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Editorials

Preterm Birth: From Prediction to Prevention

Preterm delivery—birth prior to 37 weeks of gestation—is among the strongest determinants of infant morbidity and mortality,[1–4] and it occurs in approximately 11% of US deliveries.[5] This rate is double or more that of many other developed nations,[6] and, in the United States, the rate in African-American infants (18.4% in 1992) is double that in White infants (9.1%).[5] For the very high risk condition of birth prior to 28 weeks, the ethnic disparity is nearly fourfold (1.9% vs 0.5% in 1992). Clearly, prevention of preterm birth and its consequences is an important public health goal.

From the perspective of infant health, averting preterm birth is primary prevention, intervening prior to birth to prevent morbidity in preterm infants is secondary prevention, and treatment of premature infants to minimize sequelae is tertiary prevention. Progress, however, has largely been confined to the latter 2 of these public health strategies. Secondary prevention encompasses such advances as the regionalization of perinatal and neonatal care (including maternal transport of impending preterm births) and antepartum steroid use to improve postnatal lung function. Tertiary prevention incorporates developments in neonatal intensive care such as ventilator management and surfactant treatment. It has had a substantial impact on infant mortality but has less notably affected rates of long-term sequelae. These secondary and tertiary prevention measures have lowered gestational age-specific neonatal mortality rates. As a consequence, however, an increasing number of preterm infants now survive who are at high risk of developmental disabilities.[7] Common sense argues for more attention to primary prevention through the lowering of preterm birth rates.

What types of information are needed to develop primary and secondary prevention approaches to preterm birth and its sequelae? For primary prevention, information is needed on the underlying biological causes of preterm birth and their personal and social antecedents. Unfortunately, our knowledge of the natural history of this complex and probably multi-determined health state is very limited.[8–10] As a consequence, primary prevention strategies such as social support programs[11] and home uterine monitoring for the detection and treatment of early contractions[12] have not yet proven successful.

For secondary prevention, on the other hand, information is needed on effective medical interventions that lower preterm infant morbidity and on sensitive and specific predictors of preterm birth that will allow these interventions to be applied in a timely manner to those who will benefit most.

Causation and prediction are distinct yet overlapping concepts. For successful prediction, attention is often paid to early clinical findings of the disease process. Examples include weight loss prior to cancer detection and right lower quadrant pain prior to appendix rupture. By contrast, causal models seek genuine antecedents of disease and must carefully distinguish these antecedents from factors that are consequences or epiphenomena of the disease process itself and from markers of the disease process. Predictors and markers are important elements in secondary prevention, but they are not necessarily true causes of disease. In this issue, Goldenberg et al.,[13] in referring in the title of their paper to prediction of preterm birth rather than to prevention, signal their understanding of this key distinction.

In the case of preterm birth, the distinction is perhaps more complex than in many other health states, especially since preterm birth is not in itself a disease in the usual sense but an aberration in the timing of a normal biological process. A biological factor associated with preterm delivery may be a causal factor for labor initiation both at term

Editor's Note. See related article by Goldenberg et al. (p. 233) in this issue.

and before term, or it may promote preterm birth only. Alternatively, it may be a marker not of the disease process, but of other underlying causal factors. Or it may be a marker operating in some final common pathway of the labor process of both preterm delivery and term delivery. Predictors belonging to this last category may appear late in a disease process, at a time when primary intervention is neither feasible nor wise.

Goldenberg et al. report their findings from the multicenter Preterm Prediction Study, a study in which data are collected that can provide a comprehensive assessment of the relationships of biological and psychosocial factors to preterm delivery. The authors identify 3 biological factors— bacterial vaginosis, fetal fibronectin, and short cervix—as strongly linked to spontaneous preterm births occurring at less than 32 weeks, less than 35 weeks, and less than 37 weeks. In light of the distinctions noted earlier, one is prompted to ask whether these identified entities are causal factors, markers of causal processes, or markers of early stages in the disease process. The answers to such questions will help determine whether these observations lead us to causal pathways from which primary prevention may ensue or to predictive pathways that may lead to effective secondary prevention.

The evidence for bacterial vaginosis as a causal factor is strong. Other observational studies have noted an increased risk of preterm delivery among women with bacterial vaginosis,[14–16] and, in 1 clinical trial, treatment with antibiotics lowered the risk of preterm delivery among women with this condition.[17] The suggestion in the Preterm Prediction Study that bacterial vaginosis is more strongly linked to spontaneous delivery before 32 weeks than it is to later prematurity is consistent with observations that early preterm deliveries are more often accompanied by infection in the placental/fetal membrane tissues.[18] It is implausible to think of bacterial vaginosis as merely a consequence of labor or as a component of a common labor process for preterm and full-term deliveries. Studies exploring ethnic differences in the prevalence of this infection (well documented in the Goldenberg et al. report) and its antecedents may lead to the development of primary prevention measures that go beyond reliance on antibiotic treatment.

The case for fetal fibronectin and short cervix as causal factors, or as markers of distinct causal pathology, is less convincing. Fetal fibronectin increases, and the cervix shortens, in the normal prelabor and perilabor periods of a full-term delivery,[19] suggesting that these factors are early markers of the labor process rather than markers of a unique causal pathway to preterm delivery. In the Goldenberg et al. data, by far the strongest associations of both fetal fibronectin (ascertained between 24 and 26 weeks) and short cervix (ascertained between 22 and 24 weeks) were with preterm labor occurring quite close in time to the ascertainment of these markers (i.e., between 24 and 32 weeks). There is also evidence in the data that the 2 entities may be closely linked to each other in the preterm labor process. Although short cervix and fetal fibronectin were found in common only 9% of the time in the entire study population (43 women had both risk factors among 457 who had either risk factor), they co-occurred in 29% (14 of 47) of women who had either risk factor and who delivered before 32 weeks.

The authors make a case for fetal fibronectin's having a role as a marker of upper genital tract infection. But were that the case, one might expect to find the same ethnic disparity in prevalence as was found for bacterial vaginosis (28.6% in Black subjects and 14.6% in non-Black subjects). But the ethnic difference was considerably less than that for bacterial vaginosis (7.2% vs 5.7%). No studies to this point have shown that interventions aimed to respond to fetal fibronectin or to short cervix can reduce the risk of preterm delivery. Nevertheless, fetal fibronectin and short cervix clearly have important potential as predictors that will help clinicians determine whether to use, with individual patients, the well-established secondary prevention measures referred to earlier. This study provides the strongest evidence yet of the powerful prediction offered by these clinical measures.

The Preterm Prediction Study offers a paradigm for future research on preterm delivery. The collection of biological samples, along with data on personal and social antecedents, will help to elucidate preterm delivery pathways that include both the social antecedents and the biological intermediaries. This process will be strengthened if we can distinguish the specific roles of each of the entities along the several causal pathways leading to preterm birth. □

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References

1. Copper R, Goldenberg RL, Creasy RK, et al. A multicenter study of preterm birth weight and gestational age-specific neonatal mortality. *Am J Obstet Gynecol.* 1993;168:78–84.
2. Escobar GJ, Littenberg B, Pettiti DB. Outcome among surviving very low birthweight infants: a meta-analysis. *Arch Dis Child.* 1991;66:204–211.
3. Veen S, Ens-Dokkum MH, Schreuder AM, el al. Impairments, disabilities, and handicaps of very preterm and very low birthweight infants at five years of age: the Collaborative Project on Preterm and Small for Gestational Age Infants (POP) in the Netherlands. *Lancet.* 1991;338:33–36.
4. Hack M, Klein N, Taylor HG. The long-term developmental outcomes of low birth weight infants. *Future Child.* 1995;5:176–196.
5. Ventura S, Martin J, Taffel S, et al. Advance report of final natality statistics, 1992. *Month Vital Stat Rep.* NCHS. 1994;4:375–376.
6. Paneth N. The problem of low birth weight. *Future Child.* 1995;5:19–31.
7. Bhushan V, Paneth N, Kiely JL. Recent secular trends in the prevalence of cerebral palsy. *Pediatrics.* 1993;91:1094–1100.
8. Kramer MS. Intrauterine growth and gestational duration determinants. *Pediatrics.* 1987;80: 502–511.
9. Lumley J. The epidemiology of preterm birth. *Clin Obstet Gynecol.* 1993;7:477–498.
10. Berkowitz GS, Papiernik E. The epidemiology of preterm birth. *Epidemiol Rev.* 1993;15:114–143.
11. Elbourne DR. General social support from caregivers during pregnancy. In: Chalmers I, ed. *Oxford Database of Perinatal Trials.* Ver 1.3. Oxford, England: BMJ Publishing Group; Spring 1992. Record 4169.
12. Grimes DA, Schultz KF. Randomized controlled trials of home uterine activity monitoring: a review and critique. *Obstet Gynecol.* 1992; 79:137–142.
13. Goldenberg et al. The Preterm Prediction Study: The value of new vs standard risk factors in predicting early and all spontaneous preterm births. *Am J Public Health.* 1998;88:233–238.
14. Hay PE, Lamont RF, Taylor-Robinson D, Morgan DJ, Ison C, Pearson J. Abnormal bacterial colonisation of the genital tract and subsequent preterm delivery and late miscarriage. *BMJ.* 1994;308:295–298.
15. Gravett MG, Nelson HP, Derouen T, et al. Independent associations of bacterial vaginosis and Chlamydia trachomatis infection with adverse pregnancy outcome. *JAMA.* 1986;256: 1899–1903.
16. Hillier SL, Nugent RP, Eschenbach DA, et al. Association between bacterial vaginosis and preterm delivery of a low–birth-weight infant. *N Engl J Med.* 1995;333:1737–1742.
17. Hauth JC, Goldenberg RL, Andrews WW, et al. Reduced incidence of preterm delivery with metronidazole and erythromycin in women with bacterial vaginosis. *N Engl J Med.* 1995;333: 1732–1736.
18. Hillier SL, Martius J, Krohn M, et al. A case-control study of chorioamnionitis infection and histologic chorioamnionitis in prematurity. *N Engl J Med.* 1988;319:972–978.
19. Lockwood CJ, Senyei AE, Dische MR, et al. Fetal fibronectin in cervical and vaginal secretions as a predictor of preterm delivery. *N Engl J Med.* 1991;325:669–674.