RECURRENT PRETERM BIRTH IN UTAH

by

Sara Marie Ellis Simonsen

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STATEMENT OF DISSERTATION APPROVAL

The dissertation of Sara Marie Ellis Simonsen

has been approved by the following supervisory committee members:

		Date Approved
Joseph L. Lyon	, Chair	**6/10/2011**
M. Sean Esplin	, Member	**6/10/2011**
Christina A. Porucznik	, Member	**6/10/2011**
Joseph B. Stanford	, Member	**6/10/2011**
Michael W. Varner	, Member	**6/10/2011**

and by Stephen C. Alder, Chair

of Public Health Division, Department of Family and Preventive Medicine

and by Charles A. Wight, Dean of The Graduate School.

ABSTRACT

In multiparous women, history of preterm birth is a risk factor for recurrence. We examined patterns of recurrent preterm birth by clinical presentation and additional risk factors for recurrence among 76,657 women who had their first three singleton live births in Utah, 1989– 2007. We also evaluated the association between gestational weight gain and preterm birth using a bidirectional case-crossover study to control for genetics and other time-invariant characteristics. Unadjusted and multivariable-adjusted logistic regression, multinomial regression, and conditional logistic regression were used to calculate odds ratios (OR). In our study women were likely to experience recurrent preterm birth of the same clinical subtype; however, recurrence of other clinical subtypes was also common. The highest odds of recurrence were in women with two prior preterm births of the same subtype. Additional risk factors for recurrence included a short interpregnancy interval, the presence of a preexisting maternal medical condition, history of a birth at 28–32 weeks gestation, and the presence of a fetal anomaly on the birth record for the current live birth. Risk factors varied depending upon the clinical subtype of the most recent preterm birth. Finally, we found that women who gained more weight than recommended during pregnancy were at risk for indicated preterm birth while those who gained less than recommended were at risk for spontaneous preterm birth.

For Madeleine Joy, with the hope that you will always be curious

and inspired to continue learning about our world…

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CHAPTER 1

INTRODUCTION

Preterm Birth as a Public Health Concern

Preterm birth is defined as the delivery of a live infant at less than 37 weeks of gestation.(1) Each year in the United States, more than 500,000 infants are born prematurely, with preterm birth complicating more than 1 out of every 10 live births in both Utah and the United States.(2) Preterm birth is an important public health issue because it is associated with morbidity and mortality as well as billions of dollars in health care costs. Preterm birth is second only to birth defects as the leading cause of perinatal mortality, and 75-88% of neonatal deaths occur in those born before 37 weeks gestation.(3) Preterm birth is also associated with an increased likelihood of serious neonatal morbidity including cerebral palsy and other neuro-developmental disabilities.(3, 4) In a recent study, Swamy et al. found increased mortality rates persisting from the first month of life through 5 years of age among infants born at 28-36 completed weeks gestation, and increased mortality through age 12 for infants born at 28-32 completed weeks gestation, compared with infants born at term.(5) There is also growing concern about neonatal complications in late-preterm infants (those born at 34-36 completed weeks gestation), a group previously thought to have similar morbidity and mortality as infants born at term. Recent research findings indicate that late-preterm infants have significantly increased rates of respiratory complications when compared with infants born at term. Yoder et al. reported a statistically significant increased risk for respiratory morbidity among late preterm infants born at 34 weeks (rate ratios of 35.1-41.6, depending on birth cohort) and at 35-36 weeks (rate ratios of 3.8-7.8, depending on birth cohort) compared with infants born at 39-40 weeks.(6) Finally, it is estimated that preterm birth costs approximately $26.2 billion annually in the United States, with an average of $51,600 per preterm infant.(1) For all these reasons, preterm birth is a serious clinical and public health problem.

Epidemiology of Preterm Birth

In 2008, preterm birth accounted for 12.3% of deliveries in the United States and 11.0% of deliveries in Utah. The incidence of preterm birth has increased steadily over the past decade, with an 8% increase in Utah between 1998 and 2008 and a 6% increase in the United States during the same time period.(2) Preterm birth is a heterogeneous condition and it is sometimes classified into groups based on clinical presentation. Spontaneous preterm births include deliveries initiated by spontaneous rupture of the chorioamniotic membranes before the onset of labor (preterm premature rupture of membranes or pPROM) and deliveries initiated by spontaneous preterm labor without pPROM. Medically indicated preterm births include deliveries performed via labor induction or Cesarean section for maternal or fetal conditions.(4) The most common indications for medically indicated preterm delivery are preeclampsia and fetal growth restriction; other indications include fetal distress, fetal malformations, placental abnormalities, and maternal medical conditions.(7)

Although the rates of preterm birth in the United States have increased overall, trends in these rates vary dramatically by clinical presentation.(8) Between 1989 and 2001, rates of spontaneous preterm birth remained relatively stable or decreased slightly, with Caucasians experiencing a slight 3% *increase* in spontaneous preterm birth and a 23% *decrease* in preterm birth due to PROM, and African Americans experiencing a 27% *decrease* in both spontaneous preterm birth and preterm birth due to PROM. During this same time, medically indicated preterm births *increased* 55% among Caucasians and 32% among African Americans.(8) Increases in the rates of medically indicated preterm birth have also been noted in other industrialized nations.(9-11)

It is unclear whether the overall decline in spontaneous preterm birth in the United States is due to a shift of spontaneous to indicated preterm birth through medical intervention, changes in the prevalence of underlying causes of preterm births, or both. However, the differences in preterm birth trends by clinical presentation highlight the importance of examining preterm birth both in aggregate and in analyses stratified by clinical subtype in order to more fully understand differences and similarities between preterm births with various clinical presentations—a theme throughout this dissertation.

Preterm Birth and Neonatal Mortality

Despite concern about increasing rates of preterm birth, both neonatal and infant mortality rates have declined over the last decade. In Utah, both the neonatal and infant mortality rates decreased between 1989 and 2006, with a 20.5% decrease in neonatal deaths (from 4.4/1,000 live births in 1989 to 3.5/1,000 live births in 2006) and a 37.5% decrease in infant mortality (from 8.0/1,00 live births in 1989 to 5.0/1,000 live births in 2006).(12) The trends are similar in the United States(13, 14) and in other industrialized nations.(15, 16)

The decline in neonatal and infant mortality over the last decade has been associated with the increasing rates of medically indicated preterm birth, however this association varies by maternal race(8, 10), as the rate of indicated preterm birth is increasing at a more rapid pace among Caucasians than African Americans.(8) Ananth et al. found that declines in perinatal mortality between 1989 and 2001 among Caucasians were strongly associated with increasing rates of indicated preterm birth, while the reduction in perinatal mortality among African Americans was associated with decreasing rates of spontaneous preterm birth and preterm birth initiated by PROM.(8) The reduction in neonatal mortality associated with indicated preterm birth has occurred because obstetric interventions such as labor induction or Cesarean delivery are increasingly performed due to maternal or fetal compromise. In addition, neonatal care has improved over time(16, 17), perhaps making clinicians more comfortable performing preterm inductions or operative deliveries when indicated. This interplay between preterm birth clinical subtypes and neonatal mortality also highlights the importance of studying preterm birth in analyses stratified clinical presentation.

Recurrent Preterm Birth

Recurrent preterm birth is typically defined as two or more preterm births to the same woman occurring before 37 completed weeks gestation.(7) A history of a prior preterm birth is one of the strongest predictors of preterm birth in multiparous women, and recurrence has been associated with both spontaneous and indicated preterm birth.(7, 18-25) Adams et al. found that preterm birth recurred in the second pregnancy among approximately 20% of white women and 26% of black women, with an increasing rate of recurrence among women with a younger gestational age at delivery in the first pregnancy.(18) Mercer and found that women with a preterm birth in their most recent pregnancy had a 2.5-fold increased risk for recurrent spontaneous preterm birth compared with those who had a term delivery in their most recent pregnancy. Similar to Adams et al., Mercer et al. found that risks of preterm birth in parous women were highest among those with prior preterm deliveries at early gestational ages, with an 11.6-fold increased risk in recurrence among those with a prior delivery at <28 weeks gestation.(21) Similarly, Esplin et al. found that women with a history of spontaneous preterm birth before 34 weeks gestation were at the highest risk for recurrent spontaneous preterm birth (RR=13.56).(20)

Authors have found similarly high risks for recurrent indicated preterm birth. Meis et al. found that women with a history of indicated preterm birth were at significantly increased risk for recurrent indicated preterm birth (OR=2.8). Interestingly, women with a history of spontaneous preterm birth were also at increased risk for subsequent indicated preterm birth (OR=2.45) in multivariate analysis.(22) Bloom and colleagues found that recurrent preterm birth with similar clinical presentation occurred among those with PROM (OR=5.5) and preterm labor with intact membranes (OR=7.9). The percentage of women with recurrence increased relative to the number of prior consecutive preterm births, with recurrence in 16%, 41%, 67% of those with 1, 2, and 3 prior preterm births, respectively.(23) In a study of nearly 14,000 Danish women, Kristensen et al. found that the overall risk of recurrence was similar between women who experienced spontaneous versus indicated preterm birth during their first pregnancy (15.2% and 12.8%, respectively). However, women with spontaneous preterm birth experienced recurrent spontaneous preterm birth twice as often as women with indicated preterm birth experienced recurrent indicated preterm birth (11.3% and 6.4%, respectively).(24) Ananth and colleagues also found that women with a spontaneous preterm birth in their first pregnancy had increased rates of both recurrent spontaneous (OR=3.6, 20.7%) and indicated (OR=2.5, 2.7%) preterm birth. Those with an indicated preterm birth in their first pregnancy were also at increased risk for both recurrent spontaneous (OR=1.6, 10.4%) and indicated (OR=10.6, 12.2%) preterm birth.(25)

Based on the studies described above, it is clear that both spontaneous and indicated preterm birth are risk factors for recurrent preterm birth of either type. Other risk factors for recurrent preterm birth have also been described, including Black race,(18, 26) underweight maternal body mass index (BMI),(27) weight loss between pregnancies, (28) maternal smoking,(29) number of lifetime sexual partners,(30) and short interpregnancy interval.(31) However, most research on recurrent preterm birth has focused on recurrence across two pregnancies, typically the first and second,(18, 24) or on recurrence based on the most recent pregnancy,(32) rather than examining patterns across a woman's full obstetric history. In addition, only a few studies have examined recurrent preterm birth stratified by clinical presentation.(22-25) Thus, this study was designed to further explore the patterns of recurrence and risk factors for preterm birth beyond the second pregnancy with analyses stratified by preterm birth clinical presentation, with the overall goal of providing information to aid clinicians in identifying and counseling women at risk for preterm birth.

Specific Aims

There were three unique specific aims for this study: 1) Calculate the prevalence and odds of recurrent preterm birth by clinical subtype in the second and third live births among Utah women who had their first three singleton live births in Utah between 1989 and 2007; 2) Evaluate risk factors for recurrent preterm birth in the 2nd and 3rd live births, overall and by the clinical subtype of the most recent preterm birth, among multiparous Utah women with a history of preterm birth who had their first three singleton live births in Utah between 1989 and 2007; and 3) Conduct a case-crossover study to explore the association between gestational weight gain outside of the recommended guidelines and preterm birth among Utah women who had their first three singleton live births in Utah between 1989 and 2007 and had at least one term and one preterm birth.

Methods

The methods used for each of the specific aims are described in detail in the following chapters. Briefly, maternally-linked Utah birth certificates were obtained from the Utah Population Database and were used to identify women who had their first three singleton live births in Utah between 1989 and 2007. In order to insure that the live births in the dataset were a woman's first, second, and third live births, the data were sorted by mother and date and evaluated to confirm that the reported birth order for each of the three live births in the dataset matched with the sorted order of the births.(33) Preterm birth was defined as a live birth occurring between 20 0/7 and 36 6/7 weeks gestation, using the clinical estimate of gestational age from the birth certificate. Women with births having implausible birthweight for their reported gestational age were eliminated from the dataset using published birthweight-gestational age combinations for each week of gestation.(34) Preterm births were stratified by clinical presentation into 3 groups: pPROM, spontaneous preterm labor, and medically indicated preterm birth. This stratification was done using a published algorithm (35) and with guidance from two perinatologists (committee members MSE and MWV). Unadjusted and multivariable-adjusted regression models were utilized to calculate odds ratios. For Aim 1, logistic regression and multinomial regression were utilized. For Aim 2, logistic regression models were used, and for Aim 3, conditional logistic regression was utilized.

Summary

Details about the methods used for each specific aim in addition to results and conclusions are described in Chapters 2, 3, and 4. Chapter 5 includes overall conclusions.

References

1. Behrman RE, Butler AS, Institute of Medicine (U.S.). Committee on Understanding Premature Birth and Assuring Healthy Outcomes. Preterm birth : causes, consequences, and prevention. Washington, D.C.: National Academies Press; 2007.

2. National Center for Health Statistics. Final Natality Data. Retrieved May 19, 2011 from www.marchofdimes.com/peristats.

3. Kramer MS, Demissie K, Yang H, Platt RW, Sauve R, Liston R. The contribution of mild and moderate preterm birth to infant mortality. Fetal and Infant Health Study Group of the Canadian Perinatal Surveillance System. JAMA 2000;284(7):843-9.

4. Ananth CV, Vintzileos AM. Epidemiology of preterm birth and its clinical subtypes. J Matern Fetal Neonatal Med 2006;19(12):773-82.

5. Swamy GK, Ostbye T, Skjaerven R. Association of preterm birth with long-term survival, reproduction, and next-generation preterm birth. JAMA 2008;299(12):1429-36.

6. Yoder BA, Gordon, M.C., Barth, W.H. Late-preterm birth: Does the changing obstetric paradigm alter the epidemiology of respiratory complications? Obstet Gynecol 2008;111(3):814-22.

7. Mazaki-Tovi S, Romero R, Kusanovic JP, Erez O, Pineles BL, Gotsch F, et al. Recurrent preterm birth. Semin Perinatol 2007;31(3):142-58.

8. Ananth CV, Joseph KS, Oyelese Y, Demissie K, Vintzileos AM. Trends in preterm birth and perinatal mortality among singletons: United States, 1989 through 2000. Obstet Gynecol 2005;105(5 Pt 1):1084-91.

9. Papiernik E, Zeitlin J, Rivera L, Bucourt M, Topuz B. Preterm birth in a French population: the importance of births by medical decision. BJOG 2003;110(4):430-2.

10. Joseph KS, Demissie K, Kramer MS. Obstetric intervention, stillbirth, and preterm birth. Semin Perinatol 2002;26(4):250-9.

11. Foix-L'Helias L, Blondel B. Changes in risk factors of preterm delivery in France between 1981 and 1995. Paediatr Perinat Epidemiol 2000;14(4):314-23.

12. Utah Department of Health Center for Health Data. Utah's Indicator-Based Information System for Public Health (IBIS-PH). Retrieved May 28, 2008 from ibis.health.utah.gov.

13. Alexander GR, Kogan M, Bader D, Carlo W, Allen M, Mor J. US birth weight/gestational age-specific neonatal mortality: 1995-1997 rates for whites, hispanics, and blacks. Pediatrics 2003;111(1):e61-6.

14. Demissie K, Rhoads GG, Ananth CV, Alexander GR, Kramer MS, Kogan MD, et al. Trends in preterm birth and neonatal mortality among blacks and whites in the United States from 1989 to 1997. Am J Epidemiol 2001;154(4):307-15.

15. Bell R, Glinianaia SV, Rankin J, Wright C, Pearce MS, Parker L. Changing patterns of perinatal death, 1982-2000: a retrospective cohort study. Arch Dis Child Fetal Neonatal Ed 2004;89(6):F531-6.

16. Anthony S, Ouden L, Brand R, Verloove-Vanhorick P, Gravenhorst JB. Changes in perinatal care and survival in very preterm and extremely preterm infants in The Netherlands between 1983 and 1995. Eur J Obstet Gynecol Reprod Biol 2004;112(2):170-7.

17. de Kleine MJ, den Ouden AL, Kollee LA, Ilsen A, van Wassenaer AG, Brand R, et al. Lower mortality but higher neonatal morbidity over a decade in very preterm infants. Paediatr Perinat Epidemiol 2007;21(1):15-25.

18. Adams MM, Elam-Evans LD, Wilson HG, Gilbertz DA. Rates of and factors associated with recurrence of preterm delivery. JAMA 2000;283(12):1591-6.

19. Carr-Hill RA, Hall MH. The repetition of spontaneous preterm labour. Br J Obstet Gynaecol 1985;92(9):921-8.

20. Esplin MS, O'Brien E, Fraser A, Kerber RA, Clark E, Simonsen SE, et al. Estimating recurrence of spontaneous preterm delivery. Obstet Gynecol 2008;112(3):516-23.

21. Mercer BM, Goldenberg RL, Moawad AH, Meis PJ, Iams JD, Das AF, et al. The preterm prediction study: effect of gestational age and cause of preterm birth on subsequent obstetric outcome. National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network. Am J Obstet Gynecol 1999;181(5 Pt 1):1216-21.

22. Meis PJ, Goldenberg RL, Mercer BM, Iams JD, Moawad AH, Miodovnik M, et al. The preterm prediction study: risk factors for indicated preterm births.

Maternal-Fetal Medicine Units Network of the National Institute of Child Health and Human Development. Am J Obstet Gynecol 1998;178(3):562-7.

23. Bloom SL, Yost NP, McIntire DD, Leveno KJ. Recurrence of preterm birth in singleton and twin pregnancies. Obstet Gynecol 2001;98(3):379-85.

24. Kristensen J, Langhoff-Roos J, Kristensen FB. Implications of idiopathic preterm delivery for previous and subsequent pregnancies. Obstet Gynecol 1995;86(5):800-4.

25. Ananth CV, Getahun D, Peltier MR, Salihu HM, Vintzileos AM. Recurrence of spontaneous versus medically indicated preterm birth. Am J Obstet Gynecol 2006;195(3):643-50.

26. Kistka ZA, Palomar L, Lee KA, Boslaugh SE, Wangler MF, Cole FS, et al. Racial disparity in the frequency of recurrence of preterm birth. Am J Obstet Gynecol 2007;196(2):131 e1-6.

27. Mercer BM, Macpherson CA, Goldenberg RL, Goepfert AR, Haugel-De Mouzon S, Varner MW, et al. Are women with recurrent spontaneous preterm births different from those without such history? Am J Obstet Gynecol 2006;194(4):1176-84; discussion 1184-5.

28. Merlino A, Laffineuse L, Collin M, Mercer B. Impact of weight loss between pregnancies on recurrent preterm birth. Am J Obstet Gynecol 2006;195(3):818-21.

29. Cnattingius S, Granath F, Petersson G, Harlow BL. The influence of gestational age and smoking habits on the risk of subsequent preterm deliveries. N Engl J Med 1999;341(13):943-8.

30. Yost NP, Owen J, Berghella V, Thom E, Swain M, Dildy GA, 3rd, et al. Effect of coitus on recurrent preterm birth. Obstet Gynecol 2006;107(4):793-7.

31. Smith GC, Pell JP, Dobbie R. Interpregnancy interval and risk of preterm birth and neonatal death: retrospective cohort study. BMJ 2003;327(7410):313.

32. Iams JD, Goldenberg RL, Mercer BM, Moawad A, Thom E, Meis PJ, et al. The Preterm Prediction Study: recurrence risk of spontaneous preterm birth. National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network. Am J Obstet Gynecol 1998;178(5):1035-40.

33. Adams MM, Kirby RS. Measuring the accuracy and completeness of linking certificates for deliveries to the same woman. Paediatr Perinat Epidemiol 2007;21 Suppl 1:58-62.

34. Alexander GR, Himes JH, Kaufman RB, Mor J, Kogan M. A United States national reference for fetal growth. Obstet Gynecol 1996;87(2):163-8.

35. Meirowitz NB, Ananth CV, Smulian JC, Vintzileos AM. Effect of labor on infant morbidity and mortality with preterm premature rupture of membranes: United States population-based study. Obstet Gynecol 2001;97(4):494-8.

CHAPTER 2

RECURRENT PRETERM BIRTH BY CLINICAL SUBTYPE ACROSS SINGLETON LIVE BIRTHS 1–3 IN A RETROSPECTIVE COHORT OF UTAH WOMEN

Précis

Recurrent preterm birth of the same clinical subtype is most likely, but recurrence of other clinical subtypes is also common.

Abstract

History of preterm birth is a strong predictor of subsequent preterm birth in multiparous women; however, few studies have examined recurrence patterns across etiologic subtypes beyond the second birth. We used maternally-linked birth records to describe preterm birth recurrence patterns across women's first three live births. Women in the study had three or more singleton live births in Utah (1989–2007), starting with their first birth (n=76,657). Using birth certificate data, preterm births (<37 weeks gestation) were stratified into those precipitated by prelabor rupture of the membranes (pPROM), spontaneous preterm labor (SPTL), or by labor induction or Cesarean (indicated). Multinomial regression was used to calculate adjusted odds ratios (aORs) for recurrence by subtype.

Overall, 6.5% of births were preterm with 57.2%, 28.9%, and 13.9% occurring via SPTL, pPROM, or indicated delivery, respectively. In the third birth, aORs for recurrent preterm birth of any subtype varied from 2.63 to 5.44 for women with one prior preterm birth and 9.37 to 17.50 for women with two prior preterm births. Odds of recurrence of the same clinical subtype across all births were substantial with aORs of 9.00, 5.74, and 7.71 in birth two and aORs of 45.37, 17.98, and 35.16 in birth three for pPROM, SPTL, and indicated preterm birth, respectively. In conclusion, women are likely to experience recurrent preterm birth of the same clinical subtype; however, recurrence of other clinical subtypes is also common. The highest odds of recurrence are in women with two prior preterm births of the same subtype.

Introduction

Preterm birth is defined as the delivery of a live infant at less than 37 weeks of gestation(1) and is the most common cause of perinatal death in normally formed newborns.(2) This increased mortality has been shown to persist from the first month of life through 12 years of age among preterm infants compared with infants born at term.(3) Preterm birth is also associated with an increased likelihood of serious long-term morbidity including cerebral palsy and other neuro-developmental disabilities.(2, 4) It is estimated that preterm birth costs approximately $26.2 billion annually in the United States, with an average of $51,600 per preterm infant.(1)

Recurrent preterm birth is typically defined as two or more births to the same woman occurring before 37 completed weeks gestation,(5) and a history of a prior preterm birth is one of the strongest predictors of subsequent preterm birth in multiparous women.(5-8) Preterm birth is a heterogeneous condition typically classified into subgroups based on proximate cause. Spontaneous preterm birth includes deliveries initiated by spontaneous rupture of the chorioamniotic membranes before the onset of labor (pPROM) and deliveries initiated by spontaneous preterm labor without pPROM (SPTL), while indicated preterm births include those occurring secondary to induction of labor or prelabor Cesarean delivery before 37 weeks gestation, usually due to intrauterine growth restriction, fetal compromise or maternal indications.(4)

Most studies of recurrent preterm birth have been limited in scope, focusing solely on spontaneous preterm birth, or examining only a history of any preterm birth, the outcome of the most recent delivery, or the outcome of the penultimate delivery without describing the association between a woman's full obstetric history and her risk of recurrent preterm birth.(6, 7, 9-12) In addition, there has been less attention to the proximate cause of preterm birth in recurrence studies, though a few studies have stratified recurrent preterm birth by proximate cause and have found that both spontaneous and indicated preterm birth are risk factors for recurrent preterm birth of either type.(4, 12-14) These studies have focused primarily on outcomes in the first and second pregnancy.

In this report we have investigated the risks of preterm birth recurrence in a large cohort of women having their first three singleton live births. Information on the proportion of women experiencing recurrent preterm birth by clinical subtype may be useful to clinicians counseling women at risk for recurrence, particularly women who are considering a third pregnancy after one or more preterm births.

Methods

This retrospective cohort study utilized linked Utah birth and fetal death records from 1989–2007, obtained from the Utah Population Database (UPDB). The UPDB is a data resource containing linked birth, death, fetal death, and other vital statistics data on over 6.4 million individuals (http://www.huntsmancancer.org/groups/ppr/). UPDB staff used a probabilistic record-linking program called Quality Stage, part of IBM's Websphere Information Integration Solution™, to identify unique mothers and link their births. Information on the mother's full maiden name and current surname, birth dates, birthplace, address of residence, date of previous live birth, and social security number were used for record linkage.

The initial UPDB dataset contained all live birth and fetal death records from 1989 through 2007 for residents of Utah (865,596 birth events to 443,669 unique women) (Figure 2.1). From these records, women who had a singleton first, second, and third live birth in Utah were included in the study. In women with more than three live births, only the first three were included in the dataset for analysis. Any woman delivering a multiple gestation during the time period was also excluded from analysis. In order to insure that the live births in the

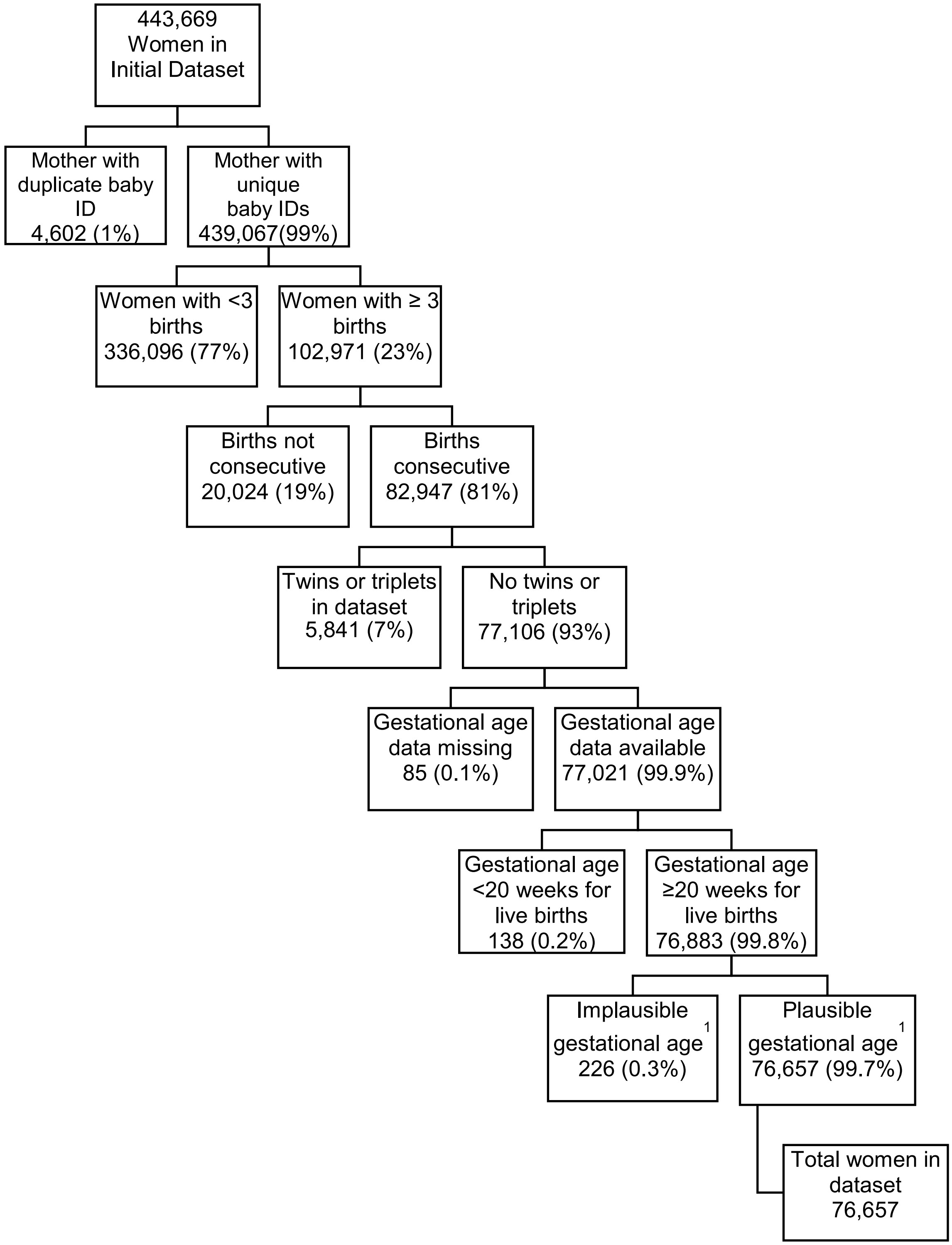

Figure 2.1: Women excluded from original dataset and reasons for exclusion. [1]Implausible birth weights for gestational age based on Alexander (1996).

dataset were a woman's first, second, and third live births, the data were sorted by mother and date and evaluated to confirm that the reported birth order for each of the 3 live births in the dataset matched with the sorted order of the births. A similar method has been recommended by Adams and Kirby for evaluating the accuracy of linked birth certificates for deliveries to the same woman.(15)

Preterm birth was defined as a live birth occurring at ≥20 and <37 weeks gestation as recorded on the birth certificate.(1) The measure of gestational age used in this study was that which was recorded on the medical record by the birth attendant, referred to as the clinical estimate of gestational age. This measure of gestational age may have been based on the woman's last menstrual period (LMP), ultrasound dating, or other clinical judgment. Women with births having implausible birthweight for their reported gestational age (n=226) were eliminated from the dataset using plausible birthweight-gestational age combinations published by Alexander (1996) for each week of gestation.(16) Women with missing gestational age data on one or more births (n=85) and women having infants with reported gestational ages <20 weeks for one or more live births (n=138) were also excluded from the dataset. See Figure 2.1.

Demographic characteristics included in this study were maternal age, self-reported race and ethnicity, marital status, and education level. Anthropometric characteristics included prepregnancy body mass index (BMI) and change in BMI category between live births. Clinical characteristics included the Kotelchuck Adequacy of Prenatal Care Utilization Index(17), time interval between pregnancies, record of a fetal anomaly on the birth certificate, maternal medical condition, and whether or not the birth was immediately preceded by a fetal death (identified by the presence of a fetal death record prior to the first live birth, between the first and second live births, or between the second and third live births with a gestational age of ≥20 weeks). The interpregnancy interval was calculated by subtracting the gestational age in the birth of interest from the time interval between the date of the previous birth and the date of the birth of interest. Maternal medical conditions were combined to create a composite variable; medical conditions included cardiac disease, acute or chronic lung disease, diabetes, hemoglobinopathy, chronic hypertension, and renal disease.

Preterm births were stratified into those precipitated by preterm premature rupture of membranes (pPROM), spontaneous preterm labor without pPROM (SPTL), and indicated preterm birth using a published algorithm(18) based on available birth certificate data and in consultation with two perinatologists (authors MSE and MWV). pPROM was defined as rupture of the membranes >12 hours before the onset of labor in women who delivered at <37 weeks gestation. Women without a record of pPROM were stratified into those who labored spontaneously prior to giving birth and those who did not. SPTL was considered to be present in the absence of labor induction or pPROM if the birth record contained evidence of tocolysis, cephalopelvic disproportion, labor augmentation, precipitous labor, prolonged labor, dysfunctional labor, vaginal birth, vaginal birth after Cesarean, vacuum-assisted delivery, or forceps-assisted delivery. Any woman without evidence of pPROM or SPTL was classified as having an indicated preterm birth; this group included women with an induction of labor and/or a primary or repeat Cesarean delivery in the absence of spontaneous labor.

The number and percentage of first, second, and third live births complicated by preterm birth overall, and by clinical subtype specifically, was calculated and reported. Logistic and multinomial regression was used to calculate unadjusted and adjusted odds ratios for recurrent preterm birth, overall, and by subtype, in the second and third births. A history of all term births was used as the referent category in these models. Because most variables were statistically significant in multivariable models due to the large sample size, variables included in adjusted models were those deemed to be clinically relevant. The aim of these models was not to adjust for all potential confounders in order to represent a causal relationship between obstetric history and subsequent pregnancy outcomes; the objective was simply to illustrate how the unadjusted odds ratios changed when adjusted for select variables of interest and to provide clinically relevant estimates of the likelihood of recurrence. Final models included maternal age, race, marital status, prepregnancy BMI, interpregnancy interval, fetal death preceding live birth, presence of a fetal anomaly, and the composite presence of a maternal medical condition. All statistical tests were two-sided and an alpha level of 0.05 was used to determine statistical significance. All statistical analyses were conducted using SAS software, Version 9.2 (SAS Institute Inc., Cary, NC).

This study was approved by the University of Utah Institutional Review Board (IRB# 00012636) and the University of Utah Resource for Genetic and Epidemiologic Research (RGE).

Results

The original dataset contained 865,596 birth events to 443,669 individual women occurring between 1989 and 2007. Figure 2.1 includes information on the women excluded from the dataset and the reasons for these exclusions. The dataset used for analysis in this study contained 230,335 birth events (229,971 live births and 364 fetal deaths) and included 76,657 women with a first, second, and third singleton live birth during the study period. Overall, 6.5% of live births (n=14,966) were preterm, with 6.3%, 6.1% and 7.2% of first, second, and third births, respectively, occurring at <37 weeks gestation. Figure 2.2 is a flow diagram that describes the number and percent of women with each preterm birth clinical subtype in the second and third live birth, stratified by the outcome in the first live birth. This figure was designed for utility in counseling patients about recurrence patterns by clinical subtype in live births two and three. The most common preterm birth subtype was SPTL, which constituted 57.2%, 61.3%, and 53.4% of first, second, and third preterm births respectively. Indicated preterm birth constituted 26.9%, 25.7%, and 33.4% of preterm births, and pPROM was the proximal cause of 15.7%, 12.9%, and 13.1% of preterm births one through three, respectively. The majority of preterm births were not recurrent preterm births; only 1.32% of second live births were recurrent preterm births

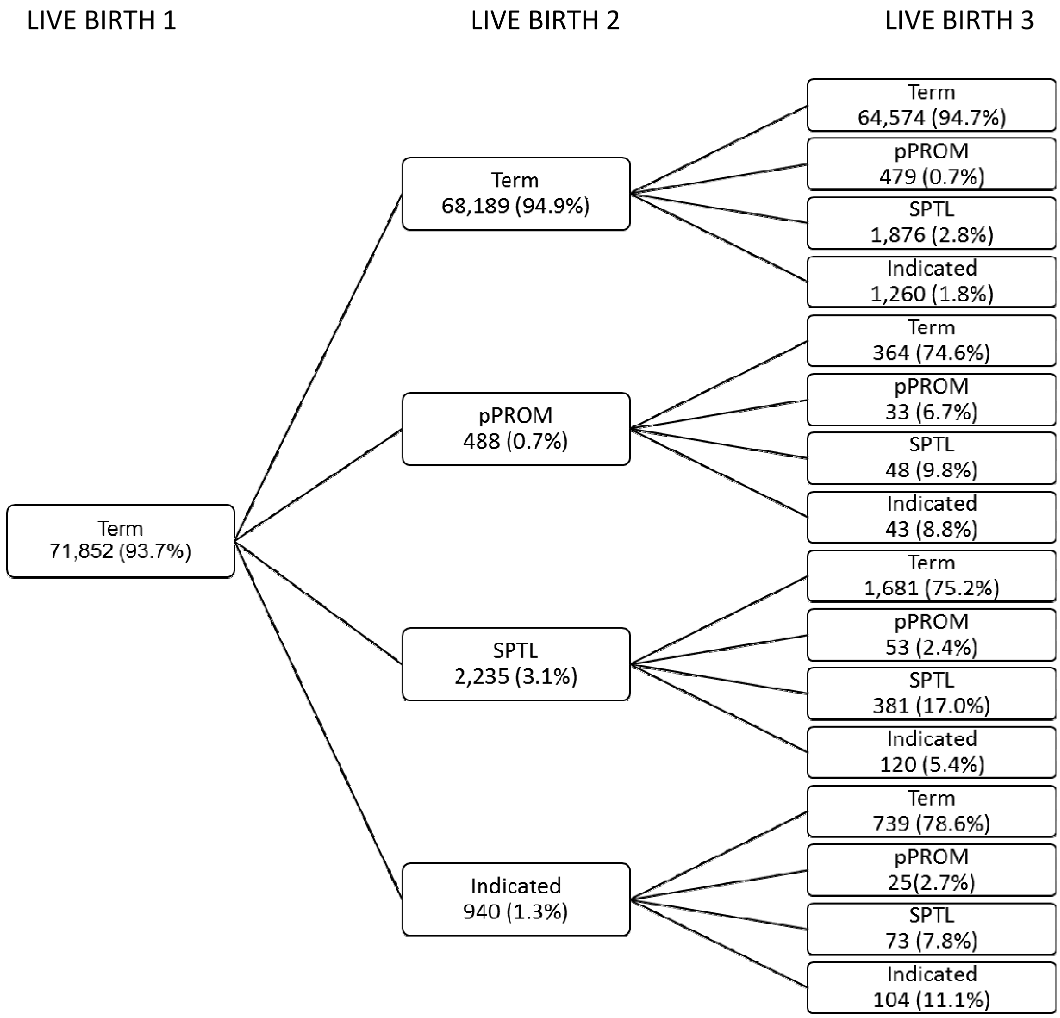

Figure 2.2: Flow diagram for recurrent preterm premature rupture of membranes (pPROM), spontaneous preterm birth precipitated by preterm labor (SPTL), and indicated preterm birth across Utah women's 1st through 3rd live births,1989-2007, stratified by outcome in first live birth (n=76,657 women)

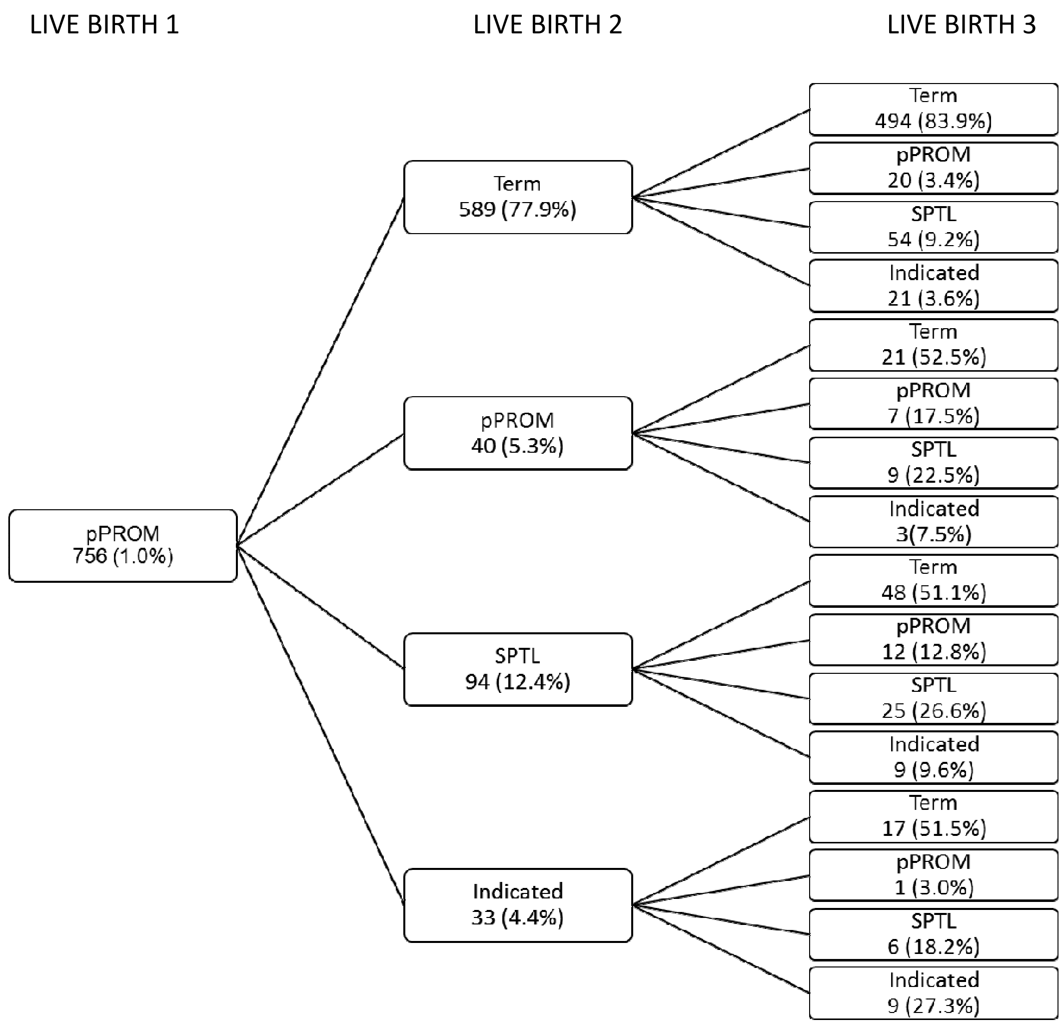

Figure 2.2 continued

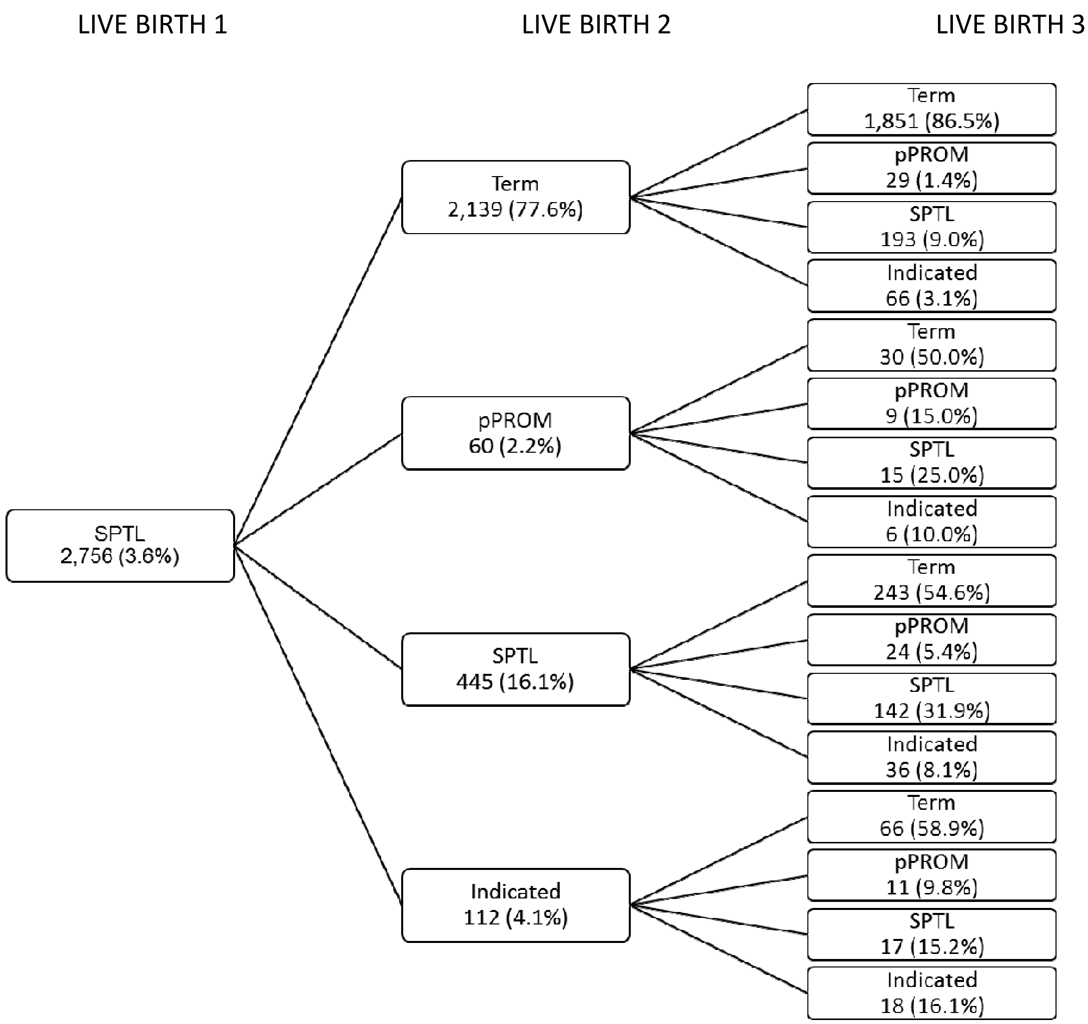

Figure 2.2 continued

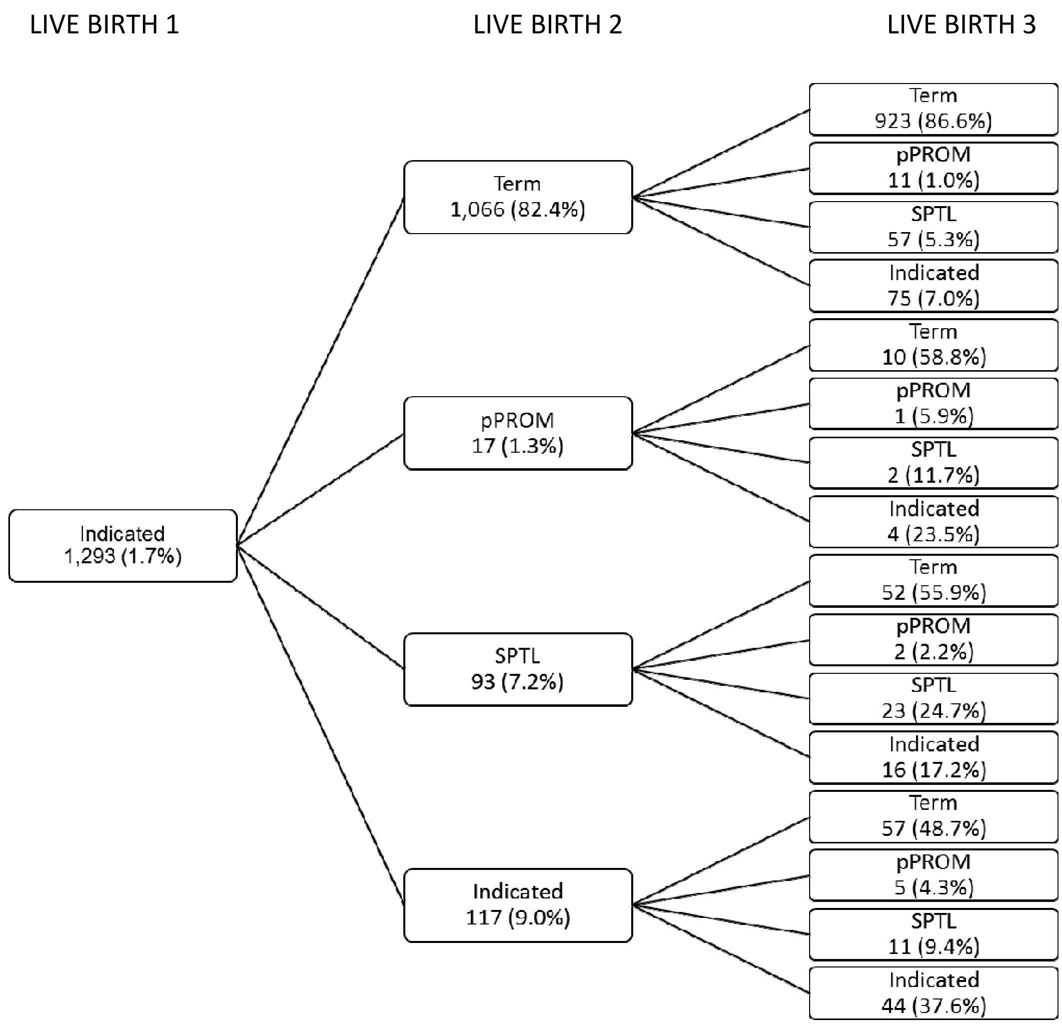

Figure 2.2 continued

(n=1,011) and 2.44% of third live births were recurrent preterm births (1.84% were a first recurrence (n=1,405) and 0.61% were a second recurrence (n=467)).

Table 2.1 contains information about the demographic, clinical, and anthropometric characteristics of the 76,657 women in the study, stratified by birth order. At their first live birth, most women in the study were under 25 years of age, non Hispanic White, and married. Self-reported race and ethnicity data varied only slightly across births. The mean age of women was 23 years at the first birth, 25 years at the second birth, and 28 years at the third birth. The proportion of women who were overweight and obese prior to becoming pregnant increased with increasing parity. The proportion of births preceded by a fetal death was extremely low at 0.17%, 0.13%, and 0.17% in births one, two, and three, respectively. Fetal anomalies identified on the birth certificate were present in 3.0% 2.6%, and 2.6% of births one through three, respectively.

Table 2.2 includes unadjusted and adjusted odds ratios for preterm birth overall, and by clinical subtype, in the second live birth stratified by the outcome of the first live birth. The ORs (both unadjusted and adjusted) were statistically significantly elevated for all clinical subtypes in women with a history of preterm birth compared to women with a history of term birth. The adjusted ORs (aOR) for recurrent preterm birth (of any subtype) in the second birth were significantly increased in women with a first birth complicated by pPROM (aOR 5.06), SPTL (aOR 4.93), or indicated preterm birth (aOR 4.00), compared with women having no history of preterm birth. When stratified by clinical subtype, the odds ratios for recurrent preterm birth were higher for the same subtype but were also

Table 2.1: Demographic, clinical, and anthropometric characteristics of Utah women whose first 3 singleton live births occurred between 1989 and 2007, by live birth number (n=76,657)

Variable	Live Birth 1 n (%)	Live Birth 2 n (%)	Live Birth 3 n (%)
Maternal Age			
<20	15778 (20.6)	3781 (4.9)	405 (0.5)
20–24	39553 (51.6)	30698 (40.1)	12739 (16.6)
25–29	18024 (23.5)	32480 (42.4)	35953(46.9)
30–34	2941 (3.8)	8462 (11.0)	22110 (28.8)
35–39	351 (0.5)	1171 (1.5)	4893 (6.4)
40+	7 (0.01)	65 (0.1)	555 (0.7)
Maternal Race			
White	73585 (96.3)		
Black	357 (0.5)		
American Indian/Alaskan Native	820 (1.1)	NA	NA
Asian	332 (0.4)		
Hawaiian/Pacific Islander	1243 (1.6)		
Other NonWhite	91 (0.1)		
Mother Hispanic/Latina	6330 (8.3)	NA	NA
Mother Married	61614 (80.4)	68132 (88.9)	69274 (90.4)
Maternal Education			
<HS Graduate	13195 (17.4)	9366 (12.3)	7851 (10.4)
HS Graduate	23134 (30.5)	24780 (32.7)	24648 (32.6)
Some College	23728 (31.2)	24029 (31.7)	24635 (32.5)
College Graduate	15894 (20.9)	17699 (23.3)	18593 (24.6)
Fetal Anomaly on Birth Certificate	2288 (3.0)	1958 (2.6)	1954 (2.6)
Live Birth Preceded by Fetal Death	131 (0.17)	103 (0.13)	130 (0.17)

Table 2.1 continued

Variable	Live Birth 1 n (%)	Live Birth 2 n (%)	Live Birth 3 n (%)
Maternal Medical Condition	2084 (2.7)	2946 (3.8)	4508 (5.9)
Prepregnancy BMI			
Underweight (<18.5)	7304 (10.2)	6255 (8.3)	4472 (6.0)
Normal Weight (18.5—24.9)	49185 (68.5)	46008 (61.3)	42554 (56.8)
Overweight (25.0—29.9)	10722 (14.9)	14320 (19.1)	16222 (21.6)
Obese (≥30)	4582 (6.4)	8517 (11.3)	11749 (15.7)
BMI Change Between Live Births			
BMI Dropped by ≥1 Category		4544 (6.5)	4658 (6.3)
BMI Stable	NA	50986 (72.4)	55104 (74.8)
BMI Increased by ≥1 Category		14911 (21.2)	13882 (18.9)
Interpregnancy Interval			
Not applicable	76519 (99.8)	NA	NA
<6 months	63 (0.08)	4973 (6.5)	3366 (4.4)
6–12 months	46 (0.06)	14692 (19.2)	10421(13.6)
13–18 months	13 (0.02)	17911 (23.4)	13355 (17.4)
19–24 months	8 (0.01)	14261 (18.6)	12732 (16.6)
25 months–36 months	5 (0.01)	14276 (18.6)	17917 (23.4)
>36 months	3 (0.00)	10544 (13.8)	18866 (24.6)

*Maternal Medical Conditions include cardiac disease, acute or chronic lung disease, pre-existing diabetes, hemoglobinopathy, chronic hypertension, and renal disease.

Table 2.2: Unadjusted and adjusted[1] odds ratios for preterm birth in the second live birth, overall and by clinical subtype[2], stratified by outcomes of the first live birth among Utah women whose first 3 singleton live births occurred between 1989 and 2007 (n=76,657)

	Outcome in 2nd Live Birth							
	Any Preterm Birth		pPROM		SPTL		Indicated	
Outcome in 1st Live Birth	OR (95% CI)	AOR[1] (95% CI)	OR (95% CI)	AOR[1] (95% CI)	OR (95% CI)	AOR[1] (95% CI)	OR (95% CI)	AOR[1] (95% CI)
Term	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
	(REF)	(REF)	(REF)	(REF)	(REF)	(REF)	(REF)	(REF)
pPROM	5.28	5.06	9.49	9.00	4.87	4.71	4.06	3.88
	(4.43–6.29)	(4.22–6.08)	(6.81–13.23)	(6.40–12.65)	(3.90–6.08)	(3.73–5.94)	(2.85–5.81)	(2.70–5.59)
SPTL	5.37	4.93	3.92	3.59	6.35	5.74	3.80	3.63
	(4.88–5.91)	(4.47–5.45)	(2.99–5.14)	(2.72–4.73)	(5.68–7.09)	(5.12–6.44)	(3.11–4.64)	(2.95–4.46)
Indicated	3.96	4.00	2.23	2.20	2.66	2.73	7.96	7.71
	(3.42–4.59)	(3.44–4.65)	(1.37–3.63)	(1.35–3.59)	(2.14–3.30)	(2.19–3.40)	(6.51–9.74)	(6.28–9.47)

[1]Adjusted for maternal age, race, marital status, prepregnancy BMI, interpregnancy interval between 1st and 2nd pregnancy, fetal death between the 1st and 2nd live births, fetal anomaly, and maternal medical condition. [2]Term=Live birth at ≥37 weeks gestation; pPROM=Live birth, <37 weeks gestation, precipitated by premature preterm rupture of membranes; SPTL= Live birth, <37 weeks gestation, precipitated by spontaneous labor; Indicated= Live birth, <37 weeks gestation, without evidence of pPROM or SPTL.

significantly elevated for all other subtypes. For example, compared with women whose first birth was term, women with a first birth complicated by pPROM had an aOR of 9.00 for recurrent pPROM in their second live birth, however these women were also at increased risk for SPTL (aOR 4.71) and indicated preterm birth (aOR 3.88). This same pattern was true for women whose first live birth ended with SPTL or indicated preterm birth. The highest odds ratios were for recurrent pPROM (aOR 9.00) and recurrent indicated preterm birth (aOR 7.71).

In the third live birth, recurrent preterm birth occurred most frequently in women with a history of two indicated preterm births; more than half of third births (51.3%) in these women were premature. With the exception of pPROM, women were most likely to repeat the most recent preterm birth subtype; women with pPROM were slightly more likely to have a subsequent SPTL preterm birth (22.5% of births with a history of two pPROMs) than they were to have a pPROM preterm birth (17.5% of such births). See Figure 2.2.

Table 2.3 includes unadjusted and adjusted odds ratios for preterm birth of all clinical subtypes in the third live birth stratified by the outcomes of the first and second live births. Women with no preterm births in their first or second live births were used as the referent category for all ORs in this table. Women with a history of two preterm births had the highest odds for recurrence of any clinical subtype. The highest aORs for any preterm birth in the third birth occurred among women with a history of two indicated preterm births (aOR=17.50), a history of pPROM followed by SPTL (aOR=17.19), a history of SPTL followed by pPROM (aOR=16.11), and a history of two pPROM preterm births (aOR=15.86).

Table 2.3: Unadjusted and adjusted[1] odds ratios for preterm birth of all clinical subtypes in the third live birth, stratified by outcomes[2] of the first and second live births among Utah women whose first 3 singleton live births occurred between 1989 and 2007 (n=76,657)

	Outcome in 3rd Live Birth	
Outcomes in 1st and 2nd Live Births	OR (95% CI)	AOR[1] (95% CI)
Term, Term	1.0 (REF)	1.0 (REF)
Term, pPROM	6.09 (4.95–7.48)	5.44 (4.38–6.75)
Term, SPTL	5.89 (5.32–6.52)	5.40 (4.86–6.00)
Term, Indicated	4.86 (4.14–5.70)	4.68 (3.97–5.52)
pPROM, Term	3.44 (2.75–4.29)	3.38 (2.69–4.24)
pPROM, pPROM	16.17 (8.69–30.11)	15.86 (8.32–30.22)
pPROM, SPTL	17.13 (11.41–25.70)	17.19 (11.21–26.36)
pPROM, Indicated	16.82 (8.49–33.32)	13.65 (6.57–28.36)

Table 2.3 continued

	Outcome in 3rd Live Birth	
Outcomes in 1st and 2nd Live Births	OR (95% CI)	AOR[1] (95% CI)
SPTL, Term	2.78 (2.44–3.16)	2.63 (2.30–3.00)
SPTL, pPROM	17.87 (10.76–29.67)	16.11 (9.57–27.11)
SPTL, SPTL	14.86 (12.29–17.96)	14.12 (11.60–17.18)
SPTL, Indicated	12.45 (8.53–18.17)	11.87 (8.03–17.55)
Indicated, Term	2.77 (2.31–3.31)	2.63 (2.19–3.17)
Indicated, pPROM	12.50 (4.76–32.87)	9.37 (3.47–25.33)
Indicated, SPTL	14.08 (9.34–21.24)	13.35 (8.64–20.62)
Indicated, Indicated	18.80 (13.07–27.06)	17.50 (11.96–25.58)

[1]Adjusted for maternal age, race, marital status, prepregnancy BMI, interpregnancy interval between 2nd and 3rd pregnancy, fetal death between the 2nd and 3rd live births, fetal anomaly, and maternal medical condition. [2]Term=Live birth at ≥37 weeks gestation; pPROM=Live birth, <37 weeks gestation, precipitated by premature preterm rupture of membranes; SPTL= Live birth, <37 weeks gestation, precipitated by spontaneous labor; Indicated= Live birth, <37 weeks gestation, without evidence of pPROM or SPTL.

Women with an intervening term birth in their second birth following a preterm first birth remained at increased risk for recurrent preterm birth in their third birth (aORs ranging from 2.63–3.38, depending on clinical subtype in the first birth); however, their odds were lower than those in women who had a term first and preterm second birth (aORs ranging from 4.68–5.44) and women with a history of two preterm births (aORs ranging from 9.37–17.50).

Table 2.4 includes unadjusted and adjusted odds ratios for preterm birth, by clinical subtype, in the third live birth stratified by the outcomes of the first and second live births. When stratified by clinical subtypes, women at the highest risk for pPROM preterm birth in their third birth were those with a history of recurrent pPROM (aOR 45.37) as well as those with SPTL in their first birth and pPROM in their second birth (aOR 37.41). The highest odds for a preterm third birth initiated by SPTL were in women with a history of recurrent SPTL (aOR 17.98) or those with a history of pPROM followed by SPTL (aOR 17.36). Women with the highest odds of indicated preterm birth in the third birth were those with a history of two indicated preterm births (aOR 35.16). Although having a term second birth following a first preterm birth lowered the odds of preterm birth in the third birth, risks were still elevated for all clinical subtypes, with adjusted OR ranges of 1.97–5.55 following pPROM and term births, 1.86–3.27 following SPTL and term births, and 1.55–3.75 following indicated and term births. In all cases, the aORs were highest for recurrence of the same clinical subtype.

Table 2.4: Unadjusted and adjusted[1] odds ratios for preterm birth in the third live birth, by clinical subtype[2], stratified by outcomes[2] of the first and second live births among Utah women whose first 3 singleton live births occurred between 1989 and 2007 (n=76,657)

	Outcome in 3rd Live Birth					
	pPROM		SPTL		Indicated	
Outcomes in 1st and 2nd Live Births	OR (95% CI)	AOR[1] (95% CI)	OR (95% CI)	AOR[1] (95% CI)	OR (95% CI)	AOR[1] (95% CI)
Term, Term	1.0 (REF)	1.0 (REF)	1.0 (REF)	1.0 (REF)	1.0 (REF)	1.0 (REF)
Term, pPROM	12.22 (8.46–17.65)	10.28 (6.96–15.17)	4.54 (3.35–6.15)	4.18 (3.06–5.71)	6.05 (4.39–8.35)	5.78 (4.14–8.06)
Term, SPTL	4.25 (3.19–5.67)	4.01 (3.00–5.37)	7.80 (6.92–8.80)	6.88 (6.07–7.79)	3.66 (3.02–4.44)	3.65 (2.99–4.45)
Term, Indicated	4.38 (2.89–6.64)	4.41 (2.90–6.71)	3.40 (2.66–4.34)	3.38 (2.63–4.34)	7.21 (5.83–8.92)	6.81 (5.46–8.50)
pPROM, Term	5.46 (3.46–8.61)	5.55 (3.50–8.78)	3.76 (2.83–5.00)	3.86 (2.90–5.15)	2.18 (1.40–3.38)	1.97 (1.23–3.18)
pPROM, pPROM	44.94 (19.01–106.21)	45.37 (18.74–109.83)	14.75 (6.75–32.25)	15.35 (6.91–34.08)	7.32 (2.18–24.58)	7.44 (2.19–25.29)

Table 2.4 continued

Outcomes in 1st and 2nd Live Births	Outcome in 3rd Live Birth: pPROM OR (95% CI)	pPROM AOR[1] (95% CI)	SPTL OR (95% CI)	SPTL AOR[1] (95% CI)	Indicated OR (95% CI)	Indicated AOR[1] (95% CI)
pPROM, SPTL	33.70 (17.79–63.85)	33.51 (17.29–64.92)	17.93 (11.03–29.14)	17.36 (10.43–28.89)	9.61 (4.71–19.63)	11.06 (5.36–22.85)
pPROM, Indicated	7.93 (1.05–59.71)	5.91 (0.76–46.17)	12.15 (4.78–30.85)	8.97 (3.23–24.93)	27.13 (12.07–61.98)	23.96 (10.27–55.93)
SPTL, Term	2.11 (1.45–3.08)	1.99 (1.36–2.93)	3.59 (3.07–4.19)	3.27 (2.80–3.85)	1.83 (1.42–2.35)	1.86 (1.44–2.40)
SPTL, pPROM	40.44 (19.10–85.64)	37.41 (17.39–80.48)	17.21 (9.25–32.04)	15.79 (8.37–29.77)	10.25 (4.26–24.67)	9.92 (4.09–24.11)
SPTL, SPTL	13.31 (8.67–20.45)	11.49 (7.31–18.06)	20.11 (16.27–24.87)	17.98 (14.45–22.38)	7.59 (5.33–10.82)	8.25 (5.76–11.83)
SPTL, Indicated	22.47 (11.79–42.81)	19.74 (9.95–39.16)	8.87 (5.19–15.14)	8.07 (4.68–13.89)	13.98 (8.28–23.61)	15.37 (9.02–26.19)

Table 2.4 continued

Outcomes in 1st and 2nd Live Births	pPROM OR (95% CI)	pPROM AOR[1] (95% CI)	SPTL OR (95% CI)	SPTL AOR[1] (95% CI)	Indicated OR (95% CI)	Indicated AOR[1] (95% CI)
Indicated,Term	1.61 (0.88–2.93)	1.55 (0.85–2.84)	2.13 (1.62–2.79)	2.14 (1.63–2.81)	4.16 (3.27–5.30)	3.75 (2.91–4.82)
Indicated, pPROM	13.48 (1.72–105.52)	9.37 (1.15–75.99)	6.88 (1.51–31.44)	5.45 (1.17–25.31)	20.50 (6.42–65.45)	15.02 (4.54–49.73)
Indicated, SPTL	5.18 (1.26–21.35)	4.92 (1.18–20.49)	15.23 (9.30–24.93)	13.82 (8.24–23.17)	15.77 (8.98–27.69)	15.53 (8.56–28.18)
Indicated, Indicated	11.83 (4.72–29.63)	11.64 (4.61–29.39)	6.64 (3.48–12.69)	6.65 (3.46–12.79)	39.56 (26.59–58.86)	35.16 (23.06–53.60)

Outcome in 3rd Live Birth

[1]Adjusted for maternal age, race, marital status, prepregnancy BMI, interpregnancy interval between 2nd and 3rd pregnancy, fetal death between the 2nd and 3rd live births, fetal anomaly, and maternal medical condition. [2]Term=Live birth at ≥37 weeks gestation; pPROM=Live birth, <37 weeks gestation, precipitated by premature preterm rupture of membranes; SPTL= Live birth, <37 weeks gestation, precipitated by spontaneous labor; Indicated= Live birth, <37 weeks gestation, without evidence of pPROM or SPTL.

Discussion

This study describes the preterm birth recurrence risks by clinical subtype across a woman's first three live births, finding that all women with a prior preterm birth had an increased risk of recurrence, regardless of the preterm birth subtype. Recurrence of the same subtype was especially likely among those with one or more pregnancies complicated by pPROM. Odds of recurrence remained elevated even among women having an intervening term birth. Previous studies have found that preterm birth is a strong predictor of both recurrent spontaneous and indicated preterm birth.(6, 10, 12-14, 19) A few studies have examined patterns of preterm birth stratified by clinical subtypes;(12-14, 19) these studies have findings similar to ours. Bloom et al. reported that recurrent preterm birth of the same clinical subtype occurred among those with pPROM (OR=5.5) and preterm labor with intact membranes (OR=7.9).(12) Meis et al. found that women with a history of indicated preterm birth had significantly increased risk for recurrent indicated preterm birth (OR=2.8) and that women with a history of spontaneous preterm birth were also at increased risk for recurrent indicated preterm birth (OR=2.45).(19) Ananth et al. reported that women with a spontaneous preterm birth in their first pregnancy had increased rates of both recurrent spontaneous (OR=3.6) and indicated (OR=2.5) preterm birth in their second birth. Similar to our findings, Ananth et al. found that those with an indicated preterm birth in their first pregnancy were also at increased risk for both recurrent spontaneous (OR=1.6) and indicated (OR=10.6) preterm birth. Our study confirms and adds to these findings by showing the consistency of these findings across 3 repeated births and among all three subtypes of preterm births. Generally, the greatest risk of recurrence is within the same subtype, but the risk of recurrence also extends to the other subtypes.

The use of linked birth certificates in this study has several strengths including the large, population-based sample which allowed for stratification into preterm birth clinical subtypes across three births and increased the generalizability of study findings. However, there are also several important limitations to using vital statistics data including concerns about the accuracy and validity of such data. Overall, studies of birth certificate data have concluded that information on birth weight, demographics, and delivery methods is accurately recorded, but that prenatal care may be over-reported and medical risk factors and labor and delivery complications may be under-reported.(20-24) Fortunately, Utah is one of two states that conduct annual data audits, comparing birth certificate data with medical records for approximately 5% of births at each hospital annually. The information from these audits is used for quality improvement (personal communication, Marie Aschliman, May 29, 2008).

The decision to use a clinical estimate of gestational age in this study rather than a LMP-based estimate may limit comparability of this study's findings to other studies using LMP-based data. The clinical estimate of gestational age is used for national reporting by the National Center for Health Statistics *only* when data on LMP are not available or are inconsistent with the infant's birth weight.(25, 26) It is important to note that studies comparing LMP-based gestational age with clinical estimates of gestational age (which may include LMP data, ultrasound data, and other clinical information) have found that clinical estimates are more highly correlated with birth weight than LMP-based estimates(27, 28) and that the clinical estimate of gestational age may be more accurate than the LMP-based gestational age estimate.(29, 30)

The etiology of preterm birth is both heterogeneous and multifactorial. The fact that women who experienced preterm birth precipitated by pPROM, spontaneous preterm labor, or preterm induction or Cesarean delivery in the absence of pPROM or labor were all at increased risk for recurrence of all other subtypes suggests that the subtypes do share at least some overlap in etiology. The high recurrence rates across all subtypes also suggest that there may be similar genetic factors for preterm birth subtypes or that stable environmental and/or behavioral risk factors act similarly across subtypes to influence these outcomes. While the objective of this study was simply to describe recurrence patterns and not to make conclusions about the causes of recurrent preterm birth, the findings will be useful to clinicians when counseling patients about patterns of recurrence based on obstetric history. Future research is needed to provide further insights into the relationship between recurrence of preterm birth subtypes and risk factors for recurrence, including genetic, environmental, and behavioral factors. This study illustrates the utility of stratifying preterm birth into three distinct clinical subtypes for such research.

References

1. Behrman RE, Butler AS, Institute of Medicine (U.S.). Committee on Understanding Premature Birth and Assuring Healthy Outcomes. Preterm birth : causes, consequences, and prevention. Washington, D.C.: National Academies Press; 2007.

2. Kramer MS, Demissie K, Yang H, Platt RW, Sauve R, Liston R. The contribution of mild and moderate preterm birth to infant mortality. Fetal and Infant Health Study Group of the Canadian Perinatal Surveillance System. JAMA 2000;284(7):843-9.

3. Swamy GK, Ostbye T, Skjaerven R. Association of preterm birth with long-term survival, reproduction, and next-generation preterm birth. JAMA 2008;299(12):1429-36.

4. Ananth CV, Vintzileos AM. Epidemiology of preterm birth and its clinical subtypes. J Matern Fetal Neonatal Med 2006;19(12):773-82.

5. Mazaki-Tovi S, Romero R, Kusanovic JP, Erez O, Pineles BL, Gotsch F, et al. Recurrent preterm birth. Semin Perinatol 2007;31(3):142-58.

6. Adams MM, Elam-Evans LD, Wilson HG, Gilbertz DA. Rates of and factors associated with recurrence of preterm delivery. JAMA 2000;283(12):1591-6.

7. Carr-Hill RA, Hall MH. The repetition of spontaneous preterm labour. Br J Obstet Gynaecol 1985;92(9):921-8.

8. Esplin MS, O'Brien E, Fraser A, Kerber RA, Clark E, Simonsen SE, et al. Estimating recurrence of spontaneous preterm delivery. Obstet Gynecol 2008;112(3):516-23.

9. Iams JD, Goldenberg RL, Mercer BM, Moawad A, Thom E, Meis PJ, et al. The Preterm Prediction Study: recurrence risk of spontaneous preterm birth. National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network. Am J Obstet Gynecol 1998;178(5):1035-40.

10. Mercer BM, Goldenberg RL, Moawad AH, Meis PJ, Iams JD, Das AF, et al. The preterm prediction study: effect of gestational age and cause of preterm birth on subsequent obstetric outcome. National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network. Am J Obstet Gynecol 1999;181(5 Pt 1):1216-21.

11. Ekwo EE, Gosselink CA, Moawad A. Unfavorable outcome in penultimate pregnancy and premature rupture of membranes in successive pregnancy. Obstet Gynecol 1992;80(2):166-72.

12. Bloom SL, Yost NP, McIntire DD, Leveno KJ. Recurrence of preterm birth in singleton and twin pregnancies. Obstet Gynecol 2001;98(3):379-85.

13. Kristensen J, Langhoff-Roos J, Kristensen FB. Implications of idiopathic preterm delivery for previous and subsequent pregnancies. Obstet Gynecol 1995;86(5):800-4.

14. Ananth CV, Getahun D, Peltier MR, Salihu HM, Vintzileos AM. Recurrence of spontaneous versus medically indicated preterm birth. Am J Obstet Gynecol 2006;195(3):643-50.

15. Adams MM, Kirby RS. Measuring the accuracy and completeness of linking certificates for deliveries to the same woman. Paediatr Perinat Epidemiol 2007;21 Suppl 1:58-62.

16. Alexander GR, Himes JH, Kaufman RB, Mor J, Kogan M. A United States national reference for fetal growth. Obstet Gynecol 1996;87(2):163-8.

17. Kotelchuck M. An evaluation of the Kessner Adequacy of Prenatal Care Index and a proposed Adequacy of Prenatal Care Utilization Index. Am J Public Health 1994;84(9):1414-20.

18. Meirowitz NB, Ananth CV, Smulian JC, Vintzileos AM. Effect of labor on infant morbidity and mortality with preterm premature rupture of membranes: United States population-based study. Obstet Gynecol 2001;97(4):494-8.

19. Meis PJ, Goldenberg RL, Mercer BM, Iams JD, Moawad AH, Miodovnik M, et al. The preterm prediction study: risk factors for indicated preterm births. Maternal-Fetal Medicine Units Network of the National Institute of Child Health and Human Development. Am J Obstet Gynecol 1998;178(3):562-7.

20. Zollinger TW, Przybylski MJ, Gamache RE. Reliability of Indiana birth certificate data compared to medical records. Ann Epidemiol 2006;16(1):1-10.

21. Reichman NE, Hade EM. Validation of birth certificate data. A study of women in New Jersey's HealthStart program. Ann Epidemiol 2001;11(3):186-93.

22. Reichman NE, Schwartz-Soicher O. Accuracy of birth certificate data by risk factors and outcomes: analysis of data from New Jersey. Am J Obstet Gynecol 2007;197(1):32 e1-8.

23. Roohan PJ, Josberger RE, Acar J, Dabir P, Feder HM, Gagliano PJ. Validation of birth certificate data in New York State. J Community Health 2003;28(5):335-46.

24. DiGiuseppe DL, Aron DC, Ranbom L, Harper DL, Rosenthal GE. Reliability of birth certificate data: a multi-hospital comparison to medical records information. Matern Child Health J 2002;6(3):169-79.

25. Wier ML, Pearl M, Kharrazi M. Gestational age estimation on United States livebirth certificates: a historical overview. Paediatr Perinat Epidemiol 2007;21 Suppl 2:4-12.

26. Martin JA. United States vital statistics and the measurement of gestational age. Paediatr Perinat Epidemiol 2007;21 Suppl 2:13-21.

27. Hammes LM, Treloar AE. Gestational interval from vital records. Am J Public Health Nations Health 1970;60(8):1496-505.

28. Taback M. Birth weight and length of gestation with relation to prematurity. JAMA 1951;146(10):897-901.

29. Klebanoff MA. Gestational age: not always what it seems. Obstet Gynecol 2007;109(4):798-9.

30. Mustafa G, David RJ. Comparative accuracy of clinical estimate versus menstrual gestational age in computerized birth certificates. Public Health Rep 2001;116(1):15-21.

CHAPTER 3

RISK FACTORS FOR RECURRENT PRETERM BIRTH IN A RETROSPECTIVE COHORT OF MULTIPAROUS UTAH WOMEN

Précis

Short interpregnancy interval and maternal medical conditions are associated with recurrent preterm birth overall; risk factors vary for recurrent spontaneous and indicated preterm birth.

Abstract

In multiparous women, history of preterm birth is a risk factor for recurrence. We examined other risk factors for recurrence in the second and third live births among multiparous women with a history of preterm birth. Maternally-linked birth records were used; multiparous women who had their first three singleton live births in Utah between 1989 and 2007 and a preterm first or second birth were included. Unadjusted and multivariable-adjusted ORs were calculated for recurrent preterm birth using variables available on the birth certificate. Results were stratified by spontaneous and indicated preterm birth. Among women with a history of preterm birth, recurrent preterm birth occurred in

21% of second live births (n=1,011) and 22% of third live births (n=1,872). In multivariable models, risk factors for recurrence included a short interpregnancy interval, the presence of a preexisting maternal medical condition, history of a birth at 28–32 weeks gestation, and the presence of a fetal anomaly on the birth record for the current live birth. Additional risk factors for spontaneous, but not indicated preterm birth included underweight prepregnancy BMI, young maternal age, and gestational weight gain that was less than appropriate for a woman's BMI and gestational age. In conclusion, risk factors for spontaneous and indicated preterm birth may vary; some of the risk factors identified in this study may be modifiable through interventions targeted at women in the interconception period.

Introduction

Preterm birth, the birth of a live infant at < 37 weeks gestation,(1) is among the leading causes of perinatal mortality with 75–88% of nonanomalous neonatal deaths resulting from preterm birth either directly or indirectly.(2) Preterm birth contributes to infant and child mortality through age 12,(3) and is associated with significant long-term morbidity including severe developmental disability(2, 4) and increased health care costs averaging $51,600 per preterm infant.(1) Amongst multiparous women, one of the strongest risk factors for preterm birth is a history of a preterm birth.(5-8) Other risk factors for recurrent preterm birth have been described, including Black race,(5, 9) underweight maternal body mass index (BMI),(10) weight loss between pregnancies, (11) maternal smoking,(12) number of lifetime sexual partners,(13) and short interpregnancy interval.(14) Much of the research on risk factors for recurrent preterm birth has been limited to outcomes in the second live birth(5, 12, 14) or has been focused on spontaneous preterm birth alone(10) or in combination with indicated preterm birth.(5, 11, 12) Thus, the purpose of this study was to build on previous research by describing risk factors for recurrent preterm birth in the second and third births and evaluating whether such risk factors vary when births are stratified by the clinical subtype (spontaneous vs. indicated) of the most recent preterm birth in the woman's history.

Methods

In this retrospective cohort study, maternally-linked Utah birth and fetal death records were obtained from the Utah Population Database (UPDB), a data resource containing linked birth, death, fetal death, and other clinical and vital statistics data (http://www.huntsmancancer.org/groups/ppr/). Probabilistic record linkage was done by UPDB staff using information on the mother's full maiden name and current surname, birth date, birthplace, address of residence, date of previous live birth, and social security number. The initial dataset contained all live birth and fetal death records from 1989 through 2007 for Utah residents (n=865,596 births among 443,669 women). From these records, women who had their first birth in Utah and a total of three or more subsequent live, singleton births during the study time period were identified. The resulting database included information on the first, second, and third singleton live births and any fetal deaths that occurred prior to the third live birth among 76,657 women (with a total of 229,971 live births and 404 fetal deaths). See Figure 2.1.

The primary outcome in this study, premature birth, was defined as a live birth occurring at ≥20 and <37 weeks gestation,(1) using the estimate of gestational age as recorded by the birth attendant. This measure of gestational age may have been based on the woman's last menstrual period, ultrasound dating, or other clinical judgment. Women with births having implausible birth weights for the reported gestational age were eliminated from the dataset (n=226) using published ranges of plausible birth weight-gestational age combinations for each week of gestation.(15) Women with missing gestational age data on one or more births were also excluded (n=85). Because the focus of this study was on recurrent preterm birth in the second and third birth, women without a history of preterm birth by their second or third birth were excluded from the dataset for analysis. Recurrent preterm birth was defined as a preterm birth preceded by one or more preterm birth irrespective of whether the woman experienced an intervening term birth. Thus, the final dataset for second birth outcomes included 4,805 women who experienced preterm birth during their first live birth (6% of women in full dataset) and the final dataset for third birth outcomes included 8,468 women who experienced their first preterm birth during either their first live birth (n=4,805, 6% of full dataset) or second live birth (n=3,663, 5% of full dataset).

Preterm births were stratified by clinical subtype. Clinical preterm birth subtypes included preterm births precipitated by preterm premature rupture of membranes (pPROM), spontaneous preterm labor, and indicated preterm birth via labor induction or Cesarean delivery without evidence of pPROM or spontaneous labor. These categories were created using a published algorithm (16) based on available birth certificate data and in consultation with two perinatologists (authors MSE and MWV). Preterm premature rupture of membranes was defined as rupture of the membranes >12 hours before the onset of labor in women who delivered at <37 weeks gestation. Women without a record of pPROM were stratified into those who labored spontaneously prior to giving birth and those who had an indicated preterm birth. Spontaneous preterm labor was considered to be present in the absence of labor induction or pPROM if the birth record contained evidence of tocolysis, cephalopelvic disproportion, labor augmentation, precipitous labor, prolonged labor, dysfunctional labor, vaginal birth, vaginal birth after Cesarean, vacuum-assisted delivery, or forceps-assisted delivery. Any birth without evidence of pPROM or spontaneous labor was classified as being indicated. Preterm births were stratified into three groups based on gestational age: late preterm births occurred between 33 and 36 completed weeks gestation, moderate preterm births occurred between 28 and 32 completed weeks gestation, and early preterm births occurred prior to 28 weeks gestation.

Risk factors considered in these analyses included demographic, clinical, and anthropometric data from the birth certificates. Demographic variables included maternal age, race, Hispanic ethnicity, educational attainment, marital status, and presence of a father on the birth record. Anthropometric data included prepregnancy body mass index (BMI), gestational weight gain during pregnancy classified as less than appropriate, appropriate, or more than appropriate for each woman's prepregnancy BMI and gestational age at birth based on 2009 guidelines published by the Institute of Medicine,(17) and change in prepregnancy BMI category between live births. Clinical variables included interpregnancy interval, maternal tobacco use during pregnancy, record of a fetal anomaly on the birth certificate, whether or not the birth was immediately preceded by a fetal death at ≥20 weeks gestation, and maternal medical conditions. The interpregnancy interval was calculated by subtracting the gestational age in the birth of interest from the time interval between the date of the previous birth and the date of the birth of interest; technically the interval between the date of one birth and the date of the last menstrual period before the next pregnancy. Maternal medical conditions were combined to create a composite variable that included cardiac disease, acute or chronic lung disease, preexisting diabetes, hemoglobinopathy, chronic hypertension, and renal disease. We also evaluated the impact of gestational age category at the most recent preterm birth and the preterm birth clinical subtype at the most recent preterm birth on the risk of recurrent preterm birth.

Bivariate analyses were conducted to evaluate factors that differed between women experiencing term versus recurrent preterm birth in their second and third births using Chi-squared tests for nominal data, Mantel-Haenszel Chi-square tests for ordinal data, and Fisher's exact tests when the expected count was less than 5 in more than 20% of cells. Descriptive statistics were reported.

Unadjusted and multivariable logistic regression models were used to calculate odds ratios (ORs) for recurrent preterm birth in the second and third births for a variety of risk factors. Our goal was to identify one set of variables to be used in models for both the second and third birth. In order to do this, we first examined all variables of interest as candidates for inclusion in separate models for the second and third birth. Initially, models including all variables were evaluated for multicollinearity using variance inflation factors (VIFs). No variables had VIF values >5, therefore, no variables were eliminated from either model for collinearity. We then used a manual backwards elimination approach, starting with all variables in each model and eliminating variables one by one until all variables remaining in the model had a p-value of <0.10. This alpha level for retention in the model was chosen a-priori to allow for the inclusion of variables with borderline p-values for exploration in stratified models; however, it is important to note that all variables had p-values <0.10 or >0.50, making the specific criteria for retention in the models somewhat inconsequential (when compared to using p-values of 0.15 or 0.20, for example). Because we sought to develop a model with the same variables for birth two and birth three, variables were retained in the final model if they had a p-value of <0.10 for *either* birth two or birth three.

Stratified analyses were conducted to evaluate whether the risk factors of interest varied by preterm birth clinical subtype. Women were stratified into three groups based on the clinical subtype of their most recent preterm birth: pPROM-initiated preterm birth, spontaneous preterm labor (SPTL)-initiated preterm birth, or medically indicated preterm birth. In these models, women with a history of the same clinical subtype who had a term birth in the pregnancy of interest were used as the referent category.

All statistical tests were two sided and an alpha level of 0.05 was used to determine statistical significance. All statistical analyses were conducted using SAS software (SAS Institute Inc., Cary, NC). This study was approved by the University of Utah Institutional Review Board (IRB# 00012636) and the University of Utah Resource for Genetic and Epidemiologic Research (RGE).

Results

In the full dataset including all 76,657 women with consecutive, singleton live births one through three, 6.5% of all births were preterm while 6.3%, 6.1% and 7.2% of first, second, and third live births, respectively, occurred between 20 and 37 weeks gestation. Recurrent preterm birth accounted for 21.6% of second *preterm* births (n=1,011 of 4,674 preterm births) and 34.1% of third *preterm* births (n=1,872 of 5,487 preterm births), but only 1.3% of second births and 2.4% of third births overall. Among recurrent preterm births in the third live birth (n=1,872), 28.1% were a first recurrence with intervening term birth (n=526), 47.0% were a first recurrence without intervening term birth (n=879), and 24.9% were a second recurrence (n=467). In the full dataset, less than 1% of women (0.61%, n=467) experienced three consecutive preterm births. Among women with a history of preterm birth, recurrent preterm birth occurred in 21% of second live births (n=1,011) and 22% of third live births (n=1,872).

In the full dataset, most women were under 25 years of age at the time of their first birth, non Hispanic White, and married. The mean age of women was 22.6 years at the first birth, 25.2 years at the second birth, and 28.3 years at the third woman's third birth. The proportion of women who were overweight or obese prior to becoming pregnant increased with increasing parity, as did the proportion of women who were married. Fetal anomalies were present in 3.0% 2.6%, and 2.6% of births 1–3, respectively. Most preterm births were late preterm births; the proportion of preterm births occurring at 33–36 weeks gestation was 84%, 89%, 90% in births one, two, and three, respectively (data not shown).

Table 3.1 includes descriptive statistics on demographic, clinical, and anthropometric factors stratified by outcome in birth two and birth three. Most of the variables in Table 3.1 were statistically significantly associated with recurrent preterm birth (p-values not shown). Exceptions include maternal race, Hispanic ethnicity, and change in prepregnancy BMI category between pregnancies; these variables all had p-values >0.05 for both second and third birth outcomes. In addition, the presence of a fetal death in the pregnancy preceding the live birth of interest was statistically significant in the third, but not the second birth. All other associations had p-values <0.05. Overall, women with recurrent preterm birth were younger, less educated, and less likely to be married or to have a father listed on the birth record. Such women were more likely to have used tobacco, to have shorter interpregnancy intervals, to have an underweight prepregnancy

Table 3.1: Demographic, clinical, and anthropometric characteristics of multiparous Utah women with a history of preterm birth, by outcome of second and third live births.

	2nd Live Birth N =4805		3rd Live Birth N=8468	
Maternal Characteristics	**Term Following Preterm Birth N =3794 (79.0%)**	**Recurrent Preterm Birth N =1011 (21.0%)**	**Term following ≥1 Preterm Birth N =6596 (77.9%)**	**Recurrent Preterm Birth N =1872 (22.1%)**
Maternal Age				
<20	291 (7.7)	125 (12.4)	75 (1.1)	37 (2.0)
20–24	1658 (43.7)	487 (48.2)	1475 (22.4)	541 (28.9)
25–29	1377 (36.3)	298 (29.5)	2981 (45.2)	798 (42.7)
30–34	399 (10.5)	92 (9.1)	1619 (24.6)	381 (20.4)
35+	69 (1.8)	9 (0.9)	445 (6.8)	114 (6.1)
Maternal Race White	3573 (95.1)	954 (94.8)	6215 (95.0)	1767 (95.3)
Maternal Ethnicity				
Hispanic	402 (10.6)	103 (10.2)	716 (10.9)	163 (8.8)
Maternal Education				
<HS Graduate	625 (16.7)	213 (21.4)	993 (15.3)	297 (16.2)
HS Graduate	1342 (35.8)	354 (35.6)	2318 (35.6)	696 (38.0)
Some College	1087 (29.0)	270 (27.1)	1938 (29.8)	535 (29.2)
College Graduate	690 (18.4)	158 (15.9)	1264 (19.4)	304 (16.6)
Mother Married	3189 (84.3)	818 (80.9)	5653 (85.7)	1548 (82.7)
No Father on Record	209 (5.5)	76 (7.5)	347 (5.3)	147 (7.9)
Maternal Tobacco Use	364 (9.7)	119 (11.8)	694 (10.6)	251 (13.6)

Table 3.1 continued

Maternal Characteristics	2nd Live Birth: Term Following Preterm Birth	2nd Live Birth: Recurrent Preterm Birth	3rd Live Birth: Term Following ≥1 Preterm Birth	3rd Live Birth: Recurrent Preterm Birth
Prepregnancy BMI				
Underweight (<18.5)	346 (9.4)	130 (13.2)	500 (7.8)	199 (10.9)
Normal Weight (18.5–24.9)	2172 (58.8)	583 (59.1)	3587 (55.7)	1003 (54.9)
Overweight (25.0–29.9)	690 (18.7)	171 (17.3)	1313 (20.4)	348 (19.1)
Obese (≥30)	485 (13.1)	103 (10.4)	1035 (16.1)	276 (15.1)
BMI Change[1]				
Decreased BMI Category	232 (6.7)	70 (7.4)	429 (6.8)	146 (8.1)
BMI Category Unchanged	2391 (69.5)	669 (71.1)	4620 (73.4)	1318 (73.5)
Increased BMI Category	817 (23.75)	202 (21.5)	1243 (19.8)	330 (18.4)
Gestational Weight Gain[2]				
Less than Appropriate	689 (18.9)	222 (23.0)	1272 (20.1)	425 (23.6)
Appropriate for BMI	1397 (38.4)	374 (38.7)	2244 (35.5)	609 (33.9)
More than Appropriate	1551 (42.7)	371 (38.4)	2802 (44.4)	765 (42.5)
Interpregnancy Interval				
<6 Months	236 (6.2)	129 (12.8)	311 (4.7)	182 (9.7)
6–12 Months	708 (18.7)	194 (19.2)	915 (13.9)	301 (16.1)
13–24 Months	1438 (37.9)	384 (38.0)	2133 (32.3)	559 (29.9)
25–36 Months	740 (19.5)	164 (16.2)	1563 (23.7)	367 (19.6)
>36 Months	672 (17.7)	140 (13.9)	1674 (25.4)	463 (24.7)
Maternal Medical Condition[3]	202 (5.3)	80 (7.9)	477 (7.2)	218 (11.7)

Table 3.1 continued

	2nd Live Birth		3rd Live Birth	
Maternal Characteristics	**Term Following Preterm Birth**	**Recurrent Preterm Birth**	**Term following ≥1 Preterm Birth**	**Recurrent Preterm Birth**
Fetal Anomaly on Record	95 (2.5)	54 (5.3)	156 (2.4)	105 (5.6)
Fetal Death in Pregnancy Preceding Live Birth	5 (0.1)	2 (0.2)	7 (0.1)	7 (0.4)
Gestational Age at Most Recent Preterm Birth				
Late (33–36 weeks)	3245 (85.5)	789 (78.0)	5805 (88.0)	1575 (84.1)
Moderate (28-32 weeks)	412 (10.9)	155 (15.3)	584 (8.9)	240 (12.8)
Early (≤28 weeks)	137 (3.6)	67 (6.6)	207 (3.1)	57 (3.0)
Preterm Birth Subtype at Most Recent Preterm Birth				
pPROM	589 (15.5)	167 (16.5)	919 (13.9)	275 (14.7)
Preterm Labor	2139 (56.4)	617 (61.0)	3875 (58.8)	1131 (60.4)
Indicated Preterm Birth	1066 (28.1)	227 (22.5)	1802 (27.3)	466 (24.9)

[1]BMI change defined as change in prepregnancy BMI category between two live births.

[2]Gestational weight gain categorized as less than appropriate, appropriate, or more than appropriate based for each woman's prepregnancy BMI and gestational age at birth.

[3]Maternal medical conditions include cardiac disease, acute or chronic lung disease, preexisting diabetes, hemoglobinopathy, chronic hypertension, and renal disease.

BMI, and to have gained less than appropriate weight during pregnancy for their BMI and gestational age. Women with recurrent preterm birth were also more likely to have a pregnancy complicated by a fetal anomaly, a preexisting medical condition, or to have had a prior preterm birth at ≤32 weeks gestation.

In multivariable modeling, all variables were initially considered for inclusion; those variables with a p-value of <0.10 in the models for either the second or third birth remained in the final model. Variables that were omitted from the individual models for both the second and third birth included maternal education, marital status, tobacco use, and change in prepregnancy BMI category between births; these variables were eliminated from the final model. Maternal race, Hispanic ethnicity, and the presence of a fetal death at ≥20 weeks gestation in the pregnancy preceding the live birth of interest had p-values of >0.10 in the model for the second live birth but had p-values of <0.10 in the model for the third live birth; thus, these variables were also included in the final model.

Table 3.2 displays unadjusted and multivariable adjusted ORs for the variables that were selected for the final model, illustrating the odds of recurrent preterm birth in the second and third birth associated with various risk factors. In multivariable adjusted analyses, six factors emerged as being statistically significant risk factors for recurrent preterm birth in both the second and third births. These factors, ordered by the magnitude of the OR in descending order, include: 1) having an interpregnancy interval of < 6 months versus 2–3 years (aOR=2.29 for birth two and 2.21 for birth three) or 6–12 months versus 2–3

Table 3.2: Unadjusted and adjusted[1] odds ratios (ORs) for preterm birth in the second and third live births among women with a history of preterm birth. Women who had term births following one or more preterm birth were used as the referent.

	2nd Live Birth		**3rd Live Birth**	
	Unadjusted OR	**Adjusted[1] OR**	**Unadjusted OR**	**Adjusted[1] OR**
Maternal Characteristics	**OR (95% CI)**	**OR (95% CI)**	**OR (95% CI)**	**OR (95% CI)**
Maternal Age				
<20	**1.99 (1.56–2.53)**	**1.44 (1.09–1.91)**	**1.84 (1.24–2.76)**	1.36 (0.88–2.11)
20–24	**1.36 (1.16–1.59)**	**1.22 (1.03–1.44)**	**1.37 (1.21–1.55)**	**1.21 (1.06–1.39)**
25–29	Referent	Referent	Referent	Referent
30–34	1.07 (0.82–1.38)	1.19 (0.91–1.57)	0.88 (0.77–1.01)	0.90 (0.78–1.04)
35+	0.60 (0.30–2.53)	0.66 (0.32–1.36)	0.96 (0.77–1.19)	0.92 (0.73–1.16)
Maternal Race Non White	0.96 (0.70–1.31)	0.92 (0.66–1.28)	0.94 (0.74–1.20)	0.78 (0.60–1.01)
Maternal Ethnicity Hispanic	0.96 (0.76–1.20)	0.85 (0.66–1.09)	0.79 (0.66–0.94)	0.70 (0.58–0.86)
Prepregnancy BMI				
Underweight (<18.5)	**1.40 (1.12–1.75)**	**1.35 (1.07–1.70)**	**1.42 (1.19–1.70)**	**1.33 (1.10–1.59)**
Normal Weight (18.5–24.9)	Referent	Referent	Referent	Referent
Overweight (25.0–29.9)	0.92 (0.76–1.12)	0.96 (0.78–1.17)	0.95 (0.83–1.09)	0.97 (0.84–1.12)
Obese (≥30)	0.79 (0.63–1.00)	0.83 (0.65–1.07)	0.95 (0.82–1.11)	0.94 (0.81–1.10)

Table 3.2 continued

	2^{nd} Live Birth		3^{rd} Live Birth	
	Unadjusted OR	**Adjusted[1] OR**	**Unadjusted OR**	**Adjusted[1] OR**
Maternal Characteristics	**OR (95% CI)**	**OR (95% CI)**	**OR (95% CI)**	**OR (95% CI)**
Gestational Weight Gain[2]				
Less than Appropriate	1.20 (1.00–1.46)	1.18 (0.97–1.44)	**1.23 (1.07–1.42)**	**1.23 (1.07–1.42)**
Appropriate for BMI	Referent	Referent	Referent	Referent
More than Appropriate	0.89 (0.76–1.05)	0.93 (0.78–1.10)	1.01 (0.89–1.13)	1.02 (0.90–1.16)
No Father on Birth Record	**1.40 (1.06–1.83)**	1.33 (0.98–1.79)	**1.53 (1.26–1.88)**	**1.29 (1.04–1.61)**
Interpregnancy Interval				
<6 Months	**2.47 (1.88–3.24)**	**2.29 (1.71–3.08)**	**2.49 (2.01–3.09)**	**2.21 (1.75–2.79)**
6–12 Months	1.24 (0.98–1.56)	1.20 (0.94–1.53)	**1.40 (1.18–1.67)**	**1.29 (1.07–1.55)**
13–24 Months	1.21 (0.98–1.48)	1.21 (0.98–1.49)	1.12 (0.96–1.67)	1.11 (0.96–1.30)
25–36 Months	Referent	Referent	Referent	Referent
>36 Months	0.94 (0.73–1.21)	0.94 (0.72–1.21)	**1.18 (1.01–1.37)**	**1.22 (1.04–1.44)**
Maternal Medical Condition[3]	**1.53 (1.17–2.00)**	**1.70 (1.28–2.25)**	**1.69 (1.43–2.00)**	**1.67 (1.39–1.99)**
Fetal Death in Most Recent Pregnancy	1.50 (0.29–7.76)	1.94 (0.36–10.50)	**3.53 (1.24–10.09)**	**2.98 (1.01–8.84)**
Fetal Anomaly on Birth Record	**2.20 (1.56–3.09)**	**2.23 (1.56–3.19)**	**2.45 (1.91–3.16)**	**2.31 (1.78–3.01)**

Table 3.2 continued

	2nd Live Birth		3rd Live Birth	
	Unadjusted OR	**Adjusted[1] OR**	**Unadjusted OR**	**Adjusted[1] OR**
	OR (95% CI)	**OR (95% CI)**	**OR (95% CI)**	**OR (95% CI)**
Gestational Age at Most Recent Preterm Birth				
Late (33–36 weeks)				
Moderate (28-32 weeks)	Referent	Referent	Referent	Referent
Early (≤28 weeks)	**1.55 (1.27–1.89)**	**1.71 (1.38–2.10)**	**1.52 (1.29–1.79)**	**1.46 (1.23-1.73)**
	2.01 (1.49–2.72)	**1.89 (1.37–2.62)**	1.02 (0.75–1.37)	1.00 (0.73-1.36)
Clinical Preterm Birth Subtype at Most Recent Preterm Birth				
pPROM	**1.33 (1.14–1.60)**	**1.32 (1.04–1.67)**	1.13 (1.00–1.27)	1.14 (0.96–1.36)
Preterm Labor	**1.35 (1.14–1.60)**	**1.33 (1.11–1.59)**	1.16 (0.98–1.37)	1.13 (0.99–1.29)
Indicated Preterm Birth	Referent	Referent	Referent	Referent

[1]Adjusted models include all variables in this table. [2]Gestational weight gain categorized as less than appropriate, appropriate, or more than appropriate based for each woman's prepregnancy BMI and gestational age at birth. [3]Maternal medical conditions include cardiac disease, acute or chronic lung disease, preexisting diabetes, hemoglobinopathy, chronic hypertension, and renal disease.

years (aOR=1.20, nonsignificant for birth two and 1.29 for birth three); 2) the presence of a fetal anomaly on the birth record (aOR=2.23 for birth two and 2.31 for birth three); 3) the presence of a preexisting maternal medical condition (aOR=1.70 for birth two and 1.67 for birth three); 4) a history of a birth at 28–32 weeks versus 33–36 weeks in the most recent preterm birth (aOR 1.71 for birth two and 1.46 for birth three); 5) having an underweight versus normal prepregnancy BMI (aOR=1.35 for birth two and 1.33 for birth three); and 6) young maternal age. Women who were <20 at the time of birth two (aOR=1.44) or birth three (aOR=1.36, not statistically significant) or age 20–24 at births two (aOR=1.22) or three (aOR=1.21) were at increased risk compared to women aged 25–29.

Two variables stood out as statistically significant risk factors for recurrent preterm birth in the second birth but not in the third birth: 1) a history of SPTL-initiated preterm birth (aOR=1.33) or pPROM-initiated preterm birth (aOR=1.32) compared with a history of indicated preterm birth and 2) a history of a preterm birth at <28 weeks gestation (aOR=1.89). Variables that were statistically significant in the third but not second birth included: 1) having an interpregnancy interval of >3 years versus 2-3 years between births two and three (aOR=1.22); 2) gaining less weight than appropriate for BMI and gestational age in birth three (aOR=1.23); 3) absence of a father on the birth record for birth three (aOR=1.29); and 4) history of a fetal death at ≥20 weeks gestation between the second and third live births (aOR=2.98).

Analyses were stratified by the clinical subtypes of the most recent preterm birth in order to evaluate risk factors in women with a history of SPTL, pPROM, and medically indicated preterm birth separately. In the second birth, recurrent preterm birth was more common among women with a history of SPTL (n=617, 22%) or pPROM (n=167, 22%) than a history of indicated preterm birth (n=227, 18%). The same was true in the third birth, recurrence was most common after a history of preterm birth initiated by SPTL (n=1,131, 23%) or pPROM (n=275, 23%) compared with indicated preterm birth (n=466, 21%).

Results of multivariable models stratified by the clinical subtype of the most recent preterm birth are shown in Tables 3.3 and 3.4. Table 3.3 includes results for women with a history of pPROM and SPTL while Table 3.4 includes results for women with a history of medically indicated preterm birth. Risk factors varied depending upon the preterm birth clinical subtype in the most recent preterm birth. In the following paragraph, aORS are listed first for outcomes in the second birth and then for outcomes in the third birth; nonsignificant aORs are noted with the abbreviation "n.s." Two variables emerged as being statistically significant for recurrent preterm birth following a history of any preterm birth clinical subtype. These variables included 1) presence of a fetal anomaly on the birth certificate (aOR=4.41 and 3.54 for pPROM, 1.89 and 2.21 for SPTL, and 2.03 (n.s.) and 2.20 for indicated preterm birth) and 2) history of a moderately preterm birth between 28 and 32 weeks gestation, compared with a late preterm birth between 33 and 36 weeks gestation (aOR=0.87 (n.s.) and 1.73 for pPROM, 2.05 and 1.32 for SPTL, and 1.73 and 1.48 for indicated preterm birth). Two additional variables were statistically significant risk factors for recurrence following indicated preterm birth and SPTL, with elevated, though nonsignificant ORs following

Table 3.3: Adjusted[1] odds ratios (ORs) for recurrent preterm birth in the second and third live births stratified by clinical presentation: pPROM vs. spontaneous preterm labor. In each stratum, women who had a term birth after a preterm birth of the same clinical subtype were used as the referent category.

	pPROM		**Spontaneous Preterm Labor**	
	Birth 2	**Birth 3**	**Birth 2**	**Birth 3**
Maternal Characteristics	**aOR (95% CI)**	**aOR (95% CI)**	**aOR (95% CI)**	**aOR (95% CI)**
Maternal Age				
<20	0.94 (0.42–2.11)	2.56 (0.74–8.96)	**1.46 (1.03–2.07)**	1.40 (0.82–2.37)
20–24	1.27 (0.82–1.97)	1.33 (0.92–1.92)	**1.25 (1.00–1.56)**	**1.23 (1.03–1.46)**
25–29	Referent	Referent	Referent	Referent
30–34	**1.98 (1.13–3.50)**	0.76 (0.51–1.11)	1.02 (0.67–1.55)	0.85 (0.70–1.03)
35+	0.55 (0.10–3.18)	1.52 (0.91–2.57)	0.47 (0.14–1.59)	0.60 (0.41–0.87)
Maternal Race Non White	1.14 (0.44–2.96)	0.81 (0.39–1.68)	0.83 (0.54–1.26)	0.77 (0.56–1.06)
Maternal Ethnicity Hispanic	1.21 (0.67–2.17)	0.93 (0.57–1.53)	0.79 (0.57–1.09)	0.60 (0.46–0.78)
Underweight BMI (<18.5)	**2.21 (1.25–3.92)**	1.47 (0.87–2.50)	1.27 (0.96–1.68)	**1.32 (1.05–1.65)**
Normal Weight BMI (18.5–24.9)	Referent	Referent	Referent	Referent
Overweight BMI (25.0–29.9)	0.86 (0.52–1.41)	1.01 (0.70–1.46)	1.14 (0.87–1.48)	1.00 (0.83–1.21)
Obese BMI (≥30)	1.08 (0.62–1.88)	1.01 (0.67–1.51)	0.69 (0.47–1.01)	0.88 (0.71–1.10)

Table 3.3 continued

	pPROM		Spontaneous Preterm Labor	
Maternal Characteristics	**Birth 2 aOR (95% CI)**	**Birth 3 aOR (95% CI)**	**Birth 2 aOR (95% CI)**	**Birth 3 aOR (95% CI)**
Gestational Weight Gain[2]				
Less than Appropriate	1.09 (0.65–1.83)	0.88 (0.58–1.32)	1.09 (0.85–1.39)	**1.39 (1.16–1.67)**
Appropriate for BMI	Referent	Referent	Referent	Referent
More than Appropriate	1.15 (0.76–1.74)	0.93 (0.67–1.28)	0.82 (0.65–1.02)	1.04 (0.88–1.22)
No Father on Birth Record	1.69 (0.84–3.38)	1.12 (0.65–1.92)	1.24 (0.84–1.84)	1.21 (0.90–1.62)
Interpregnancy Interval				
<6 Months	1.18 (0.53–2.63)	1.73 (0.89–3.35)	**2.64 (1.80–3.87)**	**2.38 (1.77–3.19)**
6–12 Months	0.88 (0.48–1.60)	1.38 (0.83–2.30)	1.37 (1.00–1.89)	**1.31 (1.04–1.66)**
13–24 Months	0.99 (0.60–1.64)	1.17 (0.76–1.29)	1.24 (0.93–1.64)	1.11 (0.91–1.35)
25–36 Months	Referent	Referent	Referent	Referent
>36 Months	0.76 (0.41–1.41)	1.54 (1.00–2.37)	0.96 (0.68–1.35)	1.15 (0.93–1.41)
Maternal Medical Condition[3]	1.07 (0.50-2.29)	1.61 (0.98–2.65)	**1.73 (1.17–2.57)**	**1.73 (1.35–2.21)**
Fetal Death in Prior Pregnancy	5.31 (0.27–104.23)	1.94 (0.17–22.83)	1.29 (0.12–13.48)	**6.53 (1.13–37.76)**
Fetal Anomaly on Birth Record	**4.41 (1.85–10.55)**	**3.54 (1.71–7.31)**	**1.89 (1.16–3.08)**	**2.21 (1.56–3.14)**

Table 3.3 continued

	pPROM		Spontaneous Preterm Labor	
	Birth 2	**Birth 3**	**Birth 2**	**Birth 3**
Maternal Characteristics	**aOR (95% CI)**	**aOR (95% CI)**	**aOR (95% CI)**	**aOR (95% CI)**
Gestational Age at Most Recent Preterm Birth				
Late (33–36 weeks)	Referent	Referent	Referent	Referent
Moderate (28-32 weeks)	0.87 (0.50–1.51)	**1.73 (1.21–2.47)**	**2.05 (1.54–2.72)**	**1.32 (1.03–1.69)**
Early (≤28 weeks)	1.03 (0.48–2.22)	0.72 (0.38–1.36)	**1.90 (1.22–2.98)**	0.92 (0.57–1.50)

[1]Adjusted models include all variables in this table.

[2]Gestational weight gain categorized as less than appropriate, appropriate, or more than appropriate based for each woman's prepregnancy BMI and gestational age at birth.

[3]Maternal medical conditions include cardiac disease, acute or chronic lung disease, preexisting diabetes, hemoglobinopathy, chronic hypertension, and renal disease.

Table 3.4: Adjusted[1] odds ratios (ORs) for recurrent preterm birth in the second and third live births among multiparous women whose most recent preterm birth was medically indicated. Women who had term births following indicated preterm birth were used as the referent category.

	Indicated Preterm Birth	
	Birth 2	**Birth 3**
Maternal Characteristics	**aOR (95% CI)**	**aOR (95% CI)**
Maternal Age		
<20	1.58 (0.86–2.92)	0.81 (0.44–1.49)
20–24	1.10 (0.77–1.57)	1.03 (0.76–1.40)
25–29	Referent	Referent
30–34	0.99 (0.60–1.63)	1.09 (0.84–1.42)
35+	0.97 (0.32–2.93)	1.24 (0.83–1.84)
Maternal Race Non White	1.21 (0.59–2.48)	0.81 (0.44–1.49)
Maternal Ethnicity Hispanic	0.74 (0.42–1.31)	0.88 (0.60–1.29)
Prepregnancy BMI		
Underweight (<18.5)	1.07 (0.60–1.91)	1.21 (0.79–1.84)
Normal Weight (18.5–24.9)	Referent	Referent
Overweight (25.0–29.9)	0.73 (0.48–1.12)	0.88 (0.66–1.17)
Obese (≥30)	0.90 (0.59–1.36)	1.00 (0.76–1.31)
Gestational Weight Gain[2]		
Less than Appropriate	1.48 (0.98–2.24)	1.09 (0.81–1.47)
Appropriate for BMI	Referent	Referent
More than Appropriate	1.11 (0.78–1.58)	1.03 (0.80–1.32)
No Father on Birth Record	1.56 (0.79–3.06)	**1.79 (1.14–2.80)**

Table 3.4 continued

	Indicated Preterm Birth	
	Birth 2	**Birth 3**
Maternal Characteristics	**aOR (95% CI)**	**aOR (95% CI)**
Interpregnancy Interval		
<6 Months	**2.37 (1.31–2.31)**	**2.06 (1.25–3.40)**
6–12 Months	1.08 (0.65–1.82)	1.21 (0.84–1.75)
13–24 Months	1.34 (0.87–2.04)	1.12 (0.83–1.50)
25–36 Months	Referent	Referent
>36 Months	1.02 (0.60–1.75)	1.25 (0.91–1.71)
Maternal Medical Condition[3]	**2.09 (1.29–3.41)**	**1.59 (1.16–2.17)**
Fetal Death in Pregnancy Preceding Live Birth	NA	1.82 (0.27–12.12)
Fetal Anomaly on Birth Record	2.03 (0.97–4.23)	**2.20 (1.35–3.60)**
Gestational Age at Most Recent Preterm Birth		
Late (33–36 weeks)	Referent	Referent
Moderate (28-32 weeks)	**1.73 (1.17–2.56)**	**1.48 (1.09–2.02)**
Early (≤32 weeks)	**3.00 (1.61–5.60)**	1.59 (0.90–2.81)

[1]Adjusted models include all variables in this table.

[2]Gestational weight gain categorized as less than appropriate, appropriate, or more than appropriate based for each woman's prepregnancy BMI and gestational age at birth.

[3]Maternal medical conditions include cardiac disease, acute or chronic lung disease, preexisting diabetes, hemoglobinopathy, chronic hypertension, and renal disease.

pPROM as well. These included 1) interpregnancy interval of <6 months (aOR=1.18 (n.s.) and 1.73 (n.s.) for pPROM, 2.64 and 2.38 for SPTL, and 2.37 and 2.06 for indicated preterm birth) and 2) the presence of a preexisting maternal medical condition (aOR=1.07 (n.s.) and 1.61 (n.s.) for pPROM, 1.73 and 1.73 for SPTL, and 2.09 and 1.59 for indicated preterm birth). Women with a history of SPTL and indicated preterm birth were also at increased risk for recurrence if their prior birth ended at <28 weeks gestation; this was not true for women with a history of pPROM (aOR=1.90 for SPTL, and 3.00 for indicated preterm birth). Women with underweight prepregnancy BMIs were at increased risk for both pPROM and SPTL (aORs=2.21 and 1.47 (n.s.) for pPROM, 1.27 (n.s.) and 1.32 for SPTL). Several additional risk factors were statistically significant following SPTL but not other preterm birth clinical subtypes. These included maternal age younger than 20 at the time of the second birth (aOR=1.46) or 20-24 at the time of the second or third birth (aOR=1.25 for the second birth and 1.23 for the third birth). In addition, women with a history of SPTL who gained less weight than recommended for their BMI and gestational age were at increased risk for recurrence in the third birth (aOR=1.39). Only one variable was a statistically significant risk factor among women with a history of pPROM: maternal age of 30-34 at the time of the second birth (aOR=1.98). Finally, only one variable emerged as being statistically significant among women with a history of indicated preterm birth: the lack of a father on the birth certificate (aOR=1.79 for the third birth outcome).

Discussion

While recurrent preterm birth is rare overall, occurring in only 1.6% of second live births and 2.4% of third live births in our dataset, it does account for a substantial proportion of all preterm births, occurring in 22% of second preterm births and 34% of third preterm births in our dataset. The association between a history of preterm birth and its recurrence is well established, (5, 8, 18-22), and has been attributed, in part, to genetic factors;(23-27) however, it is probable that common environmental or behavioral risk factors also contribute to the risk of recurrence, either independently or in combination with genetic factors.(28) Several risk factors have been associated with recurrent preterm birth in previous studies, including race,(5, 9) underweight maternal BMI,(10) weight loss between pregnancies,(11) maternal smoking,(12) and short interpregnancy interval.(14)

We sought to expand upon these findings in analyses stratified by clinical preterm birth subtype and in women experiencing recurrent preterm birth in their third live birth. We identified several variables that stood out as risk factors for recurrent preterm birth in both the second and third live birth, overall, in women with a history of spontaneous preterm birth, and in women with a history of indicated preterm birth. These factors included: 1) having an interpregnancy interval of <6 months versus 2–3 years, 2) the presence of a preexisting maternal medical condition including cardiac disease, acute or chronic lung disease, preexisting diabetes, hemoglobinopathy, chronic hypertension, or renal disease, 3) history of a birth at ≤32 weeks gestation in the most recent preterm birth (compared with 33–36 weeks gestation), and 4) the presence of a fetal anomaly on the birth record for the current live birth. Women with a history of spontaneous preterm birth via SPTL or pPROM were at increased risk for recurrence if they had an underweight prepregnancy BMI. Additional variables that were significant risk factors for all recurrence and for recurrence in women with a history of SPTL included 1) young maternal age, 2) gestational weight gain that was less than appropriate for a woman's BMI and gestational age based on the 2009 Institute of Medicine guidelines.(17)

Smith et al. found that women with an interpregnancy interval of less than 6 months were at increased risk for preterm birth at 24–32 weeks and 33–36 weeks in their second birth.(14) However, their analysis was limited to women with a term first birth, so the authors were not able to evaluate the association between interpregnancy interval and *recurrent* preterm birth. In our study, the presence of a short interpregnancy interval was one of the factors most consistently associated with recurrent preterm birth, with statistically significant aORs for preterm birth overall, indicated preterm birth, and SPTL-initiated preterm birth, and elevated, though not statistically significant aORs for pPROM preterm birth. Mercer et al. reported that recurrent preterm birth was more common among women with lower prepregnancy weight or BMI when compared to women with isolated preterm birth or term birth.(10) We verified this association in our study in analyses focused on recurrent preterm birth overall; however, in stratified analyses this association was observed among women with a history of spontaneous preterm birth, whether by pPROM or SPTL, but not among women with indicated preterm birth. Of note, women in our study with an underweight BMI in their first birth whose BMI increased to normal weight, overweight, or obese by their second birth were at decreased, though not statistically significant risk for recurrent preterm birth (OR= 0.79, 95% CI 0.54–1.15) compared to underweight women who maintained an underweight BMI. Normal weight women who moved into an underweight BMI category between births one and two were at significantly increased risk for recurrent preterm birth (OR=1.67, 95% CI 1.12–2.48). This finding was similar when looking at outcomes in the third birth among women who moved from underweight BMI to normal BMI between the second and third live births (OR=0.85, 95% CI 0.63–1.15) and normal weight women who became underweight between the second and third live births (OR=1.87, 95% CI 1.36–2.58). These findings warrant further exploration in future studies.

While other authors have reported an association between Black race and recurrent preterm birth,(5, 9) we did not find this association in our study. More than 96% of women in our study reported White race, and White women were not significantly less likely to experience recurrent preterm birth in the second or third birth than women in each racial category alone or when combined into a “non White” category. We did find that Hispanic/Latina women were at decreased risk for recurrent preterm birth when compared to non Hispanic White women in birth three overall and among women with a history of two preterm births. Women of non White race were also at decreased risk of recurrent preterm birth after a history of two prior preterm births when compared to White women. Additional research on racial disparities and recurrent preterm birth will need to occur in study populations that are more racially diverse than residents of Utah.

Numerous studies have reported an association between fetal anomalies and preterm birth,(29, 30) however, most studies of recurrent preterm birth have excluded women with one or more pregnancies complicated by a fetal anomaly. We made the decision to include such women in our study and to adjust for anomalies in multivariable analyses. We were not surprised to find that in women with a history of preterm birth, those with an anomalous fetus were more likely to deliver prematurely. In sensitivity analyses, we evaluated whether the presence of a fetal anomaly in the most recent live birth was a risk factor for recurrent preterm birth, overall and in stratified analyses. In unadjusted analyses, the history of a fetal anomaly on the birth record was not associated with recurrent preterm birth overall, or in any of the subanalyses. In multivariable analyses, the presence of a fetal anomaly at the most recent preterm birth was not statistically significant (p=0.3319 for birth 2 and 0.6721 for birth three data not shown), so would not have been included in our final multivariable models.

This study has several strengths including the large sample size which allowed for stratification of preterm births into clinical subtypes and by pattern of outcomes across the first and second live birth. In addition, birth and fetal death certificates provide population-based data, thereby increasing the generalizability of study findings. However, the use of vital statistics data involves several important limitations related to data accuracy and validity. Studies of birth certificate data quality have found that information on medical risk factors and complications may be under-reported.(27-32) Fortunately, Utah is one of two states which conducts annual data audits, comparing birth certificate data with medical records for 5% of births at each hospital annually. The information from these audits is used to correct discrepancies and for quality improvement, resulting in higher quality data (personal communication, Marie Aschliman, May 29, 2008). Concerns have also been raised about the use of gestational age data from birth certificates. We have used a clinical estimate of gestational age from the birth certificate, which has been reported to be more highly correlated with birth weight (31, 32) and more accurate than the gestational age estimates based upon patient report of last menstrual period.(33, 34)

In conclusion, this study has identified several risk factors for recurrent preterm birth that may be amenable to intervention in a preconception/ interconception model of care.(35) These factors include a focus on weight gain between pregnancies for women with an underweight BMI, provision of counseling and contraceptives as necessary to aid women in appropriately spacing their pregnancies, and treatment of maternal medical conditions to help women with a history of preterm birth achieve optimal health before becoming pregnant again. These findings should be validated with additional research, possibly including prospective studies to evaluate how interconception care focused on optimizing maternal health impacts the rates of recurrent preterm birth. In addition, the findings of this study highlight the importance of studying preterm birth stratified by clinical subtype, as important differences between subtypes would have been overlooked without such stratification.

References

1. Behrman RE, Butler AS, Institute of Medicine (U.S.). Committee on Understanding Premature Birth and Assuring Healthy Outcomes. Preterm birth : causes, consequences, and prevention. Washington, D.C.: National Academies Press; 2007.

2. Kramer MS, Demissie K, Yang H, Platt RW, Sauve R, Liston R. The contribution of mild and moderate preterm birth to infant mortality. Fetal and Infant Health Study Group of the Canadian Perinatal Surveillance System. Jama 2000;284(7):843-9.

3. Swamy GK, Ostbye T, Skjaerven R. Association of preterm birth with long-term survival, reproduction, and next-generation preterm birth. JAMA 2008;299(12):1429-36.

4. Ananth CV, Vintzileos AM. Epidemiology of preterm birth and its clinical subtypes. J Matern Fetal Neonatal Med 2006;19(12):773-82.

5. Adams MM, Elam-Evans LD, Wilson HG, Gilbertz DA. Rates of and factors associated with recurrence of preterm delivery. JAMA 2000;283(12):1591-6.

6. Carr-Hill RA, Hall MH. The repetition of spontaneous preterm labour. Br J Obstet Gynaecol 1985;92(9):921-8.

7. Mazaki-Tovi S, Romero R, Kusanovic JP, Erez O, Pineles BL, Gotsch F, et al. Recurrent preterm birth. Semin Perinatol 2007;31(3):142-58.

8. Esplin MS, O'Brien E, Fraser A, Kerber RA, Clark E, Simonsen SE, et al. Estimating recurrence of spontaneous preterm delivery. Obstet Gynecol 2008;112(3):516-23.

9. Kistka ZA, Palomar L, Lee KA, Boslaugh SE, Wangler MF, Cole FS, et al. Racial disparity in the frequency of recurrence of preterm birth. Am J Obstet Gynecol 2007;196(2):131 e1-6.

10. Mercer BM, Macpherson CA, Goldenberg RL, Goepfert AR, Haugel-De Mouzon S, Varner MW, et al. Are women with recurrent spontaneous preterm births different from those without such history? Am J Obstet Gynecol 2006;194(4):1176-84; discussion 1184-5.

11. Merlino A, Laffineuse L, Collin M, Mercer B. Impact of weight loss between pregnancies on recurrent preterm birth. Am J Obstet Gynecol 2006;195(3):818-21.

12. Cnattingius S, Granath F, Petersson G, Harlow BL. The influence of gestational age and smoking habits on the risk of subsequent preterm deliveries. N Engl J Med 1999;341(13):943-8.

13. Yost NP, Owen J, Berghella V, Thom E, Swain M, Dildy GA, 3rd, et al. Effect of coitus on recurrent preterm birth. Obstet Gynecol 2006;107(4):793-7.

14. Smith GC, Pell JP, Dobbie R. Interpregnancy interval and risk of preterm birth and neonatal death: retrospective cohort study. BMJ 2003;327(7410):313.

15. Alexander GR, Himes JH, Kaufman RB, Mor J, Kogan M. A United States national reference for fetal growth. Obstet Gynecol 1996;87(2):163-8.

16. Meirowitz NB, Ananth CV, Smulian JC, Vintzileos AM. Effect of labor on infant morbidity and mortality with preterm premature rupture of membranes: United States population-based study. Obstet Gynecol 2001;97(4):494-8.

17. Institute of Medicine. Weight gain during pregnancy: reexamining the guidelines. . Washington (DC): National Academies Press; 2009.

18. Mercer BM, Goldenberg RL, Moawad AH, Meis PJ, Iams JD, Das AF, et al. The preterm prediction study: effect of gestational age and cause of preterm birth on subsequent obstetric outcome. National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network. Am J Obstet Gynecol 1999;181(5 Pt 1):1216-21.

19. Bloom SL, Yost NP, McIntire DD, Leveno KJ. Recurrence of preterm birth in singleton and twin pregnancies. Obstet Gynecol 2001;98(3):379-85.

20. Meis PJ, Goldenberg RL, Mercer BM, Iams JD, Moawad AH, Miodovnik M, et al. The preterm prediction study: risk factors for indicated preterm births. Maternal-Fetal Medicine Units Network of the National Institute of Child Health and Human Development. Am J Obstet Gynecol 1998;178(3):562-7.

21. Kristensen J, Langhoff-Roos J, Kristensen FB. Implications of idiopathic preterm delivery for previous and subsequent pregnancies. Obstet Gynecol 1995;86(5):800-4.

22. Ananth CV, Getahun D, Peltier MR, Salihu HM, Vintzileos AM. Recurrence of spontaneous versus medically indicated preterm birth. Am J Obstet Gynecol 2006;195(3):643-50.

23. Ward K. Genetic factors in preterm birth. Bjog 2003;110 Suppl 20:117.

24. Varner MW, Esplin MS. Current understanding of genetic factors in preterm birth. Bjog 2005;112 Suppl 1:28-31.

25. Dolan SM, Hollegaard MV, Merialdi M, Betran AP, Allen T, Abelow C, et al. Synopsis of preterm birth genetic association studies: the preterm birth genetics knowledge base (PTBGene). Public Health Genomics 2010;13(7-8):514-23.

26. Haataja R, Karjalainen MK, Luukkonen A, Teramo K, Puttonen H, Ojaniemi M, et al. Mapping a new spontaneous preterm birth susceptibility gene, IGF1R, using linkage, haplotype sharing, and association analysis. PLoS Genet 2011;7(2):e1001293.

27. Day LJ, Schaa KL, Ryckman KK, Cooper M, Dagle JM, Fong CT, et al. Single-nucleotide polymorphisms in the KCNN3 gene associate with preterm birth. Reprod Sci 2011;18(3):286-95.

28. Ananth CV. Epidemiologic approaches for studying recurrent pregnancy outcomes: challenges and implications for research. Semin Perinatol 2007;31(3):196-201.

29. Dolan SM, Gross SJ, Merkatz IR, Faber V, Sullivan LM, Malone FD, et al. The contribution of birth defects to preterm birth and low birth weight. Obstet Gynecol 2007;110(2 Pt 1):318-24.

30. Grandi C, Luchtenberg G, Rittler M. The contribution of birth defects to spontaneous preterm birth. Am J Perinatol 2007;24(8):487-92.

31. Hammes LM, Treloar AE. Gestational interval from vital records. Am J Public Health Nations Health 1970;60(8):1496-505.

32. Taback M. Birth weight and length of gestation with relation to prematurity. JAMA 1951;146(10):897-901.

33. Klebanoff MA. Gestational age: not always what it seems. Obstet Gynecol 2007;109(4):798-9.

34. Mustafa G, David RJ. Comparative accuracy of clinical estimate versus menstrual gestational age in computerized birth certificates. Public Health Rep 2001;116(1):15-21.

35. Wise PH. Transforming preconceptional, prenatal, and interconceptional care into a comprehensive commitment to women's health. Womens Health Issues 2008;18(6 Suppl):S13-8.

CHAPTER 4

THE ASSOCIATION BETWEEN GESTATIONAL WEIGHT GAIN OUTSIDE OF RECOMMENDED RANGES AND PRETERM BIRTH: A BIDIRECTIONAL CASE-CROSSOVER STUDY

Précis

Women gaining more weight than recommended are at risk for indicated preterm birth while those gaining less are at risk for spontaneous preterm birth.

Abstract

In 2009, the IOM issued revised guidelines for gestational weight gain (GWG). We sought to evaluate the association between GWG outside of these guidelines and preterm birth (PTB) using a bidirectional case-crossover study to control for genetics and other time-invariant characteristics that might influence GWG and PTB. Analyses were stratified by prepregnancy BMI category, and PTBs were stratified by clinical presentation (spontaneous versus indicated) and into early PTB (<33 weeks gestation) and late PTB (33-36 weeks gestation). Data were limited to women whose first three live births occurred in Utah between 1989– 2007 and who experienced at least one term birth and one PTB. All PTBs were included as cases; bidirectional control births were used. Less

than recommended GWG was not associated with PTB except in normal weight women who were at risk for PTB overall (aOR=1.12, 95% CI 1.01–1.24), spontaneous PTB (aOR=1.15, 1.02–1.30) and late PTB (aOR=1.12, 1.00–1.25). Greater than recommended GWG was associated with late PTB among all women (aOR=1.09, 1.02–1.12) and among overweight women (aOR=1.34, 1.05–1.71). Greater than recommended GWG was also associated with indicated PTB among all women (aOR=1.26, 1.12–1.43), underweight (aOR=2.14, 1.09–4.20), normal weight (aOR=1.30, 1.07–1.56), and overweight women (aOR=1.51, 1.01–2.26). Controlling for time-invariant factors, GWG that is less than or exceeds recommendations is associated with PTB. The association between GWG and PTB varies by prepregnancy BMI category and PTB subtype. The association is most robust for greater than appropriate GWG and indicated PTB.

Introduction

In 2009, the Institute of Medicine (IOM) issued revised guidelines for gestational weight gain (GWG), with recommended ranges for total weight gain and rate of weight gain by prepregnancy body mass index (BMI) category.(1, 2) These guidelines were established, in part, by evaluating the association between GWG and five main outcomes: cesarean delivery, postpartum weight retention, preterm birth (PTB), small or large for gestational age birth, and childhood obesity. The recommendations were selected to optimize outcomes during birth and beyond, while attempting to balance the potential trade-offs between maternal and child outcomes. (1, 2) The authors point out that the association between GWG and PTB is more ambiguous than the relationships between GWG and the other outcomes studied, in part due to less extensive epidemiological evidence.(1) Overall, published studies have reported an association between both low and high GWG and PTB, with the most consistent finding in the published literature being the association between low GWG and PTB, especially among women who have low or normal prepregnancy BMIs.(3-15) However, studies have used different definitions of GWG and only a few have stratified results by clinical presentation or severity of prematurity.(4, 9, 12, 14, 15)

There were two primary objectives for this study. 1) In the context of the IOM's 2009 GWG guidelines, we sought to explore the association between preterm birth and GWG outside of recommended ranges for gestational age and BMI. 2) We also aimed to explore the utility of the case-crossover study method(16) as a way to study the association between GWG and PTB while controlling for genetics and other time-invariant characteristics that might influence this association. With this design, we were able to compare appropriateness of GWG during pregnancies that ended with PTB and pregnancies that ended with term birth in the same woman. In order to fully explore the association between GWG and preterm birth, we stratified analyses by prepregnancy BMI category and also examined preterm birth by clinical presentation (spontaneous versus medically indicated) and in two gestational age categories: early (20 0/7–32 6/7 weeks gestation) and late (33 0/7–36 6/7 weeks gestation).

Methods

This case-crossover study was nested within a historical cohort comprised of Utah residents who had their first, second, and third singleton live births in Utah between 1989 and 2007. Maternally-linked birth records were used; probabilistic record linkage was done by Utah Population Database staff using information on the mother's full maiden name and current surname, birth date, birthplace, address of residence, date of previous live birth, and social security number.(17-19)

The initial dataset contained all live birth and fetal death records from 1989 through 2007 for Utah residents. From these records, women who had their first birth in Utah and a total of three or more subsequent live, singleton births during the study time period were identified. Because our outcome of interest was preterm birth, women with births having implausible birth weights for the reported gestational age were eliminated from the dataset using published ranges of plausible birth weight-gestational age combinations for each week of gestation.(20) Women with missing gestational age data on one or more births were also excluded. The accuracy of the maternally-linked records was evaluated by sorting births to each mother by date and comparing the reported birth order with the sorted birth order.(21) See Figure 2.1. We also excluded women with a record of a fetal anomaly on one or more live births because women with pregnancies complicated by a fetal anomaly are at increased risk for preterm birth.(22, 23) In a case-crossover study, each woman contributes both case and control exposure periods. In our study we defined these case and control periods as unique pregnancies. Therefore, by definition, women without a combination of both term and preterm births were also eliminated from the dataset for analysis.

We defined case pregnancies as live births that occurred between 20 0/7 and 36 6/7 weeks gestation,(24) using the clinical estimate of gestational age as recorded by the birth attendant. This measure of gestational age could have been based on the woman's last menstrual period, ultrasound dating, or other clinical judgment. Preterm births were stratified by clinical presentation. Preterm births that were precipitated by preterm premature rupture of membranes (pPROM) or spontaneous preterm labor were defined as spontaneous preterm birth while indicated preterm births were those that occurred via labor induction or Cesarean delivery without evidence of pPROM or spontaneous labor. The clinical presentation for each preterm birth was established via birth certificate data using a published algorithm (25) with guidance from two perinatologists (authors MSE and MWV). Preterm premature rupture of membranes was defined as rupture of the membranes >12 hours before the onset of labor. Spontaneous preterm labor was considered to be present in the absence of labor induction or pPROM if the birth record contained evidence of tocolysis, cephalopelvic disproportion, labor augmentation, precipitous labor, prolonged labor, dysfunctional labor, vaginal birth, vaginal birth after Cesarean, vacuum-assisted delivery, or forceps-assisted delivery. Any birth without evidence of pPROM or spontaneous labor was classified as being indicated. Preterm births were also stratified into two groups based on gestational age: late preterm births occurred between 33 0/7 and 36 6/7 weeks gestation while early preterm births occurred between 20 0/7 and 32 6/7 weeks gestation.

Anthropometric data including prepregnancy weight, height, and GWG were self-reported on the birth certificate. When these data were not reported by the mother, the birth certificate clerk abstracted this information from the prenatal record (personal communication, Marie Ashliman, April 26, 2011). Using these data, each woman's prepregnancy BMI was calculated using her prepregnancy weight and height. Women were stratified into the following prepregnancy BMI categories for each birth: underweight (<18.5 kg/m^2), normal weight (18.5–24.9 kg/m^2), overweight (25.0–29.9 kg/m^2), and obese (≥30.0 kg/m^2). A range of recommended gestational weight gain was calculated for each week of gestation for women in each BMI category based on the IOM guidelines.(1, 2) The values used for total first trimester weight gain and rate of weekly second and third trimester weight gain for these calculations are shown in Table 4.1. With one exception, these ranges match the IOM recommendations for rate of weight gain during pregnancy.(2) The lower bound for the rate of second and third trimester weekly weight gain for normal weight women was found to be in error in the IOM report and has been revised from the reported rate(2) after discussion with the lead author, Dr. Kathleen M. Rasmussen. Each woman in the study was categorized as gaining an appropriate amount of weight, less weight than recommended, or more weight than recommended given her gestational age at birth and her prepregnancy BMI category for each live birth. This was used as our primary exposure variable in the study.

Table 4.1: Numbers used to calculate the overall range of recommended weight gain for gestational age at birth: Range of recommended first trimester weight gain and rate of weekly gestational weight gain in the second and third trimesters, by prepregnancy BMI[1]

Prepregnancy BMI	First Trimester Total Weight Gain[2]	Rate of Weekly Weight Gain During Second and Third Trimesters
Underweight (<18.5 kg/m^2)	1.0–3.0 kg	0.44–-0.58 kg/week
Normal Weight (18.5–24.9 kg/m^2)	1.0–3.0 kg	0.40–0.50 kg/week
Overweight (25.0–29.9 kg/m^2)	1.0–3.0 kg	0.23–0.33 kg/week
Obese (≥30 kg/m^2)	0.5–2.0 kg	0.17–0.27 kg/week

[1] Based on: Rasmussen KM, Abrams B, Bodnar LM, Butte NF, Catalano PM, Maria Siega-Riz A. Recommendations for weight gain during pregnancy in the context of the obesity epidemic. Obstet Gynecol 2010;116(5):1191-5.

[2]Defined as the first 14 weeks following a woman’s last menstrual period.

Unadjusted and adjusted odds ratios (ORs and aORs) for the association between GWG outside of recommended ranges and PTB were calculated using conditional logistic regression. Women gaining appropriate weight for their gestational age and prepregnancy BMI category were used as the referent category in all models. Additional variables included in the multivariable models were selected based on published literature(1) and availability on the birth certificate and included maternal age, education level, number of prior live births, and use of tobacco during the pregnancy. Multivariable models were evaluated for multicollinearity using variance inflation factors (VIFs). No variables had VIF values >2, indicating that multicollinearity was not a problem in the models.

Because the selection of control time periods can have an impact on the association between the exposure and outcome of interest in a case-crossover study, we initially calculated unadjusted and adjusted ORs for PTB in aggregate using two scenarios for selecting case births and three scenarios for selecting control births. For cases, we considered the impact of 1) including only each woman's first PTB as a case or 2) including all PTBs to each woman as cases. For controls, we considered the impact of including 1) only control births that preceded one or more case births, 2) only control births that occurred after one or more case births, and 3) bidirectional control births. The ORs varied minimally when including all PTBs versus only each woman's first PTB as cases. When comparing the ORs obtained using three different scenarios for control births (control birth before case birth, after case birth, and bidirectional), none of the models resulted in statistically significant associations for GWG and PTB. For this reason, we chose to only report effect estimates using all PTBs as cases and bidirectional controls.

Using all cases and bidirectional controls, ORs were calculated for PTB in aggregate, spontaneous PTB, indicated PTB, early PTB, and late PTB, for all women and stratified by prepregnancy BMI category. By definition, models stratified by BMI category only included women with the same BMI category in both case and control births; thus, women who changed BMI categories between births were excluded from these subanalyses.

Finally, in order to compare the results obtained via the case-crossover analysis with conditional logistic regression (where case and control data come from the same woman) to those obtained via a more traditional analysis of retrospective cohort data using logistic regression (where different women contribute case and control data), we also calculated aORs for GWG and PTB in aggregate using traditional logistic regression. We calculated aORs for live births one, two, and three, using two groups of women: 1) all women in the initial dataset who had their first three singleton, nonanomalous live births in Utah between 1989 and 2007 and 2) the same women included in the case-crossover analysis, a subset of the women from the above dataset who had at least one term and one preterm birth during their first three live births. We did these analyses separately for these two groups of women in order to examine the impact of confounding by time-invariant factors (which are adjusted for in case-crossover analyses but not in traditional logistic regression) and to explore whether the aORs differed only because of these time-invariant factors or whether the exclusion of women with all term births and all preterm births also impacted the aORs. In these traditional logistic regression models, we adjusted for maternal age, education level, number of prior live births, and use of tobacco during the pregnancy in addition to race and ethnicity—factors which have been associated with preterm birth in other studies but were not necessary to adjust for in the case-crossover analyses.(24)

All statistical tests were two sided and an alpha level of 0.05 was used to determine statistical significance. All statistical analyses were conducted using SAS 9.2 software (SAS Institute Inc., Cary, NC). This study was approved by the University of Utah Institutional Review Board (IRB# 00012636) and the University of Utah Resource for Genetic and Epidemiologic Research (RGE).

Results

The initial dataset contained all live birth and fetal death records from 1989 through 2007 for Utah residents and included 865,596 births to 443,669 women. After excluding women who did not have three consecutive live births, starting with their first within the dataset (n=360,722), women with twins or higher order multiples (n=5,841), women with live births having gestational age data that was missing (n=85), <20 weeks (n=138) or implausible given the infant's birthweight (n=226), and women with one or more fetal anomaly in the dataset (n=5,948), the full dataset included 70,709 women who had their first three consecutive, nonanomalous, singleton live births between 1989 and 2007 (n=212,127 live births). For case-crossover analyses, women without a combination of term and preterm outcomes were also excluded (n=1,176 women with three preterm births and 180,318 women with three term births). Thus, the final dataset for case-crossover analysis included 10,211 women with a combination of term and preterm outcomes in live births one through three (n= 30,633 live births).

In the full dataset including all 70,709 women with consecutive, nonanomalous, singleton live births, 5.9%, 5.8% and 6.8% of first, second, and third live births occurred between 20 and 37 weeks gestation, respectively (6.2% across all births). Among women contributing to the case-crossover analysis — those who experienced both term and preterm outcomes within three consecutive births—37.3%, 36.1%, and 43.2% of first, second, and third live births occurred preterm, respectively (38.8% across all births). Most women contributed only one case (preterm) birth (n=8,525 women, 83.5%), while 16.5% of women contributed two case births (n=1,686 women).

The case-crossover population was mostly White (94.9%) and non Hispanic (89.5%). Their mean age increased from 22 years at their first birth to 28 years at their third birth. Women's prepregnancy BMIs also increased from the first to the third birth, with the proportion of overweight women increasing from 14% to 20%, the proportion of obese women increasing from 7% to 17%, the proportion of underweight women decreasing from 14% to 8%, and the proportion of normal weight women decreasing from 66% to 56%, respectively. Table 4.2 displays demographic and anthropometric characteristics of case and control births, including all case births and bidirectional control births.

Table 4.2: Demographic and anthropometric characteristics of case and control births (n=30,633). Case births are all preterm births in dataset (n=11,897, 38.8%); control births are bidirectional (18,736, 61.2%).

	Cases **n (%)**	**Controls** **n (%)**
Maternal Age		
<20	1505 (12.7)	2418 (12.9)
20–24	4552 (38.3)	7242 (38.7)
25–29	3882 (32.6)	6193 (33.1)
30–34	1569 (13.2)	2347 (12.5)
35+	388 (3.3)	535 (2.9)
Maternal Race White	11237 (95.0)	17694 (95.0)
Maternal Ethnicity Hispanic	1231 (10.4)	1956 (10.5)
Maternal Education		
<HS Graduate	2262 (19.3)	3542 (19.1)
HS Graduate	4077 (34.8)	6519 (35.2)
Some College	3405 (29.0)	5237 (28.2)
College Graduate	1989 (17.0)	3245 (17.5)
Maternal Tobacco Use	1381 (11.7)	1977 (10.6)
Number of Previous Live Births		
0	3811 (32.0)	6400 (34.2)
1	3677 (30.9)	6534 (34.9)
2	4409 (37.1)	5802 (31.0)

Table 4.2 continued

	Cases n (%)	Controls n (%)
Prepregnancy BMI		
Underweight (<18.5)	1263 (11.1)	1864 (10.3)
Normal Weight (18.5–24.9)	6841 (59.9)	10858 (60.2)
Overweight (25.0–29.9)	1938 (17.0)	3186 (17.7)
Obese (≥30)	1380 (12.1)	2131 (11.8)
Appropriateness of GWG		
<Recommended GWG	2299 (20.6)	3519 (19.8)
GWG within Recommended Range	3963 (35.4)	6499 (36.6)
>Recommended GWG	4924 (44.0)	7739 (43.6)

Table 4.3 includes unadjusted and adjusted ORs for the association between PTB and GWG among all women. When including women in all prepregnancy BMI categories, *less* than recommended GWG was not associated with PTB in aggregate, by clinical presentation, or by gestational age category; however, *greater* than recommended GWG was associated with indicated PTB (aOR=1.26, 95% CI1.12–1.43) and late preterm birth (aOR=1.09, 95% CI 1.02–1.12). Tables 4.4 and 4.5 display unadjusted and adjusted ORs for PTB in aggregate and by clinical subtype, stratified by prepregnancy BMI. Table 4.4 includes women who were underweight or normal weight in case and control births while Table 4.5 includes women who were overweight or obese in case and control births.

When stratified by prepregnancy BMI, *less* than recommended GWG was associated with PTB overall (aOR=1.12, 95% CI 1.01–1.24) and spontaneous PTB specifically (aOR=1.15, 95% CI 1.02–1.30) among women with a normal prepregnancy BMI in case and control births. Women with underweight, overweight, or obese prepregnancy BMIs who gained *less* weight than recommended were not at significantly increased risk for PTB. Underweight, normal weight, and overweight women with *greater* than recommended GWG were at increased risk for indicated PTB, with aORs of 2.14 (95% CI 1.02–4.20), 1.30 (95% CI 1.07–1.56), and 1.51 (95% CI 1.01–2.26), respectively. This was not true for obese women. While *normal weight* women with *less* than recommended GWG were at increased risk for late PTB (aOR=1.12, 95% CI 1.00-1.25), *overweight* women with *greater* than recommended GWG were at

Table 4.3: Association between gestational weight gain (GWG) and different types of preterm birth (PTB) among women of all prepregnancy weight categories. Cases are all preterm births in the dataset with bidirectional controls. Term births and births with appropriate GWG were used as the referent.

	Unadjusted OR (95% CI)	**Adjusted[1] OR (95% CI)**
Any PTB		
<Recommended GWG	1.05 (0.97–1.13)	1.04 (0.97–1.13)
> Recommended GWG	1.06 (1.00–1.13)	1.06 (1.00–1.14)
Spontaneous PTB		
< Recommended GWG	1.08 (0.99–1.18)	1.08 (0.98–1.18)
> Recommended GWG	0.99 (0.92–1.07)	1.00 (0.93–1.08)
Indicated PTB		
< Recommended GWG	0.97 (0.84–1.13)	0.95 (0.82–1.10)
> Recommended GWG	**1.27 (1.13–1.44)**	**1.26 (1.12–1.43)**
Early PTB (20-32 wks)		
< Recommended GWG	1.16 (0.92–1.46)	1.19 (0.94–1.51)
> Recommended GWG	0.89 (0.73–1.07)	0.89 (0.74–1.08)
Late PTB (33-36 wks)		
< Recommended GWG	1.04 (0.96–1.12)	1.03 (0.95–1.12)
> Recommended GWG	**1.09 (1.02–1.17)**	**1.09 (1.02-1.12)**

[1]Adjusted for maternal age, education level, tobacco use, and parity.

Table 4.4: Association between gestational weight gain (GWG) and preterm birth (PTB) among *underweight* and *normal weight* women. Cases are all preterm births in the dataset with bidirectional controls. Term births and births with appropriate GWG were used as the referent.

	Underweight Women n=723 women[1]		**Normal Weight Women n=5,170 women[1]**	
Gestational Weight Gain	**Unadjusted OR (95% CI)**	**Adjusted[2] OR (95% CI)**	**Unadjusted OR (95% CI)**	**Adjusted[2] OR (95% CI)**
Any PTB				
< Recommended	0.86 (0.66–1.12)	0.83 (0.63–1.09)	1.10 (1.00–1.23)	**1.12 (1.01–1.24)**
> Recommended	1.29 (0.96–1.75)	1.30 (0.96–1.78)	1.08 (0.98–1.18)	1.08 (0.98–1.19)
SPTB[3]				
< Recommended	0.77 (0.58–1.04)	0.73 (0.54–1.00)	**1.14 (1.02–1.29)**	**1.15 (1.02–1.30)**
> Recommended	1.16 (0.82–1.64)	1.16 (0.82–1.65)	1.01 (0.91–1.12)	1.02 (0.92–1.14)
Indicated PTB				
< Recommended	1.52 (0.83–2.77)	1.53 (0.82–2.83)	0.98 (0.80–1.20)	0.98 (0.78–1.21)
> Recommended	**1.97 (1.04–3.76)**	**2.14 (1.09–4.20)**	**1.33 (1.11–1.59)**	**1.30 (1.07–1.56)**
Early PTB[4]				
< Recommended	1.09 (0.54–2.24)	1.08 (0.49–2.40)	1.14 (0.82–1.57)	1.17 (0.84–1.64)
> Recommended	0.91 (0.40–2.10)	1.21 (0.49–2.97)	0.95 (0.72–1.26)	0.95 (0.71–1.27)
Late PTB[4]				
< Recommended	0.83 (0.63–1.10)	0.81 (0.61–1.08)	1.11 (0.99–1.24)	**1.12 (1.00–1.25)**
> Recommended	1.33 (0.97–1.84)	1.33 (0.96–1.85)	1.10 (0.99–1.21)	1.10 (1.00–1.21)

[1]The number of women with data on GWG and at least one case and one control birth within the same prepregnancy BMI category. [2]Adjusted for maternal age, education level, tobacco use, and parity. [3]SPTB is spontaneous PTB. [4]Early PTB is 20-32 weeks gestation; late PTB is 33-36 weeks gestation.

Table 4.5: Association between gestational weight gain (GWG) and preterm birth (PTB) among *overweight* and *obese* women. Cases are all preterm births in the dataset with bidirectional controls. Term births and births with appropriate GWG were used as the referent.

	Overweight Women n=961 women[1]		**Obese Women n=830 women[1]**	
Gestational Weight Gain	**Unadjusted OR (95% CI)**	**Adjusted[2] OR (95% CI)**	**Unadjusted OR (95% CI)**	**Adjusted[2] OR (95% CI)**
Any PTB				
< Recommended	1.14 (0.82–1.60)	1.11 (0.79–1.56)	0.85 (0.64–1.14)	0.82 (0.60–1.11)
> Recommended	1.21 (0.97–1.52)	1.22 (0.97–1.53)	0.94 (0.74–1.19)	0.89 (0.70–1.15)
SPTB[3]				
< Recommended	1.14 (0.77–1.70)	1.11 (0.74–1.66)	0.92 (0.64–1.34)	0.95 (0.65–1.39)
> Recommended	1.10 (0.84–1.45)	1.12 (0.85–1.49)	0.81 (0.59–1.10)	0.78 (0.57–1.08)
Indicated PTB				
< Recommended	1.09 (0.57–2.08)	1.08 (0.55–2.11)	0.75 (0.48–1.19)	0.62 (0.37–1.03)
> Recommended	1.45 (0.98–2.13)	**1.51 (1.01–2.26)**	1.16 (0.81–1.66)	1.07 (0.72–1.59)
Early PTB[4]				
< Recommended	3.02 (0.78–11.71)	2.53 (0.54–11.75)	1.79 (0.76–4.18)	2.47 (0.87–7.03)
> Recommended	0.68 (0.35–1.32)	0.54 (0.25–1.20)	0.85 (0.43–1.67)	0.62 (0.27–1.42)
Late PTB[4]				
< Recommended	1.06 (0.75–1.51)	1.01 (0.71–1.45)	0.77 (0.57–1.05)	0.74 (0.54–1.02)
> Recommended	**1.31 (1.03–1.66)**	**1.34 (1.05–1.71)**	0.95 (0.74–1.22)	0.93 (0.72–1.22)

[1]The number of women with data on GWG and at least one case and one control birth within the same prepregnancy BMI category. [2]Adjusted for maternal age, education level, tobacco use, and parity. [3]SPTB is spontaneous PTB. [4]Early PTB is 20-32 weeks gestation; late PTB is 33-36 weeks gestation.

increased risk for late preterm birth (aOR=1.34, 95% CI 1.05–1.71). Finally, we found no statistically significant association between GWG outside of recommended ranges and early PTB, although all nonsignificant ORs were >1 in women with *less* than appropriate GWG, ranging from 1.08 (95% CI 0.49–2.40) in underweight women to 2.53 (95% CI 0.54–11.75) in overweight women and 2.47 (95% CI 0.87–7.03) in obese women.

When stratified by prepregnancy BMI, *less* than recommended GWG was associated with PTB overall (aOR=1.12, 95% CI 1.01–1.24) and spontaneous PTB specifically (aOR=1.15, 95% CI 1.02–1.30) among women with a normal prepregnancy BMI in case and control births. Women with underweight, overweight, or obese prepregnancy BMIs who gained *less* weight than recommended were not at significantly increased risk for PTB. Underweight, normal weight, and overweight women with *greater* than recommended GWG were at increased risk for indicated PTB, with aORs of 2.14 (95% CI 1.02–4.20), 1.30 (95% CI 1.07–1.56), and 1.51 (95% CI 1.01–2.26), respectively. This was not true for obese women. While *normal weight* women with *less* than recommended GWG were at increased risk for late PTB (aOR=1.12, 95% CI 1.00-1.25), *overweight* women with *greater* than recommended GWG were at increased risk for late preterm birth (aOR=1.34, 95% CI 1.05–1.71). Finally, we found no statistically significant association between GWG outside of recommended ranges and early PTB, although all nonsignificant ORs were >1 in women with *less* than appropriate GWG, ranging from 1.08 (95% CI 0.49–2.40)

in underweight women to 2.53 (95% CI 0.54–11.75) in overweight women and 2.47 (95% CI 0.87–7.03) in obese women.

In order to explore whether the association between weight gain above recommended levels and indicated PTB was due to water retention secondary to preeclampsia, we re-ran models adjusted for “pregnancy-associated hypertension.” This variable was utilized in adjusted models because the birth certificate data do not contain a variable indicating preeclampsia specifically. In models adjusted for pregnancy-associated hypertension, the association between greater than recommended GWG and indicated preterm birth persisted among all women (aOR=1.23, 95% CI 1.08–1.40), underweight women (aOR=2.10, 95% CI 1.06–4.17), and overweight women (aOR=1.56, 95% CI 1.03–2.37), but was no longer statistically significant among normal weight women (aOR=1.21, 95% CI 1.00–1.47). Data not shown.

Finally, we compared the aORS obtained via case-crossover analysis using conditional logistic regression to those obtained via traditional logistic regression where different women contribute case and control births in order to evaluate the impact of study design and analysis methods on effect estimates**.** Interestingly, we found that the ORs were most attenuated when using the case-crossover analysis. When using traditional logistic regression models limited to the same women included in the case-crossover analyses, the aORs for preterm birth in aggregate ranged from 0.93–1.22 for less than recommended GWG (versus 1.04 in the case-crossover analysis) and from 0.99–1.12 for greater than recommended GWG (versus 1.06 in the case-crossover analysis). When expanded to include all women, the aORs from traditional logistic regression were larger in magnitude and most were statistically significant, ranging from 1.20–1.34 for low GWG and 1.03–1.15 for high GWG and preterm birth. These additional analyses confirm that the association between GWG and preterm birth is modest and may be confounded by genetics or other time-invariant factors that are not adjusted for in traditional logistic regression models. See Table 4.6.

Table 4.6: Association between gestational weight gain (GWG) and preterm birth in aggregate, using three methods of analysis: 1) case-crossover analysis using conditional logistic regression, 2) traditional logistic regression using different women as cases and controls, limited to women in case-crossover analysis, and 3) traditional logistic regression using different women as cases and controls, including all women. Term births and births with appropriate GWG were used as the referent.

	< Recommended GWG AOR (95% CI)	**> Recommended GWG AOR (95% CI)**
Case-Crossover Analysis[1]	1.04 (0.97–1.13)	1.06 (0.995–1.14)
Logistic Regression: Birth 1[2]		
Women in Case-Crossover Analysis	0.93 (0.83–1.06)	**1.12 (1.02–1.23)**
All Women	**1.20 (1.09–1.32)**	**1.15 (1.07–1.24)**
Logistic Regression: Birth 2[2]		
Women in Case-Crossover Analysis	**1.22 (1.09–1.36)**	0.99 (0.90–1.31)
All Women	**1.34 (1.23–1.46)**	1.03 (0.95–1.11)
Logistic Regression: Birth 3[2]		
Women in Case-Crossover Analysis	1.05 (0.94–1.17)	1.03 (0.94–1.13)
All Women	**1.23 (1.13–1.34)**	**1.09 (1.01–1.17)**

[1]Adjusted for maternal age, education level, tobacco use, and parity.
[2]Adjusted for maternal age, education level, tobacco use, race, and ethnicity.

Discussion

This study utilized the innovative case-crossover design to address the question of whether GWG outside of the ranges recommended by the IOM for prepregnancy BMI and gestational age at delivery is associated with preterm birth, allowing for adjustment for genetics and other time-stable factors. The case-crossover study design was first utilized in 1991 to identify risk factors for myocardial infarction,(16) and has since been applied to a variety of exposure-disease relationships. However, the application of the case-crossover methodology to perinatal epidemiology is newly emerging. A PubMed search conducted on April 13, 2011 with keywords [“case-crossover” AND pregnancy] and [“case-crossover” AND birth] identified only five studies using the case-crossover methodology to study pregnancy outcomes, (26-30) with only one study focused on the outcome of preterm birth.(26)

The case-crossover design has been touted as a method ideal for the study of exposures with transient effects and outcomes with abrupt onset, (16, 31, 32) and traditionally, small time windows have been specified as case and control exposure periods. However, the application of the case-crossover methodology in studies of pregnancy outcomes has varied. Two studies have identified both case and control exposure windows within one pregnancy for each woman in the study,(26, 30) while others have used entire pregnancies to the same woman as case and control time windows(27-29) as was done in this study.

We found several statistically and clinically significant associations between GWG outside of the recommended ranges and preterm birth in this study. The only statistically significant association between PTB in aggregate and GWG *below* recommended levels was among normal weight women. We also found that normal weight women who gained *less* than appropriate weight were at increased risk for spontaneous PTB and late PTB. In contrast, overweight women who gained *more* weight than recommended were at increased risk for late preterm birth. Women gaining *more* weight than recommended were also at increased risk for indicated preterm birth. This association was true among all women, underweight, normal weight, and overweight women, and persisted in models adjusted for pregnancy-associated hypertension except among normal weight women. The association of greatest magnitude was among underweight women who gained more weight than recommended; these women were more than twice as likely to experience indicated preterm birth. These findings highlight the importance of stratifying studies of preterm birth by subtype and by examining the impact of GWG overall and in each BMI category.

In 2008, Viswanathan et al. conducted a systematic review of the published literature on GWG and pregnancy outcomes including 12 studies on the association between GWG and preterm birth.(3) The authors concluded that, overall, there is evidence to suggest an association between preterm birth and both low and high GWG. The most consistent association was between low GWG, defined as either total weight gain(5-8) or rate(9-14) of weight gain, and preterm birth, particularly in women with underweight or normal pre-pregnancy BMIs.(3) Since 2007, Savitz et. al. studied the association between preterm birth and projected 40-week gestational weight gain (defined as the average weekly GWG multiplied by 40), finding a modest association between both low (<20 kg) GWG (OR=1.4) and high (20+ kg) GWG (OR=1.3). (4) In analyses stratified by clinical presentation, the Savitz et. al. study found an association between both low *and* high GWG and spontaneous and medically indicated preterm birth.(4) While we used a different definition of GWG in our study, defining it as appropriate or inappropriate based on the 2009 Institute of Medicine Guidelines,(1, 2) our findings were similar, particularly in analyses stratified by prepregnancy BMI. However, our study revealed ORs that were somewhat attenuated compared to those published previously. In addition, our data do not support the hypothesis that underweight women with less than appropriate GWG are at increased risk for preterm birth. We found nonsignificant aORs close to 1 for underweight women with less than recommended GWG with the exception of the association between less than recommended GWG and early preterm birth in underweight women, who were 2.5 times more likely to experience early preterm birth, although the finding was not statistically significant due to a large amount of variability. It is important to note that no aORS were statistically significant for early preterm birth, likely due to the smaller number of women with this outcome. Despite the large size of our initial dataset, there were only 723 women who were in the underweight prepregnancy BMI category for at least one case and one control birth, limiting our statistical power to detect small associations among these women.

Some of the differences observed between this study and other published studies may be due to the use of the case-crossover analysis, which allowed us to evaluate the association between GWG and PTB in different pregnancies to the same woman. When we compared the case-crossover aORs to those obtained via traditional logistic regression using different women's births as cases and controls, the case-crossover analysis yielded more conservative estimates of effect. This was true when using all women in traditional logistic regression models and when limiting analyses to the same group of women included in the case-crossover analysis—those with a mix of both term and preterm births. The differences between these analyses may indicate that the association between GWG and PTB may be confounded by time-invariant factors that are controlled for using the case-crossover method.

This study has several important limitations including the use of vital statistics data. In order to minimize problems with gestational age data from the birth certificate, we used a clinical estimate of gestational age which has been reported to be more highly correlated with birth weight (33, 34) and more accurate than the gestational age estimates based upon patient report of last menstrual period.(35, 36) We also eliminated women with births having implausible birth weights for their reported gestational age using published ranges of plausible birth weight-gestational age combinations for each week of gestation.(20) Because the GWG data are self-reported, under or overreporting is possible; however, it is likely that inaccurate reporting does not vary systematically between birth certificates completed for term and preterm births . Another limitation related to GWG data from the birth certificate is the fact that the timing of the last weight measurement is not specified, so it is unclear if women are reporting their weight at the time of the delivery or at their last prenatal visit. Study strengths include the large sample size which allowed for stratification of preterm births into clinical subtypes and gestational age categories. In addition, birth records provide population-based data, thereby increasing the generalizability of study findings.

Another limitation of this study is the fact that data are limited to women who had three or more viable pregnancies during their reproductive careers. Women who have only one or two children may be systematically different from those who have three or more children. This issue, known as selective fertility, occurs when a couple makes decisions about subsequent fertility based on previous pregnancy outcomes.(37, 38) Skjærven and Melve have reported, for example, that women who have experienced perinatal death tend to have a shorter interpregnancy interval after their loss and higher parity at the end of their childbearing years, compared to women who do not experience such a loss. Conversely, women who experience preeclampsia are approximately 20% less likely to become pregnant again, compared with women who do not experience this complication.(39) Because this case-crossover study required at least one case and one control birth per woman, it was necessary to limit the study population to women with at least two live births. It is important to note, however, that such inclusion criteria may limit the generalizability of the study's findings.

The IOM's revised guidelines for GWG were established to optimize maternal and child outcomes related to a number of pregnancy complications. The GWG guidelines are based on the assumption that good outcomes occur over a range of GWG and that additional factors may need to be considered by each individual woman and her health care provider in order to balance the trade-offs between maternal and child health. (1, 2) We found modest associations between preterm birth subtypes and GWG outside of the ranges recommended by the IOM, supporting the IOM guidelines. Future research is needed to evaluate the impact of these guidelines on other pregnancy outcomes and to further explore the association between greater than appropriate GWG and indicated preterm birth observed in this study.

References

1. Institute of Medicine. Weight gain during pregnancy: reexamining the guidelines. Washington (DC): National Academies Press; 2009.

2. Rasmussen KM, Abrams B, Bodnar LM, Butte NF, Catalano PM, Maria Siega-Riz A. Recommendations for weight gain during pregnancy in the context of the obesity epidemic. Obstet Gynecol 2010;116(5):1191-5.

3. Viswanathan M, Siega-Riz AM, Moos MK, Deierlein A, Mumford S, Knaack J, et al. Outcomes of maternal weight gain. Evid Rep Technol Assess (Full Rep) 2008(168):1-223.

4. Savitz DA, Stein CR, Siega-Riz AM, Herring AH. Gestational weight gain and birth outcome in relation to prepregnancy body mass index and ethnicity. Ann Epidemiol 2011;21(2):78-85.

5. Carmichael S, Abrams B, Selvin S. The association of pattern of maternal weight gain with length of gestation and risk of spontaneous preterm delivery. Paediatr Perinat Epidemiol 1997;11(4):392-406.

6. Rosenberg TJ, Garbers S, Lipkind H, Chiasson MA. Maternal obesity and diabetes as risk factors for adverse pregnancy outcomes: differences among 4 racial/ethnic groups. Am J Public Health 2005;95(9):1545-51.

7. Jensen DM, Ovesen P, Beck-Nielsen H, Molsted-Pedersen L, Sorensen B, Vinter C, et al. Gestational weight gain and pregnancy outcomes in 481 obese glucose-tolerant women. Diabetes Care 2005;28(9):2118-22.

8. Velonakis EG, Maghiorakos P, Tzonou A, Barrat J, Proteau J, Ladopoulos I. The relation of birth weight and gestational age to biological, occupational and socioeconomic factors. Clin Exp Obstet Gynecol 1997;24(4):232-6.

9. Siega-Riz AM, Adair LS, Hobel CJ. Maternal underweight status and inadequate rate of weight gain during the third trimester of pregnancy increases the risk of preterm delivery. J Nutr 1996;126(1):146-53.

10. Kramer MS, Coates AL, Michoud MC, Dagenais S, Hamilton EF, Papageorgiou A. Maternal anthropometry and idiopathic preterm labor. Obstet Gynecol 1995;86(5):744-8.

11. Dietz PM, Callaghan WM, Cogswell ME, Morrow B, Ferre C, Schieve LA. Combined effects of prepregnancy body mass index and weight gain during pregnancy on the risk of preterm delivery. Epidemiology 2006;17(2):170-7.

12. Nohr EA, Vaeth M, Bech BH, Henriksen TB, Cnattingius S, Olsen J. Maternal obesity and neonatal mortality according to subtypes of preterm birth. Obstet Gynecol 2007;110(5):1083-90.

13. Schieve LA, Cogswell ME, Scanlon KS. Maternal weight gain and preterm delivery: differential effects by body mass index. Epidemiology 1999;10(2):141-7.

14. Stotland NE, Caughey AB, Lahiff M, Abrams B. Weight gain and spontaneous preterm birth: the role of race or ethnicity and previous preterm birth. Obstet Gynecol 2006;108(6):1448-55.

15. Rudra CB, Frederick IO, Williams MA. Pre-pregnancy body mass index and weight gain during pregnancy in relation to preterm delivery subtypes. Acta Obstet Gynecol Scand 2008;87(5):510-7.

16. Maclure M. The case-crossover design: a method for studying transient effects on the risk of acute events. Am J Epidemiol 1991;133(2):144-53.

17. Kerber RA, O'Brien E. A cohort study of cancer risk in relation to family histories of cancer in the Utah population database. Cancer 2005;103(9):1906-15.

18. Niazi TN, Cannon-Albright LA, Couldwell WT. Utah Population Database: a tool to study the hereditary element of nonsyndromic neurosurgical diseases. Neurosurg Focus 2010;28(1):E1.

19. Esplin MS, O'Brien E, Fraser A, Kerber RA, Clark E, Simonsen SE, et al. Estimating recurrence of spontaneous preterm delivery. Obstet Gynecol 2008;112(3):516-23.

20. Alexander GR, Himes JH, Kaufman RB, Mor J, Kogan M. A United States national reference for fetal growth. Obstet Gynecol 1996;87(2):163-8.

21. Adams MM, Kirby RS. Measuring the accuracy and completeness of linking certificates for deliveries to the same woman. Paediatr Perinat Epidemiol 2007;21 Suppl 1:58-62.

22. Dolan SM, Gross SJ, Merkatz IR, Faber V, Sullivan LM, Malone FD, et al. The contribution of birth defects to preterm birth and low birth weight. Obstet Gynecol 2007;110(2 Pt 1):318-24.

23. Grandi C, Luchtenberg G, Rittler M. The contribution of birth defects to spontaneous preterm birth. Am J Perinatol 2007;24(8):487-92.

24. Behrman RE, Butler AS, Institute of Medicine (U.S.). Committee on Understanding Premature Birth and Assuring Healthy Outcomes. Preterm birth : causes, consequences, and prevention. Washington, D.C.: National Academies Press; 2007.

25. Meirowitz NB, Ananth CV, Smulian JC, Vintzileos AM. Effect of labor on infant morbidity and mortality with preterm premature rupture of membranes: United States population-based study. Obstet Gynecol 2001;97(4):494-8.

26. Basu R, Malig B, Ostro B. High ambient temperature and the risk of preterm delivery. Am J Epidemiol 2010;172(10):1108-17.

27. Salihu HM, Sharma PP, Getahun D, Hedayatzadeh M, Peters S, Kirby RS, et al. Prenatal tobacco use and risk of stillbirth: a case-control and bidirectional case-crossover study. Nicotine Tob Res 2008;10(1):159-66.

28. Ananth CV, Peltier MR, Chavez MR, Kirby RS, Getahun D, Vintzileos AM. Recurrence of ischemic placental disease. Obstet Gynecol 2007;110(1):128-33.

29. Meyer KA, Williams P, Hernandez-Diaz S, Cnattingius S. Smoking and the risk of oral clefts: exploring the impact of study designs. Epidemiology 2004;15(6):671-8.

30. Hernandez-Diaz S, Hernan MA, Meyer K, Werler MM, Mitchell AA. Case-crossover and case-time-control designs in birth defects epidemiology. Am J Epidemiol 2003;158(4):385-91.

31. Szklo M, Nieto FJ. Epidemiology : beyond the basics. Gaithersburg, Md: Aspen; 2000.

32. Koepsell TD, Weiss NS. Epidemiologic methods : studying the occurrence of illness. Oxford ; New York: Oxford University Press; 2003.

33. Hammes LM, Treloar AE. Gestational interval from vital records. Am J Public Health Nations Health 1970;60(8):1496-505.

34. Taback M. Birth weight and length of gestation with relation to prematurity. J Am Med Assoc 1951;146(10):897-901.

35. Klebanoff MA. Gestational age: not always what it seems. Obstet Gynecol 2007;109(4):798-9.

36. Mustafa G, David RJ. Comparative accuracy of clinical estimate versus menstrual gestational age in computerized birth certificates. Public Health Rep 2001;116(1):15-21.

37. Skjaerven R, Wilcox AJ, Lie RT, Irgens LM. Selective fertility and the distortion of perinatal mortality. Am J Epidemiol 1988;128(6):1352-63.

38. Ananth CV. Epidemiologic approaches for studying recurrent pregnancy outcomes: challenges and implications for research. Semin Perinatol 2007;31(3):196-201.

39. Skjærven R, Melve K. Selective fertility: the examples of perinatal death and preeclampsia. Norsk Epidemiologi 2007;17(2):175-180.

CHAPTER 5

CONCLUSION

The purpose of this research was to describe patterns of recurrent preterm birth by clinical presentation, to investigate whether other factors were associated with recurrent preterm birth among multiparous women with a history of preterm birth, and to explore the association between gestational weight gain and preterm birth, in aggregate and by clinical subtype. Results of the study are summarized below.

Recurrent Preterm Birth by Clinical Presentation

Few studies of recurrent preterm birth have examined recurrence patterns by clinical presentation beyond the second birth. We used maternally-linked birth records to describe preterm birth recurrence patterns across women's first three live births for three distinct clinical presentations: preterm premature rupture of the membranes (pPROM), spontaneous preterm labor (SPTL), and medically indicated preterm birth. Our study population included 76,657 women with three consecutive, singleton live births in Utah between 1989–2007, starting with their first live birth. In this study, all women with a prior preterm birth had an increased risk of recurrence, regardless of clinical presentation. The odds of preterm birth recurrence with the same clinical presentation were substantial, with aORs of 9.00, 5.74, and 7.71 in birth two and aORs of 45.37, 17.98, and 35.16 in birth three for pPROM, SPTL, and indicated preterm birth, respectively. The highest odds of recurrence were in women with two prior preterm births of the same subtype; however, the odds of recurrence remained significantly elevated even among women having an intervening term birth (aORs ranging from 2.63–3.38, depending on clinical subtype in the first birth). These findings confirm and expand upon those of other studies. (1-9) The high recurrence rates identified in this study across preterm birth clinical subtypes suggests that there may be similar genetic factors for preterm birth subtypes or that stable environmental and/or behavioral risk factors act similarly across subtypes to influence these outcomes. It is hoped that the findings from this study, specifically the patterns of recurrence by clinical presentation, will be of use to clinicians when counseling patients about recurrence risks based on obstetric history.

Risk Factors for Recurrent Preterm Birth

Based on findings from this dissertation and other studies, it is well established that a history of preterm birth as a significant risk factor for recurrence.(1-9) Other risk factors for recurrent preterm birth have been described, including Black race,(1, 10) underweight maternal body mass index (BMI),(11) weight loss between pregnancies,(12) maternal smoking,(13) and short interpregnancy interval.(14) As with studies of recurrence patterns, most of the research on risk factors for recurrent preterm birth have been limited to outcomes in the second live birth(1, 13, 14) and have not stratified results by preterm birth clinical presentation.(1, 11-13) We used multivariable logistic regression to identify risk factors for recurrent preterm birth among multiparous women with a history of preterm birth in their first (n=4,805) or second births (n=3,663). Recurrent preterm birth accounted for 22% of second *preterm* births and 34% of third *preterm* births, but only 1% of second births and 2% of third births overall. We identified several notable risk factors for recurrent preterm birth in both the second and third live birth, including: 1) having an interpregnancy interval of <6 months versus 2–3 years, 2) the presence of a preexisting maternal medical condition including cardiac disease, acute or chronic lung disease, preexisting diabetes, hemoglobinopathy, chronic hypertension, or renal disease, and 3) history of a birth at ≤32 weeks gestation in the most recent preterm birth (compared with 33–36 weeks gestation). Women with a history of SPTL or pPROM-initiated preterm birth were at increased risk for recurrence if they had an underweight prepregnancy BMI; this was not true for women with a history of indicated preterm birth. Additional variables that were statistically significant risk factors in women with a history of SPTL included 1) young maternal age and 2) gestational weight gain that was less than appropriate for a woman's BMI and gestational age based on the 2009 Institute of Medicine guidelines.(15) Several of these risk factors may be amenable to intervention in a preconception/ interconception model of care.(16) In addition, these findings highlight the importance of studying preterm birth stratified by clinical subtype.

Gestational Weight Gain and Preterm Birth

Given the unique structure our database which included the first three consecutive, singleton live births to Utah residents occurring between 1989 and 2007, we sought to explore the utility of the case-crossover method(17) as a way to study the association between gestational weight gain (GWG) and preterm birth while controlling for genetics and other time-invariant characteristics that might influence this association. This method allowed us to compare GWG during pregnancies that ended with preterm birth and pregnancies that ended with term birth in the same woman (n=10,211 women with a mix of term and preterm outcomes in their first three nonanomalous live births). We elected to study GWG in this context because the Institute of Medicine (IOM) recently issued revised guidelines for gestational weight gain (GWG), with recommended ranges for total weight gain and rate of weight gain by prepregnancy body mass index (BMI) category.(15, 18) The only statistically significant association between preterm birth in aggregate and GWG *below* recommended levels was among normal weight women (aOR=1.12, 95% CI 1.01–1.24). We also found that *normal* weight women who gained *less* than appropriate weight were at increased risk for spontaneous preterm birth (aOR=1.15, 1.02–1.30) and late preterm birth (aOR=1.12, 1.00–1.25). In contrast, *overweight* women who gained *more* weight than recommended were at increased risk for late preterm birth (aOR=1.34, 1.05–1.71). Women gaining *more* weight than recommended were also at increased risk for indicated preterm birth. This association was true among all women (aOR=1.26, 1.12–1.43), underweight (aOR=2.14, 1.09–4.20), normal weight (aOR=1.30, 1.07–1.56), and overweight women (aOR=1.51, 1.01–2.26), and persisted in models adjusted for pregnancy-associated hypertension except among normal weight women. We obtained ORs that were somewhat attenuated in comparison to those published previously.(19-31) Interestingly, when we compared the ORs obtained via case-crossover analysis to those obtained via traditional logistic regression using different women's births as cases and controls, the case-crossover analysis yielded more conservative estimates of effect. The differences between the case-crossover analysis, traditional logistic regression analysis, and other published studies may indicate that the association between GWG and PTB is confounded by time-invariant factors that are controlled for using the case-crossover method. Although we found only modest associations, our findings do support the IOM guidelines for gestational weight gain.

Summary

This study provides new insights into preterm birth recurrence patterns by clinical presentation and risk factors for preterm birth. Study strengths and limitations are discussed in more detail in Chapters 2–4. The major study limitation is the use of vital statistics data which may have limited validity for some variables. Studies of birth certificate data quality have found that information on medical risk factors and complications, for example, may be under-reported.(27-32) Since there is no variable on the birth certificate indicating preterm labor, we derived this data using other available variables.(32) In addition, because we used birth certificate data, we did not have access to potentially useful clinical variables such as the presence of preeclampsia. Finally, birth certificate data on maternal weight and height are self-reported, thus, under or overreporting is possible. An additional limitation is the fact that data were restricted to women who had three or more viable pregnancies during their reproductive careers, limiting the generalizability of study findings, particularly those in

Chapter 4. This is because women who have only one or two children may be systematically different from those who have three or more children.(33, 34)

Study strengths include the unique database with information on each woman's first through third live births and any intervening fetal deaths at ≥20 weeks gestation, the large sample size which allowed for stratification by preterm birth clinical presentation, the use of population-based data which enhances generalizability, and the fact that Utah is one of two states which conducts annual data audits—likely resulting in higher quality vital statistics data (personal communication, Marie Aschliman, May 29, 2008). In all analyses, we used a clinical estimate of gestational age which has been reported to be more highly correlated with birth weight (35, 36) and more accurate than the gestational age estimates based upon patient report of last menstrual period.(37, 38)

The time and effort spent developing this unique database of multiparous Utah women whose first three, consecutive live births occurred between 1989 and 2007 has provided useful information about preterm birth recurrence patterns and risk factors. Study findings highlight areas where additional research is warranted. Additional research is needed to explore the indications for medically indicated preterm birth and their recurrence as well as the association between greater than appropriate gestational weight gain and recurrent preterm birth following indicated preterm birth. Finally, future prospective studies may be warranted to evaluate how interconception care focused on optimizing maternal health impacts the rates of recurrent preterm birth.

References

1. Adams MM, Elam-Evans LD, Wilson HG, Gilbertz DA. Rates of and factors associated with recurrence of preterm delivery. JAMA 2000;283(12):1591-6.

2. Carr-Hill RA, Hall MH. The repetition of spontaneous preterm labour. Br J Obstet Gynaecol 1985;92(9):921-8.

3. Mazaki-Tovi S, Romero R, Kusanovic JP, Erez O, Pineles BL, Gotsch F, et al. Recurrent preterm birth. Semin Perinatol 2007;31(3):142-58.

4. Esplin MS, O'Brien E, Fraser A, Kerber RA, Clark E, Simonsen SE, et al. Estimating recurrence of spontaneous preterm delivery. Obstet Gynecol 2008;112(3):516-23.

5. Mercer BM, Goldenberg RL, Moawad AH, Meis PJ, Iams JD, Das AF, et al. The preterm prediction study: effect of gestational age and cause of preterm birth on subsequent obstetric outcome. National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network. Am J Obstet Gynecol 1999;181(5 Pt 1):1216-21.

6. Bloom SL, Yost NP, McIntire DD, Leveno KJ. Recurrence of preterm birth in singleton and twin pregnancies. Obstet Gynecol 2001;98(3):379-85.

7. Meis PJ, Goldenberg RL, Mercer BM, Iams JD, Moawad AH, Miodovnik M, et al. The preterm prediction study: risk factors for indicated preterm births. Maternal-Fetal Medicine Units Network of the National Institute of Child Health and Human Development. Am J Obstet Gynecol 1998;178(3):562-7.

8. Kristensen J, Langhoff-Roos J, Kristensen FB. Implications of idiopathic preterm delivery for previous and subsequent pregnancies. Obstet Gynecol 1995;86(5):800-4.

9. Ananth CV, Getahun D, Peltier MR, Salihu HM, Vintzileos AM. Recurrence of spontaneous versus medically indicated preterm birth. Am J Obstet Gynecol 2006;195(3):643-50.

10. Kistka ZA, Palomar L, Lee KA, Boslaugh SE, Wangler MF, Cole FS, et al. Racial disparity in the frequency of recurrence of preterm birth. Am J Obstet Gynecol 2007;196(2):131 e1-6.

11. Mercer BM, Macpherson CA, Goldenberg RL, Goepfert AR, Haugel-De Mouzon S, Varner MW, et al. Are women with recurrent spontaneous preterm births different from those without such history? Am J Obstet Gynecol 2006;194(4):1176-84; discussion 1184-5.

12. Merlino A, Laffineuse L, Collin M, Mercer B. Impact of weight loss between pregnancies on recurrent preterm birth. Am J Obstet Gynecol 2006;195(3):818-21.

13. Cnattingius S, Granath F, Petersson G, Harlow BL. The influence of gestational age and smoking habits on the risk of subsequent preterm deliveries. N Engl J Med 1999;341(13):943-8.

14. Smith GC, Pell JP, Dobbie R. Interpregnancy interval and risk of preterm birth and neonatal death: retrospective cohort study. BMJ 2003;327(7410):313.

15. Institute of Medicine. Weight gain during pregnancy: reexamining the guidelines. . Washington (DC): National Academies Press; 2009.

16. Wise PH. Transforming preconceptional, prenatal, and interconceptional care into a comprehensive commitment to women's health. Womens Health Issues 2008;18(6 Suppl):S13-8.

17. Maclure M. The case-crossover design: a method for studying transient effects on the risk of acute events. Am J Epidemiol 1991;133(2):144-53.

18. Rasmussen KM, Abrams B, Bodnar LM, Butte NF, Catalano PM, Maria Siega-Riz A. Recommendations for weight gain during pregnancy in the context of the obesity epidemic. Obstet Gynecol 2010;116(5):1191-5.

19. Viswanathan M, Siega-Riz AM, Moos MK, Deierlein A, Mumford S, Knaack J, et al. Outcomes of maternal weight gain. Evid Rep Technol Assess (Full Rep) 2008(168):1-223.

20. Savitz DA, Stein CR, Siega-Riz AM, Herring AH. Gestational weight gain and birth outcome in relation to prepregnancy body mass index and ethnicity. Ann Epidemiol 2011;21(2):78-85.

21. Carmichael S, Abrams B, Selvin S. The association of pattern of maternal weight gain with length of gestation and risk of spontaneous preterm delivery. Paediatr Perinat Epidemiol 1997;11(4):392-406.

22. Rosenberg TJ, Garbers S, Lipkind H, Chiasson MA. Maternal obesity and diabetes as risk factors for adverse pregnancy outcomes: differences among 4 racial/ethnic groups. Am J Public Health 2005;95(9):1545-51.

23. Jensen DM, Ovesen P, Beck-Nielsen H, Molsted-Pedersen L, Sorensen B, Vinter C, et al. Gestational weight gain and pregnancy outcomes in 481 obese glucose-tolerant women. Diabetes Care 2005;28(9):2118-22.

24. Velonakis EG, Maghiorakos P, Tzonou A, Barrat J, Proteau J, Ladopoulos I. The relation of birth weight and gestational age to biological, occupational and socioeconomic factors. Clin Exp Obstet Gynecol 1997;24(4):232-6.

25. Siega-Riz AM, Adair LS, Hobel CJ. Maternal underweight status and inadequate rate of weight gain during the third trimester of pregnancy increases the risk of preterm delivery. J Nutr 1996;126(1):146-53.

26. Kramer MS, Coates AL, Michoud MC, Dagenais S, Hamilton EF, Papageorgiou A. Maternal anthropometry and idiopathic preterm labor. Obstet Gynecol 1995;86(5):744-8.

27. Dietz PM, Callaghan WM, Cogswell ME, Morrow B, Ferre C, Schieve LA. Combined effects of prepregnancy body mass index and weight gain during pregnancy on the risk of preterm delivery. Epidemiology 2006;17(2):170-7.

28. Nohr EA, Vaeth M, Bech BH, Henriksen TB, Cnattingius S, Olsen J. Maternal obesity and neonatal mortality according to subtypes of preterm birth. Obstet Gynecol 2007;110(5):1083-90.

29. Schieve LA, Cogswell ME, Scanlon KS. Maternal weight gain and preterm delivery: differential effects by body mass index. Epidemiology 1999;10(2):141-7.

30. Stotland NE, Caughey AB, Lahiff M, Abrams B. Weight gain and spontaneous preterm birth: the role of race or ethnicity and previous preterm birth. Obstet Gynecol 2006;108(6):1448-55.

31. Rudra CB, Frederick IO, Williams MA. Pre-pregnancy body mass index and weight gain during pregnancy in relation to preterm delivery subtypes. Acta Obstet Gynecol Scand 2008;87(5):510-7.

32. Meirowitz NB, Ananth CV, Smulian JC, Vintzileos AM. Effect of labor on infant morbidity and mortality with preterm premature rupture of membranes: United States population-based study. Obstet Gynecol 2001;97(4):494-8.

33. Skjaerven R, Wilcox AJ, Lie RT, Irgens LM. Selective fertility and the distortion of perinatal mortality. Am J Epidemiol 1988;128(6):1352-63.

34. Ananth CV. Epidemiologic approaches for studying recurrent pregnancy outcomes: challenges and implications for research. Semin Perinatol 2007;31(3):196-201.

35. Hammes LM, Treloar AE. Gestational interval from vital records. Am J Public Health Nations Health 1970;60(8):1496-505.

36. Taback M. Birth weight and length of gestation with relation to prematurity. J Am Med Assoc 1951;146(10):897-901.

37. Klebanoff MA. Gestational age: not always what it seems. Obstet Gynecol 2007;109(4):798-9.

38. Mustafa G, David RJ. Comparative accuracy of clinical estimate versus menstrual gestational age in computerized birth certificates. Public Health Rep 2001;116(1):15-21.