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MASTER CLASS

Prematurity and Infant Mortality

Infant mortality in the United States was more than 6 per 1,000 live births in 2004, the latest year for which data are available from the Centers for Disease Control and Prevention. This troubling rate places the United States low in the ranking of industrialized nations.

The death rate varies among different geographic areas and among various ethnic and racial groups. A common and major contributor to this relatively high infant mortality rate, however, is prematurity.

The causation of prematurity has been elusive, and therapeutic approaches have been only marginally successful. In recent years, however, a more scientific approach has been taken to understand the biology of premature labor that results in premature birth. This approach has been informing our understanding of this condition.

The National Institute of Child Health and Human Development (NICHD) has made prematurity a major part of its portfolio. The institute has a branch, in fact, whose research is dedicated to this significant obstetric problem. Many years ago, the NICHD also launched the Maternal-Fetal Medicine Units (MFMU) Network, which is a national collaborative that attempts to study difficult problems in obstetrics and tries to propose scientific solutions.

Most recently, the network engaged in a study in which it attempted to reexamine a preventive approach using hormone therapy. The network employed a randomized clinical trial methodology.

In this month's Master Class, I've invited Dr. Jay Iams, a professor of obstetrics and maternal-fetal medicine at Ohio State University, Columbus, and a member of the NICHD's MFMU Network, to address the issue of hormone prophylaxis for women who have already had one preterm birth. He will update us on the network's trial and other related research, and provide us with recommendations for applying these findings to current practice. ■

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BY JAY IAMS, M.D.

Preventing Preterm Birth

Women who deliver prematurely often attribute the birth to a recent event, such as stress at work or a fall at home. Because these events are unlikely to recur, preventive efforts in the next pregnancy may be limited to trying to reduce whatever risk was blamed for the first preterm birth, as in "I'll be more careful this time to get enough rest." Physicians often lend tacit support to this approach in the belief that there is not much we can do to prevent preterm delivery anyway.

Indeed, the majority of women who deliver prematurely will deliver at term in the next pregnancy without any intervention. However, their risk is increased, compared with that of women who delivered at term. About 15% of all preterm births in the United States occur in women who had a previous preterm birth; the risk increases in women with more than one prior preterm birth and in women whose preterm birth was early (before 32 weeks' gestation).

It's important to recognize these women as being at risk, because there is now good evidence that we can reduce the risk of recurrent preterm birth by about one-third by using prophylactic treatment with progesterone.

This development—our ability to prevent a sizeable portion of the leading cause of infant mortality in the United States—puts the onus on obstetricians to investigate each patient's history and to be aware of recent literature on the use of progesterone prophylaxis.

Information available in 2007 is stronger than it was in 2003, when the American College of Obstetricians and Gynecologists (ACOG) issued a Committee Opinion endorsing consideration of progesterone for women with a history of preterm birth.

More research is needed to fully understand how progesterone reduces the risk of preterm birth—and we must continue to monitor its long-term safety—but current evidence indicates that progesterone should be considered for women with a previous preterm birth that was spontaneous (that is, resulting from preterm labor or preterm ruptured membranes).

Risk for Recurrence

Recognizing that women with a previous preterm birth are at increased risk of having another preterm birth is the first step. However, the assessment of risk should go beyond the usual estimate that risk increases by a factor of two after a woman has one preterm birth.

We need to consider each woman's initial risk, beginning with her risk in the first pregnancy. Asian, and Hispanic, and white women, for instance, have an initial risk of preterm birth of about 10%; this rises to 20% after a history of one preterm birth. On the other hand, a black woman—regardless of her education or socioeconomic status—has a risk of preterm birth in the first pregnancy that exceeds 15%-16%; for her, a twofold increase becomes 30% or greater.

The other major component of risk assessment may well require medical records. If the first preterm baby was delivered early (before 32 weeks' gestation, and usually weighing less than 1,500 g), the risk of recurrent preterm birth rises by an additional factor of 1.5-2.0.

For a woman who is not black, then, the risk of preterm birth after a prior birth before 32 weeks can be estimated to be 25%-30%, or greater. For a black woman, the estimated risk of another preterm birth under these circumstances rises to 45%-50%.

Moreover, in women with more than one preterm birth, the risk estimate goes up by another factor of 1.5-2.0, so that a woman with two previous early preterm births may have a recurrence risk that exceeds 50%.

Knowledge of the gestational age of the previous infant at delivery and the woman's racial and ethnic background, therefore, is essential to the assessment of a woman's personal level of risk.

Determinations of risk that are as precise as possible can help guide our discussions about the potential benefits of progesterone therapy.

I like to consider preterm birth as the obstetric equivalent of a cardiac event. If a patient moves to town having had a previous heart attack, most physicians would seek and carefully examine the medical records, looking for risk factors and ways to reduce the patient's risk of another heart attack. In obstetrics, we should do the same.

Early Research

The notion that progesterone may improve pregnancy outcome has been considered for decades, most notably in papers by Dr. Arpad Csapo. Dr. Csapo's pioneering animal research led him to suggest that progesterone relaxes the uterus, and that if progesterone therapy were used, labor would occur only when the relaxing effect of progesterone is withdrawn.

In 1975, a report in the New England Journal of Medicine described the results of a small trial of 17 alpha-hydroxyprogesterone caproate (17P) for 43 women who had a history of two preterm deliveries, two miscarriages, or one miscarriage and one preterm delivery (N. Engl. J. Med. 1975;293:675-80).

The finding—that preterm delivery (defined in this study as fewer than 36 weeks' gestation) occurred in 41% of the women in the placebo group and in no women in the treatment group—stimulated interest in the use of 17P, and the treatment became popular for women with recurrent pregnancy loss.

Progesterone use fell out of favor, however, after studies linked diethylstilbestrol (DES) to uterine malformations and cervical cancer in the offspring of treated women. Even though progesterone's actions differ from those of estrogen, hormones in general were deemed to be worrisome.

The net result of this brief period of progesterone use, however, was a series of observational studies tracking the outcomes and health of individuals who were treated in the late 1970s and early 1980s as fetuses.

Although they were not rigorously scientific, the studies provided reassuring findings about the long-term safety of progesterone, as discussed in a thorough review of 17P by Dr. Paul Meis (Obstet. Gynecol. 2005;105:1128-35).

In 1990, Dr. Marc Keirse revived the idea that progesterone could be effective in protecting against preterm birth with a meta-analysis of trials employing 17P. He found "no support for the view that 17 al-

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DATA WATCH