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Risk factors associated with preterm birth after a prior term delivery

Luchin F. WONG, MD^{1,2}, Jacob WILKES Mr., BS^{3,4}, Mr. Kent KORGESKI, MS^{3,4}, Michael W. VARNER, MD^{1,2}, and Tracy A. MANUCK, MD^{1,2}

¹University of Utah, Department of Obstetrics and Gynecology, Salt Lake City, UT

²Intermountain Healthcare, Department of Maternal-Fetal Medicine, Salt Lake City, UT

³University of Utah, Department of Pediatrics, Salt Lake City, UT

⁴Intermountain Healthcare, Pediatric Clinical Program, Salt Lake City, UT

Abstract

Objective—The objective of this study was to assess for the presence of newly acquired preterm birth (PTB) risk factors among primiparous women with no prior history of PTB.

Design—Case-control study.

Setting—Deliveries occurring within a large healthcare system from 2002–2012

Population—Women with their first two consecutive pregnancies carried to 20 0/7 weeks gestation.

Methods—Those delivering the first pregnancy at term and the second preterm 20 0/7 and < 37 0/7 weeks (term-preterm cases) were compared to women with a term birth in their first two pregnancies (term-term controls). Social factors with the potential to change between the first and second pregnancies and intrapartum labour characteristics in the first pregnancy were compared between cases and controls.

Main outcome measures—Risk factors for term-preterm sequence.

Results—38215 women met inclusion criteria. 1,353 (3.8%) were term-preterm cases. Cases and controls were similar with regards to race/ethnicity and maternal age at the time of the first and second deliveries. Cases delivered their second pregnancy approximately three weeks earlier (35.7 vs. 39.1, $p < 0.001$). In multivariable models accounting for known PTB risk factors, women with a

Corresponding author: Luchin F. Wong, University of Utah Department of Ob/Gyn, 30 North Medical Drive, Suite 2B200, Salt Lake City, UT 84132, 347-563-8330 (mobile) / 801-581-8425 (office) / 801-585-2594 (fax), luchin.wong@gmail.com.

Author Affiliation Notes:

Since the study was conducted, Dr. Manuck has moved to the University of North Carolina-Chapel Hill Department of Obstetrics and Gynecology Division of Maternal Fetal Medicine (Chapel Hill, NC).

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caesarean delivery in the first pregnancy (aOR=2.20; 95% CI 1.57–3.08), new tobacco use (aOR=2.33; 95% CI, 1.61–3.38), and an interpregnancy interval < 18 months (aOR=1.37; 95% CI, 1.21–1.55) were at increased risk of term–preterm sequence.

Conclusion—Caesarean delivery in the first pregnancy, new tobacco use, and short interpregnancy interval < 18 months are significant risk factors for term-preterm sequence. Women should receive postpartum counseling regarding appropriate interpregnancy interval and tobacco cessation.

Keywords

caesarean delivery; intrapartum; preterm birth; tobacco

Introduction

Preterm birth (PTB) prior to 37 weeks gestation complicates approximately 12% of pregnancies in the United States and is a leading cause of infant morbidity and mortality.¹ Obstetric history is often used to guide subsequent pregnancy management, because a prior PTB is the strongest risk factor for subsequent PTB. Other risk factors, such as African-American race, low socio-economic status, and cervical conisation have also been associated with an increased risk of PTB, albeit to a lesser degree. However, even some seemingly ‘low risk’ women will have a PTB. Esplin et al. reported that 6.5% of pregnancies following a first term delivery deliver preterm and 5.8% of pregnancies following two consecutive term deliveries are preterm.² Little is known about why these seemingly low risk women with a proven history of term delivery then deliver preterm.

During the course of a woman’s reproductive life, she may acquire new risk factors that increase her PTB risk. These acquired risk factors are primarily those associated with lifestyle and behaviour and may include marital status, insurance status, and substance abuse.^{3–14} A detrimental change in these factors between pregnancies may place seemingly low risk women at increased risk for PTB.

Additionally, the circumstances surrounding delivery of the first infant may impact a woman’s subsequent PTB. Previous investigators have proposed an association between a prolonged second stage of labour or caesarean delivery and an increased future risk of PTB.^{15–17} It is plausible that either an inadvertently low-positioned or caudally extended caesarean hysterotomy could damage the cervix and increase the risk for cervical insufficiency and PTB in subsequent pregnancy. When a caesarean is performed during the second stage of labour, the rate of caudal hysterotomy extension is higher than when a caesarean is performed during the first stage.^{18,19} Likewise, distension of the cervix by the fetal head during a prolonged second stage could theoretically cause cervical damage regardless of the eventual mode of delivery. In one small case control study, Vyas et al. reported an association between a prolonged second stage of labour and cervical insufficiency in subsequent pregnancy.¹⁷ Thus, it is plausible that intrapartum events at term may increase a woman’s risk for subsequent PTB.

The objective of this study was to quantify the interval acquisition of PTB risk factors among secundigravid woman with a previous term birth. Of particular interest were interval development of social risk factors and intrapartum labour characteristics in the first pregnancy.

Methods

This is a case control study of women whose first two consecutive singleton pregnancies were carried to 20 0/7 weeks or greater and delivered within the Intermountain Healthcare system between 2002 and 2012. Women whose first pregnancy delivered prior to 37 0/7 weeks or required a cerclage and those who carried a fetus with major structural anomalies or aneuploidy in either the first or second pregnancy were excluded. Women whose second pregnancy was complicated by hypertension, mild preeclampsia, severe preeclampsia, superimposed preeclampsia, eclampsia, uterine rupture, or placental abruption, were also excluded to limit analysis to likely spontaneous preterm birth cases. The best obstetric estimate, utilizing last menstrual period and ultrasound parameters as appropriate, was used for dating criteria.²⁰ The study enrollment flow diagram is shown in Figure S1. This study was approved by the Intermountain Healthcare Institutional Review Board.

Term-preterm cases were identified as women whose first pregnancy (G1) was delivered at term and second pregnancy (G2) was delivered at < 20 0/7 weeks and < 37 0/7 weeks. Term-term controls were women with a term birth for both the first and second pregnancies. Intrapartum data were extracted from computerised point-of-care programs. Study data were collected and managed using REDCap (Research Electronic Data Capture) electronic data capture tools hosted at the University of Utah.²¹ A portion (2%) of these data was manually verified.

The start of the second stage of labour was defined as the earliest time at which a cervical dilation of 10 cm was recorded. Intrapartum characteristics including induction of labour, length of labour, length of second stage of labour, and mode of delivery were compared between cases and control. At the time of delivery admission for G1 and G2, maternal weight and height (including body mass index (BMI)), medical conditions, and antepartum complications were also assessed. Pre-pregnancy BMI was not reliably available for analysis. The presence of major maternal medical conditions and pregnancy complications (e.g., diabetes, hypertension, pre-eclampsia) was also assessed by ICD9 coding associated with the delivery admission for both G1 and G2.

Social habits, including tobacco, alcohol, and illicit drug use, as well as marital status and insurance type were also assessed at the time of delivery admission for both G1 and G2. Variables with the potential to change from G1 to G2 were compared between cases and controls. The interpregnancy interval was defined as the interval from delivery of G1 to last menstrual period (or the calculated last menstrual period using the best obstetric estimate) corresponding to G2.

Data were analysed using STATA version 12.0 (College Station, TX). Statistical significance was set at 0.05, and all statistical tests were two-tailed. Student's t test and chi-squared were

used as appropriate. Multivariate logistic regression was used to assess the odds of the term-preterm sequence. Models were adjusted for known PTB risk factors that were selected *a priori* as well as newly identified risk factors from univariate analysis: maternal age at first delivery, gestational age at first delivery, BMI in the first pregnancy, prostaglandin induction in the first delivery, caesarean delivery at first delivery, prolonged second stage in first delivery, new tobacco use in the second pregnancy, new alcohol use in the second pregnancy, new illicit drug use in the second pregnancy, change in marital status in the second pregnancy, interpregnancy interval less than 18 months, and vaginal trial of labour in the second pregnancy. Backwards stepwise selection with a p-value cut off of 0.20 was used to select a model. The final model adjusted for maternal age at first delivery, gestational age at first delivery, BMI in the first pregnancy, prostaglandin induction in the first delivery, caesarean delivery at first delivery, prolonged second stage in first delivery, new tobacco use in the second pregnancy, change in marital status in second pregnancy, and interpregnancy interval less than 18 months. Similar analyses were performed for term-PTB < 34 weeks sequence.

Results

We identified 35,983 women with a total of 71,966 pregnancies that met inclusion criteria (Figure S1). 1,353 (3.8%) women were term-preterm cases. Cases and controls were clinically similar with regards to race/ethnicity and maternal age at the time of the first and second deliveries (Table 1). Cases delivered G1 at 38.7 weeks (median 38.6 weeks), about 1 week earlier than controls (39.5 weeks), and delivered G2, on average, 1 week preterm (mean 35.7 weeks, median 36.2 weeks). Preterm premature rupture of membranes complicated G2 in 17.9% (242/1353) at a mean gestational age of 35.1 ± 1.8 weeks. Twenty-eight (1.8%) of the term-preterm cases delivered G2 very preterm (<32 weeks gestation). Only 4 women had a diagnosis of cervical insufficiency and/or had a cervical cerclage placed in G2 (for details, please see Table S1). Additionally, women with term-preterm sequence were more likely to have been tobacco or alcohol users in G1, unmarried in G1, be uninsured, and have a lower BMI (28.7 vs. 29.4).

There were several differences between G1 intrapartum characteristics for term-preterm cases and term-term controls (Table 2). Cases were less likely to receive prostaglandin induction of labour in G1 than controls. Among those with prostaglandin induction in G1, the mean gestational age at delivery was clinically similar between cases and controls (39.1 vs. 39.8 weeks), although the proportion of women delivering late term (> 41 weeks) in G1 was considerably greater among women with term-term sequence as compared to term-preterm cases (10.8% vs. 3.0%, $p < 0.001$). The duration of second stage of labour in G1 was also similar for both cases and controls (1.8 hours) as was the frequency of a moderately prolonged second stage < 3 hours (13.2% vs. 13.3%, $p = 0.88$), although cases had a greater frequency of prolonged second stage > 4 hours (4.2% vs. 3.8%, $p = 0.023$). However, after adjusting for potential confounders, prolonged second stage of labour 4 hours or greater did not confer a statistically significant risk for term-preterm sequence (Table 4). After adjusting for potential confounders, caesarean delivery (for any indication) conferred a 2.2-fold increase in odds for term-preterm sequence as compared to women who had a vaginal delivery.

Social risk factors with the potential to change from G1 to G2 were compared between term-preterm cases and term-term controls and are presented in Table 3. Those cases who did not report tobacco, alcohol, or illicit drug use during G1 were more likely to become new users in G2 as compared to controls. Cases were also more likely than controls to divorce between G1 and G2. Women who quit tobacco, alcohol, or illicit drug use between G1 to G2 were equally distributed between cases and controls. After adjusting for confounders, only new tobacco users remained at significantly increased odds for term-preterm sequence (Table 4). Women who became new tobacco users had a greater than two-fold increased odds for term-preterm sequence than women who remained abstinent from tobacco, aOR=2.33 (95% CI, 1.61–3.38). Similarly, women who had an interpregnancy interval less than 18 months had nearly two-fold increased odds for term-preterm sequence than controls, aOR=1.92 (95% CI, 1.68–2.20).

90 women were identified to have term-very preterm sequence (PTB < 34 weeks in G2). Unlike term-preterm sequence, the only social characteristic that changed between G1 and G2 for the term-very preterm sequence was new tobacco use (data not shown). With regards to intrapartum characteristics of G1, term-very preterm sequence was similar to term-preterm sequence with the exception of admission to delivery duration, caesarean delivery in 2nd stage among all those reaching 2nd stage, and caesarean delivery after prolonged second stage. When adjusting for potential confounders with multivariable analysis, only new tobacco use was associated with significant increased risk.

Discussion

Main Findings

In our study, we identified an association between caesarean delivery and term-preterm sequence, conferring approximately a two-fold risk. While women with a prolonged second stage of labour during G1 were more likely to experience the term-preterm sequence, this did not remain significant when adjusting for potential confounders. There also appeared to be a protective association with prostaglandin induction of labour in G1, being associated with a 23% reduction in risk of term-preterm sequence. This protective association between prostaglandin induction and term-preterm sequence may reflect an inherent cervical makeup that is more resistant to cervical remodeling. While prostaglandin induction of labour was associated with both increased rates of caesarean delivery and prolonged second stage of labour in our cohort and less frequently used among women with term-preterm sequence, this likely skews any association between term-preterm sequence and caesarean delivery or prolonged second stage of labour towards the null.

We also found that 3.1% of women who were non-smokers at the time of their first delivery became smokers at the time of their second delivery. New smokers had a greater than two-fold increased odds for term-preterm sequence as compared to their tobacco abstinent counterparts. This effect measure is roughly similar to other studies that have examined tobacco use and subsequent PTB in populations with a heterogeneous obstetric history, reporting odds ratios ranging from 1.1–1.7 for PTB.^{3,6–8} Our data suggest that the impact of new tobacco use is consistent regardless of a ‘low risk’ obstetric history and remains consistent for very preterm birth.

Finally, we found that women with an interpregnancy interval < 18 months had a significantly increased odds for term-PTB sequence. While consistent with previous literature, direct comparison regarding the magnitude of the risk is difficult given the heterogeneity in interpregnancy interval reference groups and study populations (including women with a history of term or PTB).^{22–26}

Strengths and Limitations

To our knowledge, this is the first large-scale study to examine the association between various intrapartum factors and social risk factors, particularly those with the potential to change, on the gestational age of subsequent delivery in ‘low risk’ women. Detailed antepartum and intrapartum data were collected at the time that clinical events occurred, and collection was standardised across both the first and second pregnancies carried to at least 20 weeks gestation, providing valuable clinical information regarding PTB risk.

Our study had several limitations. Due to the retrospective nature of this study, our data were limited to factors available through ICD9 coding and/or routinely captured at the point of care. Due to this, we were unable to consistently distinguish spontaneous from medically indicated (iatrogenic) PTB. However, PTB is a syndrome often consisting of more than one phenotype, with overlap between spontaneous PTB and iatrogenic PTB.²⁷ Hence, it is not always feasible to completely distinguish spontaneous from iatrogenic PTB. We also chose to consider cases of maternal abruption in G2 as iatrogenic PTB as these are mostly related to a pathologic vascular and placental process leading to rapid PTB often associated with increased perinatal morbidity in addition to the morbidity conferred by early gestational age. Another limitation is the utilisation of data based on self-reported behaviours, which are particularly susceptible to reporting and recall biases. The integrity of the data is also dependent on the individual entering the data into computerised point-of-care systems. Although we manually reviewed a portion of subjects, and focused on those for which there was missing data or data discrepancies, this may not have captured all incorrectly entered data. Finally, due to our study design, we were unable to quantify timing of adverse behaviours during pregnancy (e.g., exposure only during one trimester), nor degree of exposure (e.g., number of cigarettes smoked/day, or number of weeks smoked). We are thus unable to determine specific timing and/or thresholds of activity that may prove most detrimental with regards to PTB risk.^{3,28,29}

Interpretations

While the majority of PTB in this ‘low risk’ population is late preterm, with an average gestational age of 35.7 weeks, this is not an insignificant burden. Phibbs estimated the cost of neonatal care for preterm deliveries \$6007 and \$3444 for a 36 week delivery in 1998–2000; corrected for inflation (2014), a delivery at 35 weeks cost \$8156, and delivery at 36 weeks cost \$4676.³⁰ Even late preterm neonates and children have a significantly increased risk for major morbidity and increased utilisation of healthcare resources persisting into childhood.^{31,32}

A small number of women were diagnosed with cervical insufficiency within our study population. For this reason, we were unable to compare intrapartum factors with subsequent

risk for cervical insufficiency as Vyas et al. was able to do. In their case control study of 49 women with cervical insufficiency following a term delivery, they identified an increased odds for cervical insufficiency among women with a prolonged second stage of labour of 3 hours or greater as a significant risk factor.¹⁷ Furthermore, because the creation of our cohort was conditioned on having a second delivery ≥ 20 weeks (due to inconsistencies in delivery location and documentation in our database for pregnancies ending prior to 20 weeks gestation), we cannot accurately describe the true rate of cervical insufficiency or pregnancy losses at < 20 weeks, and is a clear limitation of this study. However, it is improbable that a true causal relationship between prolonged second stage and cervical insufficiency exists in this cohort because we had very low rates of cervical insufficiency and very early PTB (< 32 weeks gestation) in G2, despite a 13% rate of prolonged second stage ≥ 3 hours in G1 in this large cohort.

Conclusion

Caesarean delivery in the first pregnancy at term, new tobacco use, and short interpregnancy interval less than 18 months are significant risk factors for PTB, even for women with a prior term delivery and no prior history of PTB. Women with these risks for term-preterm sequence should receive postpartum counseling regarding appropriate interpregnancy interval and tobacco cessation. Tobacco abstinence should be encouraged, regardless of prior pregnancy outcome. Future studies should investigate caesarean delivery as an acquired risk factor for PTB in a prospective manner.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Tweetable Abstract

Caesarean delivery in the 1st pregnancy is a significant risk factor for preterm birth following a term delivery.

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Table 1

Maternal demographic & pregnancy characteristics, comparing term-preterm cases to term-term controls. Data are n(%) unless otherwise specified.

	Term-Preterm Cases n=1,353 (%)	Term-Term Controls n=34,630 (%)	p-value
Caucasian	1,122 (83.1%)	28,539 (82.7%)	0.699
G1 – Maternal age, y (mean ± SD)	23.7 ± 4.0	24.4 ± 4.0	<0.001
G1 – Mean delivery gestational age, wks (median)	38.7 (38.6)	39.5 (39.5)	<0.001
G1 – Tobacco use	46 (3.4)	529 (1.5)	<0.001
G1 – Alcohol use	169 (12.5)	3,509 (10.1)	0.005
G1 – Illicit drug use *	2 (0.15)	21 (0.06)	0.213
G1 – Married	1,026 (75.8)	28,612 (82.6)	< 0.001
G1 – Private insurance	934 (69.0)	26,425 (76.3)	< 0.001
G1 – Body mass index (kg/m²) †	28.7 ± 5.3	29.4 ± 5.0	< 0.001
G1 – Any hypertension in pregnancy ‡	111 (8.2)	2,777 (8.0)	0.806
G2 – Maternal age, y (mean ± SD)	26.1 ± 4.2	27.0 ± 4.1	<0.001
G2 – Mean delivery gestational age, wks (median)	35.7 (36.2)	39.1 (39.1)	<0.001

* Fisher's exact test

† Body mass index at time of delivery admission

‡ Includes hypertension, mild preeclampsia, severe preeclampsia, superimposed preeclampsia, and eclampsia

Table 2

Univariable analyses comparing intrapartum characteristics of the 1st delivery between term-preterm cases and term-term controls. Data are n(%) unless otherwise specified.

Characteristics of the 1 st delivery	Term-Preterm Cases n=1,353 (%)	Term-Term Controls n=34,630 (%)	p-value
Induction of labour with prostaglandins *	102 (8.4)	4,048 (13.0)	< 0.001
Mechanical (Foley bulb) induction *	5 (0.4)	171 (0.6)	0.516
Length of 2 nd stage, hrs ($\pm$ SD) †	1.8 $\pm$ 1.2	1.8 $\pm$ 1.1	0.518
2 nd Stage of labour 3 hrs ‡	147 (13.2)	3,718 (13.3)	0.882
2 nd Stage of labour 4 hrs ‡	47 (4.2)	1,052 (3.8)	0.023
2 nd Stage of labour 5 hrs ‡	14 (1.3)	278 (1.0)	0.397
2 nd Stage of labour 6 hrs ‡	3 (0.3)	70 (0.3)	0.907
Admission to delivery, hrs ($\pm$ SD) *	9.7 $\pm$ 5.4	11.0 $\pm$ 6.8	< 0.001
Caesarean delivery	225 (16.6%)	6,171 (16.6%)	0.991
Caesarean delivery *	138 (11.3)	3,685 (11.8)	0.576
Caesarean delivery in 2 nd stage ‡	67 (5.7)	1,172 (3.9)	0.003
Caesarean delivery in 2 nd stage ‡	67 (42.4)	1,172 (28.3)	< 0.001
Caesarean delivery after 3 hrs in 2 nd stage §	46 (26.1)	743 (16.4)	< 0.001
Caesarean delivery after 4 hrs in 2 nd stage §	32 (47.1)	389 (27.7)	0.001

* Among those with a vaginal trial of labour (31,178 women had term G1, 1,222 women had preterm G1)

† Among those reaching 2nd stage of labour (29,838 women had term G1, 1,186 women had preterm G1)

‡ Among those with caesarean delivery for any indication (4,146 women had term G1, 158 women had preterm G1)

§ Among all women with 2nd stage of labour 3 hrs (4,522 women had term G1, 176 women had preterm G1)

§ Among all women with 2nd stage of labour 4 hrs (1,407 women had term G1, 68 women had preterm G1)

Table 3

Univariable analyses comparing changes in social characteristics between term-preterm cases and term-term controls. Data are n(%).

Social Characteristics that changed between G1 and G2	Term- Preterm Cases n=1,353 (%)	Term-Term Controls n=34,630 (%)	p-value
New tobacco user	42 (3.1)	411 (1.2)	< 0.001
New alcohol user	110 (8.1)	2,271 (6.6)	0.022
New illicit drug user *	3 (0.22)	17 (0.05)	0.038
Lost private insurance	98 (7.2)	2,966 (8.6)	0.087
Newly divorced/separated	17 (1.3)	263 (0.8)	0.041
Quit tobacco use	6 (0.4)	157 (0.5)	0.958
Quit alcohol use	98 (7.2)	2,125 (6.1)	0.097
Quit illicit drug use *	2 (0.2)	19 (0.1)	0.186
Interpregnancy interval < 18 months	743 (54.9)	17,059 (49.3)	< 0.001

*
Fisher's exact test

Table 4

Multivariable regression examining intrapartum and social factors associated with PTB following term delivery

Characteristics of G1	aOR *	95% CI	p-value
G1 – Delivery gestational age (wk)	0.48	0.45–0.51	< 0.001
G1 – Maternal age (yr)	0.96	0.95–0.98	< 0.001
G1 –Body mass index (kg/m ²) [†]	0.98	0.97–0.99	0.003
G1 – Prostaglandin induction of labour	0.77	0.62–0.96	0.018
G1 – 2 nd stage of labour 4 hours	1.24	0.91–1.70	0.181
G1 – Caesarean delivery	2.20	1.57–3.08	< 0.001
New tobacco user	2.33	1.61–3.38	< 0.001
Got divorced	1.63	0.93–2.87	0.088
Interpregnancy interval < 18 months	1.37	1.21–1.55	< 0.001

* New alcohol use, new illicit drug use, and vaginal trial of labour were considered for the regression model but not included in the final model as these variables did not remain significant

[†] Body mass index at time of delivery admission