THE MASTER CLASS

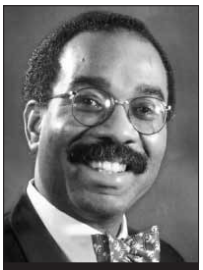
A Practical Perspective on a Complicated Problem

The health of any country is judged by the survival of its infants. The United States spends 15% of its gross national product on health care, yet it ranks 21st in the world in its infant mortality rate of 8 deaths per 1,000 live births, according to the World Health Organization. The two main contributors to this death rate are prematurity and birth defects.

Aggressive research programs are aimed at trying to understand the pathophysiology of preterm birth, and clinical interventions have been introduced in an attempt to reduce this unacceptably high rate of preterm birth.

Washington Clark Hill, M.D., the guest expert for the Master Class this month, has long studied preterm labor in the context of both singleton and multiple gestations. He has published comprehensive overviews of research on the complications of tocolysis and the prevention and treatment of preterm labor.

A graduate of Temple University School of Medicine in Philadelphia, Dr. Hill did his residency training at William Beaumont Army Medical Center in El Paso, Tex., before completing a fellowship in maternal-fetal medicine at the University of California, San Francisco.



BY E. ALBERT REECE, M.D., PH.D, M.B.A.

He is director of the perinatal center and the division of maternal-fetal medicine at the Sarasota (Fla.) Memorial Hospital. Dr. Hill brings a clinical and practical perspective to this complicated problem. His insights will allow us to disentangle fact from fiction and what works from what doesn't.

DR. REECE, who specializes in maternal-fetal medicine, is the vice chancellor and dean of the college of medicine at the University of Arkansas in Little Rock.

Managing Preterm Labor in Multiple Gestations

Preterm labor is one of the most important and vexing challenges complicating pregnancy. Premature babies account for an estimated 6%-10% of births, yet they account for 70%-85% of neonatal morbidity and mortality.

In multiple gestations, which are increasingly common as a result of delayed childbearing and the use of assisted reproductive technologies, preterm labor is an even greater risk. The literature points to an incidence of preterm labor of 20%-75% in multiple gestations. Although these figures may be somewhat high, I think it is safe to say that at least 1 in 10 multiple gestations seen at my institution are complicated by preterm labor. Not all of these patients will be admitted or will deliver early, but the very common nature of this problem and the potentially lethal consequences of premature multiple deliveries make this an issue that every physician and institution should approach carefully.

BY WASHINGTON C. HILL, M.D.

First, it is important to consider the delivery goal of a multiple gestation pregnancy. Overall, most twins are delivered at 37-38 weeks. For triplets, the gestational age is closer to 34 weeks, and quadruplets are born at around 30 weeks. These are reasonable numbers applicable to community practice.

If a patient arrives in preterm labor, you have to decide what to do, considering her situation and the capabilities of your local hospital and medical staff. It is clear that premature babies fare best when they are cared for in the institution where they are born. If someone needs to be transferred, it should be the mother, not the baby.

Obviously, if a patient carrying twins presents in labor at 35 or 36 weeks, most obstetricians would be inclined to do very little to cut short the labor, because—in the absence of other complications—these babies are likely to do well. However, if she presents at 29 weeks, it would make sense to be more aggressive.

Can the patient be safely and aggressively managed for preterm labor in her local community? The answer hinges on the plan for delivery if the treatment fails. Each hospital and service has to pick a gestational age at which neonatal survival is acceptably high. Then, options for the mother should be discussed with her and with the neonatal intensive care unit at your hospital or the institution to which she will be transferred.

Depending on the circumstances, the treatment of preterm labor may be undertaken for several reasons:

- To delay delivery until the patient can be transferred to a tertiary medical center with a high-level neonatal intensive care unit.
- To delay delivery 24-48 hours for the administration of corticosteroid therapy.
- To reduce the strength and frequency of uterine contractions, enabling the fetus to further develop in the uterus.
- To minimize hospital stays for the mother and the neonate.
- To reduce the risk of neonatal morbidity and mortality by preventing preterm delivery, the most dangerous complication of multiple gestation pregnancies.

When I consult with a woman in preterm labor, I go through a list of available options. Unfortunately, a careful review of the literature reveals few really good, effective treatments.

Although new ideas emerge every few years, not many interventional strategies have withstood attempts to corroborate results from single institutions. It may be tempting to "just do something," but we owe it to our patients to stick to scientifically valid and efficacious treatments.

Bed Rest

Bed rest or activity restriction will not prevent preterm labor. Rest neither lengthens gestation nor reduces neonatal morbidity in multiple gestation pregnancies. In some studies these patients did worse.

If a patient carrying multiples has a short cervix and threatened preterm labor, there is some evidence to support getting her off her feet rather than having her continue working at a very active job.

Once a multiple pregnancy is complicated by preterm labor, hospitalization may be necessary for observation and implementation of a treatment course.

Hydration

There is no evidence that hydration is an effective treatment for preterm labor. In fact, the initial administration of bolus intravenous fluids may pose some risk to patients with multiple gestations. These patients already have an increased blood volume and could develop pulmonary edema from fluid overload if tocolytic therapy is initiated after unnecessary fluids are administered.

Progesterone

A study by Paul J. Meis, M.D., and colleagues (N. Engl. J. Med. 2003;348:2379-85) suggests recurrent preterm birth in singleton pregnancies can be prevented by 17 ζ-hydroxyprogesterone caproate. The jury is still out on whether progesterone can be useful in managing active or threatened preterm labor in a multiple gestation pregnancy.

Studies are underway that may provide us with more guidance in the use of this agent. However, no evidence exists that it is safe and efficacious in multiple gestation pregnancies, so I suggest its use be reserved for patients in clinical trials.

Antibiotics

It is tantalizing to believe antibiotics would be helpful in preventing or treating preterm labor. Many researchers theorize that intrauterine infection or fetal infection may be responsible for preterm labor, particularly in pregnancies that are not complicated by multiple fetuses. However, the data do not show that antibiotic treatment is any more efficacious than placebo in prolonging pregnancy or preventing preterm delivery.

Tocolytics

The use of tocolytics to decrease or halt preterm labor is controversial in multiple gestations as well as in singleton pregnancies because the drugs pose risks to the mother and, in some cases, to the fetus. However, the available data support the position that tocolytic agents work for a short period—about 48 hours, although Roger B. Newman, M.D., and colleagues have shown that some multiple gestations can be prolonged for more than 7 days (Am. J. Obstet. Gynecol. 1989;161:547-55; "Multifetal Pregnancy: A Handbook for Care of the Pregnant Patient" [Philadelphia: Lippincott Williams & Wilkins, 2000]).

Each tocolytic agent carries its own benefits, risks, contraindications, and adverse effects profile. Numerous sources are available for this information; for quick reference; I recently published a summary in chart form (Clin. Obstet. Gynecol. 2004;47:216-26). Keep in mind that women with multiple gestations have an elevated risk of cardiovascular complications, such as pulmonary edema resulting from anemia, lower colloid oncotic pressure, and higher blood volume.

I would take a middle-of-the-road approach in choosing an agent or agents for tocolysis. For example, oral terbutaline, oral calcium channel blockers, and oral Indocin have been well-studied and widely used, with varying levels of success.

COURTESY DR. WASHINGTON HILL

A twin pregnancy at 25 weeks' gestation shows discordancy for fetal size. The patient presented in preterm labor and will be followed closely.

John P. Elliott, M.D., and Tari Radin, Ph.D., studied a small number of high-order multiple gestations and found similar levels of serum magnesium in triplets and quadruplets and in singleton pregnancies after the administration of magnesium

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sulfate for tocolysis (J. Reprod. Med. 1995;40:450-2). However, they concluded that higher levels of magnesium sulfate are needed in multiple gestations to inhibit labor. They suggested administration at infusion rates of 4-5 g/h in triplet and quadruplet pregnancies.

Research on combination tocolytic therapy has produced conflicting results. Most of the studies on this topic are dated, limited in scope, and not specifically focused on multiple gestations. Some concerns, however, have been raised. For example, magnesium sulfate administered in conjunction with nifedipine can result in significant neuromuscular blockage and a subsequent marked hypotensive effect.

My recommendation is to administer combination tocolytic therapy only with great caution, using agents such as intravenous magnesium sulfate with oral terbutaline or indomethacin. The mother and fetus also should be monitored closely by professionals well-versed in side effects linked to this form of therapy.

Should tocolytic therapy be maintained after successful cessation of labor? A careful reading of the available evidence suggests the answer is no. In well-designed studies, maintenance tocolytic therapy has reduced neither preterm deliveries nor perinatal morbidity or mortality.

Corticosteroids

Corticosteroids are among the few noncontroversial agents for use during preterm labor. These agents—which clearly reduce the incidence and severity of neonatal respiratory distress syndrome, intraventricular hemorrhage, necrotizing enterocolitis, and neonatal mortality—should be administered to any patient in preterm labor at 24-34 weeks, using the same regimen as in singleton gestations.

The accepted corticosteroid treatment consists of two intramuscular doses of betamethasone or four intramuscular doses of dexamethasone.

In higher-order gestations, Dr. Elliott and Dr. Radin have observed that betamethasone can increase uterine contractions and advance labor in patients with frequent contractions. They therefore recommend that corticosteroids be reserved in these pregnancies for patients having fewer than three contractions per hour (Obstet. Gynecol. 1995;85:250-54). Uterine activity in higher-order gestations should be closely monitored following the administration of corticosteroids.

It once was suggested that multiple courses of prenatal corticosteroids might be of benefit. This recommendation is no longer made, because there is no good evidence for enhanced efficacy and because repeated doses are associated with clear risks, including decreased fetal growth and reduced birth weight.

Adjunctive Treatments

Isolated studies have suggested a role in preterm labor for such interventions as vaginal lever pessaries, blood transfusions, and cerclage. None of these have been put to rigorous scientific scrutiny. Cerclage obviously has no role in patients who do not have an incompetent cervix, or in such specific cases as the previable delivery of one dichorionic twin when a delayed-interval delivery of the second twin is desired.

Treating the Whole Patient

Not infrequently, preterm labor in a multiple gestation pregnancy requires the prolonged hospitalization of the mother, who may be a busy professional woman or the parent of other small children. Spending 5-10 weeks in hospital is a long, frustrating time, replete with boredom and anxiety.

At my institution, a clinical nurse specialist who was concerned with the psychosocial effect of hospitalization on the women in our unit proposed what has become a highly successful multidimensional program: Mom Matters. The program offers support, diversion, and empathy in the form of wheelchair outings, Internet access, flexible visitation for family members (including children), manicures, pedicures, movies, and get-togethers.

The success of our program and the gratitude expressed by the mothers on our service have convinced me that this is a kind and therapeutic approach worth considering and implementing elsewhere.

The Future

The road to safe and effective therapy for preterm labor has been a long and frustrating one. I am hopeful that researchers are now on the right track, focusing on subtle indications of infection and other potential causes of preterm labor.

In multiple gestations, of course, preterm labor is often caused simply because there are too many fetuses in the womb. Uterine overdistension will not be an easy problem to overcome, except by reducing multiple gestations. Many of our colleagues in reproductive endocrinology have gotten the message that implanting too many embryos is unwise and unethical.

I believe that in the coming years, we will gain a better understanding of organic causes of preterm labor, permitting us to customize therapy according to individual circumstances of each pregnancy. ■