Recurrence risk for preterm delivery

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OBJECTIVE: To estimate recurrence risk of preterm delivery in third births.

STUDY DESIGN: We conducted a population-based cohort study of Missouri mothers who delivered 3 consecutive singleton live births during 1989-1997. The recurrence risk was computed for 4 cohorts based on prior preterm delivery status and adjusted using Mantel-Haenszel stratified analysis.

RESULTS: The study population included 19,025 third births. The recurrence risk ranged from 42% (for women with 2 prior preterm deliveries), through 21% (term/preterm) and 13% (preterm/term), to 5% (term/term). The recurrence risk was highest (57%) for women with 2 prior very preterm deliveries (21-31 weeks) and lowest (33%) for those with 2 prior moderate preterm deliveries (32-36 weeks). The recurrence risk was less pronounced for women with 1 prior very or moderate preterm delivery.

CONCLUSION: These data show a strong association between prior preterm delivery and recurrence risk, which is affected by the frequency, order, and severity of prior preterm births.

Key words: gestational age at delivery, prematurity, preterm delivery, recurrence, risk factors

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Preterm delivery is the leading cause of morbidity and mortality in newborns.[1,2] Premature infants are prone to developmental and cognitive abnormalities. Infants who deliver at earlier gestations incur longer length of stays in the hospital and higher health care costs. Furthermore, the incidence of preterm delivery has significantly increased. In the United States, the risk for preterm birth (<37 weeks of gestation) steadily increased from 1992 to 2002.[3] In 2003, 12.1% of live births in the United States are born preterm. This concerning trend is a major public health issue and has led to the recommendation in Healthy People 2010 to decrease the risk of preterm delivery to less than 7.6% of live births.[4]

Previous studies have shown that prior preterm delivery confers an increased risk of recurrent preterm delivery in subsequent pregnancies.[4-21] Evidence from population-based studies regarding the risk of recurrent preterm delivery in multiparous women is largely limited to first and second pregnancies, with insufficient data relating to gestational age.[6,13,22] Little is known about the risk of a third preterm delivery. Bakketeig et al[23] found that the risk of preterm delivery in the third birth was similar to the risks for a second preterm delivery. They also demonstrated that the risk of a third preterm baby was high (28%) when the first and second births were preterm; however, that study did not determine if the risk of a third preterm baby was modified by gestational age of prior preterm deliveries. Other studies delineating the risk of recurrent preterm labor in third and subsequent pregnancies were limited to hospital-based studies, which may not be generalizable to the general population.[9,10,12,24]

Our objective was to evaluate the risk of preterm delivery in third birth and to determine if the risk is was modified by frequency, severity, and order of prior preterm deliveries. We hypothesized that a history of previous preterm delivery would confer an increased risk of preterm delivery in third birth and that the risk of preterm delivery would increase with decreasing gestational age of prior births.

Materials and Methods

We conducted a population-based cohort study of preterm births in multiparous women. The study population was obtained from the Missouri maternally linked cohort, which links sibling birth certificate data to common maternal identifiers.[25] The study population included all mothers who were residents of Missouri and who delivered 3 consecutive singleton live births (>20 weeks gestation) during 1989-1997. The study was restricted to this 9-year period because the clinical estimate of gestational age at delivery was first recorded on the Missouri birth certificate in 1989 and the last year of available data for this cohort was 1997. Mothers with multiple gestations were excluded from the study, to eliminate nonindependent events. Mothers with missing information regarding gestational age at delivery or other potential risk factors (listed below) were excluded from our sample.

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The study population was divided into 4 cohorts: (1) women with both first and second births preterm, (2) women with the second birth preterm, (3) women with the first birth preterm, and (4) women with neither birth preterm. This latter cohort was selected as the reference population. Preterm delivery was defined as a birth prior to 37 weeks gestation.

The study cohorts were further divided into subgroups by gestational age at delivery: very preterm (21-31 weeks), moderate preterm (32-36 weeks), and term (≥37 weeks).

There are 2 ways to determine gestational age from birth certificates: clinical estimate of gestational age and last menstrual period (LMP). Gestational age at delivery was based on the clinical estimate of gestational age, which is considered a more accurate covariate than "length of pregnancy," which is based on the date of last menses.

The clinical estimate of gestational age is a more precise measure because it includes LMP along with clinical factors, such as ultrasound. LMP is based solely on patient recall. Clinicians use the best clinical estimate of gestational age, rather than LMP alone, to determine the gestation of the newborn. Furthermore, the ranges of the 2 estimates differed. Clinical estimate ranged from 21-44 weeks, while LMP ranged from 17-52 weeks. Corrections to "clinical estimates" were requested of hospital birth certificate coordinators by the State of Missouri whenever "impossible data" were identified.

All data were obtained from birth certificates in the Missouri maternally linked cohort. Maternal risk factors included age, race, ethnicity, marital status, income, and cigarette and alcohol use during pregnancy. Maternal age was divided into 4 categories (<19, 19-31, 32-36, >36 years) to explore its potential nonlinear relationship with preterm delivery.[15,22,24] The standard racial and ethnic classification set forth by the 1997 US federal Office of Management and Budget (OMB) standards was not used. Instead, maternal race and ethnicity were combined and categorized as non-Hispanic black, non-Hispanic white, or other. Low income was defined as participation in Medicaid, the Women, Infants and Children program, or governmental food program.

Prior studies have identified other obstetrical and medical factors associated with preterm delivery, including prepregnancy body mass index, birth interval, prenatal care utilization, chronic hypertension, preeclampsia, insulin-dependent diabetes mellitus, and premature rupture of membrane.[1,10,14,17,18,26,27] Prenatal care utilization was determined using the Kotelchuck index[28], which combines the month when the prenatal care began and the number of prenatal visits and classifies care as inadequate, intermediate, adequate, or adequate plus. We assessed the frequency of preeclampsia and premature rupture of membranes for the 4 study cohorts, but did not include either risk factor as a potential confounder when evaluating the effect of prior preterm delivery on recurrence of preterm delivery because preterm premature rupture of membranes and severe preeclampsia lie in the causal pathway for preterm birth.

The percentages of the 4 study cohorts with specific demographic, medical, and obstetrical characteristics were computed. A chi-square test was used to assess differences between the 3 study cohorts and the reference cohort. The preterm delivery risk in the third birth (%) was computed for each study cohort. Relative risks (RR) were estimated to measure the strength of association between prior preterm delivery status and preterm delivery risk for the third birth. The RRs were calculated by dividing the preterm delivery risk in the third birth for each study cohort by the preterm delivery risk in the third birth for the reference cohort. The 95% confidence intervals (CI) were estimated to determine the precision of each RR. Mantel-Haenszel stratified analysis[29] was used to adjust the relative risk for potential confounders if the adjusted relative risk differed by 10% from the crude relative risk. All analyses were performed using SAS software (version 9.0; SAS Institute, Cary, NC).

This study was conducted at Saint Louis University. The Saint Louis University institutional review board classified this project as exempt under 45 CFR 46.101(b) of the US Department of Health and Human Services regulations for the protection of human subjects.

Results

Our study population consisted of 19,763 women from the Missouri maternally linked cohort who delivered 3 consecutive singleton live births during 1989-1997. We excluded 738 (3.7%) women with incomplete data; these were more likely to be non-Hispanic black, younger, single, low income, cigarette smokers, and to have shorter birth intervals, preeclampsia, premature rupture of membranes, and a history of preterm delivery. Many of these are risk factors for a recurrent preterm delivery.

The frequencies of demographic, obstetrical, and medical factors associated with preterm delivery are shown in Table 1 for all third births. Women with prior preterm deliveries (cohorts 1-3) were more likely to be non-Hispanic black, younger, single, low income, leaner, and to have shorter birth intervals and inadequate prenatal care during their third pregnancy. Women with 2 prior preterm deliveries (cohort 1) or their first delivery occurring preterm (cohort 3) were more likely to present with chronic hypertension or preeclampsia. Women with 2 prior preterm deliveries (cohort 1) or their second delivery occurring preterm (cohort 2) were more likely to experience premature rupture of membranes. All characteristics, except alcohol use, were significantly different ($P < .05$) among the 4 cohorts.

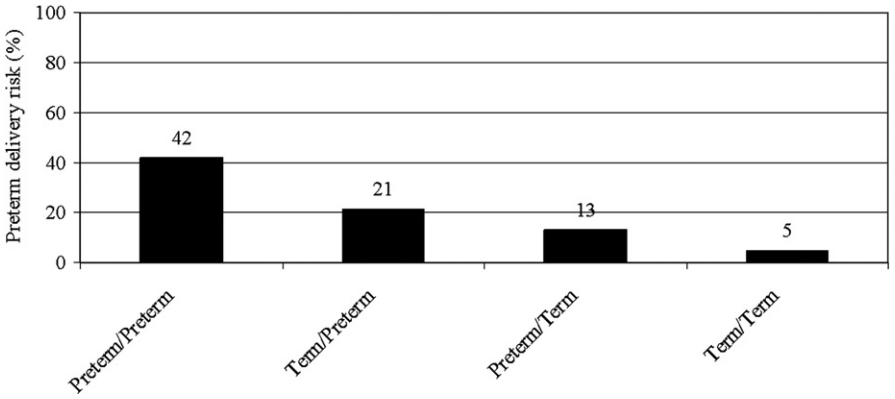
The preterm delivery risk for all third births among women with complete data (n = 19,025) was 6.7%. The preterm delivery risk was 42% in cohort 1 (preterm/preterm), 21% in cohort 2 (term/preterm), 13% in cohort 3 (preterm/term), and 5% in cohort 4 (term/term) (Figure 1). We then analyzed the data to account for missing information. We compared those mothers with missing information to those with complete data. The results did not change within

TABLE 1
Demographic, medical, and obstetric characteristics of the study population

	Cohort: Preterm Delivery Status of Birth 1/Birth 2			
	1: Preterm/Preterm (n = 305)	2: Term/Preterm (n = 1010)	3: Preterm/Term (n = 1084)	4: Term/Term (n = 16,626)
Demographic characteristics, %				
Maternal race/ethnicity				
non-Hispanic black	43	35	26	17
non-Hispanic white	55	63	72	81
other	2	1	2	2
Maternal age (years)				
14-18	14	11	9	5
19-31	74	78	74	75
32-36	9	9	14	17
37-44	3	2	2	3
Married	46	52	62	72
Low income	68	71	61	53
Cigarette use	21	30	23	23
Alcohol use	2	1.3	1.9	1.5
Medical and obstetric characteristics, %				
Body mass index (kg/m^2)				
<19.8	28	26	17	16
19.8-26.0	48	50	51	51
26.1-29.0	8	10	12	12
>29.1	16	13	21	21
Interval between 1st and 2nd births (months)				
<18	48	42	33	27
18-23	15	21	24	25
>23	37	37	43	47
Interval between 2nd and 3rd births (months)				
<18	30	31	22	23
18-23	21	20	22	21
>23	50	49	56	56
Prenatal care utilization				
inadequate	23	23	17	14
intermediate	13	12	13	15
adequate	22	35	42	50
adequate plus	42	31	29	20
Chronic hypertension	2.3	0.5	1.3	0.5
Preeclampsia	4.6	1.8	4.3	1.7
Insulin-dependent diabetes	0.7	0.7	1	0.4
Premature rupture of membranes	6.6	4.1	2.8	1.7

Chi-square *P* values < .02 for comparisons of frequency of characteristics, except alcohol use, by preterm delivery status.

FIGURE 1
Preterm delivery risk for third births in cohorts 1-4



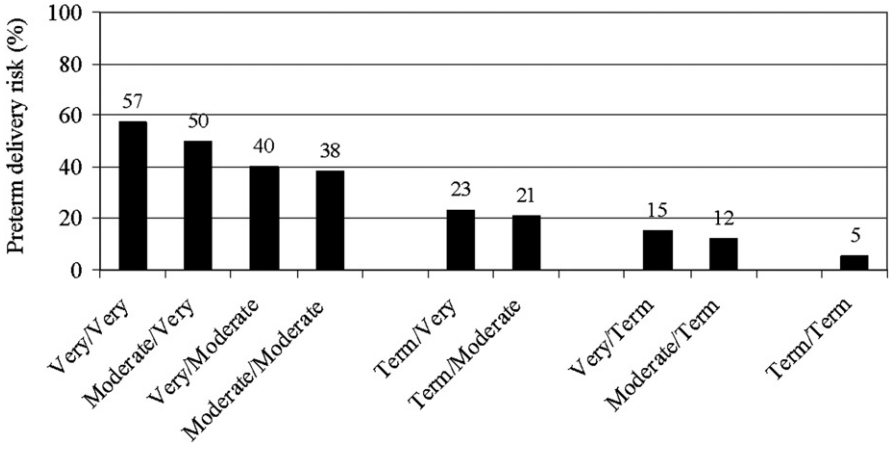
Prior preterm delivery status.

each of the 4 cohorts. The recurrence risk in each cohort remained the same. Thus, excluding mothers with missing information did not affect our results.

Within cohort 1, the preterm delivery risk for the third pregnancy was highest (57%) for those with 2 prior very preterm deliveries (21-31 weeks) and lowest (33%) for those with 2 prior moderate preterm deliveries (32-36 weeks). The preterm delivery risk was less pronounced for cohorts 2 and 3, in which only 1 prior delivery was either very (21-31 weeks) or moderate preterm (32-36 weeks), thus showing a dose-response relationship (Figure 2).

Women with 2 prior preterm deliveries had the highest relative risk (adjusted RR 6.7, 95% CI 5.7-7.7) for a subsequent preterm delivery, compared with women with no prior preterm deliveries (Table 2). The relative risk for a preterm delivery in the third birth was higher if the second birth was preterm (3.6, 3.1-4.1) than if the first birth was preterm (2.4, 2.1-2.9), compared with women with no prior preterm deliveries. A similar relationship was evident when prior preterm delivery was stratified by order and gestational age of the prior preterm deliveries. The highest relative risk (8.3, 6.0-11.6) for a subsequent preterm delivery occurred among women with 2 prior very preterm deliveries, whereas the relative risk was 6.3 (5.2-7.7) for women with 2 prior moderate preterm deliveries. The effect size was smaller for women with 1 prior preterm delivery but was also dependent upon the order and gestational age (very vs moderate) of the prior preterm delivery. All relative risks were adjusted for maternal race, ethnicity, and marital status, which were the only confounders to change the size of the crude relative risk by 10% or more.

FIGURE 2
Preterm delivery risk for third births in cohorts 1-4



Prior preterm delivery status by order and gestational age at delivery.

Comment

Our data show a strong association between prior preterm delivery and recurrence risk in the third birth. This association is affected by 3 risk factors: the frequency of prior preterm deliveries, the severity of preterm delivery as measured by the gestational age, and the order in which the prior preterm delivery occurred. Women with 2 prior preterm deliveries had the highest overall risk, 42%, for recurrent preterm delivery. This risk was inversely related to the gestational ages of their prior preterm births, ranging from 38 to 57%. The overall recurrence risk for women with 1 prior preterm delivery was less than half the magnitude of those with 2 prior preterm deliveries. Although this risk was higher for women with their second birth preterm (21%) than those with their first birth preterm (13%), the recurrence risk for either cohort appeared to be less affected by the gestational ages of the prior preterm delivery.

Bakketeig et al[23] reported similar, albeit lower, risks of preterm delivery for the second and third births and showed that the recurrence risk was high (28%) when the first and second births were preterm. In contrast to our analysis, their study did not determine if the risk of a third preterm infant was modified by gestational age at delivery.

Furthermore, we have shown that having 1 prior term delivery reduces the risk of preterm birth compared with cohort 1, with the greatest reducing effect being a term delivery in the most recent pregnancy. Moreover, 2 prior consecutive term deliveries confer an even lower risk of preterm birth in the third pregnancy (Figure 2).

Clinically, it seems reasonable that patients with recurrent preterm delivery

TABLE 2
Crude and adjusted relative risks for preterm delivery of third births by order and gestational age of prior preterm deliveries

Preterm delivery status of birth 1/birth 2	n	cRR	aRR*	95% CI
Cohort 1: preterm/preterm	305	8.6	6.7	5.7-7.7
very preterm/very preterm	30	11.7	8.3	6.0-11.6
moderate preterm/very preterm	36	10.3	7.3	5.2-10.2
very preterm/moderate preterm	60	8.3	6.2	4.5-8.6
moderate preterm/moderate preterm	179	7.9	6.3	5.2-7.7
Cohort 2: term/preterm	1,010	4.4	3.6	3.1-4.1
term/very preterm	148	4.8	4	3.0-5.4
term/moderate preterm	862	4.3	3.5	3.0-4.1
Cohort 3: preterm/term	1,084	2.7	2.4	2.1-2.9
very preterm/term	164	3.2	2.8	2.0-4.1
moderate preterm/term	920	2.6	2.4	2.0-2.8
Cohort 4: term/term	16,626	1	1	reference

aRR, adjusted relative risk; *CI*, confidence interval; *cRR*, crude relative risk; *n*, third births.

* Adjusted for maternal race, ethnicity, marital status.

have risk factors and biologic mechanisms that are less susceptible to modification than those with only 1 prior preterm birth. Meis et al.[30] showed, in a subset of women with prior spontaneous preterm birth, that recurrence might be prevented with progesterone therapy,[30] although the mechanism of action remains unclear. Mercer et al.[26] showed that patients with recurrent spontaneous preterm births are more likely to have lower body mass indices, shorter cervixes, and more advanced Bishop scores early in pregnancy than women with isolated spontaneous preterm birth. Consistent with these studies, our data indicate that these patients may be biological proxies for research about modifiable risk factors, the preventive mechanism of progesterone therapy, and understanding the contributions of body composition, uterine, cervical, and genetic predispositions.

Like all observational studies, our study has its strengths and limitations. Studies using birth certificate data are criticized for underreporting specific medical procedures and specific medical diagnoses. Nonetheless, they can be very useful for population trend analyses of demographic data. Although our preterm delivery risks were estimated for all Missouri residents during 1989-1997, our results may not be generalizable to other populations. The preterm delivery risk for Missouri (11.6%) was similar for all women in the United States (11.4%) in 1997, but state-specific risks ranged from 7.6% (Vermont) to 15.6% (Mississippi) for the same year.[3] The lower-than-expected preterm delivery risk of 6.7% for our study population may reflect the eligibility criteria, which excluded women with multiple gestations, births <20 weeks gestation, and stillbirths. Second, our cohort included women with 3 consecutive singleton live-births, but did not differentiate between women with or without prior pregnancy losses. Third, our gestational age at delivery estimates used to identify the frequency, severity, and order of prior preterm deliveries and the preterm delivery status for the third birth were based on birth certificate data. We cannot verify that all clinicians use the same method for estimating the gestational ages in our study population. Finally, our analysis was limited to information from birth certificate data, which prevented us from adjusting our relative risk estimates for other potential confounders, such as multiple first trimester losses, assisted reproductive technologies, subclinical intraamniotic infections, shortened cervical length, presence of fetal fibronectin, substance abuse, and domestic violence.

Despite these limitations, our results are population based (n ~ 17,000) and have epidemiologic significance. We showed a strong association between prior preterm delivery and recurrence risk in the third birth. This association was affected by the frequency, order, and severity of prior preterm deliveries. The significance of this study lies in the fields of maternal-fetal medicine and public health.

Our study has clinical implications for management. "At risk" patients are easily identified and should be encouraged to seek timely preventive obstetric care. Physicians may use evidence-based use of cerclage, progesterone therapy, or antibiotic therapy. Based on a given patient's reproductive history, physicians should consider special individualized counseling tailored to that patient's risk, see her more often (as indicated), and teach signs and symptoms appropriate to the risk for recurrent preterm delivery. Consultation and/or direct management by maternal-fetal medicine specialists is recommended. Moreover, to avoid delays in obstetric interventions, arrangements for timely patient access to obstetric care should be provided. The timely and appropriate use of antenatal ste-

roids, antibiotics, and tocolytic agents in conjunction with appropriate transfer to a tertiary care perinatal center may then optimize the outcome for a preterm infant.

Preterm delivery remains the leading cause of neonatal morbidity and mortality. With these data, clinicians should be better able to counsel mothers who have had prior preterm deliveries. Public health professionals may be better able to educate the public and make recommendations to clinicians, professional organizations, and policy makers regarding prematurity prevention and areas for future research. ■

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Discussion

Fredrik Broekhuizen, MD.

Members and guests of the Central Association: I thank you for the opportunity to discuss this paper.

I will try to approach this paper from 2 different angles. The first, a response as a practicing clinician: how do the author's findings change my approach to the prevention of preterm birth? The second, a response as a reviewer of the methodology used in this paper: what are the limitations of a vital statistics database in obstetrical research?

I was not surprised by the conclusion of this paper: The more prior preterm deliveries at an earlier gestational age, the higher the risk for a repeat preterm delivery, with risks ranging from 13 to 57%, dependent on history. The frequency of prior preterm deliveries, the severity of preterm delivery, and the order in which they occurred determined the risk. These findings are no surprise to a clinician, but do not translate into an innovative algorithm for the management of the patient at risk for preterm birth.

Our present understanding of preterm birth as multifactorial in origin with no

identifiable single prevention strategy for each risk factor has left us currently in practice with biological markers for risk, such as cervical length measurements or fetal fibronectin status, or the application of 17 hydroxyprogesterone as a prevention/reduction strategy without a clear understanding of its preventive action. This paper encourages further research in the quest to better identify clinical subtypes with different etiologies for preterm birth and possible etiology-directed interventions. It does not help the current practitioner at this time.

What about the limitations of an obstetrics vital statistics database for obstetrical research? This particular database—a Missouri cohort from 1989 to 1997—has been used by others, and in a recent article Ananth et al[1] concluded from the same database that medically induced preterm birth carried a similar risk in a future pregnancy for recurrent preterm birth as spontaneous preterm birth. That finding is actually more intriguing for the clinician than the finding in this paper, suggesting common etiologies at a genomic or proteomic level,[3] where research in markers for inflammation may provide clinical clues in the future.

Nevertheless, all vital statistics database studies have significant limitations and should be used only to generate hypotheses, not to test them. The advantage of a vital statistics database is its size and numbers. On the other hand, there is the lack of data validity, and both misclassification and missing data are common.

The authors pointed out several limitations to their study, but did not include a reference to the validity or lack thereof of the data in the dataset used and did not describe missing data explicitly and how they were accounted for in the design and analysis of the study. I would like the authors to comment.

Methods have been described to address and correct the issue of gestational age inaccuracy, which tends to occur most often with very low birthweight births. It is not clear from the manuscript if any methods were used? Can the authors clarify this point?

I congratulate the authors for their epidemiological approach to the subject and their thoughtful analysis.

A word of caution—and I have no doubt the authors realize this. It was recently pointed out by Dr Kenneth Schoendorf[2] from the National Center for Health Statistics that "although birth and death certificates ostensibly provide a multitude of clinically relevant data, the method of collection renders them unsuitable for research intended to directly evaluate or guide clinical practice."

This important fact is illustrated by the fundamentally flawed study using birth certificate data that linked prostaglandin use for induction with increased risk for uterine rupture in vaginal birth after cesarean patients.[4] This study impacted clinical and medicolegal practice immediately. The fact that since then 2 large observational studies using primary data have disputed these results has not undone the harm done in clinical and medicolegal practice.

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Ms Cooke (Closing).

My coauthors and I would like to thank the Central Association of Obstetricians and Gynecologists for this opportunity to present our work. Also, we would like to thank Dr. Fredrik Broekhuizen for his thoughtful discussion and the other reviewer for his or her constructive criticisms and insights. Our responses are incorporated into the revised full length manuscript.