

1 The diagnosis and management of preterm labor with intact membranes

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INTRODUCTION

A preterm birth is one that occurs between fetal viability and 37 completed weeks of gestation (1–4). Delivery of a previable conceptus represents a spontaneous abortion rather than a preterm birth. Although the definition of “viability” varies among countries and even medical centers, the central idea is that a nonviable infant is so immature that there is no likelihood of survival in the extrauterine environment despite all medical support.

Prior to modern developments in neonatal care, a nonviable infant was defined as one weighing less than 500 g (see below). This definition is discouraged because preterm delivery should be defined by gestational age at birth, rather than birth weight. Although some have proposed to define a preterm birth as one that occurs between 20 and 37 weeks of gestation, we prefer to define preterm birth as one occurring between 24 and 37 weeks of gestation. Some neonates can survive if born around 24 weeks of gestation, but none at 20 weeks (5–8). This definition may need to be revised in the future if technological advances allow substantial survival of neonates born at less than 24 weeks of gestation.

A birthweight of 500 g has historically been used to define viability. However, this approach has limitations since viable neonates born after 24 weeks of gestation may be affected by intrauterine growth restriction (IUGR) and have birthweights below 500 g. Conversely, some previable infants may weigh more than 500 g. The threshold of 500 g is valuable when there is uncertainty about gestational age. An accurate definition of preterm birth has implications for the calculation of vital statistics and comparisons of the rates of preterm delivery among different countries and populations, an issue that is often overlooked (1).

Spontaneous Vs. Indicated Preterm Birth

Preterm births can be spontaneous or “indicated.” Spontaneous preterm labor can occur with either intact or prelabor rupture of the (fetal) membranes (PROM). “Indicated” preterm births are those that result from induced preterm labor or preterm cesarean delivery for maternal or fetal indications, such as pre-eclampsia and/or IUGR (3,9–13). Other causes include severe medical or surgical complications of pregnancy, some congenital anomalies, and complications of twin gestations (in particular, complications of monochorionic twins).

Of all preterm deliveries, spontaneous preterm labor with intact membranes occurs in 45% (23.2–64.1%), spontaneous

preterm labor following PROM occurs in 30% (7.1–51.2%), and preterm birth as a result of an indicated delivery occurs in 25% (18.7–35.2%) (14,15). In the United States, the rate of preterm delivery has increased by 14% since 1990—this has been attributed to “indicated” preterm births of singleton gestations, multiple gestations, and increased numbers of older parturients (16). Preterm births have been classified by gestational age. Table 1 presents the classification of preterm birth according to gestational age at birth and the contribution of each stratum (3).

THE COMMON PATHWAY OF TERM AND PRETERM LABOR

The traditional view that has dominated the study of preterm parturition is that spontaneous labor at term and preterm labor fundamentally involves the same processes, albeit occurring at different gestational ages. Indeed, term and preterm labor share a common pathway. We have defined the “common pathway of parturition” as the anatomic, biochemical, endocrinologic, and clinical events that occur in the fetus and/or mother in both term and preterm labor (17–22). Broadly conceptualized, the common pathway of parturition can be considered to have uterine (maternal and fetal) and extrauterine components. The uterine components (which are a subject of wide attention in clinical obstetrics) include increased uterine contractility, cervical ripening, and decidual/membrane activation (17,18). The extrauterine components include endocrinologic and metabolic changes associated with labor. For example, labor is associated with increased caloric metabolic expenditures (21), and an increase in maternal and fetal cortisol (20).

A fundamental difference between term and preterm labor is that the former results from “physiologic activation” of the common pathway, while the latter results from a pathologic process (pathologic activation) that extemporaneously activates one or more components of the common pathway (22).

Activation of the uterine components of the common pathway of parturition may be synchronous or asynchronous. Synchronous activation will result in clinical spontaneous preterm labor, and asynchronous activation will result in a different phenotype. For example, predominant activation of the membranes would lead to preterm PROM, of the cervix to cervical insufficiency, or of myometrium to preterm uterine contractions (Figs. 1 and 2). The activation of each component

This work is based on several review articles and chapters published previously by the first author in other publications. This work has been modified and adapted for this textbook. The original chapters are referenced and contain a more extensive discussion of the subject. This chapter has a clinical emphasis. The work has been primarily done by Roberto Romero, who is a government employee, and therefore, is not subject to copyright.

Table 1 Classification of Preterm Birth According to Gestational Age at Birth and the Contribution of Each Stratum

Proposed classification	Gestational age at birth (in weeks)	Frequency
Extreme preterm birth	<28	5%
Very early preterm birth	28 to 30-6/7	15%
Early preterm birth	31 to 33-6/7	20%
Late preterm birth	34 to 36-6/7	60–70%

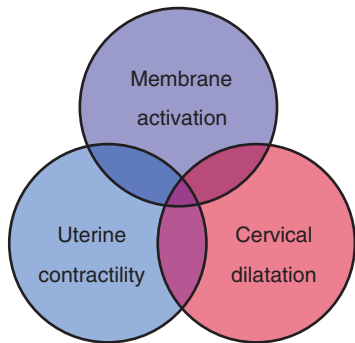


Figure 1 Uterine components of the common pathway of parturition. *Source:* From Ref. 22.

confers a different risk for impending preterm delivery. For example, rupture of membranes is followed by the onset of labor in most cases within a short period of time. In contrast, most patients who present with increased uterine contractility without cervical change at an early gestational age deliver at term. Acute cervical insufficiency (formerly called “cervical incompetence”) may lead to late spontaneous abortion or early preterm delivery days or weeks after the diagnosis (23,24).

SPONTANEOUS PRETERM LABOR AS A SYNDROME

Preterm labor with intact membranes is a “syndrome” caused by multiple etiologies. The term “syndrome” refers to a combination of symptoms or signs identified as a discrete clinical entity (25). Symptoms and signs of preterm labor include increased uterine contractility, changes in cervical status (dilatation and effacement), and/or changes in membrane status (i.e., activation, which can be expressed subclinically as a positive fetal fibronectin, or overtly, such as rupture of membranes).

The proposed etiologies of the preterm labor syndrome are presented in Figure 3. The main causes are (i) intra-amniotic infection/inflammation (26–57); (ii) vascular disease mediated through ischemia (58–64); (iii) uterine overdistension [twin gestations (65), patients with polyhydramnios (66,67), and Müllerian duct abnormalities (68)]; (iv) stress (69–73); (v) cervical disease [congenital after diethylstilbestrol exposure (74–79), post-traumatic after conization (80–88), etc. (89)]; (vi) hormonal disorders that mediate a suspension of progesterone actions (90–98); (vii) allergic disease (99–107); and (viii) an abnormal allogeneic response in which there is a rejection-like mechanism by the maternal immune system of the conceptus (108–112).

We also believe that the entire spectrum of the mechanisms of the preterm labor syndrome has not been fully elucidated. In addition, some patients have preterm labor because more than

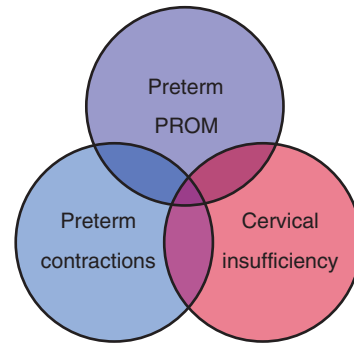


Figure 2 Clinical manifestations of preterm activation of the common pathway of parturition. *Source:* From Ref. 22.

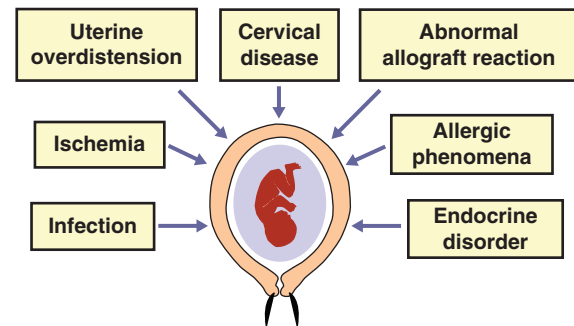


Figure 3 The preterm parturition syndrome. *Source:* From Ref. 25.

one mechanism of disease operates simultaneously. For example, subclinical intra-amniotic infection leads to preterm labor through an inflammatory mechanism that involves chemokines, cytokines, and prostaglandins; yet, one of the effects of IL1 β (a cytokine involved in preterm parturition) can decrease progesterone action through activation of NF κ B (113–115). This transcription factor may lead to preterm cervical ripening and also to the activation of membrane and decidua. The interested reader is referred to recent reviews of the mechanisms responsible for the preterm labor syndrome (3,116).

There is an extensive body of epidemiologic literature identifying risk factors for preterm labor and delivery—for example, individuals of African-American origin (12,117–119), those with a low body mass index (120–124), or patients who smoke during pregnancy (125–127) are at increased risk (Table 2 lists commonly identified risk factors). Yet, the precise pathologic mechanism responsible for the increased risk has not been elucidated.

THE DIAGNOSIS OF PRETERM LABOR

The Importance of Diagnosis

The clinical diagnosis of preterm labor is important because patients at risk for preterm delivery can be offered (i) admission to the hospital, (ii) assessment for intra-amniotic infection, (iii) steroids, (iv) tocolysis, (v) antibiotic prophylaxis against group B streptococci, (vi) transport to a tertiary care center, and (vii) the option of magnesium sulfate for neuroprotection.

Criteria to Increase the Index of Suspicion

Preterm labor is suspected in patients with preterm gestations (before 36-6/7 weeks of gestation) who present with symptoms of increased uterine contractility, vaginal bleeding, pelvic

*Table 2 Risk Factors Associated with Preterm Delivery***Sociobiological variables**

Age <17 years, >35 years
 Low BMI or pre-pregnancy weight <50kg (<120lbs)
 Poor nutritional status
 Single marital status
 Lower socioeconomic status
 Lower education
 Smoking
 Heavy alcohol consumption
 Illicit drug use (cocaine, heroin, etc.)
 Social factors (e.g., poor access to care, physical abuse)
 Working conditions—shift work, standing for long periods of time (>8 hours)

Past obstetric/gynecologic history

Prior preterm birth
 Multiple therapeutic and/or spontaneous abortions
 Uterine anomalies
 Cervical surgery (cone biopsy, LEEP)

Characteristics of current pregnancy

Short inter-pregnancy interval (<6 months)
 In vitro fertilization/assisted reproductive techniques
 Multiple gestation
 Fetal conditions (e.g., structural malformations, chromosomal abnormalities, IUGR, fetal demise)
 Antepartum hemorrhage
 Amniotic fluid abnormalities—polyhydramnios, oligohydramnios
 Maternal medical conditions (e.g., hypertension, diabetes, asthma, thyroid disease)
 Maternal abdominal surgery
 Psychological factors (e.g., stress, depression)
 Infections during pregnancy (e.g., chlamydia, gonorrhea, trichomonas, bacterial vaginosis, asymptomatic bacteriuria, urinary tract infection, pyelonephritis, severe viral infections)
 Short cervical length
 Positive fetal fibronectin between 22 and 34 weeks
 Preterm contractions

Abbreviations: LEEP, loop electrosurgical excision procedure; IUGR, intrauterine growth retardation.

pressure and/or pain, expulsion of the mucus plug, and leakage of amniotic fluid. The latter is particularly important because if rupture of membranes is present, the management and prognosis are different from those of patients with preterm labor and intact membranes (15,128). For example, tocolysis is not indicated in patients with preterm prelabor rupture of membranes (129) (see the chapter on preterm PROM in this book).

“Threatened Preterm Labor,” “False Preterm Labor,” and “Rule out preterm labor”

Some authors and textbooks have employed these terms because approximately 15% of pregnant women present with symptoms and signs consistent with preterm labor, yet they do not deliver preterm (130). Results of randomized clinical trials of beta-adrenergic agents have shown that 47% to 50% of patients admitted with symptoms of preterm labor randomized to placebo treatment deliver at term (131). Some investigators have interpreted such findings as indicating that these patients were in “false preterm labor” or “threatened preterm labor” because they delivered at term when treated with placebo (intravenous hydration). However, there is an

implicit problem in requiring that a patient delivers preterm for the diagnosis of preterm labor to be correct: such view would imply that preterm labor inevitably leads to preterm delivery. In the pre-antibiotic era, pyelonephritis was associated with preterm labor and delivery. After the introduction of antibiotics (132), pyelonephritis has been associated with preterm labor but not necessarily preterm birth (133,134). This indicates that labor has a reversible phase in which early treatment may prevent preterm delivery (135).

The pathologic process responsible for preterm labor can have a spectrum of severity. Mild insults that can be managed by the homeostatic system do not lead to preterm delivery, but more severe insults would be required for progression to preterm delivery. A pregnant woman who sustains mild abdominal trauma (such as an automobile accident or a fall) may experience increased uterine contractility which eventually subsides. However, if the trauma leads to preterm separation of the placenta (abruptio placentae), preterm labor/delivery may occur.

True or False Labor: a Diagnostic Challenge

The diagnostic dilemma described in the previous paragraph is not exclusive to preterm labor, but it also applies to labor at term. Labor is a retrospective diagnosis that can be made with certainty only when the patient has delivered or when delivery is inevitable (e.g., a patient with preterm labor and advanced cervical dilation who has spontaneous rupture of membranes or, alternatively, a patient with preterm labor who is in the second stage of labor). Except for these rare circumstances, physicians will often encounter a patient who has some degree of activation of the three components of the terminal pathway of parturition (increased uterine contractility, cervical changes, and/or membrane decidual activation) and will need to decide whether or not to initiate therapeutic intervention.

The diagnosis of labor at term is also challenging. Nonetheless, the risk of an inaccurate diagnosis is lower because a fetus at term does not require steroids and other interventions which may be beneficial to the preterm neonate. Thus, the diagnosis of “false labor” at term carries different consequences from a misdiagnosis of preterm labor. Patients diagnosed with “false labor” at term typically present as if they were in the latent phase of labor and stop contracting after the administration of sedation, analgesia, or during a period of observation. Yet this diagnosis of “false labor” is not always correct; many labor wards have at least one story of a patient sent home who has delivered a few hours later outside the hospital or on her way back to the hospital. Since the neonates are born at term, such diagnostic errors generally do not have serious consequences; however, the possibility of shoulder dystocia, other obstetrical complications, or neonatal emergencies can transform this situation into a tragedy.

Does “False Preterm Labor” have Any Consequences?

Clinicians believe that an episode of preterm labor that resolves itself is benign. Yet these patients remain at risk for recurrent episodes of preterm labor and, more importantly, preterm delivery (136–138). An explanation for this is that a subclinical pathologic process may underline an episode of preterm labor. If the pathologic process worsens, this eventually may lead to preterm labor and delivery.

Synchronous and Asynchronous Activation of the Common Pathway

Activation of the common pathway of labor can occur with recruitment of the three components (i.e., synchronous) or with activation of mainly one component (i.e., asynchronous) (Figs. 1 and 2). The phenotypic definitions of the preterm labor syndrome depend on the specific pathway activated.

Most physicians and patients focus on increased uterine contractility as a sign of preterm labor—such symptoms are easily detected by patients and verifiable by the health-care provider. In contrast, cervical ripening (effacement and dilatation) is largely subclinical, and its diagnosis requires a pelvic examination or transvaginal sonography. Some patients may present with a short cervix (and even visible membranes) in the absence of demonstrable contractions—this phenotype is consistent with cervical insufficiency, typically occurring in the midtrimester.

Similarly, mild activation of the decidual/membrane component of the common pathway of labor is largely subclinical and can be detected by an elevation in the concentration of molecules involved in extracellular matrix degradation, such as fetal fibronectin (139–143), IL-6 (144–148), and matrix metalloproteinases (MMPs) (149–151) in the cervicovaginal fluid. Most asymptomatic patients with a positive fetal fibronectin after 22 weeks of gestation do not deliver preterm (even though the relative risk for preterm delivery is increased) (143,152,153). This indicates that decidual/membrane activation of this common pathway can occur without leading to inevitable preterm labor and delivery.

The Clinical Diagnosis of Preterm Labor

With the introduction and widespread utilization of tocolytic agents, several definitions of preterm labor were proposed. Notably, in 1975, Ingemar Ingemarsson (154) proposed that the criteria for the diagnosis should include (i) painful regular uterine contractions occurring at intervals of less than 10 minutes for at least 30 minutes by external tocography, (ii) a cervix that is effaced or almost effaced and dilated at least 1 to 2 cm, (iii) intact membranes, and (iv) a gestational age between 28 and 36 weeks. This definition was the basis for a randomized, double-blinded clinical trial of terbutaline in women with preterm labor and intact membranes (154). The gestational age limitation reflected neonatal survival at the time. Importantly, two components of the common pathway were required for the diagnosis (increased myometrial contractility and cervical change). Gonik and Creasy wrote a clinical opinion in 1986 (155), in which they proposed a definition of preterm labor that has been used subsequently in the literature. The definition is based on uterine contractility and cervical change, and was proposed to select patients for tocolytic treatment. A change in cervical status was required because of the concern about overtreating patients with painful Braxton-Hicks contractions without other evidence of preterm labor (156–158).

Uterine Contractility

Increased uterine contractility can be present in the absence of cervical change. Two types of uterine contractions have been identified using electromyography (159): (i) “contractures,” which are epochs of myometrial activity leading to a modest increase in intrauterine pressure and are of long duration, and

(ii) “contractions,” which are of short duration but increase intrauterine pressure. A switch from a predominant “contracture pattern” to a predominant “contraction pattern” can occur during normal labor or be induced by pathologic events such as intra-abdominal surgery, infection, or food withdrawal. The molecular basis of this switch is thought to be the development of gap junctions, which increase the transmission of cell-to-cell communication in the myometrium during labor. Efforts to differentiate contractures from contractions using clinically available external tocodynamometry have failed to distinguish between the patient at risk for preterm delivery and the one who is not at risk (160). Therefore, uterine contractility alone is not sufficient to reliably diagnose preterm labor. Recent modalities that use external electromyography may improve such a diagnosis, but these techniques are not yet clinically available (161–165).

Sonographic Cervical Length

The most important advance in the diagnosis of preterm labor has been the introduction of transvaginal sonography (79,166–168). Many investigators have shown that transvaginal sonography is more accurate than digital examination of the cervix (to assess dilatation and effacement) in predicting the risk of preterm birth (168,169). The data consistently indicate that women with a long cervix (defined as >30mm) have a likelihood of preterm delivery of less than 5% (169,170). In contrast, women with preterm uterine contractions and with a cervical length of <15mm have a probability of preterm delivery of 63% (171). Figure 4 illustrates the probability of preterm delivery in patients presenting with an episode of preterm labor—the shorter the cervix, the greater the risk of preterm delivery (168,172–174). Moreover, the shorter the cervix and the earlier the gestational age at presentation, the greater the risk of intra-amniotic infection (175).

Fetal Fibronectin

Another test frequently used to assess the risk of preterm delivery is fetal fibronectin. This glycoprotein is present in the

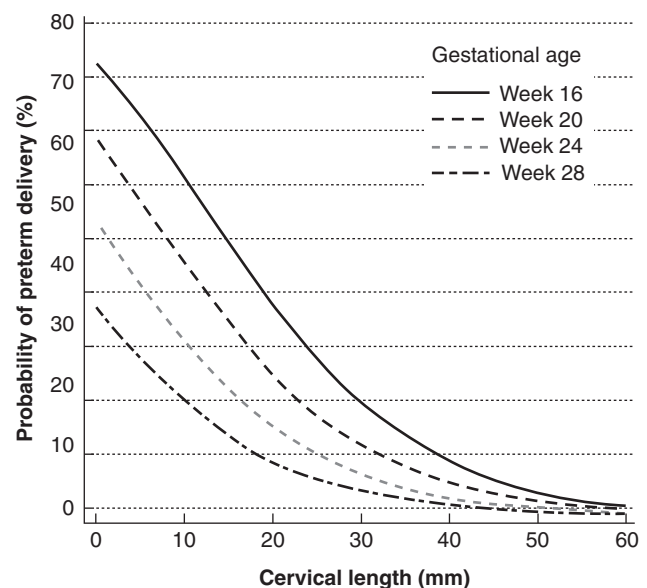


Figure 4 Predicted probability of delivery before 32 weeks of gestation, by cervical length (mm) and time of measurement (week of pregnancy), in women with a prior preterm birth. Source: From Ref. 504.

trophoblast–decidua interface and, like all fibronectins, acts as cellular “cement” to anchor trophoblast cells to the uterine wall (decidua). Decidual/membrane activation is a process whereby extracellular matrix is dissolved at this interface. Such a process is teleologically intended to weaken the membranes for membrane rupture during labor and also to prepare the membranes for separation from the uterine cavity after delivery. This intercellular “cement” has a unique glycosylation pattern, which is different from other fibronectins, and that is why it is called “fetal” fibronectin. Fortuitously, fetal fibronectin can be detected in vaginal and cervical fluids (142). It is interesting that fetal fibronectin can be detected between 16 and 20 weeks of gestation in normal pregnancy (176). However, normally it becomes undetectable (using a cut-off of 50 ng/mL) after 22 weeks of gestation and becomes detectable again at term prior to the onset of labor (142,177).

After 22 weeks of gestation, a positive fetal fibronectin in cervicovaginal fluid is associated with an increased risk for preterm delivery in symptomatic and asymptomatic patients (142,178–182). However, the proportion of patients with a positive fetal fibronectin who will deliver preterm is small (low positive predictive value) in both symptomatic and asymptomatic patients (143,152,153). In contrast, this test is considered more valuable in identifying patients at low risk for preterm delivery (high negative predictive value) (183–185). The value of this test relates to its ability to identify the patient unlikely to deliver, therefore avoiding unnecessary intervention. The results of fetal fibronectin may be affected by a history of sexual intercourse within 24 hours (186), a pelvic examination during the same period of time, or vaginal bleeding. Each of these conditions may lead to what has been called a “false-positive” test (187). In contrast, the use of lubricant may lead to

a false-negative result. Amniotic fluid contains fetal fibronectin in high concentrations (187). Therefore, a positive test can occur if there is membrane rupture or if the sample is contaminated with amniotic fluid (187).

Combined Use of Cervical Sonography and Fetal Fibronectin in the Diagnosis of Preterm Labor

Several studies have examined the value of combining these tests to predict preterm delivery. A study by Gomez et al. (171) indicated that (i) cervical length in labor is a strong predictor of preterm delivery; (ii) a short cervix (defined as a cervical length of <15 mm) identifies patients at high risk of impending preterm delivery (within 48 hours or 7 days of admission); (iii) a long cervix (defined as cervical length of 30 mm or more) identifies patients at low risk of preterm delivery; (iv) a positive fetal fibronectin is also associated with spontaneous preterm delivery, but the likelihood ratio of a positive test is substantially lower for fetal fibronectin than for a short cervix (i.e., 3.6 vs. 9.2 for delivering at <35 weeks of gestation) (see Tables 3 and 4 for a detailed comparison of cervical length and vaginal fetal fibronectin); and (v) the combined use of sonographic cervical length and fetal fibronectin improves the prediction of preterm delivery over that provided by each test alone; however, this effect was observed only when the cervical length was <30 mm (171,188). Therefore, there does not seem to be a justification for performing a fetal fibronectin when the cervical length is 30 mm or more.

Our practice is to perform a vaginal speculum examination to exclude rupture of membranes (assess the presence of pooling and nitrazine testing, and collect samples for ferning) and obtain samples for microbiology (including group B streptococcus (GBS), and if the prevalence justifies, gonorrhea

Table 3 Risk of Spontaneous Preterm Delivery Within 48 hours, 7 days, and 14 days According to Cervical Length Results and Vaginal Fibronectin Determination

	Delivery within 48 hours	LR		Delivery within 7 days	LR		Delivery within 14 days	LR	
		+	–		+	–		+	–
Cervical length <15 mm	36.7% (11/30)	6.7		56.7% (17/30)	8.7		56.7% (17/30)	6.9	
Cervical length ≥15 mm	3.2% (6/185)		0.4	5.9% (11/185)		0.4	9.2% (17/185)		0.5
Cervical length <30 mm	13.9% (15/108)	1.9		23.1% (25/108)	2.0		26.9% (29/108)	1.9	
Cervical length ≥30 mm	1.9% (2/107)		0.2	2.8% (3/107)		0.2	4.7% (5/107)		0.3
Vaginal fetal fibronectin (+)	19.2% (10/52)	2.8		34.6% (18/52)	3.5		42.3% (22/52)	3.9	
Vaginal fetal fibronectin (–)	4.3% (7/163)		0.5	6.1% (10/163)		0.4	7.4% (12/163)		0.4
Prevalence of the outcome	7.9% (17/215)			13.0% (28/215)			15.8% (34/215)		

Abbreviation: LR, Likelihood ratio.

Table 4 Risk of Spontaneous Preterm Delivery <32 and <35 weeks According to Cervical Length Results and Vaginal Fibronectin Determination

	Delivery <32 weeks	LR		Delivery <35 weeks	LR	
		+	–		+	–
Cervical length <15 mm	58.3% (7/12)	14.3		63.3% (19/30)	9.2	
Cervical length ≥15 mm	2.2% (2/89)		0.2	8.1% (15/185)		0.5
Cervical length <30 mm	18.4% (9/49)	2.2		27.8% (30/108)	2.0	
Cervical length >30 mm	0% (0/52)		0.1	3.7% (4/107)		0.2
Vaginal fetal fibronectin (+)	30.4% (7/23)	4.5		40.4% (21/52)	3.6	
Vaginal fetal fibronectin (–)	2.6% (2/78)		0.3	8% (13/163)		0.5
Prevalence of the outcome	8.9% (9/101)			15.8% (34/215)		

Abbreviation: LR, Likelihood ratio.

Table 5 Frequency of Spontaneous Preterm Delivery According to Cervical Length (Cut-off 30mm) and Vaginal Fibronectin Results

Cervical length <30mm	Fetal fibronectin +	Delivery within 48 hours	Delivery within 7 days	Delivery within 14 days	Delivery <32 weeks	Delivery <35 weeks
No	No	2.2% (2/93)	2.2% (2/93)	3.2% (3/93)	0% (0/47)	1.1% (1/93)
No	Yes	0% (0/14)	7.1% (1/14)	14.3% (2/14)	0% (0/5)	21.4% (3/14)
Yes	No	7.1% (5/70)	11.4% (8/70)	12.9% (9/70)	6.5% (2/31)	17.1% (12/70)
Yes	Yes	26.3% (10/38)	44.7% (17/38)	52.6% (20/38)	38.9% (7/18)	47.4% (18/38)
Prevalence of the outcome		7.9% (17/215)	13.0% (28/215)	15.8% (34/215)	8.9% (9/101)	15.8% (34/215)

Table 6 Frequency of Spontaneous Preterm Delivery According to Cervical Length (Cut-off 15mm) and Vaginal Fibronectin Results

Cervical length <15mm	Fetal fibronectin +	Delivery within 48 hours	Delivery within 7 days	Delivery within ≤14 days	Delivery ≤32 weeks	Delivery ≤35 weeks
No	No	2.0% (3/149)	3.4% (5/149)	4.7% (7/149)	1.4% (1/74)	4.7% (7/149)
No	Yes	8.3% (3/36)	16.7% (6/36)	27.8% (10/36)	6.7% (1/15)	22.2% (8/36)
Yes	No	28.6% (4/14)	35.7% (5/14)	35.7% (5/14)	25% (1/4)	42.9% (6/14)
Yes	Yes	43.8% (7/16)	75% (12/16)	75% (12/16)	75% (6/8)	81.3% (13/16)
Prevalence of the outcome		7.9% (17/215)	13.0% (28/215)	15.8% (34/215)	8.9% (9/101)	15.8% (34/215)

and *Chlamydia trachomatis*). We collect a sample using a Dacron swab, and save it to assess fetal fibronectin concentration and perform an endovaginal ultrasound examination to measure cervical length. This is followed by a digital examination if the membranes are intact.

Approximately 50% of patients presenting with preterm contractions will have a cervical length of 30 mm or more, and this will make testing for fetal fibronectin unnecessary (171). However, if the cervical length is <30 mm, a fetal fibronectin test may be performed to improve the assessment of the likelihood of preterm delivery. The magnitude of the increase is presented in Tables 5 and 6 and in Figure 5. A practical approach is to restrict fetal fibronectin testing between 20 and 30 mm (188), because the patients who have a cervical length below 20 mm are already at high risk of preterm delivery, and the management would not be affected by the improvement in risk estimation derived from the performance of the two tests. This method is consistent with the study of Hincz et al. (189), who proposed a two-step approach.

Preterm labor is a worldwide challenge, and the performance of tests for the diagnosis of preterm labor should consider the availability of resources. In most countries, assessment of preterm labor can be conducted with transvaginal sonography without the performance of a fetal fibronectin test. Cervical length can be determined with transvaginal sonography or even with transperineal sonography in centers that do not have an endovaginal probe (190). Ultrasound is widely available in virtually all obstetrical units, and the results can be obtained immediately. An immunoassay for fetal fibronectin or another analyte can be expensive and impractical. The recent development of a bedside test for fetal fibronectin has clinical appeal (191,192).

DIAGNOSTIC WORKUP OF PRETERM LABOR

The clinical assessment of patients presenting with symptoms of preterm labor should include (i) a history of previous pregnancies and risk factors (e.g., prior preterm delivery, prior second-trimester abortion); (ii) current pregnancy status; (iii) presenting complaint(s); (iv) physical examination;

(v) monitoring of fetal heart rate and uterine contractions; (vi) vaginal examination (speculum and/or digital); (vii) collection of cervicovaginal samples for microbiology (streptococcus group B (GBS), chlamydia, gonorrhea, Gram stain for bacterial vaginosis (BV)); (viii) urinalysis, culture, and sensitivity; (ix) amniocentesis; (x) fetal fibronectin; and (xi) ultrasound (estimated fetal weight, number of fetuses, placental location, fetal presentation and lie, amniotic fluid volume, and transvaginal cervical length).

Evaluation for Subclinical Intra-amniotic Infection

Intra-amniotic infection is a frequent and important cause of premature labor and delivery (33,193–203). Most of these infections are subclinical in nature, and only 12.5% of patients with a positive amniotic fluid culture for microorganisms will have a fever or meet the definition of clinical chorioamnionitis (193). Patients with intra-amniotic infections are more likely to deliver despite the administration of tocolytic agents (204), mothers are at an increased risk for pulmonary edema (205–211) and neonates for sepsis and other neonatal complications, such as intraventricular hemorrhage and periventricular leukomalacia.

Amniocentesis is offered to patients to assess the microbial state of the amniotic cavity and fetal lung maturity. The amniotic fluid is considered to be sterile for bacteria. Therefore, the identification of bacteria by culture (33,193,212) or microbial footprints with molecular techniques (213–216) is evidence that microbial invasion of the amniotic cavity has occurred. These infections result, in the majority of cases, from microorganisms normally present in the vagina, which cross the endocervical canal and intact membranes and gain access to the amniotic cavity (196). Microorganisms can proliferate and gain access to the fetus. Aspiration of infected fluid may lead to congenital pneumonia (217), but other infections such as otitis, conjunctivitis, and omphalitis can occur by direct spread of microorganisms from infected amniotic fluid. Seeding from any of these sites to the fetal circulation may lead to bacteremia and sepsis. The frequency of intra-amniotic infection in patients with preterm labor and intact membranes is approximately 10% (193,218); however, the lower the gestational

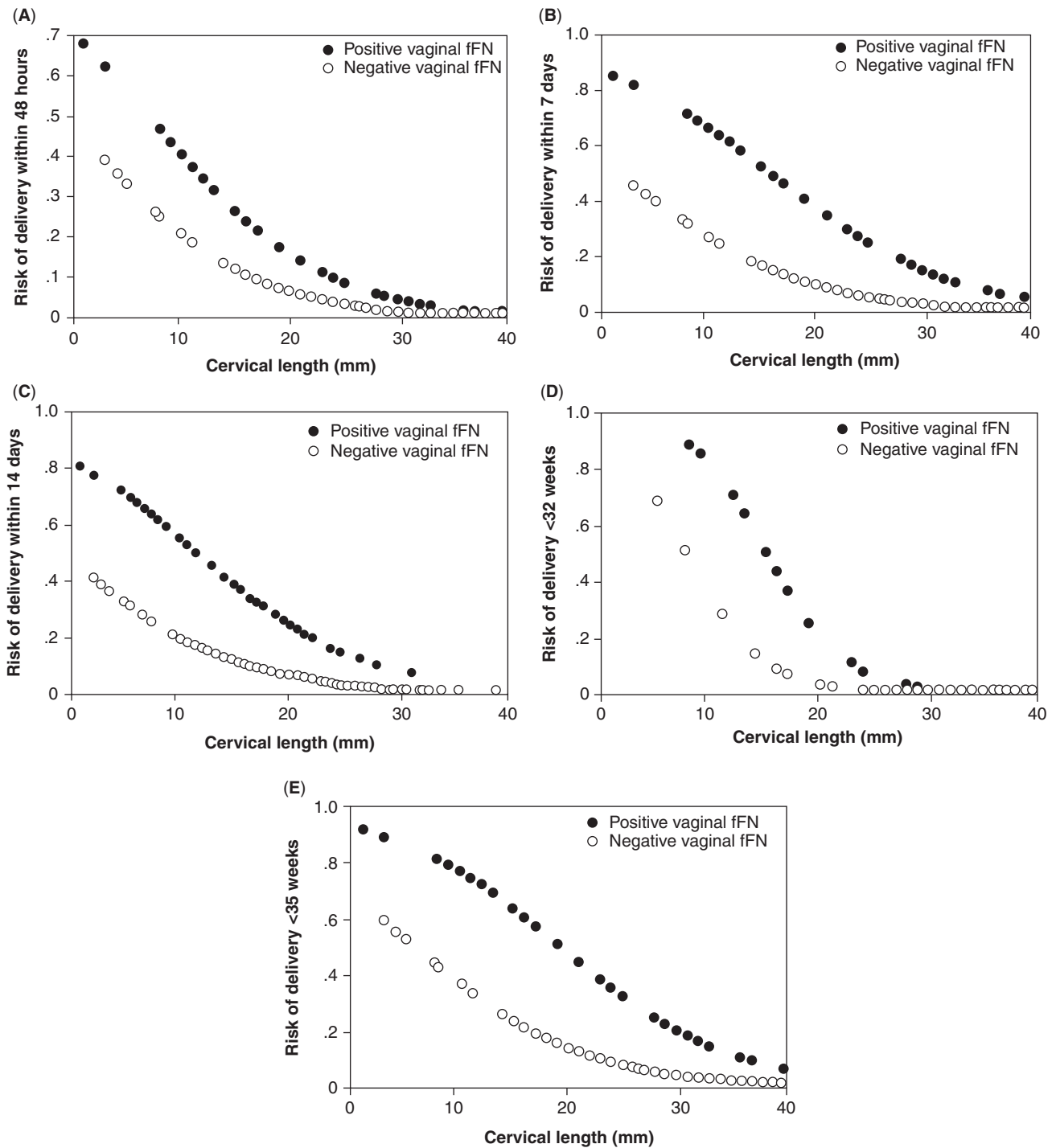


Figure 5 Risk of spontaneous preterm delivery within (A) 48 hours, (B) 7 days, (C) 14 days, (D) delivery <32 weeks, and (E) <35 weeks, according to cervical length results and vaginal fetal fibronectin (fFN) determination. Source: From Ref. 171.

age at presentation and the shorter the cervix, the higher the frequency of intra-amniotic infection and intra-amniotic inflammation (219). The organisms most frequently found in the amniotic cavity are genital mycoplasmas (33,51,193,195,200,220) and aerobic and anaerobic infections. Fungi have been identified in pregnancies with a retained intrauterine contraceptive device (221–225).

Amniocentesis is easy to perform in patients with preterm labor and intact membranes. The likelihood of infection is assessed by rapid tests, such as a Gram stain of amniotic fluid (204), amniotic fluid white blood cell count (226), and a

glucose determination (227). A positive Gram stain of amniotic fluid has a specificity of 99% for intra-amniotic infection (false-positive rate 1%) (193). However, it has a limited sensitivity because genital mycoplasmas cannot be seen on a Gram stain due to their small size. Gram stain examinations must be performed by experienced laboratory staff, because artifacts and crystals of the reagents may be confused with bacteria by inexperienced individuals.

Neutrophils are not normally present in amniotic fluid. The presence of neutrophils is indicative of intra-amniotic inflammation (226). An amniotic fluid white blood cell count

can be performed easily in a hemocytometer chamber, which is universally available in hospitals worldwide. It is the same chamber used to perform white blood cell counts in peripheral blood. In patients with intact membranes, a white blood cell count above 50 cells/mm³ has a sensitivity of 80% and a specificity of 87.6% in the detection of a positive amniotic fluid culture (226). If patients have an elevated white blood cell count, but the Gram stain is negative, an infection with genital mycoplasmas must be suspected.

Glucose is a normal constituent of amniotic fluid, and the concentration of glucose decreases with advancing gestational age (227). In the presence of infection or inflammation, the concentrations of glucose in the amniotic fluid decreases (227). This has been attributed to a combination of the consumption of glucose by microorganisms and by activated neutrophils involved in host defense and microbial killing. A glucose concentration can be performed by standard analyzers, and it is important to alert laboratories that the amniotic fluid glucose concentration is much lower than that of plasma or serum. A glucose concentration of <14mg/dL has a high sensitivity and specificity for the detection of intra-amniotic infection (212,228,229).

The determination of amniotic fluid interleukin-6 (IL-6) is a sensitive method to detect intra-amniotic inflammation. A concentration above 2.6ng/mL identified patients at risk for a positive amniotic fluid culture or impending delivery (218). Moreover, these patients are at increased risk for perinatal morbidity or mortality. Importantly, patients with an elevated amniotic fluid IL-6 and a negative amniotic fluid culture have a similar outcome as patients with a positive amniotic fluid culture (218). This suggests that there may be infections that cannot be detected with current methods (230) or, alternatively, that intra-amniotic inflammation due to non-infectious etiology is present (231–233) and this is associated with adverse outcome.

Neutrophils produce a collagenase, which is called matrix metalloproteinase 8 (MMP-8). MMP-8 has been proven to be an excellent marker for intra-amniotic infection/inflammation (234,235). Amniotic fluid MMP-8 >30 ng/mL has a sensitivity of 82.4%, specificity of 78%, positive predictive value of 36%, and negative predictive value of 97.7% for the prediction of intra-amniotic infection, defined as positive amniotic fluid culture (235). A rapid test (MMP-8 PTD Check test; SK Pharma Co. LTD, Korea) has been produced (236,237), which has high sensitivity and specificity, as well as likelihood ratios for a positive and a negative result (238).

Amniotic fluid cultures should be performed for aerobic and anaerobic bacteria, as well as for genital mycoplasmas. Bacteria take time to grow and results may take several days. Molecular microbiologic techniques are becoming available and would allow detection of bacteria and identification of the organisms in 8 hours or less (239,240).

The detection of microorganisms or intra-amniotic inflammation is a poor prognostic sign. Patients with preterm labor with intact membranes and documented intra-amniotic infection/inflammation are unlikely to respond to tocolysis (193,218,239,241) and are at risk of developing pulmonary edema (205,242,243) if attempts are made to delay delivery with tocolysis. Therefore, our approach is to suspend the administration of tocolysis in these patients. We continue to administer steroids because there is evidence that they cross

the placenta and may downregulate the fetal inflammatory response syndrome (244). In patients with preterm PROM, the management depends upon gestational age. The higher the gestational age (e.g., >33 weeks), the better the outcome if the decision is to deliver the patient. On the other hand, at a gestational age of <32 weeks, treatment must be individualized. We have previously reported that it is possible to eradicate intra-amniotic infection in patients with preterm PROM (245,246), as well as in patients with a sonographic short cervix with antibiotic treatment (247).

Amniotic fluid can also be tested for fetal lung maturity. This can be done with the standard tests, including the lecithin/sphingomyelin (L/S) ratio, phosphatidylglycerol, TDx-FLM surfactant albumin ratio, and lamellar body count. In the presence of lung maturity, heroic measures with aggressive tocolysis should be considered carefully.

Performance of amniocentesis in patients with preterm labor is valuable to identify patients at risk for intra-amniotic infection/inflammation and can be performed by individuals with expertise in ultrasound and invasive procedures. We explain to patients that examination of amniotic fluid is necessary to detect the presence of infection and identify the microorganism, and that infection is a frequent cause of preterm delivery. Although a randomized clinical trial of amniocentesis versus management without amniocentesis has not been performed, we believe that amniocentesis is indicated to identify intra-amniotic infection/inflammation. In any other specialty in medicine, identification of infection and the microorganism is undertaken. It is only in obstetrics that some are hesitant to identify this process. We believe that the benefits of identifying intra-amniotic infection/inflammation and establishing fetal lung maturity outweigh the risks of amniocentesis, which is today a minimally invasive procedure (248–252).

TREATMENT OF PRETERM LABOR

Glucocorticoids

The idea that glucocorticoid administration could induce fetal lung maturity was first proposed by Liggins et al. more than 50 years ago (253). While studying the mechanisms of the onset of parturition in sheep, Liggins reported that administration of steroids to the fetal sheep induced preterm labor and that neonatal lambs born under these circumstances had inflated rather than collapsed lungs. Aeration of the lungs was attributed to the effects of steroids in inducing the production of pulmonary surfactant. This observation was followed by a randomized clinical trial in humans in which betamethasone was reported to decrease the rate of respiratory distress syndrome (254). Subsequently, multiple randomized clinical trials using either betamethasone or dexamethasone were reported (254–275). Systematic reviews of such trials have been performed since 1990, and they have consistently concluded that the beneficial effects of corticosteroids in neonatal outcome extend beyond inducing fetal lung maturity (276,277). Glucocorticoid receptors are expressed in many organs; and hence, the potential benefit in reducing morbidity such as intraventricular hemorrhage, necrotizing enterocolitis, etc.

The most recent systematic analysis reported by Roberts and Dalziel (276) included the review of 21 trials (3885 women and 4269 infants). Administration of corticosteroids was associated with a significant reduction in neonatal death, respiratory

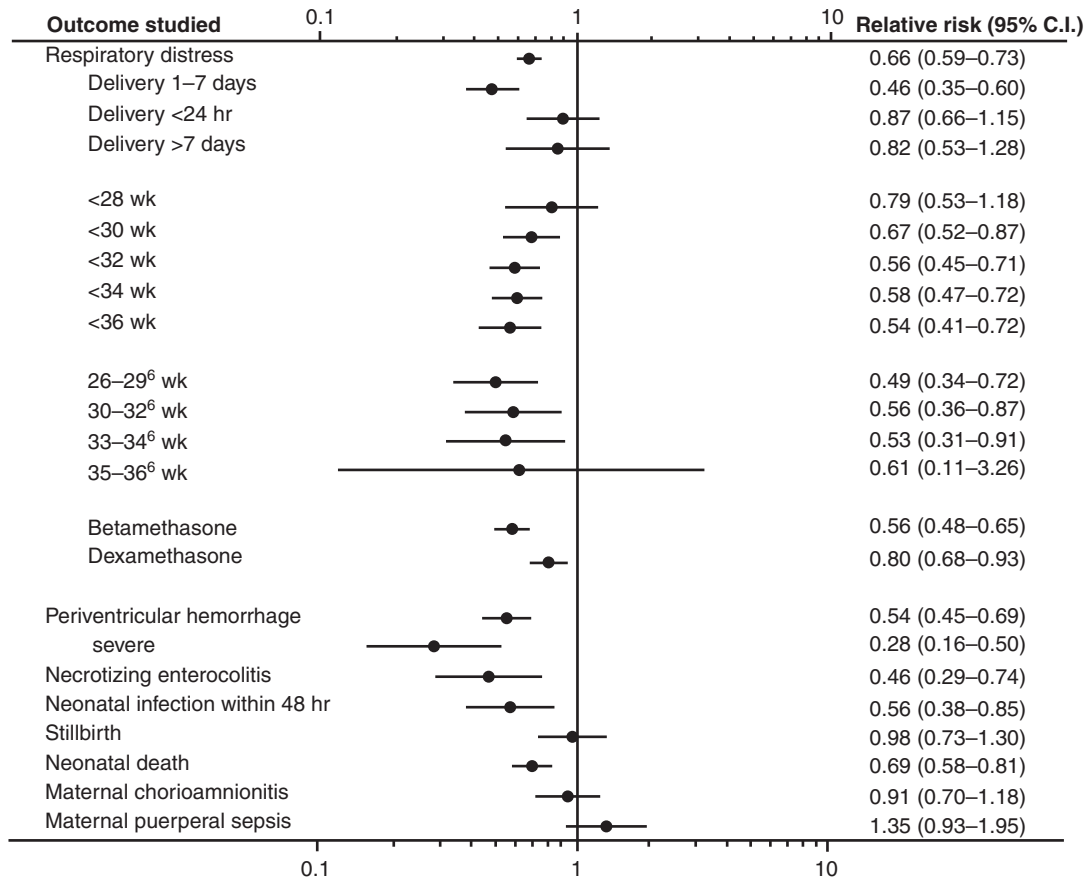


Figure 6 Impact of antenatal corticosteroids before anticipated preterm birth on perinatal outcomes. Abbreviation: C.I., confidence interval. Source: From Ref. 276.

distress syndrome, intraventricular hemorrhage, necrotizing enterocolitis, admission to neonatal intensive care unit, and neonatal infection within the first 48 hours of life (Fig. 6) (276). In addition, these benefits accrue without an increased risk of clinical chorioamnionitis, puerperal sepsis, or the risk of stillbirth.

The agents administered are either dexamethasone or betamethasone because they cross the placenta readily, are weaker immunosuppressors than other glucocorticoid steroids, and have a longer duration of action than cortisol. The standard dosage of betamethasone consists of two intramuscular 12-mg doses (24 hours apart), while four intramuscular doses of 6 mg of dexamethasone should be administered at 6-hour intervals. Oral administration of dexamethasone is not recommended, because it has been associated with an increased risk of neonatal intraventricular hemorrhage (IVH) and sepsis compared with intramuscular administration (278,279).

Betamethasone is preferred over dexamethasone because its administration results in a greater reduction in respiratory distress syndrome and puerperal infection (280) while the use of dexamethasone is associated with a lower frequency of intraventricular hemorrhage than betamethasone. However, most investigators believe that there is still equipoise between the two drugs (255,276,280–283).

Glucocorticoids provide beneficial effects to patients between 24 and 33-6/7 weeks of gestation (276). Some data suggest that there are beneficial effects at 23 weeks of gestation (284), while more studies are required to establish efficacy between 34 and 36-6/7 weeks of gestation (285,286).

Long-term follow-up studies have not uncovered complications in children exposed to a single course of antenatal steroids, and one study has followed these infants for 30 years (287).

Although many believe that the benefits of antenatal steroid administration occur after 24 hours of initiation of therapy, there is evidence that when delivery occurs between the first and second dose of betamethasone, there is still a reduction in the rate of neonatal death, intraventricular hemorrhage, and the need for vasopressors (288). Therefore, benefits accrue even if 48 hours have not elapsed since the administration of the first dose of steroids. On the other hand, the beneficial effects of antenatal corticosteroids are not demonstrable in babies born more than 7 days after treatment, and the birth weight is significantly reduced (276,289).

Should Steroid Administration Be Repeated After 7 days?

Several randomized clinical trials have been conducted to address this question. Moreover, a systematic review including five trials has been reported (290). The trial reported by Crowther et al. (291) (Australasian Collaborative Trial of Repeat Doses of Steroids) randomized 982 women (1146 neonates) at less than 32 weeks of gestation who had received a single course of antenatal corticosteroids to receive weekly betamethasone or placebo (291). Repeated corticosteroids led to a significant reduction in the rate of respiratory distress syndrome (33% vs. 41%; $p = 0.01$), severe lung disease (12% vs. 20%; $p = 0.0003$), less frequent oxygen therapy (56% vs. 63%; $p = 0.03$), and shorter duration of mechanical ventilation ($p = 0.01$) (291).

In contrast, a randomized controlled trial conducted in the United States by Wapner et al. (292) randomly assigned 495 women at 23 weeks of gestation to receive either betamethasone or placebo weekly between 7 and 10 days after the initial dose of steroids. The primary outcome of the trial was neonatal morbidity as a composite score. There was no difference between those patients allocated to repeat steroids versus placebo (8% vs. 9.1%; $p = 0.6$) (292). Neonates in the repeat steroid group had a significantly lower frequency of surfactant administration, mechanical ventilation, continuous positive airway pressure, and pneumothorax. However, the frequency of small for gestational age (<10th percentile) was higher in infants exposed to repeated doses of steroids than in the control group. Importantly, the frequency of cerebral palsy was higher in neonates that received four or more courses of maternal corticosteroids, but this was not statistically significant [2.4% (6/248) vs. 0.4% (1/238)] (293). There were no differences in physical or neurocognitive outcomes in this trial. By contrast, Crowther et al. (294) noted a higher frequency of children with behavioral problems (e.g., attention deficit and emotional reactivity), but no differences in the frequency of cerebral palsy [repeat steroids, 4.2% (22/521) vs. 4.8% (25/528)].

There are several differences in these two trials. The dose in the study of Crowther et al. was 11.4 mg/week of betamethasone, while the study of Wapner et al. used 24 mg/week. Also, more women received four or more doses of steroids in the Wapner et al. trial than those in the Crowther et al. trial.

Murphy et al. (295) reported results of a randomized clinical trial of the multiple courses of antenatal corticosteroids for preterm birth. In this study, 1858 women between 25 and 32 weeks who were undelivered 14 to 21 days after the initial dose of steroids were randomized to repeat doses of steroids ($n = 973$) or placebo ($n = 921$) every 14 days until 33 weeks of gestation or delivery, whichever came first. The primary endpoint was a composite of perinatal morbidity and mortality. Infants exposed to multiple courses of steroids had similar morbidity and mortality rates to those allocated to placebo (12.9% vs. 12.5%). In this study, exposure to steroids was associated with a lower birth weight, lower length at birth, and smaller head circumference. The authors concluded that multiple courses of steroids could not be recommended.

An individual patient meta-analysis is in progress but results are not available at the time of this writing. The American Congress of Obstetricians and Gynecologists has recommended that only one course of betamethasone (12 mg in two doses, 24 hours apart) should be given to women in preterm labor. In contrast, in Australia and New Zealand, repeat doses are given weekly to women at risk up to 32 weeks of gestation.

Another strategy for repeat steroids is what is referred to as “rescue” therapy. In this instance, repeat steroids are administered only to patients with impending delivery. In a study by Garite et al. (296), patients who were diagnosed to have an episode of preterm labor at less than 33 weeks and received a complete course steroids before 30 weeks more than two weeks ago were randomized to receive either a single “rescue” course of betamethasone (12 mg; 2 doses, 24 hours apart) or placebo. Patients with rupture of membranes, advanced cervical dilatation (>5 cm), and chorioamnionitis

were excluded. Of the 433 patients randomized (223 to “rescue” steroids and 214 to placebo), 55% in each group delivered at less than 34 weeks of gestation. In the rescue group there was a significant reduction in the primary outcome (composite neonatal morbidity below 34 weeks) (43.9% vs. 63.6%; OR 0.45; 95% CI, 0.27–0.75; $p = 0.002$). There was also a significant decrease in respiratory distress syndrome, ventilatory support, and surfactant use (296). This observation suggests that “rescue” therapy can be considered with an understanding that prediction of the patient who is at risk of impending delivery is difficult.

TOCOLYTIC THERAPY

The basic premise behind the use of tocolytic treatment is that the administration of pharmacologic agents can inhibit myometrial contractions, prolong pregnancy, and reduce the rate of neonatal morbidity and mortality. Intravenous alcohol was the first agent introduced to delay preterm delivery (297). Its use was accompanied by an unacceptable rate of maternal complications. Since that time, multiple pharmacologic agents have been used, including beta-adrenergic agents, magnesium sulfate, oxytocin receptor antagonists, calcium-channel blockers, nitroglycerin, and prostaglandin synthase inhibitors. Decades of research indicate that tocolysis can prolong pregnancy for 48 hours to 7 days (298–301). This prolongation of gestation is considered beneficial, because it allows the transfer of patients to a tertiary care facility and, importantly, the administration of corticosteroids. The hope that the use of tocolysis would reduce the rate of preterm birth has not been realized. It is possible that the ideal agent has not been identified. Alternatively, it is possible that tocolysis, as a strategy, would not succeed if a serious pathologic process which has led to activation of the myometrium and other components of the common pathway of parturition is not treated. For example, the administration of beta-adrenergic agents in patients with documented intrauterine infection is not effective in prolonging pregnancy and may result in an increased rate of maternal pulmonary edema (205,242,243). Therefore, many studies of tocolysis are confounded by including patients who will not benefit from inhibition of uterine contractility.

Beta-adrenergic Receptor Agonists

The first and only agent approved for tocolysis in the United States by the Food and Drug Administration (FDA) was ritodrine, a selective beta-2 adrenergic agent. This drug is no longer marketed in the United States. This class of agents achieves myometrial relaxation by binding to the beta-2 adrenergic receptor and increasing the levels of intracellular cyclic adenosine monophosphate, which, in turn, activates protein kinase, inactivates myosin light-chain kinase, and inhibits myometrial contractility (302–304). Agents in this class include terbutaline and fenoterol (4). A meta-analysis including 11 randomized clinical trials (1320 women) in which beta-adrenergic agents were compared with placebo indicates that these agents reduce the rate of delivery within 48 hours, but not within 7 days (300). There was no evidence of a significant decrease in perinatal or neonatal morbidity and mortality.

The use of beta-adrenergic agents is associated with maternal and fetal side effects. The most common are maternal and fetal tachycardia, tremor, headache, nausea,

vomiting, hypokalemia (301), and hyperglycemia (300,301). Hypotension due to peripheral vasodilatation is a common problem (305). Maternal cardiac arrhythmias and myocardial ischemia have been reported during the course of tocolysis with these agents (306). The onset of chest pain should be taken seriously during the course of therapy. Because of metabolic effects (hyperglycemia) of beta-adrenergic agents, it is best to use other agents in patients with glucose intolerance. Neonatal side effects include hypoglycemia (4), hypocalcemia (4), and myocardial damage (case reports) (307).

There is no evidence that maintenance treatment with either oral or subcutaneous beta-adrenergic agents is beneficial. Some have used subcutaneous terbutaline administered via a pump; however, randomized clinical trials do not show evidence of efficacy (308,309). Recently, the FDA has issued a black-label warning for terbutaline administration based upon reports of some maternal deaths associated with its use (310,311). Fenoterol is used in Europe, and there is considerable experience with this agent in Germany.

A common practice in patients who present with preterm uterine contractions is to administer a single subcutaneous dose of terbutaline. Patients in whom contractions persist are at increased risk for preterm delivery (312).

Magnesium Sulfate

This tocolytic agent can cause a reduction in uterine contractility *in vitro* and *in vivo* (313). Magnesium hyperpolarizes the cellular membrane and inhibits myosin light-chain kinase activity by competing with intracellular calcium (314–316). Despite its wide utilization in the United States, the largest randomized clinical trial in which magnesium sulfate was compared with placebo concluded that magnesium sulfate was not effective in prolonging pregnancy (317). Meta-analyses of randomized trials in which magnesium was compared with placebo or other agents do not show differences in prolongation of pregnancy for 48 hours (318). Maternal and neonatal side effects of magnesium sulfate are well known since this drug is used to prevent seizures in pre-eclampsia. Common side effects include nausea and vomiting, a metallic taste in the mouth, lethargy, and hot flashes. Pulmonary edema has been reported in patients receiving this drug. Since magnesium crosses the placenta, prolonged administration can lead to hypermagnesemia in the neonate. A systematic review reported by Crowther et al. (318) in which more than 2000 women were included in 23 trials concluded that magnesium was not effective in preventing preterm delivery and was associated with an increased risk of death (fetal and pediatric) (RR 2.8; 95% CI, 1.20–6.62). Grimes and Nanda have called for a discontinuation of magnesium sulfate as a tocolytic agent (319). There is no evidence that oral magnesium administration can prevent preterm birth or is effective for maintenance of tocolysis.

Calcium-Channel Blockers

These agents inhibit uterine contractility by blocking the calcium channels and, thereby, the influx of calcium through the cell membrane as well as the release of intracellular calcium from the sarcoplasmic reticulum (320,321). Nifedipine is the most popular agent used as a tocolytic agent. Its use is based on comparative trials with beta-adrenergic agents.

A recent systematic review indicates that nifedipine is as effective as beta-adrenergic agents in delaying delivery for 48

hours (298). However, nifedipine was superior to beta-adrenergic receptor agonists in delaying delivery of 7 days within initiation of therapy and also in improving clinically important neonatal outcomes such as respiratory distress syndrome, necrotizing enterocolitis, intraventricular hemorrhage, jaundice, admission to the neonatal intensive care unit (NICU), and length of stay in the NICU. Moreover, nifedipine use was associated with fewer maternal side effects and a lower rate of discontinuation of treatment than beta-adrenergic agents. Follow-up of infants exposed to either nifedipine or beta-adrenergic agents showed no difference in neurodevelopmental status at 2 years of age (322), or psychological or motor function at 9 to 12 years of age (323). There are insufficient data to assess the efficacy of nifedipine against oxytocin receptor antagonists or nitric oxide. There was no evidence that maintenance therapy with nifedipine was efficacious. The proposed dose of administration is 10 mg orally or sublingually. If contractions persist, this dose can be repeated every 15 to 20 minutes up to a maximal total dose of 40 mg during the first hour of treatment, then 20 mg orally every 6 to 8 hours for 2 to 3 days. The side effects of nifedipine include headache, flushing, dizziness, hypotension, and nausea (324). Suppression of maternal heart rate, contractility, and left ventricular systolic pressure may also occur. Concurrent administration of magnesium with calcium-channel blockers may result in neuromuscular blockade and pulmonary edema (325,326). However, a retrospective case-control study concluded that the use of nifedipine and magnesium sulfate together in patients with pre-eclampsia does not increase the risk of serious magnesium-related effects including neuromuscular blockade (327).

Prostaglandin Synthase Inhibitors

Prostaglandins are considered the universal mediators of labor and can induce uterine contractility and cervical ripening. The therapeutic target is the cyclooxygenase (COX) enzyme, which catalyzes the conversion of arachidonic acid to the intermediate product of prostaglandins, PGH. There are two COX enzymes, COX-1 and COX-2. The former is the constitutive enzyme, and the second is the inducible enzyme. Indomethacin is a non-specific inhibitor of COX, while nimesulide is a specific inhibitor of COX-2. One of the randomized clinical trials in which indomethacin was compared with placebo concluded that indomethacin resulted in a reduction in the rate of preterm birth (defined as <37 gestational weeks) (328,329). However, this trial included only 36 women, and there was no difference in neonatal outcome. Comparative trials (with either beta-adrenergic agents or magnesium sulfate) show that COX inhibitors reduced the rate of preterm birth before 37 weeks and the frequency of adverse events (329). However, there was no demonstrable improvement in neonatal outcome. Two studies comparing non-selected COX inhibitors versus COX-2 inhibitors did not demonstrate differences in maternal and neonatal outcome (329–331). It is recognized that the trials have been of small sample size.

Adverse events include nausea, vomiting, heartburn, gastrointestinal bleeding, and impairment of platelet function (prolonged bleeding time). Indomethacin should not be administered in patients with peptic ulcer, kidney, or liver

disease. The drug crosses the placenta readily, and the most common side effects include stenosis of the fetal ductus arteriosus and oligohydramnios (328,332). There is also a concern about impairment of platelet function in the neonates (333). However, a meta-analysis of 28 studies showed no significant differences in the rates of intraventricular hemorrhage, patent ductus arteriosus, necrotizing enterocolitis, and neonatal mortality between the two groups (334). The standard recommendation is not to use the agent after 32 weeks of gestation or longer than 50mg (4). Indomethacin is used as an acute tocolytic. The oral dose of indomethacin is a 50 mg loading dose, followed by 25 to 50mg every 6 hours for 48 hours (total duration of treatment). The drug can also be administered rectally as a suppository.

Nitric Oxide Donors

Nitric oxide can induce relaxation of smooth muscle by increasing cyclic guanosine monophosphate, which inhibits myosin light-chain kinases. Nitroglycerin is a nitric oxide donor. The initial trials with nitroglycerin for tocolysis suggested that it was comparable with ritodrine (335). A randomized, double-blind, placebo-controlled trial was conducted in which patients ($n = 153$) with preterm labor (between 24 and 32 weeks of gestation) were randomized to receive transdermal nitroglycerin (0.4mg/h) or placebo patches (336). The primary endpoint of this study was a composite of neonatal morbidity and mortality. Infants born to mothers allocated to transdermal nitroglycerin had a significantly lower composite neonatal outcome compared with placebo (RR 0.29, 95% CI 0.08–1.00; $p = 0.048$). The number needed to treat was 10. Preterm birth prior to 28 weeks of gestation was reduced by 50% (RR 0.50, 95% CI 0.23–1.09). Patients receiving nitroglycerin had significantly more maternal side effects than those allocated to placebo. The most common side effects were headache and local irritation from the patch. Importantly, in this trial, none of the subjects received other tocolytics from randomization to delivery. Therefore, this is a unique trial in the history of tocolytic therapy. Long-term follow-up of infants enrolled in a previous trial of nitroglycerin patches versus beta-adrenergic agonists showed that there was no significant difference in psychometric testing at the age of 2 (337).

Oxytocin Receptor Antagonists

Oxytocin is a powerful stimulant of myometrial contractions. Its receptor is widely distributed in myometrium and decidua. Atosiban, an oxytocin receptor antagonist, can block spontaneous and oxytocin-induced uterine contractility. This agent is used widely in Europe, but is not available in the United States.

Comparative randomized clinical trials in which patients were allocated to beta-mimetic agents or atosiban indicated that atosiban had the same efficacy, but fewer maternal adverse events (338–341). These studies were conducted by a worldwide atosiban versus beta-adrenergic agonists study group and included comparisons of this agent with ritodrine, salbutamol, and terbutaline. Tocolytic effectiveness was similar in terms of gestational age at delivery, but maternal side effects, particularly cardiovascular adverse events, were less frequent in patients allocated to atosiban than in patients allocated to

beta-adrenergic agents (8.3% vs. 81.2%, $p < 0.001$) (341). This was associated with a lower rate of discontinuation of treatment due to side effects (1.1% vs. 15.4%, $p = 0.0001$).

A large randomized clinical trial in which patients in preterm labor were allocated to either atosiban- or placebo-initiated treatment showed that atosiban-treated patients were significantly less likely to deliver within 24 hours, 48 hours, and 7 days than patients with placebo-initiated treatment (342). There was no difference in the interval from enrollment to delivery between the two groups. In this study, the rate of fetal/infant death was greater in patients allocated to atosiban than placebo. This was attributed to an excess number of patients with gestational ages less than 24 weeks allocated to the atosiban arm compared with the placebo-initiated treatment. Similarly, there was an excess of infection-associated preterm labor and delivery in patients allocated to atosiban. This concern for safety was probably the reason the FDA did not approve atosiban in the United States. Another randomized clinical trial in which patients with an episode of preterm labor were treated with atosiban and subsequently randomized to either maintenance therapy with atosiban (subcutaneous pump) or placebo showed that maintenance therapy was not associated with a reduction in the rate of preterm delivery (343). However, in this trial, prolonged exposure to atosiban did not result in an excess of fetal or infant death. This finding, coupled with the extensive experience in Europe with atosiban, makes it unlikely that there is a toxic effect of atosiban on the fetus.

Antibiotics in Preterm Labor

Several randomized clinical trials have tested the effect of antibiotics versus placebo in patients with an episode of preterm labor (344–354). A systematic review of such intervention demonstrated that antibiotic administration (ampicillin and/or erythromycin) does not reduce the rate of preterm delivery or neonatal complications. The largest trial conducted to date is the ORCALE II trial (346), in which 6295 women were randomized to placebo, amoxicillin/clavulanic acid, erythromycin, and the combination of amoxicillin/clavulanic acid and erythromycin.

The study that followed the infants enrolled in the ORACLE II trial at the age of 7 years indicated that those exposed to antibiotics have an increased rate of cerebral palsy, which was modest in magnitude, but statistically significant (355). This unexpected observation suggests that antibiotic administration to women without demonstrable infection could cause harm. However, the precise mechanism by which antibiotic administration can cause neurologic injury is unknown. One possibility is that antibiotics may cause the release of microbial products, which could initiate an inflammatory reaction, and change the nature of the host–microbial interaction in normal pregnancy and fetal life. These observations, and the lack of efficacy of adjuvant antibiotics in the prevention of preterm delivery and neonatal morbidity, suggest that antibiotics should not be used in patients with preterm labor and intact membranes. However, this does not apply to the prevention of vertical transmission of GBS. Antibiotic administration is effective in reducing the rate of neonatal GBS sepsis and should be used in patients at risk (356–361). The recommended treatment is penicillin G 5 million units intravenously, followed by 2.5 to 3 million units every 4 hours. Patients allergic

to penicillin can receive either clindamycin (900mg IV every 8 hours) or erythromycin (500mg IV every 6 hours), if the isolate microorganism is susceptible to clindamycin or erythromycin, or vancomycin (1g IV every 12 hours) if the isolate microorganism is resistant to the clindamycin or erythromycin or in cases of unknown susceptibility (362).

Magnesium Sulfate for Neuroprotection

Preterm delivery is a major risk factor for cerebral palsy. Several randomized clinical trials have been conducted to test the effect of magnesium sulfate in the prevention of cerebral palsy after a report by Nelson and Grether (363) suggesting that *in utero* exposure to magnesium sulfate was associated with a lower rate of cerebral palsy in infants born weighing less than 1500g.

A systematic review of six trials (364), involving 4796 women and 5357 infants, indicated that antenatal magnesium sulfate was associated with a significant reduction in the risk of cerebral palsy (RR 0.69, 95% CI 0.55–0.88), moderate or severe cerebral palsy (RR 0.64, 95% CI 0.44–0.92), and substantial gross motor dysfunction (RR 0.60, 95% CI 0.43–0.83). There was no overall difference in the risk of total pediatric mortality (RR 1.01, 95% CI 0.89–1.14). Minor side effects were more frequent among women receiving magnesium sulfate. Therefore, we recommend the use of magnesium sulfate for neuroprotection in women at high risk for preterm delivery before 34 weeks of gestation. The loading dose of magnesium sulfate is 6g and the maintenance dose 1 to 2g/h, for 24 hours. This treatment should be restricted to patients expected to deliver within 24 hours. It has been used in patients with both intact and ruptured membranes. Using this approach, it has been estimated that the incremental cost of preventing one case of cerebral palsy would be approximately \$10,291 (95% CI \$6135–\$29,685) (364).

Prediction of Spontaneous Preterm Delivery

The risk factors associated with preterm delivery/preterm PROM (3) include a sonographic short cervix (2,166–169, 173,174,247), African-American race (365–368), and a prior history of preterm delivery (2,369). There is conflicting evidence of the efficacy of antibiotic treatment for BV in women with a prior preterm birth. Some studies suggest a benefit to the use of antibiotics for these patients (370–372) and others have not shown this benefit (373–376). A systematic review of seven randomized clinical trials demonstrated no evidence of benefit for screening or treating low-risk pregnant women who are asymptomatic for BV. Furthermore, they found no advantage to screening for and treating BV in the general population of pregnant women who are asymptomatic for BV (373).

Fetal fibronectin has been used in the evaluation of asymptomatic women to predict their risk of preterm delivery. Numerous meta-analyses (176,184,377–380) have concluded that cervicovaginal fetal fibronectin testing might be clinically useful in the prediction of preterm birth, with an emphasis given to the high negative predictive value of the test, particularly in women who are symptomatic of threatened preterm labor and for delivery within 7 to 10 days of sampling. Kurtzman et al. (381) have proposed the use of quantitative fetal fibronectin screening in asymptomatic women with a

prior preterm delivery. This group demonstrated that quantitative fetal fibronectin assessment at 24 weeks of gestation could be used to predict the risk of spontaneous preterm delivery before 34 weeks of gestation, and that this risk increased as the quantity of fetal fibronectin (FFN) increased [compared with an FFN = 0 ng/mL; RR 2.42 (FFN 1–49ng/mL; 95% CI 0.76–5.66), 4.68 (FFN 50–199ng/mL; 95% CI 1.28–10.95), and 9.94 (FFN>200ng/mL; 95% CI 2.90–19.67)] (381).

Recently, Conde-Agudelo and Romero conducted a systematic review and meta-analysis of 15 studies investigated the accuracy of cervicovaginal fetal fibronectin in predicting preterm birth in women with multiple gestations (382). This study demonstrated that among asymptomatic women with multiple or twin pregnancies, the pooled sensitivities, specificities, and positive and negative likelihood ratios for predicting preterm birth before 32, 34, and 37 weeks of gestation ranged from 33% to 45%, 80% to 94%, 2.0 to 5.5, and 0.68 to 0.76, respectively. Among women with twin pregnancies and threatened preterm labor, the test was most accurate in predicting spontaneous preterm birth within 7 days of testing (pooled sensitivity, specificity, and positive and negative likelihood ratios of 85%, 78%, 3.9, and 0.20, respectively).

These findings provided evidence that cervicovaginal fetal fibronectin has limited accuracy in predicting spontaneous preterm birth in both asymptomatic and symptomatic women with multiple pregnancies because the likelihood ratios for positive and negative test results generated only minimal to moderate changes in the pretest probabilities of preterm birth. The test is most accurate in predicting spontaneous preterm birth before 32 weeks of gestation in asymptomatic women with multiple or twin pregnancies, and spontaneous preterm birth within 7 days of testing in women with twin pregnancies and threatened preterm labor (382).

A Short Sonographic Cervical Length: a Powerful Predictor of Preterm Delivery

Cervical sonography is the most objective and reliable method to assess cervical length (168,172–174,383,384). Furthermore, cervical length is the most powerful predictor of spontaneous preterm delivery. The shorter the sonographic cervical length in the midtrimester, the higher the risk of spontaneous preterm labor/delivery (168,173,174,383). There is no agreement as to what is a sonographic short cervix. For example, Iams et al. (174) proposed that a cervix of 26mm or shorter at 24 weeks of gestation increases the risk for spontaneous preterm delivery (RR 6.19, 95% CI 3.84–9.97). The prevalence of spontaneous preterm delivery (defined as <35 weeks) in this study was 4.3%, and the positive predictive value was 17.8% for a cervical length of ≤ 25 mm at 24 weeks of gestation (174). Thus, most women with a short cervix (defined as ≤ 25 mm) and no history of previous preterm birth will not deliver a preterm neonate. Other investigators have proposed a cut-off of 15mm (173,383), because a cervical length of 15mm or less is associated with nearly a 50% risk of spontaneous preterm delivery at 32 weeks of gestation or less, when neonatal morbidity is substantial (171,173,219,247,383,385–390). To et al. (385) have developed a method to assess the risk of preterm delivery for individual patients using sonographic

cervical length and other maternal risk factors such as maternal age, ethnic group, body mass index, cigarette smoking, and previous cervical surgery. Importantly, sonographic cervical length is the single most powerful predictor for preterm birth in the index pregnancy (172,384) and is far more informative than a history of previous preterm birth (172,385,391). This has implications in the selection of patients for future trials and the interpretation of past trials. Specifically, all trials conducted to date (392–396), except one (397), have identified patients for study based upon a history of previous preterm birth. As much as preterm birth is a syndrome, it is likely that the risk conferred by a previous preterm delivery may vary within and between populations. This may explain the apparent contradictory results between trials [i.e., conflicting reports of trials of vaginal progesterone (395,396) and the wide range of preterm birth among control groups (394–396)].

Sonographic cervical length is not a screening test for spontaneous preterm delivery because only some of the patients who will have a spontaneous preterm birth have a short cervix in the midtrimester. However, sonographic cervical length is a method for risk assessment for spontaneous preterm delivery. Its importance derives from the observation that, as a fraction of patients with a history of previous preterm birth who shorten their cervix during the index pregnancy may benefit from therapeutic cervical cerclage (398,399), patients with a short cervix may benefit from vaginal progesterone administration to reduce the rate of spontaneous preterm birth (397).

Cervical ultrasound is a powerful tool in performing risk assessment for spontaneous preterm birth. It is simple to perform, inexpensive when performed at the time of second-trimester screening for anomalies, informative, and can provide an estimate of risk in primigravidae. We believe that measuring cervical length should be part of standard sonographic examination in the midtrimester. Other tools may help to refine the estimation of risk. Such tools can range from vaginal fibronectin (219,400), the collascope (165,401–403), amniotic fluid analysis (220,226,227,235,238,404–407), and the presence/absence of “amniotic fluid sludge” (408,409), to genetic analysis of DNA variants of the progesterone receptor (410–413). These may help determine patients who will respond to progestogens or other treatments and those who will not and realize “personalized perinatal medicine” in the 21st century.

Amniotic Fluid “Sludge”

Particulate matter in the amniotic fluid is present in about 4% of pregnancies during transvaginal ultrasound in the first and early second trimesters (414). Particulate matter in the first two trimesters of pregnancy has been associated with intra-amniotic bleeding (415,416) and the acrania-anencephaly sequence (417), and has been observed in women with high concentrations of maternal serum α -fetoprotein (418). In contrast, in the last trimester of pregnancy, particulate matter and “echogenic amniotic fluid” have been attributed to the presence of vernix caseosa and/or meconium (419–422), and with a lecithin–sphingomyelin ratio indicative of lung maturity (423,424).

Amniotic fluid “sludge” is defined as particulate matter seen in the proximity of the internal cervical os during a

transvaginal sonographic examination of the cervix and occurs in 1% of uncomplicated pregnancies (408) (Fig. 7). The first description of amniotic fluid sludge was in patients in preterm labor. Espinoza et al. (408) conducted a retrospective study of 84 patients in preterm labor with intact membranes. The prevalence of amniotic fluid sludge was 22.6% (19 of 84) in patients with preterm labor. Patients with amniotic fluid sludge had a higher frequency of positive amniotic fluid cultures [33.3% (6 of 18) vs. 2.5% (1/40), $p = 0.003$] and histological chorioamnionitis [77.8% (14 of 18) vs. 19% (11 of 58), $p < 0.001$], and a higher rate of spontaneous preterm delivery within 48 hours [42.9% (6 of 14) vs. 4.4% (2 of 45), $p = 0.001$], within 7 days [71.4% (10 of 14) vs. 115.6% (7 of 45), $p < 0.001$], less than 32 weeks [75% (9 of 12) vs. 25.8% (8 of 31), $p = 0.005$], and less than 35 weeks [92.9% (13 of 14) vs. 37.8% (17 of 45), $p < 0.001$] than those without amniotic fluid “sludge.” Stepwise logistic regression analysis indicated that the presence of sludge was independently associated with the likelihood of spontaneous delivery within 48 hours and 7 days, but not less than 32 weeks or less than 35 weeks. Survival analysis demonstrated that patients with amniotic fluid “sludge” had a shorter examination-to-delivery interval compared with those without “sludge” [sludge median: 1 day

(interquartile range: 1–5 days) versus no sludge, median: 33 days (interquartile range: 18–58 days); $p < 0.001$]. These results indicate that amniotic fluid “sludge” during transvaginal examination of the cervix is a risk factor for intra-amniotic infection, histological chorioamnionitis, and impending preterm delivery (408).

The presence of amniotic fluid “sludge” on transvaginal examination in asymptomatic patients is also associated with delivery within 14 days of ultrasound and preterm delivery at less than 32 and less than 34 weeks (409,425). Amniotic fluid sludge has also been identified as an independent risk factor for spontaneous preterm delivery at less than 28 weeks, less than 32 weeks, and less than 35 weeks of gestation; and for preterm PROM; intra-amniotic infection; and histological chorioamnionitis (409). Furthermore, asymptomatic patients with amniotic fluid sludge had shorter ultrasound-to-delivery and ultrasound-to-preterm PROM intervals than those without sludge (409,425).

Recently, amniotic fluid sludge has been demonstrated to represent a biofilm (426,427). A sample of sludge was retrieved by transvaginal amniotomy under ultrasound guidance from a patient at 28 weeks with spontaneous labor and clinical chorioamnionitis. Grossly, the sludge had a “pus-like” appearance and the Gram stain showed gram-positive bacteria. The amniotic fluid culture was positive for *Streptococcus mutans*, *Mycoplasma hominis*, and *Aspergillus flavus*. Of interest, the results of the amniocentesis performed at the time of admission for preterm labor were negative for intra-amniotic infection (426,427). The aspirated sludge was then analyzed further. Scanning electron microscopy showed flocs of amniotic fluid sludge that consisted of bacterial cells and the exopolymeric matrix material that are typical of a biofilm (Fig. 8) (427). The evidence that sludge represents a biofilm in this case includes the following: (i) the presence of bacteria detected by fluorescence *in situ* hybridization, with the use of a probe against the conserved sequence of prokaryotes; (ii) bacterial aggregates were separated by material that resembled

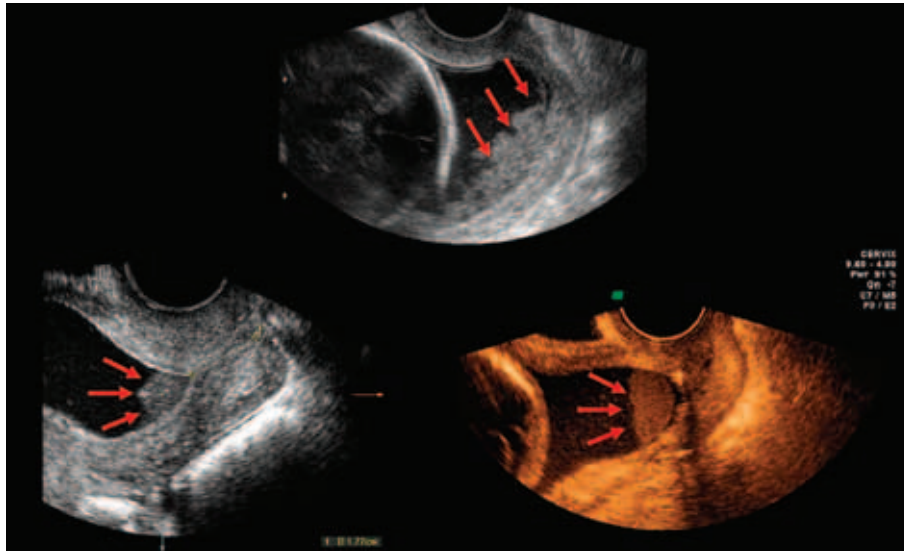


Figure 7 Amniotic fluid “sludge” seen in proximity of the internal cervical os during a transvaginal sonographic examination of the cervix. Source: From Ref. 505.

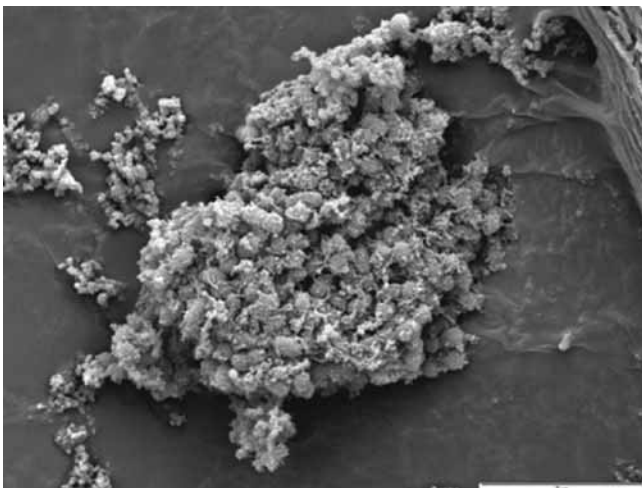


Figure 8 Examination of sludge using scanning electron microscopy. Source: From Ref. 427.

a matrix; and (iii) lectin-based identification of exopolymeric matrix that stained with wheat germ agglutinin (427).

The clinical significance of this relates to the challenges encountered with diagnosis and treatment of this condition. First, the diagnosis of microbial invasion in the presence of biofilms is extremely challenging, and current cultivation techniques are inadequate to detect such infections. The consequences are that the frequency of infection of the amniotic cavity may be underestimated and that molecular microbiologic techniques will be required to improve diagnosis. Second, the optimal treatment of biofilm-related infections represents a challenge in clinical medicine. Antimicrobial agents appear to be inactivated or fail to reach bacteria within a biofilm. Interestingly, bacteria within biofilms have increased resistance to antimicrobial compounds even though the same bacteria can be sensitive to the same agent if grown under standard conditions (428–431). Thus, the difficulties in treating intra-amniotic infection may be due to the refractoriness of biofilms to conventional antibiotic treatment. Third, biofilms in the amniotic fluid may

represent a unique form of these structures, which can be dislodged by fetal movement, resulting in seeding of planktonic bacteria and the eliciting of an inflammatory response.

Progestogens for the Prevention of Preterm Birth

The importance of progesterone in the maintenance of mammalian pregnancy is well-established (90,97,116,432–446), and the suspension of progesterone action is believed to be central to the initiation of parturition in most mammalian species, including primates (90,97,410,436,438,442,443,447). Yet the precise mechanism for this in humans has not been elucidated (90,97,98,436,439,443,448–451).

Progestogen (a term that, like progestins, describes both “natural” progesterone and synthetic compounds with progesterone action) (452) administration to prevent spontaneous abortion (453–465) and preterm birth (392–395,397, 454,466–469) has been a subject of investigation for several decades. The use of progesterone in the first trimester of pregnancy to “support corpus luteum function” is a well-established clinical practice (453,455,456,460,461,463,465,470), and formulations of progesterone for this indication have been approved by the FDA (<http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm>) and regulatory agencies in Europe and other countries (471).

The results of the early trials for the use of progestogens for the prevention of preterm birth or recurrent abortion were contradictory; as were the meta-analyses of such trials (470,472,473). For example, the meta-analysis of Goldstein et al. (473) included trials employing several progestational agents and could not demonstrate a beneficial effect of progesterone on the prevention of preterm birth. The meta-analysis of Professor Marc Keirse (472) focused only on studies of 17 alpha-hydroxyprogesterone caproate and examined its effect on different endpoints: “early curtailment of gestation, whether by miscarriage (<20 weeks or <500g) or by preterm birth (<37 weeks).” Despite these encouraging results, little clinical research on the subject was conducted for more than a decade.

The Use of Progestogens in Women with a Prior History of Preterm Birth

In 2003, two trials were reported in women with a prior history of preterm birth. The first study Fonseca et al. (395) randomized 142 women with risk factors for preterm birth to receive 100 mg vaginal progesterone or placebo between 24 and 34 weeks of gestation (395). In this trial, the rate of preterm delivery at both <37 and <34 weeks was significantly lower in women allocated to progesterone treatment than to placebo [<37 weeks, progesterone 13.8% (10/72) vs. placebo 28.5% (20/70), $p = 0.03$; and <34 weeks, progesterone 2.8% (2/72) vs. placebo 18.6% (13/70), $p = 0.002$].

Another trial (by Meis et al.) (394) evaluated the use of weekly injections of 17 alpha-hydroxyprogesterone caproate (250 mg IM between 16 and 36 weeks, $n=310$; and placebo, $n = 153$) in women with a prior preterm birth. The authors reported a reduction in the rate of preterm birth before 37 (36.3% vs. 54.9%, RR 0.66, 95% CI 0.54–0.81) and 35 (20.6% vs. 30.7%, RR 0.67, 95% CI 0.48–0.93) weeks of gestation.

The largest randomized clinical trial in which patients with a history of a previous spontaneous preterm delivery were allocated to receive vaginal progesterone (90 mg/day) in a bioadhesive formulation/gel or placebo was conducted by O'Brien et al. (396) The primary endpoint for the trial was preterm delivery (≤ 32 weeks). All patients had transvaginal sonography to determine the cervical length at enrollment and at 28 weeks. Randomization-to-delivery interval in patients who received tocolytic therapy for preterm labor or shortening of the cervix was considered a secondary outcome.

This multinational trial involved 53 centers and 659 women with a singleton pregnancy who were randomized, between 18 and 22 completed weeks of gestation, to receive daily treatment with vaginal progesterone gel or placebo (396). Progesterone or placebo was self-administered either until delivery, 37 weeks of gestation, or the occurrence of premature rupture of membranes. Vaginal progesterone did not reduce the rate of preterm birth at ≤ 32 , ≤ 35 , or ≤ 37 weeks of gestation. Moreover, there was no difference in neonatal and maternal outcomes. The results of this study conflict with those of the initial trial reported by Fonseca et al. (395).

The Use of Progestogens to Prevent Preterm Birth in Multiple Gestations

Multiple gestation is a risk factor for preterm birth (369,474–486). Uterine overdistention has been implicated as a mechanism responsible for the excess rate of preterm labor in this subset of patients (22,487,488). Progesterone down-regulates the expression of contraction-associated proteins (113–115,489–491); therefore, it is possible that progestogens may reduce the rate of preterm birth in multiple gestations. Consequently, investigators have tested whether progestogens can prevent preterm birth in these pregnancies (397,466,468).

More than 25 years ago, Hartikainen-Sorri et al. (466) reported a double-blind, placebo-controlled clinical trial of 17 alpha-hydroxyprogesterone caproate administration in 77 women with twin pregnancies enrolled between 28 and 33 weeks of gestation. Weekly intramuscular injection of 250 mg of 17 alpha-hydroxyprogesterone caproate or placebo were initiated at the time of enrollment and discontinued at 37 weeks of gestation or when delivery

occurred before term. The administration of 17 alpha-hydroxyprogesterone caproate did not reduce the rate of preterm birth (<37 weeks) or perinatal morbidity.

The issue has been revisited recently. Rouse et al. (468) reported a multicenter, placebo-controlled, double-blind, randomized clinical trial of 17 alpha-hydroxyprogesterone caproate for prevention of preterm birth in twin pregnancies, which included 655 women enrolled between 16 and 20 completed weeks of gestation. Patients were allocated to receive weekly injection of 250 mg of 17 alpha-hydroxyprogesterone caproate or placebo until 34 completed weeks of gestation or delivery. The primary outcome was a composite of fetal death or delivery before 35 completed weeks of gestation, which occurred in 41.5% (135/325) of patients in the 17 alpha-hydroxyprogesterone caproate group and in 37.3% (123/330) of those in the placebo group [RR 1.1 (95% CI 0.9–1.3)]. No benefit to the use of 17 alpha-hydroxyprogesterone caproate was demonstrated in twins.

In a sub-analysis of their randomized trial of vaginal progesterone versus placebo in 24 women with twin gestations and a short cervix (≤ 15 mm), Fonseca et al. (397) reported that progesterone administration was associated with a non-significant reduction in the rate of preterm delivery.

Norman et al. (492) reported the results of a randomized clinical trial of vaginal progesterone in 500 women with twin gestations. The use of vaginal progesterone beginning at 24 weeks of gestation was not associated with a reduction in the risk of preterm delivery before 34 weeks of gestation. Collectively, the results of these studies indicate that prophylactic progesterone administration does not reduce the rate of preterm delivery in women with twin pregnancies.

Recently, Caritis et al. (493) reported that the use of 17 alpha-hydroxyprogesterone caproate in triplet gestations did not reduce the rate of preterm delivery.

Sonographic Cervical Length to Identify the Patients who may Benefit from Progesterone Treatment

Facchinetti et al. (494) reported the results of a randomized prospective clinical trial in which women with preterm labor and intact membranes (25 to 33-6/7 weeks) were allocated to either observation or intramuscular administration of 341 mg of 17 alpha-hydroxyprogesterone caproate twice a week until 36 weeks of gestation or delivery, and sonographic cervical length measured at discharge as well as at 7 (7–9) and 21 (18–21) days later. Patients allocated to receive 17 alpha-hydroxyprogesterone caproate had a longer sonographic cervical length than those in the observation group. These findings, coupled with experimental data, suggest that progesterone may have major effects in the uterine cervix.

Two clinical lines of evidence support that cervical status may identify the patient who could benefit from progestogen administration (397,495). First, a recent randomized clinical trial reported by Fonseca et al. (397) indicates that vaginal progesterone reduces the rate of preterm birth by 44% (from 34.4% in the placebo group to 19.2% in the progesterone treatment group) in women with a sonographic short cervix. Second, a secondary analysis of a study by DeFranco et al. (495) suggests that patients with a short cervix may benefit from vaginal progesterone administration.

Fonseca et al. (397), working with the Fetal Medicine Foundation Second Trimester Screening Group, conducted a randomized, double blind, placebo-controlled trial in which women with a short cervix (≤ 15 mm by transvaginal ultrasound), between 20 and 25 weeks of gestation, were allocated to daily vaginal administration of 200 mg of micronized progesterone or placebo (safflower oil) from 24 to 34 weeks. The frequency of spontaneous preterm delivery at < 34 weeks (primary endpoint for the trial) was significantly lower in the progesterone group than that in the placebo group [19.2% (24/125) vs. 34.4% (43/125); $p = 0.007$]. A secondary analysis of this trial indicated that among women without a history of delivery before 34 weeks, the incidence of preterm birth was significantly lower in women receiving progesterone than in those allocated to placebo [17.9% (20/112) vs. 31.2% (34/109); RR 0.57, 95% CI 0.35–0.93; $p = 0.03$]. The trial was not designed to test whether progesterone administration could reduce neonatal morbidity and such a reduction was not observed (397).

DeFranco et al. (495) reported a retrospective analysis of the effect of vaginal progesterone on pregnancy outcome (preterm birth and infant outcome) as a function of cervical length. The hypothesis for this study was that the effect of prophylactic vaginal progesterone may vary according to cervical length. To test this concept, all patients eligible to participate in the trial of O'Brien et al. (396) had a sonographic measurement of the cervix at the time of enrollment. Patients without a previous preterm birth and a cervical length of ≤ 25 mm were subjected to a separate randomization procedure (to vaginal progesterone or placebo) and excluded from the main trial. The rationale for this was that the main trial tested the effect of vaginal progesterone on patients with a history of preterm delivery regardless of cervical length. However, after the completion of the main trial, only nine patients had been enrolled in the "short cervix only" arm of the trial. Analysis of the effect of progesterone on nine patients with a short cervix was not meaningful. Therefore, the investigators modified their initial plan so that the analysis included women enrolled in the main trial (and therefore, with a history of previous preterm birth). The authors divided the patient population into quartiles according to cervical length at enrollment and tested whether outcomes were different as a function of cervical length (the lowest quartile was a cervical length of ≤ 32 mm). Although there was a delay in delivery, progesterone administration did not result in a significant difference in outcome in patients in the lowest quartile.

The authors (495) then explored the effect of vaginal progesterone as a function of cervical length using two new cut-offs: ≤ 30 and < 28 mm. For the cut-off of 30 mm, there was a trend for a longer randomization-to-delivery interval in women allocated to progesterone than those allocated to placebo (Wilcoxon $p = 0.043$, log-rank $p = 0.057$) (432). However, there was no difference in the frequency of preterm delivery at ≤ 32 weeks.

With the second cut-off (< 28 mm), patients who had received vaginal progesterone had a lower rate of spontaneous preterm delivery at ≤ 32 weeks of gestation. Though this was not observed for preterm delivery defined as ≤ 35 weeks or ≤ 37 weeks. It is noteworthy that the frequency of newborn intensive care unit admission was lower in women with a

cervical length of ≤ 30 and < 28 mm and who had received progesterone treatment than in those allocated to the placebo group. The same was the case for the duration of newborn intensive care unit length of stay (495). This analysis provided the first hint that vaginal progesterone administration may improve infant outcome in properly selected patients. It is important to stress, however, that these conclusions were derived from a secondary analysis that was intended to be hypothesis-generating (496).

Hassan et al. (497) conducted a multicenter, randomized, placebo-controlled trial that enrolled 465 asymptomatic women with a singleton pregnancy and a sonographic short cervix (10–20 mm) at 19 to 23–6/7 weeks of gestation. Women were randomly allocated to receive vaginal progesterone gel ($n = 235$) or placebo ($n = 223$) daily from 20 to 23–6/7 weeks to 36–6/7 weeks, preterm rupture of membranes, or delivery, whichever occurred first. The primary endpoint was preterm birth before 33 weeks of gestation. Women allocated to receive vaginal progesterone had a lower risk of preterm birth before 33 weeks than those allocated to placebo [8.9% ($n = 21$) vs. 16.1% ($n = 36$), relative risk (RR) 0.55, 95% confidence interval (CI) 0.33–0.92, $p = 0.02$]. The effect remained significant after adjustment for co-variables (adjusted RR 0.52, 95% CI 0.31–0.91, $p = 0.02$). Vaginal progesterone was also associated with a significant reduction in the risk of preterm birth before 28 (5.1% vs. 10.3%, RR 0.50, 95% CI 0.25–0.97, $p = 0.04$) and 35 weeks (14.5% vs. 23.3% RR 0.62, 95% CI 0.42–0.92, $p = 0.02$), respiratory distress syndrome (3.0% vs. 7.6% RR 0.39, 95% CI 0.17–0.92, $p = 0.03$), any morbidity or mortality event (7.7% vs. 13.5% RR 0.57, 95% CI 0.33–0.99, $p = 0.04$), and birth weight < 1500 g [6.4% (15/234) vs. 13.6% (30/220), RR 0.47, 95% CI 0.26–0.85, $p = 0.01$]. There were no differences in the incidence of adverse events between the groups. The conclusion of this study was that the administration of vaginal progesterone gel to women with a sonographic short cervix in the midtrimester is associated with a 45% reduction in the risk of preterm birth before 33 weeks of gestation and improved neonatal outcomes.

In conclusion, patients with a previous history of spontaneous preterm delivery can be offered 17 alpha-hydroxyprogesterone caproate for the prevention of recurrent preterm delivery (394). It is important to counsel the patients following the determinations of the FDA indicating that this agent reduces the risk of preterm birth in subsequent pregnancies (394), but there is no solid evidence of improvement in neonatal outcome (394). Patients should also be counseled about the safety signal identified by the FDA, namely, a potential increase in the risk of pregnancy loss in the midtrimester (498).

Patients with a short cervix (10–20 mm) should be offered vaginal progesterone for the prevention of preterm birth and improvement in infant outcome. The approach of universal screening with transvaginal cervical length in the midtrimester followed by the use of vaginal progesterone appears to be cost-effective and allows the prevention of preterm delivery in nulliparous women (497,499,500).

Mode of Delivery

Preterm birth per se is not an indication for cesarean delivery. In the last two decades, there has been an interest in determining whether cesarean delivery could improve the

outcome of preterm birth. Efforts to conduct randomized clinical trials have not been effective in enrolling patients. Grant et al. (501), while conducting a systematic review of six trials of elective versus selective cesarean delivery, for infants less than 30 weeks of gestation, emphasized the difficulties in the execution of the trial and recommended that decision making should be individualized taking into account par-enteral preferences.

Therefore, cesarean delivery is currently performed for obstetrical indications, such as breech presentation, and fetal distress. The performance of a cesarean section in an early preterm gestation (<30 weeks) is often associated with an incision in the uterine corpus, because the lower uterine segment is not formed. This would increase the risk of uterine rupture in subsequent pregnancies, as well as complications associated with implantation of the placenta on the uterine scar (502). There is little evidence that the fetus may benefit from cesarean delivery and, therefore, the increased maternal risk for subsequent pregnancies does not appear to be justified.

In terms of the management of a vaginal delivery, some evidence suggests that delivery with intact membranes may improve umbilical artery pH by reducing the effect of mechanical forces on the fetus and umbilical cord. There is little evidence that the performance of a “prophylactic” outlet forceps or “elective” episiotomy improves neonatal outcome. Vacuum extraction is considered to be contraindicated in preterm neonates.

Timing of clamping of the cord deserves consideration. Randomized clinical trials of delayed versus early cord clamping indicate that delayed clamping is associated with a reduction in the need for transfusions of the infant for anemia (RR 2.01, 95% CI 1.24–3.27), neonatal hypotension (RR 2.58, 95% CI 1.17–5.67), and IVH (RR 1.74, 95% CI 1.08–2.81) (503).

SUMMARY

It is becoming increasingly clear that preterm labor, preterm PROM, and cervical insufficiency are syndromes caused by multiple pathologic processes leading to increased myometrial contractility, cervical remodeling, and/or membrane activation. The clinical presentation will depend upon the nature and timing of the insults on the various components of the common pathway of parturition. This view has important implications for the understanding of the biology of preterm parturition, as well as its diagnosis, treatment, and prevention.

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