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An Examination of Inter-pregnancy Intervals as a Risk Factor for Stillbirth

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Maternal and Child Health Certificate

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A.B., Bryn Mawr College, 2013
M.P.H., Emory University Rollins School of Public Health, 2015

Faculty Thesis Advisor: Dr. Carol J. Rowland Hogue, Ph.D., M.P.H.

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ABSTRACT

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Context: It is estimated that 1 in 160 pregnancies in the United States annually end in stillbirth (SB, fetal death ≥ 20 weeks gestation). The causal risk factors of SB are unknown, however, short and long inter-pregnancy intervals (IPI) have commonly been reported as risk factors for other adverse perinatal outcomes.

Objective: This analysis seeks to examine the association between IPI and SB risk among an ethnically, racially, and geographically diverse population.

Methods: The Stillbirth Collaborative Research Network (SCRN) study was a multi-site, population-based case-control study from March 2006 to September 2008 with surveillance for all stillbirths at 59 tertiary care hospitals over 5 catchment areas ensuring access to at least 90% of deliveries. This analysis was restricted to singleton pregnancies among multiparous or multigravid women. Exclusion criteria included pregnancy terminations, incarcerated women, or those who were unable to provide informed consent. Weighted logistic regression models were used to depict the association of short and long intervals on stillbirth risk. Weighted backward elimination for interaction and weighted all-possible subsets approach to confounding were conducted at a 5% significance level. All models were created using SAS 9.3.

Results: Compared with IPI between 18-23 months, short intervals (<6 months) and long intervals (60-100 months) were associated with increased risk of stillbirth (Odds Ratio [OR]: 1.6; 95% Confidence Interval [CI]: 0.8, 3.2) and (OR: 2.4; 95%CI: 1.3, 4.7) respectively, controlling for age, race, education, insurance, BMI, smoking status, alcohol consumption, marital status, use of assisted reproductive technologies, and prior pregnancy outcome. Final models controlled for all ten covariates of interest and were selected based on HL statistics and AUC. True confounders differed between short and long intervals. For the combined analysis, the relationship between IPI and SB risk was confounded by age, BMI, education and prior pregnancy outcome; when restricted to short intervals, confounders in this study included age, insurance, and prior pregnancy outcome. The relationship between long intervals and SB was not confounded by any of the suspected covariates.

Conclusions: Short and long IPI contributed to an increased risk of SB controlling for selected covariates. However, only long intervals were associated with a statistically significant increase in SB risk.

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TERMS AND DEFINITIONS

Child Mortality - death of a child before his/her fifth birthday.

Early Term Birth - birth between 37-38 weeks completed gestation.

Full Term Birth – birth between 39-40 weeks completed gestation.

Gestational Age (GA) - period between the date of the last menstrual period and date of delivery, usually measured in weeks.

Infant Mortality – death of a child before his/her first birthday

Late Term Birth – birth at 41 weeks completed gestation.

Low Birth Weight (LBW) - infant born under 2,500 grams.

Maternal death - the death of a woman while pregnant or within 365 days of termination of pregnancy, irrespective of the duration and site of the pregnancy, from any cause related to or aggravated by pregnancy or its management but not from accidental or incidental causes* (U.S. adopted 1999).

Direct maternal death- maternal death due to obstetric complications during pregnancy, labor or puerperium (6 weeks post-partum) or from any treatment received.

Indirect maternal death- maternal death due to a preexisting or newly developed health problem unrelated to pregnancy.

Late maternal death- maternal death 42 – 365 days after delivery.

Neonatal Death- death of a child prior to 28 days.

Early Neonatal Death (END) – death of a child prior to 7 days of life.

Late Neonatal Death (LND) - death of a child between 7-27 days of life.

Post Term Birth – birth at 42 weeks or more completed gestation.

Preterm Birth (PTB) - birth occurring prior to 37 weeks completed gestation.

Very Preterm Birth- birth occurring prior to 32 weeks completed gestation.

Early Preterm Birth- birth occurring from 32-34 weeks completed gestation.

Late Preterm Birth – birth occurring between 34-36 weeks completed gestation.

Iatrogenic Preterm Birth- preterm birth caused by medical or obstetric complications

Preterm Premature Rupture of the Membranes (PPROM) - rupture of the amniotic sac prior to the 37 weeks completed gestation

Spontaneous Preterm Birth (SPTB) – spontaneous onset of labor prior to 37 completed weeks gestation. Not caused by medical or obstetric complications or premature rupture of the membranes.

Small for Gestational Age (SGA) – infant less than 10th percentile weight for gestational age

Stillbirth Collaborative Research Network (SCRN)

Stillbirth (SB) - fetal death at 20 weeks or more gestation.

Early Fetal Death (EFD) - stillbirth occurring between 20 and 27 weeks completed gestation

Late Fetal Death (**LFD)** – stillbirth occurring at 28 or more weeks completed gestation

INTRODUCTION

Stillbirth is defined as a fetal death at or greater than 20 weeks gestation (SCRN, 2014). Stillbirth is a critical public health issue as the loss of a child not only affects mothers, but also families and communities. In 2011, Lawn et al. estimated that approximately 3 million families around the world will be affected by stillbirth every year; this is equivalent to approximately 7,000 stillbirths per day (Lancet, 2011). The Global Alliance to Prevent Prematurity and Stillbirth (GAPPS) estimates that 98% of stillbirths occur in the developing world. Stillbirth is also a problem in developed countries, as 1 in 160 babies in the United States are stillborn (Lancet, 2011).

The intra-partum period is the time from the onset of labor until the birth of the infant and the delivery of the placenta (CDC, 2013). This period is often considered a critical "window of intervention" as nearly 50% of stillbirths, 75% of maternal deaths, and 25% of newborn deaths occur during this period. Intervention during this critical period is estimated to address and perhaps even prevent 2.3 million maternal and child deaths (Lancet, 2011).

Before 2012, stillbirths were not included in any global health agendas, including the United Nations Millennium Development Goals and the Global Burden of Disease (Lawn, 2011). As a result, millions of deaths remain uncounted. The lack of global public health attention to stillbirth prevents assessment of the prevalence, etiology and causal risk factors, and scope of the emotional, mental, and physical toll

on mothers and families. An incomplete understanding of stillbirth and possible risk factors also impedes a woman's ability to take control over her reproductive health.

Two articles published in Lancet in 2011 stated that both mother and child are at greater risk of mortality at the onset of labor, than at any other stage in the lifecycle (Lawn et al., 2011; Patterson et al., 2011). Lawn et al. published an article in 2006, which stated that nearly 1 in 3 stillborn infants were alive before the onset of labor, which suggests the infant death may be attributed to causes that are often associated with maternal and neonatal mortality (Lawn, 2011). Public health efforts to elucidate the causal factors of stillbirth and development of evidence-based interventions to prevent stillbirths could contribute to the reduction of maternal and neonatal mortality thereby strengthening the argument in support of making stillbirth a public health priority.

The emotional costs of stillbirth and the subsequent effect on physical, emotional, and mental health alone, make this an important public health issue. The grief experienced after a stillbirth is overwhelming and *often hidden* (Scott, 2011). The death of a live-born child is most often shared by families and communities as these parties have had a chance to bond with the child, whereas a stillborn child is a loss felt most closely by the parents. In much of the western world, a life is considered valuable at the time a woman becomes pregnant. Generally, a woman's pregnancy is celebrated in anticipation of a live-born infant. As a result, a stillbirth is often unacknowledged, unexpected, obscure, and complex (Cacciatore et al., 2009; Raedestad et al., 1996). A 2011 Lancet review regarding the perceptions of stillbirth

worldwide found that in some countries the birth of a stillborn child is so incomprehensible that the delivery of a stillborn baby is often treated as a non-event (Froen et al. 2011). In some cases, a stillborn child is disposed of without a name or ritual recognition. This reaction from one's family or community may aggravate and deepen a mother's sorrow. In countries in which a woman's value is determined by her ability to bear children, a stillborn child may result in social stigma, blame, and marginalization as her "role" in society may be considered unmet (Froen et al. 2011). In addition to grief, a mother who suffers a stillbirth is likely to experience other adverse health outcomes including depression and post-traumatic stress disorder (Hogue et al., 2014; Turton et al., 2009; Badenhorst et al., 2006; LaRoche et al., 1984). These perceptions regarding stillbirth serve to elucidate the possible emotional and mental effects on mothers and communities. Further exploration of the psychological effects of stillbirth could provide essential information leading toward the improvement of medical, clinical, and societal responses to stillbirth (Froen et al., 2011).

CHAPTER 1: THE STILLBIRTH COLLABORATIVE NETWORK

In response to lack of knowledge regarding the scope and causal factors of stillbirth, the National Institute of Child Health and Human Development (NICHD) established the Stillbirth Collaborative Research Network (SCRN) in 2003.

The SCRN is a multisite, population-based, case-control study of stillbirths in the United States. Primary investigators and researchers were from Brown University, Emory University, University of Texas Medical Branch at Galveston, University of Texas Health Sciences Center at San Antonio, University of Utah, National Institute of Child Health and Human Development (NICHD), and the Research Triangle Institute (RTI). The SCRN catchment areas were required to contain at least 6,000 births per year in urban areas and at least 3,000 births from rural areas. The SCRN investigators selected 59 hospitals for study purposes in order to recruit at least 90% of deliveries in the catchment areas. Cases were defined as *women who experienced a fetal death at 20 or more completed weeks gestation*. Controls were defined as *women who delivered a live birth at 20 weeks or more completed gestation*. Women who resided in one of the catchment areas were at least 13 years of age and identified for participation prior to discharge from the study hospital were included into the SCRN study. Women experiencing fetal death less than 20 weeks gestation, whose delivery resulted from termination of a living fetus, or who were discharged prior to the study consent, or those for whom informed consent was not obtained due to mental or linguistic barriers were excluded from the study. Women who were incarcerated were also excluded from

the study. For consenting participants, maternal interviews were conducted to collect demographic information, prior medical history, and psychosocial information. Following these interviews, maternal and neonatal information was compiled from chart abstraction. Placental examinations were then performed by SCRN pathologists for all deliveries. Lastly, post-mortem examinations were conducted for fetal deaths and placental examinations were conducted for all deliveries by SCRN pathologists.

The primary goal of the SCRN was to study the etiology and epidemiology of stillbirth in the United States. The specific aims of the SCRN were threefold: 1) To determine the causal factors associated with stillbirth using a standardized stillbirth post-mortem protocol, 2) estimate the incidence of stillbirth, and 3) elucidate the risk factors for stillbirth. Within the specified aims of the SCRN, the researchers were guided by specific research questions. Examples include an examination of racial disparities in stillbirth, the association between prenatal environmental and interpersonal stressors and stillbirth, and the relationship of placental abnormalities and stillbirth (SCRN, 2011).

KNOWN RISK FACTORS OF STILLBIRTH

The following section will provide necessary introduction to the epidemiology of stillbirth. The review will first discuss the known and suspected risk factors of stillbirth. Chapter 2 will offer an introduction to risk factors of stillbirth that remain unexplored and poorly understood.

Many studies have examined risk factors for stillbirth (Hogue et al., 2014; Flenady et al., 2011; SCRN, 2011; McCowan et al., 2013; Bring et al., 2013; Varner et al., 2014; Cnattinguis et al., 2002; Fretts, 2005; Silver et al., 2007; Smith et al., 2007). A review of the evidence regarding stillbirth published in 2007 by Silver et al., stated that genetics, infection, maternal characteristics, and obstetric complications are risk factors for stillbirth.

Genetics

A considerable proportion of stillbirths can be attributed to genetic causes. Approximately 6-12% of stillbirth can be attributed karyotypic abnormalities (Wapner et al., 2002; Christiaens et al., 2003). It is difficult to study cell karyotypes; therefore it is likely these percentages are underestimates. Chromosomal abnormalities that result in physical or structural defects in the stillborn are easier to identify. The genetic abnormalities that are common among stillbirths include monotrisomy X, trisomy 13, trisomy 21, and trisomy 23. Chromosomal abnormalities also contribute to severe malformations and deformations. Genetic abnormalities of the placenta and chromosomal micro deletions have yet to be explored as risk factors of stillbirth.

SCRN investigators found that single-nucleotide polymorphism (SNP) oligonucleotide microarray analysis is more likely to provide a genetic diagnosis of stillbirth. Unlike karyotype analysis, microarray analysis does not require live cells and can detect small duplications and deletions. Micro array analysis increased the diagnosis of genetic abnormalities by 41.9% among all stillbirths; 34.5% in

antepartum stillbirths; and by 53.8% in stillbirths with anomalies as compared to karyotype analysis (Reddy et al. 2012).

Infection

Stillbirths that occur early on in gestation are more likely to be associated with infection. Mechanisms by which infections may cause stillbirth include direct infection, placental damage and maternal illness during pregnancy. In developing countries, ascending bacterial infections are commonly cited as a risk factor for stillbirth. In developing countries, Escherichia coli and Group B Streptococci are among the most commonly infectious causes of stillbirth (Gibbs, 2002; Goldenberg, 2003). Pregnant mothers without a prior history of malaria may also be at risk for stillbirth. Viral risk factors are generally difficult to study; however Parvovirus B-19 has been found to be significantly associated with stillbirth (Enders, 2004). Parvovirus B-19 can be diagnosed via blood test; however clinicians most commonly diagnose it if redness or rash is visible on the baby's cheek. The virus can infect the infant by crossing the placenta or directly attacking the infant's cardiac tissue. As stated previously, the earlier in gestation the stillbirth, the most likely it will be associated with infection (Enders, 2004). SCRN investigators found that among stillbirths that were associated with infection, 20-22% of stillbirths occurred prior to 23 weeks completed gestation whereas 5-12% occurred at 24 weeks or more completed gestation (Silver et al., 2007).

Hemorrhage

Fetal-maternal hemorrhage is a possible complication of labor and delivery. Mothers who undergo Caesarian section and those who experience placental abruption or trauma to the abdomen during pregnancy have a greater risk of maternal hemorrhage (Owen et al., 1989; Laubeet al., 1982). Hemorrhage may be prevented by monitoring during prenatal care, and providing safe, quality healthcare for mothers (Stillbirth Collaborative Research Network Writing Group, 2011).

Maternal Characteristics and Diseases

Maternal age is a well-known risk factor for adverse birth outcomes (Stephansson et al., 2001; Hansen et al., 1986; Raymond et al., 1994). In a 1986 review of the effects of maternal age on pregnancy outcomes, Hansen concluded that compared to women under 35 years of age, the stillbirth rate of women between 35-39 years of age increased 2-fold; and the stillbirth rate among women 40 years and older increased 3-4 fold. Non-Hispanic African American women have a 2 fold risk of stillbirth when compared to non-Hispanic white women suggesting race is a significant risk marker of stillbirth (Willinger, 2009; SCRN, 2011). Other maternal characteristics that may contribute to stillbirth rates include pre-pregnancy obesity and co-morbid conditions including diabetes and hypertension. Women with Type-2 diabetes are at 2.5 fold odds of having a stillbirth when compared to non-diabetic women after controlling for adequate prenatal care and diabetes management (Cundy et al., 2000). More women are entering the workforce

and postponing motherhood to older ages. In addition, the incidence of diabetes and obesity are on the rise globally. It is quite likely that maternal age and chronic disease status are risk factors that will become increasingly more relevant. Other maternal diseases that have a significant association with stillbirth include thyroid disease, cardiovascular disease, kidney disease, Lupus, thrombophilias and asthma (Fretts, 2005; SCRN, 2011; Simpson, 2002).

SCRN investigators found that race, previous stillbirth, diabetes, age, blood type, maternal weight, and not living with a partner were independently associated with stillbirth. Non-Hispanic Black women has a 2-fold odds of stillbirth when compared to Non-Hispanic White women (AOR: 2.12; 95% CI: 1.41, 3.20). Women who had a previous stillbirth were at a 6-fold odds of stillbirth[1] (AOR: 5.91; 95% CI: 3.18, 11.00). Nulliparous women with a previous loss prior to 20 weeks gestation had a 3-fold odds of stillbirth[2] (AOR: 3.13; 95% CI: 2.06, 4.75) whereas nulliparous women without a previous loss prior to 20 weeks gestation had a 2-fold odds of stillbirth [3](AOR: 1.98, 95% CI: 1.51, 2.60). Diabetic women had a 2.5-fold odds of stillbirth (AOR: 2.50, 95% CI: 1.39, 4.48). Mothers over the age of 40 were 2.4 times as likely to have a stillborn child as mothers between the age of 20-34 years (AOR: 2.41, 95% CI: 1.24, 4.70). Women with AB blood-type had a 2-fold odds of stillbirth when compared to women with O blood-type (AOR: 1.96, 95% CI: 1.16, 3.30). Obese mothers (BMI= 30-34) also had a 2-fold odds of stillbirth when compared to normal weight (BMI=18.5-24.9) mothers (AOR: 1.72; 95%CI: 1.22, 2.43). Women who did

[1] Compared to multiparous women
[2] Compared to multiparous women without a previous loss prior to 20 weeks gestation
[3] Compared to multiparous women with a previous loss prior to 20 weeks gestation

not live with a partner were 1.6 times as likely to have a stillbirth as women who were married (AOR: 1.62; 95% CI: 1.15, 2.77) (SCRN, 2011).

Risk Behaviors

Cigarette smoking, recreational drug use, and consumption of alcohol are commonly studied in epidemiological studies. Among smokers the odds of stillbirth is 1.6 times that of non-smokers (1.2, 2.3) (Gardosi, 1998; Wisborg 2001; Lee, 1998). Mothers who abuse cocaine during pregnancy are 6 times as likely to suffer a stillbirth (Lutiger, 2005). Some studies show that alcohol consumption during pregnancy increase the risk of stillbirth, while others studies show a protective effect. These studies may suffer from confounding bias. The evidence regarding marijuana use is conflicting. Despite the varying conclusions, there is a large body of research and general public health education encouraging mothers not to engage in smoking, alcohol use, or recreational drug use during pregnancy (Wisborg, 2001; Lutiger 2005; Lee, 1998; Fergusson, 2002; Faden, 1997; Kesmodel, 2002; Whitehead, 2003).

SCRN investigators found that mothers who had a history of drug addiction were 2 times as likely to have a stillbirth as women who never abused drugs (AOR:2.08; 95% CI: 1.12, 3.88). Mothers who smoked during 3 months prior to pregnancy were 1.6 times as likely to have a stillborn child as mothers who smoked fewer than 10 cigarettes a day (AOR:1.55; 95% CI: 1.02,2.35) (SCNR, 2011). SCRN investigations revealed the most common individual drug was tetrahydrocannabinolic acid (THCA), the active ingredient in marijuana. THCA was

associated with a 2.3-fold odds of stillbirth (OR: 2.34; 95%CI: 1.13, 4.81) (Varner et al., 2014).

Developing and Developed Countries

Prevention of stillbirth must consider the social, cultural, political and economic context of the study location, as the risk factors of stillbirth differ between developing and developed countries. In order of attributable risk, stillbirth in developing countries can be attributed to: 1) obstructed or prolonger labor, 2) congenital infections, 3) hypertensive disorders, 4) poor nutritional status, 5) history of stillbirth, 6) congenital abnormalities, 7) malaria, and 8) sickle-cell disease. In developed countries stillbirth can be attributed to: 1) congenital and karyotypic abnormalities, 2) growth restriction in utero, 3) chronic disease and comorbid diseases, 4) hypertensive disorders, 5) congenital infections, 6) smoking, and 7) multiple gestation. (Smith et al., 2007).

Investigators from the Stillbirth Research Collaborative Network found that the causes of death differed between antepartum and intrapartum stillbirths. Intrapartum stillbirths were associated with obstetric complications and infectious causes, whereas antepartum stillbirths were more commonly caused by placental complications and fetal/genetic structural abnormalities (Stillbirth Collaborative Research Network Writing Group, 2011)

Many of the risk factors discussed in this section are modifiable. To have significant impact stillbirth interventions must consider which risk factors have the greatest attributable risk as well as the socio-cultural context of the study location.

The Stillbirth Collaborative Research Network has significantly contributed to the existing body of literature regarding stillbirth. Recently, stillbirth has been added to major global health agendas. It is therefore expected that the importance of stillbirth will continue to gain recognition and as a consequence it is expected that monitoring and surveillance of stillbirth will improve.

CHAPTER 2: REVIEW OF THE LITERATURE REGARDING INTER-PREGNANCY INTERVALS

Inter-pregnancy interval (IPI) is the time between pregnancies. Inter-pregnancy interval is calculated by subtracting the date of the last menstrual period of the index pregnancy from the date the pregnancy prior to the index pregnancy ended. Women who suffer a stillbirth often experience urgency to become pregnant again quickly, in order to avoid long-term grief or stigma and marginalization from their communities. A growing body of literature suggests that a shortened inter-pregnancy interval (IPI) may increase the likelihood of adverse birth outcomes including preterm birth[4] (PTB), low birth weight[5] (LBW), small for gestational age[6], and infant and neonatal morbidity and mortality[7]. Few studies have investigated the role of IPI on risk of stillbirth (James, 1968; Fedrick, 1973; Spiers, 1976; Erickson, 1978; Fortney, 1984; Miller 1991). Most of the articles are quite old, and the results regarding whether IPI is a risk factor for stillbirth are conflicting. In addition the data reported were published long before stillbirth gained public health attention and before standardized definitions and methodologies could contribute to adequate surveillance and monitoring.

[4] Birth occurring prior to 37 weeks completed gestation
[5] Infant born under 2,500 grams
[6] Infant less than the 10th percentile weight for gestational age
[7] Death of a child before his/her 1st birthday

In fact, a comprehensive review of the literature resulted in only one relatively recent article that investigated the association between IPI and risk of stillbirth (Boerma et al., 1992; Conde-Agudelo et al., 2006; Conde-Agudelo et al., 2012; DeFranco et al., 2014; DeFranco et al., 2007; Fowler et al., 2004; Fuentes-Afflick et al., 2000; Gemmill et al., 2003; Grisaru-Granovsky et al., 2009; Hogue et al., 2011; Hussaini et al., 2013; Khoshnood et al., 1998; Kozuki et al., 2013; Nerlander et al., 2014; Rodrigues et al., 2008; Smith et al., 2003; Smits et al.,2001; Stephanson et al., 2003; Wong et al., 2014; Zhu et al., 2005; Zhu et al.,1999). The study was published in 2003, by Drs. Olof Stephansson, Paul W. Dickman, and Sven Cnattingius. Stephansson et al., conducted a population-based study in Sweden of first and second singleton deliveries occurring between 1983 and 1997. Stillbirth was defined as a fetal death at 28 or more completed weeks of gestation. Inter-pregnancy interval was defined as the time that elapsed between the birth of the first child and estimated conception date of the following child. Logistic regression analysis was conducted to model the association between IPI and adverse birth outcomes in the second pregnancy. Adverse outcomes in the first pregnancy included: SB, PTB, small for gestational age (SGA) and neonatal death. Early neonatal deaths[8] (END) were limited to live-born infants. All logistic models controlled for IPI, maternal age at delivery, smoking status, education level, mother's residential status with the father of the child, mother's country of birth, diabetes, hypertensive disorders, and year of second delivery and previous

[8] Death of a child prior to 7 days of life

pregnancy outcome. Effect modifiers tested the interaction between IPI and adverse pregnancy outcomes from the first pregnancy (SB, END, PTB and SGA). Wald tests for significance were conducted to evaluate possible effect modifiers. Odds ratios and 95% confidences intervals were calculated using SAS (SAS Institute, Cary, NC).

Stephansson et al. studied 410,021 births, of which 1,062 were stillbirths, equivalent to a rate of 2.6 per 1,000 livebirths. The reference group for IPI was 12-35 months. When compared to the reference group, short intervals (0-3 months) and long intervals (36-71 months) and very long intervals (72 months or longer) were associated with an increased risk of stillbirth. The odds of stillbirth were 1.6 (95%CI:1.1, 2.5), 1.2 (95%CI:1.0, 1.4), and 1.5 (95%CI:1.1, 2.1) respectively controlling for smoking, maternal age, education level, cohabitation with the biological father, mother's country of birth, diabetes, hypertension, year of second delivery, and outcome of the first pregnancy. Crude odds ratios were 1.3 (95%CI: 1.3, 2.7), 1.2 (95%CI: 1.1, 1.5), and 1.8 (95%CI: 1.4, 2.4) respectively. The results from the study supported the existing literature on risk factors for stillbirth. Smoking, higher maternal age, diabetes status and hypertensive disorders were significantly associated with stillbirth. Inter-pregnancy interval was influenced by previous history of SB, SGA, END, PTB, smoking status, education level, and non-cohabitation with the biological father, greater maternal age, and diabetes and hypertensive disorders (Stephanson, 2003).

The findings from this study suggest that the relationship between IPI and stillbirth is heavily confounded, and that assessment of confounding and effect modification should be a priority in future modeling and evaluation of this research

question. The large sample size and strong registry and record linkage system contributes to the power of this study. One limitation of the study was information regarding prior spontaneous or induced abortions. Spontaneous abortions have been found to be associated with adverse birth outcomes as well as shortened IPI, and these may have contributed to misclassification of IPI thereby underestimating the effect of short IPI and overestimating the effect of long IPI. In addition, gestational age may be subject to bias in cases where GA could not be confirmed by ultrasound. It is also possible that selection bias exists as this was a cohort study and women with short IPI were more likely to be included in the study.

INTER-PREGNANCY INTERVALS AND ADVERSE BIRTH OUTCOMES

The following section will review the literature regarding the association between IPI and adverse birth outcome to highlight the relevance of studying IPI as a possible risk factor for stillbirth.

Khoshnood et al. published an article in 1998 that examined the effects of short inter-pregnancy intervals on the risk of PTB and LBW among Non-Hispanic Whites, African Americans, Native Americans, Mexicans and Puerto Ricans in the United States. They used logistic regression analysis to calculate adjusted odds ratios and corresponding 95% confidence intervals. When compared to mothers with IPI greater than 12 months, mothers with IPI less than 6 months had an increased risk of low birth weight and preterm birth. The authors found that the risk of very low-birth weight (<1500 grams) increased by 30-60%; the risk of very preterm birth (<32 weeks) increased by 20-70% among mothers who had IPI less

than 6 months when controlling for maternal age, education, marital status, parity, prenatal care, smoking, and previous preterm delivery. The odds of VLBW among Puerto Rican mothers with IPI less than 6 months was greater than any other racial group (AOR: 1.6; 95%CI: 1.2, 2.2). Mexican mothers with IPI less than 6 months also had an increased odds of VLWB (AOR: 1.5; 95%CI: 1.3, 1.6). Similar trends were noted for VPTB. Puerto Rican and Mexican mothers with IPI less than 6 months had the greatest odds of VPTB (AOR: 1.7; 95%CI: 1.4, 2.1) and (AOR: 1.4; 95%CI: 1.3, 1.5) respectively. These results are adjusted odds ratios as compared with reference group with and inter-pregnancy interval of >12 months and controlled for maternal age, education, marital status, parity, prenatal care, smoking, and previous preterm delivery.

In 2000 Fuentes-Afflick et al., evaluated whether IPI were associated with the risk of PTB. The researchers investigated over 200,000-singleton births among Mexican Hispanic and Non-Hispanic White women who had at least one previous livebirth. When compared to mothers with IPI between 18-59 months, IPI less than 6 months was associated with a 47% increase in odds of VPTB (AOR: 1.5; 95%CI: 1.3, 1.7) and IPI greater than 59 months was associated with a 45% increase in odds of VPTB (AOR: 1.5; 95%CI: 1.3, 1.6) when adjusting for age, education, birthplace, parity, previous PTB or SGA, utilization of prenatal care, and infant sex. Hispanic women had a 30% increase in odds of VPTB (AOR: 1.3; 95%CI: 1.2, 1.6) when compared to white women adjusting for age, education, birthplace, parity, previous PTB or SGA, utilization of prenatal care, and infant sex. In this study it was found

that women with IPI between 18-59 months had the lowest risk of adverse birth outcomes (Fuentes-Afflick et al., 2000).

A retrospective cohort study in Scotland, published in 2003, found that when compared to women with IPI 18-23 months, women with IPI less than 6 months had a 2.2 fold odds of VPTB (AOR: 2.2; 95%CI: 1.4, 3.6); a 1.6 fold odds of LPTB (AOR: 1.6; 95%CI: 1.3, 2.0); a 3.6-fold odds of perinatal deaths unrelated to congenital abnormalities (AOR: 3.6; 95%CI: 1.2, 10.7). These results were adjusted for age, marital status, height, socioeconomic, deprivation category, smoking, previous birth weight, and previous caesarian section. The results of this study were found to be statistically significant. A major strength of this study is the sample size: 89,143 women having second births in 1992-1998 and who conceived within five years of their first birth were studied. Stratification by IPI and outcome resulted in small numbers for analysis (Smith et al., 2003).

A nationwide, case-control study in Portugal, published in 2008 examined the relationship between short inter-pregnancy intervals on the occurrence of SPTB and PPROM. The authors found when compared to mothers with IPI greater than 6 months, mothers with IPI less than or equal to 6 months had nearly a 4-fold odds ratio for early SPTB (AOR:3.6; 95%CI: 1.4, 8.9) when controlling for age, education, prior spontaneous birth, antenatal care, smoking habits, BMI, and gestational weight gain. The authors also found that for a short IPI (<6 months) risk of PPROM was 4-fold (OR: 4.3; 95%CI: 1.8, 10.0). These findings are consistent with the results from the previous studies. The confidence intervals are wide suggesting the presence of

bias. Further evaluation of confounding and possible effect modification should be prioritized in future replication of this research question (Rodrigues et al., 2007).

In 2005, Zhu published a study that reviewed the relationship between IPI and adverse birth outcomes including: LBW, PTB, and SGA. Three studies were reviewed: a 1999 cross-sectional study from Utah, a 2001 cross-sectional study from Michigan, and a 2003 retrospective study from Michigan. The studies stratified and controlled for maternal reproductive risk factors. A review of the results from these studies revealed a J-shaped relationship between IPI and LBW, PTB and SGA. The risks of LBW, SGA, and PTB were high when the inter-pregnancy interval was less than 3 months. The risk of adverse outcome decreased as IPI increased; the lowest risk was seen for IPI between 18-23 months. After 23 months, the risk of adverse birth outcomes increased linearly. This review also found that the median IPI in all three studies and among all racial groups was approximately 20 months, which is within the range of the optimal IPI associated with the lowest risk for adverse birth outcomes (18-23) (Zhu, 2005).

In 2007, Conde-Agudelo et al. published a systematic review of observational studies that examined the association between inter-pregnancy intervals and adverse pregnancy outcomes. The review included studies published 1966 and 2006. The authors found inter-pregnancy intervals between 18-23 months were associated with the lowest risk of adverse birth outcomes. In addition, women with IPI less than six months had a greater odds of PTB (OR: 1.4; 95%CI: 1.2, 1.6); LBW (OR: 1.6; 95%CI: 1.4, 1.9); and SGA (OR: 1.3; 95%CI: 1.2, 1.3). Intervals between 6-17 months and longer than 59 months were also found to pose significant increases

in risk of PTB, LBW, and SGA. Conde-Agudelo et al., also discovered J-shaped relationships between IPI and PTB, LBW, SGA, fetal death, and early neonatal death. These findings are consistent with previous studies (Zhu, 2005; Smith et al., 2003; Rodrigues et al., 2007; Fuentes-Afflick et al., 2000).

In a 2007 population-based cohort study in Missouri, DeFranco et al. evaluated whether the risk of PTB increased for a mother with short IPI and found IPI less than 6 months increased the odds of PTB (AOR:1.5; 95%CI:1.4, 1.6); moderate[9] PTB (AOR:1.5; 95%CI: 1.3, 1.6); very[10] PTB (AOR:1.6; 95%CI:1.4, 1.8) and extreme[11] PTB (AOR:1.4; 95%CI:1.1, 1.8) when controlling for previous PTB, prenatal care, race and age. Consistent with other studies, the lowest risk was observed among mothers with IPI greater than 18 weeks completed gestation.

In 2009 Grisaru-Granovsky et al. published a longitudinal cohort study investigating the relationship of IPI on PTB, SGA, early neonatal death and congenital malformations. The results were consistent with previous studies: IPI less than 6 months was associated with a significant increase in risk, although the odds ratios are smaller than findings in other studies. For example the odds ratio for PTB was 1.2 (1.2, 1.3); VPTB 1.2 (1.1, 1.4); SGA 1.1 (1.1, 1.2); congenital malformations 1.1 (1.0, 1.2). Early neonatal deaths also posed a significant increase in odds for IPI less than 6 months 1.6 (1.2, 2.2). Inter-pregnancy intervals greater than 60 months indicated an increase in risk of adverse outcomes, however all measures of association were below an odds ratio of 1.50. This may be a result of

[9] Moderate preterm birth was defined as 32-35 weeks completed gestation.
[10] Very preterm birth was defined as 28-32 weeks completed gestation.
[11] Extreme preterm birth was defined as 20-28 weeks completed gestation.

selection bias and confounding. All the women included in this study had complete coverage for prenatal and labor and delivery services. Confounders that were not controlled for due to inconsistencies in the data included socio-demographic factors, and information regarding spontaneous and induced abortions. Abortion information could contribute to misclassification of IPI and possible spurious association between IPI and adverse birth outcomes. While the measures of association are smaller in magnitude relative to similar studies, IPI was found to be significantly associated with SGA, PTB, and END.

Hussaini et al. published a case-control study in 2012 that sought to evaluate the relationship between IPI and infant mortality in Arizona. When compared to intervals between 18-23 months, shorter intervals, specifically IPI <6 months, 7-11 months and 12-17 months significantly increased the odds of neonatal mortality. When compared to the optimal IPI, infant mortality was 76% higher for IPI less than 6 months and 85% higher for IPI 12-17 months controlling for maternal medical risks, smoking, race, gestational weight gain, prenatal care, prior history of PTB, number of living children, marital status, age, mother's education, insurance status, and geographic area of mother's residence. The full logistic model contained IPI as a predictor of infant mortality and adjusted for the confounders listed previously as well as known risk factors: PTB, LBW, and SGA. Infant mortality was increased by 68% for IPI < 6 months, 67% for IPI 6-11 months, and 48% for IPI 12-17 months. Longer IPI did not predict higher infant mortality in the fully adjusted model. It is important to note that the majority of infant mortality in this study population occurred during the neonatal period. The authors found severe increase in odds of

PTB, LBW and SGA among short IPI. This may suggest that post-neonatal mortality is associated with complications following PTB, LBW, and SGA.

A meta-analysis conducted in 2012 found that IPI less than 6 months and IPI between 6-11 months were significantly associated with an increased odds of extreme preterm birth (AOR:1.6; 95% CI:1.4, 1.8) and (AOR:1.2; 95% CI: 1.0, 1.5). Inter-pregnancy intervals less than 6 months and between 6-11 months were also significantly associated with moderate preterm birth (AOR:1.4, 95%CI:1.2, 1.7) and (AOR:1.1; 95% CI: 1.0, 1.2) respectively. Similar results were found for low birth weight (<6 m AOR: 1.4; 95%CI: 1.3, 1.6) and (6–11 m AOR: 1.1; 95%CI: 1.1, 1.2). Wendt et al. abstracted 43 stillbirth and early neonatal death studies. Among the articles that met the inclusion criteria, the overall odds ratio for stillbirth was (OR: 1.4; 95% CI: 1.1, 1.7) and the odds ratio for early neonatal death was (OR: 1.3; 95% CI: 1.0, 1.6). The results from this study support the conclusion that mothers should recuperate from birth for at least a year before conceiving another child. Most of the articles reviewed in this analysis were from developed countries; only three were from low and middle income countries, suggesting the need for future studies in low income settings as a methods of determining an ideal IPI for perinatal survival and quality of life in the developing world (Wendt et al., 2012).

A 2013 study investigating the correlates of short pregnancy intervals in the United States found that young mothers (15-19 years), those who reported the pregnancy was unintended, and those who became mothers after 20 years of age, were significantly more likely to have shorter pregnancy intervals when controlling for socio-demographic and childbearing characteristics. The study found that 55%

of pregnancies with short IPI were unintended. This is likely to have implications for future public health intervention as reduction of unintended pregnancies through contraceptive use may reduce short IPI as well. Interestingly, intended pregnancies with short IPI (45%) were more likely to occur among financially advantaged mothers; in addition, these mothers tended to be 30 years or older, college graduates and not using Medicaid to pay for delivery.

A 2014 population-based retrospective cohort study of singleton births in Ohio found that the odds of neonatal morbidity were lowest for an IPI between 12-24 months. Compared to the reference interval (12-24 months) the crude odds ratio of neonatal morbidity for an IPI less than 6 months was 1.5 (1.5-1.6) and 1.6 (1.5-1.6) for an IPI greater than or equal to 60 months. After adjusting for gestational age, race, maternal age, and prior preterm birth, the odds of neonatal morbidity for a woman with an IPI of less than 6 months was 1.4 (1.3 1.5) and 1.3 (1.3, 1.4) for IPI greater than or equal to 60 months. These results suggest that the odds of neonatal morbidity are greatest among short and long IPI. In addition IPI length is a significant contributor to neonatal morbidity independent of gestational age. This finding further supports the importance of birth planning and spacing (DeFranco, 2014).

Two studies published in July of 2014, three days apart from the other, came to opposing conclusions regarding the effects of IPI on adverse birth outcomes. In an evaluation of the relationship between short inter-pregnancy intervals and preterm birth in US adolescents between 2007 and 2008 Nerlander et al. found that IPI was significantly associated with preterm birth. More specifically, when controlling for

maternal race, age, previous preterm birth, marital status, smoking, and prenatal care, an IPI of less than 3 months was associated with an odds of moderate[12] preterm birth 1.89 (1.70, 2.10) and the odds of very preterm birth 2.52 (1.98, 3.22) relative to IPI of 18-23 months. IPI between 3-5 months were associated with a 1.68-fold odds (1.35, 2.10) of very preterm birth controlling for maternal race, age, previous preterm birth, marital status, smoking, and prenatal care. Inter-pregnancy interval greater than 36 months was also significantly associated with an increased odds of very preterm birth (AOR: 1.62; 95%CI: 1.22, 2.17) when controlling for maternal race, age, previous preterm birth, marital status, smoking, and prenatal care. This study noticed a U-shaped trend in the relationship between IPI and PTB; short and long intervals were associated with the greatest risk of PTB (Nerlander et al., 2014). A retrospective studied published three days after the Nerlander et al study sought to evaluate the relationship between IPI and SGA, PTB, and LBW. In this study, conditional logistic regression analysis was used to evaluate the risk of adverse birth outcomes. The authors confirmed previous studies that showed a J-shaped relationship between IPI and adverse birth outcomes, but suggested that a possible spurious relationship was a result of inadequate adjustment for confounding of maternal factors that are often difficult to measure. The authors hypothesized that much of the variation between birth outcomes might be explained by risk factors that vary greatly between individual women but persist between pregnancies. They identified that among women who had 3 prior births, each mother could be used as her own control for individual risk factors that were

[12] Moderate preterm birth was defined as a preterm birth occurring between 32 and 36 weeks.

suspected to contribute to the J-shaped trend in previous studies. They found a much weaker measure of effect for short intervals on the odds of PTB and LBW as had previously been reported by other studies. The unmatched model adjusted for parity, socioeconomic status, birth year, maternal age, ethnicity, and previous birth outcome. The matched model adjusted for parity, socioeconomic status, birth year and maternal age. The unmatched analysis revealed that relative to the optimal interval (18-23 months) IPI of less than 6 months resulted in a 1.4-fold odds ratio for PTB (95%CI:1.3, 1.5); a 1.3-fold odds ratio for LBW (95%CI:1.2, 1.4); and a slight decreased risk of SGA (OR:0.9; 95%CI: 0.9, 1.1). In the matched analysis, the relationship between IPI less than 6 months and PTB was nearly null (1.1; 0.9, 1.34). Similar results were found for LBW (OR: 1.0; 95%CI: 0.8, 1.3) and SGA (OR: 1.1; 95%CI: 0.9, 1.3). Both the matched and unmatched analysis found increased odds of SGA and LBW with IPI greater than 59 months, whereas the results for PTB were found to be significantly weaker in the matched model than the unmatched model. The methods used in this study adjust more fully for individual maternal confounders that may impact the relationship between IPI and adverse birth outcomes. The results from this study support the findings from previous studies that the optimal inter-pregnancy interval is 18-23 months; however this study questions the causal effect of short and long IPI on adverse birth outcomes. Further research is needed to elucidate the possible causal relationship between IPI and adverse birth outcomes.

It is evident from a review of the literature that some uncertainty remains regarding whether short IPI are associated with an increased risk of adverse birth

outcomes. However among the studies that suggest an increased risk exists for women with shorter pregnancy intervals, there is consensus regarding hypothesized mechanisms to explain the increase risk of adverse birth outcomes associated with short IPI. The following section will provide a brief summary of those hypotheses.

CHAPTER 3: HYPOTHESIZED MECHANISMS BY WHICH INTER-PREGNANCY INTERVALS MAY CONTRIBUTE TO ADVERSE BIRTH OUTCOMES

Evidence suggests that short and long term intervals between pregnancies are both associated with an increased risk of various adverse perinatal, infant, and maternal outcomes, albeit perhaps for different reasons. Substantial debate regarding the potential causal mechanisms by which short and long IPI may contribute to adverse birth outcomes exists in the literature. The hypotheses are often either biological or behavioral.

With respect to short intervals, the first, commonly cited hypothesis is often referred to as *maternal depletion syndrome*. Adequate supply of nutrients in the mother's body is necessary to support the proper growth and development of the fetus during pregnancy. An inadequate supply can result in a state of biological competition, in which the mother and infant are competing for nutrients, thereby decreasing the well-being of the mother and increasing the risk of adverse health outcomes for the infant. It is hypothesized that shorter intervals between pregnancies and periods of lactation are not long enough for the mother to recover from the physiological stresses of the preceding pregnancy (Winkvist et al., 2003). If a mother's nutritional supply is compromised at the time of conception her ability to support optimal fetal growth may be restricted, thereby increasing the infant's risk of adverse perinatal outcomes (Conde-Agudelo et al., 2012).

The second hypothesis is a component of nutrition depletion syndrome. Namely to the insufficient renewal of the mother's folate supply (Smits et al., 2004). Dr. Godfrey Oakley has popularized the finding that insufficient folate supply in

pregnant women leads to neural tube birth defects (NTD). Folate is needed both during pregnancy to promote the proper development of the fetus's neural tube and also after birth for the mother. During her fifth month of pregnancy red blood cells and serum folate concentration are diluted because of increased blood volume. Higher blood volume persist for several weeks following delivery. Conceptions during this period of folate depletion are suggested to be at greater risk for adverse perinatal outcomes.

A third depletion hypothesis relates to the duration, frequency, and intensity of lactation. Breastfeeding can further deplete maternal folate supply. The depletion of folate stores may be more severe in women who are chronically malnourished; regardless, it is suggested that the effect of short IPI on the risk of perinatal outcomes may be greater among mothers who breastfeed if their folate supply is not adequately restored through vitamin supplementation and nutrient rich foods. If a mother's folate supply is deficient before conception, she may be at greater risk for maternal folate deficiency which may contribute to PTB, SGA, LBW and NTD (Smits et al., 2004; Conde-Agudelo et al., 2012, Wendt et al., 2012).

Breast-feeding overlap is defined as the "continuation of breastfeeding into the first, second, and third trimester of pregnancy" (Conde-Agudelo, 2012). One study found that breastfeeding overlap was common among mothers who had shorter IPI than among mothers who had IPI greater than 24 months (Boerma et al., 1992). A study in Peru evaluating the effects of breastfeeding overlap on perinatal outcomes found that infants whose mother breastfed through pregnancy gained 125 grams less (8, 241) than infants whose mothers did not breastfeed through

pregnancy (Marquis et al. 2003). Other studies have shown that breastfeeding through pregnancy changes the composition of breast milk and may limit the nutritional value and immune benefits of breast milk (Marquis et al. 2003; Ismail et al., 2009).

It has also been hypothesized that IPI less than 18 months may not afford the woman's muscles enough time to recuperate from the first birth, resulting in cervical insufficiency or the "inability of the uterine cervix to retain a pregnancy in the absence of contractions" (Conde-Agudelo et al., 2012; Ludmir et al. 2000).

Vertical transmission of infections has also been hypothesized to mediate the association between short IPI and adverse perinatal outcomes. A 2004 study by Fowler et al. studied the association between IPI and congenital cytomegalovirus (CMV) infection. Women in whom CMV seroconversion had occurred within 2 years of pregnancy had a 4-fold odds of having a CMV infected infant (OR: 3.8; 95% CI: 1.6, 9.0) as mothers who became pregnant more than 2 years after the index pregnancy. The authors assumed that the risk of exposure to CMV was constant over time, suggesting that CMV infection that occurs within 2 years of conception increases the risk of congenital CMV. While the results of this study support the hypothetical causal mechanism, the authors fail to control for common confounders including maternal age and race (Fowler et al. 2004). Another study published in 2008 examined maternal risk factors that contribute to the reoccurrences of group B streptococci (GBS) in subsequent pregnancies. The study found that women with IPI less than 12 months were 1.6 times (95% CI: 1.1, 2.4) as likely to have reoccurring GBS as women who had IPI greater than 36 months. The results suggest that

recurrent GBS associated with short IPI may increase the risk of neonatal infection and corresponding adverse perinatal outcomes (Cheng et al., 2008).

With respect to increased risk of adverse perinatal outcomes associated with longer IPI, a common hypothesis is a result of women's physiological regression. That is, a mother's physiological processes are primed for fetal growth during pregnancy and shortly thereafter. If a woman does not get pregnant again with a reasonable interval, her capacity to support proper growth and development of the fetus diminishes. This hypothesis is supported by the observation that risk of adverse perinatal outcomes for longer IPI and are similar to the outcomes common to primigravid women (Zhu et al. 1999). Other hypothesis regarding longer IPI involve the mother's innate capability to have a healthy pregnancy as well as the known excess risk associated with advanced maternal age.

There is no clear evidence that explains the mechanisms through which either short and long intervals between pregnancies are associated with increased risk of adverse maternal and perinatal outcomes. In addition, the literature examining whether IPI is a risk factor for adverse perinatal outcomes is conflicting. The purpose of the introduction was to provide the necessary context for why stillbirth is a public health concern and shed light on the existing gaps in knowledge regarding stillbirth. Chapter 1 served to provide background on the Stillbirth Collaborative Network and elucidate the known risk factors for stillbirth. Chapter 2 sought to justify why this thesis will examine IPI as a risk factor for stillbirth by providing a review of the literature regarding the relationship between IPI and other adverse perinatal outcomes. Chapter 3 explored the possible causal mechanisms by which IPI may

impact perinatal outcomes. This background knowledge may aid in the assessment of confounding and effect modification when evaluating whether inter-pregnancy intervals are a risk factor for stillbirth.

The purpose of this thesis is to evaluate the impact of short and long inter-pregnancy intervals on the outcome of stillbirth using data collected in the Stillbirth Collaborative Research Network (SCRN) study. We hypothesize that short and long inter-pregnancy intervals increase the risk of stillbirth when controlling for demographic and maternal characteristics. The following section will provide an in-depth examination of the methods used to evaluate this research question.

CHAPTER 4: METHODS

STUDY DESIGN

This study was conducted using data from the Stillbirth Collaborative Research Network (SCRN) study. The SCRN study was conducted between March 2006 and September 2008. The Stillbirth Collaborative Research Network is a multi-site, population-based, case control study with prospective enrollment of livebirths and stillbirths at the time of delivery. Stillbirth Collaborative Research Network investigators established catchment areas that contained at least 6,000 births per year for urban areas and at least 3,000 births for rural areas. The catchment areas included portions of 5 states including: Rhode Island, Massachusetts, Georgia, Texas, and Utah. Investigators selected 59 hospitals for enrollment. These hospitals ensured access to at least 90% of all pregnancies ending in either a live birth or stillbirth to residents of the various catchment areas (Parker et al., 2011).

STUDY POPULATION

Study participants consisted of women who resided in one of the catchment areas, were at least 13 years of age, and identified for participation prior to discharge from the study hospital. Cases were defined as *women who experienced a fetal death at 20 or more completed weeks gestation*. Controls were defined as *women with a live birth at 20 weeks or more completed gestation*. Women excluded from the study consisted of those experiencing fetal death less than 20 weeks gestation, or whose delivery resulted from termination of a living fetus, or who were discharged prior to the study consent, or those for whom informed consent was not

obtained due to mental or linguistic barriers. Women who were incarcerated were also excluded from the study (Parker et al., 2011).

SAMPLING CONTROLS

Stillbirth Collaborative Research Network investigators carefully sampled livebirths to ensure: 1) sufficient controls at various gestational ages for future gestation-specific analysis, 2) uniform numbers of controls among various racial/ethnic groups, and 3) real-time sampling of controls. Oversampling of livebirths between 20-31 completed weeks gestation was conducted due to the difference in gestational age distribution between stillbirths and livebirths. The original study design resulted in 2:1 livebirths to stillbirths (≥32 completed weeks gestation) between non-Hispanic White women and Hispanic women. The ratios between non-Hispanic White and non-Hispanic Blacks was closer to 1:1. Due to the increased burden of stillbirth among African Americans, SCRN investigators developed an addendum to double the number of African Americans in the sample of livebirths (≥32 weeks completed gestation) (Parker et al., 2011).

ANALYSIS WEIGHTS

Analysis weights were developed to account for differences in timing of enrollment across the 59 hospitals, variation in participation rates, and different sampling probabilities among livebirths by gestational age and race.

EXCLUSIONS

Stillbirth Collaborative Research Network investigators identified 953 eligible deliveries with stillbirths and 3088 deliveries with live births. Two hundred and ninety women who had stillbirths and 1156 women with livebirths were excluded as they did not meet the eligibility criteria or refused to participate in the study, reducing the number of stillbirths to 663 and the number of livebirths to 1932. Of the pregnancies enrolled, 49 cases and 116 controls were excluded from analysis due to incomplete maternal interview and chart abstraction. In the end 614 cases and 1816 controls had complete or partial maternal interview and chart abstraction.

Information regarding case status, maternal demographics, and time between pregnancies was collected from standardized screening, maternal interview and chart abstraction forms.

This analysis was restricted to singleton pregnancies among multiparous or multigravida women who had complete information regarding the date the pregnancy prior to the index ended and estimated date of last menstrual period. Discrepancies were found between pregnancy number and the date the pregnancy ended. It was expected that the most recent birthdate would have the largest pregnancy number associated with it. In some cases the most recent pregnancy date was misclassified and was not always associated with the largest pregnancy number. For this reason the data were sorted by the date the previous pregnancy ended and only the most recent pregnancy was included for analysis purposes. All other pregnancies were excluded from analysis. Adhering to this exclusion criteria

resulted in a loss of 358 cases and 1,102 controls; leaving 256 cases and 714 controls for analysis.

DATA DESCRIPTION

Stillbirth was defined as a fetal death at or greater than 20 weeks completed gestation. Gestational age was determined by the multiple sources including assisted reproductive technology with documentation of the first day of ovulation or embryo transfer, estimated date of last menstrual period based on maternal interview, and certain date of last menstrual period based on obstetric sonograms.

The exposure, inter-pregnancy interval was evaluated as the number of months between the date the pregnancy prior to the index pregnancy ended and the estimated date of last menstrual period. The interval was first calculated in days and then converted into months. It was assumed that one month was equivalent to 30 days. Few study participants had certain dates of last menstrual period and therefore estimated date of last menstrual period was used to calculate inter-pregnancy interval.

Inter-pregnancy interval was a continuous variable categorized into 6 categories: <6 months, 6-11 completed months, 12-17 completed months, 18-23 completed months, 24-59 completed months and 60-100 completed months. The reference category for inter-pregnancy interval is 18-23 months. Short inter-pregnancy intervals included: < 6 completed months, 6-11 completed months, and 12-17 completed months. Long pregnancy intervals included: 24-59 month, and 60-100 months.

Information regarding maternal characteristics was derived from the standardized maternal interview form. Ten additional maternal characteristics were evaluated as potential effect modifiers and confounders. These included: age, race, BMI, education level, insurance status, smoking status, alcohol status, marital status, use of assisted reproductive technology (ART) and prior pregnancy outcome.

Maternal age was defined as the age at the start of the interval. Age was calculated by taking the difference between the date of the pregnancy prior to the index ended subtracted by the mother's date of birth. Maternal age was then categorized into five categories: less than 20 years, 20-23 years, 24-27 years, 28-31 years, ≥ 32 years. These age categories were evenly distributed across the sample and had greater than 30 observations, allowing for sufficient power during analysis.

All other variables pertain to the subsequent (index) pregnancy. Race/ethnicity was divided into four categories including: non-Hispanic white, non-Hispanic black, Hispanic, and Other. Body mass index (BMI), at initiation of the subsequent (index) pregnancy, was classified as underweight (<18.5 kg/m^2), normal weight (18.5-24.9 kg/m^2), overweight (25- 29.9 kg/m^2), obese (30-34.9 kg/m^2), and very obese (≥ 35 kg/m^2). Education level was divided into three categories: 0-11 years (none, primary and some secondary school), 12 years (completed secondary), and ≥ 13 years (some college). Insurance status was divided into three categories including: no insurance, any public or private assistance, and VA/commercial health insurance/HMO. Smoking status was defined as smoking during 3 months prior to or during pregnancy and categorized into three categories: ≥ 10 cigarettes, < 10 cigarettes and non-smoker. Alcohol consumption was defined as alcohol use during

3 months prior to pregnancy and categorized into three categories: did not drink, drank/no binging, and binged. Marital status was split into three categories: not married or cohabitating, cohabitating, and married. Use of assisted reproductive technologies was a dichotomous variable (yes/no). Lastly, prior pregnancy outcome was defined using pregnancy outcome and gestational age data from the maternal interview form. Prior pregnancy outcome was divided into four categories: early terminations (<20 weeks), spontaneous abortion, ectopic pregnancy and molar pregnancy were grouped into one category. The other categories included: full term (≥ 37 weeks) livebirths, preterm (20-36 weeks) livebirths, and preterm stillbirths.

STATISTICAL ANALYSIS

All analyses were conducted using Statistical Analysis Software (SAS) Version 9.3. Logistic models were first created for the overall or crude effect of both short and long inter-pregnancy intervals and stillbirth. This analysis evaluated the risk of stillbirth across all six categories of inter-pregnancy interval: <6 months, 6-11 months, 12-17 months, 18-23 months, 24-59 months and 60-100 months. For the purposes of discussion, this model will be referred to as Model 1.

This analysis was also restricted to evaluate the risk for exclusively short intervals and exclusively long intervals. Short and long intervals were evaluated separately as it was assumed that the etiology of their effect on stillbirth risk might differ. The evaluation of short inter-pregnancy intervals on stillbirth risk restricted the analysis to: <6 months, 6-11 months, 12-17 months, and 18-23 months. This model will be referred to as Model 2. Similarly the evaluation of long inter-

pregnancy intervals restricted the analysis to: 18-23 months, 24-59 months and 60-100 months. This model will be referred to as Model 3.The reference category for inter-pregnancy interval for all three models was 18-23 months.

Interaction and confounding were then evaluated separately for all three models. Interaction assessment involved a weighted chunk test followed by a weighted backward elimination of individual interaction terms. Interaction terms included product terms between exposure (inter-pregnancy interval) and key covariates: age, race, BMI, education level, insurance status, smoking status, alcohol status, marital status, use of assisted reproductive technology (ART) and prior pregnancy outcome. All interaction terms were evaluated at a 5% significance level.

The chunk test revealed no significant interaction. Nonetheless, I ran a weighted backward elimination (BWE) on each individual interaction term. Previous SCRN publications have evaluated interaction at a 0.20 significance level. At an alpha of 0.20, interaction existed between inter-pregnancy interval and prior pregnancy outcome. However for the purposes of this analysis significance was evaluated at an alpha level of 0.05. No significant interaction was found after conducting a chunk test and subsequent BWE when the analysis was restricted to only short and long intervals.

Following the interaction assessment, an all-possible subsets approach was conducted to evaluate confounding for the three models. Separate confounding assessments were conducted for the three models as it was assumed that confounders may vary between short and long intervals and their relationship to stillbirth risk.

To assess collinearity, variance inflation factors for each predictor were examined. Collinearity was diagnosed if condition indexes (CNIs) were greater than 30 and there were 2 or more variance decomposition proportions (VDPs) greater than 0.5. Final models were selected based on Hosmer Lemeshow (HL) Goodness of Fit Test, and area under the curve using Receiver Operating Curves (ROC) was applied to the final models for assessment of statistical significance.

CHAPTER 5: RESULTS

DESCRIPTIVE STATISTICS

A weighted total of 970 .4 pregnancies were included in this analysis, with 714.1 controls and 256.3 cases. Descriptive statistics for the study participants are shown in Table 1. Among cases and controls 69.0% of women were between the ages of 20-31 years, with a mean age of 25.6 years. Mean IPI was 29.0 months; 48% had long inter-pregnancy intervals between 24-100 months, 40% had IPIs less than 18 months, and 12.4% of all pregnancies had ideal IPIs between 18-23 months. The preceding pregnancy outcome was 78% full-term livebirths, 10% previous spontaneous abortion, ectopic pregnancy, or molar pregnancy, 10% pre-term livebirth, and 2% previous stillbirth.

Chi square tests for association between covariates and the outcome of interest are also summarized in Table 1. There were statistically significant differences in the distribution of inter-pregnancy interval (χ^2 =34.5, p= <0.0001), race (χ^2 =19.3, p= 0.0002), marital status (χ^2 =14.3, p= 0.0008), maternal BMI (χ^2 =13.9, p= 0.0076), smoking status (χ^2 =8.9, p= 0.0117), and prior pregnancy outcome (χ^2 =66.9, p= <0.0001) between stillbirths and livebirths. There was no evidence of statistically significant differences in distribution of maternal age, education, insurance status, alcohol status, and use of ART between stillbirths and livebirths.

Chi square tests for association between covariates and inter-pregnancy intervals are presented in Table 2. There were statistically significant differences in the distribution of maternal age (χ^2 =39.4, p= 0.006), education (χ^2 =25.0, p=

0.0.0054), maternal BMI (χ^2 =32.5, p= 0.0387), alcohol status (χ^2 =25.3, p= 0.0048), and prior pregnancy outcome (χ^2 =183.3, p= <0.0001) across inter-pregnancy intervals. Prior pregnancy outcome (p-value <0.001) and maternal BMI (p-value 0.01-0.04) were strongly associated with both inter-pregnancy interval and stillbirth.

LOGISTIC MODELS FOR INTER-PREGNANCY INTERVALS

Crude Model

Table 3 summarizes the results of Model 1 which models the odds of stillbirth across both short and long intervals. The crude model examines the relationship between IPI and stillbirth not controlling for any confounder. In this model there is a statistically significant increase in risk of stillbirth for both short intervals (<6 months) and long intervals (60-100 months). Women with IPI less than 6 months had a 3.3-fold odds (95%CI: 1.8, 6.0) and women with IPIs between 60-100 months had a 2.5-fold odds (95%CI: 1.4, 4.4) when compared with women with IPI between 18-23 months.

Adjusted Models

The gold standard for Model 1 controlling for all ten suspected covariates[13] revealed an increase in stillbirth risk for intervals <6 months and intervals between 60-100 months. Intervals <6 months were associated with a 1.6-fold odds (95%CI:

[13] age, race, BMI, education, insurance, smoking status, alcohol, marital status, ART use and prior pregnancy outcome

0.8, 3.2), while intervals between 60-100 months were associated with a 2.6-fold odds (95%CI: 1.3, 4.8). While there was an increase in stillbirth risk for shorted intervals, this result was not statistically significant. The other intervals presented an insignificant null relationship between IPI and stillbirth: 6-11 months (OR: 1.0; 95%CI: 0.5, 1.9), 12-17 months (OR: 1.2; 95%CI: 0.6, 2.7), and 24-59 months (OR: 1.0; 95%CI: 0.6, 1.7). Hosmer Lemeshow (HL) goodness of fit and examination of receiving operating curves was applied to the gold standard for model 1. Hosmer Lemeshow goodness of fit resulted in a p-value of <0.001 and area under the curve (AUC) of 0.664.

Age, BMI, education, and prior pregnancy outcome were true confounder's (i.e. Failing to control for these covariates would result in a greater than 10% change in effect). This adjusted model confirmed that short intervals (<6 months) were associated with a 1.7-fold odds ratio for stillbirth although this finding was not statistically significant (95% CI: 0.9, 3.3). In addition, long intervals (60-100 months) were significantly associated with a 2.5-fold odds ratio with 95% confidence interval of (95%CI: 1.3, 4.6). The other intervals presented an insignificant null relationship between IPI and stillbirth: 6-11 months (OR: 1.1; 95%CI: 0.6, 2.0), 12-17 months (OR: 1.2; 95%CI: 0.7, 2.2), and 24-59 months (OR: 1.0; 95%CI: 0.6, 1.7). Hosmer Lemeshow goodness of fit resulted in a p-value of <0.001; ROC curves revealed an AUC of 0.646.

The adjusted model had greater precision than the gold standard model, similar fit and slightly lower AUC. The gold standard model controlling for all

suspected confounders was selected as the final model based on HL goodness of fit and greater AUC.

LOGISTIC MODELS FOR SHORT INTER-PREGNANCY INTERVALS

Crude Model

Table 4 summarizes the results of Model 2 which models the odds of stillbirth across short intervals. The crude model examines the relationship between IPI and stillbirth not controlling for any confounder. In this model there is a statistically significance increase in risk of stillbirth for short intervals (<6 months). Women with IPI less than 6 months have a 3.3-fold odds ratio for stillbirth (1.8, 6.0). Inter-pregnancy intervals between 6-11 months had a 1.4-fold odds ratio for stillbirth (95%CI 0.8, 2.5) and 12-17 months had a 1.2-fold odds ratio for stillbirth (95%CI: 0.7, 2.1). Both the results for 6-11 months and 12-17 months were statistically insignificant.

Adjusted Models

The gold standard for Model 2 controls for age, race, BMI, education, insurance, smoking status, alcohol, marital status, ART use and prior pregnancy outcome. Inter-pregnancy intervals <6 months were associated with a 1.6 fold odds of stillbirth. While there was an increase in stillbirth odds for shortest interval, this result was not statistically significant (95%CI: 1.3, 4.8). Inter-pregnancy intervals between 6-11 months (OR: 1.0; 95%CI: 0.5, 1.9) and 12-17 months (OR: 1.2; 95%CI:

0.6, 2.1) had statistically insignificant and near null relationships with stillbirth. Hosmer Lemeshow goodness of fit resulted in a p-value of 0.001; ROC curves revealed an AUC of 0.72.

Age, insurance, and prior pregnancy outcome were true confounders. This adjusted model proved that short intervals (<6 months) were associated with an increase in stillbirth odds (AOR: 1.7) although this finding was not statistically significant (95%CI: 0.89, 3.32). The other intervals presented an insignificant, null relationship between IPI and stillbirth: 6-11 months (OR: 1.1; 95%CI: 0.6, 2.0) and 12-17 months (OR: 1.2; 95%CI: 0.7, 2.2). Hosmer Lemeshow goodness of fit resulted in a p-value of 0.005; ROC curves revealed an AUC of 0.64.

Despite the slight improvement in precision in the adjusted model, the gold standard model had better fit and greater AUC and therefore was selected as the final model for short inter-pregnancy intervals as a risk factor for stillbirth.

LOGISTIC MODELS FOR LONG INTER-PREGNANCY INTERVALS

Crude Model

Table 5 summarizes the results of Model 3 which models the odds of stillbirth across long intervals. The crude model examines the relationship between IPI and stillbirth not controlling for any confounder. In this model there is a statistically significant increase in odds of stillbirth for long intervals between 60-100 months (OR: 2.5; 95%CI: 1.4, 4.4). Inter-pregnancy intervals between 24-59 months had a statistically insignificant and null association with stillbirth with an OR of 1.0 and corresponding 95% confidence interval of (0.6, 1.7).

Adjusted Models

The gold standard for Model 3 controls for age, race, BMI, education, insurance, smoking status, alcohol, marital status, ART use and prior pregnancy outcome. In this model there is a statistically significant increase in odds of stillbirth for long intervals between 60-100 months (OR: 2.4; 95%CI: 1.3, 4.7). Inter-pregnancy intervals between 24-59 months had a statistically insignificant and null association with stillbirth with an OR of 1.0 and corresponding 95% confidence interval of (0.6, 1.7). Lemeshow goodness of resulted in a p-value of 0.0001 ROC curves revealed an AUC of 0.66.

None of the 10 suspected covariates acted as confounders for the relationship between long inter-pregnancy intervals and stillbirth. For this reason, Hosmer Lemeshow goodness of fit tests and examination of ROC curves to measure area under the curve were applied to both the crude model and the gold standard model.

The crude model had an HL goodness of fit p-value of 0.0054 and an AUC of 0.57 whereas the gold standard model had an HL goodness of fit p-value of 0.0001 and an AUC of 0.66. The gold standard model was selected as the final model to demonstrate the relationship between long inter-pregnancy intervals and risk of stillbirth.

CHAPTER 6: DISCUSSION

The results of this study suggest that inter-pregnancy intervals less than 6 months and an IPI between 60-100 months are associated with an increased risk of stillbirth controlling for age, race, education, insurance, BMI, smoking, alcohol, marital status, ART, and prior pregnancy outcome. However, only the results for IPIs between 60-100 months were statistically significant. These results are similar to the conclusions drawn by Stephansson et al. in which a statistically significant increase in risk of stillbirth was apparent among women who had IPIs between 0-3 (OR: 1.6; 95%CI: 1.1, 2.5) and IPIs ≥ 72 months (OR: 1.5; 95% CI: 1.1, 2.1).

A number of women were excluded from this analysis as they possessed characteristics that could bias the results. Only singleton births were included in the study as multiple gestation births are reported to have higher rates of adverse birth outcomes including PTB and LBW (Cnattingus, 2002; SCRN, 2007). Women in this study had IPIs less than 9 years because women with IPIs greater than 9 years may suffer from infertility or require assisted reproductive technologies.

The research explaining why long inter-pregnancy intervals act as a risk factor for adverse birth outcomes is disputed. Some authors suggest that parous women with long inter-pregnancy intervals behave as nulliparous women with regard to risk of pregnancy complications and adverse birth outcomes (Conde-Agudelo et al., 2006 ;Zhu et al., 1999; Zhu et al., 2005; Zhu et al., 2006;). This hypothesis states that after delivery a mother gradually loses her 'child-bearing' capabilities that developed during the preceding pregnancy. The results from this

study suggest that this 'window of opportunity' diminishes as a woman's pregnancy interval approaches 60 months.

As other studies have done (Boerma et al., 1992; Conde-Agudelo et al., 2006; Conde-Agudelo et al., 2012; DeFranco et al., 2014; DeFranco et al., 2007; Fowler et al., 2004; Fuentes-Afflick et al., 2000; Gemmill et al., 2003; Grisaru-Granovsky et al., 2009; Hogue et al., 2011; Hussaini et al., 2013; Khoshnood et al., 1998; Kozuki et al., 2013; Nerlander et al., 2014; Rodrigues et al., 2008; Smith et al., 2003; Smits et al.,2001; Stephanson et al., 2003; Wong et al., 2014; Zhu et al., 2005; Zhu et al.,1999), this study chose the IPI of 18-23 months to be the reference group. However, unlike some previous research, there was little difference in the odds of stillbirth for intervals from 6-17, 18-23, or 24-59 months.

Other studies that have evaluated the risk of IPI on adverse perinatal outcomes including: PTB and LBW; in these studies intervals between 6-17 and 24-59 months were generally associated with an increased risk of adverse birth outcomes. Because the SCRN study was a case-control study of stillbirths, it was not possible to examine other adverse perinatal outcomes.

The results from this study also suggest differences in confounders between short intervals and long intervals. Confounders of short intervals included age, insurance, and prior pregnancy outcome. However, there was no evidence that any of the ten tested covariates were confounders of an association of long inter-pregnancy intervals with stillbirth. Conversely, when short and long intervals were included in one model, we found that age, BMI, education and prior pregnancy outcome confounded the association between "risky" intervals and the referent

interval of 18-23 months. Women who were teenagers at the birth of the preceding pregnancy were more likely than women in their twenties to have either long or short IPI. This may reflect differences in life course between women who had a pattern of early childbearing from those who postponed the second pregnancy until after achieving educational or other goals. Older women, who are known to have higher risk of stillbirth, had less time to complete childbearing before ending their potential reproductive lifespan; unsurprisingly, they had shorter IPI than their younger counterparts. Women who were at IPI extremes were more likely to have less than a high school education and less likely to have some college education than women in the referent interval or 18-23 months. Additionally, women with higher BMI (overweight, obese, or very obese) were more likely than women with normal BMI to have both short and long inter-pregnancy intervals. This may be because obese women, who have a higher risk of stillbirth, have difficulty getting pregnant which may contribute to longer intervals between pregnancies. Women with higher BMI may also have difficulty carrying a child to term. A woman with both high BMI and lacking success in carrying a child to term may experience urgency to become pregnant again quickly, in order to avoid long-term grief or stigma and marginalization from her community. An additional explanation why BMI confounds the relationship between IPI and SB may be that BMI is an indicator for unhealthy lifestyle behaviors or lower SES that may contribute to shortened inter-pregnancy intervals.

Whether the effect of inter-pregnancy interval on adverse pregnancy outcomes is causal or not remains disputed. The risk of adverse pregnancy

outcomes increases with maternal characteristics including age, BMI, chronic disease, infections or placental complications. Most of the women in this study had a full-term livebirth. These women were less likely to have shorter inter-pregnancy intervals. Women who suffered a previous stillbirth, spontaneous abortion, ectopic pregnancy or molar pregnancy, women were more likely to have short IPIs (p-value= 0.0007). Prior studies have investigated the factors that influence IPI including prior pregnancy outcomes pressure from family members to get pregnant. Some studies suggest that inter-pregnancy intervals may be influenced by changes in partner (Basso et al., 2001; Skjaerven et al., 2002; Zhang et al., 2007). There was no obvious trend in IPI among women who has a preterm livebirth. The risk of stillbirth was greater for women who had a prior stillbirth at short and long intervals (<6 month and 60-100 months). The finding that longer intervals were associated with marital status and cohabitation (p= 0.0003) may complement such studies, although I was not able to control for changes in partners

CHAPTER 7: STRENGTHS AND WEAKNESSES

One of the strengths of the analysis is the fact that the data were collected from the largest population-based study of stillbirth in the U.S. to date. The multi-site study design enabled a large sample size thus contributing to the power and generalizability of the results. Detailed information from both maternal interviews and chart abstraction enabled control for prior risk factors of stillbirth to allow for a more accurate, in-depth analysis of the effect of inter-pregnancy interval on stillbirth risk. The SCRN study was specifically designed to evaluate the etiology of stillbirth whereas other studies on stillbirth may rely on pooling data from multiple databases that often have fragmented information regarding maternal and obstetric characteristics.

In this study only the information regarding the most recent pregnancy was used for analysis, perhaps limiting the degree of recall bias in regards to the details of that pregnancy including but not limited to: birth outcome, gestational age and date of birth. The degree to which recall bias or possible misclassification exists in this study however is dependent on the number of pregnancies a mother was asked to recall.

Limitations of this study include the retrospective collection of maternal demographic and obstetric information. Some women in this study had up to 17 pregnancies. Detailed information regarding pregnancy history was supposed to be recorded in chronological order; therefore the most recent pregnancy or the pregnancy most relevant for this analysis would happen towards the end of the maternal interview. Recalling the details of previous pregnancies is time consuming

for both researchers and mothers. In addition, recalling adverse pregnancy outcomes may be emotionally exhausting for mothers. Information regarding the date the pregnancy ended, gestational age, and birth outcome may all be subject to misclassification or recall bias.

In addition, inter-pregnancy interval required calculating the number of months between the date the pregnancy prior to the index ended and the estimated date of last menstrual period. Last menstrual period was either based on maternal interview (estimated LMP) or ultrasound (certain LMP). An estimated LMP was missing less often than the certain date of LMP. Because estimated LMP was based on maternal interviews it may be subject to recall bias.

Prior studies have concluded that inter-pregnancy intervals are strongly influenced by changes in partner. The finding that longer intervals were associated with marital status and cohabitation may be consistent with results from those studies. I was not however able to account for temporal changes in marital status, insurance status, education, BMI smoking status, alcohol consumption, or changes in how participants identify in regards to racial/ethnic origin. For the purposes of this analysis, these factors were assumed to remain constant.

While the sample size allowed for sufficient power when evaluating stillbirth risk across various inter-pregnancy intervals, the sample size did not support further stratification of stillbirth risk by other covariates of interest (i.e. age and prior pregnancy outcome).

In conclusion short and long inter-pregnancy intervals were associated with an increased risk of stillbirth when controlling for age, race, BMI, education level,

insurance status, smoking status, alcohol consumption, marital status, ART use and prior pregnancy outcome. These results contribute to the gap in knowledge regarding risk factors of stillbirth and more specifically, the impact of inter-pregnancy intervals on stillbirth.

CHAPTER 8: FUTURE PUBLIC HEALTH IMPLICATIONS

For nine months women and families prepare for the healthy and safe delivery of their child. Planning for birth is a multi-step process; eating and lifestyle behaviors are often altered, time and money are often spent developing clean, and safe spaces in the home for the baby to eat and sleep. In addition, families and communities begin to discuss names for the child and dream about the child soon to be born. The anticipated arrival of a child can be a joyous and unifying occasion for mothers and communities. It is for this reason that the unexpected birth of a stillborn child is both a tragic and traumatic loss at the individual, community, and societal levels.

Many of the known risk factors of stillbirth, including but not limited to: placental abruption, maternal infection, genetic or chromosomal abnormalities, chronic disease and various maternal characteristics can be prevented with frequent medical monitoring of the mother. In fact, much of the decline in stillbirths in the United States since the 1950s can be attributed in part to improved monitoring and treatment of maternal BMI, blood pressure, and diabetes. Early genetic screening and proper monitoring of maternal vital signs may help to reduce the risk of stillbirth.

The Stillbirth Collaborative Research Network Study was designed to address the gap in knowledge regarding the prevalence, etiology, causal risk factors, and scope of the emotional, mental, and physiological toll of stillbirth on mothers and communities. This research seeks to examine the relationship between inter-

pregnancy interval and stillbirth. The impact of birth spacing on low-birth weight and preterm birth has been widely studied. These studies have shown that shorter (generally <6 months) and longer (generally >59 months) intervals are associated with a greater risk of both low-birth weight infants and preterm infants. This study contributes to the body of knowledge regarding the implications of proper birth spacing on the reduction of adverse perinatal outcomes, as it was found that shorter (<6 months) and longer (>59 months) intervals are associated with an elevated risk of stillbirth. However, the public health implications of this study extend beyond addressing the gap in knowledge regarding the risk factors of stillbirth.

Investing in the healthy development and delivery of a child is costly. In 2013, a report was published by Truven Health Analytics entitled *The Cost of Having a Baby in the United* States. It was estimated that in the United States, 4 million women give birth each year. The cumulative cost for 4 million annual births in the United States was reported to be well over $50 billion. A family that loses a child may require additional medical services to address mental and physiological factors that may act as risk factors for future adverse perinatal and maternal outcomes. Apart from the emotional loss associated with stillbirth, the financial costs associated with preparing for a new baby are substantial. More knowledge regarding risk factors associated with stillbirth and recommendations that mothers can follow to prevent an adverse outcome may reduce the financial burdens of pregnancy.

Adequate birth spacing may help to reduce the risk of adverse perinatal and maternal health outcomes. In addition, healthier mothers and healthier babies may help reduce healthcare expenditures associated with pregnancy in the United States. It is for this reason that governments, businesses, and academic institutions should enact family and baby friendly policies that afford mothers the opportunity to have children at the ideal reproductive ages and with ideal inter-pregnancy intervals. Healthy, happy mothers are more productive in the workplace and may generate greater economic revenue. Healthier mothers also give birth to healthier babies who have the capacity to be productive citizens. Promoting policies that allow women to bear children at appropriate ages and afford ideal birth spacing without forfeiting their academic and professional development should be seen as an immediate and long term investment in the growth of healthy nations.

In addition, this research may help to inform future theoretical frameworks that explain the possible causal mechanisms for birth spacing on stillbirth. Thus, results from this study may also help to develop translation and guidance documents to help inform clinical and public health leadership regarding appropriate education and counseling about the benefits of proper birth spacing intervals.

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TABLES

Table 1. Socio-demographic and Pregnancy Characteristics of Study Participants by Outcome								
	Stillbirths		**Livebirths**		**Total**		**Chi-Square**	**P Value**
	n	**%**	**n**	**%**	**n**	**%**		
	256	26.4	714	73.6	970.4	100		
Inter-pregnancy Intervals								
<6 months	43.8	17.1	51.2	7.2	95.1	9.8	36.4681	<0.0001
6-11 months	33.6	13.1	93.6	13.1	127.2	13.1		
12-17 months	38.8	15.2	126.0	17.6	164.6	17.0		
18-23 months	25.0	9.8	96.2	13.5	121.2	12.4		
24-59 months	73.3	28.5	282	39.4	355.1	36.6		
60-100 months	41.8	16.3	65.6	9.2	107.3	11.1		
Maternal Age								
<20	35.3	13.8	97.6	13.5	132.2	13.6	5.2000	0.2674
20-23	51.3	20.0	172.0	24.1	223.2	23.0		
24-27	58.5	22.8	183.0	25.6	241.2	24.9		
28-31	68.0	26.5	146.0	20.4	213.5	22.0		
>= 32	43.2	16.9	117.0	16.4	160.3	16.5		
Maternal Race								
Non-Hispanic White	91.6	35.7	310.0	43.4	401.3	41.4	19.3405	0.0002
Non-Hispanic Black	49.8	19.4	66.0	9.2	115.8	11.9		
Hispanic	98.7	38.6	287.0	40.2	385.9	39.8		
Other	16.3	6.3	51.2	7.2	67.5	6.9		
Marital Status*								
Married	149.0	58.2	485	68.0	634	65.4	14.2655	0.0008
Cohabitating	58.0	22.6	154	21.6	212	21.9		
Not married or cohabitating	49.1	19.2	74.2	10.4	123.3	12.7		

Maternal Education*								
0-11 (none, primary, some secondary)	64.0	25.0	135.0	19.0	199.0	20.6	4.5644	0.0900
12 (completed secondary)	70.0	27.3	195.0	27.4	264.0	27.4		
>= 13 (college)	122.0	47.7	382.0	53.6	503.0	52.0		
Maternal BMI								
<18.5 (underweight)	4.6	1.8	22.0	3.1	26.5	2.8	13.8995	0.0076
18.5-24.9 (normal)	88.9	35.2	332.0	46.8	420.8	43.7		
25-29.9 (overweight)	65.6	26.1	164.0	23.1	229.8	23.8		
30-34.9 (obese)	46.3	18.3	102.0	14.3	147.8	15.4		
>=35 (very obese)	46.9	18.6	90.3	12.7	137.2	14.3		
Maternal Insurance*								
Any Public/Private Assistance	135.0	53.0	341	47.8	475.7	49.2	2.5952	0.2732
VA/Commercial health insurance/HMO	106.0	41.7	339	47.6	445.1	46.0		
No insurance	13.5	5.3	32.6	4.6	46.1	4.8		
Smoking Status*								
Smoked during 3 months prior/during pregnancy, >= 10 cigarettes	26.7	10.4	39.2	5.5	65.9	6.8	8.9031	0.0117
Smoked during 3 months prior/during pregnancy, <10 cigarettes	20.2	7.9	42.1	5.9	62.3	6.4		
Did not smoke	209	81.7	630	88.6	839.8	86.8		
Alcohol Status*								
Binge drinking	39.9	15.7	112.0	15.7	151.6	15.7	0.7761	0.6784
Moderate drinking	48.2	19.0	154.0	21.6	201.8	20.9		
No drinking	165	65.3	447.0	62.7	612.1	63.4		
ART Use								
Yes	7.9	3.1	21.2	3.0	29.1	3.0	0.0108	0.9174

No	248.0	96.9	693.0	97.0	941.3	97.0		
Prior Pregnancy Outcome*								
SA, EP, or MP	48.8	19.0	53.8	7.6	102.5	10.6	66.9186	<0.0001
Full Term Livebirth	157.0	61.2	598.0	84.0	754.9	78		
Preterm Livebirth	37.3	14.5	56.1	8.0	93.4	9.6		
Previous Stillbirth	13.3	5.2	4.1	0.6	17.5	1.8		

*Missing values in dataset

Table 2. Chi-square test for association comparing covariates with inter-pregnancy interval

	<6 months		6-11 months		12-17 months		18-23 months		24-59 months		60-100 months			
	N	%	N	%	N	%	N	%	N	%	N	%	Chi Square	P Value
Maternal Age														
<20	12.2	12.9	16.7	13.1	20.6	12.5	11.8	9.8	52.1	14.7	18.7	17.4		
20-23	16.1	16.9	28.2	22.2	37.1	22.6	31.3	25.8	81.7	23.0	81.7	26.9		
24-27	18.0	19.0	30.2	23.7	39.6	24.1	28.4	23.5	84.8	23.9	40.1	37.4	39.3818	0.0060
28-31	28.9	30.4	23.8	18.7	33.8	20.6	25.0	20.6	87.9	24.8	14.0	13.1		
>= 32	19.8	20.9	28.3	22.3	33.4	20.3	24.7	20.4	48.5	13.7	5.6	5.2		
Maternal Race														
Non-Hispanic White	29.9	31.5	44.4	34.9	76.2	46.3	61.5	50.7	153.5	43.2	35.9	33.5		
Non-Hispanic Black	14.3	15.1	19.2	15.1	21.7	13.2	10.7	8.8	33.4	9.4	16.6	15.5	21.3852	0.1250
Hispanic	44.1	46.6	53.9	42.4	60.1	36.5	39.0	32.2	142.1	40.0	46.6	43.4		
Other	6.7	7.1	9.7	7.6	6.6	4.0	10.0	8.3	26.2	7.4	8.2	7.6		
Marital Status*														
Married	55.5	58.4	73.7	57.7	105.5	64.1	82.2	67.8	253.3	71.6	63.8	59.5		
Cohabitating	21.7	22.8	34.2	26.9	36.6	22.2	23.9	19.8	66.1	18.7	29.5	27.5	15.4828	0.1154
Not married or cohabitating	17.9	18.9	19.3	15.2	22.5	13.7	15.0	12.4	34.6	9.8	13.9	13.0		
Maternal Education*														
0-11 (none, primary, some secondary)	29.6	31.5	29.4	23.1	27.9	17.1	15.6	12.9	69.9	19.8	26.2	24.5		
12 (completed secondary)	23.2	24.7	39.3	30.9	41.7	25.5	32.6	26.9	88.4	25.0	39.2	36.5	24.9846	0.0054
>= 13 (college)	41.2	43.8	58.5	46.0	94.1	57.5	72.9	60.2	194.8	55.2	41.9	39.0		

Maternal BMI*														
<18.5 (underweight)	1.8	1.9	1.7	1.4	6.6	4.0	3.8	3.1	9.5	2.7	3.2	3.0		
18.5-24.9 (normal)	32.2	34.2	52.9	42.3	91.2	55.4	62.7	52.1	142.9	40.1	38.8	36.7		
25-29.9 (overweight)	21.9	23.3	31.5	25.2	36.1	22.0	22.6	18.8	89.9	25.6	27.5	26.0	32.4582	0.0387
30-34.9 (obese)	17.7	18.8	17.9	14.3	17.1	10.4	12.2	10.1	61.9	17.6	21.0	19.9		
>=35 (very obese)	20.5	21.8	21.1	16.9	13.6	8.2	19.0	15.8	47.7	13.6	15.2	14.4		
Maternal Insurance*														
Any Public/Private Assistance	38.8	41.4	45.9	36.5	77.9	47.3	59.5	49.1	183.7	51.9	39.2	36.5		
VA/Commercial health insurance/HMO	49.7	53.0	73.4	58.3	78.0	47.5	57.6	47.5	156.5	44.2	60.3	56.2	16.1517	0.0954
No insurance	5.3	5.6	6.7	5.3	8.5	5.2	4.1	3.4	13.7	3.9	7.8	7.3		
Smoking Status*														
Smoked during 3 months prior/during pregnancy, >= 10 cigarettes	6.2	6.5	13.9	11.0	7.3	4.4	6.9	5.7	19.9	5.6	11.7	10.9		
Smoked during 3 months prior/during pregnancy, <10 cigarettes	5.3	5,6	6.9	5.4	9.4	5.7	9.2	7.6	27.2	7.7	4.3	4.0	11.1101	0.3490
Did not smoke	83.6	87,9	106.3	83.6	147.9	89.8	105.1	86.7	305.7	86.7	91.3	85.1		
Alcohol Status*														
Binge drinking	7.1	7.5	17.1	13.8	26.3	16.0	29.6	24.4	55.7	15.8	15.9	14.8		
Moderate drinking	16.3	16.3	19.5	15.6	26.2	15.9	29.9	24.7	81.3	23.1	28.5	26.5	25.2751	0.0048
No drinking	71.6	75.3	88.6	70.8	112.0	68.1	112.0	50.9	215.1	61.1	62.9	58.7		
ART Use														
Yes	3.8	4.0	1.3	1.0	5.7	3.5	3.9	3.3	13.0	3.7	1.3	1.2	3.9632	0.5547

No	91.2	95.9	125.9	99.0	158.9	96.5	117.2	96.5	342.0	96.3	105.9	98.8		
Prior Pregnancy Outcome*														
SA, EP, or MP	42.1	44.3	22.3	17.6	14.3	8.7	9.0	7.4	9.8	2.8	4.9	4.7	183.3338	<0.0001
Full Term Livebirth	42.5	44.7	82.2	64.5	133.6	81.6	101.6	83.8	308.1	86.8	86.9	81.4		
Preterm Livebirth	4.2	4.5	20.9	16.5	11.2	6.8	9.3	7.6	33.6	9.5	14.2	13.4		
Previous Stillbirth	6.2	6.6	1.7	1.3	4.7	2.8	1.3	1.1	3.6	1.0	0.0	0.0		

*Missing values in dataset

Table 3. Odds Ratios for Stillbirth Associated with Inter-pregnancy Interval

	Crude [a]		Gold Standard [b]		Adjusted [c]	
	OR	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**
< 6 MONTHS	3.3	(1.8, 6.0)	1.6	(0.8, 3.2)	1.7	(0.9, 3.3)
6-11 MONTHS	1.4	(0.8, 2.5)	1.0	(0.5, 1.9)	1.1	(0.6, 2.0)
12-17 MONTHS	1.2	(0.7, 2.1)	1.2	(0.6, 2.7)	1.2	(0.7, 2.2)
18-23 MONTHS	REFERENCE		REFERENCE		REFERENCE	
24-59 MONTHS	1.0	(0.6, 1.7)	1.0	(0.6, 1.7)	1.0	(0.6, 1.7)
60-100 MONTHS	2.5	(1.4, 4.4)	2.6	(1.3, 4.8)	2.5	(1.3, 4.6)

[a] Model contains only exposure and outcome of interest.

[b] Model controls all confounders: age, race, education, insurance, BMI, smoking, alcohol, marital status, ART, and prior pregnancy outcome. Hosmer Lemeshow p-value <0.001 and area under the curve of 0.664.

[c] Model controls for true confounders: age, BMI, education, and prior pregnancy outcome. True confounders are those that resulted in >10% change in effect. Hosmer Lemeshow p-value <0.001 and area under the curve of 0.646.

Table 4. Odds Ratios for Stillbirth Associated with Short Inter-Pregnancy Intervals

	Crude [a]		Gold Standard [b]		Adjusted [c]	
	OR	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**
< 6 MONTHS	3.3	(1.8, 6.0)	1.6	(0.8, 3.2)	1.7	(0.9, 3.3)
6-11 MONTHS	1.4	(0.8, 2.5)	1.0	(0.5, 1.9)	1.1	(0.6, 2.0)
12-17 MONTHS	1.2	(0.7, 2.1)	1.2	(0.6, 2.1)	1.2	(0.7, 2.2)
18-23 MONTHS	REFERENCE		REFERENCE		REFERENCE	

[a] Model contains only exposure and outcome of interest.

[b] Model controls all confounders: age, race, education, insurance, BMI, smoking, alcohol, marital status, ART, and prior pregnancy outcome. Hosmer Lemeshow p-value 0.0001 and area under the curve of 0.720.

[c] Model controls for true confounders: age, insurance, and prior pregnancy outcome. Hosmer Lemeshow p-value 0.005 and area under the curve of 0.644.

Table 5. Odds Ratios for Stillbirth Associated with Long Inter-pregnancy Interval

	Crude [a]		Gold Standard [b]	
	OR	**95% CI**	**OR**	**95% CI**
18-23 MONTHS	REFERENCE		REFERENCE	
24-59 MONTHS	1.0	(0.6, 1.7)	1.0	(0.6, 1.7)
60-100 MONTHS	2.5	(1.4, 4.4)	2.4	(1.3, 4.7)

[a] Model contains only exposure and outcome of interest. HL p-value of 0.0054 and AUC of 0.57.

[b] Model controls for age, race, education, insurance, BMI, smoking, alcohol, marital status, ART, and prior pregnancy outcome.

FIGURES

Figure 1. Directed Acyclic Graph (DAG) Depicting the Association between Inter-Pregnancy Interval and Stillbirth

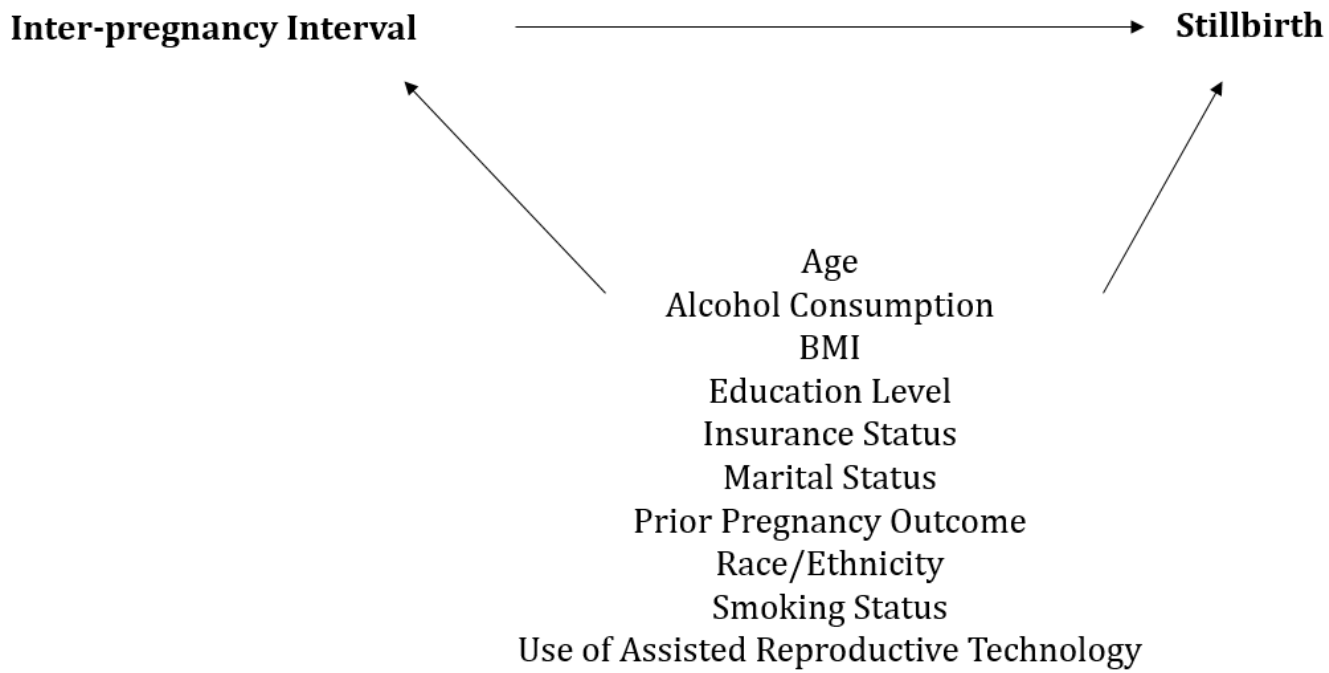
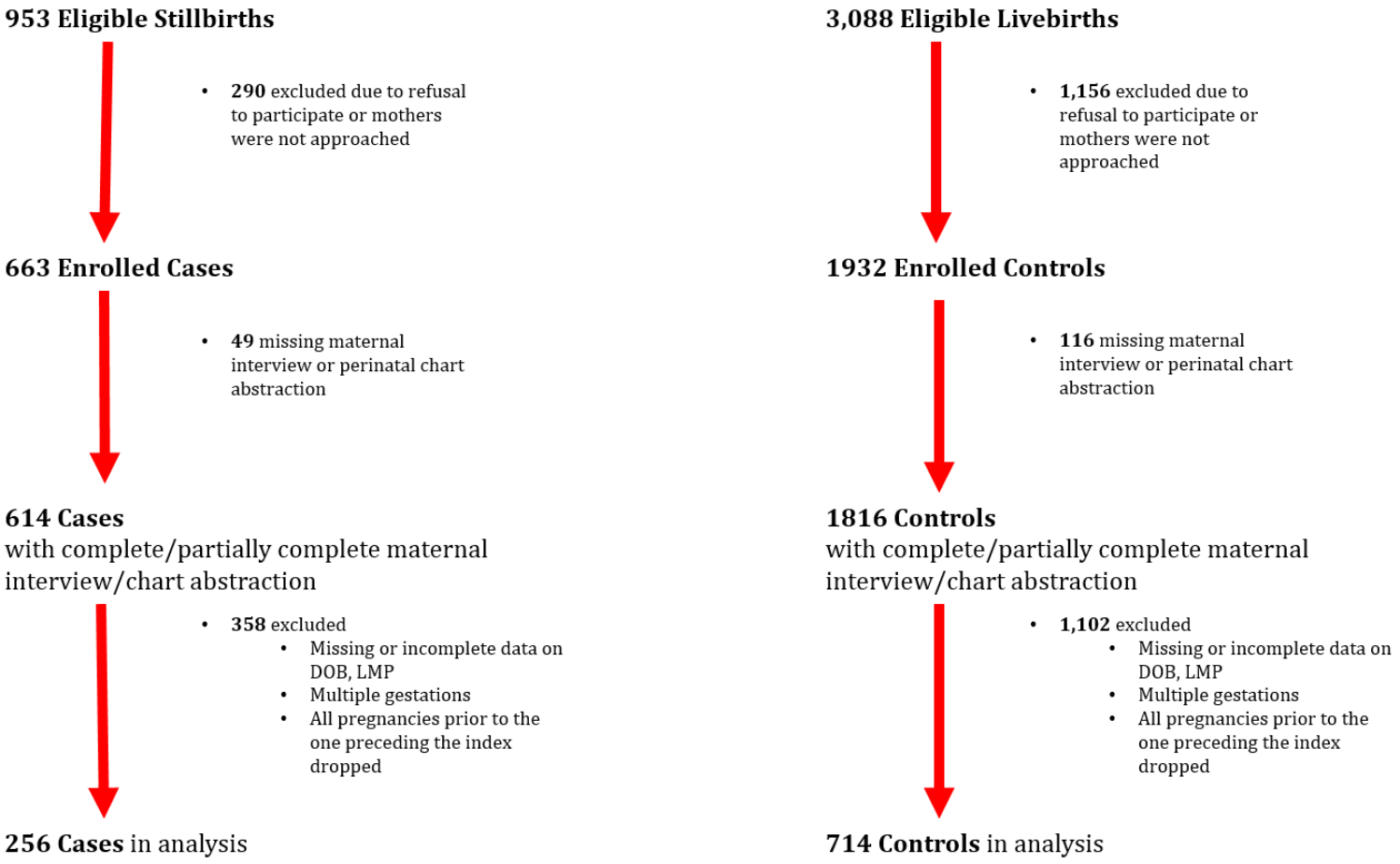


Figure 2. Enrollment and Inclusion of Cases and Controls in Regression Analysis



APPENDIX

INSTITUTIONAL REVIEW BOARD (IRB) PROTOCOL

TO: Carol Hogue, PhD
Principal Investigator
Epidemiology

DATE: September 4, 2014

RE: **Amendment Approval**
AM7_IRB00000764
IRB00000764
Stillbirth Collaborative Research Network Case-Control Study of Stillbirth

Thank you for submitting an amendment request. The Emory IRB reviewed and approved this amendment under the expedited review process on **9/4/2014**. This amendment includes the following:

- Changes to Study Team members:
  - Add Alexa Freedman
- Changes to Study Sites:
  - Remove Emory University Hospital, EUH Midtown, Children's Healthcare of Atlanta, and Grady Health System
  - Add Emory Children's Center and Rollins School of Public Health

Important note: If this study is NIH-supported, you may need to obtain NIH prior approval for the change(s) contained in this amendment before implementation. Please review the NIH policy directives found at the following links and contact your NIH Program Officer, NIH Grants Management Officer, or the Emory Office of Sponsored Programs if you have questions.

Policy on changes in active awards: http://grants.nih.gov/grants/guide/notice-files/NOT-OD-12-129.html

Policy on delayed onset awards: http://grants.nih.gov/grants/guide/notice-files/NOT-OD-12-130.html

In future correspondence with the IRB about this study, please include the IRB file ID, the name of the Principal Investigator and the study title. Thank you.

Sincerely,

Samuel Roberts, BA CIP
Senior Research Protocol Analyst
This letter has been digitally signed

CC: Berry Jacquelyn Epidemiology
Stoll Barbara Pediatrics - Main