



Multiple Mechanisms of Preterm Labor Other Than Intrauterine Infection

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Abstract

The causes of preterm labor and delivery have multiple antecedents and contributing factors. Spontaneous preterm labor with intact fetal membranes more commonly occurs in association with multifetal pregnancy, intrauterine infection, cervical insufficiency, hydramnios, and uterine abnormality. Also, the degree of uterine stretch in cases of multifetal pregnancy, hydramnios, or uterine abnormality affects the course of preterm labor. The risk of preterm labor is known to be increased by several maternal infections (e.g., urinary tract infection) as well as appendicitis and periodontal disease. Maternal infections other than intrauterine infection may cause endotoxin-induced uterine attack leading to preterm labor. Other contributing factors that affect the frequency of preterm labor are several genetic factors, environmental factors, the interval between pregnancies, and prior preterm birth. The latter is one of the most important risk factors for preterm labor: The recurrent risk of preterm delivery is threefold greater for women with a previous preterm delivery than for women whose first delivery was at term. Also, the maternal lifestyle factor of insufficient as well as excessive maternal weight gain increases the risk. This chapter introduces these multiple mechanisms of preterm labor and delivery, with the exception of intrauterine infection.

Keywords

Preterm labor · Multifetal pregnancy · Hydramnios · Uterine abnormalities · Urinary tract infection · Appendicitis · Periodontal disease · Inadequate maternal weight gain · Prior preterm birth

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8.1 Multiple Mechanisms of Preterm Labor and Delivery

Direct causes of preterm births other than maternal or fetal indications are spontaneous preterm labor with intact membranes, idiopathic preterm premature rupture of membrane (PPROM), and twins or higher-order multifetal births. Among preterm births, 40–45% are due to spontaneous preterm labor and 30–35% are due to preterm membrane rupture [1]. More than one in every two twins and more than nine of every ten triplets are born preterm or with low birth weight in the USA [2]. The causes of preterm labor and delivery have multiple antecedents and contributing factors [3]. The common findings associated with spontaneous preterm labor with intact fetal membranes are multifetal pregnancy, intrauterine infection, cervical insufficiency, hydramnios, and uterine abnormalities. Several maternal illnesses including infections (e.g., urinary tract infection), appendicitis, and periodontal disease increase the risk of preterm labor, and several genetic and environmental factors affect the frequency of preterm labor. These wide-ranging factors all lead to premature cervical dilation and effacement and premature activation of uterine contractions [4]. However, the findings of recent animal studies support the notion that preterm birth is not always an acceleration of the normal process. The four major causes of preterm birth are uterine distention, maternal-fetal stress, premature cervical changes, and infection, and the etiology determines which of the various pathways that induce early parturition is activated [4]. In the following sections, we look in more detail at some of the specific antecedents and contributing factors to preterm labor and delivery other than intrauterine infection.

8.2 Multifetal Pregnancy

Twins or higher-order multifetal births account for approximately 3% of neonates born in the USA [2], and preterm delivery continues to be the major cause of the high rates of perinatal morbidity and mortality associated with multifetal pregnancies. Preterm labor affects up to 50% of twin deliveries, 75% of triplet deliveries, and 90% of quadruplet deliveries [5]. Similar to cases of singleton preterm labor, intraamniotic infection is documented in approximately one-third of twin pregnancies [6]. In multifetal pregnancies, the causes of preterm labor are related to the effects of uterine stretch, with early uterine distention thought to act in initiating the expression of contraction-associated proteins in the myometrium [7]. More recent reports suggest that as uterine stretch increases, levels of gastrin-releasing peptides increase and promote myometrial contractility. The influence of uterine stretch on the cervix should also be considered, because premature stretch may be the starting point of events that accelerate the timing of uterine activation, including cervical ripening [4].

8.3 Hydramnios

Hydramnios is an abnormal increase in amniotic fluid volume that complicates 1–2% of pregnancies [8]. Its underlying causes include fetal anomalies in

approximately 15% of cases and diabetes in 15–20%. Although a diagnosis of exclusion, idiopathic hydramnios accounts for up to 70% of hydramnios cases. Maternal symptoms typically appear only when hydramnios is severe or develops rapidly: Acute hydramnios tends to develop earlier in pregnancy and may cause preterm labor, whereas the gradual accumulation of excessive abdominal distention in chronic hydramnios tends not to cause much discomfort [4]. The causes of preterm labor in hydramnios are related to the effect of uterine stretch as well as to multifetal pregnancy [4].

8.4 Uterine Abnormalities

The population-based prevalence of congenital uterine abnormalities is 0.4–10%, but these abnormalities occur at a significantly higher rate in woman with recurrent miscarriage [9]. In the general population, the most common finding is arcuate uterus, followed in order by septate, bicornuate, didelphic, and unicornuate uterus. These Mullerian anomalies carry significant obstetric risks, including first- and second-trimester miscarriage, malpresentation, fetal-growth restriction, fetal demise, prematurity, ruptured membranes, and preterm delivery [10]. The causes of preterm labor in cases of uterine abnormality are also related to the effect of uterine stretch and to multifetal pregnancies [4].

8.5 Maternal Infections Other Than Intrauterine Infection

Several maternal infections increase the preterm labor risk. Endotoxins released in bacterial infections readily stimulate myometrial contractility. Also, other mechanisms may allow bacteria into the intrauterine cavity during pregnancy: there may be ascending infection, retrograde flow of infection into the peritoneal cavity via the fallopian tubes, or transfer of maternal systemic infection via the placenta [11].

8.5.1 Urinary Tract Infections

Urinary tract infections are the most common bacterial infections seen in pregnant women. Almost all urinary tract infections are due to ascending infection by bacteria in the normal vulvar flora. Most urinary tract infections present as asymptomatic bacteriuria without significant symptoms, but they can sometimes cause clinical infections such as cystitis and pyelonephritis. Several studies have investigated whether asymptomatic bacteriuria affects maternal and fetal perinatal outcomes. Although there is no consensus yet, the results of some studies suggest that asymptomatic bacteriuria is associated with preterm delivery and low birth weight [12]. Acute pyelonephritis is one of the most important bacterial infections encountered in pregnant patients and can sometimes become serious. Endotoxins induce uterine contractions, but most infections are transient and most begin resolving with fluid replacement and antibiotics [13]. Tocolytic therapy for

pregnant women with pyelonephritis should be selected carefully because beta agonists can cause pulmonary edema associated with vascular hyperpermeability in these patients [14].

8.5.2 Appendicitis

Diagnosis of appendicitis is much more difficult in pregnant women than non-pregnant women. This is because the cardinal symptoms of appendicitis, nausea and vomiting, are difficult to differentiate from symptoms caused by uterine enlargement during a normal pregnancy, and the enlarged pregnant uterus can shift the position of the appendix [15]. However, many studies have shown that peritonitis caused by appendiceal perforation is associated with very poor maternal and fetal outcomes. Therefore, it is important to quickly initiate surgical treatment when appendicitis is suspected even if a definitive diagnosis has not been reached [16]. Appendicitis during pregnancy is known to increase the risk of miscarriage and preterm delivery. This risk is even more pronounced when peritonitis occurs due to appendiceal perforation. In a large study of 908 pregnant women with appendicitis, rates of preterm delivery and low birth weight were 1.5–2 times higher in the appendicitis group than in the control group [17].

8.5.3 Periodontal Disease

Several recent studies have noted an association between periodontal disease and preterm delivery [18]. Offenbacher et al. found that the rate of preterm delivery was about seven times higher in pregnant women with periodontal disease than in those without periodontal disease [19]. Hautz et al. found that 24 of 28 pregnant women who delivered at 32 weeks or earlier had periodontal disease, and their rate of preterm delivery was four times higher than that in pregnant women without periodontal disease [20]. Research indicates that this could be due to the association between intraoral bacteria, particularly *Fusobacterium nucleatum* and *Capnocytophaga* species, and upper reproductive tract infection. There is no consensus regarding the effect of periodontal disease prevention on preterm delivery. A meta-analysis of prevention and treatment of periodontal disease showed a reduced rate of preterm delivery, but a randomized controlled trial showed no significant difference [21].

8.6 Lifestyle Factors

Inappropriate gestational weight gain is known to be a lifestyle factor that increases the risk of preterm delivery [22]. Other maternal lifestyle factors that have been implicated in preterm delivery include smoking, young age, old age, poverty, and short height. There are varying opinions regarding whether working conditions

during pregnancy are associated with preterm delivery, but one study showed that working more than 40 h a week in a job that requires standing for long periods increases the rate of preterm delivery [23]. Systems for predicting preterm delivery based on combinations of these risk factors have been devised, but none has been found effective to date.

8.7 Genetic Factors

For some time, the hypothesis that genetic factors are involved in preterm delivery has frequently been proposed. The findings that preterm delivery tends to recur, patients can have a family history, and incidence differs between races support this hypothesis. Several studies on the association between mutations and preterm delivery have been published over the past several years especially [4].

8.8 Interval Between Pregnancies

It has been known that a short interval between pregnancies is associated with the rate of preterm delivery in patients with a history of preterm delivery. Recent studies have shown that the interval between pregnancies is associated with poor perinatal outcomes regardless of history of preterm delivery. A meta-analysis from 2006 showed that the risk of preterm delivery or low birth weight increases when the interval between pregnancies is <18 months or more than 59 months [24].

8.9 Prior Preterm Birth

The most important risk factor is a history of preterm delivery. Prior preterm delivery during the second trimester in particular is strongly correlated with preterm delivery in the next pregnancy, as it increases risk by six to eight times. A study of 16,000 deliveries at Parkland Hospital showed that pregnant women with a history of preterm delivery had a threefold higher risk of preterm delivery of the next pregnancy than those who previously delivered at term. In addition, more than one-third of pregnant women with two prior preterm deliveries had a preterm delivery in the next pregnancy [4, 25]. A retrospective study conducted by Ananth et al. in 2006 that investigated outcomes of the next pregnancy after preterm delivery in about 150,000 deliveries showed that the rate of spontaneous preterm delivery of the next pregnancy was 3.6 times higher in women with a prior spontaneous preterm delivery [26]. Risk of recurrent preterm birth is influenced by three factors: the frequency of prior preterm deliveries, severity as measured by gestational age, and the order in which the prior preterm delivery occurred [27]. Thus, an individual woman's risk for recurrent preterm birth is influenced by her past number and term births.

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