The Preterm Parturition Syndrome

Preterm Labor Has Multiple Causes

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

Dr. Roberto Romero: The common pathway of parturition consists of the anatomical, physiological, 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 (dilation and effacement), and membrane/decidual activation. In most women, these components are typically activated in a synchronous manner in spontaneous labor. Most women admitted in labor have uterine contractions, cervical changes—and sometimes—rupture of membranes.

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.

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

Dr. Roberto Romero: 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 chorioamniotic 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 prematurity. A transcriptional profile is a snapshot of genes that are being upregulated or downregulated at a particular point in time.

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**Factors Responsible for Preterm Labor**

![Diagram of Factors Responsible for Preterm Labor]

**Cervical pathologies**
- Infection
- Uterine overdistention
- Allergic phenomena
- Ischemia
- Abnormal allograft reaction
- Endocrine disorders

**Source:** Dr. Romero

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**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. 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 rejection-like process is a fascinating challenge. However, ob-gyns know that the frequency of adverse pregnancy outcomes is higher in mothers who have had 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 preecclampsia and growth restriction, but also preterm labor.

**What is the mechanism linking uterine overdistention with premature labor?**

**RR:** Premature rupture of the membranes (pPROM) is a risk factor for preterm birth, and we believe that if the cause of preterm birth is in the membranes, then bed rest will not cure it. 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 labor is in the membranes, and the patients who may benefit from this intervention.

**What is the evidence and importance of hormonal manipulation in preterm 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 Hofel 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 Paipernik 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.**

**What is the final message that you would like the health care providers to try and understand?**

**RR:** It is important to remember that a short cervix is not synonymous with cervical insufficiency, and the ways these affect the initiation of preterm and term labor.