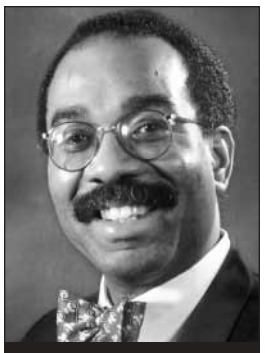
MASTER CLASS


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

Preterm Labor Has Multiple Causes

In July's Master Class, the specific role of infection in preterm labor was discussed at length by Dr. Roberto Romero, chief of the Perinatology Research Branch at the National Institute of Child Health and Human Development, and professor of obstetrics and gynecology at Wayne State University in Detroit.

Although infection is a leading—and perhaps the best understood—cause of spontaneous preterm labor and delivery, it is not the only cause. Research from Dr. Romero's group and others increasingly point to several disease mechanisms with genetic and environmental components that can be responsible for what we now know as the preterm parturition syndrome.

I am pleased to welcome back Dr. Romero, an international authority on the syndrome.

In this month's discussion, Dr. Romero provides an overview of evolving knowledge about the syndrome and details current scientific progress in the understanding of the noninfectious causes that may be important in the process of preterm labor. ■

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The Preterm Parturition Syndrome

Dr. E. Albert Reece: What is the common pathway of parturition?

Dr. Roberto Romero: The common pathway of parturition consists of the anatomical, physiologic, biochemical, and clinical events that occur in the mother and/or fetus in both term and preterm labor. The uterine components of this pathway include increased uterine contractility; cervical ripening (dilatation and effacement); and membrane/decidual activation. In most women, these components are typically activated in a synchronous manner in spontaneous labor at term. Indeed, most women admitted in labor have uterine contractions, cervical changes and—sometimes—rupture of membranes.


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However, in some cases the activation of the common pathway may be asynchronous. For example, a patient may have increased uterine contractility, but the cervix undergoes very little change over time. This is what is called a prolonged latent phase of labor. In 10% of cases, patients have spontaneous rupture of membranes without myometrial contractility. This is evidence that membrane/decidual activation has occurred without recruitment of the myometrium.

Asynchronous activation is more common in the preterm gestation. Many patients with suspected preterm labor will present with increased uterine contractility without cervical changes. Others will present with the clinical picture of cervical insufficiency (which used to be called cervical incompetence). Finally, some women will present with preterm premature rupture of the membranes (pPROM), which is premature membrane/decidual activation.

EAR: What is the importance of the concept of the common pathway?

RR: Much of the clinical management and research in understanding the causes of premature labor, treatment, and prevention has been focused on the elements of the common terminal pathway. For example, we have used uterine monitors to detect an increase in uterine contractility and tocolytic agents to treat increased myometrial contractility. We use ultrasound to identify patients with a short cervix who are at risk for preterm delivery. In some cases, we have placed cervical cerclage in patients at risk. Finally, we have used fetal fibronectin to detect decidual/membrane deactivation. A positive fetal fibronectin is an indicator that disruption of the choriodecidual interface has occurred. Yet these interventions aim to treat preterm labor as a symptom, without first identifying and understanding the underlying pathology that sets it in motion. Progress on this front is now being made.

EAR: What is the difference between spontaneous labor at term and preterm labor?

RR: We propose that spontaneous labor at term is the inevitable process that occurs when the capacity of the mother to support the fetus in utero has been reached. In other words, when the fetus has achieved maturity and is ready to face extrauterine life, it signals the onset of labor and engages the cooperation of the mother in this process.

In contrast, we propose that premature labor results from a pathologic insult that activates the common pathway of parturition. Before the development of newborn special care units, extreme prematurity was nearly always lethal. Thus, being born preterm is likely to result from such a severe pathologic process that it threatens the survival of the mother and/or baby.

In summary, spontaneous labor at term results from physiologic activation of the common pathway, whereas preterm labor would result from pathologic activation of the pathway.

EAR: What is the evidence that premature labor is a heterogeneous condition?

RR: My laboratory and other groups have generated evidence that the pattern of uterine gene expression—also known as the transcriptional profile—is different in patients with different causes of premature labor. A transcriptional profile is a snapshot of genes that are being upregulated or downregulated at a particular point in time.

We have demonstrated experimentally that the transcriptional profile in the uteri of mice that go into labor as a result of infection is different from the transcriptional profile of mice that go into labor because of ovariectomy (a model of progesterone withdrawal).

We have also examined the transcriptional profile of the chorioamniotic membranes in women with preterm labor and intact membranes vs. women with pPROM, in each case studying women with and without histologic chorioamnionitis. These studies have demonstrated that the patterns of gene expression are very different in these four groups, even though the clinical presentations are similar.

Collectively, the observations in patients and animals suggest that premature labor is a heterogeneous condition. Although they share a common pathway (uterine contractility and cervical dilatation and/or membrane rupture or activation), there are multiple causes for the preterm parturition syndrome.

Using the tools of high-dimensional biology, we have learned that premature labor is not simply labor before its time, but rather a disease state. It is caused by different pathologic processes with both environmental components and genetic components. For example, in infection-induced preterm labor (OB.GYN. NEWS, July 1, 2006, p. 42), the environmental component is represented by the microorganisms that cause the infection. The genetic component is the factor that predisposes some women to have an intrauterine infection or to respond more severely to that infection.

We have not one patient, but two. Accumulating evidence indicates that the fetus plays a central role in the initiation of labor in both animals and humans.

A prime example of the importance of genetics lies with the fetus. In pregnancy, we have not one patient, but two. Accumulating evidence indicates that the fetus plays a central role in the initiation of labor in both animals and humans. In humans, mothers of fetuses who have mounted a severe fetal inflammatory response are more likely to go into labor than are mothers of fetuses who have not mounted a fetal inflammatory response to infection. The magnitude and severity of the inflammatory response are under genetic control.

Thus, in pregnancy, the genetic makeup of two hosts—mother and child—plays a role in determining the susceptibility and response to infection. It is a unique situation in medicine.

EAR: Why do you call preterm parturition a syndrome?

RR: The current taxonomy of disease in obstetrics is largely based on the symptoms and signs exhibited by the mother, not the mechanisms of disease responsible for the clinical presentations. A syndrome is a combination of symptoms and signs that form a distinct clinical picture indicative of a particular disorder. Implicit in this definition is the fact that a syndrome can have multiple causes. Our emphasis in referring to premature parturition as a syndrome is that it will help both patients and physicians readjust the unreasonable expectation that one test can diagnose or identify all women at risk, and that one treatment will be effective for all women in premature labor, regardless of the cause.

EAR: In the last Master Class, we spoke about the role of infection and inflammation as a cause of premature labor. You have shared with us a figure that shows other causes of preterm parturition. I would like to discuss the other causes with you. Can you tell us how uterine ischemia and/or vascular pathology cause premature labor?

RR: Placental histology suggests that vascular lesions involving maternal or fetal circulation constitute the second most common apparent cause of preterm labor and pPROM, after inflammation.

Research in this area has focused on elevated rates of vascular abnormalities in women with spontaneous preterm labor with intact membranes and pPROM, compared with women who deliver at term. The vascular lesions have been found on both the maternal and fetal side. For example, thrombosis of the decidual vessels attached to the placenta and failure of physiologic transformation in the myometrial segment of the spiral arteries are generally considered maternal lesions. Abnormalities in the fetal circulation linked to preterm labor include a decreased number of arterioles in the villi and fetal arterial thrombosis.

Whereas uteroplacental ischemia is the driver of vascular events, the leading can-

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didate to explain the molecular mechanisms responsible is the renin-angiotensin system; in severe uteroplacental ischemia, the enzyme thrombin is emerging as an important activator of preterm labor associated with vaginal bleeding.

The work of Dr. Mark Phillippe and Dr. Michal Elovitz has demonstrated in animal models and in vivo investigations that whole blood—but not heparinized blood—raises contractile activity of the uterine muscle, and that such increased uterine activity can be blocked with a thrombin antagonist.

Moreover, women with preterm labor have higher concentrations of thrombin-antithrombin (TAT) complexes in amniotic fluid and in maternal plasma than do women without preterm labor. Similarly, Dr. Todd Rosen and Dr. Charles Lockwood have provided evidence that women destined to develop pPROM have higher concentrations of thrombin weeks before the development of complications. Therefore, thrombin is a potential initiator not only of the rupture of membranes (via stromal cells and matrix metalloproteinase 1), but also of uterine contractility and preterm labor.

The thrombin connection would help to explain why retroplacental hematomas in early pregnancy are associated with preterm delivery, and why vaginal bleeding in the first or second trimester is a risk factor for preterm birth with intact or ruptured membranes.

EAR: What is the evidence that uterine overdistention is a cause of preterm parturition?
RR: Obstetricians and midwives know that multiple gestation is a risk factor for preterm delivery, and that the higher the order of multiple gestation, the greater the risk for preterm birth. Patients with polyhydramnios resulting from a congenital fetal anomaly are also at risk for spontaneous preterm labor and delivery. These two conditions are probably mediated by uterine overdistention. It is likely that the same is the case for patients who have müllerian duct abnormalities in which the uterine cavity is small. One example is congenital hypoplastic uterus and another is the abnormal uterus resulting from diethylstilbestrol exposure.

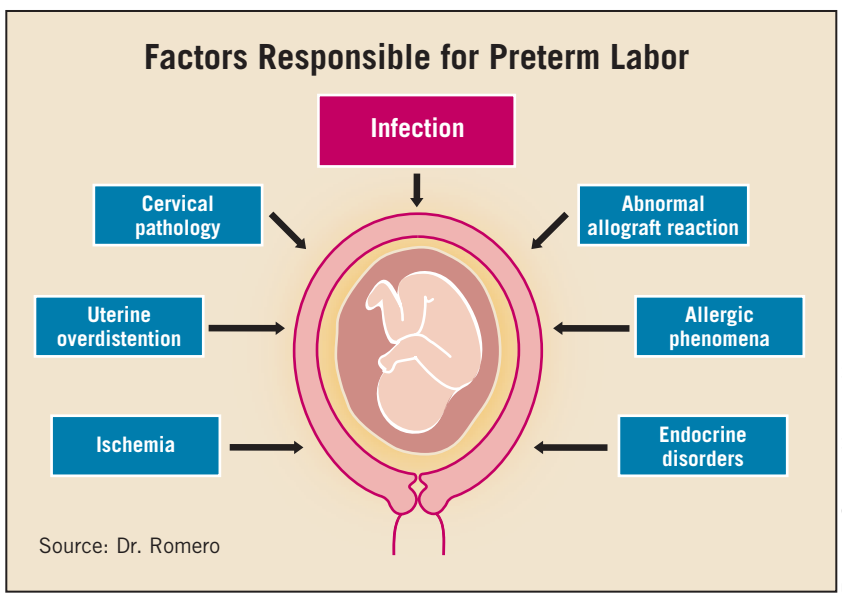
EAR: What is the mechanism linking uterine overdistention with premature labor?
RR: This is an area that requires further work. In general terms, mechanical signals triggered by uterine stretch may lead to preterm labor—as in multiple gestations and polyhydramnios—although the precise mechanisms involved remain unknown.

Experimental distention of the uterus with a saline-filled balloon rapidly prompted regular uterine contractions in women carrying live term fetuses or dead fetuses. All were delivered within 21 hours.

Stephen Lye, Ph.D., and his group at the University of Toronto have found increased expression of oxytocin receptor, connexin 43, and the c-fos mRNA in the myometrium. Gillian Bryant-Greenwood, Ph.D., at the University of Hawaii, Honolulu, has shown that stretching of the chorioamniotic membranes in experimental models can increase the expression of interleukin-8 and also another cytokine called visfatin, which can have important effects on the integrity of the membranes.

EAR: I noticed that cervical pathology is also a potential cause of the preterm parturition syndrome. Is this the same as cervical insufficiency?
RR: Yes. Cervical insufficiency is also a cause of the preterm parturition syndrome and can result from congenital disorders, surgical trauma, trauma, or infection. Although cervical length has been touted as a predictor of preterm birth, it is important to remember that a short cervix is not always a ripe cervix. Once again, more research is needed to identify the events that occur as a result of cervical insufficiency, and the ways these affect the initiation of preterm and term labor.

EAR: What about abnormal allograft reaction?
RR: The fetoplacental unit has been called "nature's most successful transplant," or—more accurately—a "semiallograft." The mechanisms that bring about tolerance of this semiallograft are poorly understood. However, transplants of solid organs are tolerated through the establishment of microchimerism in the transplanted organ as well as in the host. Therefore, we consider that microchimerism in pregnancy is probably important for tolerance of the fetoplacental unit. However, I anticipate that under pathologic conditions—just as in the case of transplants—tolerance of the fetoplacental unit may break down, which in turn may lead to a unique form of rejection of the fetoplacental unit. Unraveling the mechanisms of this rejectionlike process is a fascinating challenge. However, ob.gyns. know that the frequency of adverse pregnancy outcomes is higher in mothers who have pregnancies after embryo or egg donation. Under these circumstances, the placenta and fetus are totally foreign because they do not have the normal 50% genetic endowment from the mother. The complications noticed in these pregnancies include not only preeclampsia and growth restriction, but also preterm labor.



EAR: What is the evidence that an allergic phenomenon could be associated with premature labor, and could antihistamines be a treatment for premature labor?
RR: This idea came to me after seeing the relative of an obstetrician who went into premature labor after eating shellfish to which she was allergic. Around that time, we observed that a group of women in premature labor had eosinophils in the amniotic cavity. Eosinophils are associated with an allergiclike phenomenon and are not normally present in the amniotic cavity. The evidence to support biologic plausibility was generated in our work with Dr. Robert Garfield and Dr. Egle Bytautiene. We were able to demonstrate that guinea pigs allergic to egg proteins (ovalbumin) went into premature labor when challenged with the allergen during pregnancy. Premature labor could be prevented by the administration of an antihistamine in these animals.

We have interpreted this as evidence that some patients with premature labor may have an allergiclike reaction or type I hypersensitivity reaction. The nature of the allergen may vary. However, we know that allergens can cross the placenta. For example, dust mite antigen has been demonstrated in the amniotic fluid of women in the midtrimester of pregnancy. Also, there is evidence that the fetus is able to recognize and mount an immune response to allergens in utero.

In response to your question, we have treated with antihistamines some patients who have a typical allergiclike history along with premature labor, and this has resulted in the disappearance of uterine contractions. However, these are anecdotal reports, and I would like to stress that our interest in this mechanism of disease stems from the importance of demonstrating that a common mechanism of disease, such as allergy, can be a cause of the preterm parturition syndrome. This should not be surprising, because the uterus is bestowed with mast cells, the key effector cells of an allergic response, and the uterus has all the components required to generate an allergiclike immune response.

EAR: What is the evidence and importance of hormonal dysfunction in premature parturition?
RR: Progesterone withdrawal and/or deficiency has not yet been specifically demonstrated as an initiator of spontaneous parturition in humans. However, the role of progesterone in maintaining pregnancy is unquestionable.

Indeed, suspension of progesterone action through the administration of progesterone receptor inhibitors and progesterone receptor antagonists can induce activation of the components of the common pathway of parturition in animals and humans.

The progesterone/estradiol and progesterone/estriol ratios in amniotic fluid are lower in laboring than in nonlaboring subjects, and the progesterone/estriol ratio is lower in preterm labor followed by preterm delivery compared with preterm labor followed by term delivery, suggesting that these hormones are important in determining the duration of pregnancy.

Trials of progesterone administration to prevent preterm delivery have shown interesting results. Specifically, two recent randomized clinical trials demonstrated that vaginal suppositories containing natural progesterone, or injections of a progesterone, 17 α-hydroxyprogesterone caproate, to women at risk for preterm delivery seem to reduce the rate of spontaneous preterm delivery. Moreover, in the trial using 17 α-hydroxyprogesterone caproate, infants of mothers treated with this compound had a lower rate of necrotizing enterocolitis, intraventricular hemorrhage, and the need for supplemental oxygen. Further research is needed to identify the ideal progesterone regimen and the patients who may benefit from this intervention.

EAR: What about stress as a cause of premature labor?
RR: Epidemiologic studies have indicated that women exposed to stressful conditions during pregnancy have a mild increase in the rate of spontaneous preterm labor. The work of Dr. Pathik Wadhwa and Dr. Cal Hobel has been seminal in this area.

The precise mechanisms whereby stress causes premature labor implicate corticotropin-releasing hormone (CRH), which is produced by the hypothalamus and—importantly—by the placenta. Dr. Roger Smith's work in Australia has proposed that CRH is the regulator of a placental clock. Dr. Felice Petraglia in Italy has also contributed significantly to establish a link between CRH and premature labor.

The clinical implications of this work are related to the epidemiologic observations reported by Dr. Emile Papiernik in France, noting that women who are prescribed rest during pregnancy had a lower frequency of preterm delivery. This interesting experience has not been explored in the United States.

However, a targeted intervention to the patient at risk—such as the woman who must stand or do significant physical work during pregnancy—may be beneficial. However, bed rest per se is not an effective treatment to prevent all causes of premature labor. It is easy to understand that if the cause of preterm parturition is infection, then bed rest will not cure it.

EAR: What is the final message that you would like the readers of OB.GYN. NEWS take with them?
RR: Preterm labor is not just labor before its time, but is the result of a pathologic process. The challenge for health care providers is to try to identify why a women is in premature labor, what specific mechanism of disease may be involved, how sick the fetus is, and whether the benefits of pregnancy prolongation outweigh the risk of prematurity. The administration of steroids has been demonstrated to reduce the rate of adverse neonatal outcomes, and it is indicated when the patient is at risk for preterm delivery. ■