Further Characterization of Preterm Birth Clinical Phenotypes:

A Descriptive Study

By

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CHAPTER ONE

BACKGROUND & SIGNIFICANCE

Preterm birth (PTB) is defined by the World Health Organization (WHO), March of Dimes (MOD), and the Centers for Disease Control (CDC) as birth before 37 weeks of gestation. Worldwide, approximately 15 million newborns are born preterm every year (Blencowe et al., 2013). In the United States (U.S.), PTB is a major challenge in that it not only represents 9.8% of (e.g., 1 in 10) births, but it also is the leading cause of neonatal mortality and morbidity, costing over $26 billion each year (Anderson et al., 2018; Behrman & Butler, 2007; Liu et al., 2012; MacDorman, Matthews, Mohangoo, & Zeitlin, 2014). In spite of ongoing advances in perinatal care and related technologies, the PTB rate is not decreasing and, equally significant, is that nearly 70% of PTBs have no known risk factor (Ferrero et al., 2016; MOD, 2018). Of equal concern is the increased prevalence of PTB in African-Americans compared to all other ethnicities (MOD, 2018), which calls into question a myriad of health care and equity issues. To date, several risk factors and underlying biological processes have been linked to or associated with PTB; however, this information has not translated into the ability to predict or prevent PTB (Di Renzo et al., 2011).

PTB is clearly a significant obstetric and public health issue in need of continued exploration. Further, infants born preterm, as well as their mothers, are at increased risk for short- and long-term complications, including lifelong comorbidities (Table 1.1) (Catov et al., 2013; Slattery & Morrison, 2002). These complications and comorbidities, in turn, result in significant and ongoing costs, to the health care system, the family, and the children.

Table 1.1

Short- and Long-Term Complications and Comorbidities Associated with PTB

Short-term	Long-term
Infant	
Anemia of prematurity	Behavioral and psychological issues
Apnea of prematurity	Cerebral palsy
Hyperbilirubinemia	Chronic lung disease
Hypo-/hyperglycemia	Hearing loss
Intraventricular hemorrhage	Impaired cognitive skills
Necrotizing enterocolitis	Impaired vision
Neonatal demise	Poor dental health
Respiratory distress syndrome	
Retinopathy of prematurity	
Sepsis	
Temperature instability	
Mother	
	Cardiovascular disease
	Risk of subsequent PTB

One of the challenges arising from previous programs of research is that PTB has been approached as if it were a single outcome, defined and primarily understood in terms of timing, rather than being understood through the myriad of pathways that led to the outcome. This single outcome approach has created imprecision in understanding the etiology, prediction, prevention, and/or treatment of PTB. In the last 10 years, researchers and clinicians have begun to shift from viewing PTB as a single outcome to recognizing that PTB is instead a complex syndrome with variable phenotypic expression and pathways (e.g., preeclampsia, infection/inflammation).

Clinical phenotypes are used to further categorize the presentation or expression of a disease or disorder.

To date, PTB has been linked to several socio-demographic risk factors (e.g., poverty, low body-mass index, smoking), physiological risk factors (e.g., sexually-transmitted/genital infections, shortened cervix, male fetal sex) and medical comorbidities (e.g., systemic lupus erythematosus, chronic hypertension, diabetes mellitus), as well as familial predisposition/family history and/or previous history of PTB (Di Renzo et al., 2011). Accordingly, current prevention efforts have primarily focused on reducing modifiable risk factors (e.g. smoking cessation), expanding preventive strategies (e.g. treating STIs), and early identification and treatment of non-modifiable risk factors (e.g. cervical cerclage for shortened cervix) (Barros et al., 2010). Of note is that each of these factors, when examined individually, has little to no predictive value and therefore is not significant when screened in all pregnant women (Ferrero et al., 2016). The remaining challenge is that almost 70% of PTBs remain classified as *idiopathic*, having no known risk factor, underlying biological process, or proximal determinant (Ferrero et al., 2016).

Current approaches to understanding PTB have not only begun to identify specific proximal determinants or clinical phenotypes, but also link them with associated labor pathways, including spontaneous preterm labor (SPTL) and/or iatrogenic (medically-indicated) preterm labor (IPTL) (Figure 1.1) (Barros et al., 2015; Esplin, 2014; Esplin, 2016; Esplin et al., 2015; Henderson, McWilliam, Newnham, & Pennell, 2012; Kramer et al., 2012; Manuck et al., 2015; Myatt et al., 2012; Villar et al., 2012).

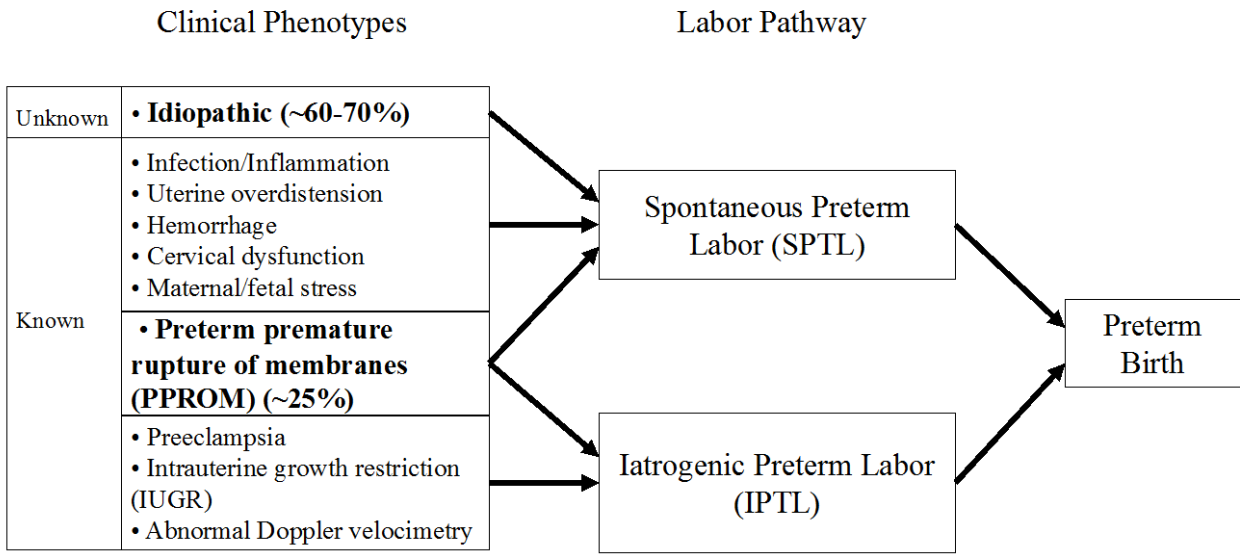

Figure 1.1. Clinical Phenotypes and Associated Labor Pathways

The clinical phenotype that remains elusive and in need of more description is Idiopathic PTB. In recent years, as others have begun to take a closer look at the complexity of PTB, there also appears to be an emerging subset of socio-demographic variables (e.g. fetal sex), clinical characteristics (e.g. maternal autoimmune disorder), and perinatal interventions (e.g. Tdap vaccine) that may provide additional insight into PTB clinical phenotypes (Table 1.2).

Table 1.2

Emerging Sociodemographic Variables, Clinical Characteristics, and Perinatal Interventions

Sociodemographic variable	Clinical characteristic	Perinatal intervention
Maternal age	First pregnancy	Tdap
	Autoimmune disorder	Influenza vaccine
	Fetal maturity/gestation	
	Fetal sex	

Specific Aims

The goal of this study was to further characterize PTB clinical phenotypes. The study focused specifically on two clinical phenotypes - *Idiopathic PTB* and *Preterm Premature Rupture of Membranes* (*PPROM)* using an established, open-source template, expanded to include a select subset of emerging socio-demographic variables, clinical characteristics, and perinatal interventions. The long-term goal is a clear characterization of PTB as a complex syndrome that enables clinicians and researchers to understand the risks, proximal determinants, and trajectories within/across PTB, identify those at risk for PTB earlier, and create tailored or clinical phenotype-specific clinical interventions to reduce the incidence of PTB and its cost to the child, family, and society. The specific aims of this study were to:

1. Describe broad sociodemographic variables, clinical characteristics, and perinatal interventions within the *Idiopathic* PTB clinical phenotype.

    Rationale: According to PTB literature, Idiopathic PTB currently makes up the largest (~60-70%) and least understood PTB clinical phenotypic pathway. Beginning with a comprehensive description using an expanded, standardized

template is the first step in gaining additional insight into this otherwise elusive category.

2. Identify differences in a focused subset of emerging sociodemographic variables, clinical characteristics, and perinatal interventions between:
    a. *Idiopathic* and non-Idiopathic PTB clinical phenotypes.
    b. *PPROM* and non-PPROM PTB clinical phenotypes.

    Rationale: Collecting a focused subset of contemporary and/or emerging variables on the two most common PTB phenotypes allows for a first-level comparison within/across selected clinical phenotypes.

Summary

There is an urgent need to further characterize the various PTB clinical phenotypes as well as their identified determinants/risks, labor pathways, and trajectories. Preterm birth is a significant public health issue, yet our current lack of understanding regarding PTB risk factors and/or underlying biologic triggers hinders our ability to predict and prevent preterm delivery. By further characterizing PTB clinical phenotypes and trajectories, we can advance the science toward improved PTB prediction, prevention, and treatment.

This study focused on selected PTB clinical phenotypes and a subset of emerging socio-demographic variables, clinical characteristics, and perinatal interventions. Continued exploration is needed to gain a more nuanced understanding of known PTB clinical phenotypes. Without such knowledge, there will be no upstream progress toward developing preventive interventions targeted to high-risk pregnancies or tailored to the individual PTB clinical phenotype.

CHAPTER TWO

LITERATURE REVIEW

This chapter begins with a brief overview of preterm birth (PTB), including its definition and significance. This introductory overview is followed by a focused review of what is currently known about the various clinical phenotypes, proximal determinants, and associated labor pathways that lead to PTB. A subset of novel and/or emerging maternal/fetal variables are discussed. These variables are only beginning to be considered in PTB research efforts.

Preterm Birth

PTB is defined as delivery prior to 37 weeks of completed gestation (MOD, 2018). Worldwide, over 15 million infants are born preterm and PTB accounts for ~90% of neonatal mortality and morbidity (Blencowe et al., 2013; Lawn, Gravett, Nunes, Rubens, & Stanton, 2010). In spite of ongoing advancements in perinatal healthcare and research, the PTB rate is not decreasing and in fact has increased for two years in a row (Anderson et al., 2018; Martin, Hamilton, Osterman, Driscoll, & Drake, 2018; MOD, 2018). The significance of this persistent rate is that these preterm infants are at risk for immediate-, short-term, and long-term adverse outcomes, including intraventricular hemorrhage, respiratory distress syndrome, cerebral palsy, and bronchopulmonary dysplasia (Slattery & Morrison, 2002). Long-term adverse outcomes in mothers who deliver preterm include a greater risk of delivering preterm in subsequent pregnancies and cardiovascular disease (Catov et al., 2013; Catov, Snyder, Bullen, Barinas-Mitchell, & Holzman, 2019).

There is an inverse relationship between gestational age at birth and incidence of mortality and morbidity related to prematurity; the shorter the neonate's gestation, the higher the risk of poor health-related outcomes. Accordingly, PTB, while defined by time/completed weeks

of gestation, is further subdivided into four time-related subgroups: 1) extremely, 2) very, 3) moderate, and 4) late preterm (Table 2.1). While the extremely preterm subgroup accounts for only about 6% of all PTBs, newborns in this group have the greatest risk of mortality and morbidity.

Table 2.1

Preterm Birth Sub-Classifications

Extremely Preterm	Very Preterm	Moderate Preterm	Late Preterm
<28 weeks (~6%)	>28 and <32 weeks (~11%)	>32 and <34 weeks (~13%)	34-36 weeks (~70%)

Preterm Birth Clinical Phenotypes

Historically, PTB has been conceptualized as a single outcome, exclusively defined by gestational age at birth, rather than the result of multiple underlying causes. Recently, several clinical phenotypes have been identified by their underlying biologic process and/or suspected proximal pathology (e.g., infection/inflammation, cervical dysfunction, uterine overdistention). There is heterogeneity in the literature regarding PTB phenotype description. Overlap between the phenotype definitions and inconsistent phenotype classification inhibits the ability to produce reliable and replicable results. Precise and consistent descriptions are crucial for advancing PTB research and producing actionable knowledge.

Expanding upon an established PTB research template introduced by Myatt et al (2012), PTB can be categorized into 10 clinical phenotypes based upon the clinical phenotype or proximal determinant of early delivery that results in one of two labor pathways (i.e., spontaneous or iatrogenic) (Figure 2.1). Six clinical phenotypes exclusively result in spontaneous

preterm labor (SPTL) (e.g., idiopathic, uterine overdistention). Three clinical phenotypes exclusively result in iatrogenic (medically-indicated/induced) preterm labor (IPTL) (e.g., preeclampsia). One clinical phenotype, preterm premature rupture of membranes (PPROM), can result in either SPTL or IPTL. This dissertation focuses on the *Idiopathic* and *PPROM* clinical phenotypes, as they represent the largest proportion of PTB and are the ones that are least understood.

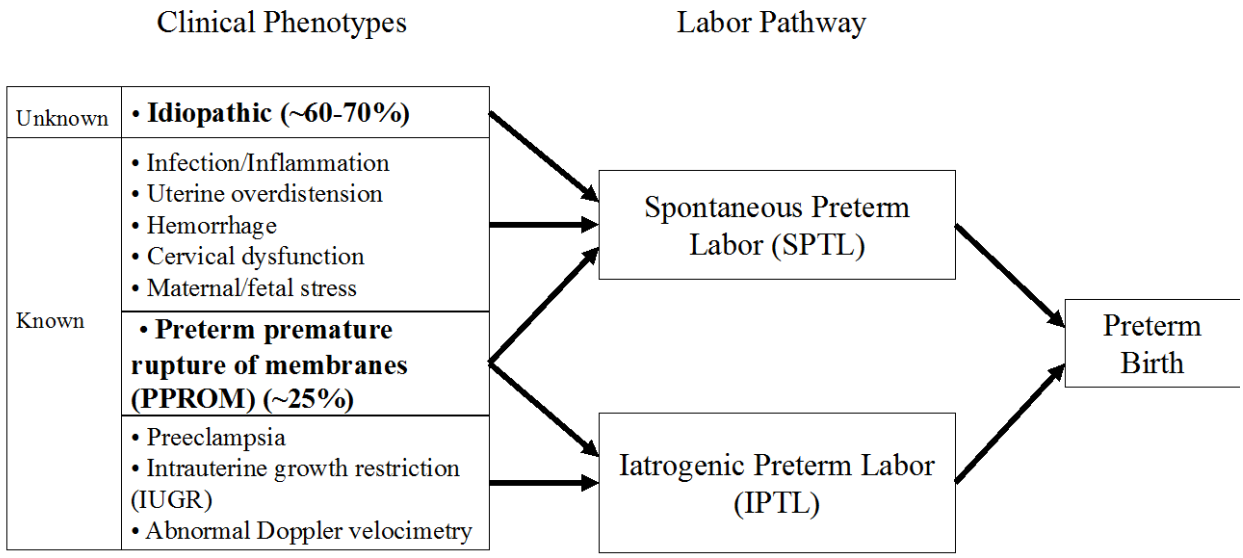

Figure 2.1. Clinical Phenotypes and Associated Labor Pathways in PTB

Spontaneous Preterm Labor

Spontaneous preterm labor (SPTL) is defined as the onset of labor <37 weeks of gestation and is responsible for over 50% of all PTBs (Ananth, Joseph, Oyelese, Demissie, & Vintzileos, 2005). There are known factors associated with SPTL (e.g., smoking, low socioeconomic status) (McCowan et al., 2009; Slattery & Morrison, 2002); however, SPTL is more frequent in

populations with no known risk factors (Ferrero et al., 2016; Moutquin, 2003). SPTL can be divided into phenotypes based upon unknown (Idiopathic) or known proximal determinants or underlying pathobiological mechanisms: infection/inflammation, uterine overdistention, hemorrhage, cervical dysfunction, and maternal/fetal stress. Each phenotype will be described in detail with corresponding supporting literature.

Unknown (Idiopathic) Proximal Determinant(s) leading to SPTL

Idiopathic clinical phenotype is a comprehensive term for a PTB that does not fall into any other clinical phenotype. The data are inconsistent when reporting the prevalence of idiopathic PTB, but it has been reported that up to 70% of all PTBs have no known biologic origin (Ferrero et al., 2016).

Known Proximal Determinant(s) Leading to SPTL

Infection/inflammation

Maternal and/or amniotic infection and the accompanying inflammatory response associated with infection are thought to be a leading risk factor of preterm birth (Simmons, Rubens, Darmstadt, & Gravett, 2010; Thaxton, Nevers, & Sharma, 2010). There remain many challenging questions for determining the role of infection/inflammation in PTB, including which infectious organisms are involved and the critical locus of an infection (Cappelletti, Della Bella, Ferrazzi, Mavilio, & Divanovic, 2016). Multiple sources of infection (e.g., intrauterine, systemic) have been shown to have a negative effect on pregnancy; however, the exact loci of infection remains poorly understood (Cappelletti et al., 2016).

The presence of an infection is detected in at least 25% of PTBs (Cappelletti et al., 2016; Goncalves, Chaiworapongsa, & Romero, 2002). Moreover, 79% of all extreme PTBs (<28 weeks) test positive for an infection and are refractory to standard anti-laboring medications and

interventions. While intrauterine infection is highly associated with SPTL, less than 1% of non-laboring women have the presence of microbes in the amniotic fluid (Cappelletti et al., 2016; Romero, Espinoza, Kusanovic, et al., 2006). While there is a clear association between intrauterine infection (e.g., chorioamnionitis) and PTB (Kacerovsky et al., 2014), infection-driven parturition remains undefined. Given the high correlation between intrauterine bacterial infections and PTB, there has been an interest in administering antibiotics to prevent premature parturition; however, earlier clinical trials have determined there was no reduction in PTB rates in pregnancies who received antibiotic therapy (Simcox, Sin, Seed, Briley, & Shennan, 2007). While systemic infections in mothers (e.g., pneumonia, sepsis) have a significantly high ability to influence PTB, the overall occurrence is relatively low, likely due to early clinical diagnosis and prophylactic treatment of infection.

Much research has examined various biomarkers, specifically pro-inflammatory cytokines (e.g., interleukin-1 (IL-1), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF-α)) and matrix metalloproteinase (MMP) activity. Yet, the exact influence of inflammation on PTB remains unknown.

Chronic inflammation and immunologic anomalies that occur in the absence of infection have also been implicated in PTB (Romero, Espinoza, Kusanovic, et al., 2006). Researchers continue to have an interest in exploring the effect of autoimmune diseases and other diseases inherent to chronic inflammation on early parturition (Moore & Gainer, 2014; Scott, 2002; Stokkeland et al., 2016).

An inflammatory response secondary to maternal/fetal intolerance, similar to transplant rejection, has become an area of interest in PTB research (Romero, Espinoza, Kusanovic, et al., 2006). Maternal recognition of fetal allograft can cause the maternal production of cytotoxic

antibodies and forms a physiological barrier to immunoglobulins (Aksel, 1992). This immunologic maternal response to the fetus has been linked to pregnancy loss, intrauterine growth restriction (IUGR), and preeclampsia (Chen, Wilson, Cumming, Walker, & McKillop, 1994).

While there are a number of studies examining the effect of infection/inflammation on the incidence of PTB, this research has produced little actionable knowledge. Figure 2.2 depicts the multiple factors that are associated with infection/inflammation.

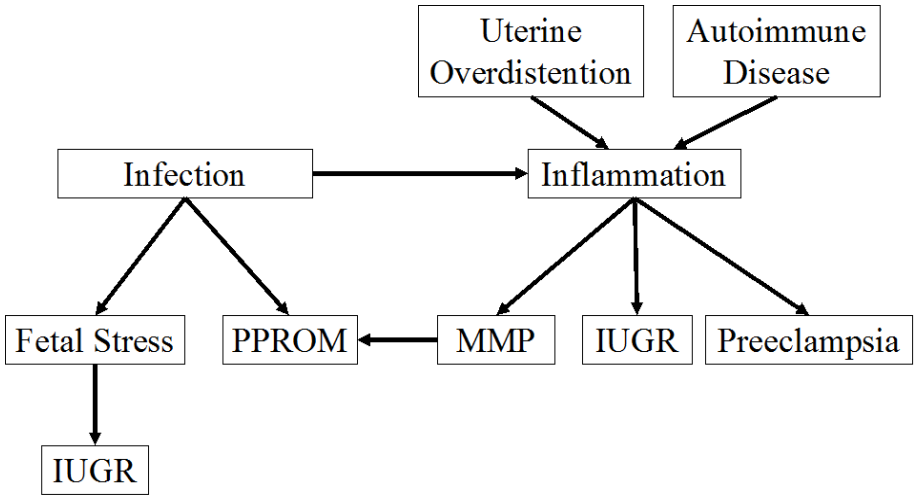

Figure 2.2. Infection/Inflammation Clinical Phenotype

KEY: *PPROM*: Preterm Premature Rupture of Membranes; *IUGR*: Intrauterine Growth Restriction; *MM*P: Matrix Metalloproteinase

Uterine overdistention

Mechanical stress due to uterine overdistention (e.g., multiple pregnancy, polyhydramnios) contributes to SPTL (Adams Waldorf et al., 2015). Mechanical stress activates biochemical receptors in smooth muscle (Farrugia et al., 1999; Hu, Bock, Wick, & Xu, 1998) and is known to influence fetal membrane rupture (Romero, Espinoza, Kusanovic, et al., 2006).

Women pregnant with twins are over 50% more likely to deliver preterm than singleton pregnancies (Goldenberg et al., 1996). Moreover, polyhydramnios occurs in less than 1% of all pregnancies but has been linked to an increased risk of PTB (Hill, Breckle, Thomas, & Fries, 1987; Kirkinen & Jouppila, 1978; Phelan, Park, Ahn, & Rutherford, 1990).

Uterine overdistention from multiple pregnancies and polyhydramnios induces the release of inflammatory cytokines, including IL-6, TNF-α, and prostaglandin E2, which then influences the onset of SPTL (Adams Waldorf et al., 2015). Despite this knowledge, the ability to predict which pregnancies with multiples or polyhydramnios will deliver preterm has yet to be elucidated. Figure 2.3 illustrates the association between uterine overdistention clinical phenotype and other known associations with PTB.

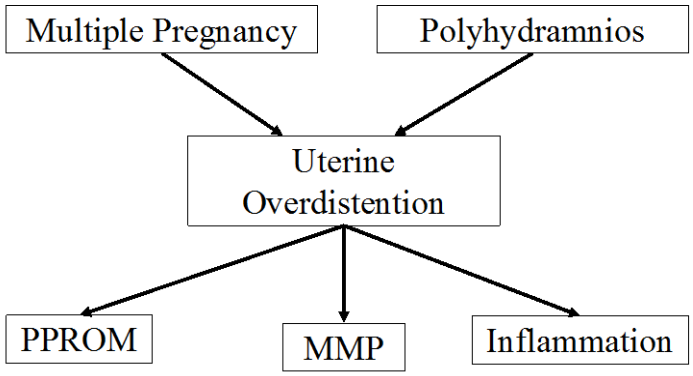

Figure 2.3. Uterine Overdistention Clinical Phenotype

KEY: *PPROM:* Preterm Premature Rupture of Membranes; *MMP*: Matrix Metalloproteinase

Hemorrhage

Approximately 25% of women experience vaginal bleeding in the first half of pregnancy (Bushtyreva, Kuznetsova, Barinova, Kovaleva, & Dmitrieva, 2015). Additionally, bleeding prior to 24 weeks of gestation is associated with an increased risk of PTB even among otherwise low

risk women (Hackney & Glantz, 2011). The primary causes of hemorrhage during pregnancy are subchorionic hemorrhage, subchorionic hematoma, and placental abruption.

Subchorionic hemorrhage, defined as fluid separating of the chorionic membrane from the myometrium resulting in vaginal bleeding, is significantly associated with early spontaneous miscarriage and PTB (Bushtyreva et al., 2015; Nagy, Bush, Stone, Lapinski, & Gardo, 2003). While many studies have found that subchorionic hemorrhage is associated with an increased risk of adverse pregnancy outcomes (e.g., preeclampsia, shortened cervix, IUGR) (Bushtyreva et al., 2015; Palatnik & Grobman, 2015), these associations remain unclear due to heterogeneity of definitions of subchorionic hemorrhage, volume discrepancies, and controlling of confounding variables between these studies (Kyser, 2012).

Subchorionic hematoma (SCH) is the most common cause of subchorionic hemorrhage and affects approximately 3.1% of all pregnancies (Nagy et al., 2003). Bushtyreva et al. (2015) studied pregnancy outcomes among women with SCH and found that women with SCH whose pregnancy progressed to the second trimester had a significantly higher risk of preterm delivery than the control group of normal pregnancy (Bushtyreva et al., 2015). SCH is also associated with other pregnancy complications, including shortened cervix, pregnancy-induced hypertension (PIH), and IUGR (Bushtyreva et al., 2015; Palatnik & Grobman, 2015).

A meta-analysis of 218 publications focused on early pregnancy vaginal bleeding and the risk of PTB determined that the odds of PTB increases with the severity of bleeding (Hackney & Glantz, 2011), while another study found no association between severity of bleeding and the risk of adverse pregnancy outcomes (Kyser, 2012). A study on the prediction of PTB showed that first and second trimester vaginal bleeding does not significantly increase the risk of PTB; however, the risk of PTB was significantly associated with vaginal bleeding in subgroups (e.g.,

multiparity) (Goldenberg et al., 1996). This knowledge suggests that using vaginal bleeding to predict PTB across all pregnancies is limited. Additionally, the prevention of PTB and other complications secondary to subchorionic hemorrhage is limited as there are no known clinical interventions to prevent adverse pregnancy outcomes (Kyser, 2012).

Placental abruption is when the placenta separates from the uterine wall before parturition and results in maternal hemorrhage. Approximately 1% of all pregnancies are complicated by placental abruption, with the risk increasing with increased parity. There are varying degrees of placental separation, with a higher percentage of separation resulting in higher risks of adverse pregnancy outcomes, including PTB and IUGR. While smoking tobacco and hypertension are thought to be linked to placental abruption, the exact etiology remains unknown and most women have no known risk factors (Ananth, Smulian, & Vintzileos, 1999).

Figure 2.4 demonstrates the heterogenous nature of the known risk factors/clinical characteristics that are associated with the hemorrhage clinical phenotype.

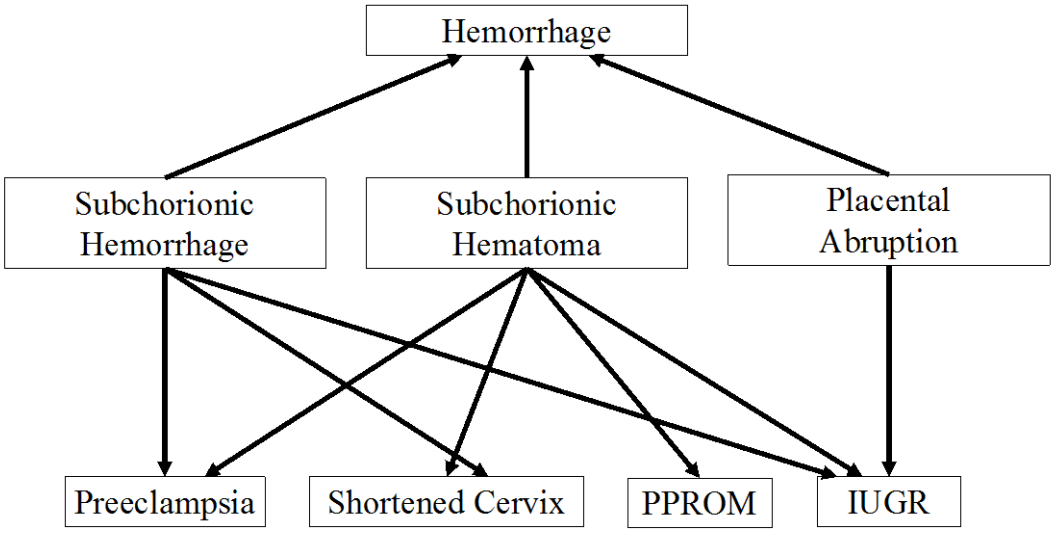

Figure 2.4. Hemorrhage Clinical Phenotype

KEY: *PPROM*: Preterm Premature Rupture of Membranes; *IUGR:* Intrauterine Growth Restriction

Cervical dysfunction

Cervical insufficiency, predominantly cervical shortening, has been implicated in recurrent mid-trimester pregnancy loss, PPROM, and bulging membranes in the absence of labor in low- and high-risk populations (Bohiltea et al., 2016; Iams et al., 1996; Mella & Berghella, 2009; Romero, Espinoza, Erez, & Hassan, 2006). Cervical shortening in the first trimester is commonly caused by SCH (Bushtyreva et al., 2015; Palatnik & Grobman, 2015). Additional causes of cervical insufficiency include certain congenital disorders (e.g., incompetent cervix), surgery, or traumatic damage to the cervical tissue; however, mid-trimester cervical insufficiency is commonly associated with a pathobiological process, most commonly intrauterine infection (Bohiltea et al., 2016; Romero, Espinoza, Kusanovic, et al., 2006). Despite this knowledge, there is insufficient evidence that routine cervical length screening on all pregnant women effectively predicts and/or prevents PTB (Berghella, Baxter, & Hendrix, 2013; Crane & Hutchens, 2008).

In singleton pregnancies, placement of a cervical cerclage has historically been shown to significantly reduce the risk of PTB in women with high-risk pregnancies (Alfirevic, Stampalija, & Medley, 2017; Berghella, Odibo, To, Rust, & Althuisius, 2005; Berghella, Rafael, Szychowski, Rust, & Owen, 2011; Owen et al., 2001), although cerclage significantly increases the risk of PTB in multiple pregnancies (Berghella et al., 2005). Cerclage placement does not prevent PTB in all women, and guidelines re: placement and management of cerclages are not based on large randomized trials (Bohiltea et al., 2016). While studies have concluded that vaginal progesterone reduces the rate of PTB in women with known shortened cervix (Hassan et al., 2011; Romero et al., 2012), the overall effectiveness of cerclage versus vaginal progesterone is unknown (Alfirevic et al., 2017).

While cervical dysfunction is a known risk factor for PTB, routine screening for all pregnancies is not well supported by scientific literature; it is known that intrauterine infection is responsible for many cervical abnormalities, suggesting that the underlying pathobiological process of PTB is highly linked to infection and/or inflammation. As illustrated in Figure 2.5, there are multiple pathobiological influences on cervical insufficiency, yet, this information has not resulted in the ability to predict who will deliver preterm.

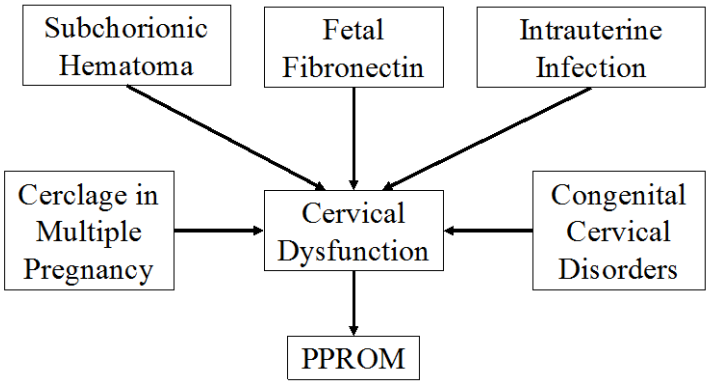

Figure 2.5. Cervical Dysfunction Clinical Phenotype

KEY: *PPROM*: Preterm Premature Rupture of Membranes

Maternal/fetal stress

Maternal and fetal stress induce a physiological response that can cause adverse pregnancy outcomes (e.g., PTB, IUGR) (Levine, Alderdice, Grunau, & McAuliffe, 2016; Wright et al., 2010). *Maternal* stressors include low socioeconomic status (SES), domestic violence, and depression/anxiety (Dole et al., 2003; Henrichs et al., 2010; Wright et al., 2010). Moreover, non-Hispanic, African-American women have a higher incidence of psychological and environmental stress and are at a higher risk of PTB compared to all other races/ethnicities (Dole et al., 2003; Wheeler, Maxson, Truong, & Swamy, 2018). *Fetal* stressors include reduced uterine circulation,

intrauterine growth restriction (IUGR), and fetal inflammatory response syndrome (FIRS) (Levine et al., 2016).

Maternal stress has been linked to increased uterine artery resistance, which contributes to preeclampsia and IUGR (Aardema et al., 2004). Additionally, maternal stress induces the production of corticotropin-releasing hormone, which can have negative effects on pregnancy outcomes, primarily spontaneous PTB, IUGR, and preeclampsia (Bartha, Comino-Delgado, Gonzalez-Mena, Lopez, & Arrabal, 1998; Diego et al., 2006; Dole et al., 2003; Henrichs et al., 2010; Kivlighan, DiPietro, Costigan, & Laudenslager, 2008; Rondo et al., 2003; Sandman, Davis, Buss, & Glynn, 2012; Wadhwa et al., 2004). Stress-induced corticotropin-releasing hormone can result in reduced uteroplacental perfusion, which increases the risk of preeclampsia and IUGR (Goland et al., 1993; Hobel, Dunkel-Schetter, Roesch, Castro, & Arora, 1999; Levine et al., 2016; Lockwood, 1999; Majzoub et al., 1999). Figure 2.6 illustrates the association between socio-economic variables and clinical characteristics and maternal/fetal stress clinical phenotype.

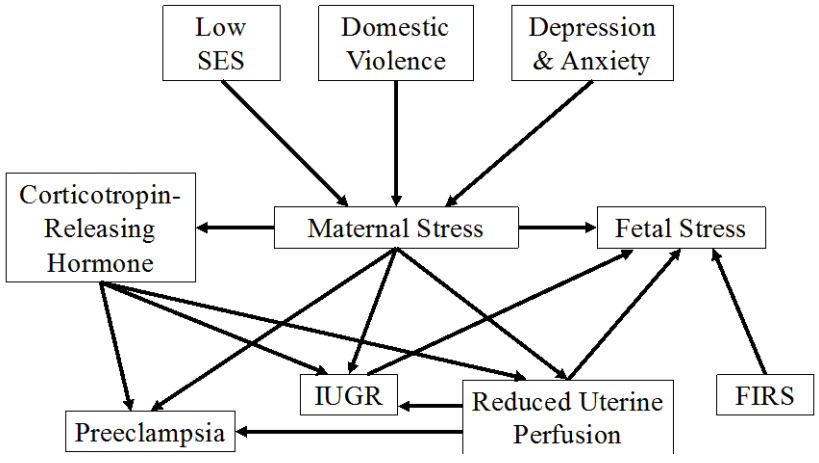

Figure 2.6. Maternal/Fetal Stress Clinical Phenotype

KEY: *SES:* Socioeconomic Status; *IUGR:* Intrauterine Growth Restriction; *FIRS:* Fetal Inflammatory Response Syndrome

Iatrogenic (Medically-Indicated/Induced) Preterm Labor

Iatrogenic preterm labor (PTL) is the umbrella term for medically indicated and/or induced preterm (<37 weeks of gestation) labor due to maternal or fetal complications. The three complications presented include preeclampsia, IUGR, and abnormal Doppler velocimetry.

Known Proximal Determinants Leading to Iatrogenic Preterm Labor (PTL)

Preeclampsia

Preeclampsia is characterized as new-onset hypertension after 20 weeks of gestation. In 2013, the American College of Obstetricians and Gynecologists altered the preeclampsia guidelines to include women without proteinuria, after it was noted that many women with severe preeclampsia did not present with proteinuria. When women have preeclampsia, the odds of preterm birth are 4-5 times higher than pregnancies without preeclampsia (Davies, Bell, & Bhattacharya, 2016; Hofmeyr, Matjila, & Dyer, 2017). Although preeclampsia occurs in 3-6% of pregnancies, it remains poorly understood (Ananth & Basso, 2010; Wallis, Saftlas, Hsia, & Atrash, 2008). More recent studies have determined that preeclampsia is in itself a syndrome with many underlying and intertwining associations (Figure 2.7) (Hofmeyr et al., 2017; Myatt et al., 2012). As previously described, reduced uteroplacental perfusion is often an early indicator of preeclampsia; however, not all women who develop preeclampsia have a high resistance index diagnosed by uterine artery Doppler velocimetry (DeCarolis et al., 2007; Myatt & Roberts, 2015; Stubert et al., 2014). Additional known complications that can result in preeclampsia are an increase in corticotropin-releasing hormone from maternal stress and SCH (Tuuli, Norman, Odibo, Macones, & Cahill, 2011).

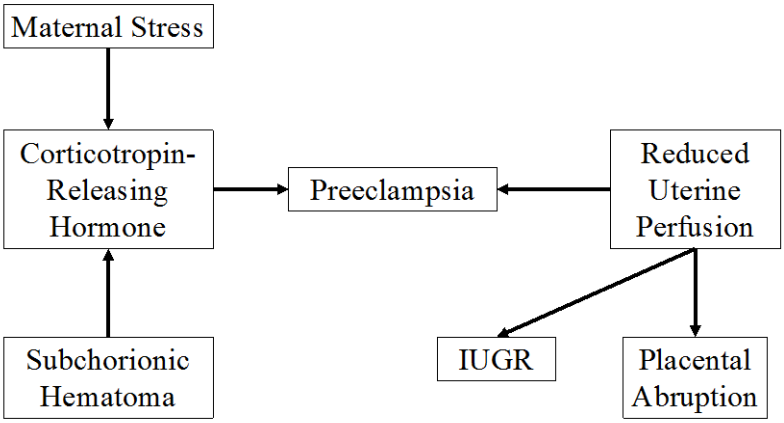

Figure 2.7. Preeclampsia Clinical Phenotype

KEY: *IUGR*: Intrauterine Growth Restriction

Intrauterine Growth Restriction

IUGR is defined as neonatal birth weight less than the 10th percentile on a standardized measurement scale (Capucci et al., 2011). The strongest relationship between IUGR and the risk of PTB occurs before 34 weeks of gestation (Zeitlin, Ancel, Saurel-Cubizolles, & Papiernik, 2000). Twenty-three percent of preterm neonates are identified as IUGR; however, not all IUGR fetuses require induction (Zeitlin et al., 2000). It is likely that the prevalence of IUGR is underestimated, as IUGR statistics do not include fetal demise (Zeitlin et al., 2000). Additionally, corticotropin-releasing hormone has been found to be elevated in pregnancies complicated by IGUR (Goland et al., 1993; Hobel et al., 1999; Lockwood, 1999; Majzoub et al., 1999). Figure 2.8 portrays the multiple known or suspected clinical characteristics associated with IUGR.

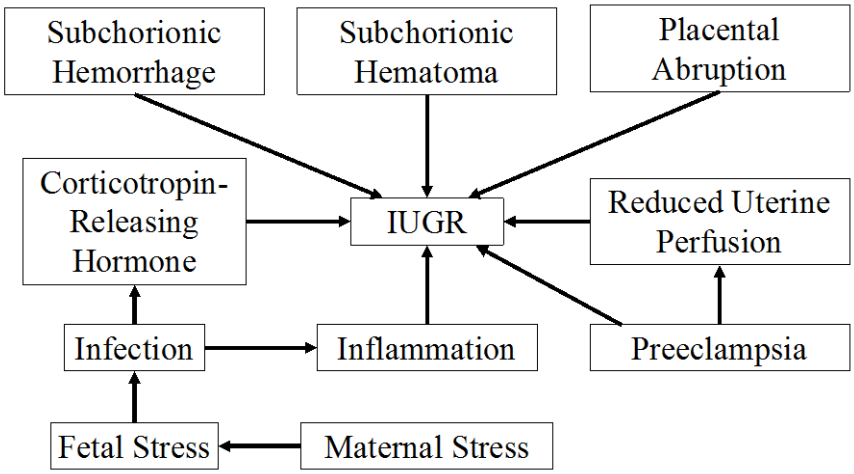

Figure 2.8. Intrauterine Growth Restriction Clinical Phenotype

KEY: *IUGR:* Intrauterine Growth Restriction

Abnormal Doppler velocimetry

Doppler velocimetry is a non-invasive method of studying uteroplacental perfusion and is measured by a resistance index. Figure 2.9 reports the various sources and potential outcomes of an abnormal Doppler velocimetry reading. Reduced uteroplacental circulation is known to be a precursor to adverse pregnancy outcomes, specifically IUGR and preeclampsia (Capucci et al., 2011; Hollis, Prefumo, Bhide, Rao, & Thilaganathan, 2003; Stubert et al., 2014), and abnormal uteroplacental perfusion can identify preeclampsia and IUGR before clinical signs emerge (DeCarolis et al., 2007; Hollis et al., 2003; Stubert et al., 2014). However, not all pregnancies with reduced uteroplacental perfusion result in IUGR or preeclampsia.

Performing uterine artery Doppler studies in high risk populations can potentially increase the predictive value of adverse maternal and neonatal outcomes; however, the efficacy of predicting PTB overall is limited, as most pregnancies are not complicated by reduced uteroplacental circulation (Axt-Fliedner et al., 2005). As previously mentioned, abnormal

uteroplacental perfusion can also be influenced by maternal stress (Aardema et al., 2004; Harville et al., 2008).

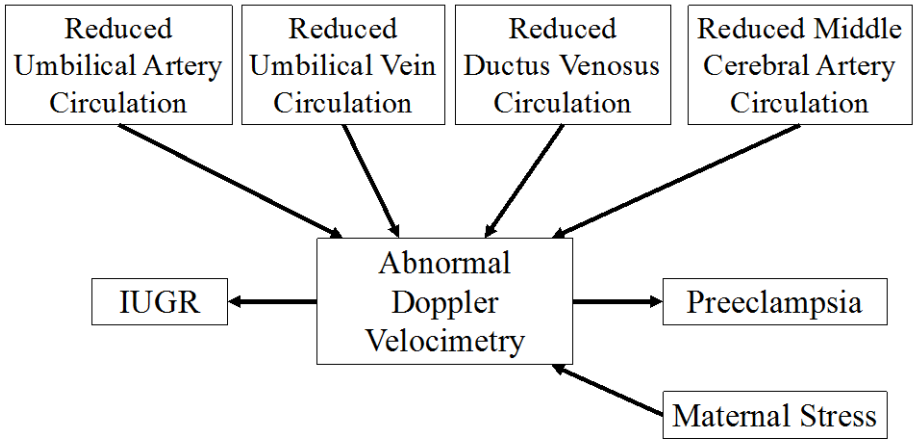

Figure 2.9. Abnormal Doppler Velocimetry Clinical Phenotype

KEY: *IUGR*: Intrauterine Growth Restriction

Preterm Premature Rupture of Membranes

Preterm premature rupture of membranes (PPROM) is fetal membrane rupture prior to <37 weeks of gestation and prior to the onset of labor. PPROM leads 25-30% of PTBs (Martin, 2017) and 50 -75% of pregnancies complicated by PPROM deliver within one week, even with conservative management (Lamont, 2003; Medina & Hill, 2006; Mercer, 2003). Of note, is PPROM can result in either SPTL or IPTL, which differentiates it from idiopathic and other known PTB phenotypes.

There are known risk factors associated with PPROM (Nakubulwa, Kaye, Bwanga, Tumwesigye, & Mirembe, 2015; Tuuli et al., 2011); however, most women who develop PPROM have no known risk factors (French & McGregor, 1996). Pregnancies complicated by PPROM are not only at a significantly increased risk for preterm delivery, but the frequency of

early-onset neonatal sepsis is also significantly higher among women with a longer duration of membrane rupture (Ashraf, ul Haq, Ashraf, Sajjad, & Ahmen, 2015).

Activation of the inflammatory cascade is suspected to play a significant role in reducing the integrity of the fetal membranes that contribute to premature rupture (Bhat et al., 2013; El-Haieg, Zidan, & El-Nemr, 2008; Goldenberg, Culhane, Iams, & Romero, 2008). While infection is thought to be a risk factor for PPROM, only 30% of PPROM pregnancies also have intrauterine infections (Romero et al., 1998).

While the exact role of inflammation is unknown, the current literature reports that the proinflammatory cytokine interleukin-6 (IL-6) is potentially involved in PPROM. (Fortunato, Menon, & Lombardi, 2002; Kacerovsky et al., 2014; Kacerovsky et al., 2015; Kacerovsky et al., 2015). A systemic fetal inflammatory response triggers the production of IL-6, which has been shown to cause PPROM (Gomez et al., 1998). Production of these proinflammatory cytokines has been shown to play an important role in early parturition and PPROM; however, the underlying mechanisms influencing their activation are poorly understood.

Matrix Metalloproteinases (MMPs) are proteins similar to human interstitial collagenase and serve as mediators of tissue damage. Some studies have concluded that MMPs influence the degeneration of the extracellular matrix of the fetal membranes.(Vadillo-Ortega & Estrada-Gutierrez, 2005) Several additional studies indicate that MMPs contribute to the weakening of the amnion and chorion membranes (Borg, Gravino, Schembri-Wismayer, & Calleja-Agius, 2013; French & McGregor, 1996; Goldenberg et al., 2008; Lamont, 2003; Menon & Fortunato, 2007; Mercer, 2003). Additionally, evidence suggests infection plays a role in PPROM by triggering the inflammatory cascade resulting in the activation of MMPs, which subsequently reduces the tensile strength of the fetal membranes (Vadillo-Ortega & Estrada-Gutierrez, 2005).

MMPs have been shown to be abnormally present in many cases of PPROM compared with PTL with intact membranes and term membrane rupture. (Arechavaleta-Velasco, Ogando, Parry, & Vadillo-Ortega, 2002; Athayde et al., 1999; Athayde, 1998; Canzoneri et al., 2013; Fortunato & Menon, 2001; Fortunato, Menon, Bryant, & Lombardi, 2000; Jabareen, Mallik, Bilic, Zisch, & Mazza, 2009; Maymon, Romero, Pacora, Gervasi, Bianco, et al., 2000; Maymon, Romero, Pacora, Gervasi, Edwin, et al., 2000; Maymon, Romero, Pacora, Gervasi, Gomez, et al., 2000; Maymon, Romero, Pacora, Gomez, et al., 2000; Maymon et al., 2001; Soydinc et al., 2012; Soydinc & Gul, 2013; Vadillo-Ortega, 1996; Xu, 2002) While MMP activity has been shown to be abnormally high in PPROM, the underlying reasons why they are elevated have not been elucidated. The ability to use MMP as a predictor of PTB is limited, as most studies measured MMP values after fetal membrane rupture.

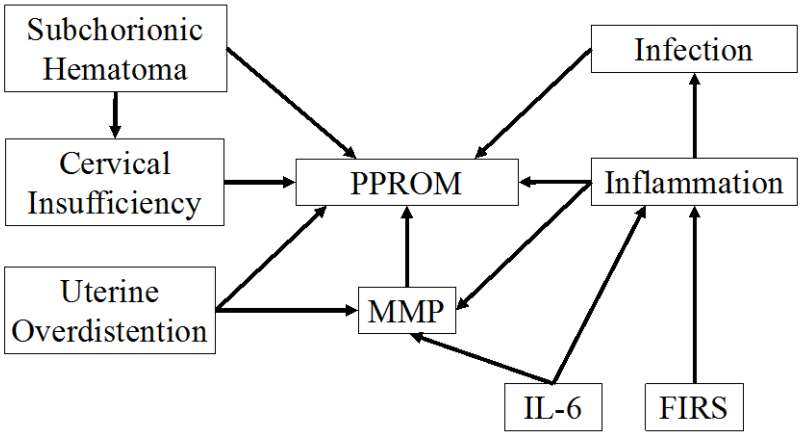

Figure 2.10. Preterm Premature Rupture of Membranes (PPROM) Clinical Phenotype

KEY: *PPROM:* Preterm Premature Rupture of Membranes; *MMP*: Matrix Metalloproteinase; *IL-6*: Interleukin-6; *FIRS*: Fetal Inflammatory Response Syndrome

Summary of PTB Literature

To date, research has primarily defined and studied PTB as a single outcome. This restricted lens has resulted in inconsistent definitions and classifications of PTB and contributed to imprecision in understanding the etiology of PTB. As this literature review has demonstrated, there is a great deal of heterogeneity and overlap in the known influencing factors associated with PTB. Figures 2.2-2.10 illustrate the heterogenous nature of the known/suspected socio-demographic and clinical characteristics associated with PTB. This heterogeneity further indicates a lack of current understanding of PTB, as these known influencing factors only represents ~30-40% of all PTBs.

Preterm Birth as a Complex Syndrome

Until recently, clinicians and epidemiologists have combined all PTBs into one category, presupposing it has a single underlying pathology. Current research has shown that PTB is a collection of many intermingled signs/symptoms and has been classified as a syndrome (Myatt et al., 2012; Romero, Dey, & Fisher, 2014; Romero, Espinoza, Kusanovic, et al., 2006). Conceptualizing PTB as a syndrome is an emerging phenomenon that requires a new look at which socio-demographic variables, clinical characteristics, and perinatal interventions differentiate individual PTB clinical phenotypes. There is a great deal of heterogeneity in the underlying etiologies of preterm deliveries and each PTB is possibly the result of many interacting factors. This heterogeneity makes prediction and prevention difficult to ascertain. Additionally, a limitation in PTB research overall is that “fetal demise at <20 weeks” is not included in most PTB studies. It is likely that the same pathobiological causes of various PTB phenotypes are also responsible for early-gestation fetal demise.

Phenotype Classification for Complex Diseases

There are multiple studies that encourage the use of phenotype classification to divide complex diseases with unknown etiologies by underlying pathobiological causes (Li, Lewinger, Gauderman, Murcray, & Conti, 2011; Perez-Gracia et al., 2010). Phenotype classification has been shown to further characterize trait-associated variants within complex diseases (Morita & Kumuro, 2016).

Phenotype Classification in Preterm Birth Research

There are several publications that illustrate the importance of using a standardized template when collecting data and/or seeking to further characterize PTB and its clinical phenotypes (Kramer et al., 2012; Manuck et al., 2015; Villar et al., 2012). Consistent and efficacious classification systems for clinical phenotyping should focus on maternal, fetal, and placental characteristics (Esplin, 2016). Distal determinants or risk factors (e.g., smoking, ethnicity) should be collected as variables but not included in the phenotype classifications.

To date, there has been one study that used cluster analysis of spontaneous PTB, which revealed five clusters or clinical phenotypes: 1) maternal stress, as determined by psychiatric medications taken during pregnancy, self-reported severe stress, and the Beck Depression Index score indicating severe depression; 2) PPROM; 3) familial factors, characterized by the history of a spontaneous PTB in one first degree relative; and 4) maternal comorbidities, characterized by diabetes mellitus, chronic hypertension, autoimmune diseases, and chronic renal failure. The fifth cluster was characterized by multiple determinants, including infection, decidual hemorrhage, and placental dysfunction (Esplin et al., 2015). A parallel prospective study of SPTL identified nine phenotypes and determined that 78% of women presented with ≥2 phenotypes and only 4.2% had no identified phenotype (Manuck et al., 2015).

Clearly, there is inconsistency in phenotype classification in PTB literature (Table 2.2). Several publications reference spontaneous PTB (Esplin, 2014; Esplin, 2016; Manuck et al., 2015), while others define the same process as SPTL (Henderson et al., 2012; Kramer et al., 2012; Myatt et al., 2012). Some literature defines medically-indicated/induced PTL as iatrogenic, but not all report phenotypes associated with the labor pathway (Barros et al., 2015; Esplin, 2016; Myatt et al., 2012).

Table 2.2

Various Phenotype Classification Systems in PTB Research

Phenotypes	Henderson 2011	Myatt 2012	Villar 2012	Kramer 2012	Esplin 2014	Manuck 2015	Esplin 2015	Barros 2015
Infection/inflammation		●	●	●		●	●	●
Maternal stress		●		●		●	●	
Fetal stress		●	●					
Decidual hemorrhage		●				●	●	
Uterine distention		●	●			●	●	
Cervical dysfunction		●				●	●	
Placental dysfunction			●			●	●	
PPROM	●		●	●		●	●	
Maternal comorbidities			●			●	●	
Familial factors						●	●	
Preeclampsia			●					●
Multiple births			●					●
Extrauterine infection								●
Chorioamnionitis			●					●
IUGR			●					●
Antepartum stillbirth								●
Spontaneous PTL/PTB	●			●	●			
Iatrogenic	●	●	●	●				
Idiopathic		●						
Polyhydramnios			●					
Fetal anomaly			●					
Alloimmune fetal anemia			●					
Gestational age				●				

PPROM: Preterm Premature Rupture of Membranes; IUGR: Intrauterine Growth Restriction; PTL: Preterm Labor; PTB: Preterm Birth

Open-Source Standardized Template for PTB Research

The complexity of PTB creates an argument for categorizing the phenomenon into very specific, clinically relevant phenotypes aimed at identifying rare variants associated with PTB. The concept of PTB phenotype classification is in its early stage in PTB research; however, it has already informed the development of an open-source, standardized template for PTB clinical phenotype research. This dissertation expands upon this template by including PPROM as a phenotype and by including novel and/or emerging variables.

Novel and/or Emerging Variables

This dissertation integrates three emerging variables that are supported in the literature: 1) fetal sex as a biological variable; 2) immunizations received during pregnancy; and 3) maternal autoimmune disorders.

Fetal sex as a biological variable

There has been growing interest in evaluating sex as a biological variable (Clayton, 2016; Tannenbaum, Schwarz, Clayton, de Vries, & Sullivan, 2016), including fetal sex (Challis, Newnham, Petraglia, Yeganegi, & Bocking, 2013; Saif et al., 2015; Wainstock, Shoham-Vardi, Glasser, Anteby, & Lerner-Geva, 2015). Sex has also been recognized by the National Institutes of Health (NIH) as an important inclusion in epidemiological studies (DiPietro & Voegtline, 2017). Several studies have determined that male fetuses are more likely to deliver preterm than female fetuses, although the underlying mechanisms are not known (Brettell, Yeh, & Impey, 2008; Di Renzo, Rosati, Sarti, Cruciani, & Cutuli, 2007; Vatten & Skjaerven, 2004; Zeitlin, Ancel, Larroque, & Kaminski, 2004; Zeitlin et al., 2002). Sex is an attribute that influences and is influenced by genetics, anatomy, and physiology; as such, fetal sex warrants consideration as a biological variable in PTB research.

Immunizations received during pregnancy

Multiple studies have supported the inclusion of immunizations received during pregnancy in epidemiological research. There is evidence to suggest that influenza vaccine can reduce influenza-associated PTB (Nordin et al., 2014; Savitz, Fell, Ortiz, & Bhat, 2015; Swamy & Beigi, 2015); however, the results are not conclusive (Nunes & Madhi, 2015). Additionally, the rate and severity of pertussis is increasing and is associated with an increased risk of PTB (Munoz et al., 2014). It is currently standard practice to administer Tdap vaccine during pregnancy to protect both the mother and fetus; however, while no adverse pregnancy outcomes are being reported (Sukumaran et al., 2015; Swamy & Beigi, 2015), further monitoring of the efficacy and safety of vaccine administration during pregnancy is needed.

Maternal autoimmune disorders

There has been growing interest in studying how maternal autoimmune disorders affect pregnancy outcomes. For example, pregnant women with autoimmune connective tissue conditions (e.g., systemic lupus erythematosus, polymyositis) (Scott, 2002), undiagnosed celiac disease (Moore & Gainer, 2014), rheumatoid arthritis (Aljary, Czuzoj-Shulman, Spence, & Abenhaim, 2018), and those diagnosed with autoimmune hepatitis are at a higher risk of PTB (Stokkeland et al., 2016). Given what is known about the association between PTB and inflammation (Goldenberg et al., 2008), studying the relationship between maternal autoimmune diseases and PTB is warranted.

Conclusion

This focused literature review highlights the heterogenous nature of PTB and the importance of moving beyond the conceptualization of PTB as a single outcome. The primary objective of this dissertation was to further characterize PTB clinical phenotypes, particularly the

two clinical phenotypes that make up the majority – Idiopathic and PPROM. Ultimately, the long-term goal is to clearly characterize PTB as a complex syndrome, enabling clinicians and researchers to understand the risks, proximal determinants, and trajectories within/across PTB, identify those at risk for PTB early, and create tailored or phenotype-specific intervention that ultimately reduce the incidence of PTB and its cost to the child, family, and society.

CHAPTER THREE

RESEARCH DESIGN & METHODS

Research Design

A retrospective, descriptive chart review was used to collect data and further characterize the *Idiopathic PTB* and *PPROM* clinical phenotypes. An established open-source template for clinical studies in PTB informed the chart review. This template was expanded to include a subset of emerging socio-demographic variables, clinical characteristics, and perinatal interventions, creating the study's data abstraction form.

Data Collection

Data were collected at Baptist Health Lexington in Lexington, KY. Both Baptist Health Lexington and Oregon Health & Science University Institutional Review Board (IRB) approvals were obtained prior to beginning data collection (Appendices A & B).

Sample

There was no direct contact with participants. Eligible birth records were identified by screening the neonatal intensive care unit (NICU) in-born patient log for inclusion/exclusion criteria (Table 3.1). The patient log was securely located on the G-drive at Baptist Health-Lexington. The patient log for 2018 was reviewed and neonatal charts were filtered to include gestational ages <37 weeks.

Once eligible neonatal records were identified for inclusion, the linked maternal medical record numbers (MRNs) were identified. Maternal records were then reviewed. Only needed data was extracted manually from maternal electronic health records (EHRs) using a chart abstraction tool (Appendix C). Data collected on the abstraction form was entered into an Excel file with variable labels and stored on a password-protected computer.

Table 3.1

Sample Inclusion/Exclusion Criteria

Inclusion	Exclusion
Delivered between 23-36^6 weeks	Delivered <23 weeks
	Delivered ≥37 weeks

Sample size

An *a priori* sample size calculation with an anticipated effect size = 0.5, statistical power = 0.8, and $\alpha = .05$ indicated a minimum sample of 128 (64/group) would be needed for the comparative analyses between Idiopathic/non-Idiopathic and PPROM/non-PPROM groups in Specific Aim 2. There were 258 deliveries within the gestational age range stated in the inclusion criteria; 77 were labeled *Idiopathic*. The total number of PPROM charts obtained from 2018 was below the minimum sample size required, therefore, the timeline for chart collection was expanded to include the first six months of 2019. Out of 119 deliveries in 2019, 21 were PPROM (18.4%). After the additional PPROM records from 2019, there were 71 charts labeled as PPROM and 209 labeled non-PPROM. The additional PPROM records were used exclusively for the comparative analyses in Aim 2b.

Data Collection Instruments

Data was gathered directly from Baptist Health EHRs and recorded on a data abstraction form (Appendix C). As noted earlier, the form was developed using an established, open-source template for clinical studies in PTB and then expanded to include a subset of emerging socio-demographic variables, clinical characteristics, and perinatal interventions. A pilot trial of the chart abstraction form was performed in 10 charts. From the pilot, it was determined that one

infection, cytomegalovirus CMV), was not routinely monitored for and/or documented and was, therefore, removed from the desired dataset.

Clinical Phenotype Assignment

Each record was reviewed to determine clinical phenotype assignment. The most proximal reason for the preterm delivery (e.g., IUGR, fetal stress), as indicated in physician progress notes, was selected for phenotype assignment. Of note, however, was that SPTL, PPROM, and preeclampsia each has a separate diagnosis code, which were used for phenotype assignment. Maternal charts that were listed as having SPTL with no other known determinants were categorized as *Idiopathic*. *PPROM* was assigned if the rupture of fetal membranes occurred prior to the onset of preterm labor.

Methods

In this section, each study aim is presented, followed by the statistical analysis performed.

Specific Aim 1. Describe sociodemographic variables, clinical characteristics, and perinatal interventions within the *Idiopathic* PTB clinical phenotype.

Analysis

Using the data abstraction tool, each socio-demographic variable, clinical characteristic, and perinatal interventions was analyzed using Stata v15.1 Descriptive statistics were used, differentiated by data type (e.g., categorical data will be reported using proportions). Table 3.2 identifies the socio-demographic variable, clinical characteristic, and perinatal interventions collected on the data abstraction tool that are considered continuous variables, while Table 3.3 identifies those variables considered to be categorical.

Table 3.2

Data Abstraction Tool: Continuous Variables

Maternal age (years)	Gravida	Parity
Fetal maturity (at birth)	Body mass index	White blood cells
Red blood cells	Hemoglobin	Hematocrit
Mean platelet volume	Platelets	Birth weight (grams)

Table 3.3

Data Abstraction Tool: Categorical Variables

Month of delivery	Race	Ethnicity
Singleton/multiples	Blood type	Type of delivery
Tobacco use	Alcohol use	Illicit drug use
Chronic hypertension	Obesity	Abnormal pap of cervix
Hypothyroidism	Sexually-transmitted infection	Autoimmune disorder
Group B streptococcus	History of previous PTB	Immunizations
Fetal sex		

Specific Aim 2: Identify differences in a <u>focused subset</u> of socio-demographic variables, clinical characteristics, and perinatal interventions between:

a. ***Idiopathic* and non-Idiopathic PTB clinical phenotypes.**

b. ***PPROM* and non-PPROM PTB clinical phenotypes.**

Analysis

For the first comparison [Idiopathic vs. *non*-Idiopathic] of the focused subset of variables (Table 3.4) in this aim any PTB that had a known clinical phenotype/proximal determinant (e.g., preeclampsia, hemorrhage) was labelled *non-Idiopathic* or "known" (Figure 3.1).

Table 3.4

Data Abstraction Tool: Focused Subset of Emerging Sociodemographic Variables, Clinical Characteristics, and Perinatal Interventions

Sociodemographic variable	Clinical characteristics	Perinatal intervention
Maternal age	First pregnancy	Tdap
	Autoimmune disorder	Influenza vaccine
	Fetal maturity/gestation	

Any PTB data set that did not have a clearly identified or known clinical phenotype proximal determinant was labelled *Idiopathic*. For the second comparison in this aim [PPROM vs. *non*-PPROM], any PTB that had been clearly identified as PPROM retained that label, while all other PTB data were labelled non-PPROM. Independent t-tests were used for comparing continuous data and χ^2 were used for categorical data (Table 3.5). All statistical analyses were accomplished using Stata v15.1. Effect sizes for continuous data were calculated using Cohen's *d*, where 0.2 indicates a small effect, 0.5 a medium effect, and 0.8 a large effect (Rice & Harris, 2005). Effect

sizes for categorical data were calculated using Cramer's V (φ_c). Cramer's V has a range of 0-1, where 0 shows little association and 1 shows strong association (Ferguson, 2009).

Table 3.5

Analysis of Focused Subset of Emerging Sociodemographic Variables, Clinical Characteristics, and Perinatal Interventions

Continuous (*t*-tests)	Categorical (χ^2)
Maternal age (years)	First pregnancy (Y/N)
Fetal maturity/gestation (weeks)	Fetal sex (F/M/both)
	Autoimmune disorder (Y/N)
	Tdap (Y/N)
	Influenza vaccine (Y/N)

Ethical considerations

Because the chart review used data directly from EHRs, there was no direct contact with participants. However, pregnant women, neonates and minors are all considered vulnerable subjects; therefore, careful attention was given to protect the data. While there was access gained into EHRs of identified participants, no protected health information (PHI) was collected for export. There is always a potential risk for loss of confidentiality; however, all data files were assigned a unique study code, which was not associated with the patient MRN or any other identifiable or PHI data to minimize the possibility of identifying individual participants.

Potential risks

The potential risk of loss of confidentiality to human subjects in this retrospective chart review was minimal. No PHI was obtained. For example, maternal age (in years) and month of delivery was collected, but no date of birth (maternal) or date of delivery (neonate) was included. There were no potential physical risks to participants.

Protection against risk

Completed chart abstraction forms were kept securely in the possession of the study team. All electronic files, including databases for analysis, were kept in password-protected files. Every precaution was taken to protect data and ensure confidentiality and no data was collected beyond what was proposed as necessary to conduct this chart review. Data was stored and managed in a secure Excel file and access to data was restricted to the research team only. Protection of all participants was best ensured by securely storing all data per OHSU and Baptist Health protocol. We estimated the risk in the proposed study to be minimal. Data reporting in presentations and publications will include only aggregate data.

Potential study benefits

Participants did not directly benefit from the proposed chart review. This chart review used de-identified data collected from Epic EHRs; however, achieving the specific aims of this study has the potential to inform clinicians, researchers, and policymakers as the ultimate goal is to be able to clearly identify women with a greater risk for PTB and intervene to prevent it. Due to the low likelihood of risk and a high potential benefit to society, the risk-benefit ratio of this chart review was high.

CHAPTER FOUR

RESULTS

In this chapter, the results begin with a description of the sample and setting, followed by a discussion of findings organized by specific aim. The findings will be discussed in Chapter 5.

Sample/Setting

A total of 258 neonatal records (January – December 2018) from Baptist Health Lexington in Lexington, KY were identified from the NICU log as meeting inclusion criteria. Each record was then matched with maternal charts and data was recorded using the data abstraction tool. The resultant sample (n=258) is described using sociodemographic variables, clinical characteristics, and perinatal interventions (Table 4.1).

First-round analysis

Data were reviewed upfront to assess for missing data, the appropriateness of the mean as the measure of central tendency, the shape of the distribution, and the overall integrity of the data. The majority of charts documented BMI (n = 224; 87%), so this variable was retained. The BMI was most often recorded on the anesthesia record; however, these records were not always complete and not all women received labor anesthesia. One chart did not have a blood type or complete blood count recorded due to a precipitous vaginal delivery, where the infant delivered before laboratory tests could be drawn. All other charts had no missing data.

Table 4.1

Sample Characteristics

Sociodemographic variables	***n* (%)**	**Mean ± SD**	**Range**
Maternal age (years)		27.7 ± 6	17 - 43
Race			
White	233 (90.3)		
Black or African-American	22 (8.53)		
Asian	2 (0.78)		
Pacific Islander	1 (0.4)		
Ethnicity			
Non-Hispanic	253 (98.1)		
Hispanic	5 (1.9)		
Gravida		2.54 ± 1.7	1 - 11
Parity		2.16 ± 1.4	1 – 10
Tobacco use	58 (22.5)		
Alcohol use	1 (1.3)		
Drug use			
THC	26 (10.1)		
Opioid agonist	5 (2)		
Opioids	3 (1.2)		
Methamphetamine	4 (2.6)		
THC & Cocaine	1 (0.4)		
History of preterm birth			
No	143 (55.4)		
Yes	58 (22.5)		
History of spontaneous abortion	57 (22.1)		
Fetal maturity/gestation (weeks)		33.2 ± 2.2	24.3 – 36.6
PTB sub-classification			
Extremely preterm (<28 weeks)	6 (2.3)		
Very preterm (28-32^6 weeks)	82 (31.8)		
Moderate preterm (33-34^6 weeks)	112 (43.4)		
Late preterm (35-36^6 weeks)	58 (22.5)		
Clinical characteristics	***n* (%)**	**Mean ± SD**	**Range**
Single/multiples pregnancies			
Single	208 (80.6)		
Twins	48 (18.6)		
Triplets	2 (0.78)		

Blood type			
O-positive	111 (43.2)		
A-positive	83 (32.3)		
B-positive	27 (10.5)		
A-negative	14 (5.5)		
O-negative	11 (4.3)		
AB-positive	5 (2)		
B-negative	5 (2)		
AB-negative	1 (0.4)		
Autoimmune disorder	18 (7)		
Type of delivery			
Cesarean section	182 (70.5)		
Vaginal	76 (29.5)		
Body-mass index		34.2 ± 8.8	16.7 – 70.7
White blood cells (10^9/L) (reference range: 4.5-11 x 10^9/L)		13.2 ± 4.1	4 – 30.8
Red blood cells (million/mcL) (reference range: 4.2-5.4 million/mcL)		4.1 ± 2.1	2.56 – 36.8
Hemoglobin (g/dL) (reference range: 12-15.5 g/dL)		11.5 ± 1.35	6.9 – 15
Hematocrit (vol%) (reference range: 37-48%)		34.8 ± 3.6	22.3 – 45.4
MPV (fL) (reference range: 9.4-12.3 fL)		10.8 ± 1	8.4 – 13.9
Platelets (10^3/mm^3) (reference range: 150-450 10^3/mm^3)		233 ± 66.4	83 – 492
Sexually-transmitted infections	48 (18.6)		
Group B streptococcus			
Unknown/not checked	190 (73.6)		
Negative	49 (18.99)		
Positive	19 (7.4)		
Fetal maturity/gestation (weeks)		33.2 ± 2.2	24.3 – 36.6
Fetal sex			
Female	120 (46.5)		
Male	122 (47.3)		
Both (multiples)	16 (6.2)		

Perinatal interventions	N (%)
Immunizations	
None in prenatal record	163 (63.2)
Influenza only	21 (8.1)
Tdap only	24 (9.3)
Tdap administered after delivery	24 (9.3)
Tdap/influenza recommended, no follow-up	10 (3.9)
Both Tdap & Influenza	16 (6.2)

Phenotype distribution

The distribution of the clinical phenotypes in this study sample was not consistent with the distribution reported in PTB literature (Table 4.2). Idiopathic PTB accounted for only ~30% of PTB in this sample, half the typical percentile (65-70%), while preeclampsia accounted for a third (33%) of PTB in this sample, two – three times the typical percentile (10-15%). The lower-than-anticipated incidence of idiopathic and higher-than-anticipated incidence of preeclampsia are notable. One might speculate that these differences may be reflective of the overall health of Kentucky residents. According to the United Health Foundation (UHF, 2018), Kentucky ranks number 45 out of the 50 United States in overall health, reporting higher-than-average rates of obesity, chronic hypertension, and smoking, all of which may contribute to increased rates of preeclampsia (Ankumah & Sibai, 2017; Spradley, 2017; Vieira et al., 2017). In particular, there were 22 (26.8%) mothers with preeclampsia who also had chronic hypertension. In short, Kentucky ranks very low in overall health, therefore, the population from which the sample was drawn for this study is typically more obese with more chronic hypertension and obesity-related co-morbidities when compared to the nation as a whole (UHF, 2018).

Table 4.2.

Primary Phenotype Distribution

	N	Study %	*National %*
1. Idiopathic	77	29.8	*65-70*
2. PPROM	50	19.3	*25-30*
3. Cervical dysfunction	2	0.78	-
4. Hemorrhage	12	4.7	-
5. Uterine overdistention	3	1.2	-
6. Infection/inflammation	1	0.4	-
7. Maternal/fetal stress	7	2.7	-
8. Preeclampsia	85	33	*10-15*
9. IUGR	13	5	-
10. Abnormal Doppler velocimetry	8	3.1	-

Specific Aim 1: Describe broad sociodemographic variables, clinical characteristics, and perinatal interventions within the *Idiopathic* PTB clinical phenotype.

Seventy-seven maternal records (29.8%) in this sample were identified as Idiopathic PTB. Sociodemographic variables, clinical characteristics, and perinatal interventions are listed in Table 4.3 along with overall sample findings. Of note was the slightly higher number of female newborns in the Idiopathic PTB group. This latter finding was particularly interesting in that male sex has been suggested as a risk factor for PTB. In both the overall sample and in the Idiopathic PTB subgroup, there were more females than males.

Table 4.3

Idiopathic PTB Subgroup (n=70) Sociodemographic Variables, Clinical Characteristics, and Perinatal Interventions

Sociodemographic variables	***n* (%)**	**Mean ± SD**	**Range**	***Overall sample***
Maternal age (years)		27.5 ± 6.3	19 – 42	*27.7 ± 6*
Race				
White	68 (88.3)			*233 (90.3)*
Black/African-American	7 (9.2)			*22 (8.53)*
Asian	1 (1.3)			*2 (0.78)*
Pacific Islander	1 (1.3)			*1 (0.4)*
Ethnicity				
Non-Hispanic	76 (98.7)			*253 (98.1)*
Hispanic	1 (1.3)			*5 (1.9)*
Gravida		2.9 ± 2.1	1 –11	*2.54 ± 1.7*
Parity		2.64 ± 1.9	1 – 10	*2.16 ± 1.4*
Tobacco use	20 (26)			*58 (22.5)*
Alcohol use	1 (1.3)			*1 (1.3)*
Drug use				
THC	9 (12.7)			*26 (10.1)*
Opioid agonist	3 (3.9)			*5 (2)*
Opioids	3 (3.9)			*3 (1.2)*
Methamphetamine	2 (2.6)			*4 (2.6)*
THC & Cocaine	1 (1.3)			*1 (0.39)*
History of previous PTB				
No	40 (52)			*143 (55.4)*
Yes	20 (26)			*58 (22.5)*
History of previous SAB	17 (22)			*57 (22.1)*

Clinical characteristics	***n* (%)**	**Mean ± SD**	**Range**	***Overall sample***
Single/multiples pregnancy				
Singleton	54 (70.1)			*208 (80.6)*
Twins	23 (29.9)			*48 (18.6)*
Triplets	0 (0%)			*2 (0.78)*
Blood type				
O-positive	41 (54)			*111 (43.2)*
A-positive	19 (25)			*83 (32.3)*
B-positive	7 (9.2)			*27 (10.5)*

A-negative	3 (4)			*14 (5.5)*
O-negative	3 (4)			*11 (4.3)*
AB-positive	2 (2.6)			*5 (2)*
AB-negative	1 (1.3)			*1 (0.4)*
B-negative	0 (0)			*5 (2)*
Autoimmune disorder	4 (5.2)			*18 (7)*
Type of delivery				
Cesarean section	41 (53.2)			*182 (70.5)*
Vaginal	36 (47.8)			76 (29.5)
Body-mass index		32.7 ± 9.8	16.7 – 60.9	*34.2 ± 8.8*
White blood cells (10^9/L) (reference range: 4.5-11 x 10^9/L)		13.3 ± 4.5	5.99 – 30.8	*13.2 ± 4.1*
Red blood cells (million/mcL) (reference range: 4.2-5.4 million/mcL)		3.97 ± 0.43	2.9 – 5.01	*4.1 ± 2.1*
Hemoglobin (g/dL) (reference range: 12-15.5 g/dL)		11.4 ± 1.35	8 – 15	*11.5 ± 1.4*
Hematocrit (vol%) (reference range: 37-48%)		34.8 ± 3.5	25.2 – 44	*34.8 ± 3.6*
MPV (fL) (reference range: 9.4-12.3 fL)		10.7 ± 0.95	8.4 – 13.9	*10.8 ± 1*
Platelets (10^3/mm^3) (reference range: 150-450 10^3/mm^3)		236 ± 66.6	147 - 452	*233 ± 66.4*
Sexually-transmitted infections	20 (26)			*48 (18.6)*
Group B streptococcus				
Unknown/not checked	48 (62.3)			*190 (73.6)*
Negative	23 (29.9)			*49 (18.99)*
Positive	6 (7.8)			*19 (7.4)*
Fetal maturity (weeks)		33.1 ± 2.3	26.5 – 36.6	*33.2 ± 2.2*
Fetal sex				
Female	41 (53.3)			
Male	28 (36.4)			*120 (46.5)*
Both (multiples)	8 (10.4)			*122 (47.3)*
				16 (6.2)

Perinatal interventions	**N (%)**	***Overall sample***
Immunizations		
None in prenatal record	55 (71.4)	*163 (63.2)*
Influenza only	7 (9.1)	*21 (8.1)*
Tdap only	4 (5.2)	*24 (9.3)*

Tdap administered after delivery	6 (7.8)	*24 (9.3)*
Tdap/influenza recommended, no follow-up	3 (3.9)	*10 (3.9)*
Both Tdap & Influenza	2 (2.6)	*16 (6.2)*

Specific Aim 2a: Identify differences in a focused subset of emerging sociodemographic variables, clinical characteristics, and perinatal interventions between Idiopathic and *non*-Idiopathic clinical phenotypes.

In this specific aim, comparative statistics were used to ascertain differences between a subset of emerging sociodemographic variables, clinical characteristics, and perinatal interventions of the 77 (29.8%) PTB records identified as Idiopathic PTB and the 181 (70.2%) identified as *non*-Idiopathic. The *sociodemographic* variable of interest was maternal age; the *clinical characteristics* of interest included first pregnancy, concurrent or history of maternal autoimmune disorder, fetal maturity, fetal sex; and *perinatal interventions* included immunizations (e.g., the pregnant woman having received the Tdap and/or influenza vaccine). T-tests were used for continuous data and χ^2 for categorical data. Effect sizes were calculated using Cohen's *d* for continuous data and Cramer's V (φ_c**)** for categorical data (Table 4.4).

Table 4.4

Idiopathic vs. non-Idiopathic PTB Comparisons of Selected Sociodemographic Variables, Clinical Characteristics, and Perinatal Interventions

Sociodemographic variable	**N (%)**	**Mean ± SD**	***p*-value**	**Cohen's *d***
Maternal age (years)				
Idiopathic		27.5 ± 6.3	0.69	0.055
Non-Idiopathic		27.8 ± 6		

Clinical characteristics	**N (%)**	**Mean ± SD**	***p*-value**	**Cohen's *d*/φ_c**
First pregnancy				
Idiopathic	20 (26)		0.191	-0.081
Non-Idiopathic	62 (34.3)			
Autoimmune disorder				
Idiopathic	4 (5.2)		0.464	-0.046
Non-Idiopathic	14 (7.7)			
Fetal maturity/gestation (weeks)		33 ± 2.2	0.25	0.002
Idiopathic		33.1 ± 3.2		
Non-Idiopathic				
Fetal sex				
Idiopathic				
Female	41 (53.2)			
Male	28 (36.4)			
Both (multiples)	8 (10.4)			
Non-Idiopathic			**0.031**	0.16
Female	79 (43.6)			
Male	94 (51.9)			
Both (multiples)	8 (4.4)			

Perinatal interventions	**N (%)**	***p*-value**	**φ_c**
Tdap vaccine			
Idiopathic	8 (10.4)	0.063	-0.116
Non-Idiopathic	36 (19.9)		
Influenza vaccine			
Idiopathic	9 (11.7)	0.428	-0.049
Non-Idiopathic	28 (15.5)		

There was a significant difference in female fetal sex between groups, with female fetal sex found more often in the Idiopathic group compared to all other combined clinical phenotypes. This finding is inconsistent with PTB literature, which reports that there is an increased risk of PTB with male fetal sex across phenotypes (Brettell et al., 2008; Di Renzo et al., 2007; Vatten & Skjaerven, 2004; Zeitlin et al., 2004; Zeitlin et al., 2002). As previously noted, there were more females than males in the overall study sample, which is distinctly different from national findings. There were no other significant differences and all estimated effect sizes were in the small range.

Specific Aim 2b: Identify differences in a focused subset of emerging sociodemographic variables, clinical characteristics, and perinatal interventions between PPROM and *non*-PPROM clinical phenotypes.

The total number of PPROM charts obtained from 2018 (n=50) was below the minimum sample size required to allow for an exploration of differences, therefore, the timeline for chart collection was expanded to include the first six months of 2019 to increase the number of PPROM participants. Out of 119 PTB records in the expanded time period, 21 (18.4%) PTB records were identified as PPROM. This percentile was similar to the PPROM distribution from 2018 (19.3%) and again lower than the national percentiles (25-30%). In this comparison, the number of PPROM records were 71 and the number of *non*-PPROM charts was 209. The additional PPROM records were used exclusively for the comparative analyses in Aim 2b and not added to the overall sample.

Table 4.5

PPROM vs. non-PPROM Comparisons of Selected Sociodemographic Variables, Clinical Characteristics, and Perinatal Interventions

Sociodemographic variable	**N (%)**	**Mean ± SD**	***p*-value**	**Cohen's *d***
Maternal age (years)				
PPROM		28.6 ± 6.17	0.222	-0.168
Non-PPROM		27.6 ± 5.96		

Clinical characteristics	**N (%)**	**Mean ± SD**	***p*-value**	**Cohen's *d*/φ_c**
First pregnancy				
PPROM	13 (18.3)		**0.007**	-0.161
Non-PPROM	74 (35.4)			
Autoimmune disorder				
PPROM	3 (4.3)		0.451	-0.045
Non-PPROM	14 (12.7)			
Fetal maturity/gestation (weeks)				
PPROM		33.1 ± 1.9	0.669	0.059
Non-PPROM		33.2 ± 2.2		
Fetal sex				
PPROM				
Female	36 (50.7)			
Male	32 (45.1)			
Both (multiples)	3 (4.2)		0.753	0.045
Non-PPROM				
Female	98 (46.9)			
Male	98 (46.9)			
Both (multiples)	13 (6.2)			

Perinatal interventions	**N (%)**	***p*-value**	**φ_c**
Tdap vaccine			
PPROM	15 (22.1)	0.405	0.0498
Non-PPROM	35 (16.7)		
Influenza vaccine			
PPROM	15 (21.1)	0.119	0.093
Non-PPROM	28 (13.4)		

There was a statistically significant difference between the PPROM and *non*-PPROM participants in regard to first pregnancy, with first pregnancy more likely to be found in the *non*-PPROM group. This finding is consistent with the larger PPROM literature, which consistently reports that the risk of PPROM increases with subsequent pregnancies (Di Renzo et al., 2011). There were no other significant differences and all estimated effect sizes were in the small range.

Post hoc **analyses**

After the analyses were completed on the focused subset of variables, additional exploratory comparisons were completed on the remaining variables on the chart abstraction tool.

Idiopathic clinical phenotype

Comparative analyses between Idiopathic and *non*-Idiopathic were run on all remaining variables to test for any significant differences.

GBS status

There was a significant difference between GBS status and the Idiopathic clinical phenotype, however, the effect size was small ($p = 0.009$; $\varphi_c = 0.191$). The largest χ^2 contribution was GBS negative status within the Idiopathic clinical phenotype, where there were significantly more than expected who tested positive for GBS and fewer than expected were not tested for GBS status. There was a larger-than-expected proportion of women who were GBS negative and fewer-than-expected with GBS unknown/not checked in the Idiopathic clinical phenotype when compared to all other phenotypes. One likely explanation for this is that GBS status is not routinely checked during pregnancy until the end of the third trimester, meaning that women who delivered in the second or early part of the third trimester would not have yet been tested for GBS status in keeping with prenatal care routines. Additionally, given the large

proportion of women with preeclampsia, most of whom end up with induced labor/cesarean-sections under emergent situations, checking GBS status may not be a top priority and may be implausible given the time required to ascertain GBS status within many labs. Thus, a larger number of women who present with PTL with unknown distal determinants will more likely be admitted to the antepartum unit with an attempt to delay delivery while corticosteroids are administered to enhance fetal lung development. Additionally, an attempt to delivery vaginally, whenever possible, means that the neonate will be more likely to pass through the vaginal canal, where exposure to GBS, and subsequent risk for GBS-sepsis, is increased when compared to other phenotypes that are likely to result in C-sections.

STIs during pregnancy

Having an STI at some point during the pregnancy was associated with the Idiopathic clinical phenotype with a small degree of association ($p = 0.047$; $\varphi_c = 0.124$). There was a higher incidence of STIs at some point during pregnancy in the Idiopathic clinical phenotype when compared to all other phenotypes. In this case, there was treatment for an STI at some point during the pregnancy; STIs were not present upon delivery, and therefore, are not considered an indication for assignment to the infection/inflammation clinical phenotype. While the difference was statistically significant, the degree of association was small. A potential reason for association could be that the presence or treatment of a genitourinary infection at any point during the pregnancy does contribute to the onset of SPTL. It is possible that this association would be different with a larger study sample.

Blood type distribution

There was a difference in blood type distribution within the Idiopathic clinical phenotype when compared to the sample overall and the general population. While this difference was not

statistically significant, it is still worth mentioning. The American Red Cross reports that ~37% of the White population has O-positive blood type (ARC, 2019); however, the percentage of O-positive blood type in the overall sample was 43%, and within the Idiopathic clinical phenotype 53.9%. Given that 90.3% of this sample was White, it is surprising that the proportion of those with O-positive blood type is greater than that of the overall White population. It is recommended to examine blood type in future PTB studies with larger sample sizes. All other comparative analysis results between Idiopathic and *non*-idiopathic clinical phenotypes were non-significant.

PPROM clinical phenotype

Comparative analyses between PPROM and *non*-PPROM were run on all measured variables to test for any significant differences.

Mean platelet volume (MPV)

Results of a two-sample t-test comparing MPV in the PPROM and *non*-PPROM clinical phenotypes showed a statistically significant relationship with a small effect size (10.6 ± 1 and 10.9 ± 0.98, respectively; $p = 0.0274$; Cohen's $d = 0.3$). Results showed significantly lower MPV levels in PPROM versus *non*-PPROM clinical phenotypes. PPROM literature is inconsistent when reporting MPV levels and PPROM. MPV levels have been found to be significantly lower in PPROM pregnancies than those without PPROM (Ekin, Gezer, Kulhan, Avci, & Taner, 2015); while another study found that MPV levels were elevated in PPROM (Dundar et al., 2018). While there is inconsistency in literature, researchers have begun to look at MPV levels as a way to predict those at risk of developing PPROM (Ekin et al., 2015).

Platelets

PPROM was associated with significantly higher platelets than *non*-PPROM, however the effect size was small (251.4 ± 66 and 230.6 ± 65.6, respectively; $p = 0.0114$; Cohen's $d = -0.0441$), which is consistent with PPROM literature that examines platelet levels when compared to *non*-PPROM PTB (Dundar et al., 2018; Ekin et al., 2015).

Abnormal Pap smear of the cervix

There was higher incidence of abnormal pap smear of the cervix in women who presented with PPROM than *non*-PPROM, with a small degree of association ($p = 0.011$; $\varphi_c = 0.153$). Having a history of abnormal Pap smear of the cervix was significantly more likely in the PPROM group versus *non*-PPROM, with a small effect size. Cervical abnormalities, including shortened cervix, are known risk factors for PPROM (Bohiltea et al., 2016; Iams et al., 1996). Evaluating the relationship between a history of cervical abnormalities is warranted in a future study with a larger sample size. All other comparative analyses between PPROM versus *non*-PPROM clinical phenotypes were non-significant.

Preeclampsia clinical phenotype

Due to the large number of preeclampsia records collected, comparative analyses of the selected subset from Aim 2, as well as post hoc analyses, were performed on the Preeclampsia clinical phenotype versus *non*-preeclampsia clinical phenotypes. There were 82 charts labeled Preeclampsia and 176 charts labeled *non*-preeclampsia.

Focused subset

Results from the comparative analyses of the focused subset from Aim 2 are listed in

Table 4.6

Preeclampsia vs. non-Preeclampsia Comparisons of Selected Sociodemographic Variables, Clinical Characteristics, and Perinatal Interventions

Sociodemographic variable	**N (%)**	**Mean ± SD**	***p*-value**	**Cohen's *d***
Maternal age (years)				
Preeclampsia		28 ± 5.7	0.604	-0.07
Non-preeclampsia		27.6 ± 6.1		

Clinical characteristics	**N (%)**	**Mean ± SD**	***p*-value**	**Cohen's *d*/φ_c**
First pregnancy				
Preeclampsia	37 (45)		**0.002**	0.196
Non-preeclampsia	45 (25.5)			
Autoimmune disorder				
Preeclampsia	5 (6.1)		0.705	-0.024
Non-preeclampsia	13 (7.4)			
Fetal maturity/gestation (weeks)				
Preeclampsia		33.2 ± 1.95	0.975	-0.0004
Non-preeclampsia		33.2 ± 2.3		
Fetal sex				
Preeclampsia				
Female	34 (41.4)			
Male	45 (54.9)			
Both (multiples)	3 (3.7)		0.185	0.114
Non-preeclampsia				
Female	86 (48.9)			
Male	77 (43.8)			
Both (multiples)	13 (7.4)			

Perinatal interventions	**N (%)**	***p*-value**	**φ_c**
Tdap vaccine			
Preeclampsia	19 (23.2)	0.075	0.111
Non-preeclampsia	25 (14.2)		
Influenza vaccine			
Preeclampsia	15 (18.3)	0.216	0.077
Non-preeclampsia	22 (12.5)		

Women in the preeclampsia clinical phenotype were significantly more likely to be primiparous when compared to all other combined phenotypes, however, the effect size was small. Consistent with preeclampsia literature, primiparity was associated with a higher risk of developing preeclampsia when compared to *non*-preeclampsia clinical phenotypes (English, Kenny, & McCarthy, 2015). All other analyses were non-significant.

Post hoc analysis

Beyond the focused subset, comparative analyses were performed on the remaining variables on the chart abstraction tool. There were three comparisons of note: chronic hypertension, obesity, and BMI. Twenty-seven percent of women with preeclampsia also had chronic hypertension, compared to 7.4% of all other phenotypes. Additionally, 59.8% of women with preeclampsia had "obesity" listed as a medical co-morbidity, compared to 20.5% of *non*-preeclamptic women (Table 4.7).

Table 4.7

Preeclampsia vs. non-Preeclampsia Co-Morbidities

	N (%)	**Mean ± SD**	***p*-value**	**Cohen's *d*/φ_c**
Chronic hypertension				
Preeclampsia	22 (26.8)		**<0.0001**	0.264
Non-preeclampsia	13 (7.4)			
Body-mass index (BMI)				
Preeclampsia		37.7 ± 9.1	**<0.0001**	-0.65
Non-preeclampsia		32.3 ± 8		
Obesity listed as co-morbidity				
Preeclampsia	28 (59.8)		**<0.0001**	0.4
Non-preeclampsia	36 (20.5)			

To gain deeper insight into the three comparisons that yielded medium effect sizes, further analyses were done using logistic regression.

Obesity as a co-morbidity

A logistic regression model found that women with an increased BMI had an increased risk of preeclampsia compared to women without preeclampsia (OR = 1.08; z = 4.17; p = <0.0001). Additionally, women who had obesity as a co-morbidity were nearly six times more likely to become preeclamptic in pregnancy (OR = 5.78; 95% CI [3.25-10.2]; p = <0.0001) than women without preeclampsia. These findings are consistent with preeclampsia literature, wherein obesity is associated with an increased risk of pregnancy-induced preeclampsia and chronic hypertension with superimposed preeclampsia (Ankumah & Sibai, 2017; Spradley, 2017; Vieira et al., 2017). Preexisting health conditions, such as obesity and chronic hypertension, might skew these results and embellish the association with preeclampsia.

Chronic hypertension with superimposed preeclampsia

A logistic regression showed that women with chronic hypertension were nearly five times more likely to develop preeclampsia (OR = 4.89; 95% CI [2.3-10.3]; p = <0.0001) than women without. Women with chronic hypertension have a known risk for developing preeclampsia secondary to the underlying hypertension (Ankumah & Sibai, 2017; Guedes-Martins, 2017). There was a high proportion of women who had chronic hypertension with superimposed preeclampsia in this sample. It is likely that the pathobiological processes that are responsible for pregnancy-induced hypertension/preeclampsia are different than chronic hypertension that then leads to preeclampsia (Guedes-Martins, 2017). It is recommended in future studies to separately analyze chronic hypertension and true pregnancy-induced hypertension to aid in isolating the underlying distal determinants that contribute to the onset of preeclampsia.

PTB sub-classifications

In prior analyses, gestational age was reported as a continuous variable; however, there are benefits to also examining gestational age as a categorical variable, broken down by PTB sub-classifications (Table 4.8), as pathobiological determinants of PTB may vary depending on gestation.

Table 4.8

Preterm Birth Sub-Classifications

1) Extremely Preterm	2) Very Preterm	3) Moderate Preterm	4) Late Preterm
<28 weeks	$28 – 32^6$ weeks	$33 – 34^6$ weeks	$35 – 36^6$ weeks
7 (2.5%)	88 (31.4%)	125 (44.6%)	60 (21.4%)

Phenotype assignment associations by PTB sub-classifications

PTB sub-classification association studies were performed using χ^2 and found that there were no statistically significant differences in sub-classifications between the Idiopathic versus *non*-idiopathic, PPROM versus *non*-PPROM, and Preeclampsia versus *non*-preeclampsia clinical phenotypes.

Table 4.9

Phenotype Assignment by PTB Sub-Classifications

	***p*-value**	φ_c
Idiopathic vs *non*-idiopathic	0.814	0.060
PPROM vs *non*-PPROM	0.431	0.103
Preeclampsia vs *non*-preeclampsia	0.069	0.166

Mean comparisons by PTB sub-classifications

Maternal age was analyzed to determine if there was a significant difference in mean maternal age between PTB sub-classifications (Table 4.10). A one-way ANOVA indicated equal variances and a statistically significant difference in maternal age between the sub-classification factor groups with a small degree of association ($F[3, 254] = 3.63$; $p = 0.0136$; eta-squared (η^2) = 0.041). The three parametric assumptions of ANOVA were not violated: 1) all observations were independent; 2) the dependent variable followed a normal distribution in the population; and 3) the homogeneity of variance assumption was not violated (Bartlett's $p = 0.436$). Pairwise comparison indicated that there was a statistically significant contrast in the mean age between 'moderate preterm' and 'extremely preterm' sub-classifications, indicating younger maternal age was associated with extremely preterm deliveries.

There was an association between younger maternal age and the "very preterm" sub-classification, however, the effect size was small. Additionally, the proportion of "extremely preterm" was low in this study, as Baptist Health-Lexington only accommodates greater than 28 weeks of gestation; therefore, the "extremely preterm" admissions were few and transferred to a Level IV NICU immediately. PTB literature indicates that there is an association between younger maternal age and the risk of delivering preterm (Chantrapanichkul & Chawanpaiboon, 2013), although it has yet to be evaluated between PTB sub-classifications. Many PTB studies use maternal age as a confounding variable. It is recommended that future studies that include a larger sample and a larger proportion of "very preterm" should include maternal age as a predictor variable to evaluate a possible link between completed gestation and maternal age.

Differences in complete blood count results between PTB sub-classifications were analyzed using one-way ANOVAs and found that there was a significant difference in WBCs

and platelets between sub-classifications. The one-way ANOVA ($F[2, 252] = 4.63$; $p = 0.0036$) comparing WBCs between sub-classifications indicated unequal variances (Bartlett's $p = <0.0001$) and a small effect size ($\eta^2 = 0.052$). The results of a pairwise comparison found that the mean WBC levels in "very preterm" were significantly higher than "late preterm." This is possibly due to the fact that reportedly ~80% of all PTBs at <28 weeks test positive for an intrauterine infection (Cappelletti et al., 2016). Given that infection and/or inflammation is known to contribute to the onset of early labor, it would be beneficial to compare WBCs by PTB sub-classifications to find if there is a correlation between earlier gestation delivery and infection/inflammation. A larger sample size overall and within the "very preterm" population would be optimal. There may also be potential benefit in exploring inflammation factors beyond the WBC, as the WBC increases normally during birth processes and thus may not be the best marker to help differentiate physiology versus pathophysiology. Other infectious markers (e.g., C-reactive protein, IL-6) could be used to capture pathophysiological processes in future studies.

The one-way ANOVA ($F[3, 252] = 3.37$; $p = 0.0191$) examining platelet levels between sub-classifications indicated equal variances (Bartlett's $p = 0.091$), with a small effect size ($\eta^2 = 0.0386$). Pairwise comparison found that "moderate preterm" was associated with significantly lower platelet levels with a small degree of association when compared to "extremely preterm" and "very preterm." To date, there are no known studies that support or refute this finding. Comparing maternal platelet levels between PTB sub-classifications in future studies with a larger sample and a more accurate sub-classification distribution (i.e., more "extremely preterm") would be beneficial.

All other differences in complete blood count levels between sub-classifications were non-significant; therefore, pairwise comparisons and η^2 for RBC, hemoglobin, hematocrit, and MPV were not evaluated.

Table 4.10

Mean Comparisons by PTB Sub-Classification

	ANOVA *p*-value	**Bartlett's test**	**(η^2)**
Maternal age	**0.0136**	$p = 0.436$	0.041
White blood cells (10^9/L) (reference range: 4.5-11 x 10^9/L)	**0.0036**	$p = <0.0001$	0.052
Red blood cells (million/mcL) (reference range: 4.2-5.4 million/mcL)	0.0718	$p = <0.0001$	-
Hemoglobin (g/dL) (reference range: 12-15.5 g/dL)	0.474	$p = 0.222$	-
Hematocrit (vol%) (reference range: 37-48%)	0.564	$p = 0.234$	-
MPV (fL) (reference range: 9.4-12.3 fL)	0.164	$p = 0.323$	-
Platelets (10^3/mm^3) (reference range: 150-450 10^3/mm^3)	**0.0191**	$p = 0.091$	0.0386

CHAPTER FIVE

DISCUSSION

The final chapter of this dissertation revisits preterm birth (PTB) maturity as an important health issue and then summarizes key findings and discusses them in relation to this larger literature. A subset of insights and findings is particularly highlighted, as each has the potential to inform further next steps: 1) an upfront modification of the initial phenotype/labor pathway, 2) the potential impact of overall health status in Kentucky, and 3) the use of fetal maturity versus maternal gestation in the identification of PTB. The chapter ends with a discussion of the strengths and limitations of the study, as well as the research and clinical implications and recommendations for future research.

Preterm birth is an important health issue

As introduced in Chapter 1, PTB is an important health issue and represents ongoing challenges for researchers. PTB is not only common, occurring in ~10% (1 in 10) births; it is also the leading cause of neonatal mortality and morbidity, costing over $26 billion each year (Anderson et al., 2018; Behrman & Butler, 2007; Liu et al., 2012; MacDorman et al., 2014). Further, infants born preterm, as well as their mothers, are at increased risk for short- and long-term complications that include lifelong comorbidities (Catov et al., 2013; Slattery & Morrison, 2002). These complications and comorbidities, in turn, result in significant and ongoing costs, not only to the health care system, but also to the family and children.

While news media and medical summary lines often report, “The majority of preterm survivors are found to *do well* and have *fairly normal lives*”, this statement can be “deeply deceptive” (Gunter, 2019). To put a more human face to this somewhat misleading statement, a mother and obstetrician recently described that ‘doing well’ involved 11-13 weeks of intensive

care and over 40 medical appointments in just the first three months home from the hospital (Gunter, 2019). My own experience as a neonatal intensive care (NICU) nurse for over 10 years not only can attest to this mother's statement, but also informs my program of research and this dissertation as despite ongoing advances in perinatal care and related technologies, the rate of PTB has not decreased (Ferrero et al., 2016; MOD, 2018). Of equal concern is the increased prevalence of PTB in African-Americans compared to all other ethnicities (MOD, 2018), which calls into question a myriad of health care and equity issues.

While several risk factors and underlying biological processes have been linked to or associated with PTB, this information has not translated into the ability to predict or prevent PTB (Di Renzo et al., 2011). Further, ~70% of PTBs remain classified as *idiopathic*, having no known risk factor, underlying biological process, or proximal determinant (Ferrero et al., 2016). In short, PTB is clearly a significant obstetric and public health issue in need of continued exploration, as attempted with this dissertation.

An ongoing challenge in research is that PTB has been approached as if it were a single outcome, defined and primarily understood in terms of timing, rather than being understood through the myriad of pathways that led to the outcome. This 'single outcome' approach has created imprecision in understanding the etiology, prediction, prevention, and/or treatment of PTB as well as challenges for researchers. More recently, researchers and clinicians have begun to shift from viewing PTB as a single outcome to recognizing that PTB is instead a complex syndrome with variable phenotypic expression and pathways (e.g., preeclampsia, infection/inflammation) (Barros et al., 2015; Esplin, 2014; Esplin, 2016; Esplin et al., 2015; Henderson et al., 2012; Kramer et al., 2012; Manuck et al., 2015; Myatt et al., 2012; Villar et al., 2012). By further characterizing PTB clinical phenotypes and trajectories, we can advance the

science toward improved PTB prediction, prevention, and treatment. This dissertation represents one small step.

Key findings

In this focused study, using a retrospective chart review, the emphasis was on selected PTB clinical phenotypes and a subset of emerging sociodemographic variables, clinical characteristics, and perinatal interventions in one hospital in Kentucky. The data was recorded using an open-source template, which was expanded to include the subset of variables. As noted above, the study represents a small step toward advancing our understanding of PTB as a complex syndrome.

The key findings included overall sample characteristics, the discovery of inconsistent nomenclature in health record documentation, variation in clinical phenotype distribution in the study sample compared to national distribution percentages, the inconsistent documentation of immunizations in prenatal health records, and the high incidence of chronic hypertension in the sample population. Each of these findings is discussed.

Overall sample characteristics

The focused subset of sociodemographic variables, clinical characteristics, and perinatal interventions overall and within the idiopathic clinical phenotype (Table 5.1).

Table 5.1

Focused subset of sociodemographic variables, clinical characteristics, and perinatal interventions in the overall sample and within idiopathic clinical phenotype

Sociodemographic variable	**Mean ± SD**		**Range**
Maternal age			
Overall sample	27.7 ± 6		17 – 43
Idiopathic	27.5 ± 6.3		19 – 42
Clinical characteristics	***n* (%)**	**Mean ± SD**	**Range**
First pregnancy			
Overall sample	82 (32)		
Idiopathic	20 (26)		
Autoimmune disorder			
Overall sample	18 (7)		
Idiopathic	4 (5.2)		
Fetal maturity/gestational age (weeks)			
Overall sample		33.2 ± 2.2	24.3 – 36.6
Idiopathic		33.1 ± 2.3	26.5 – 36.6
Fetal sex			
Overall sample			
Female	120 (46.5)		
Male	122 (47.3)		
Both (multiples)	16 (6.2)		
Idiopathic			
Female	41 (53.2)		
Male	28 (36.4)		
Both (multiples)	8 (10.4)		

Perinatal interventions	***n* (%)**
Tdap vaccine	
Overall sample	44 (17.1)
Idiopathic	8 (10.4)
Influenza vaccine	
Overall sample	37 (14.3)
Idiopathic	8 (10.4)

Within the focused subset, the most notable difference between the overall sample and within the idiopathic clinical phenotype was fetal sex. The sample was equal female/male distribution in the sample overall (46.5%, 47.3%, respectively); however, within the idiopathic clinical phenotype, the female/male distribution was notably unequal (53.2%, 36.4%, respectively). This difference was shown to be statistically significant, however, the implication of this difference is yet to be understood. PTB literature states that male fetal sex is associated with an increased risk of PTB. It is possible that male fetal sex increases the risk of iatrogenic PTL, and, therefore, results in the unequal fetal sex distribution within the idiopathic clinical phenotype.

In addition to the focused subset, there were several notable findings within the overall sample and within the selected phenotypes. The sample was predominantly White (90.3%) and non-Hispanic (98.1%). The homogeneity of the sample is relatively consistent with the overall race percentages reported in Kentucky demographics, wherein Whites represent 87.3% of the population (WPR, 2019). Over half of sample population (55.4%) had no prior history of PTB, which is a known risk factor. This study showed that the first pregnancy was more likely to be in the non-PPROM group, which is consistent with larger literature that the risk of PPROM increases with subsequent pregnancies. In addition, this study found that women in the preeclampsia phenotype were more likely to be primiparous, which is also consistent with literature PTB literature.

Blood type distribution in this study was different within the idiopathic clinical phenotype when compared to the sample overall and the general population. National statistics reports that ~37% of the White population have O-positive blood type, whereas the percentage of women with O-positive blood type in the overall sample was 43% and within the idiopathic

clinical phenotype was 53.9%. While these differences did not indicate statistical significance, it is still an interesting finding.

The C-section rate in the overall sample was over 70%, but only 53.2% within the idiopathic clinical phenotype. This is likely due to emergency C-sections in the case of iatrogenic PTL phenotypes (e.g., IUGR, preeclampsia). Women in the idiopathic clinical phenotype present with spontaneous PTL, which would potentially indicate a lower risk of requiring a C-section.

Results from this study showed that there was a statistically significant difference in MPV between PPROM and the sample overall. Literature inconsistently reports the relationship between MPV and PPROM; some studies conclude that PPROM is associated with an increased MPV, while other studies conclude that it is associated with a decreased MPV. This study indicated that MPV were significantly lower in the PPROM group.

Inconsistent nomenclature

The data collection process brought to light several instances in which the language used to describe and document pregnancy characteristics and outcomes in the health record were inconsistent. For example, some physicians/healthcare providers used the term “preterm premature rupture of membranes (PPROM)” synonymously with “preterm rupture of membranes (PROM)”. The improper blurring of these two diagnoses creates imprecision, not only in how maternal charts are labeled and identified, but also in how diagnoses are monitored and evaluated in both clinical and research efforts. The distinction between these two diagnoses is important, as PPROM indicates that the fetal membranes ruptured prior to the onset of spontaneous *preterm* labor or iatrogenic preterm labor (PTL), while PROM indicates that the fetal membranes ruptured spontaneously before the onset of labor at *term* gestation. The distinction is important in that there may indeed be two different mechanisms and confounding them may overlook them.

Another example of inconsistent nomenclature was the variable use of the terms preterm labor, preterm onset of labor, and premature onset of labor. It has been suggested in PTB literature not to describe PTB as "premature" as PTB is defined by time (i.e., pre-term gestation), while "premature" denotes under-developed. As researchers move away from PTB being understood as a single outcome defined by time and shift to a more nuanced assessment of fetal maturity, careful use of preterm versus premature will be warranted.

Consistency in nomenclature is important in PTB research and ongoing inconsistencies may contribute to persistent misunderstandings. Equally challenging are the inconsistencies within and across different hospital systems in terms of location of information, as much of the information gleaned from the charts reviewed for this study also required a great deal of "sifting" through progress notes.

Overall phenotype distribution

The overall phenotype distribution in this study was very different from what was expected, based on PTB literature and national statistics. The largest phenotype noted was preeclampsia, making up 33% of the sample. This statistic was drastically different than PTB literature, which reports preeclampsia to affect only ~10-15% of all PTBs. The higher-than-anticipated number of preeclampsia occurrences in this study sample may likely be attributed to the high incidence of chronic hypertension (27% in this sample). It is also possible that rates of preeclampsia have increased due to the recent (2013) introduction of an expanded definition of preeclampsia, which now includes women with and without proteinuria, rather than requiring proteinuria be present.

Also of note was the decreased number of idiopathic and PPROM phenotypes in comparison to national percentiles. In this sample, 29.8% of the sample were considered

idiopathic, which is well below national statistics (65-70%); 19.35 were considered PPROM, which is also below national statistics (25-30%).

Immunization administration and tracking

One surprising finding from this study was the low number of women who were given the Tdap and/or Influenza vaccines (17.1% and 14.3%, respectively). Sixty-three percent of the 258 prenatal records and hospital EHRs made no mention of vaccinations before, during, or after pregnancy. Offering the Tdap vaccine during pregnancy has been considered a standard of practice in prenatal visits, as well as offering an inactive influenza vaccine during influenza season; however, the hospital charts did not highlight vaccines administered as part of prenatal care. This lack of emphasis may be unique to Kentucky in that immunization reporting and tracking is not a requirement at this time, and the statewide database is still in its infancy.

Given the fact that Tdap and Influenza vaccine administration are considered standards of practice during pregnancy, the findings of this study indicate this is an area that needs significant improvement in terms of vaccine administration and/or tracking. Obstetric health care practitioners should be routinely addressing vaccinations in prenatal records, whether they were administered or offered and the patient declined. Such documentation is needed to continue to monitor the potential impact and/or role, if any, of perinatal vaccines on PTB.

Chronic hypertension with superimposed preeclampsia

The higher-than-average rate of preeclampsia found in this study could be attributed to the poor health of the Kentucky population overall. The Center for Disease Control (CDC) reports health statistics of each state and ranks them compared to the national average. According to the CDC, heart disease, which includes chronic hypertension, in Kentucky ranks 9th overall (CDC, 2018). In this study, 27% of women in the preeclampsia clinical phenotype also

had chronic hypertension, which makes it difficult to attribute whether or not the preeclampsia was superimposed and actually due to the underlying cardiac disease, rather than a unique phenotype. This is one example that illustrates why continued exploration is needed to gain a more nuanced understanding of known PTB clinical phenotypes. Without such knowledge, there will be no upstream progress toward developing preventive interventions targeted to high-risk pregnancies or tailored to the individual PTB clinical phenotype.

Modification of the initial phenotype/labor pathways

In Chapter One, 10 PTB clinical phenotypes were introduced with the associated labor pathways. These phenotypes were based on prior literature, which previously noted that PPROM led to either SPTL or IPTL (Figure 5.1).

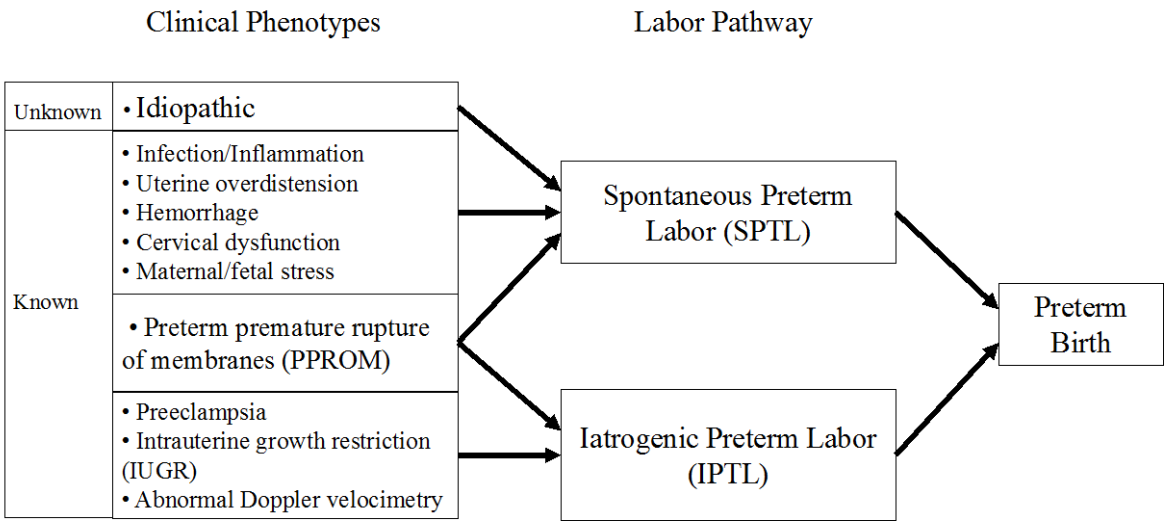

Figure 5.1. PTB Clinical Phenotypes/Known Proximal Determinants and Associated Labor Pathways

However, results of this chart review found that 71.4% of women in the maternal/fetal stress clinical phenotype also could lead to IPTL due to maternal/fetal complications (e.g., intrahepatic cholestasis, diabetic retinopathy, oligohydramnios). Thus, the clinical phenotype and subsequent labor pathway figure was adjusted to reflect the incidence of maternal/fetal stress leading to either labor pathway (Figure 5.2).

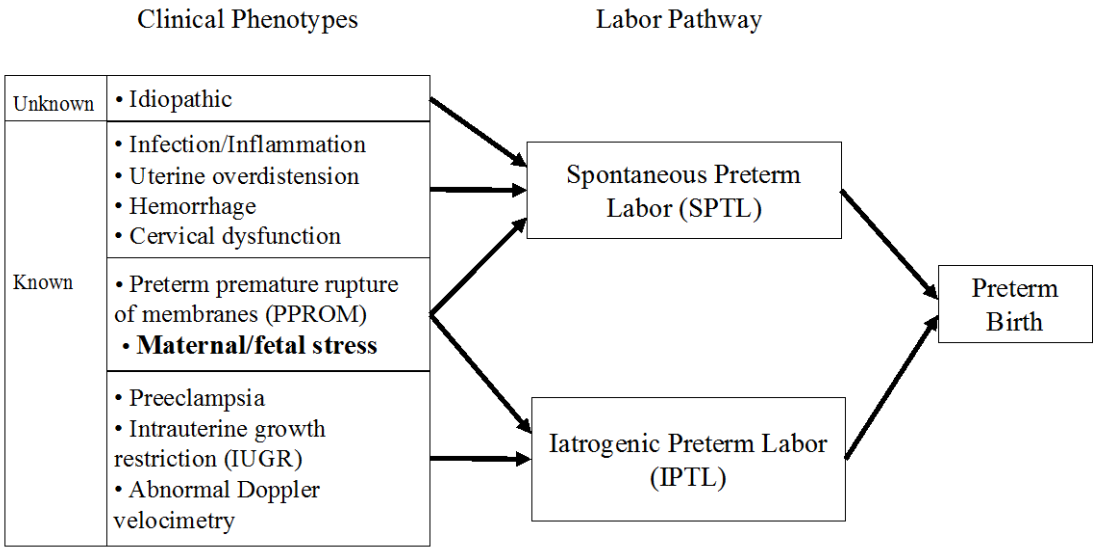

Figure 5.2. Adjusted PTB clinical phenotypes/known proximal determinants and associated labor pathways

Potential impact of overall health status in Kentucky

Kentucky ranks very low in overall health when compared to the nation as a whole, ranking 5th in adult obesity and 3rd in childhood obesity (NHANES, 2018). In 2017, the leading cause of death in Kentucky was heart disease, and ranked 9th in the U.S. (CDC, 2018). In this study, 33% of this sample were in the preeclampsia clinical phenotype, which is well above the 10-15% consistently reported in literature.

PTB in Kentucky versus the U.S. overall

The March of Dimes develops PTB report cards for the U.S. overall, as well as for each individual state (MOD, 2018). Grading assignment is determined by comparing the current PTB rate as reported in 2017 and the target PTB rate of 8.1% by the year 2020. The PTB rate in the U.S. overall in 2017 was 9.9% and received a grade 'C'; Kentucky state saw a PTB rate of 11.1%, and within Lexington/Fayette county, where this study was conducted, the PTB rate received a 'D' grade also, with a PTB rate of 11.2% (MOD, 2018). Additionally, the infant mortality rate (deaths per 1000 live births) within the state of Kentucky is 6.5, compared to the national average of 5.8 (CDC, 2018). It is possible that there would be a difference in phenotype distribution if data were collected from one of the states with lower rates of obesity, heart disease, and PTB.

Fetal Maturity **vs** ***Maternal Gestation*** **in the Identification of PTB**

PTB is currently defined by time, using maternal gestation age (time) as a measurement of term, pre-term, or unviability; however, in clinical practice, fetal maturity is not always consistent with maternal gestation. This distinction is important because medical decisions (e.g. administration of surfactant to neonate) often revolve around the *expected* fetal maturity based upon gestation. While some neonatologists and neonatal nurse practitioners are turning towards conservative management and intervening based upon the neonate's clinical status, the overall standard of practice at many NICUs still bases interventions based upon maternal gestation, regardless of the neonate's clinical status. This ongoing practice can lead to either over-treatment or under-treatment of the neonate. There have been multiple discussions over the past several decades about how to best address a discrepancy in fetal maturity and maternal gestational age;

yet, documentation and treatment continues to lean toward maternal gestation, although the subject remains a topic of ongoing discussion.

Of note, in this study, there were no reports of fetal maturity measurement, as clinical practice has steered away from the conventional methods of fetal maturity assessment (e.g., Ballard, fetal lung maturity). Maternal gestation was used exclusively to determine fetal status and subsequent clinical interventions.

A potential exists for a prospective study wherein neonates would be consistently treated based solely upon their clinical status (fetal maturity). Neonatal outcomes could then be compared to neonates who were treated with protocols based upon maternal gestational/fetal age. Ideally, such an effort would take the form of a multi-site study, where one subset of NICUs consistently treats based upon neonatal clinical status (fetal maturity) and the other paired subset of NICUs treats based upon set maternal gestational age protocols.

There have been several attempts to develop an assessment tool that could accurately determine gestational age based upon neonatal characteristics or maturity. Currently, the two most prominent tools are the Ballard and Dubowitz postnatal assessment tools (Ballard, Novak, & Driver, 1979; Dubowitz, Dubowitz, & Goldberg, 1970). Each tool includes physical and neuromuscular criteria obtained from examining the neonate (Table 5.2).

Table 5.2

Ballard and Dubowitz Physical and Neuromuscular Criteria

	Ballard assessment	**Dubowitz assessment**
Physical criteria	Skin, lanugo, plantar crease, breast maturity, eye and/or ear firmness, genitals	Edema, skin texture, skin color, skin opacity, lanugo, plantar creases, nipple formation, breast size, ear form, ear firmness, genitals
Neuromuscular criteria	Posture, square window (wrist), arm recoil, popliteal angle, scarf sign, heel-to-ear	Posture, square window, ankle dorsiflexion, arm recoil, leg recoil, popliteal angle, heel-to-ear, scarf sign, head lag, ventral suspension

While both of these tools have been widely used over the past 40+ years, their accuracy was brought into question years ago, particularly in the preterm/low birth weight population. Two studies conducted in the nineties fueled this caution. One study (Sanders et al., 1991) assessed 110 preterm neonates and compared Ballard and Dubowitz scores to maternal prenatal measures of gestational age (e.g., last menstrual period, best obstetric estimate). Their study found that less than 10% of the postnatal measures (e.g., Ballard, Dubowitz) agreed with the prenatal measures, and less than 55% agreed within 2 weeks. Both of these postnatal assessment measurement tools were found to overestimate gestational age (Sanders et al., 1991). Another study (Alexander, de Caunes, Hulsey, Tompkins, & Allen, 1992) used the Ballard assessment

tool to compare with prenatal gestation measures that included 4,193 neonates ranging from 28-44 weeks. This study also found that the Ballard assessment consistently overestimated gestational age of preterm births (Alexander et al., 1992).

More recently, a systematic review of 78 studies on gestational age assessment (Lee et al., 2017) found that the Ballard assessment overestimated gestational age ± 3.8 weeks when compared with ultrasound and ± 4.2 weeks when compared with last menstrual period. The Dubowitz score dated within ± 2.6 weeks when compared with ultrasound and ± 2.9 weeks when compared with last menstrual period. Further, this review found that newborn assessments underestimated gestational age in IUGR infants and overestimated gestational age in preterm infants (Lee et al., 2017). Noting early discrepancies, a revised Ballard assessment tool was introduced that was intended to improve accuracy by expanding to include additional scoring categories for extremely preterm infants (Ballard et al., 1991). However, this new Ballard tool was also found to overestimate gestational age (Lee et al., 2017).

The lack of an accurate or consistently useful fetal maturity assessment tool does not preclude the need for continued discussion and research on the best approach to understanding PTB pathways and outcomes. Recent progress in the use of non-invasive fetal lung maturity using ultrasound (e.g., thoracic wall movement, nasal fluid flow velocity waveforms) has been found to accurately determine fetal lung development when compared to the traditional test using lecithin/sphingomyelin (L/S) determination from amniotic fluid (La Torre et al., 2003). Researchers have also found that gray level histogram width was a reliable measure of fetal lung development (Serizawa & Maeda, 2010), both of which will continue to contribute to ongoing discussions on gestational age vs fetal maturity.

Study strengths and limitations

This study is the first known study that characterizes the idiopathic clinical phenotype individually and compared to non-idiopathic on sociodemographic variables, clinical characteristics, and perinatal intervention. In addition, the study also took a closer look at PPROM vs non-PPROM using the same set of variables. A specific strength was the use of an established open-source template for data collection in an attempt to address nomenclature.

The main limitation was the sample. While adequate numbers were obtained for comparative analyses, the distribution of clinical phenotypes and the disproportionately small number of "extremely preterm" charts need to be taken into account in the discussion. Another limitation is that there was inconsistency in the nomenclature and charting methods between care providers and EHRs do not explicitly specify the most proximal cause of delivery for the less prevalent clinical phenotypes (e.g., cervical dysfunction). Manually sifting through progress notes was required to determine the most proximal cause of delivery; therefore, accurate phenotype was challenging. An additional limitation is the ethnic homogeneity of the overall sample available in Kentucky, which does not accurately reflect the U.S. population as a whole, especially Black or African Americans who have poorer PTB outcomes.

Clinical implications

PTB as a complex syndrome

Historically, PTB has been viewed as a single outcome, defined by time; yet, it is evident that PTB has many underlying and intermingling causes. Viewing PTB through a different lens, both clinically and scientifically, has the potential to yield very new findings. For example, have

an ICD-10 code for each identified clinical phenotype, based upon the most proximal cause of delivery.

Fetal maturity as an indicator for clinical intervention

It is evident that using maternal gestation to determine the clinical interventions for the neonate is problematic, as maternal gestation dates may not always be accurate, and they do not implicitly guarantee the maturity of the fetus. Medical interventions should be based upon the neonate's overall clinical picture, rather than based solely upon gestation. There is a need to develop tools to assess both fetal maturity and maternal gestation to inform clinical care, to mitigate both over- and under-treatment of the neonate. Such tools would also shift the conversation surrounding fetal viability, as it currently is defined as <23 weeks of gestation.

Documentation of vaccines

It is important for clinicians to document vaccines in the prenatal record in such a way that perinatal charts can capture it. Both Tdap and Influenza vaccines are now part of standard prenatal care. Given the abundant evidence that supports the positive effects of both and no apparent increased risk in neonatal outcomes, educating women on the safety and efficacy of the inactivated influenza vaccine should continue to be a priority in prenatal care visits during influenza season. Studies have shown that maternal Tdap administration protects the newborn against infant pertussis in the first year of life (Baxter, Bartlett, Fireman, Lewis, & Klein, 2017; Hardy-Fairbanks et al., 2013), with no indication of adverse pregnancy outcomes (McHugh et al., 2019). Maternal Tdap during pregnancy was 91.4% effective within the infant's first two months of life, and 60% effective within the first year of life. In the United States, DTaP vaccine administration is recommended at 2 months of age; therefore, maternal Tdap protects an infant before it is old enough to receive the pertussis vaccine (Baxter et al., 2017). Further, pregnant

women are considered a priority population to receive the inactivated influenza vaccine, as maternal influenza infection has adverse effects on pregnancy outcomes, and the risk of fetal death nearly doubles with maternal influenza diagnosis (Haberg et al., 2013). While numerous studies have found that maternal influenza vaccine administration is beneficial in preventing maternal infection and infant infection via transplacental antibody transfer (Haberg et al., 2013), women often report concerns about the potential risks to the fetus and opt to not receive the vaccine. Studies of the effects of maternal influenza vaccine on adverse pregnancy outcomes concluded that there were no significant differences in PTB rates, low-birth weight, spontaneous abortions, and small-for-gestational age between the vaccinated and unvaccinated groups (Dodds et al., 2012; Donahue et al., 2019; Haberg et al., 2013; Jeong, Jang, Jo, & Jang, 2019; Legge, Dodds, MacDonald, Scott, & McNeil, 2014; McHugh et al., 2019). Some studies reported a decreased risk of PTB in women who received the influenza vaccine (Legge et al., 2014; Omer et al., 2011).

Recommendations for future studies

Recommendations for future studies include: 1) obtain a larger and/or more heterogenous sample; 2) have uncomplicated, term births as a control group to measure associations between distal determinants and PTB; 3) exclude multiples pregnancies to isolate pathobiological determinants that are involved in PTB, rather than mechanical; 4) categorize and analyze separately pregnancy-induced hypertension and chronic hypertension with superimposed preeclampsia; and 5) extend the gestational range to include <23 weeks, as it is likely that the same pathobiological factors in PTB and intrauterine fetal demise are similar.

The opportunity to obtain larger samples sizes for PTB observational studies is limited, as there is currently no way to parse apart each clinical phenotype based on ICD-10 codes, which leaves the researcher to dig through EHR progress notes to find the most proximal cause of the preterm delivery. Currently, there is one overarching ICD-10 code for PTB, and it is defined by time (i.e., delivery before 37 weeks of gestation), with the exception of PPROM and preeclampsia, which have their own ICD-10 codes. As PTB science moves towards separating phenotypes accurately and consistently, clinicians can begin to categorize each PTB into the corresponding phenotype within the EHR, and eventually develop ICD-10 codes that are phenotype-specific. Having phenotype-specific ICD-10 codes will enable researchers to access biorepository data and collect very large samples, which will enhance the ability to use biomedical informatics and robust statistical clustering techniques (e.g., latent class analysis) to determine heterogeneity in an otherwise seemingly homogenous group.

Larger prospective studies using selected predictors based on findings in this and other PTB studies would help foster translational science to produce actionable knowledge to predict, prevent, and/or treat PTB.

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Appendix

Record ID	Record ID
Maternal age	**Maternal age**
Month of delivery	Month of delivery
Race	Race
Ethnicity	Ethnicity
Gravida	**Gravida**
Parity	Parity
Fetal maturity/gestational age	**Fetal maturity/gestational age**
Single or multiples	Single or multiples
Allergies	Allergies
Blood type	Blood type
Labor pathway	Labor pathway
Cause of delivery	Cause of delivery
BMI	BMI
Tobacco	Tobacco
ETOH	ETOH
Illicit drugs	Illicit drugs
Existing medical condition	Existing medical condition
Autoimmune disorder	**Autoimmune disorder**
WBC	WBC
RBC	RBC
Hemoglobin	Hemoglobin
Hematocrit	Hematocrit
MPV	MPV
Platelets	Platelets
Blood glucose	Blood glucose
GBS	GBS
History of PTB	History of PTB
Immunizations	**Immunizations**
Fetal sex	**Fetal sex**
Birth weight	Birth weight

***Bolded** indicates Aim 2 focused subset variables

APPROVAL TO RELY ON AN EXTERNAL

June 17, 2019

Dear Investigator:

On 6/17/2019, the IRB reviewed the following submission:

Type of Review:	Initial Study
Title of Study:	[BHL - IAA] Further Characterization of Preterm Birth Phenotypes: A Descriptive Study
Principal Investigator:	Martha Driessnack
IRB ID:	STUDY00019764
Funding:	None
IND, IDE, or HDE:	None

Your request that the Oregon Health & Science University (OHSU) IRB rely on the review of Baptist Health Lexington IRB for the study referenced above was approved by the OHSU IRB.

No human subjects research may be conducted until the Baptist Health Lexington IRB approves the overall study and the addition of our site for the study.

The OHSU IRB expects that review of this study will occur according to all applicable federal, state, and local laws and regulations, and per any applicable agreements.

Requirements under HIPAA:

If your study involves the collection, use, or disclosure of Protected Health Information (PHI), you must comply with all applicable requirements under HIPAA. See the HIPAA and Research website and the Information Privacy and Security website for more information.

Sincerely,
The OHSU IRB Office

Institutional Review Board (IRB) Authorization Agreement

OREGON HEALTH & SCIENCE UNIVERSITY
OHSU
Research Integrity Office
Mail code **L106-RI** 3181 S.W. Sam Jackson Park Road Portland, Oregon 97239-3098
tel: 503 494-7887 | fax: 503 346-6808

Use this form when OHSU is waiving IRB oversight. An agreement template from the reviewing institution may be used instead of this form.

Name of Institution or Organization Providing IRB Review (Institution/Organization A):

Baptist Health-Lexington	
IRB Registration#:	**IRB000002954**
Federalwide Assurance (FWA) #:	**FWA00003601**

Name of Institution Relying on the Designated IRB (Institution B):

Oregon Health & Science University	
FWA #:	**FWA00000161**

The Officials signing below agree that *Oregon Health & Science University* may rely on the designated IRB for review and continuing oversight of its human subjects research described below: (*check one*)

(x) This agreement is limited to the following specific protocol(s):

OHSU eIRB #: STUDY00019764

Name of Research Project: Further characterization of selected preterm birth phenotypes: a descriptive study

Name of Principal Investigator: Martha Driessnack, Ph.D., P.P.C.N.P.-B.C.

Sponsor or Funding Agency: **n/a** Award Number, if any: ____

(___) Other *(describe):* _____

The review performed by the designated IRB will meet the human subject protection requirements of Institution B's OHRP-approved FWA. The IRB at Institution/Organization A will follow written procedures for reporting its findings and actions to appropriate officials at Institution B. Relevant minutes of IRB meetings will be made available to Institution B upon request. Institution B remains responsible for ensuring compliance with the IRB's determinations and with the Terms of its OHRP-approved FWA. This document must be kept on file by both parties and provided to OHRP upon request.

Signature of Signatory Official (Institution/Organization A):

Date: 5-10-2019

Print Full Name: **William Sisson, MBA, FACHE** Institutional Title: **President**

Signature of Signatory Official (Institution B):

David Holmgren

Digitally signed by David Holmgren
DN: cn=David Holmgren, o=OHSU, ou=IRB, email=holmgred@ohsu.edu, c=US
Date: 2019.05.13 14:03:39 -07'00'

Date: 5-13-2019

Print Full Name: **David P. Holmgren** Institutional Title: **IRB Manager**

BAPTIST HEALTH
LEXINGTON

1740 Nicholasville Road
PHONE: 859.260.6100
Lexington, KY 40503

May 24, 2019

Susan Elaine Frase, RN, BSN, PhD Candidate
OHSU School of Nursing
3455 SW US Veterans Hospital Rd
Portland, OR 97239

RE: #1548 - Further Characterization of Preterm Birth Phenotypes: A Descriptive Study **(**Reference#015296

) Dear Ms. Frase,

Your new protocol listed above was approved under the expedited review process on 05/24/2019 and will be reported at the 06/20/2019 meeting of the Baptist Health Lexington Institutional Review Board.

The IRB approval for this protocol will expire on 05/23/2020. Please submit your continuation request by 05/09/2020 in order to avoid lapses in approval of your research.

As principal investigator, you are responsible for complying with IRB decisions, conditions and requirements. The protocol procedures should be implemented as approved by the IRB and any other changes in this protocol, including closure, must be reported promptly to the IRB through iRIS, the IRB submission system. No change may be initiated without review by the IRB, except where necessary to eliminate apparent immediate hazard to the participant. In addition, any unanticipated problem involving risk to the participant or others must be reported immediately to the IRB

If you have any questions, please contact the IRB office at 859-260-6074.

Sincerely,

Signature applied by Dee Beckman on 05/24/2019 12:22:14 PM EDT

Dee Beckman, DNP, MBA, MSN, RN, NE-BC
IRB Chairperson

BAPTIST HEALTH
LEXINGTON

1740 Nicholasville Road
PHONE: 859.260.6100
Lexington, KY 40503

June 24, 2019

Susan Elaine Frase, RN, BSN, PhD Candidate
OHSU School of Nursing
3455 SW US Veterans Hospital Rd
Portland, OR 97239

RE: #BHL-19-1548 (Reference#015484) - Further Characterization of Preterm Birth Phenotypes: A Descriptive Study

Dear Ms. Frase,

Your amendment for the protocol listed above, request to increase N to 137, was approved under expedited review on 06/24/2019. This will be reported at the Baptist Health Lexington Institutional Review Board meeting on 07/18/2019. With this submission, you have continued approval until 05/23/2020.

As you are aware, any change in this protocol must be reported promptly to the IRB. No change may be initiated without review by the IRB, except where necessary to eliminate apparent immediate hazard to the participant. In addition, any unanticipated problem involving risk to the participant or others must be reported immediately to the IRB.

If you have any questions, please contact the IRB office at 859-260-6074.

Sincerely,

Signature applied by Dee Beckman on 06/24/2019 08:34:28 AM EDT

Dee Beckman, DNP, MBA, MSN, RN, NE-BC
IRB Chairperson

BAPTIST HEALTH
LEXINGTON

1740 Nicholasville Road
PHONE: 859.260.6100
Lexington, KY 40503

June 28, 2019

Susan Elaine Frase, RN, BSN, PhD Candidate
OHSU School of Nursing
3455 SW US Veterans Hospital Rd
Portland, OR 97239

RE: #BHL-19-1548 (Reference#015552) Further Characterization of Preterm Birth Phenotypes: A Descriptive Study

Dear Ms. Frase,

Your amendment for the protocol listed above, request to collect data on mothers who delivered between 34-34.6 weeks, was approved under expedited review on 06/28/2019. This will be reported at the Baptist Health Lexington Institutional Review Board meeting on 07/18/2019. With this submission, you have continued approval until 05/23/2020.

As you are aware, any change in this protocol must be reported promptly to the IRB. No change may be initiated without review by the IRB, except where necessary to eliminate apparent immediate hazard to the participant. In addition, any unanticipated problem involving risk to the participant or others must be reported immediately to the IRB.

If you have any questions, please contact the IRB office at 859-260-6074.

Sincerely,

Signature applied by Dee Beckman on 06/28/2019 08:51:37 AM EDT

Dee Beckman, DNP, MBA, MSN, RN, NE-BC
IRB Chairperson

BAPTIST HEALTH
LEXINGTON

1740 Nicholasville Road Lexington, KY 40503
PHONE: 859.260.6100

July 1, 2019

Susan Elaine Frase, RN, BSN, PhD Candidate
OHSU School of Nursing
3455 SW US Veterans Hospital Rd
Portland, OR 97239

RE: #BHL-19-1548 (Reference#015557) Further Characterization of Preterm Birth Phenotypes: A Descriptive Study

Dear Ms. Frase,

Your amendment for the protocol listed above, request to increase number of charts enrolled to 280 from 200, was approved under expedited review on 07/01/2019. This will be reported at the Baptist Health Lexington Institutional Review Board meeting on 07/18/2019. With this submission, you have continued approval until 05/23/2020.

As you are aware, any change in this protocol must be reported promptly to the IRB. No change may be initiated without review by the IRB, except where necessary to eliminate apparent immediate hazard to the participant. In addition, any unanticipated problem involving risk to the participant or others must be reported immediately to the IRB.

If you have any questions, please contact the IRB office at 859-260-6074.

Sincerely,

Signature applied by Dee Beckman on 07/01/2019 10:35:36 AM EDT

Dee Beckman, DNP, MBA, MSN, RN, NE-BC
IRB Chairperson