The Risk of Preterm Birth Across Generations

T. FLINT PORTER, MD, ALISON M. FRASER, MPH, CHERI Y. HUNTER, RYK H. WARD, PhD, AND MICHAEL W. VARNER, MD

Objective: To examine the risk of preterm birth for mothers who themselves were born before term.

Methods: Data were taken from a linked data base of birth certificates composed of two cohorts: 1) a parental cohort of women born between 1947 and 1957 and 2) their offspring born between 1970 and 1992. "Preterm mothers" were women in the parental cohort who were born at less than 37 weeks' gestation. "Term mothers" were women in the parental cohort born at or after 38 weeks' gestation. Preterm mothers and term mothers were matched for birth year, county of birth, marital status, parity, and age. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated for the risk of preterm delivery in preterm mothers. Multiple logistic regression was used to assess the interaction of concomitant variables with the risk of premature delivery.

Results: The risk of preterm birth was significantly higher in preterm mothers than in term mothers (OR 1.18; 95% CI 1.02, 1.37). This risk increased as the gestational age at the mothers' birth decreased (less than 30 weeks': OR 2.38; 95% CI 1.37, 4.16). The interaction between maternal age and parity increased the risk of preterm delivery at less than 34 weeks in some age and parity strata.

Conclusion: An increased risk of preterm delivery exists for women who themselves were born before 37 weeks' gestation. This risk is inversely correlated with the maternal gestational age at birth and is influenced by maternal age and parity. (Obstet Gynecol 1997;90:63–7. © 1997 by The American College of Obstetricians and Gynecologists.)

Preterm birth and low birth weight (LBW) are among the leading causes of perinatal morbidity and mortality and remain among the most pressing problems facing obstetricians.[1] These factors are responsible for nearly 70% of all neonatal mortality, and as much as 85% after excluding deaths associated with congenital malformations.[2] Morbidity is related primarily to birth weight as a reflection of gestational age at delivery.[3,4] Unfortunately, many different pathologic mechanisms lead to preterm birth, making the evaluation of treatment and prevention strategies difficult.[5]

Most preterm birth prevention programs have attempted to identify women who are likely to deliver prematurely based on the presence of numerous risk factors,[6–9] including low socioeconomic status, maternal age less than 18 or greater than 40 years, increasing parity, race, previous preterm labor and delivery, multiple gestation, uterine malformations, and bacterial vaginosis.[5,10–12] The most important of these factors is a history of preterm delivery,[13–15] which may be influenced by genetic and environmental determinants.[16] However, the intergenerational predisposition to preterm birth has not been well established, with some investigators finding a significant effect[17–19] and others finding no effect.[20] Recent epidemiologic studies have indicated that the intrauterine environment has an important impact on the risk of adult morbidity, which may extend to reproductive outcomes as well.[21]

The objective of our study was to define the extent to which maternal predisposition influences the risk of preterm birth in women who themselves were born before term. In addition, we examined the interaction of maternal age and parity with the risk of preterm birth.

Materials and Methods

A linked data base of Utah birth certificates was established that encompasses two distinct cohorts: a cohort of offspring composed of all births occurring between 1970 and 1992 and a parental cohort composed of births occurring between 1947 and 1957. The time span for the offspring cohort was longer than for the parental cohort to include all births from women in the parental cohort during their reproductive years. Information from linked birth certificates was obtained according to a protocol described previously.[22] This project was approved by the University of Utah Institutional Review

From the Departments of Obstetrics and Gynecology and Human Genetics, University of Utah School of Medicine, Salt Lake City, Utah.

The authors would like to acknowledge the Geary family, whose gift helped support this research.

0029-7844/97/$17.00
PII S0029-7844(97)00215-9

Board in agreement with the Utah State Department of Health.

Women selected as "preterm mothers" were born between 1947 and 1957, were known to have had at least one live birth between 1970 and 1992, and were born before 37 weeks' gestation (36 completed weeks) or had a description of prematurity listed on their birth certificate.

Women selected as "term mothers" were born between 1947 and 1957, were known to have had at least one live birth between 1970 and 1992, and themselves were delivered after 38 weeks' gestation, with no mention of prematurity on the birth certificate. A ratio of two term mothers for every preterm mother was used. To avoid confounding, we matched term mothers to preterm mothers for maternal age (±1 year), marital status, birth year (±1 year), county in which the delivery occurred, and parity (±1). Counties were categorized as frontier, rural, or urban on the basis of the population density per square mile. The population densities for frontier, rural, and urban counties were 2.5, 14.7, and 416.2 persons per square mile, respectively. Other variables that may be associated with preterm delivery were not assessed (eg, smoking, alcohol use) because they were not recorded on birth certificates in 1947–1957. Only white women were included in this analysis.

Because of the inherent inaccuracy of birth certificate records, we took great care to limit the number of misclassifications of both preterm mothers and term mothers. Births less than 2500 g were excluded when the gestational age was listed as 38 weeks or greater. For those identified as "premature" but with delivery listed as more than 37 weeks' gestation, the record was checked manually to verify prematurity. Women delivered before 37 weeks by induction or cesarean were excluded from analysis. In addition, women selected as term mothers had no record of any sisters who were delivered prematurely, although some sisters may have been missed because of out-of-state birth.

The gestational age at delivery of the offspring was classified according to the gestational age at delivery of the mothers. Only singleton births were included. Simple odds ratios (ORs) and 95% confidence intervals (CIs) for premature delivery were calculated for preterm mothers versus term mothers. Stepwise multiple logistic regression analysis was used to identify potential concomitant variables that modified the intergenerational risk for preterm delivery. Conditional multiple logistic regression was used to assess the interaction of these variables with the risk of preterm birth. Statistical analysis was performed using the BMDP statistical program (Los Angeles, CA).

Table 1. Matched Variables for Preterm Mothers and Term Mothers

Variable	Preterm mothers (%) (n = 1405)	Term mothers (%) (n = 2781)
Age (y)		
≤17	3.2	3.0
18–19	11.5	11.6
20–24	34.1	34.5
25–29	23.9	23.9
≥30	27.3	27.0
Marital status		
Married	99.1	99.2
Unmarried	0.4	0.3
Unknown	0.6	0.5
Parity		
0	28.8	29.2
1	25.3	25.3
2	19.4	19.5
3	12.2	12.3
4+	13.5	13.0
Unknown	0.9	0.8
Geographic locale*		
Frontier	24.3	24.1
Rural	18.4	18.6
Urban	57.4	57.3

* Counties are categorized based on the population density per square mile. The population densities for frontier, rural, and urban counties are 2.5, 14.7, and 416.2 people per square mile, respectively.

Results

In the period 1947–1957, 29,247 white women were identified from Utah birth certificates who subsequently gave birth to 100,335 offspring in Utah during the period 1970–1992. There were 1487 women born between 1947 and 1957 who met the criteria as preterm mothers and gave birth to offspring in the 1970–1992 period. We were able to match 1353 of these to 2697 term mothers who were born after 38 weeks' gestation during the same period and who gave birth to offspring in the 1970–1992 period. In the offspring cohort, 4891 children were born to preterm mothers and 9585 children were born to term mothers. Demographics for the preterm mothers and term mothers are presented in Table 1. The groups were similar with regard to age, multiple births, marital status, parity, and geographic locale of birth.

Figure 1 presents the distribution of gestational ages at birth of the preterm mothers. Gestational age for this group ranged between 20 and 36 weeks, with most between 30 and 36 weeks (91%). The period between 36 and 37 weeks' gestation (36 completed weeks) represented more than 50% of preterm mothers. Figure 2 illustrates the distribution of gestational ages at birth of the offspring of both preterm mothers and term mothers. The distribution for preterm offspring is shifted to the left, toward younger gestations, compared with the

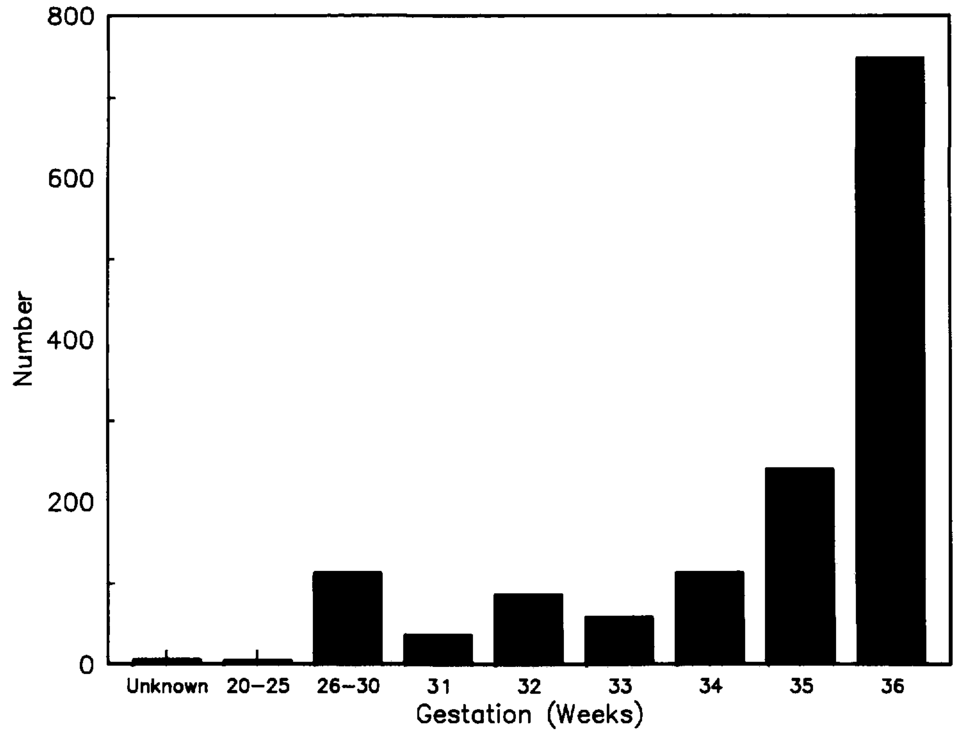

Figure 1. Distribution of the gestational ages of preterm mothers. Gestational ages for this group ranged between 20 and 36 weeks, with most between 30 and 36 weeks (91%). The period between 36 and 37 weeks' gestation (36 completed weeks) represents more than 50% of preterm mothers.

distribution for term offspring. For example, the frequency of preterm offspring is greater than that of term offspring (9.3% versus 4.4%; P = .025) at 36 completed weeks and less.

The preterm mothers' risk of preterm delivery stratified by their own gestational weeks at birth is presented in Table 2, with ORs and 95% CIs. As the preterm mothers' gestational ages at birth decreased, the OR for preterm delivery of their own offspring significantly increased, indicating an inverse relation

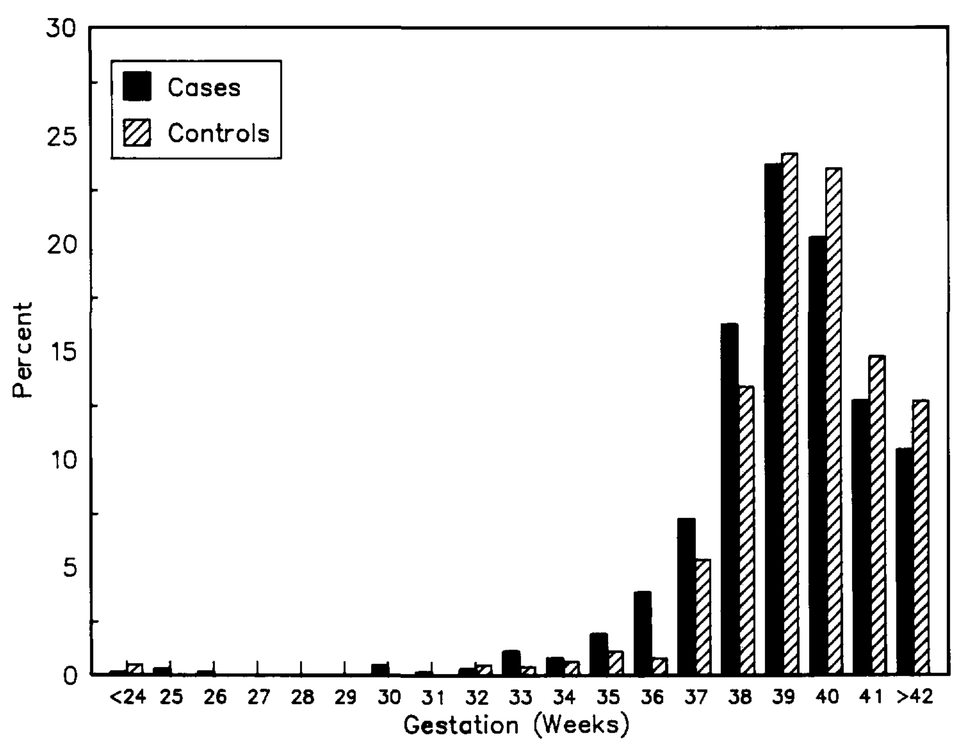

Figure 2. Distribution of the gestational ages of preterm offspring compared with term offspring. The distribution for preterm offspring is shifted to the left, toward younger gestations, compared with the distribution for term offspring. The frequency of preterm offspring is greater than that of term offspring (9.3% versus 4.4%; P = .025) at 36 completed weeks or less.

Table 2. Premature Birth for Preterm Mothers Stratified by Gestational Week at Birth

Gestational age (wk)	No. of offspring of preterm/term mothers	OR	95% CI
<37	773/13,340	1.18	1.02, 1.37
<36	375/5627	1.36	1.13, 1.64
<35	250/3480	1.47	1.17, 1.84
<34	173/2505	1.45	1.10, 1.96
<33	145/2035	1.68	1.25, 2.27
<32	94/1282	2.02	1.30, 2.94
<31	79/996	2.44	1.61, 3.78
<30	45/592	2.38	1.37, 4.16

OR = odds ratio; CI = confidence interval.

between gestational week and the risk for preterm birth. Statistical significance was achieved in all gestational week strata.

Multiple logistic regression was used to assess the interaction of variables with the intergenerational risk of preterm delivery. The following variables were selected for analysis based on inspection of the model: urban/rural, parity, and maternal age. Only parity and maternal age were found to approach statistical significance ($P = .05$ and $P = .06$, respectively). After including these variables, the overall fit of the model improved ($\chi^2 = 18$, degrees of freedom = 8, $P < .01$). The model indicated that increasing offspring-specific parity exacerbated the intergenerational risk, from 1.5 for a parity of 0 to 3.2 for a parity of 3. On the other hand, increasing age of the preterm mothers decreased the intergenerational risk, from 2.9 in women less than 17 years of age to 1.5 in women aged 25–29 years.

Discussion

This linked intergenerational data base, containing gestational age at birth as well as some other obstetric indices, has allowed a systematic study of the risk of preterm birth across generations. We found that women who themselves were born before 37 weeks' gestation had a significantly increased likelihood of preterm delivery of their own offspring. In addition, increased maternal age and parity had an effect on the subsequent risk of preterm delivery for those women born at younger gestational ages (less than 34 weeks). The cohort design of this study minimized ascertainment bias in this population, and although some may question the accuracy of birth certificate records, their objective nature eliminated recall bias.

Birth weight, reflecting the intrauterine environment, has been postulated to influence eventual adult health outcomes and also may exert influence on reproductive outcomes.[21] Several investigators have found strong familial tendencies in birth weight in successive pregnancies of the same mother[15,17,20,23] and across generations.[14,24–26] However, there has been less conclusive evidence about these influences on gestational age at birth.[17,18,20,25,26] An earlier study examining small for gestational age infants and/or preterm LBW infants concluded that a familial component exists for both fetal growth restriction and preterm birth.[17] Critics cited potential recall bias because the data were obtained by maternal self-report.[23] Later reports used actual birth registry data but contained limited information on the potentially important effects of parity, maternal age, and other obstetric factors.[18,20,25] Using Amish birth certificate records, one group found that preterm birth was related to maternal inbreeding, whereas LBW was related to paternal inbreeding.[18] In a later study of linked maternal and offspring birth records, investigators found that maternal birth weight correlated highly with offspring birth weight but exerted only minimal influence on the duration of gestation.[25] More recently, Magnus et al[20] failed to find a correlation between the gestational age at birth of mothers and their subsequent propensity to deliver preterm infants. This study limited both maternal age and parity by including only women in younger age groups and by excluding multiparas.

In contrast, we found that the maternal gestational age at birth influences the risk of preterm delivery. For women who themselves were born before 37 weeks' gestation, the risk of preterm delivery was increased nearly 20%. Their offspring were born at earlier gestations compared with the offspring of women who were born at 38 weeks' gestation or later. The risk of preterm birth increased as maternal gestational age at birth decreased, more than doubling for women born before 32 weeks. Furthermore, maternal age and parity exerted additional effects on the risk of preterm delivery. In our population, increasing parity was associated with an increased intergenerational risk for preterm delivery, whereas increasing maternal age of the preterm mothers was associated with a decreased risk.

Our findings may differ from those of previous reports for several reasons. We collected data from an intergenerational set of linked birth certificate records, thereby limiting the unreliability of maternal recall. We were able to include all offspring of preterm mothers and term mothers, allowing and adjusting for the influence that parity might have in determining risk. Furthermore, by including women in different age groups, we were able to assess the effect that maternal age may have on risk. Our preterm mothers and term mothers were matched for important demographic variables, thus limiting the role that environment may play in determining risk.[16,27] Finally, our study was large and inclusive, allowing an adequate number of preterm mothers matched to twice as many term mothers.

The inherent inaccuracies of birth certificates must be acknowledged, especially in those records from earlier time periods (parental cohort) when gestational age assessment was more difficult. We attempted to minimize the effects of misclassification by manually verifying records in which estimated gestational age and coded prematurity conflicted and by excluding those records in which birth weight was not appropriate for gestational age. In addition, we stratified groups in the aggregate rather than in mutually exclusive gestational age groups (eg, less than 36 weeks, less than 35 weeks versus 35–36 weeks, 34–35 weeks), as the latter would be less accurate. The impact of misclassification inaccuracies should be more pronounced at older gestational ages than at earlier gestational ages because it is more difficult to misclassify a 32-week infant as being term than a 36-week infant.

Although the mechanisms of the genetic involvement in preterm birth are poorly understood, efforts at testing women with a familial history of preterm birth for numerous markers are under way. Understanding the intergenerational risk for preterm birth will aid in this research by identifying families at the highest risk. Other research efforts in the prevention, prediction, and treatment of preterm labor also may be enhanced. Finally, this information may be of benefit in counseling women who have an increased risk of preterm labor based on their maternal history.

References

1. Institute of Medicine. Preventing low birth weight. Washington, DC: National Academy Press, 1985.
2. Berkowitz GS, Papiernik E. Epidemiology of preterm birth. Epidemiol Rev 1993;15:414–43.
3. Escobedo MB. Follow up of prematurely born infants. Clin Obstet Gynecol 1988;31:662–7.
4. Klein JM. Neonatal morbidity and mortality secondary to premature rupture of membranes. Obstet Gynecol Clin North Am 1992;19:265–80.
5. Savitz DA, Blackmore CA, Thorp JM. Epidemiologic characteristics of preterm delivery: Etiologic heterogeneity. Am J Obstet Gynecol 1991;164:467–71.
6. Main DM, Richardson DK, Hadley CB, Gabbe SG. Controlled trial of a preterm labor detection program: Efficacy and costs. Obstet Gynecol 1989;74:873–7.
7. Tucker JM, Goldenberg RL, Davis RO, Copper RL, Winkler CL, Hauth JC. Etiologies of preterm birth in an indigent population: Is prevention a logical expectation? Obstet Gynecol 1991;77:343–7.
8. Fangman JJ, Mark PM, Pratt L, Conway KK, Healey ML, Oswald JW, et al. Prematurity prevention programs: An analysis of successes and failures. Am J Obstet Gynecol 1994;170:744–50.
9. Creasy RK, Gummer BA, Liggins GC. System for predicting spontaneous preterm birth. Obstet Gynecol 1980;55:692–5.
10. Migone A, Emanuel I, Mueller B, Daling J, Little RE. Gestational duration and birthweight in white, black and mixed-race babies. Paediatr Perinat Epidemiol 1991;5:378–91.
11. MacGregor JA, French JI, Jones W, Milligan K, McKinney PJ, Patterson E, et al. Bacterial vaginosis is associated with prematurity and vaginal fluid mucinase and sialidase: Results of a controlled trial of clindamycin cream. Am J Obstet Gynecol 1994;170: 1048–60.
12. Mclean M, Walters WAW, Smith R. Prediction and early diagnosis of preterm labor: A critical review. Obstet Gynecol Surv 1993;48: 209–25.
13. Frederick J, Anderson ABM. Factors associated with spontaneous preterm birth. Br J Obstet Gynaecol 1976;83:342–50.
14. Carr-Hill RA, Hall M. The repetition of spontaneous preterm labor. Br J Obstet Gynaecol 1985;92:921–8.
15. 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.
16. Wildschut HIJ, Lumey LH, Lunt PW. Is preterm delivery genetically determined? Paediatr Perinat Epidemiol 1991;5:363–72.
17. Johnstone F, Inglis L. Familial trends in low birthweight. BMJ 1974;3:659–61.
18. Khoury MJ, Cohen BH. Genetic heterogeneity of prematurity and intrauterine growth retardation: Clues from the Old Order Amish. Am J Obstet Gynecol 1987;157:400–10.
19. Klebanoff MA, Meirik O, Berendes HW. Second-generation consequences of small for dates births. Pediatrics 1989;84:343–7.
20. Magnus P, Bakketeig LS, Skjaerven R. Correlations of birth weight and gestational age across generations. Ann Hum Biol 1993;20: 231–8.
21. Martyn CN, Barker DJ, Jespersen S, Greenwald S, Osmond C, Berry C. Growth in utero, adult blood pressure, and arterial compliance. Br Heart J 1995;73:116–21.
22. Varner MW, Fraser AM, Hunter CY, Corneli PS, Ward RK. The inter-generational predisposition to operative delivery. Obstet Gynecol 1996;87:905–11.
23. Little RE. Birthweight and gestational age: Mother's estimate compared with state and hospital records. Am J Public Health 1986;76:1350–1.
24. Klebanoff MA, Graubard BI, Kessel SS, Berendes HW. Low birthweight across generations. JAMA 1984;252:2423–7.
25. Klebanoff MA, Yip R. Influence of maternal birth weight on rate of fetal growth and duration of gestation. J Pediatr 1987;111:287–92.
26. Alberman E, Emanuel I, Filakti H, Evans SJ. The contrasting effects of parental birthweight and gestational age on the birthweight of offspring. Paediatr Perinat Epidemol 1992;6:134–44.
27. Little RE, Sing CF. Genetic and environmental influences on human birth weight. Am J Hum Genet 1987;40:512–26.

Address reprint requests to:
T. Flint Porter, MD
Department of Obstetrics and Gynecology
University of Utah School of Medicine
Room 2B 200, 50 North Medical Drive
Salt Lake City, UT 84132
E-mail: flint.porter@hsc.utah.edu

Received December 10, 1996.
Received in revised form March 13, 1997.
Accepted March 21, 1997.