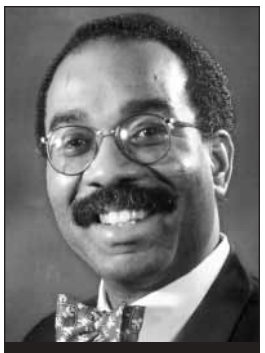

BY E. ALBERT REECE, M.D., PH.D., M.B.A.

MASTER CLASS

The Changing Approach to Preterm Labor

Preterm delivery accounts for a significant component of infant mortality in the world. In this, the United States has not been spared; in fact, our country ranks a dismal 21st internationally in infant mortality, with prematurity as a major contributor.

Historically, obstetrics has approached this problem from a therapeutic perspective: If you see a contraction, try to stop it. In large measure, we have been unsuccessful, staving off delivery by a mean of approximately 2 days despite our best efforts. Although this window can allow for the stabilization of patients, arranging for their transfer to appropriate delivery sites, and initiating required medications, it does not solve the problem of prematurity.

By focusing on the symptoms of premature labor, we have not paused sufficiently to ask basic questions about potential causes and triggers that could help us to develop preventive strategies and targeted treatments for what is clearly a multifactorial syndrome.

This is all changing. The National Institutes of Health saw this as such a priority that it formed a Perinatology Research Branch within the National Institute of Child Health and Development and chose international authority Dr. Roberto Romero to lead it. The Centers for Disease Control and Prevention and the March of Dimes have similarly launched research initiatives and made the prevention of prematurity a priority.

Much progress has been made, with Dr. Romero's team taking a role in the forefront. I am very pleased to welcome Dr. Romero, professor of ob.gyn. at Wayne State University in Detroit and chief of the Perinatology Research Branch at NIH, as this month's guest professor. We will review advances in our understanding of the biology of prematurity as a syndrome and offer potential treatment implications, beginning with a focus on infection.

In September, we will similarly review the other contributors to the prematurity syndrome. ■

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The Role of Infection

Dr. E. Albert Reece: How important is infection as a mechanism of disease in premature labor?

Dr. Roberto Romero: Intrauterine and systemic infections are a leading cause of spontaneous preterm labor and delivery. Indeed, infections and inflammation are the only mechanisms of disease for which a clear causal link with prematurity has been established. Moreover, a clear molecular pathophysiology has been described.

EAR: How frequent is intrauterine infection in spontaneous preterm birth?

RR: It has been estimated that one of every four preterm births occurs to mothers with intraamniotic infection (defined as a positive amniotic fluid culture for microorganisms). Under normal circumstances, the amniotic cavity does not contain bacteria, just as cerebrospinal fluid does not. However, approximately 12% of women presenting with an episode of preterm labor will have a positive amniotic fluid culture for microorganisms. The organisms most frequently isolated are genital mycoplasmas, particularly *Ureaplasma urealyticum*. Among women with preterm premature rupture of membranes (PROM), one of every three will have a positive amniotic fluid culture for microorganisms at the time of presentation. *U. urealyticum* is the most common microorganism isolated from the amniotic cavity.

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EAR: Is there a particular subgroup of women in whom intrauterine infection is more prevalent?

RR: The earlier the gestational age at which a patient presents with preterm labor and intact membranes or preterm PROM, the higher the likelihood of a positive amniotic fluid culture. For example, infection and/or inflammation is present in close to 70% of women presenting around 24 weeks of gestation, but is much rarer in patients presenting after 34 weeks.

EAR: Among women who present with a clinical picture of acute cervical insufficiency, also known as an "incompetent cervix," how common are infections?

RR: Studies by our group and others indicate that approximately 50% of women presenting with a dilated cervix and bulging membranes before 24 weeks of gestation will have a positive amniotic fluid culture for microorganisms. It is important to realize that rupture of membranes after a cervical cerclage may be the result of a subclinical infectious process, rather than the consequence of cerclage placement.

EAR: What proportion of intrauterine infections manifest themselves with clinical chorioamnionitis?

RR: Most intrauterine infections are subclinical in nature. Our work indicates that among women with intraamniotic infection and preterm labor with intact membranes, only 12% will have a positive amniotic fluid culture. Among women with preterm PROM, only 20% will have clinical signs of chorioamnionitis when a positive amniotic fluid culture is present.

EAR: If most infections are subclinical in nature, how can they be detected?

RR: The most accurate method to detect the presence of intraamniotic infection is analysis of amniotic fluid. Amniotic fluid is normally sterile for bacteria. It is possible to isolate some viruses from amniotic fluid, but generally, cultures for viruses are not performed in patients with preterm labor and preterm PROM. Amniotic fluid should be cultured for aerobic and anaerobic bacteria, as well as for *Mycoplasma* species. Detection of mycoplasmas is important, because they are the most common organisms found in the amniotic fluid. Commercially available systems exist that can be implemented in U.S. laboratories.

EAR: The results of cultures take several days to become available. Thus, rapid tests are required to assess the likelihood of infection or inflammation. What tests would you recommend for this purpose?

RR: A positive Gram stain has 99% specificity, but 20% sensitivity in the detection of intraamniotic infection. The low sensitivity is because the Gram stain cannot detect mycoplasmas since these organisms are too small to be seen with light microscopy. However, the take-home message is that a positive Gram stain is virtually always associated with a positive culture and that false positives are rare. The current approach to the detection of infection and/or inflammation in the amniotic fluid includes other tests that are routinely performed for the analysis of cerebrospinal fluid in all hospitals in the United States. Such tests include a white blood cell (WBC) count of amniotic fluid, and a glucose determination.

EAR: How can the clinician interpret the results of an amniotic fluid WBC and an amniotic fluid glucose determination?

RR: White blood cells—such as neutrophils, monocytes, or eosinophils—are not normally present in the amniotic fluid. Therefore, a high count of white blood cells is an indicator that intraamniotic inflammation is present. We recommend that an amniotic fluid sample be sent to the clinical hematology laboratory, that a WBC count be performed in the standard hemacytometer chamber, and that this be followed by a differential count. When the WBC count is greater than 50 cells/L in patients with intact membranes—or greater than 30 in patients with preterm PROM—the likelihood of a positive amniotic fluid culture is high.

In terms of the amniotic fluid glucose concentration, under normal circumstances glucose is present in the amniotic fluid. The lower the amniotic fluid glucose value, the higher the likelihood of intraamniotic infection or inflammation. For example, glucose values less than 14 mg/dL in women with intact membranes—or less than 10 mg/dL in women with preterm PROM—suggest that intraamniotic infection and/or inflammation is present.

EAR: Are there other tests, such as measurements of cytokines or other proteins, that can be used to detect inflammation in the amniotic fluid?

RR: The concentrations of a cytokine, such as interleukin-6, can be used to detect inflammation. Similarly, we have developed a rapid test that can be used at the bedside to detect inflammation by detecting the concentration of an enzyme produced by neutrophils. This enzyme is MMP-8 (matrix metalloproteinase-8).

These tests can be valuable in the context of midtrimester amniocentesis. The rate of pregnancy loss after a midtrimester amniocentesis has been estimated to be 0.5%-1%; such losses have mistakenly been thought to be always procedure related. However, we have found that among women who have midtrimester amniocenteses, those who have an elevated IL-6 or MMP-8 concentration are more likely to lose their pregnancy or have a spontaneous abortion shortly after the procedure. In these circumstances, determination of IL-6 or MMP-8 in the amniotic fluid stored by the genetic laboratories may be helpful for the patient and physician to identify that intraamniotic inflammation was a cause of the pregnancy loss. This may also have medicolegal implications.

EAR: How common is intraamniotic infection and/or inflammation in women having genetic amniocenteses in the midtrimester of pregnancy?

RR: The frequency of intraamniotic infection has been estimated to be 0.9%; the frequency of intraamniotic inflammation is about 1.2%. The most common organism found in the amniotic fluid is *U. urealyticum*. Intraamniotic infection and/or inflammation is more common in women who have discolored amniotic fluid at the time of genetic amniocentesis. It is important to realize that these infections are subclinical and that sometimes, patients with these infections rupture their membranes within hours or days of the procedure.

EAR: Can treatment be offered to these patients with midtrimester intraamniotic infections?

RR: Recent evidence from Dr. Sonia Hassan in our group indicates that the administration of antibiotics to the mother can eradicate intraamniotic infection in the midtrimester. Women with a short cervix detected by ultrasound were found to have microorganisms in 9% of cases. Patients were offered treatment with antibiotics and a repeat amniocentesis was performed

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Continued from previous page

to be sure that the infections were eradicated. Most women treated in this fashion had eradication of their intraamniotic infection and their pregnancy went to term.

EAR: How frequently are intrauterine infections confined to the amniotic fluid, and how often is the fetus involved?

RR: A study conducted in the United Kingdom in women with preterm PROM indicated that approximately 30% of patients had microorganisms in the amniotic fluid. Of these, 30% had positive fetal blood cultures. This means that 10% of all fetuses with preterm PROM will have fetal bacteremia. Clearly, this represents a minimum estimate of the frequency of fetal infection, a result of the limitations of standard techniques and the difficulties in isolating relevant microorganisms from fetal blood.

EAR: What is the importance of congenital neonatal infections?

RR: Sepsis is a more serious disease in neonates than in adults. Neonates have been generally considered immunosuppressed hosts, and the lethality of sepsis in neonates is high. There is now accumulating evidence that neonates with sepsis are more likely to develop cerebral palsy and bronchopulmonary dysplasia or chronic lung disease.

EAR: How important is intrauterine infection as a cause for cerebral palsy?

RR: It has been estimated that as many as 20% of all cases of cerebral palsy result from infection. Moreover, this applies to term neonates as well as to preterm neonates. Therefore, the traditional paradigm—that intrapartum asphyxia was the leading cause of cerebral palsy—is probably not correct. Obstetricians need to be aware that undiagnosed infections can be a cause for cerebral palsy because this has medicolegal implications.

EAR: What is the link between infection and the brain injury associated with cerebral palsy?

RR: Microorganisms involved in cases of intraamniotic infection can invade the human fetus. When the fetus breathes or swallows infected amniotic fluid, microorganisms may be entering the fetal compartment. Once microorganisms invade the fetus, they elicit a fetal inflammatory response syndrome (FIRS), which is the counterpart of the systemic inflammatory response syndrome (SIRS) in the adult. In FIRS one of the most critical organs affected is the brain. Microorganisms or their products that gain access to the fetal brain can induce damage of neurons or white matter in utero. Damage to the white matter in utero is also known as periventricular leukomalacia (PVL) and is the most important predictor of cerebral palsy. There is evidence that cytokines, chemokines, and other inflammatory products—such as reactive oxygen metabolites—can cause damage to the glia or to neurons, which is responsible for the cognitive abnormalities, including mental retardation.

EAR: If most intrauterine infections are subclinical, how can an obstetrician determine whether or not a neonate had intrauterine infection after birth?

RR: One possibility is to look at the placenta. Inflammation in the placenta can be of maternal origin or of fetal origin. Histologic chorioamnionitis is inflammation of the chorioamniotic membranes caused by maternal cells and is, therefore, a maternal inflammatory response. By contrast, funisitis—inflammation of the umbilical cord—is a fetal inflammatory response. Therefore, the presence of funisitis, diagnosed by examination of the placenta, indicates that the fetus was exposed to microorganisms before birth, or that the fetus mounted a FIRS. This is the reason why we call funisitis the hallmark of FIRS. The practical implication of this is that the examination of the placenta may be helpful in understanding what happened before birth. This is particularly important, given that funisitis has been associated with the subsequent development of cerebral palsy. The medicolegal implications of this are apparent. Because there is no known treatment for funisitis, there is no evidence that any intervention by obstetricians can prevent cerebral palsy associated with or induced by intrauterine infection.

EAR: Do systemic infections cause premature labor?

RR: Systemic clinical infections—such as pyelonephritis, pneumonia, malaria, and appendicitis—have been associated with premature labor and delivery. However, there is recent evidence that subclinical distant infections may also be a cause of premature labor and delivery. Specifically, periodontal disease, which is a chronic inflammatory process, has been associated with the subsequent development of preterm labor as well as with small-for-gestational-age infants. ■

In September's Master Class: Dr. Reece will query Dr. Romero about the other important causes of preterm parturition, rounding out our exploration of the syndrome.