Adverse Birth Outcomes Among Nulliparous vs. Multiparous Women

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ABSTRACT

Objectives. Previous studies indicate that nulliparous women (i.e., women having no previous births) are at higher risk for adverse birth outcomes than multiparous women (i.e., women having had at least one previous birth). We examined whether part of the difference in adverse outcome rates is attributable to nulliparous women with poor pregnancy outcomes being less likely (through choice or fecundity differences) to have a subsequent live birth within the same time period as nulliparous women without adverse outcomes.

Methods. Using deterministic matching, we linked nulliparous women from the North Carolina Detailed Birth Record to subsequent births. We employed statistical and simulation-based analyses to estimate first birth outcome rate differences between nulliparous women who did have a subsequent live birth vs. those who did not. Our Markov simulations focused on preterm birth (PTB).

Results. Among nulliparous women who were not linked to a second birth, maternal age-adjusted rates of multiple adverse outcomes were all statistically higher compared with rates for linked women. These results also held in race/ethnicity-specific analyses. Simulations found that the relative risk of PTB associated with a history of PTB was underestimated if some women who would have been at risk for PTB did not experience a second birth.

Conclusions. The observed differences in rates of adverse outcomes between nulliparous and multiparous women are partly attributable to higher-risk women not having a subsequent live birth, either by choice or due to fecundity differences.

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Preterm birth (PTB; gestation <37 weeks) and low birthweight (LBW; birthweight <2,500 grams) are associated with significant short- and long-term morbidity and mortality,[1–14] as well as substantial economic costs.[15] Crude rates of PTB and LBW are higher among nulliparous women (i.e., women having no previous births) than among multiparous women (i.e., women having had at least one previous birth) (Table 1).[16,17] The most consistent risk factor for PTB is a history of PTB,[15] and some interventions have been shown to be effective in this population.[18] However, approximately one-third of all pregnancies are first pregnancies.[16] A recent systematic review found significantly elevated risks for nulliparous compared with multiparous women for LBW (summary odds ratio [OR] = 1.41, 95% confidence interval [CI] 1.26, 1.58) and small-for-gestational-age births (summary OR=1.89, 95% CI 1.82, 1.96), but not for PTB (summary OR=1.13, 95% CI 0.96, 1.34).[17]

Three possible explanations may account for an excess risk of adverse outcomes in nulliparous women. First, other factors associated with an increased risk for PTB and/or LBW, such as young maternal age,[15] a history of infertility,[19] or hypertensive disorders of pregnancy,[16] are more prevalent in nulliparous women. Second, there may be something unique about first pregnancies, independent of other causal factors (e.g., increased risk of preeclampsia). If so, quantifying this risk and understanding its etiology are important for developing strategies to prevent PTB/LBW attributable to nulliparity alone. Finally, women who experience an adverse outcome in their first birth may be less likely to get pregnant again or may be more likely to have a spontaneous abortion, induced abortion, or stillbirth. If this theory is the case, then the risk associated with nulliparity alone will be overestimated, and the risk of recurrence will be underestimated.

We explored the plausibility of differential progression to a second live birth as a factor in the observed association between nulliparity and adverse pregnancy outcomes, using both statistical and simulation approaches.

Table 1. Pregnancy outcomes by parity among singleton births in the U.S., 2006[a]

Outcome	*Rate among nulliparous women (percent)*	*Rate among multiparous women (percent)*	*Relative rate for nulliparous women*
Gestation <37 weeks[b]	9.22	8.67	1.06
Gestation <34 weeks[b]	2.66	2.05	1.30
Birthweight <2,500 grams	7.59	5.70	1.33
Birthweight <1,500 grams	1.41	0.94	1.50

[a]National Center for Health Statistics (US). Natality public-use files 1990–2006. Hyattsville (MD): Centers for Disease Control and Prevention (US), NCHS, Division of Vital Statistics; 2006.

[b]Based on a clinical estimate of gestation

METHODS

Causal model

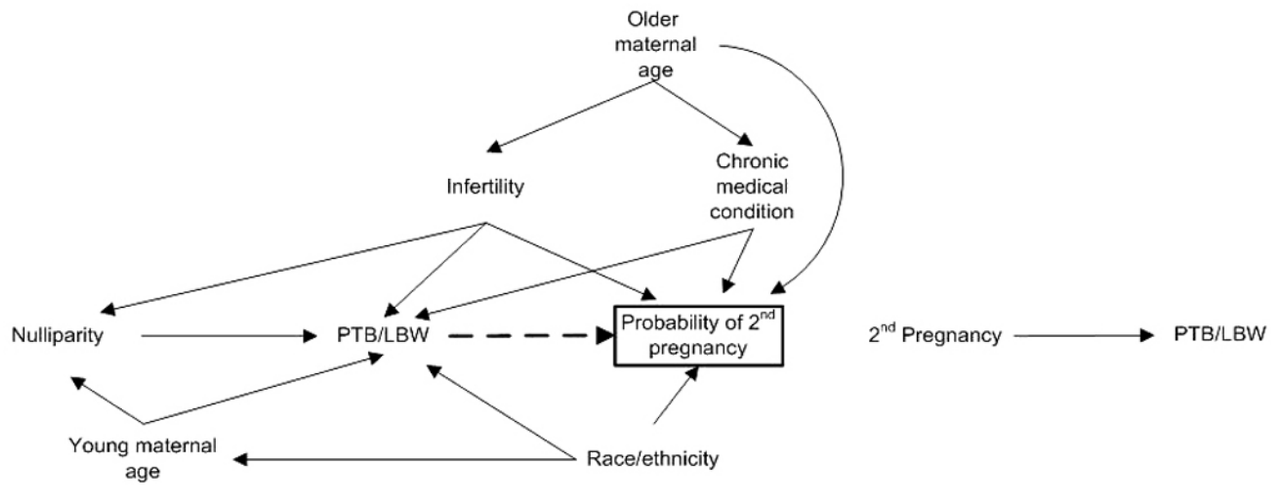
We used the directed acyclic graph (DAG) approach[20,21] to describe a plausible causal model for nulliparity as an independent risk factor for PTB/LBW and to identify potential sources of bias. Figure 1 depicts a causal DAG for the effect of nulliparity on PTB. As described by Hernan et al.,[22] selection bias occurs in the presence of conditioning on a common effect of at least two variables, one of which is either the exposure or the cause of the exposure and the other of which is either the outcome or the cause of the outcome. In this case, the exposure of interest is nulliparity, and the potential common effect is the probability of a second birth. There are multiple pathways by which such conditioning can occur. For example, infertility is causal of nulliparity and also affects the likelihood of a second birth, while older maternal age, which affects the likelihood of a second birth through age-related effects on fecundity, also increases the risk of chronic medical conditions (e.g., hypertension) that would lead to an increased risk of PTB/LBW.

Linking first and second births

The North Carolina (NC) Detailed Birth Record provides demographic, health, and obstetrics information on all live births occurring in NC. We used data on births occurring in NC during 1990–2007.

We linked multiple births occurring to the same mother using individual identifiers within the birth record. Our matching algorithm employed various combinations of the maternal identifiers of full name, maiden name, state and date of birth, and obstetrics history, including birth order and date of last live birth. Initially, second births were linked to first births that matched exactly on all matching criteria, with subsequent linkages allowing for various combinations of disagreement between select variables and accounting for minor spelling and data entry errors. In all stages, the date of last live birth recorded for the second birth was required to match the date of birth for the associated first birth. Pairs of linked births that did not match exactly on all identifying fields were reviewed by two programmers, and non-exact matches were only

Figure 1. Directed acyclic graph of the potential causal pathways for the association between nulliparity and PTB/LBW[a]



[a]Factors such as older maternal age and infertility are in the causal pathway for both PTB/LBW and the probability of a second pregnancy, leading to the possibility of selection bias.

PTB = preterm birth

LBW = low birthweight

retained when consensus on matching was reached. Additional details on the matching process are available from the authors upon request.

The linked birth data enabled us to assess the effect of first pregnancy outcomes on the likelihood of a second recorded birth within five years. We restricted our analysis to singleton first births to non-Hispanic white (NHW) and non-Hispanic black (NHB) women. (We excluded Hispanic women from analysis because rapidly rising immigration rates make it very likely that a previous Hispanic birth did not occur in NC.) We further restricted our analysis to women aged 15–34 years during their first birth, to minimize the effect of declining fecundity after age 35 years and increasing utilization of infertility treatment on pregnancy timing. Although the linkage to subsequent births included data through 2007, we only included first births occurring between 1990 and 2000 to capture subsequent births that may have occurred even after a relatively long internatal period. We excluded records with a birthweight of <400 grams, an estimate of <24 weeks gestation, or any missing data on any outcomes of interest. These restrictions eliminated 0.4% of otherwise qualifying births.

Association of outcome with linkage status

Using the linked birth data, we compared pregnancy outcomes among first births linked to a second birth with first births not linked to a second birth. The following outcomes were considered: PTB, late PTB (34–36 completed weeks gestation), very PTB (VPTB; <34 weeks gestation), LBW, and very LBW (VLBW; birthweight <1,500 grams). We used logistic regression controlling for maternal age to produce age-adjusted ORs and 95% CIs to compare the odds of adverse birth outcomes by linkage status. Age-adjusted ORs are presented for all births, and separately for NHW and NHB births. The analysis was repeated restricting to only first births with no maternal medical complications reported and only first births with at least one maternal medical complication reported. All statistical analyses were performed using SAS® version 9.2.[23]

Association of outcome with time to next reported birth

To estimate how much of the gap in adverse birth outcome rates between nulliparous and multiparous women might be attributable to differential rates of second birth, we used the linked data to perform survival analysis using time to next birth stratified by gestational age (VPTB, late PTB, and full-term birth) and birthweight (VLBW, birthweight 1,500–2,499 grams, and normal birthweight ≥2,500 grams) of the first birth. For first births linked to a second birth, the date of conception of the second birth was estimated using the date of birth and gestational age at delivery; the internatal spacing between the first and second birth was calculated as the number of completed months between delivery of the first infant and estimated conception of the second. Internatal spacing was censored

to 60 months. For first births not linked to a second birth, the internatal spacing was set to 60 months and marked as censored data. The impact of a preterm first birth on time to the next birth was estimated using proportional hazard models, controlling for maternal age at first birth, race/ethnicity, and their interaction.

Simulating effect of differential second birth rates on estimated relative risk

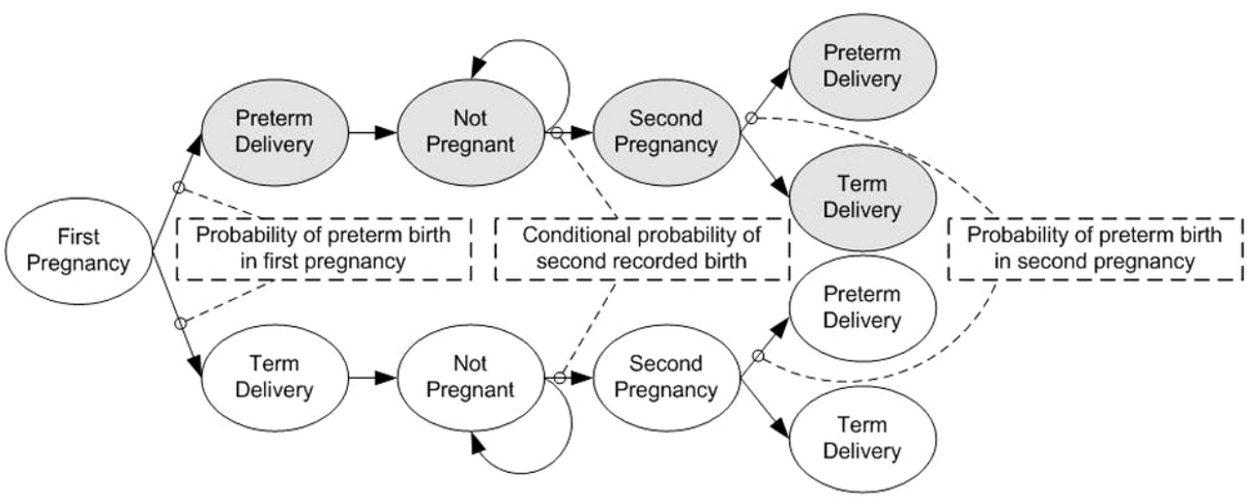
To estimate the potential impact of differential subsequent birth rates on the association between adverse pregnancy outcomes in the first and subsequent births, we constructed a simple Markov model[24] (Figure 2) using TreeAge Pro 2009.[25] The model simulates a cohort of women after their first birth, stratified by gestational age (full-term vs. preterm). We assumed an overall preterm delivery rate in the first birth of 12%, and relative risk (RR) of a PTB in women with a history of PTB in their first birth of 1.5,[26] but we assumed in the base case scenario that the overall PTB rate was identical in both first and second births.

We used the observed overall annual conditional probability of a second birth in the dataset. In the base case, we assumed that the hazard ratio for this probability was 1.0 for women with full-term and preterm first births. Using the model, we calculated an overall five-year probability of births, the PTB rate for those births, and RRs associated with nulliparity and a history of PTB. By varying the modeled hazard ratio in the simulation, we were able to estimate the effect of differential second birth rates on estimates of the RRs associated with nulliparity and a history of PTB.

RESULTS

The final dataset included 426,259 first births, of which 62.2% were forward-linked to a second birth. The 2002 National Survey of Family Growth indicated that 31.2% of mothers aged 15–44 years have not had a second birth,[27] suggesting that our forward-linking rate was quite good. To provide additional context, among second births in NC during 1990–2007 meeting similar restrictions and with a date of late live birth in 1990 or later, the backward-linked success rate (i.e., the proportion of second births for which we were able to identify the associated first birth) was 81.2%; a large portion of the lower backward-linking success rate was likely due to the high rate of in-migration to NC during the time period under study. The correlation of county-level backward-linking success rate with county-level migration to NC based on 2000 U.S. Census data[28] was −0.79 ($p<0.0001$). Linking second births to the associated first birth was more successful for NHB, unmarried, and lower educational attainment

Figure 2. Markov state-transition model used for estimating the potential effect of decreased probability of second birth after adverse outcome of first birth on "observed" association between parity and adverse outcomes[a]



[a]Arrows indicate allowed transitions between different states after each Markov cycle. After each post-delivery cycle, women can either remain not pregnant (curved arrow) or become pregnant (straight arrow). The ratio of the conditional probabilities of becoming pregnant in women with a full-term vs. preterm first pregnancy is the hazard ratio. The ratio of the probability of preterm birth between first and second pregnancies, or between second births in women with a prior full-term vs. preterm birth, is the relative risk. By fixing the probabilities of preterm delivery in both pregnancies and varying the hazard ratio, one can observe the effect of differential rates of second births on estimates of relative risk.

women, all of which were factors associated with higher rates of poor birth outcomes. We used the forward-linking data in our analyses.

Table 2 provides summary statistics on the first births used in the linked analyses. The vast majority of births (72.9%) were to NHW women. Dramatic differences in maternal demographic characteristics existed between the NHW and NHB nulliparous women. Forward-linking rates did not differ by race/ethnicity, with 62.0% of NHW and 63.0% of NHB first births being linked to a second birth.

Among all first births, the rates of PTB, VPTB, LBW, and VLBW were 10.3%, 3.0%, 7.7%, and 1.4%, respectively. The crude rates of each outcome by linking status and stratified by race/ethnicity are presented in Table 3. As expected, the rates of adverse pregnancy outcomes were higher among NHB births than among NHW births. Overall and by race/ethnicity, the rate of adverse birth outcomes was consistently higher among first births that were not linked to a second birth than among first births that were linked to a second birth. With the exception of late PTB among NHB births, the differences in these crude rates between linked and unlinked births were significant ($p<0.05$).

Table 4 presents age-adjusted ORs (AORs) of PTB and LBW for unlinked vs. linked births, before and after stratifying for the presence of a maternal medical condition in the first birth. For each group, non-linkage was associated with a higher likelihood of PTB or LBW in the first birth, indicating that adverse outcomes in the first birth were associated with the decreased likelihood of a second birth. These differences in the likelihood of a second birth after PTB or LBW in the first birth were exacerbated by the presence of maternal medical complications, suggesting that both maternal and neonatal outcomes affected the probability of a subsequent birth. Earlier gestational age or lower birthweight was associated with a higher rate of non-linkage. For example, for women without medical complications, not being linked to a second birth was associated with a 5% increase in the odds of late PTB in the first birth (34–36 weeks gestation; AOR=1.05, 95% CI 1.02, 1.09) vs. a 23% increase in the odds of VPTB (<34 weeks gestation; AOR=1.23, 95% CI 1.17, 1.30). These findings were consistent for both the NHW and NHB populations.

Table 5 shows the conditional probability of a second birth in each of the first five years after the index delivery, stratified by age and history of PTB at first birth. Women younger than 25 years of age with a history of PTB were more likely to have a second birth conceived within the first year after delivery than women of the same age with a full-term birth, but annual birth rates in subsequent years were lower for women with a history of PTB across all age groups, with the difference increasing with maternal age. These general patterns were similar when stratified further by race/ethnicity. In a proportional hazards model using months as the time interval, a history of PTB or LBW was associated with a lower 60-month probability of a second birth after adjusting for age at first delivery, race/ethnicity (NHW and NHB only), and age-race/ethnicity interactions; as with the logistic regression results, the association was stronger with earlier gestational age or lower birthweight (Table 6).

In the simulation model, we fixed the RR of PTB in first vs. second births at 1.0 and the RR of PTB in a second birth given a history of PTB at 1.5; then, we varied the hazard ratio for a second birth from 1.0 to 0.8 (within the range observed in Table 6). Lower hazard ratios resulted in higher calculated RRs for nulliparity (although this increase was quite small) and lower calculated RRs for a history of PTB; this effect was increased at higher RRs for a history of PTB (Table 7). Varying the "true" RR for nulliparity, or for the rates of PTB in the first birth, did not alter the effect of a lower hazard ratio on calculated RRs.

Table 2. Summary statistics of 1990–2000 North Carolina first births to women <35 years of age for inclusion in a linked analysis, by race/ethnicity

		Maternal race/ethnicity	
Demographic	*All (percent)*	*Non-Hispanic white (percent)*	*Non-Hispanic black (percent)*
N	426,259	310,735	115,524
Percent	100.0	72.9	27.1
Maternal age (in years)			
15–19	26.3	20.4	42.3
20–24	31.9	31.2	34.0
25–29	27.0	31.0	16.0
30–34	14.8	17.5	7.8
Maternal education			
<Ninth grade	2.2	2.0	2.7
Some high school	18.5	15.2	27.5
Completed high school	34.5	33.0	38.5
Some college	22.7	23.5	20.5
Completed college	22.0	26.2	10.7
Not married	37.8	23.0	77.6
Reported tobacco use	14.2	17.0	6.7
Linked to a subsequent birth	62.2	62.0	63.0

Table 3. Crude outcome rates among 1990–2000 North Carolina first births to women <35 years of age, by linking status[a] and race/ethnicity

	All		*Non-Hispanic white*		*Non-Hispanic black*	
Outcome	*Unlinked* N *(percent)*	*Linked* N *(percent)*	*Unlinked* N *(percent)*	*Linked* N *(percent)*	*Unlinked* N *(percent)*	*Linked* N *(percent)*
Total births	161,045 (100.0)	265,214 (100.0)	118,242 (100.0)	192,493 (100.0)	42,803 (100.0)	72,721 (100.0)
PTB (<37 weeks gestation)	17,638 (11.0)	26,151 (9.9)	11,184 (9.5)	16,021 (8.3)	6,454 (15.1)	10,130 (13.9)
Late PTB (34–36 weeks gestation)	12,159 (7.6)	18,965 (7.2)	8,150 (6.9)	12,246 (6.4)	4,009 (9.4)	6,719 (9.2)
Very PTB (<34 weeks gestation)	5,479 (3.4)	7,186 (2.7)	3,034 (2.6)	3,775 (2.0)	2,445 (5.7)	3,411 (4.7)
Birthweight <2,500 grams	13,560 (8.4)	19,154 (7.2)	8,101 (6.9)	10,933 (5.7)	5,459 (12.8)	8,221 (11.3)
LBW (1,500–2,499 grams)	10,895 (6.8)	16,075 (6.1)	6,683 (5.7)	9,372 (4.9)	4,212 (9.8)	6,703 (9.2)
Very LBW (<1,500 grams)	2,665 (1.7)	3,079 (1.2)	1,418 (1.2)	1,561 (0.8)	1,247 (2.9)	1,518 (2.1)

[a]"Linked" refers to a first birth for which a subsequent birth to the same woman could be found; "unlinked" refers to a first birth for which a subsequent birth to the same woman could not be found.

PTB = preterm birth

LBW = low birthweight

Table 4. Age-adjusted odds ratios for outcomes among 1990–2000 North Carolina first births to women <35 years of age not linked to a second birth compared with those linked to a known second birth, overall and stratified by reported maternal medical complications

	All	*Non-Hispanic white*	*Non-Hispanic black*
Outcome	*AOR (95% CI)*	*AOR (95% CI)*	*AOR (95% CI)*
All first births			
PTB (<37 weeks gestation)	1.16 (1.14, 1.18)	1.16 (1.13, 1.19)	1.13 (1.09, 1.17)
Late PTB (34–36 weeks gestation)	1.10 (1.07, 1.12)	1.10 (1.07, 1.13)	1.07 (1.02, 1.11)
Very PTB (<34 weeks gestation)	1.32 (1.28, 1.37)	1.34 (1.28, 1.41)	1.23 (1.17, 1.30)
Birthweight <2,500 grams	1.23 (1.20, 1.26)	1.24 (1.21, 1.28)	1.14 (1.10, 1.19)
LBW (1,500–2,499 grams)	1.18 (1.15, 1.21)	1.20 (1.16, 1.24)	1.10 (1.06, 1.15)
Very LBW (<1,500 grams)	1.47 (1.40, 1.55)	1.51 (1.40, 1.62)	1.31 (1.22, 1.42)
First births with no reported maternal medical complications			
PTB (<37 weeks gestation)	1.10 (1.07, 1.13)	1.10 (1.07, 1.14)	1.07 (1.02, 1.12)
Late PTB (34–36 weeks gestation)	1.05 (1.02, 1.09)	1.06 (1.03, 1.11)	1.02 (0.97, 1.08)
Very PTB (<34 weeks gestation)	1.23 (1.17, 1.30)	1.25 (1.17, 1.34)	1.16 (1.08, 1.26)
Birthweight <2,500 grams	1.17 (1.13, 1.21)	1.18 (1.13, 1.23)	1.11 (1.05, 1.17)
LBW (1,500–2,499 grams)	1.14 (1.10, 1.18)	1.15 (1.10, 1.20)	1.08 (1.02, 1.15)
Very LBW (<1,500 grams)	1.35 (1.24, 1.47)	1.38 (1.23, 1.54)	1.23 (1.08, 1.39)
First births with any reported maternal medical complications			
PTB (<37 weeks gestation)	1.22 (1.18, 1.26)	1.21 (1.16, 1.26)	1.20 (1.14, 1.27)
Late PTB (34–36 weeks gestation)	1.14 (1.09, 1.18)	1.13 (1.08, 1.18)	1.14 (1.06, 1.22)
Very PTB (<34 weeks gestation)	1.37 (1.30, 1.44)	1.39 (1.29, 1.49)	1.28 (1.19, 1.39)
Birthweight <2,500 grams	1.26 (1.22, 1.31)	1.28 (1.22, 1.34)	1.17 (1.11, 1.24)
LBW (1,500–2,499 grams)	1.19 (1.15, 1.24)	1.22 (1.16, 1.28)	1.11 (1.04, 1.18)
Very LBW (<1,500 grams)	1.50 (1.40, 1.61)	1.54 (1.40, 1.69)	1.35 (1.22, 1.50)

AOR = adjusted odds ratio

CI = confidence interval

PTB = preterm birth

LBW = low birthweight

Table 5. Conditional probability and crude hazard ratio of a subsequent pregnancy by time since first birth among second births occurring in North Carolina in 1990–2007 and linked to a first birth in 1990–2000, with maternal age <35 years at first delivery, stratified by maternal age at first delivery and history of PTB

	Probability (percent) of second birth within time period											
	15–19 years of age		*20–24 years of age*		*25–29 years of age*		*30–34 years of age*		*Crude hazard ratio PTB vs. full-term first birth*			
Number of years since first birth	*Full-term birth*	*PTB*	*Full-term birth*	*PTB*	*Full-term birth*	*PTB*	*Full-term birth*	*PTB*	*15–19 years of age*	*20–24 years of age*	*25–29 years of age*	*30–34 years of age*
<1	14.2	16.2	9.7	10.6	8.1	8.1	8.2	7.4	1.14	1.09	1.00	0.90
1–2	19.1	18.8	15.1	13.7	19.3	15.5	20.2	15.1	0.98	0.91	0.81	0.75
2–3	17.0	16.0	14.2	12.2	18.7	15.3	17.2	12.9	0.94	0.85	0.82	0.75
3–4	14.9	13.9	12.0	10.5	13.9	11.9	10.9	8.3	0.93	0.87	0.85	0.76
4–5	12.8	12.1	9.6	9.3	9.9	8.8	6.5	5.6	0.95	0.97	0.89	0.87
Within 5	57.3	56.7	47.7	45.0	53.2	47.2	49.5	40.8	0.99	0.94	0.89	0.82

PTB = preterm birth

DISCUSSION

Our analyses suggest that women experiencing an adverse outcome in their first birth are less likely to have a second birth within five years than women with healthy infants born at ≥37 weeks gestation, and that this trend leads to subsequent overestimation of the risk associated with nulliparity alone. Among nulliparous women who we were unable to link to a second birth, rates of poor pregnancy outcomes (PTB, VPTB, LBW, and VLBW) were all higher compared with linked women. Non-linkage was higher and, among those who were linked to a second birth, the time to recorded subsequent birth was longer in women with infants born at younger gestational ages and/or lower birthweights. The risk of non-linkage was highest in women with both medical complications and more severe adverse perinatal outcomes, suggesting that both maternal and neonatal outcomes influenced the probability of a second birth.

Table 6. Hazard ratio for second birth within 60 months of first birth, stratified by gestational age and birthweight category of first birth,[a] among all second births occurring in North Carolina in 1990–2007 linked to a first birth in 1990–2000 and restricted to women <35 years of age at first birth

Outcome of first birth	*Hazard ratio (95% CI)*
Gestational age	
Full-term birth (≥37 weeks gestation)	1.00
PTB (<37 weeks gestation)	0.92 (0.91, 0.93)
Late PTB (34–36 weeks gestation)	0.95 (0.93, 0.96)
Very PTB (<34 weeks gestation)	0.86 (0.84, 0.88)
Birthweight	
Birthweight ≥2,500 grams	1.00
Birthweight <2,500 grams	0.90 (0.89, 0.92)
LBW (1,500–2,499 grams)	0.92 (0.90, 0.94)
Very LBW (<1,500 grams)	0.83 (0.80, 0.86)

[a]Adjusted for maternal age at first birth, race/ethnicity, and age-race/ethnicity interaction

CI = confidence interval

PTB = preterm birth

LBW = low birthweight

Limitations

This study was subject to several limitations. For one, there was a higher probability of birth within the first year after delivery among women in the youngest age groups. Younger women with PTB may be more likely to have shorter interpregnancy intervals.[29] There are a variety of possible explanations for this occurrence, including higher fecundity, lower use of effective contraception, or higher rates of VPTB/VLBW and subsequent higher neonatal and infant mortality among younger women. We were unable to estimate the potential impact of differential rates of spontaneous or induced abortion, or of stillbirth, in women based on a history of PTB in the first birth on these estimates. As pregnancies with these outcomes are not typically included in either the numerator or denominator of calculations of preterm rates, this inability to estimate would not substantially affect our estimates of differential live birth rates on estimates of RR of PTB. In the case of stillbirth, although PTB is associated with an increased risk of stillbirth,[30] the baseline low risk of stillbirth means that the absolute number of "missed" outcomes because of failure to capture stillbirths was likely too small to have a substantive effect on our findings.

Additionally, some of the women in the unlinked category may have had a subsequent birth that we were not able to find. If it is true that women who have more than one birth are less likely to experience adverse pregnancy outcomes in the first birth (as our data suggest), then the inclusion of some women who actually had second births in the unlinked category would have caused the rates of outcomes among unlinked first births in this analysis to be reduced from the true values. Thus, the significant differences we found between outcome rates among unlinked vs. linked births would likely be even larger if we were able to find some of the missing subsequent second births.

Finally, our findings would themselves be biased if women with adverse outcomes in the first birth were more likely to be unlinked because of factors such as relocation out of state rather than differential rates of second birth. Residential mobility during pregnancy was relatively low,[31] but there are no recent U.S. data on the effect of chronic illness in either mothers or infants on residential mobility.[32]

CONCLUSIONS

Previous studies suggest that nulliparous women are at higher risk for adverse birth outcomes compared with multiparous women. Our results suggest that some of the observed association between nulliparity and certain adverse outcomes may be overestimated; this finding is consistent with the only recent large study to control for potential confounders associated with nulliparity, which found no independent effect after adjustment.[33] If women with known and unknown risk factors for adverse outcomes are less likely to have a second birth after a first birth marked by an adverse outcome, then the prevalence of those risk factors will be lower in women having two or more births, lowering the absolute incidence of adverse outcomes and falsely elevating the estimated association based on parity alone. More importantly, overestimation of the association between parity and PTB leads to underestimated risk associated with a history of PTB, which is presumably due to the presence of causal factors present in both pregnancies.

Although both the observed difference in subsequent birth rates and the modeled impact on RRs were fairly small, these findings have clinical and public health implications. First, they suggest that further research into causal mechanisms for PTB/LBW associated solely with nulliparity, rather than with conditions that are more common in nulliparous women, is unlikely to have a major impact. Second, depending on the study design and sample size, failure to account for this selection bias might lead to underestimation of a potentially important association, particularly a common exposure with a small but significant increased risk, which could have a large attributable proportion. Finally, these results emphasize that, particularly for idiopathic PTB, factors such as nulliparity, which is unique to a single pregnancy, may be less important than genetic, social, environmental, or other exposures that are present in both first and subsequent pregnancies.

Table 7. Simulation results showing calculated RRs for PTB in first pregnancy compared with second pregnancy, and for PTB in second pregnancy given a history of PTB in first pregnancy[a]

	True RR[b]=1.5		*True RR[b]=1.8*		*True RR[b]=2.0*	
Hazard ratio for second birth if first birth was PTB	*Calculated RR for PTB in first pregnancy compared with second pregnancy*	*Calculated RR for PTB in second pregnancy given history of PTB in first pregnancy*	*Calculated RR for PTB in first pregnancy compared with second pregnancy*	*Calculated RR for PTB in second pregnancy given history of PTB in first pregnancy*	*Calculated RR for PTB in first pregnancy compared with second pregnancy*	*Calculated RR for PTB in second pregnancy given history of PTB in first pregnancy*
1.0	1.000[c]	1.50[c]	1.000[c]	1.80[c]	1.000[c]	2.00[c]
0.9	1.004	1.38	1.006	1.66	1.008	1.84
0.8	1.008	1.26	1.012	1.51	1.016	1.68

[a]Overestimation of the risk of PTB in first pregnancies and underestimation of the risk associated with PTB increase as the true RR of PTB associated with a history of PTB increases, and as the likelihood of a second pregnancy after a first PTB decreases.

[b]For PTB in second pregnancy given a history of PTB in first pregnancy. "True" parameter values are those used in the model; "calculated" parameter values are those calculated from the model results when the hazard ratio and RR associated with a history of PTB are varied.

[c]Calculated RR = true RR when hazard ratio = 1.0.

RR = relative risk

PTB = preterm birth

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REFERENCES

1. Hack M, Klein NK, Taylor HG. Long-term developmental outcomes of low birth weight infants. Future Child 1995;5:176-96.
2. Avchen RN, Scott KG, Mason CA. Birth weight and school-age disabilities: a population-based study. Am J Epidemiol 2001;154:895-901.
3. Crofts BJ, King R, Johnson A. The contribution of low birth weight to severe vision loss in a geographically defined population. Br J Ophthalmol 1998;82:9-13.
4. Doussard-Roosevelt JA, Porges SW, Scanlon JW, Alemi B, Scanlon KB. Vagal regulation of heart rate in the prediction of developmental outcome for very low birth weight preterm infants. Child Dev 1997;68:173-86.
5. Kuban KC, Leviton A. Cerebral palsy. N Engl J Med 1994;330:188-95.
6. Lemons JA, Bauer CR, Oh W, Korones SB, Papile LA, Stoll BJ, et al. Very low birth weight outcomes of the National Institute of Child Health and Human Development Neonatal Research Network, January 1995 through December 1996. Pediatrics 2001;107:e1.
7. Lorenz JM, Wooliever DE, Jetton JR, Paneth N. A quantitative review of mortality and developmental disability in extremely premature newborns. Arch Pediatr Adolesc Med 1998;152:425-35.
8. Ment LR, Vohr B, Allan W, Westerveld M, Katz KH, Schneider KC, et al. The etiology and outcome of cerebral ventriculomegaly at term in very low birth weight preterm infants. Pediatrics 1999;104(2 Pt 1):243-8.
9. Resnick MB, Gueorguieva RV, Carter RL, Ariet M, Sun Y, Roth J, et al. The impact of low birth weight, perinatal conditions, and sociodemographic factors on educational outcome in kindergarten. Pediatrics 1999;104:e74.
10. Ross G, Lipper EG, Auld PA. Social competence and behavior problems in premature children at school age. Pediatrics 1990;86:391-7.
11. Saigal S, Hoult LA, Streiner DL, Stoskopf BL, Rosenbaum PL. School difficulties at adolescence in a regional cohort of children who were extremely low birth weight. Pediatrics 2000;105:325-31.
12. Weiss JL, Malone FD, Emig D, Ball RH, Nyberg DA, Comstock CH, et al. Obesity, obstetric complications and cesarean delivery rate—a population-based screening study. Am J Obstet Gynecol 2004;190:1091-7.
13. Osmond C, Barker DJ, Winter PD, Fall CH, Simmonds SJ. Early growth and death from cardiovascular disease in women. BMJ 1993;307:1519-24.
14. Barker DJ, Martyn CN, Osmond C, Hales CN, Fall CH. Growth in utero and serum cholesterol concentrations in adult life. BMJ 1993;307:1524-7.
15. Behrman RE, Butler AS. Preterm birth: causes, consequences, and prevention. Washington: National Academies Press; 2006.
16. National Center for Health Statistics (US). Natality public use files 1990–2006. Hyattsville (MD): Centers for Disease Control and Prevention (US), NCHS, Division of Vital Statistics; 2006.
17. Shah PS. Parity and low birth weight and preterm birth: a systematic review and meta-analyses. Acta Obstet Gynecol Scand 2010;89:862-75.
18. Dodd JM, Flenady V, Cinotta R, Crowther CA. Prenatal administration of progesterone for preventing preterm birth in women considered to be at risk of preterm birth. Cochrane Database Syst Rev 2006;1:CD004947.
19. Myers ER, McCrory DC, Mills AA, Price TM, Swamy GK, Tantibhedhyangkul J, et al. Effectiveness of assisted reproductive technology. Rockville (MD): Department of Health and Human Services (US), Agency for Healthcare Research and Quality; 2008.
20. Shrier I, Platt RW. Reducing bias through directed acyclic graphs. BMC Med Res Methodol 2008;8:70.
21. Greenland S, Pearl J, Robins JM. Causal diagrams for epidemiologic research. Epidemiology 1999;10:37-48.
22. Hernan MA, Hernandez-Diaz S, Robins JM. A structural approach to selection bias. Epidemiology 2004;15:615-25.
23. SAS Institute, Inc. SAS®: Version 9.2. Cary (NC): SAS Institute, Inc.; 2009.
24. Sonnenberg FA, Beck JR. Markov models in medical decision-making: a practical guide. Med Decis Making 1993;13:322-38.
25. TreeAge Software, Inc. TreeAge Pro 2009. Williamstown (MA): TreeAge Software, Inc.; 2009.
26. Iams JD, Berghella V. Care for women with prior preterm birth. Am J Obstet Gynecol 2010;203:89-100.
27. Chandra A, Martinez GM, Mosher WD, Abma JC, Jones J. Fertility, family planning, and reproductive health of U.S. women: data from the 2002 National Survey of Family Growth. Vital Health Stat 2005;23:1-160.
28. Census Bureau (US). Census 2000 summary file 3. Washington: Census Bureau; 2003.
29. Smith GC, Pell JP, Dobbie R. Interpregnancy interval and risk of preterm birth and neonatal death: retrospective cohort study [published erratum appears in BMJ 2003;327:851]. BMJ 2003;327:313.
30. Reddy UM, Laughon SK, Sun L, Troendle J, Willinger M, Zhang J. Prepregnancy risk factors for antepartum stillbirth in the United States. Obstet Gynecol 2010;116:1119-26.
31. Chen L, Bell EM, Caton AR, Druschel CM, Lin S. Residential mobility during pregnancy and the potential for ambient air pollution exposure misclassification. Environ Res 2010;110:162-8.
32. Halliday TJ, Kimmitt MC. Selective migration and health in the USA, 1984–93. Popul Stud (Camb) 2008;62:321-34.
33. Ananth CV, Peltier MR, Getahun D, Kirby RS, Vintzileos AM. Primiparity: an "intermediate" risk group for spontaneous and medically indicated preterm birth. J Matern Fetal Neonatal Med 2007;20:605-11.