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Vaginal progesterone to reduce the rate of preterm birth and neonatal morbidity: a solution at last

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Preterm delivery: an important healthcare issue for women & their families

Preterm delivery has been, and remains, the most important challenge to modern obstetrics. In 2009, 13 million babies were born preterm: 11 million in Africa and Asia and 500,000 in the USA [1]. The highest rates of preterm birth are in Africa (11.9%) and North American (10.6%).

Premature neonates are at increased risk of death and short-term complications such as respiratory distress syndrome, Intraventricular hemorrhage, neonatal sepsis and necrotizing enterocolitis. Long-term complications include neurodevelopmental disorders such as cerebral palsy, chronic lung disease, blindness and deafness [2]. The financial cost of preterm birth has been estimated to be US $26 billion per year in the USA alone, but that is only part of the story: the less-appreciated burden of preterm birth is borne by the families caring for preterm babies.

Why has a problem affecting one in ten pregnancies been so difficult to solve?

Preterm birth is defined by the gestational age at which it occurs (<37 weeks of gestation). This is an unusual way of defining a disease in medicine. The norm is to identify pathologic disorders with discreet symptoms and signs caused by specific mechanisms of disease (e.g. *Mycobacterium tuberculosis* causes lung inflammation [pneumonia] and destruction and can be cured by the administration of antibiotics; atherosclerosis can cause multiple myocardial infarctions and cardiac failure. The symptoms and treatment of cardiac failure under these circumstances are well known). The use of age to define preterm birth recognizes only one of the problems – namely, that the greater the organ immaturity at the time of birth, the higher the risk of death and short- and long-term complications. However, age alone does not tell us why the preterm birth occurred, and this has profound consequences as to the prognosis of the newborn and the likelihood that we will ever be able to prevent the different types of preterm birth.

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When we look at the other end of the spectrum of life (i.e., geriatrics), the older an individual is, the more likely it is that she/he would have disease due to organ senescence or cumulative insults experienced during life. Yet, we do not define disease purely on the basis of age, and we treat an elderly individual differently if the cause of the disorder is cardiac failure, pneumonia, renal failure or cancer, and so forth. In obstetrics, we may be guilty of oversimplification by not considering the cause of preterm birth or other obstetrical syndromes with sufficient depth to allow meaningful prevention.

It is now clear that preterm birth is not a single condition. Two-thirds of preterm births occur because women go into spontaneous preterm labor (with intact or ruptured membranes). The remainder are due to preterm deliveries indicated for potentially life-threatening complications of the mother, such as pre-eclampsia or fetal complications, such as intrauterine growth restriction. The complexity of the problem extends further than just whether a preterm birth was spontaneous or induced. A deeper examination reveals that preterm labor with intact membranes, premature rupture of membranes, pre-eclampsia and intrauterine growth restriction are all syndromes caused by multiple mechanisms of disease: 'the great obstetrical syndromes' [3,4]. Therefore, since preterm birth is not a single condition, there will never be a single test to predict it, a single intervention to treat it, or one approach to prevent it all. I believe that oversimplification of the nature of disease in obstetrics has been an obstacle to progress, but with an improved understanding of the unique features of obstetrical disorders, forward movement has begun.

The rediscovery of progesterone as a hormone important for pregnancy maintenance

Progesterone was discovered as a hormone produced by the corpus luteum, essential or pregnancy maintenance. Removal of the ovary with the corpus luteum in the first trimester of pregnancy leads to spontaneous abortion, unless progesterone is replaced. The name of the hormone is intended to remind us of its crucial role in pregnancy ('pro'-in favor; '-gest' –gestation; '-one' –ketone chemical structure). In most mammalian species, progesterone concentrations in peripheral blood drop before the onset of labor at term (a progesterone withdrawal). Nonetheless, this does not occur in human, and therefore, the role of progesterone in pregnancy maintenance beyond the first trimester lost support a few decades ago.

The key concept is that a subset of preterm deliveries are caused by a progesterone deficiency, which is largely subclinical in nature, but can be detected by changes in the uterine cervix observed with ultrasound in the midtrimester (a short cervix). The basis for this hypothesis is that the administration of progesterone receptor antagonists (e.g., RU-486 any time during pregnancy leads to cervical ripening (which includes shortening), and sometimes, the onset of labor. For these reasons, it was proposed that patients with a short cervix may have a progesterone deficiency, which may be corrected by the administration of this hormone in close proximity to the cervix.

A short cervix measured by transvaginal sonography is the most powerful predictor of spontaneous preterm birth

Several cohort studies have now provided incontrovertible evidence that women with a short cervix, detected by transvaginal ultrasound in the midtrimester of pregnancy (18–24 weeks of gestation), are at risk for spontaneous preterm delivery [6–9]. For example, a cervix should be longer than 30 mm during normal pregnancy. Women with a cervix of 15 mm or less have a 50% chance of having a preterm delivery at less than 33 weeks of gestation [6]. This knowledge has not been introduced into routine clinical practice because there was no

intervention to reduce the rate of preterm birth in these women. Indeed, the risk assessment of preterm birth has been largely based on asking patients if they had had a previous preterm birth; such history increases the risk of a recurrent preterm birth. Unfortunately, this approach does not address women who are pregnant for the first time. The advantage of cervical sonography is that it can be used in all patients – nulliparous and parous – and a short cervix predicted preterm delivery in both.

Vaginal progesterone reduces preterm birth & neonatal morbidity in women with a short cervix

The first randomized clinical trial to formally test the effect of progesterone was reported by Fonseca *et al.* from the Fetal Medicine Foundation in the UK [10]. Patients with a cervix of less than 15 mm were randomized to receive vaginal progesterone or placebo. Women allocated to progesterone had a significant reduction (44%) in the rate of preterm birth at less than 34 weeks of gestation (primary endpoint of the trial) [10]. Although this trial did not show an improvement in neonatal outcome, the findings were promising. A secondary analysis of another randomized clinical trial by DeFranco *et al.* suggested that women with a short cervix would benefit from vaginal progesterone gel, and that such treatment could improve neonatal outcome [11,12].

The most recent installment is the PREGNANT trial – which was a multi-institutional, international clinical trial in which more than 30,000 women were screened for cervical length to identify those who had a cervix between 10–20 mm in the midtrimester of pregnancy [13]. Patients allocated to vaginal progesterone gel (90 mg) had a 45% reduction in the rate of preterm birth at less than 33 weeks of gestation (primary endpoint of the trial), and a reduction in the rate of preterm delivery at 35 weeks [13]. Importantly, vaginal progesterone administration was associated with a 50% reduction in the rate of preterm birth at less than 28 weeks of gestation, when infants are at greater risk for short- and long-term complications. All these findings were significant, as was the reduction in the rate of respiratory distress syndrome by 61%. The profile of drug-related adverse events was similar in the vaginal progesterone gel and placebo groups. Moreover, a recent study from Copenhagen has reported that an 18 month follow-up of infants exposed to vaginal progesterone at higher doses than those used in the PREGNANT trial did not yield any differences in physical or neurobehavioral examinations [14]. This result is consistent with the long experience of using progesterone in the first trimester of pregnancy to support women who conceived with assisted reproductive technologies.

The authors of randomized clinical trials of vaginal progesterone have now joined efforts to conduct an individual patient meta-analysis – the results of this meta-analysis will be forthcoming, but patients and physicians should be reassured to know that vaginal progesterone reduces the rate of preterm birth at 35, 34, 32 and 28 weeks of gestation, reduces the rate of respiratory distress syndrome, admission to the Newborn Intensive Care Unit, mechanical ventilation and composite neonatal morbidity. There is remarkable consistency in the results of these trials [Romero R, Nicolaides K; Pers. Comm.].

There is no evidence from randomized clinical trials that 17-alpha-hydroxyprogesterone caproate can reduce the rate of preterm birth in women with a short cervix. This synthetic progestin has been approved for use in women with a prior history of preterm birth, but questions of efficacy and safety remain (see FDA statistical review [101]). One trial designed to confirm the findings of the effectiveness and safety of 17-alpha-hydroxyprogesterone caproate in women with a prior history of preterm birth is in progress (see [102]).

What are the clinical implications of such trials?

It is now possible to implement a universal screening process to assess the risk of preterm birth for all pregnant women [15]. This can be accomplished by performing an ultrasound examination in the midtrimester of pregnancy and measuring the uterine cervix. This step is simple, well-accepted by women and takes 5 min to perform. Women with a short cervix (10–20 mm) can be treated with vaginal progesterone, which reduces the risk of early preterm birth and neonatal complications.

Is this approach cost-effective?

Two studies have recently been published, which indicate that universal screening with cervical length and vaginal progesterone is cost-saving [16,17]. The most recent estimate is that such a policy would save more than $19 million per 100,000 women examined [15,16]. Further studies are required to take into account the results of the individual patient meta-analysis, and such studies are forthcoming.

Future perspective

Although the administration of vaginal progesterone has been effective in the reduction of the rate of preterm birth in singleton gestations, this has not been the case for either natural [18] or synthetic progestogens (17-alpha-hydroxyprogesterone caproate) in twin gestations [19–21]. However, there are indications that the negative trials in twin gestations may be due to the inclusion of all twins, rather than focusing on those who can benefit: mothers with twin gestations and a short cervix [14,22]. Randomized clinical trials are now being planned to address this urgent question, given that twins contribute disproportionately to preterm birth.

Cervical cerclage has been used for decades in obstetrics, and its role has remained poorly defined. Recent evidence suggests that a subgroup of women with a history of preterm birth and a cervix of less than 25 mm may benefit from this procedure [23]. Of course, the question of whether cerclage is better than vaginal progesterone, or whether the two strategies should be used in combination, remains open for further study.

Conclusion

After many efforts to attempt to reduce the rate of preterm birth and neonatal morbidity, a strategy to identify the patient at risk with cervical ultrasound in the midtrimester and a targeted intervention with vaginal progesterone have been shown to reduce the rate of preterm birth and neonatal morbidity [13] and be cost effective [16]. This advance addresses the problem of the prevention of preterm birth in women with a short cervix. Vaginal progesterone is not the solution to prevent all preterm births; however, it is a firm step forward. Other approaches will be necessary to identify women at risk for preterm birth due to other causes, and different interventions will be needed to prevent them [24].

Dedication

The Perinatology Research Branch of Eunice Kennedy Shriver National Institute of Child Health and Human Development conducted the clinical trial in this Editorial. The Branch was established during the tenure of Dr. Bernadine Healy as Director of NIH, as part of her initiative to expand research in women’s health. The author would like to dedicate this Editorial to Bernadine, in recognition of her vision, leadership and contributions to women’s health.

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