Estimating Recurrence of Spontaneous Preterm Delivery

Michael S. Esplin, MD, Elizabeth O'Brien, PhD, Alison Fraser, MPH, Richard A. Kerber, PhD, Erin Clark, MD, Sara Ellis Simonsen, RN, MSPH, Calla Holmgren, MD, Geraldine P. Mineau, PhD, and Michael W. Varner, MD

OBJECTIVE: To identify factors associated with spontaneous preterm birth and to estimate the risk of its recurrence for the second through fourth births among women in Utah who had a first and any subsequent birth between 1989 and 2001, using a retrospective cohort study design.

METHODS: Utah state birth records were reviewed to identify women with a first live birth and at least one subsequent live birth from 1989 to 2001. Recurrence risks for spontaneous preterm birth were calculated for first through fourth births. Then all parties (1–12) and multiple maternal risk factors were used to estimate recurrence risks for pre-term birth outcomes by multinomial regression. Recurrence risks for early and late spontaneous preterm birth were calculated. Recurrence also was evaluated as the fraction attributable to previous spontaneous preterm birth. Using the identified factors, the sample was divided and the model was estimated for a subset of births (1989–1999); its predictive value was tested on the remaining births (2000–2001).

RESULTS: Women who experienced a spontaneous preterm birth before 34 weeks of gestation in their first or second live birth had the highest rate of recurrence. Spontaneous preterm birth before 34 weeks was the highest risk factor for recurrence of early spontaneous preterm birth (relative risk 13.56, 95% confidence interval 11.5–16.0), and, in general, risks were highest for recurrences of same gestational age outcomes.

CONCLUSION: A history of a live spontaneous birth before 34 weeks of gestation is a strong predictor of subsequent spontaneous preterm birth. A model of clinical risk factors may be used to identify women at increased risk for recurrent spontaneous preterm birth.
(Obstet Gynecol 2008;112:516–23)

LEVEL OF EVIDENCE: II

Spontaneous preterm birth is the leading cause of perinatal morbidity and mortality in nonanomalous newborns. Compared with neonates born at term, those born prematurely have a 40-fold increase in neonatal mortality[1,2] and are at significantly increased risk for major complications such as cerebral palsy, chronic respiratory illness, blindness, and deafness[3] Furthermore, long-term neurologic and developmental deficits have been identified in as many as 70% of children with very low (less than 800 grams) birth weight.[4] These complications are associated with billions of dollars in direct and indirect costs and unrealized human potential each year in the United States.

Several investigators have used clinical scoring systems to identify women at risk for spontaneous preterm birth.[5] Despite initial enthusiasm for these approaches, results have shown poor sensitivity and specificity in prospective evaluation.[6,7] However, historical factors such as a previous spontaneous preterm birth remain the most predictive of subsequent complications. An ideal predictive test would identify patients at risk for spontaneous preterm birth early in pregnancy, including the first, and carry little risk to the patient and fetus. The ability to precisely identify women at risk for spontaneous preterm birth would allow the development of effective ongoing surveillance and potential inter-

From the University of Utah Health Sciences Center, Department of Obstetrics and Gynecology; the University of Utah-Huntsman Cancer Institute; the University of Utah Department of Family and Preventive Medicine, Public Health Program; and the University of Utah-Huntsman Cancer Institute, Department of Oncological Sciences, Salt Lake City, Utah.

Partial support for the Utah Population Database is provided by Huntsman Cancer Foundation at the University of Utah, Salt Lake City, Utah.

Corresponding author: Michael S. Esplin, MD, Department of Obstetrics and Gynecology, 30 North 1900 East, Room 2B200, Salt Lake City, Utah 84132; e-mail: mesplin@hsc.utah.edu.

Financial Disclosure
The authors have no potential conflicts of interest to disclose.

ISSN: 0029-7844/08

vention while avoiding unnecessary treatments and expense.

In this study, we estimated the risk of spontaneous preterm birth and its recurrence among women who had a first plus at least one other live singleton birth recorded in Utah during the period 1989–2001. We identified maternal and fetal health factors associated with early (less than 34 weeks) or late (34 to 36 weeks) spontaneous preterm birth. We then used these factors to test a clinical model of spontaneous preterm birth risk and recurrence and evaluated the model's predictive capabilities.

MATERIALS AND METHODS

The Utah Population Database is a unique resource of linked records that includes birth, death, and other vital data for more than 6.4 million individuals and extensive pedigree information on many. We have used this data resource in previous studies of familial predisposition to complications of pregnancy, including preeclampsia, preterm delivery, cesarean section, and forceps delivery.[8–11] The protocol for this study and the use of the database were approved by the institutional review boards at the University of Utah Health Sciences Center and the Resource for Genetic Epidemiology.

From the Utah Population Database we identified women who had a first live birth and at least one subsequent live birth in Utah during the period 1989–2001. All clinical information came directly from state birth records that are linked annually to the Utah Population Database. In the state of Utah, maternal characteristics recorded on the birth certificate include age at delivery, height, weight, marital status, parity, use of substances such as tobacco, alcohol or other drugs, obstetric and medical history, plus maternal and neonatal complications at that birth. Maternal histories then were created by linking all records of births to the same mother together in correct sequence, including term births, fetal deaths where certified, multiple births, and other births involving "indicated" procedures.

The focus of this study was restricted to "spontaneous" preterm births, distinct from "indicated" births involving conditions such as preeclampsia, multiple gestations, or fetal complications because these frequently are managed by early labor induction or other procedures that affect gestational age. Thus, our analysis seeks predictors of "spontaneous" birth events–without induction or other "indicated" interventions–resulting in singleton live births from 20 to less than 37 weeks of gestation. As a general rule, gestational age was based on last menstrual period; however, to maintain the greatest accuracy, records for which the neonatal weight at delivery was less than 5% or more than 95% were further reviewed; if alternative evidence of concordant gestation for weight estimates were recorded (clinical gestation and gestation based on estimated due date), these were used. Extent of prenatal care was determined by the month that prenatal care was initiated.

To capture the burden of recurrent spontaneous preterm birth events, as well as the recurrent effects of particular maternal conditions on spontaneous preterm birth, we used multinomial logistic regression to estimate effects of 20 variables for two outcomes (Stata 8.0, StataCorp LP, College Station, TX): early spontaneous preterm birth (less than 34 weeks of gestation) and late spontaneous preterm birth (less than 37 weeks of gestation), compared with term birth (more than 36 weeks of gestation). Forward stepwise regression was used to establish a minimal set of risk factors significantly associated with spontaneous preterm birth from the very large number of maternal and fetal conditions recorded on birth records. Multinomial regression was used to analyze a final set of 20 variables, including maternal history indicators, for early and late spontaneous preterm birth outcomes. Here, early and late outcome groups overlap, in that spontaneous preterm births less than 34 weeks are included in outcomes less than 37 weeks. Births within a maternal history were not considered independent but rather repeated observations on the same individual. Standard errors were adjusted for clustering on mothers for this reason. Results of the multinomial regression analysis are reported as relative risks (RRs) according to stata's mlogit model (stata 8.0, StataCorp LP, College Station, TX).

Pair-wise recurrence risks of spontaneous preterm birth for parities one through four were estimated for both early and late preterm outcomes. All risk estimates pertain to spontaneous, singleton, live births, relative to having a term birth. Risk estimates are reported for each ordered pair and outcome, eg, first live birth compared with second, third, and fourth live births, second compared with third and fourth live births, and third compared with fourth live birth.

To estimate the proportion of spontaneous preterm births attributable to a history of spontaneous preterm birth, we computed the probability of causation [(OR−1)/OR] (OR, odds ratio) for each case of spontaneous preterm birth. The average probability of causation across all cases is an estimate of the population-attributable risk.[12]

Finally, we performed a basic test of the predictive value of our regression results by dividing the

cohort into subsets: births in years 1989 through 1999 (n=205,952) provided an estimation sample; births in years 2000 through 2001 (n=42,079) provided a validation sample. We fit the model on the estimation sample, the major portion of the cohort, then tested its predictive value on the validation sample, the final 2 years of birth outcomes information. Estimates of sensitivity (portion of true positives correctly classified) and specificity (portion of true negatives correctly classified) were calculated for various threshold values across the receiver operating characteristic space range, from 0 to 1. The area under the curve was calculated to demonstrate the difference between the estimated curve and a flat, 45-degree line, indicating the level of prediction by random classification.

RESULTS

There were a total of 544,325 deliveries in the state of Utah between January 1, 1989, and December 31, 2001. We identified 249,610 live singleton births during this period that met study criteria; these included 98,724 women who had their first parity and one or more subsequent births in the observation period. The quality of the data was very good: 96.5% of all women had complete, sequential information for parities one and two, 89.6% for parities one through three, and 81% for parities one through four. There were 3,657 early preterm deliveries (less than 34 week group) and 13,636 late preterm deliveries (34–36 week group). The average number of live births per participant during the study period, which was included in the analysis, was 2.6 (range of 2.0 to 12.0). The mean maternal age at the time of the first live birth was 22.6 years. The race of women included in the study was 94% white and 6% other. Hispanic ethnicity was identified by 8.4% of the population (see Table 1).

The overall crude rate of spontaneous preterm birth among live births included in the analysis was 11.3%. The pair-wise analysis shows the proportion of second, third, and fourth live birth outcomes compared with the first, parities three and four compared with two, and four compared with three (see Tables 2–4). Although every measure was taken to ensure that Tables 2–4 correctly specify all paired parities, fully continuous sequences cannot be inferred for every maternal history because some contain missing data points. For instance, any birth that did not occur in Utah is not included in our Utah birth records. This might occur if, for example, a particular maternal history recorded births one and three, but not two, so that only births one and three would be included in our records and in these comparisons. Additionally, births of multiples, fetal deaths, and induced preterm birth are not enumerated in the paired events in Tables 2–4. These tables also show how rapidly the number of birth events decline as parities progress beyond two.

Among women who had a full term first birth, 5.3% had a spontaneous preterm birth (early or late) at the second live parity, 6.8% at the third live parity, and 7.4% at the fourth live parity. The highest risk of recurrence was for early spontaneous preterm birth at the second parity after an early spontaneous preterm birth at first parity (RR 17.4) and a 35% recurrence of any (early or late) spontaneous preterm birth (Table 2). High recurrence risks also were shown at higher parities after an early spontaneous preterm birth outcome: the risk of early spontaneous preterm birth at third parities was very high after a second parity early spontaneous preterm birth (RR 32.4), with a 44% recurrence of any spontaneous preterm birth; at fourth parity the risk of early spontaneous preterm birth was high after a third parity early spontaneous preterm birth (RR 42.3), with a 52% recurrence of any spontaneous preterm birth. Overall, women who experienced an early spontaneous preterm birth were at much higher risk of recurrence at their next live birth compared with women who had a late premature birth, and much more so than those who had a term birth.

Thirteen maternal characteristics from birth records emerged as significant predictors of early or late spontaneous preterm birth in the study population. Of these, some were social and lifestyle related: level of education, marital status, tobacco use, prepregnancy body mass index, whether non-white, month prenatal care was initiated, and length of birth interval. The following biological factors also were included in the final model: maternal health histories of diabetes, cerclage, uterine bleeding, cardiac disease, chronic and pregnancy-related hypertension, and any record of a prior certified fetal death (stillborn infants at 20 weeks of gestation or more are recorded with a fetal death certificate in the state of Utah). To these 13 characteristics and conditions indicated on birth records, we added four variables to determine the effect of timing of maternal history effects on recurrence of spontaneous preterm birth. These four indicate whether the "last" birth of the maternal history was an early or late spontaneous preterm birth and whether any "prior" to the last was an early or late spontaneous preterm birth, where "last" and "prior" births are nonoverlapping sets. We also established the effects of biological conditions

Table 1. Characteristics of Women in the Study Cohort*

	Outcome			
	Less Than 34 wk	34–36 wk	Term	Total
Mean age, y				
Mother	24.2	24.6	24.9	
Father	27.2	27.4	27.7	
Married (%)	76.6	81.7	86.4	
Mo prenatal care initiated	2.5	2.6	2.6	
Education, y				
Mother	12.7	13.0	13.3	
Father	13.4	13.5	13.8	
Mothers' race/ethnicity (%)				
Caucasian	1.8	5.4	92.8	
Non-caucasian	2.3	6.1	91.7	
Hispanic	2.4	5.9	91.6	
Total	1.8	5.4	92.8	
Live singleton births				
Indicated	281	1,810	0	2,091
Not indicated	3,376	11,826	232,317	247,519
Total	3,657	13,636	232,317	249,610
Live singleton birth order				
First	1,791	5,329	91,604	98,724
Second	1,183	5,083	88,220	94,486
Third	477	2,189	36,225	38,891
Fourth	158	760	12,332	13,250
More than fourth	48	275	3,936	4,259
Total	3,657	13,636	232,317	249,610
Multiple births				
Indicated	55	232	0	287
Not indicated	933	1,699	1,593	4,225
Total				4,512
Certified fetal deaths				
Singleton fetal deaths	248	59	88	395
Multiple births with fetal death	82	11	7	100
Unclassifiable				6
				501

* Women in the study cohort (n = 98,724) all had a first live single on birth, and at least one subsequent (live singleton) birth, in Utah during the study period, 1989–2001. Among mothers in the study cohort, 94% are Caucasian, 6% are non-Caucasian, and 8.4% are self-reported as Hispanic. Maternal histories range from 2–12 live, singleton births (n = 249,610). Certified fetal deaths of singleton births (n = 395) are included in the multinominal regression analysis.

over maternal histories with reference to "last" and "prior" parities for early and late spontaneous preterm birth outcomes. Thus, a final set of 20 variables was analyzed using multinomial regression.

Results of a multinomial regression analysis for the 20 factors are given in Table 5. Effect estimates associated with spontaneous preterm birth outcomes are reported in Table 5 as RRs with associated 95% confidence intervals. Factors were drawn from birth records and included in the model if they were significantly positive or protective (by forward stepwise regression) for spontaneous preterm birth in this population. Table 5 shows that a last live birth at less than 34 weeks of gestation confers a high recurrence risk of early spontaneous preterm birth (RR 13.6) and an elevated risk of any spontaneous preterm birth (less than 37 weeks) (RR 5.6). A late spontaneous preterm birth at the last live birth also confers an elevated risk of early (RR 5.3) or any (RR 5.1) spontaneous preterm birth. The persistent risk of spontaneous preterm birth attributable to any history of a live premature birth is further captured in the risk effects of a prior spontaneous preterm birth. Excluding the last live birth, the risk of recurrence is still elevated for any (less than 37 weeks) premature live birth outcome (RR 2.9) with a prior early spontaneous preterm birth, as well as for an early (less than 34 weeks) premature outcome (RR 2.2) with a prior late spontaneous preterm birth.

In addition to a history of preterm outcomes, other factors associated with an increased risk of

Table 2. Outcome of First Live Birth Compared With Outcomes of Second, Third, and Fourth Live Births

	Subsequent Births								
	2nd Birth			3rd Birth			4th Birth		
1st Birth	SPTB(e)	SPTB(l)	Term	SPTB(e)	SPTB(l)	Term	SPTB(e)	SPTB(l)	Term
SPTB(e)	299 (17.9)	288 (17.3)	1,082 (64.7)	65 (8.9)	119 (16.3)	548 (74.9)	7 (3.2)	35 (15.8)	179 (81.0)
RR	17.39	4.05	0.65	6.14	3.03	0.80	1.83	2.78	0.87
95% CI	(15.33–19.68)	(3.56–4.59)	(0.63–0.74)	(4.69–7.93)	(2.48–3.69)	(0.72–0.90)	(0.73–3.84)	(1.89–3.99)	(0.71–1.07)
SPTB(l)	175 (3.9)	901 (19.9)	3,454 (76.2)	75 (3.8)	290 (14.8)	1,593 (81.4)	26 (3.8)	112 (16.5)	541 (79.7)
RR	3.75	4.66	0.80	2.65	2.76	0.87	2.21	2.90	0.86
95% CI	(3.21–4.36)	(4.34–5.01)	(0.77–0.84)	(2.08–3.34)	(2.44–3.12)	(0.82–0.93)	(1.44–3.27)	(2.35–3.54)	(0.77–0.96)
Term	906 (1.0)	3,750 (4.5)	83,308 (94.7)	530 (1.4)	1,965 (5.4)	34,184 (93.2)	218 (1.7)	718 (5.7)	11,674 (92.6)
RR	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
95% CI	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref

SPTB(e), early spontaneous preterm birth at less than 34 weeks of gestation; SPTB(l), late spontaneous preterm birth at 34–36 weeks of gestation; Term, birth at more than 36 weeks of gestation; RR, relative risk; CI, confidence interval.
Number and percentage of cases is given for each pair of outcomes.

preterm birth included a prior, but especially a last, fetal death, maternal tobacco use, and a history of several maternal health factors including diabetes, hypertension (both associated with and independent of pregnancy), cardiac disease, uterine bleeding, and cerclage. The contribution and significance of factors vary depending on whether they were estimated for early spontaneous preterm birth alone or for early and late spontaneous preterm birth combined.

Table 6 gives estimates for the portion of early and late spontaneous preterm births due to previous experience of spontaneous preterm birth. Approximately 14.7% of early and 14% of late outcomes are estimated to result from having had a previous spontaneous preterm birth.

When evaluated for an estimation sample (births in 1989 through 1999), our regression model in 20 factors (above) associated with increased risk for spontaneous preterm birth was applied to a validation sample (births occurring in 2000 through 2001). A basic test of predictive capability for early (less than 34 weeks) spontaneous preterm birth outcomes gave a sensitivity of 12%, a specificity of 98%, and a positive predictive value of 28% in Table 7.

DISCUSSION

We found that women who had an early spontaneous preterm birth (less than 34 weeks of gestation) were at greatest risk of a recurrence, especially for their next live birth. Although the tendency for gestational age and birth weight to repeat among births of a maternal history has been noted by others,[13] our study evaluated the risk of recurrent spontaneous preterm birth in consecutive second, third, and fourth live births. Despite the risk of recurrence in this population, the majority (65%) of women experienced a normal term delivery in their subsequent birth. Our rate of recurrence in the second live birth was similar to that

Table 3. Outcome of Second Live Birth Compared With Outcomes of Third and Fourth Live Births

	Subsequent Births					
	3rd Birth			4th Birth		
2nd Birth	SPTB(e)	SPTB(l)	Term	SPTB(e)	SPTB(l)	Term
SPTB(e)	207 (30.8)	88 (13.1)	378 (56.2)	26 (11.6)	33 (14.7)	166 (73.8)
RR	32.36	3.12	0.59	7.77	2.66	0.79
95% CI	(27.56–37.87)	(2.47–3.91)	(0.52–0.67)	(4.97–11.69)	(1.79–3.84)	(0.65–0.97)
SPTB(l)	96 (4.4)	716 (32.6)	1,383 (63.0)	37 (5.3)	129 (18.3)	537 (76.4)
RR	4.60	7.79	0.66	3.54	3.32	0.82
95% CI	(3.71–5.65)	(7.15–8.48)	(0.62–0.78)	(2.47–4.93)	(2.73–4.02)	(0.73–0.92)
Term	325 (0.9)	1,431 (4.2)	32,435 (94.9)	168 (1.5)	624 (5.5)	10,509 (93.0)
RR	1.00	1.00	1.00	1.00	1.00	1.00
95% CI	Ref	Ref	Ref	Ref	Ref	Ref

SPTB(e), early spontaneous preterm birth at less than 34 weeks of gestation; SPTB(l), late spontaneous preterm birth at 34–36 weeks of gestation; Term, birth at more than 36 weeks of gestation; RR, relative risk; CI, confidence interval.
Number and percentage of cases is given for each pair of outcomes.

Table 4. Outcome of Third Live Birth Compared With Outcome of Fourth Live Birth

	4th Birth		
3rd Birth	SPTB(e)	SPTB(l)	Term
SPTB(e)	97 (41.3)	26 (11.1)	112 (47.7)
RR	42.31	2.65	0.50
95% CI	(33.04–53.82)	(1.70–3.99)	(0.40–0.63)
SPTB(l)	26 (3.7)	278 (39.6)	398 (56.7)
RR	3.80	9.49	0.60
95% CI	(2.46–5.61)	(8.23–10.92)	(0.53–0.98)
Term	109 (1.0)	466 (4.2)	10,597 (94.9)
RR	1.00	1.00	1.00
95% CI	Ref	Ref	Ref

SPTB(e), early spontaneous preterm birth at less than 34 weeks of gestation; SPTB(l), late spontaneous preterm birth at 34–36 weeks of gestation; Term, birth at more than 36 weeks of gestation; RR, relative risk; CI, confidence interval.
Number and percentage of cases is given for each pair of outcomes.

described by Adams and colleagues, who found a recurrence rate of 19–26% in the second delivery in their population.

In our analysis, the level of prematurity in the last live birth is a strong predictor of recurrent spontaneous preterm birth. This finding confirms a report by Bakketeig and colleagues,[14] who also showed that an early spontaneous preterm birth between 23 and 27 weeks of gestation gave the highest risk of recurrence (RR range 2.4–3.1) for subsequent births. However, that study does not provide information regarding the proximity of a preterm delivery on later birth outcomes. The relative risk for an early spontaneous preterm birth in our study was high at parities two through four, particularly if the last live birth was an early spontaneous preterm birth (RR 17.4). Lower risks are shown, in general, for nonconsecutive parities (RR range 1.8–6.1). Thus, both the proximity and the severity of any previous spontaneous preterm birth must be considered when counseling patients about their risk for spontaneous preterm birth.

When complicating the last birth, diabetes, hypertension, and cardiac disease all contribute significantly to risk of spontaneous preterm birth, both early and late. Although misclassification of indicated preterm births as spontaneous preterm births may explain this association, it is also plausible that the underlying chronic disease may increase the risk of spontaneous preterm birth. Possible mechanisms include an increased propensity for inflammation/infection and stress-induced early activation of the hypothalamic-pituitary-adrenal axis. Further analyses are needed to examine more precisely the interactions between these features of maternal health and pregnancy outcomes. Together with the effects of proximity and severity, these findings are also consistent with the hypothesis that early and late spontaneous preterm births may have different etiologies.

Table 5. Multinomial Logistic Regression for Spontaneous Preterm Birth at Less Than 34 Weeks of Gestation and at Less Than 37 Weeks of Gestation*

Factor	SPTB Less Than 34 wk	SPTB Less Than 37 wk
Last birth less than 34 wk of gestation	13.56 (11.5–16.00)	5.64 (5.03–6.32)
Prior birth less than 34 wk of gestation	3.18 (2.20–4.60)	2.93 (2.41–3.55)
Last birth less than 37 wk of gestation	5.25 (4.59–6.00)	5.06 (4.72–5.43)
Prior birth less than 37 wk of gestation	2.25 (1.76–2.89)	2.74 (2.43–3.09)
Last birth resulted in fetal death	4.32 (2.32–8.02)	2.15 (1.36–3.40)
Prior birth resulted in fetal death	1.39 (1.25–1.54)	1.20 (1.14–1.26)
Married at time of delivery	0.61 (0.53–0.71)	0.78 (0.72–0.84)
Maternal education (y)	0.92 (0.89–0.94)	0.94 (0.93–0.95)
Last birth complicated by diabetes	1.89 (1.30–2.76)	1.95 (1.62–2.35)
Prior birth complicated by uterine bleeding	1.27 (0.96–1.70)†	1.21 (1.05–1.40)
Cerclage during last pregnancy	5.52 (2.22–13.70)	1.51 (.62–3.68)†
Any maternal tobacco use	1.73 (1.49–2.00)	1.36 (1.26–1.47)
Length of birth interval (mo)	0.99 (0.99–0.99)	0.99 (0.99–0.99)
Number of mo prenatal care received	0.89 (0.85–0.93)	0.97 (0.95–0.99)
Maternal prepregnancy body mass index (mean for all deliveries)	0.99 (0.98–1.00)	0.98 (0.97–0.99)
Non-white race	0.98 (0.88–1.08)†	1.14 (1.09–1.20)
History of cardiac disease	1.88 (0.55–6.43)†	1.94 (1.16–3.25)
Prior birth affected by chronic hypertension	0.63 (.08–4.60)†	2.07 (1.23–3.48)
Last birth affected by chronic hypertension	2.75 (1.59–4.76)	2.07 (1.50–2.86)
Last birth affected by pregnancy-related hypertension	1.50 (1.25–1.81)	1.43 (1.30–1.57)

SPTB, spontaneous preterm birth; last, the birth before the index birth; prior, all birth(s) before "last."
Results are given as Relative Risks (RRs) with 95% confidence interval, adjusted for nonindependent observations by clustering on mothers.
*All index births were live, singleton, spontaneous births, parity more than 1.
† Effect not significant for outcome.

Table 6. Cases and Attributable Cases Given for Each Spontaneous Preterm Birth Outcome Conditioned on Previous Outcomes

Previous Outcome		Outcome			
		SPTB Less Than 34 wk		SPTB Less Than 37 wk	
SPTB Less Than 34 wk	SPTB Less than 37 wk	Cases	AtbCases	Cases	AtbCases
No	No	3,008		1,200	
No	Yes	365	279	1,792	1,384
Yes	No	244	219	551	433
Yes	Yes	40	39	93	88
Total		3,657	14.7%	13,636	14.0%

SPTB, spontaneous preterm birth; AtbCases, attributable cases.
Attributable cases are those estimated to be due to previous spontaneous preterm birth. Overall, 14% of all spontaneous preterm births, whether early or late, are attributable to previous spontaneous preterm birth.

Several risk-scoring systems to predict spontaneous preterm birth have been reported in the literature. Creasy[5] suggests that a combination of clinical markers could predict the occurrence of spontaneous preterm birth with excellent sensitivity and specificity, but such a result has not been duplicated in subsequent prospective trials.[6,7] These systems have included previous spontaneous preterm birth as a major risk factor but do not include effects of proximity or severity of previous preterm outcomes in the assessment of risk. The current effort takes into account these as well as other weighted risk factors identified in this large statewide population and was able to identify recurrent spontaneous preterm birth with sensitivity and specificity similar to previously reported tests based on single biologic markers.

This study does have several limitations, including the relatively homogeneous population that has been studied. It is possible that the current clinical model may not perform as well in other, more heterogeneous populations. Another concern is the accuracy of data regarding gestational age as recorded on birth certificates. We addressed this limitation by reviewing multiple lines of evidence to resolve nonconcordant gestational ages and birth weights when possible. Also, it is difficult to fully evaluate all stillbirths, miscarriages, and pregnancy terminations from birth certificate data, so all index cases in the study were limited to live birth events. Certified fetal deaths were evaluated for their contributions to risk in the multinomial logistic regression analysis, even though they constitute some unknown portion of all fetal deaths. Including fetal deaths as predictors in the regression analysis revealed that a history of fetal death also increases the risk of spontaneous preterm birth, both early and late. As with any study based on maternal histories, comparisons are limited as parity increases because women conclude child bearing at different parities, and the decision when to do so may be conditioned by what outcomes they have experienced already. Our findings with respect to recurrence rates are in keeping with those of other large, population-based cohort studies.[13–16] This is reassuring; however, the approach must be tested in more populations, and we must draw from new data sources before true efficacy can be

Table 7. Multinomial Regression Model Fit to Estimation Sample (Births 1989–1999) and Used to Predict Early Spontaneous Preterm Birth (Less Than 34 Weeks of Gestation) in Validation Sample (Births 2000–2001)

	SPTB		No SPTB				
Cutoff	True Positive	False Negative	False Positive	True Negative	% Sensitivity	% Specificity	PPV (%)
0.01	373	301	10,085	31,320	55.3	75.6	3.8
0.02	199	475	3,266	38,139	29.5	92.1	5.7
0.05	86	588	771	40,634	12.7	98.1	10.0
0.10	43	631	631	41,166	6.4	99.4	15.2
0.20	12	662	31	41,374	1.8	99.9	27.9

SPTB, spontaneous preterm birth; PPV, positive predictive value.
PPV is the proportion of true positives out of all (true and false) positively classified early spontaneous preterm birth.
The area under the corresponding receiver operating characteristic curve=.72.
Sensitivity 100%, all true positives correctly classified; specificity100%, no false positives identified.

established. Lastly, there may be other confounders that were not controlled for in the multivariate analysis.

The size of this study population and the statistical approach used in this analysis better clarified the effects of maternal history on spontaneous preterm birth, and in this regard the study improves our ability to counsel women about spontaneous preterm birth recurrence risks. However, our approach shares the main limitation of all clinical-based prediction models that have gone before: it offers no better means of predicting spontaneous preterm birth for first births or any sporadic event in the absence of clinical indicators or recurring complications. It is clear from these studies that additional information from new data sources is required to advance the predictive model capabilities for all parities, including the first. As genomic and proteomic studies in particular help to better characterize the molecular boundaries of labor, we expect that significant progress also will be made in predicting preterm birth.[17] Indeed, the results of this analysis suggest designs for further molecular-level studies. This analysis clearly distinguishes women with respect to variation in risk of spontaneous preterm birth outcomes and recurrences; next it would be useful to conduct association studies to determine whether risk groups also vary at the molecular level in ways that indicate signature etiologies of pending preterm birth events.

REFERENCES

1. Goldenberg RL, Rouse DJ. Prevention of premature birth. N Engl J Med 1998;339:313–20.
2. Rush RW, Keirse MJ, Howat P, Baum JD, Anderson AB, Turnbull AC. Contribution of preterm delivery to perinatal mortality. Br Med J 1976;2:965–8.
3. European Community collaborative study of outcome of pregnancy between 22 and 28 weeks' gestation. Working Group on the Very Low Birthweight Infant. Lancet 1990;336:782–4.
4. Lipper EG, Ross GS, Auld PA, Glassman MB. Survival and outcome of infants weighing less than 800 grams at birth. Am J Obstet Gynecol 1990;163:146–50.
5. Creasy RK, Gummer BA, Liggins GC. System for predicting spontaneous preterm birth. Obstet Gynecol 1980;55:692–5.
6. Main DM, Gabbe SG. Risk scoring for preterm labor: where do we go from here? Am J Obstet Gynecol 1987;157:789–93.
7. Holbrook RH Jr, Laros RK Jr, Creasy RK. Evaluation of a risk-scoring system for prediction of preterm labor. Am J Perinatol 1989;6:62–8.
8. Porter TF, Fraser AM, Hunter CY, Ward RH, Varner MW. The risk of preterm birth across generations. Obstet Gynecol 1999;90:63–7.
9. Esplin MS, Fausett MB, Fraser A, Kerber R, Mineau G, Carrillo J, et al. Paternal and maternal components of the predisposition to preeclampsia. N Engl J Med 2001;344:867–72.
10. Varner MW, Fraser AM, Hunter CY, Corneli PS, Ward RH. The intergenerational predisposition to operative delivery. Obstet Gynecol 1996;87:905–11.
11. Aagaard-Tillery KM, Stoddard GJ, Holmgren C, Lacoursiere DY, Fraser A, Mineau GP, et al. Preeclampsia and subsequent risk of cancer in Utah. Am J Obstet Gynecol 2006;195:691–9.
12. Bruzzi P, Green SB, Byar DP, Brinton LA, Schairer C. Estimating the population attributable risk for multiple risk factors using case-control data. Am J Epidemiol 1985;122:904–14.
13. Adams MM, Elam-Evans LD, Wilson HG, Gilbertz DA. Rates of and factors associated with recurrence of preterm delivery. JAMA 2000;283:1591–6.
14. Bakketeig LS, Hoffman HJ, Harley EE. The tendency to repeat gestational age and birth weight in successive births. Am J Obstet Gynecol 1979;135:1086–103.
15. 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;341:943–8.
16. Winkvist A, Mogren I, Högberg U. Familial patterns in birth characteristics: impact on individual and population risks. Int J Epidemiol 1998;27:248–54.
17. Esplin MS, Varner MW. Genetic factors in preterm birth–the future. BJOG 2005;112:97–102.