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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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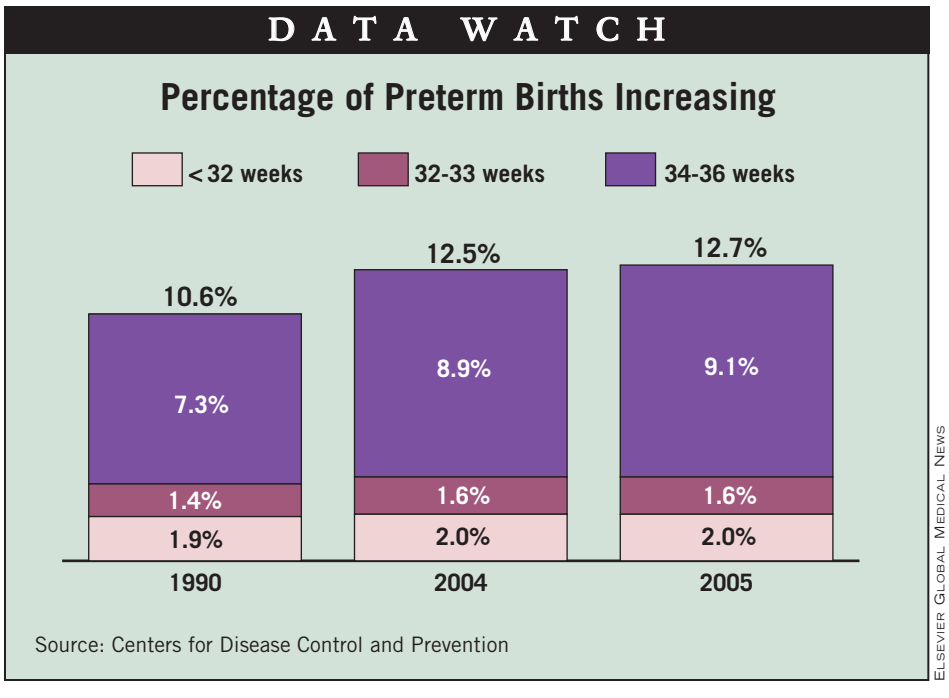
DATA WATCH



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pha-hydroxyprogesterone caproate protects against miscarriage," but said that trials did collectively "suggest that that [the therapy] does reduce the occurrence of preterm birth." (Br. J. Obstet. Gynaecol. 1990;97:149-54).

His review prompted investigators to start looking at progesterone again. Perhaps it had been discarded a little too early, they thought.

More Recent Studies

The study that eventually led to the reintroduction of progesterone for the prevention of spontaneous preterm birth—and the study that led to the cautious endorsement of progesterone therapy by ACOG—was a much larger, randomized, double-blind trial conducted by the Maternal-Fetal Medicine Units (MFMU) Network of the National Institute of Child Health and Human Development, and published in the New England Journal of Medicine in 2003.

Investigators enrolled women at 19 clinical centers who had had at least one previous spontaneous preterm delivery and randomized them, using a 2:1 ratio, to receive weekly injections of 17P (250 mg) or a placebo. Treatment was begun between 16 and 20 weeks and was continued until either delivery or 37 weeks' gestation. (N. Engl. J. Med. 2003;348:2379-85).

The study planned to enroll 500 women, but enrollment was stopped at approximately 450 women by an independent data-monitoring panel when data showed that the rate of preterm delivery (defined as fewer than 37 weeks' gestation) was almost 55% in the one group but just over 36% in the other group. When the data were unmasked, the treatment group was found to have the lower rate of recurrent preterm birth.

This reduction in preterm birth of about one-third took members of the MFMU Network by surprise. When Dr. Meis, the lead author on this paper, first proposed in the mid-1990s that the network study 17P, network investigators—myself included—expected to find minimal, if any, benefit of 17P prophylaxis.

The network, in existence since the late 1980s, is known for conducting unbiased research on interventions that are part of routine obstetric care but are not yet backed by rigorous study. Rarely had the network published a study showing benefit for interventions or processes that many had hoped would be proven beneficial. (For this reason, study designers did not incorporate a full array of outcomes measures—particularly long-term outcomes measures—in the study of 17P.)

Also surprising was a secondary finding that progesterone was more effective in preventing premature births in women whose previous premature delivery occurred earlier than 32 weeks' gestation than in women whose previous delivery occurred later.

Our original theory was based on the expectation that progesterone would act primarily as a uterine relaxant, so—if progesterone worked—we thought it would likely be most effective in women whose previous premature delivery occurred later in gestation (after 32-34 weeks). To our surprise, the network study found that the earlier the previous preterm birth occurred, the more likely progesterone would be to prevent another preterm birth.

Some criticized the study, usually for reasons related to misunderstandings of the rigorous rules under which the MFMU Network operates. The study was stopped and restarted, for instance, because the initial supplier of 17P could not guarantee its purity and therapeutic effect. This required us to set these data aside and start all over again with study medication provided by a new supplier whose product was consistently prepared.

Critics have also said that the high rates of preterm birth raise suspicions about the study's design. What has not been appreciated, however, is that the mean gestational age of previous preterm deliveries was 31 weeks in both the treatment and placebo groups. Moreover, a significant portion (30%-40%) of women in both groups had more than one previous preterm birth, and almost 60% of the women enrolled were black.

The rate of premature birth in the placebo group was thus exactly what one would expect to see in such a study population, based on existing epidemiologic literature. These women were exactly the kind of patients one would expect to sign up for a research trial: women whose index pregnancy resulted in an early preterm birth, an experience they were anxious to avoid.

PHOTODISC, INC.

Prematurity is a common and major contributor to the relatively high U.S. infant mortality rate. Therapeutic approaches have been only marginally successful.

The Issue Today

Two additional studies published just this year have addressed the issue of progesterone use in women with two other high-risk conditions: multiple gestations and a short cervix.

The trial of progesterone therapy for twin pregnancy—again using 17P—found no benefit for 17P prophylaxis in a study conducted by the MFMU Network (N. Engl. J. Med. 2007;357:454-61). This suggests to me that the mechanism of early delivery of twins is likely to be somewhat different from the mechanism of early delivery in women with a singleton preterm birth.

The recent trial of progesterone therapy for a short cervix, which was conducted by the Fetal Medicine Foundation in England, reported positive results. In this trial, 250 women with a cervical length of 15 mm or less were randomly assigned to receive vaginal progesterone (not 17P) or placebo (N. Engl. J. Med. 2007;357:462-9).

Spontaneous delivery before 34 weeks' gestation was less frequent in the progesterone group (19%) than in the placebo group (34%).

The exact mode of action of 17P therapy in preventing preterm birth is unknown, but we do know that progesterone does many things. It relaxes the uterus and, we now know, it alters or blunts the body's response to inflammation.

My interpretation of the research to date is that progesterone is effective when inflammation is the key element of the pathway to preterm birth (as is often the case for a short cervix) and that it does not work when uterine stretch and contractions are the critical pathway elements (as in twins).

These and other studies need to be repeated and confirmed, however. The MFMU Network has just begun a study of 17P injections for women with a short cervix who are pregnant for the first time. If it turns out that progesterone really does help prevent premature birth in women with a short cervix, then measurement of the cervix using transvaginal ultrasonography could be a useful test to identify women who might benefit from 17P prophylaxis.

For now, I believe that any woman with a previous spontaneous preterm birth should be informed of progesterone therapy. The higher her risk for recurrence—the earlier her previous preterm birth, for instance, or the higher the number of previous preterm births—the more likely it is that she might benefit from this therapy.

A woman whose previous preterm delivery occurred at 35 weeks' gestation, for instance, may well choose to decline the therapy. My discussions with women who have this history are more of a conversation than a recommendation. On the other hand, a woman with two previous preterm births, both before 32 weeks' gestation, should be strongly urged to have the therapy.

Again, a personal estimate of recurrence risk forms the basis for these recommendations. There are currently no data available to support the use of cervical ultrasound in women with a prior preterm birth to identify women who are more or less likely to benefit from progesterone prophylaxis, so we offer it to any woman with an appropriate history. Someday, we may be able to use progesterone more selectively than we do today.

There is no evidence to suggest that progesterone will help women with preterm labor or ruptured membranes in the current pregnancy, so we do not use it in these women.

Any risks of progesterone therapy are primarily theoretical, based on concern about continuing a pregnancy in which inflammation may favor allowing delivery. Fortunately, there are no signs of that in the original Meis study or in the two more recent large studies in women with twins and a short cervix.

A study recently published of the babies born in the 2003 Meis study found no differences in neurologic development between those who received progesterone and those who took placebo. MFMU Network investigators evaluated the children with various neurologic, physical, and developmental examinations, up to the ages of 4-6 years.

I tell my patients that potential risks continue to be monitored, but that progesterone prophylaxis is backed by a lot more evidence than are many other treatments and practices that are considered "standard" in obstetrics today. ■

Take Home Points For Prevention

- When caring for a woman with a prior preterm birth, take a thorough history of the entire pregnancy, and look for events that might have contributed. Think like an internist who is taking care of someone with a previous heart attack: Are these risks still present? Can they be eliminated or reduced?
- Estimate each woman's individual risk of recurrent preterm birth, taking into account the gestational age at the time of the previous preterm birth, her racial/ethnic background, and the number of prior preterm births.
- Consider and discuss supplemental progesterone prophylaxis with women who have had a prior spontaneous preterm birth, especially women who have had a prior early (before 32 weeks) preterm birth, or more than one prior preterm birth. Think of spontaneous preterm birth as one that did not follow a specific indication for delivery, such as fetal distress, preeclampsia, or bleeding due to placenta previa. Spontaneous preterm births are those between 17 and 36 weeks that followed premature cervical dilation and effacement with or without contractions, or preterm premature rupture of membranes.
- Don't use progesterone prophylaxis in women with multiple gestation.
- Don't use progesterone prophylaxis in women with preterm labor in the current pregnancy, or as a tocolytic.