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Spontaneous preterm labor can be predicted and prevented

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Who would have thought 30 years ago that the major advances in the prediction and prevention of the most important problem in obstetrics, spontaneous preterm parturition, would occur through the utilization of ultrasound? This brief narrative describes what has happened, how it unfolded and what lies ahead.

The clinical presentations of spontaneous labor at term and preterm labor are similar in most cases, characterized by the onset of regular uterine contractions. Thus, it was logical to assume, at first, that preterm labor results from a premature activation of the myometrium and that preterm delivery could be prevented by decreasing or arresting uterine contractility. Multiple pharmacologic approaches were tested, including intravenous alcohol, beta-adrenergic agents, anti-prostaglandins, oxytocin receptor antagonists, calcium channel blockers, and nitric oxide donors. All of these agents decreased the frequency of uterine contractions but not the rate of preterm delivery or neonatal morbidity. This led to the conclusion that increased uterine contractility was not the primary cause of premature labor but rather the clinical manifestation of an underlying pathologic process. Further, this concept became easy to accept after recognizing that some women with preterm labor had intra-amniotic infection. Tocolytic agents were shown to be ineffective in delaying delivery in such cases and could cause maternal complications, such as pulmonary edema[1]. Based on these observations, a proposal emerged: there is a fundamental difference between labor at

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term and preterm labor, the former being the result of physiologic activation of the mechanisms of labor and the latter the consequence of activation of labor due to infection or other, yet unrecognized, mechanisms of disease. This provided the basis for the hypothesis that spontaneous preterm parturition is a syndrome caused by one or more pathologic insults[2, 3]. This conceptual framework shifted the focus of research in parturition to the causes responsible for spontaneous preterm labor, emphasizing infection and inflammation. These were the first mechanisms of disease to be causally linked to the syndrome, largely because infection can be easily detected (under normal circumstances, bacteria should not be present in amniotic fluid; therefore, their detection is evidence of a pathologic state). Unraveling the other pathologic processes that could lead to preterm labor proved challenging and fascinating. Potential causes of the syndrome, subsequently recognized, included cervical disease, decline in progesterone action, uterine over-distension, vascular disorders, breakdown of maternal-fetal tolerance, and even allergy-like insults.

Additional insights emerged from comparative studies in term labor and preterm labor. It was recognized that the main clinical entities that lead to spontaneous preterm delivery are increased uterine contractility (often referred to as threatened preterm labor), cervical insufficiency, and preterm prelabor rupture of the membranes (PPROM). The clinical presentations reflected activation of each of the components of what was called ‘the common pathway of labor,” which includes uterine contractility, cervical ripening, and membrane-decidual activation. These components become activated synchronously in spontaneous labor at term, yet asynchronous activation is associated with PPROM, cervical insufficiency, and threatened preterm labor without cervical changes. Strategies for detecting early preterm labor aim to identify the activation of each of the three components, including tocodynamometers or electromyography for the myometrium; sonographic examination for the cervix; and determination of extracellular matrix proteins, such as fibronectin and insulin-like growth factor-binding protein-1, for the detection of membrane-decidual activation. Of these approaches, the one that has yielded important clinical advances is examination of the cervix using ultrasound.

Thirty years have passed since the first report that sonographic measurement of cervical length can help identify patients at risk for preterm delivery after adjusting for parity and obstetric history[4]. Clinical studies worldwide confirmed this observation, which led to randomized clinical trials of the efficacy of vaginal progesterone for the prevention of spontaneous preterm birth in women with a short cervix[5, 6]. These studies were informed by a body of basic and clinical research, which showed that progesterone was important in the regulation of cervical ripening and, specifically, that administration of anti-progestogens induces cervical ripening across pregnancy and that these changes are not often associated with an increase in uterine contractility[7]. Such findings became the basis of another thesis: a decline in progestogen action may be responsible for a subset of patients who had a sonographic short cervix and subsequently delivered preterm. Systematic reviews and meta-analyses have subsequently shown that administration of vaginal progesterone to women with a sonographic short cervix decreases the rate of preterm delivery and neonatal morbidity. Analyses of cost-effectiveness revealed that universal cervical length screening, coupled with the administration of vaginal progesterone, is cost-effective, and implementation research has demonstrated that the introduction of cervical length

assessment reduces the rate of preterm birth in patients with a sonographic short cervix. However, they have yet to embrace universal cervical length assessment during the mid-trimester of pregnancy. Cervical length measurement is simple to perform and inexpensive when incorporated into second-trimester anomaly screening, and it can provide an estimate of the risk for preterm delivery in all pregnant women[8].

The realization of the vision that universal cervical length measurement could be an important step toward achieving personalized obstetrical care in the 21st century is near, given that it is now possible to provide an individualized estimate of risk of preterm delivery based on cervical length and maternal characteristics[9–12]. The development of methods to identify patients who will or will not respond to vaginal progesterone is also important. This will likely be achieved by using biophysical and biochemical methods.

Progress over the last three decades has also allowed us to refine the role of cervical cerclage in obstetrical practice. The efficacy of this treatment has been a subject of controversy for decades. We now know that it is effective in preventing preterm birth in patients who present with acute cervical insufficiency (readily diagnosed with ultrasound) and that it reduces preterm delivery in women with a history of preterm birth and a sonographic short cervix[13]. Indirect meta-analyses suggest that vaginal progesterone and cerclage are equally effective in these patients and that cerclage may have a role in the prevention of preterm birth in patients who do not respond to vaginal progesterone.

This journey of discovery began in large measure when infection was causally linked to preterm labor. What progress has been made on this front? We now know that intra-amniotic infection is present in approximately one-third of all patients who deliver preterm and that it is sub-clinical in 80% of cases. Specific microorganisms responsible have been identified, the most common of which are genital mycoplasmas rather than the typical bacteria involved in neonatal sepsis, such as group B streptococcus and *Escherichia coli*. Genital mycoplasmas are commensal members of the lower genital tract microbiota in women with a normal pregnancy and use an ascending pathway to gain access to the amniotic cavity[14]. A reliable diagnosis requires analysis of the amniotic fluid to detect inflammation, using a white blood cell count and a concentration of glucose or proteins, such as interleukin-6[15] or matrix metalloproteinase-8[16], for which rapid tests are now available. Bacteria can be detected by cultivation or by utilizing new molecular methods based on polymerase chain reaction of microbial genes. Amniotic fluid ‘sludge,’ detected by ultrasound, has emerged as a risk factor for intra-amniotic inflammation, allowing the identification of microbial biofilms in amniotic fluid[17]. Importantly, experimental[18,19] and clinical[20–22] evidence now indicates that intra-amniotic infection and inflammation can be eradicated with the administration of antibiotics to patients with documented infection or inflammation and that this treatment can lead to term delivery. Whether changes in the cervical and vaginal microbiome and local immune response can be used in the prediction of preterm delivery and in the prevention of infection-related preterm delivery is a frontier[23,24]. The recognition that intra-amniotic infection and inflammation can lead to a fetal systemic inflammatory response syndrome[25], which may involve multiple organ systems, including the fetal brain, was an important step given recent experimental evidence that downregulation of the inflammatory response in neonates, using nanodevices[26] or cell-based therapy[27], can be treat neuroinflammation and

prevent cerebral palsy. Additional biomarkers and interventions need to be developed to address the other mechanisms responsible for the spontaneous preterm parturition syndrome, such sterile intra-amniotic inflammation.

In the last three decades, we have learned that the foremost problem of obstetrics, spontaneous preterm parturition, is tractable and that spontaneous preterm labor can be predicted and prevented in a subset of patients. Many of these advances first appeared in the pages of *Ultrasound in Obstetrics and Gynecology* and were presented at the annual congresses of ISUOG. It is now accepted that no single test can predict all cases of spontaneous preterm parturition and that no single intervention can prevent all of them. Progesterone is effective in a subset of patients with a sonographic short cervix but not in those with a history of preterm birth but without a short cervix. Antibiotics can be effective in patients with intra-amniotic infection and intra-amniotic inflammation but not in those without these pathologic processes. The lessons learned in the study of spontaneous preterm parturition are applicable to the other great obstetrical syndromes, such as preeclampsia, fetal growth disorders, and fetal death. Imaging, largely through ultrasound, has been an extraordinary tool for discovery in obstetrics[28].

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