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The Changing Face of Preterm Birth

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IN THE OCTOBER 2007 issue of *Pediatrics*, Edison et al¹ reported a remarkable association between low maternal serum cholesterol levels and preterm birth. Because preterm birth is the single largest factor worldwide in infant mortality² and morbidity,³ this finding could have important consequences. The authors used an elegant approach with an existing cohort of women who had undergone a prenatal maternal serum screening analysis and provided a unique opportunity to correlate maternal serum cholesterol levels in early pregnancy with adverse birth outcomes. Because this finding was observed only in individuals of European ancestry, it will need to be replicated in other high-risk populations (eg, black Americans, preferably in a prospective manner). As the authors noted, the mechanism remains speculative but is biologically credible, because cholesterol is a precursor of placental progesterone, which is critical to the maintenance of pregnancy and is also a major component of plasma membranes in maternal decidual tissue. Although the association of low maternal serum cholesterol with preterm labor (as well as low birth weight) was unexpected, the finding opens the door to identification of a high-risk group of mothers in whom early interventions, including nutritional modifications or progesterone supplementation, might be effective in diminishing the subsequent occurrence of preterm labor.

Environmental components to preterm labor risk have long been recognized and include nutrition, infection, stress, trauma, and drug use. A genetic component is recognized but has been less well studied. A low maternal serum cholesterol level has multiple and overlapping etiologies, including maternal nutrition and genetic factors.⁴ It seems likely that the highest-risk group may well be those who have a combination of contributory dietary factors and a genetic predisposition to a low cholesterol level. Currently, there are active efforts by the World Health Organization, the National Institutes of Health, the Centers for Disease Control and Prevention, and the March of Dimes to better identify gene/environment etiologies for preterm birth and provide to the public information on the scope of the problem and the importance of recognizing early risk factors. Recent advances in genetics and environmental bioassays⁵ now make it practical to identify genetic and environmental interactions by using large sample collections and genetic tools such as genome-wide association analysis.⁶

The application of these unique and powerful genetic techniques to common, complex traits such as preterm labor⁷ afford opportunities to prospectively identify high-risk populations and engage in preventative environmental interventions. The success in decreasing neural tube defects after the introduction of folic acid food fortification has provided a model approach. Given the well-recognized risks between cardiovascular disease and elevated cholesterol,

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interventions to raise cholesterol might best be conducted only in high-risk populations of women with low serum cholesterol levels early in pregnancy. This makes it imperative to identify the genetic underpinnings so that just as there is currently screening for Rh incompatibility, HIV status, and birth defects in early pregnancy, similar screening could be performed for mothers through simple assays of cholesterol levels and genetic predispositions to identify groups of women who would benefit from current or prepregnancy dietary counseling or, possibly, interventions with supplements of progesterone. Progesterone supplementation decreases the risk for preterm labor in some (previous preterm birth, short cervix) but not all high-risk groups⁸ so this might be a consideration in a low maternal serum cholesterol population.

Preterm labor continues to be a major international health crisis, the frequency of which has seen a dramatic rise in developed countries over the last 2 decades,⁹ increasing the numbers of infants at risk for its many morbid consequences. In addition, there is a vast difference in maternal and perinatal health status in high-versus low-resource settings. This disparity represents one of the starkest inequities of our time. Approximately 530 000 women and 3 million newborns die each year as a result of complications related to pregnancy and childbirth.¹⁰ Most of these deaths occur in developing countries among populations of lower socioeconomic status. However, even in wealthier countries differentials in pregnancy and newborn outcomes across socioeconomic strata persist. These alarming discrepancies indicate that perinatal health inequities are problems that transcend public health concerns alone and are a major social injustice.

Although research in maternal and perinatal health has made significant progress in recent years, most progress has been driven by the needs of health systems that operate in high-resource settings. This has resulted in the production of pregnancy- and childbirth-related interventions that translate poorly in low-resource settings and exacerbate the persistent gaps in women's and infants' reproductive health conditions around the world. The paucity of research funding and resultant efforts targeted at conditions that disproportionately affect women in low-resource settings has impeded the development of effective, affordable, and feasible preventive strategies. The research agenda for maternal and perinatal health in the future must be defined with a larger focus, one that targets the needs of all populations and especially those that are most vulnerable and in greatest need of affordable interventions. Successful implementation of this larger focus could lead to significant reductions in maternal and perinatal mortality, a goal that has yet to be achieved despite decades of international commitment.¹¹ In addition, this new focus could have the added benefit of significantly reducing underlying causes of morbidity, disabilities, and associated health care costs in the more developed world. Results of the Edison et al study may well translate across socioeconomic strata and have wide application. These results could support the implementation of nutritional interventions among pregnant women to reduce the risk of preterm birth. Furthermore, it is possible that the effect of low cholesterol levels on preterm birth could be even larger among populations with inadequate nutritional status, which suggests that relatively simple, affordable, and culturally acceptable nutritional interventions could contribute substantially to reducing the risk of preterm birth among those populations most in need. The authors' results also provide insights into the pathophysiology of parturition and suggest pathways to investigate for genetic contributors to preterm labor, as well. Although the results need confirmation, the Edison et al article provides critical data for beginning to understand and quickly apply information on the joint genetic and environmental mechanisms that cause this problem of major clinical and social importance.

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