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ISUOG – 30th Anniversary Opinion Article

Spontaneous preterm parturition can be predicted and prevented

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Word Count: 1,526

Keywords: biomarker, cerclage, cervical length, great obstetrical syndromes, intra-amniotic infection, progesterone, sterile intra-amniotic inflammation, ultrasound

This is the author manuscript accepted for publication and has undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1002/uog.23565

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Spontaneous preterm parturition can be predicted and prevented

Who would have thought, thirty 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? Herein, a 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, with the onset of regular uterine contractions. Thus, it was logical to conclude 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 agents decreased the frequency of uterine contractions but not the rate of preterm delivery or neonatal morbidity. That led us to conclude that increased uterine contractility was not the primary cause of premature labor but rather the clinical manifestation of an underlying pathologic process. This was easy to accept after recognizing that some women with premature 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, we propose that there is a fundamental difference between labor at term and premature labor: the former is the result of physiologic activation of the mechanisms of labor, whereas the latter is the consequence of activation of labor due to infection or other yet unrecognized mechanisms of disease. This was the basis for the proposal that premature 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 preterm labor, with an emphasis on infection and inflammation, because it

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was the first mechanism of disease to be causally linked to spontaneous preterm labor (largely because infection was easy to define; under normal circumstances bacteria should not be present in amniotic fluid and its detection is evidence of a pathologic state, infection). Unraveling the other pathologic processes, which could lead to premature labor, proved challenging and fascinating. Potential causes, which were subsequently recognized, included cervical disease, a decline in progesterone action, uterine over-distension, vascular disorders, a breakdown in maternal-fetal tolerance, and even allergy-like insults.

Other insights emerged from comparative studies of term labor to preterm labor. The main clinical entities that lead to spontaneous preterm delivery are 1) increased uterine contractility (often referred to as threatened preterm labor), 2) cervical insufficiency, and 3) preterm prelabor rupture of the membranes, or preterm PROM. We realized that these clinical presentations reflected activation of one of the components of what we had called 'the common pathway of labor," which includes uterine contractility, cervical ripening, and membrane and decidual activation. These components become activated synchronously in spontaneous labor at term, yet asynchronous activation explains preterm PROM, cervical insufficiency, and threatened preterm labor without cervical changes. Strategies for detecting early preterm labor aim to identify the activation of each component: (1) tocodynamometers or electromyography for the myometrium; (2) sonographic examination for the cervix; and (3) 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 with ultrasound.

Thirty years have passed since the first report that sonographic cervical length identifies patients at risk for preterm delivery after adjusting for parity and obstetric history[4]. Clinical studies

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worldwide confirmed this observation, which led to randomized clinical trials of the efficacy of vaginal progesterone in women with a short cervix in the prevention of spontaneous preterm birth[5, 6]. These studies were informed by a body of basic and clinical research that showed that progesterone was important in the regulation of cervical ripening (namely, 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]. This was the basis for the thesis that a decline in progestogen action may be responsible for a subset of patients who had a short sonographic 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 decreased the rate of preterm delivery and neonatal morbidity. Cost-effective analyses have shown that universal cervical length screening, coupled with the administration of vaginal progesterone, is cost-saving and implementation research has demonstrated that the introduction of cervical length assessment reduces the rate of preterm birth. Moreover, professional organizations have recommended the use of vaginal progesterone to reduce 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 is simple to perform, inexpensive when done during second-trimester anomaly screening, and can provide an estimate of risk for preterm delivery in all pregnant women[8].

The realization of the vision that universal cervical length 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]. The development of methods to identify the patient who will and will

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not respond to vaginal progesterone is also important. We believe that this will be possible by using biophysical and biochemical methods.

Progress over the last three decades has also allowed us to refine the role of cerclage in obstetrical practice. The efficacy of this operation has been controversial 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 also reduces preterm delivery in women with a history of preterm birth and a sonographic short cervix[10]. Indirect meta-analyses suggest that vaginal progesterone and cerclage are equally effective in these patients and that the operation 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 by realizing that infection was causally linked to premature 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. The specific microorganisms have been identified; the most common of which are genital mycoplasmas rather than the typical bacterial involved in neonatal sepsis such as group B streptococcus or *Escherichia coli*. Genital mycoplasmas are commensal members of the lower genital tract microbiota in normal pregnant women and use an ascending pathway to gain access to the amniotic cavity[11]. A reliable diagnosis requires analysis of amniotic fluid to detect inflammation using a white blood cell count, glucose determination or proteins such as interleukin-6[12] or matrix metalloproteinase-8[13] for which there are now rapid tests. Bacteria can be detected by culture or using new molecular methods base on PCR of microbial genes. Amniotic fluid ‘sludge’, detected by ultrasound, has emerged as a risk factor for intra-amniotic inflammation and allow the identification of microbial biofilms in amniotic fluid[14]. Importantly, there is now

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experimental[15, 16] and clinical evidence[17-19] 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 to predict preterm delivery and to prevent infection related preterm delivery is a frontier[20, 21]. The recognition that intra-amniotic infection and inflammation can lead to a fetal systemic inflammatory response syndrome[22], which may involve multiple organ systems including the fetal brain was an important step given recent experimental evidence that down regulation of the inflammatory response in neonates with nanodevices[23] or cell-based therapy[24] can be treat neuroinflammation and prevent cerebral palsy. Additional biomarkers and interventions need to be developed to address the other mechanisms of disease responsible for the preterm parturition syndrome such sterile intra-amniotic inflammation.

In these three decades, we have learned that the most important problem of obstetrics, preterm delivery, is tractable, and that spontaneous preterm labor can be predicted and prevented in a subset of patients. Many of these advances, presented at annual congresses of ISUOG, have appeared on the pages of *Ultrasound in Obstetrics and Gynecology*. It is now accepted that no single test can predict all cases of 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 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 extraordinary tool for discovery in obstetrics[25].

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