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# Progesterone to prevent spontaneous preterm birth

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SUMMARY

Preterm birth is the leading cause of perinatal morbidity and mortality worldwide, and its prevention is an important healthcare priority. Preterm parturition is one of the 'great obstetrical syndromes' and is caused by multiple etiologies. One of the mechanisms of disease is the untimely decline in progesterone action, which can present as a clinically silent sonographic short cervix in the midtrimester. The detection of a short cervix in the midtrimester is a powerful risk factor for preterm delivery. Vaginal progesterone can reduce the rate of preterm delivery by 45% and the rate of neonatal morbidity (admission to the neonatal intensive care unit, respiratory distress syndrome, need for mechanical ventilation, etc.). To prevent one case of spontaneous preterm birth <33 weeks of gestation, 11 patients with a short cervix would need to be treated (based on an individual patient meta-analysis). Vaginal progesterone reduces the rate of spontaneous preterm birth in women with a short cervix, both with and without a prior history of preterm birth. In patients with a prior history of preterm birth, vaginal progesterone is as effective as cervical cerclage to prevent preterm delivery. 17α-Hydroxyprogesterone caproate has not been shown to be effective in reducing the rate of spontaneous preterm birth in women with a short cervix.

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## 1. Introduction

Preterm birth (<37 weeks of gestation) is the leading cause of perinatal morbidity and mortality worldwide, and affects 5–18% of all pregnancies [1]. In 2009, 13 million neonates were born preterm, which included 11 million in Africa and Asia and 500,000 in the USA [2]. The highest rates of preterm birth are in Africa (11.9%) and North America (10.6%) [2]. Short- and long-term complications of preterm birth are well known to obstetricians and pediatricians [3–10]. The financial cost of preterm birth has been estimated to be $26 billion per year in the USA alone [11]. Families bear a less appreciated burden of preterm birth, which is caring for preterm infants.

The challenge of the prediction and prevention of preterm birth has been difficult to address. Recent developments suggest that it is possible to identify a subset of patients at risk for preterm delivery, and to prevent this adverse pregnancy outcome with the use of progestogens. In this article, we review an important conceptual framework about spontaneous preterm birth – specifically, the role of progestogens to prevent preterm delivery.

## 2. Defining a medical disorder (preterm birth) on the basis of gestational age alone: a pitfall

Preterm birth is defined by the gestational age at which it occurs (conventionally <37 weeks of gestation); yet, age is an unusual way of defining disease in medicine [3]. The norm is to identify pathologic conditions associated with discrete symptoms and signs caused by specific mechanisms of disease [3]. For example, *Mycobacterium tuberculosis* is able to induce lung inflammation (pneumonia), which is clinically manifested by fever, cough, expectoration, etc., and can be cured with the administration of antibiotics. Using age to define a medical condition or disease state recognizes only one of its 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 [3]. However, the age at birth, by itself, is not informative as to why preterm birth occurred. The causes of preterm birth have important implications for the prognosis of the newborn [12–20].

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Similarly, at the other end of the life spectrum (i.e. geriatrics), the older an individual, the more likely it is that he/she will have a disease state (secondary to senescence); yet, disease is not defined purely on the basis of age [3]. An elderly individual is treated differently if the cause of the symptoms (e.g. cough) is cancer, congestive heart failure or pneumonia. One of the issues impeding progress in the prevention of preterm birth is the failure to consider the specific causes responsible for this condition [21].

## 3. Preterm birth is not a single condition

Two-thirds of preterm births occur because women go into spontaneous labor with intact or ruptured membranes; the other third result from indicated preterm deliveries for potentially life-threatening conditions (e.g. pre-eclampsia) or fetal complications (e.g. intrauterine growth restriction) [3]. The complexity of the problem extends further – spontaneous preterm labor, prelabor rupture of membranes (PROM), pre-eclampsia, and intrauterine growth restriction are all syndromes caused by multiple etiologies. We have coined the term 'great obstetrical syndromes' to reframe the concept of obstetrical disease [21–23]. Such syndromes are characterized by: (i) multiple etiologies; (ii) a long preclinical stage; (iii) frequent fetal involvement; (iv) clinical manifestations that are often adaptive in nature; and (v) gene–environment interactions that may predispose to the syndromes [21–23].

## 4. Preterm parturition syndrome

We have proposed that preterm labor is a syndrome characterized by activation of the common pathway of parturition, which we have defined as the anatomical, biochemical, endocrinological, and clinical events that occur in term and preterm parturition [21,24,25]. The uterine components of the common pathway include: (i) increased uterine contractility; (ii) cervical ripening; and (iii) decidual membrane activation (Fig. 1) [21,24,25]. A crucial difference between term and preterm labor is that the former represents 'physiologic activation of the common pathway', whereas the latter represents a pathologic process ('pathologic activation that extemporaneously activates components of the common pathway') (Fig. 2) [24–26].

Activation of the different uterine components of the common pathway of parturition may be synchronous or asynchronous [27]. Synchronous activation results in clinical spontaneous preterm labor, whereas asynchronous results in a different clinical presentation (referred to, by some, as a phenotype). For instance, predominant activation of the membranes would lead to preterm PROM; of the cervix, to cervical insufficiency; and of the myometrium, to increased preterm uterine contractions (Fig. 3) [24]. The activation of each component confers a different risk for impending preterm delivery. For example, in most cases, the rupture of membranes is followed by the onset of labor within a short period of time. By contrast, most patients who present with increased uterine contractility at an early gestational age deliver at term. Acute cervical insufficiency (formerly called 'cervical incompetence') may lead to a late spontaneous abortion or early preterm delivery within days or weeks after the diagnosis [25,28–31]. An isolated short cervix in the midtrimester is an example of asynchronous activation of the common pathway of parturition because, in general, patients do not have increased uterine contractility or evidence of ruptured membranes. The mechanisms of disease responsible for the preterm parturition syndrome are shown in Fig. 4 [32], and the evidence in support of this has been reviewed elsewhere [21].

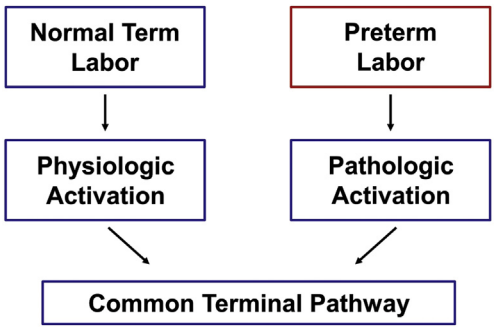


**Fig. 2.** Normal spontaneous labor at term results from physiologic activation of the common pathway of parturition. By contrast, preterm labor begins because of a pathologic insult, resulting in the initiation of labor. Reproduced with permission from Romero et al. [25].

## 5. Progesterone: a key hormone for pregnancy maintenance

Progesterone was discovered as a hormone produced by the corpus luteum, essential for pregnancy maintenance [33–39].

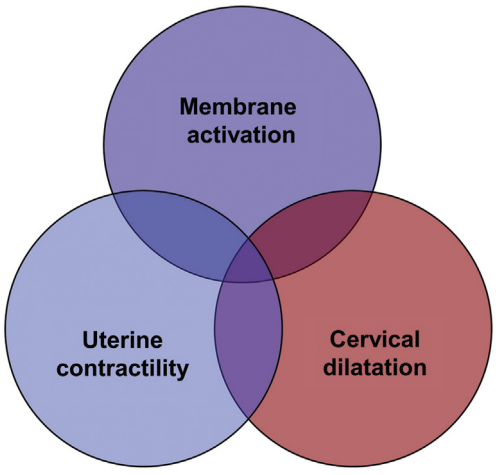


**Fig. 1.** Uterine components of the common pathway of parturition. Reproduced with permission from Romero et al. [24].

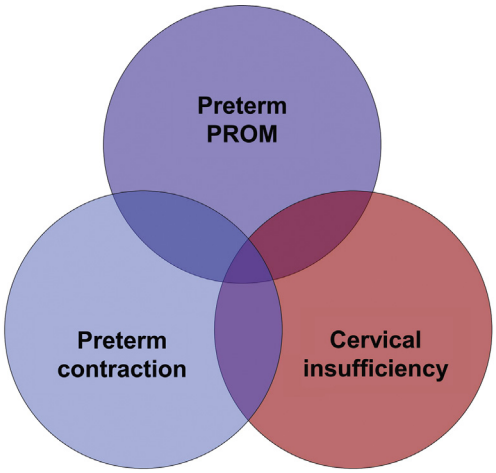


**Fig. 3.** Clinical manifestations of preterm activation of the common pathway of parturition. PROM, prelabor rupture of membranes. Reproduced with permission from Romero et al. [24].