any	0.701	[0.0472,10.43]
Number of Previous Miscarriages		
0	1	[1,1]
1	0.823	[0.0481,14.09]
2	0.515	[0.00371,71.61]
3 or more	0.212	[0.000339,132.3]
Any Previous **Stillbirths**		
None	1	[1,1]
Any	264614.5***	[2966.6,23603157.8]
Mode of Delivery		
Vaginal or Other	1	[1,1]
Caesarean	0.745	[0.416,1.335]
Onset of Labour		
Induced	1	[1,1]
No labour	2.05	[0.868,4.842]
Spontaneous	1.175	[0.560,2.468]
Any Morbidities Before Current Pregnancy		
None	1	[1,1]
Any	1.011	[0.578,1.769]

Any Morbidities Before and During Current Pregnancy				
None			1	[1,1]
Any			0.949	[0.547,1.645]
Any Pregnancy Related Complications of Current Pregnancy				
None			1	[1,1]
Any		1.790*		[1.031,3.107]
Observations	282		282	
df_m				
df_r	1		34	
Exponentiated coefficients; 95% confidence intervals in brackets				
* p < 0.05, ** p < 0.01, *** p < 0.001				

Table 15. Neonatal study, Poisson regression of new interpregnancy intervals and preterm birth, previous term birth population

Preterm Birth	Crude	95% CI	Full	95% CI
IPI (Months)				
0 to 11	0.839	[0.591,1.192]	0.665*	[0.469,0.944]
12 to 19	1	[1,1]	1	[1,1]
20 to 59	0.748	[0.559,1.001]	0.763*	[0.584,0.996]
City, Country				
Kilifi, Kenya			1	[1,1]
Mae Sot, Thailand			0.575*	[0.356,0.929]
Nairobi, Kenya			2.421***	[1.436,4.082]
Oxford, UK			1.262	[0.751,2.120]

Pelotas, Brazil	1.306	[0.834,2.046]
Maternal Age Group 10-year Intervals		
20 to 29		
30 to 40	1	[1,1]
	0.854	[0.620,1.178]
Previous Pregnancy Maternal Age Group 10-year Intervals		
29 or less		
30 to 40	1	[1,1]
	1.146	[0.831,1.580]
Pre-pregnancy BMI		
Normal		
Underweight	1	[1,1]
Overweight	1.217	[0.703,2.108]
Obese	0.998	[0.767,1.297]
	0.819	[0.616,1.089]
Marital Status		
Not Married/Cohabiting		
Married/Cohabiting	1	[1,1]
	0.651	[0.408,1.036]
Highest Education Attained		
Less than Highschool		
Highschool	1	[1,1]
Professional or University	0.728	[0.514,1.031]

Student/Housework/Other	0.580*		[0.366,0.919]
Occupational Status			
Blue-Collar		1	[1,1]
White-Collar	0.633*		[0.420,0.956]
		0.947	[0.710,1.262]
Tobacco Use During Pregnancy			
No Tobacco Use			
Tobacco Use		1	[1,1]
		0.862	[0.607,1.225]
Alcohol Use During Pregnancy			
No Alcohol Use			
Alcohol Use		1	[1,1]
		1.523	[0.816,2.841]
Gravida			
1			
2		1	[1,1]
3 or more		0.99	[0.639,1.535]
		0.772	[0.390,1.528]
Parity			
0			
1		1	[1,1]
2		0.867	[0.559,1.347]
3 or more		1.723	[0.935,3.173]

Number of Previous Terminations		
None	1	[1,1]
Any	0.673	[0.369,1.227]
Number of Previous Miscarriages		
0	1	[1,1]
1	1.341	[0.933,1.927]
2	0.991	[0.558,1.761]
3 or more	1.335	[0.648,2.752]
Any Previous Stillbirths		
None	1	[1,1]
Any	1.057	[0.664,1.682]
Mode of Delivery		
Vaginal or Other	1	[1,1]
Caesarean	2.321***	[1.686,3.195]
Onset of Labour		
Induced	1	[1,1]
No labour	0.550**	[0.364,0.831]
Spontaneous	1.243	[0.864,1.790]
Any Morbidities Before Current Pregnancy		
None	1	[1,1]
Any	0.99	[0.765,1.282]

Any Morbidities Before and During Current Pregnancy				
None			1	[1,1]
Any			1.178	[0.911,1.523]
Any Pregnancy Related Complications of Current Pregnancy				
None			1	[1,1]
Any			4.010***	[3.047,5.277]
Observations	1339		1316	
df_m				
df_r	2		33	
Exponentiated coefficients; 95% confidence intervals in brackets				
* p < 0.05, ** p < 0.01, *** p < 0.001				

Table 16. Neonatal study, Poisson regression of new interpregnancy intervals and preterm birth, previous preterm birth population

Preterm Birth	Crude	95% CI	Full	95% CI
IPI (Months)				
0 to 11	1.304	[0.869,1.956]	1.363	[0.893,2.079]
12 to 19	1	[1,1]	1	[1,1]
20 to 59	0.873	[0.585,1.301]	1.062	[0.674,1.674]
City, Country				
Kilifi, Kenya			1	[1,1]
Mae Sot, Thailand			0.747	[0.358,1.561]
Nairobi, Kenya			1.571	[0.666,3.703]

Oxford, UK		1.139	[0.498,2.604]
Pelotas, Brazil		0.77	[0.351,1.691]
Maternal Age Group 10-year Intervals			
20 to 29		1	[1,1]
30 to 40		0.779	[0.449,1.351]
Previous Pregnancy Maternal Age Group 10-year Intervals			
29 or less		1	[1,1]
30 to 40		1.227	[0.685,2.197]
Pre-pregnancy BMI			
Normal		1	[1,1]
Underweight		1.239	[0.588,2.607]
Overweight		0.984	[0.667,1.452]
Obese	0.513**		[0.314,0.839]
Marital Status			
Not Married/Cohabiting		1	[1,1]
Married/Cohabiting		0.961	[0.402,2.295]
Highest Education Attained			
Less than Highschool		1	[1,1]
Highschool		1.229	[0.657,2.298]
Professional or University		1.039	[0.459,2.354]
Student/Housework/Other			
Occupational Status		1	[1,1]

Blue-Collar	1.03	[0.605,1.754]
White-Collar	0.985	[0.616,1.575]
Tobacco Use During Pregnancy		
No Tobacco Use	1	[1,1]
Tobacco Use	0.897	[0.536,1.500]
Alcohol Use During Pregnancy		
No Alcohol Use	1	[1,1]
Alcohol Use	0.000000305***	[5.01e-08,0.00000186]
Gravida		
1	1	[1,1]
2	1.168	[0.629,2.169]
3 or more	0.882	[0.356,2.186]
Parity		
0	1	[1,1]
1	0.968	[0.542,1.728]
2	1.789	[0.747,4.284]
3 or more		
Number of Previous Terminations	1	[1,1]
None	1.361	[0.838,2.209]
Any		
Number of Previous Miscarriages		

0		1	[1,1]
1		1.072	[0.640,1.797]
2		1.063	[0.375,3.011]
3 or more		2.057	[0.717,5.900]
Any Previous Stillbirths			
None		1	[1,1]
Any		0.873	[0.551,1.382]
Mode of Delivery			
Vaginal or Other		1	[1,1]
Caesarean		1.157	[0.651,2.057]
Onset of Labour			
Induced		1	[1,1]
No labour		1.938	[0.897,4.191]
Spontaneous	2.566*		[1.188,5.544]
Any Morbidities Before Current Pregnancy			
None		1	[1,1]
Any		0.91	[0.634,1.306]
Any Morbidities Before and During Current Pregnancy			
None		1	[1,1]
Any		0.998	[0.710,1.403]

Any Pregnancy Related Complications of Current Pregnancy				
None			1	[1,1]
Any		2.038***		[1.364,3.046]
Observations	184		183	
df_m				
df_r	2		33	
Exponentiated coefficients; 95% confidence intervals in brackets				
* p < 0.05, ** p < 0.01, *** p < 0.001				

Table 17. Neonatal study, Poisson regression of new interpregnancy intervals and preterm birth, previous early pregnancy loss population

Preterm Birth	Crude	95% CI	Full	95% CI
IPI (Months)				
0 to 9	1	[1,1]	1	[1,1]
10 to 59	0.726	[0.459,1.148]	0.752	[0.438,1.292]
City, Country				
Kilifi, Kenya			1	[1,1]
Mae Sot, Thailand			2.231	[0.663,7.503]
Nairobi, Kenya			2.852	[0.657,12.37]
Oxford, UK			1.257	[0.373,4.235]
Pelotas, Brazil			2.415	[0.615,9.481]

Maternal Age Group 10-year Intervals			
20 to 29		1	[1,1]
30 to 40		1.162	[0.531,2.544]
Previous Pregnancy Maternal Age Group 10-year Intervals			
29 or less		1	[1,1]
30 to 40		0.539	[0.219,1.328]
Pre-pregnancy BMI			
Normal		1	[1,1]
Underweight		0.385	[0.137,1.085]
Overweight	0.465*		[0.254,0.852]
Obese		1.111	[0.626,1.975]
Marital Status			
Not Married/Cohabiting		1	[1,1]
Married/Cohabiting		0.674	[0.306,1.482]
Highest Education Attained			
Less than Highschool		1	[1,1]
Highschool		0.781	[0.267,2.286]
Professional or University		0.989	[0.249,3.920]
Occupational Status			
Student/Housework/Other		1	[1,1]
Blue-Collar		0.675	[0.297,1.537]

White-Collar		0.954	[0.524,1.737]
Tobacco Use During Pregnancy			
No Tobacco Use		1	[1,1]
Tobacco Use		0.944	[0.364,2.448]
Alcohol Use During Pregnancy			
No Alcohol Use		1	[1,1]
Alcohol Use	4.382**		[1.670,11.50]
Gravida			
1		1	[1,1]
2		0.653	[0.208,2.056]
3 or more		0.723	[0.225,2.327]
Parity			
0		1	[1,1]
1	8.32e-08***		[1.11e-08,0.000000624]
2	0.00000163***		[8.88e-08,0.0000299]
3 or more		2.664	[0.260,27.33]
Number of Previous Terminations			
None		1	[1,1]

Any		1.473	[0.456,4.756]
Number of Previous Miscarriages			
0		1	[1,1]
1		0.997	[0.293,3.393]
2		1.711	[0.272,10.78]
3 or more		6.556	[0.854,50.35]
Any Previous Stillbirths			
None		1	[1,1]
Any	0.000000102***		[1.56e-08,0.000000671]
Mode of Delivery			
Vaginal or Other		1	[1,1]
Caesarean	0.389*		[0.174,0.870]
Onset of Labour			
Induced		1	[1,1]
No labour	3.095*		[1.137,8.424]
Spontaneous	2.191*		[1.079,4.448]
Any Morbidities Before Current Pregnancy			
None		1	[1,1]
Any		0.777	[0.424,1.423]

Any Morbidities Before and During Current Pregnancy			
None		1	[1,1]
Any		1.223	[0.726,2.061]
Any Pregnancy Related Complications of Current Pregnancy			
None		1	[1,1]
Any		3.783***	[2.012,7.113]
Observations	197	190	
df_m			
df_r	1	33	
Exponentiated coefficients; 95% confidence intervals in brackets			
* p < 0.05, ** p < 0.01, *** p < 0.001			

CHAPTER 6: CONCLUSION OF DISSERTATION

SUMMARY

The goal of this dissertation was to investigate the relationship between interpregnancy intervals (IPI) and preterm and whether that relationship was modified by previous pregnancy outcomes. Current recommendations from the WHO have identified an IPI of less than two years as harmful for women with a previous live birth and to avoid an IPI of less than 6 months for women with a termination or loss.

This study was not able to statistically prove the selected windows for the women with previous term or preterm births, the lowest points of the spline curves were below the 24 months WHO minimum. This suggest that the WHO's recommendation is potentially shifting women into a higher risk group than is necessary, and this is supported by the work of Conde-Agudelo et al., who found in their seminal study found that short IPIs of 12 to 23 months had to lowest rates of preterm birth (18). These recommendations were created with the intent of avoiding short IPI, ignoring the risk of longer IPIs, and thus assume that selecting a short IPI cut-off that is above the found minimums is safe due to uniform risk after their defined short IPI. This assumption is flawed, and potentially harmful.

This dissertation discussed three major areas of interest. In the first aim, we evaluated the literature for gaps and assess the potential effect of previous pregnancy history on the relationship between PTB and IPI. In the second aim, we investigated the potential determinants of short IPI in the INTERBIO-21st Fetal Study cohort. Aim 3, we evaluated the whether the 12-to-24 interval identified by Conde-Agudelo et al. was associated with a lower risk of PTB and explored novel methods of identifying new optimal IPI window(18). Our hypothesis was that optimum IPI was

potentially modified by previous pregnancy outcomes. Our results from Aims 1 and 2 suggest that our hypothesis was potentially true, as we did see differences in associations across pregnancy history. Aim 3 supported found that women with previous early pregnancy loss had a fundamentally different optimal IPI than women with a previous live birth (either term or preterm). Aim 3 also provided some indication that there were potential differences in optimal IPI between women with a previous preterm and term birth with the INTERBIO-21st Fetal Study. The Neonatal Study did not support the same conclusions, with the exception to women with a previous early pregnancy loss.

Strengths and Limitations

Our results should be interpreted along its strengths and limitations. First, our study utilized a unique, international, and diverse cohort which utilized standardized measures which contributed to a high level of internal validity in our study. The limited numbers of women who eligible for analysis potentially prevented us from establishing statistical significance. The directions of effect in the Fetal Study results suggest that our methods did improve our ability to select an optimal IPI interval, though further research is required. Second, the end date of the immediately previous pregnancy was established using maternal recall and supplemented using hospital records(84). This allowed a high degree of confidence and accuracy and mitigated the risk of overestimating the length of IPI. Additionally, gestational ages were measured using standardized methods and ultrasound methods in all participating sites, allowing for consistent gestational age measurement regardless socio-economic differences across sites. Both factors allowed for accurate IPI estimation and evaluation of effect for an international population. Third, the use of restricted cubic spline curves allowed for a more organic understanding of the risk of PTB across IPI, which the use of predefined intervals does not allow.

Suggestions for Future Research

The results of this dissertation indicate many areas of future research. More research is needed to evaluate the relationship between maternal depletion and the "J-shaped" nature of IPI for women with previous live births. One method would be to utilize a study, such as the INTERBIO-21st Project, and measure levels of nutrients, lipids, and vitamins present in women of various IPIs. While this study was not able to define the optimum IPI utilizing the rules established in Aim 3, future studies can investigate how to set an optimum IPI utilizing restricted cubic splines. Future studies should implement maternal recall and evaluate the potential differences in reported IPI lengths between maternal records and maternal recall. Lastly, studies should evaluate the determinants of IPI in larger prospective studies.

Conclusions

Aim 1 of the dissertation indicated that the relationship between found associations between IPI and adverse pregnancy outcomes could be modified depending on the pregnancy outcome used to define the start of the IPI.

Aim 2 found that the determinants of short IPI, less than 18 months, differed across previous pregnancy outcomes. The differences in risk indicators suggested that potentially women different previous pregnancy outcomes may not have the same relationship to IPI. The differences between previous love births and previous early pregnancy losses had been noted, though the literature largely treated them the same. Additionally, recommendations created by the WHO misinterpreted the dangers of short IPI for women with a previous early pregnancy loss or termination.

In Aim 3, our study showed that the relationship between IPI and PTB was modified by previous pregnancy outcomes, particularly for women with a previous early pregnancy loss compared to women with a previous live birth, and that recommendations need to reflect these

differences. The identified IPI of 0-to-9 months was shown to be protective for women with a previous early pregnancy loss, and this is a potentially actionable IPI as the mean IPI of women in this group was 11 months. The lack of clear association for women in either previous live birth group could potentially be attributed to insufficient numbers, and a study which addresses these issues could establish an optimal IPI.

The current recommendations held by the WHO are potentially problematic for women with a previous abortion, as this study shows that an IPI of less than 9 months is protective for women with a previous early pregnancy loss, meaning that these recommendations are pushing women into higher periods of risk unnecessarily. Recommendations for IPI need to take into account previous pregnancy history and further research is needed to better understand what the optimum IPI windows are for women with different pregnancy histories.

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APPENDIX 1.

Search Strategies

Search Terms and databases

Unless otherwise stated, search terms are free text terms.

Abbreviations:

'$': stands for any character; '?': substitutes one or no character; adj: adjacent (i.e. number of words within range of search term); exp:

exploded MeSH; MeSH: medical subject heading (MEDLINE medical index term); pt: publication type; sh: MeSH; tw: text word

PubMed

(

(

(

(interpregnan*[tw] OR inter-pregnan*[tw] OR "birth spacing*"[tw] OR "birth interval*"[tw] OR

"pregnancy spacing*"[tw] OR "pregnancy interval*"[tw])

AND

(interval*[tw] OR spacing*[tw])

)

OR

("Birth Intervals"[Mesh])

)

AND

(

(

("Infant, Low Birth Weight"[MeSH] OR "Infant, Premature"[MeSH])

OR

(

(

(prematur*[tw] OR preterm[tw] OR pre-term[tw] OR “low birth weight*”[tw] OR “low birthweight*”[tw])

AND

(neonat*[tw] OR newborn*[tw] OR infan*[tw] OR “Infant, Newborn”[MeSH])

)

OR

(“small for gestational age”[tw] OR (“small”[tw] AND “gestational age”[tw]))

)

)

OR

(

(“Premature Birth”[MeSH] OR “Obstetric Labor, Premature”[MeSH])

OR

(

(prematur*[tw] OR preterm[tw] OR pre-term[tw])

AND

(“Parturition”[MeSH] OR parturition*[tw] OR birth*[tw] OR “Delivery, Obstetric”[MeSH] OR obstetric*[tw] OR deliver*[tw] OR “Labor, Obstetric”[MeSH] OR labor*[tw] OR labour*[tw])

)

)

OR

(

(“Maternal Mortality”[MeSH])

OR

(

(maternal[tw])

AND

(outcome*[tw] OR death*[tw] OR mortalit*[tw])

)

)

OR

(

(“Pregnancy Complications”[MeSH] OR “Pregnancy Outcome”[MeSH] OR “Infant Mortality”[MeSH] OR “Fetal Mortality”[MeSH] OR “Infant Death”[MeSH] OR “Abortion, Induced”[MeSH])

OR

(

(

(“Infant”[MeSH] OR infant*[tw] OR newborn*[tw] OR neonat*[tw] OR “Fetus”[MeSH] OR fetus*[tw] OR fetal[tw] OR feti[tw] OR foet*[tw] OR “Pregnancy”[MeSH] OR pregnan*[tw] OR prenat*[tw] OR pre-nat*[tw] OR antenat*[tw] OR ante-nat*[tw] OR perinat*[tw] OR peri-nat*[tw] OR “Parturition”[MeSH] OR parturition*[tw] OR birth*[tw] OR “Delivery, Obstetric”[MeSH] OR obstetric*[tw] OR deliver*[tw] OR “Labor, Obstetric”[MeSH] OR labor*[tw] OR labour*[tw])

AND

(outcome*[tw] OR mortalit*[tw] OR death*[tw] OR complicat*[tw] OR terminat*[tw])

)

OR

(miscarr*[tw] OR abort*[tw] OR stillb*[tw])

)

)

)

)

NOT

("Animals"[MeSH] NOT "Humans"[MeSH])

manually limited to 1980

Embase

1 ((interpregnanc* or inter-pregnanc* or birth* or pregnanc*) adj2 (interval* or spacing*)).mp.

2 premature labor/ or prematurity/

3 exp low birth weight/

4 exp abortion/

5 exp induced abortion/

6 exp pregnancy termination/

7 pregnancy outcome/

8 pregnancy complication/

9 fetus mortality/ or infant mortality/ or maternal mortality/ or exp perinatal mortality/

10 ((prematur* or preterm or pre-term) adj2 (birth* or parturition* or delivery or labo?r)).mp.

11 ((prematur* or preterm or pre-term or low birth weight or low birthweight) adj2 (neonat* or

newborn* or infant*)).mp.

12 "small for gestational age".mp.

13 (miscarr* or abort* or stillb* or ((f?etal or f?tus) adj (death* or mortality))).mp.

14 ((f?tal or f?tus* or f?ti or pregnan* or prenatal or pre-natal or antenatal or ante-natal or

perinatal or peri-natal or birth* or obstetric* or parturition* or labo?r) adj2 (complicat* or

outcome* or mortalit* or death*)).mp.

15 ((infant* or newborn* or neonat*) adj2 (complicat* or outcome* OR death* OR

mortalit*)).mp.

16 (maternal adj2 (outcome* or death* or mortalit*)).mp.

17 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16

18 1 and 17

19 exp animals/ not human/

20 18 not 19

22 limit 20 to yr="1980 -Current"

The Cochrane Library

1 ((interpregnanc* OR inter-pregnanc* OR birth* OR pregnanc*) NEAR/2 (interval* OR spacing*)):ti,ab,kw

2 ([mh “birth intervals”])

3 {OR #1, #2}

4 ([mh “animals”] NOT [mh “humans”])

5 #3 NOT #4

Web of Science

1 TI=((interpregnanc* OR inter-pregnanc* OR birth* OR pregnanc*) NEAR/2 (interval* OR

spacing*))

2 AB=((interpregnanc* OR inter-pregnanc* OR birth* OR pregnanc*) NEAR/2 (interval* OR

spacing*))

3 AK=((interpregnanc* OR inter-pregnanc* OR birth* OR pregnanc*) NEAR/2 (interval* OR

spacing*))

4 #1 OR #2 OR #3

5 TI=((prematur* OR preterm OR pre-term) NEAR/2 (birth* OR parturition* OR delivery

OR labo$r))

6 AB=((prematur* OR preterm OR pre-term) NEAR/2 (birth* OR parturition* OR delivery

OR labo$r))

7 AK=((prematur* OR preterm OR pre-term) NEAR/2 (birth* OR parturition* OR delivery

OR labo$r))

8 TI=((prematur* OR preterm OR pre-term OR “low birth weight” OR “low birthweight”)

NEAR/2 (neonat* OR newborn* OR infant*))

9 AB=((prematur* OR preterm OR pre-term OR “low birth weight” OR “low birthweight”)

NEAR/2 (neonat* OR newborn* OR infant*))

10 AK=((prematur* OR preterm OR pre-term OR “low birth weight” OR “low birthweight”)

NEAR/2 (neonat* OR newborn* OR infant*))

11 TI=("small for gestational age")

12 AB=("small for gestational age")

13 AK=("small for gestational age")

14 TI=(miscarr* OR abort* OR stillb* OR ((f$etal OR f$tus) NEAR/0 (death* OR

mortalit*)))

15 AB=(miscarr* OR abort* OR stillb* OR ((f$etal OR f$tus) NEAR/0 (death* OR

mortalit*)))

16 AK=(miscarr* OR abort* OR stillb* OR ((f$etal OR f$tus) NEAR/0 (death* OR

mortalit*)))

17 TI=((f$tal OR f$tus* OR f$ti OR pregnan* OR prenatal OR pre-natal OR antenatal OR ante-natal OR perinatal OR peri-natal OR birth OR obstetric* OR parturition* OR labo?r) NEAR/2 (complicat* OR outcome* OR mortalit* OR death*))

18 AB=((f$tal OR f$tus* OR f$ti OR pregnan* OR prenatal OR pre-natal OR antenatal OR ante-natal OR perinatal OR peri-natal OR birth OR obstetric* OR parturition* OR labo?r) NEAR/2 (complicat* OR outcome* OR mortalit* OR death*))

19 AK=((f$tal OR f$tus* OR f$ti OR pregnan* OR prenatal OR pre-natal OR antenatal OR ante-natal OR perinatal OR peri-natal OR birth OR obstetric* OR parturition* OR labo?r) NEAR/2 (complicat* OR outcome* OR mortalit* OR death*))

20 TI=((infant* OR newborn* OR neonat*) NEAR/2 (complicat* OR outcome* OR death* OR mortalit*))

21 AB=((infant* OR newborn* OR neonat*) NEAR/2 (complicat* OR outcome* OR death* OR mortalit*))

22 AK=((infant* OR newborn* OR neonat*) NEAR/2 (complicat* OR outcome* OR death* OR mortalit*))

23 TI=(maternal NEAR/2 (outcome* OR death* OR mortalit*))

24 AB=(maternal NEAR/2 (outcome* OR death* OR mortalit*))

25 AK=(maternal NEAR/2 (outcome* OR death* OR mortalit*))

26 #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25

27 #4 AND #26

28 SU=Veterinary Sciences

29 WC=Veterinary Sciences

30 #28 OR #29

31 #27 NOT #30

32 #31

[with date limiter set]

Scopus

1 TITLE-ABS-KEY((interpregnanc* OR inter-pregnanc* OR birth* OR pregnanc*) W/2 (interval* OR spacing*))

2 TITLE-ABS-KEY((prematur* OR preterm OR pre-term) W/2 (birth* OR parturition* OR delivery OR labo*r))

3 TITLE-ABS-KEY((prematur* OR preterm OR pre-term OR “low birth weight” OR “low birthweight”) W/2 (neonat* OR newborn* OR infant*))

4 TITLE-ABS-KEY("small for gestational age")

5 TITLE-ABS-KEY(miscarr* OR abort* OR stillb* OR ((f*etal OR f*tus*) W/1 (death* OR mortalit*)))

6 TITLE-ABS-KEY((f*etal OR f*etus* OR f*eti OR pregnan* OR prenatal OR pre-natal OR antenatal OR ante-natal OR perinatal OR peri-natal OR birth OR obstetric* OR parturition* OR labo*r) W/2 (complicat* OR outcome* OR mortalit* OR death*))

7 TITLE-ABS-KEY((infant* OR newborn* OR neonat*) W/2 (complicat* OR outcome* OR death* OR mortalit*))

8 TITLE-ABS-KEY(maternal W/2 (outcome* OR death* OR mortalit*))

9 #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 (must put this in the “Combine Searches” box)

10 #1 AND #9

11 SUBJAREA(VETE)

12 #10 AND NOT #11

13 PUBYEAR > 1979

14 #12 AND #13