

Preterm labor: Diagnostic and therapeutic options are not all alike

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Practice recommendations

- Consider progesterone to reduce the risk of recurrent preterm delivery (**A**).
- Consider calcium channel blockers (CCBs) as initial therapy for preterm labor; though these are Class C agents in pregnancy, CCBs are at least as effective as other agents and cause no known fetal or neonatal side effects (**A**).
- Consider tocolytic therapy for preterm labor, to prolong pregnancy for 2 to 7 days and thereby permit administration of antenatal corticosteroids and transfer to a tertiary center, if needed (**A**). Maintenance and recurrent use of tocolytics has not proven beneficial and should be avoided (**A**).

Despite diagnostic and therapeutic advances in premature labor, the rate of preterm delivery has increased in the United States. Preterm delivery, defined as birth before 37 weeks gestation, occurs in about 12% of

pregnancies,¹ and it is the leading cause of mortality among non-anomalous fetuses.² Among premature newborns who survive, 10% to 15% have significant handicaps.³ Long-term sequelae include visual or hearing impairment, chronic lung disease, developmental delay, and cerebral palsy.⁴ The annual cost of premature birth in the United States exceeds \$5 billion, and the rate of preterm delivery has increased in recent years.^{5,6} Specific maternal attributes increase risk of preterm delivery, though these factors need not be present for premature delivery to occur.

Standard techniques of physical diagnosis may not accurately detect preterm labor, either missing the diagnosis or prompting unnecessary hospitalization and treatment. Select imaging studies can more reliably indicate a true need for intervention.

This article reviews the risk factors for preterm birth, the tests available to accurately diagnose preterm labor, and the medications available to prevent or postpone premature delivery.

■ RISK FACTORS

Preterm delivery is categorized as spontaneous or indicated. Almost 75% of preterm births occur after spontaneous preterm labor or preterm premature rupture of the membranes (PPROM). The remaining 25% of early births are elective due to conditions potentially harmful to either the mother or the fetus.⁷

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TABLE 1

Maternal risk factors for spontaneous preterm birth

Risk factor	Odds ratio
Bacterial vaginosis at <16 weeks	7
Periodontal infection	4
Prior preterm birth	4
Prepregnancy BMI <20	3
Interpregnancy interval <6 mo	2
Bleeding in 2nd trimester	2
African-American race	2
Psychiatric disorder	1.6
Cigarette smoking	1.5
Gestational diabetes	1.2

Sources: Iams 2002⁷; Leitch et al 2003⁸; Jeffcoat et al 2001⁹; Moutquin 2003¹⁰; Smith et al 2003¹¹; Kelly et al 2002¹²; Hedderson et al 2003.¹³

Maternal risk factors for spontaneous preterm births are listed in **Table 1**.⁷⁻¹³ The risk factors for preterm labor and PPRM are similar, with the exception that those whose membranes rupture prematurely are more likely to be indigent, to smoke cigarettes, and to have bleeding in the current pregnancy.

Not all preterm births carry the same risks.

Early preterm birth—delivery before 32 weeks—is associated with clinical or subclinical infection, short cervical length, and the presence of fetal fibronectin in the cervicovaginal secretions. It tends to recur and leads to long-term fetal morbidity. **Late** preterm birth—delivery after 32 weeks but before 37 weeks—is associated with increased uterine contractions, tends to mimic normal labor, and is less likely to cause peripartum morbidity.⁷ Despite these known risk factors, women can experience preterm labor without exhibiting any of them.

■ INCREASING THE ACCURACY OF DIAGNOSIS

Uterine contractions before 37 weeks and concomitant change in cervical dilation or effacement as detected by digital examination comprise the standard definition of preterm labor.

Caveats with clinical evaluation

The problem with the definition above is that women may not perceive contractions, and that contractions are at times difficult to differentiate from benign Braxton-Hicks contractions of normal pregnancy. Moreover, digital assessment of the cervix lacks reproducibility when the dilation is <3 cm or effacement is < 80%.⁷ Clinical evaluation alone can easily suggest prematurity when it is absent and miss it when it is present.⁷

Imaging and lab evaluation more telling

The ability to diagnose preterm labor improves with the use of transvaginal cervical sonography or measurement of fetal fibronectin.

Lesser cervical length means greater risk.

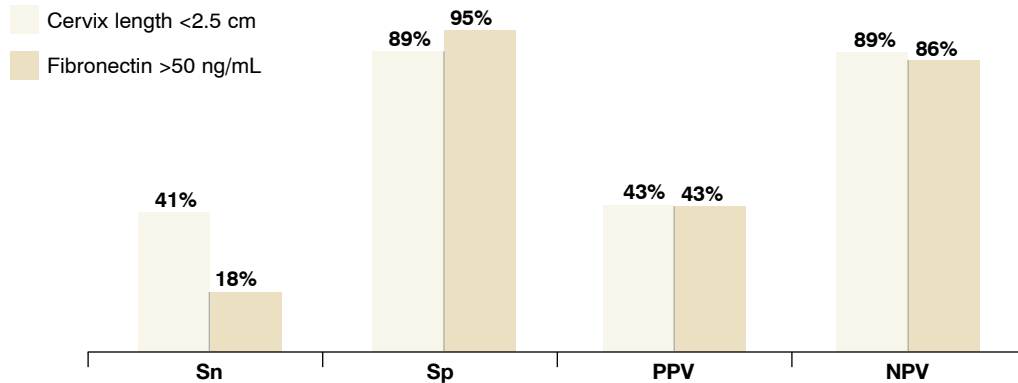
Likelihood of preterm delivery is inversely proportional to cervical length measured at 18 to 28 weeks. A length of ≤ 2.5 cm is the threshold for abnormal condition (level of evidence [LOE]: 2).⁶

Fibronectin detected late may mean delivery early. Fibronectin, an extracellular glycoprotein described as the glue that attaches the fetal membrane to the underlying uterine decidua, is normally absent in cervicovaginal secretions between weeks 22 and 37 of pregnancy. Its presence (≥ 50 ng/mL) between 22 to 24 weeks is a predictor of spontaneous preterm birth; its absence makes premature delivery unlikely (LOE: 2).

Imaging and test results justify management decisions. The predictive accuracies of abnormal cervical length and of the presence of fibronectin are depicted in the **Figure**.⁷ The major benefit of these two tests is when they are normal (cervical length >2.5 cm or negative fetal fibronectin), unnecessary intervention is avoided.¹⁴ If, for example, a patient is having contractions and the cervical length is greater than 2.5 cm, or fetal

FIGURE

Value of transvaginal cervical imaging and fetal fibronectin measurement in predicting spontaneous preterm birth



Cervical imaging and fetal fibronectin measurements at 22 to 24 weeks; preterm birth defined as before 35 weeks.

Sn, sensitivity; Sp, specificity; PPV, positive predictive value; NPV, negative predictive value.

Source: adapted from Iams 2002.⁷

fibronectin is absent, tocolytics can be discontinued and hospitalization avoided.

■ PREVENTING PRETERM LABOR

Progestational agents

Many authors have advocated the use of progestational agents to inhibit premature labor. Progesterone's presumed mechanisms are inhibition of the oxytocin effect of prostaglandin F_{2a} and stimulation of α -adrenergic receptors, thereby increasing the α -adrenergic tocolytic response.^{15,16} Natural progesterone appears to be free of any untoward teratogenic, metabolic, or hemodynamic effects.¹⁷

Studies favoring progesterone. Two double-blind, placebo-controlled studies assessed the use of 17 α -hydroxyprogesterone caproate in preventing premature labor in high-risk populations. These patients had histories of preterm deliveries or spontaneous abortions.

Weekly intramuscular (IM) injections of 250 mg were started at 12 to 16 weeks gestation and given until 37 weeks or delivery, whichever came first. In both studies, the rate of premature deliveries was significantly lower in the treated group than the control group (number needed to treat [NNT]=2.4 and

4.6). In addition, neither mothers nor infants experienced adverse effects attributable to 17 α -hydroxyprogesterone caproate (LOE: 2).^{18,19} However, these studies were small—43 and 79 patients.

A large double-blind, placebo-controlled, randomized study established the effectiveness of 17 α -hydroxyprogesterone caproate in preventing preterm delivery.²³ Four hundred fifty-nine pregnant women with a history of preterm delivery were randomized to receive weekly injections of 17 α -hydroxyprogesterone caproate 250 mg or placebo beginning at 16 to 20 weeks gestation and continuing to 36 weeks. Significantly fewer women in the treated group than the control group gave birth before 37 weeks, 36.3% v 54.9%, respectively (NNT=6; LOE: 1). Perhaps more importantly, treatment resulted in significant reductions in birth weight <2500 g (NNT=7), necrotizing enterocolitis (NNT=38), need for supplemental oxygen (NNT=11), and intraventricular hemorrhage (NNT=26). Swelling, bruising, or rash at the injection site were the most common adverse effects of 17 α -hydroxyprogesterone caproate administration.

Vaginal progesterone suppositories have also been shown to decrease the rate of preterm birth

TABLE 2

Evidence generally supports progesterone in prevention of preterm labor

Study	Treatment	Comment	NNT	LOE
Johnson ¹⁸	Weekly IM 250 mg injections of 17 α -hydroxyprogesterone caproate	Decreased preterm delivery	2.4	2
Yemeni ¹⁹	Weekly IM 250 mg injections of 17 α -hydroxyprogesterone caproate	Decreased preterm delivery	4.6	2
Hauth ²⁰	Weekly IM 1000 mg injections of 17 α -hydroxyprogesterone caproate	Did not decrease preterm delivery	N/A	2
Hartikainen-Sorri ²²	Weekly IM 250 mg injections of 17 α -hydroxyprogesterone caproate	Did not decrease preterm delivery	N/A	2
Meis ²³	Weekly IM 250 mg injections of 17 α -hydroxyprogesterone caproate	Decreased preterm delivery	6	1
da Fonseca ¹⁷	Daily 100 mg progesterone vaginal suppositories	Decreased preterm delivery	7	1

NNT, number needed to treat; LOE, level of evidence; IM, intramuscular; N/A, not applicable.

in patients at increased risk.¹⁷ da Fonseca et al noted that among 142 women who had 1 prior preterm birth, prophylactic cerclage, or uterine malformation, daily use of a 100-mg vaginal progesterone suppository compared with placebo significantly decreased the likelihood of delivery prior to 37 weeks, 14% v 28% (NNT=7; LOE: 1). Adverse effects of progesterone suppositories were not mentioned.

Studies lacking clear benefit. Another investigator enrolled 168 active-duty military women into a randomized double-blind study that evaluated weekly IM injections of 1000 mg 17 α -hydroxyprogesterone caproate or placebo beginning between 16 and 20 weeks gestation.²⁰ The study population was chosen based on a report that active-duty pregnant military personnel had an increased number of pregnancy complications including low birth-weight infants and increased premature delivery.²¹ In contrast to the previous studies, no significant difference in premature labor or perinatal mortality was seen between the 2 groups (LOE: 2). Perhaps although active-duty personnel are at a higher risk for preterm labor, the

risk is not as high as it is with previous preterm birth, prior spontaneous abortion, and so forth.

An additional small study of 77 women with twin pregnancies investigated the use of 17 α -hydroxyprogesterone caproate to prevent preterm delivery.²² Patients were randomized to receive weekly injections of 17 α -hydroxyprogesterone caproate 250 mg or placebo from the 28th gestational week until the 37th week or delivery. The mean duration of pregnancy did not differ between the two groups of women, nor did perinatal mortality (LOE: 2).

Evidence generally supports use of progesterone. Based on available data, consider administering progesterone to women at high risk for preterm delivery to prevent recurrent preterm birth (SOR: A). These data are summarized in **Table 2**.

Hydroxyprogesterone caproate in oil is commercially available in the United States in 125 mg/mL and 250 mg/mL strengths. It is not, however, approved by the Food and Drug Administration (FDA) for the prevention of preterm labor.

Progesterone suppositories are also not FDA approved, and they are commercially unavailable

in the US. Therefore, they have to be extemporaneously compounded.

Treating bacterial vaginosis may not prevent preterm labor

Bacterial vaginosis (BV) during pregnancy has been associated with preterm birth, and antibiotics have been thought perhaps to reduce this risk. A systematic review of 10 trials including 4249 pregnant women with BV showed that, although antibiotics eradicated BV, they did not significantly reduce the risk of birth before 32, 34, or 37 weeks (LOE: 1).²⁴ This was true even for women with a history of preterm delivery. However, antibiotics did decrease the risk of PPRM. The authors concluded that evidence does not support screening all pregnant women for asymptomatic BV to prevent preterm birth.

Treating asymptomatic bacteriuria may prevent preterm labor

Asymptomatic bacteriuria in pregnant women has also been associated with preterm birth. One review of 14 trials comparing antibiotic treatment with placebo in this patient population—though not of high quality—demonstrated decreased incidences of pyelonephritis and preterm birth or low birth weight (LOE: 1).²⁵

■ TREATING PRETERM LABOR

The primary goal of using tocolytics in preterm labor is to prolong pregnancy for 2 to 7 days, permitting administration of corticosteroids and transfer to a tertiary care center when necessary. Recommendations for the treatment of preterm labor are summarized in **Table 3**.

Calcium channel blockers safe, effective

Calcium channel blockers (CCBs) are nonspecific smooth muscle relaxants. They prevent the influx of extracellular calcium ions into the myometrial cell, thereby exerting their tocolytic effect. Nifedipine is the most widely studied CCB in the management of preterm labor.

A systematic review of 12 randomized con-

trolled trials including 1029 women demonstrated that CCBs significantly reduced the rate of preterm delivery within 7 days of the start of treatment and before 34 weeks gestation (LOE: 1).²⁶ Compared with betamimetics, CCBs caused fewer maternal adverse effects, and decreased the frequency of neonatal respiratory distress syndrome, necrotizing enterocolitis, intraventricular hemorrhage, and jaundice. The authors concluded that CCBs are preferable to betamimetics for tocolysis.

Calcium channel blockers have also been compared with magnesium. Eighty women at 20 to 34 weeks gestation with documented cervical change were randomized to receive nifedipine or magnesium.²⁷ No difference in tocolytic efficacy was observed between the treatments, but there were significantly fewer maternal side effects among the nifedipine-treated patients (LOE: 2).

CCBs appear not to adversely affect the human fetus.^{28,29} There was no significant increase in congenital anomalies among 586 mothers who had been exposed to CCBs compared with 907 controls: 2.6% vs 2.4%, respectively (LOE: 2).³⁰ CCBs are effective at reducing the rate of preterm delivery, decreasing neonatal morbidity and mortality, and are well tolerated by both mother and baby. Although some other tocolytics (such as beta-agonists and prostaglandin inhibitors) prolong pregnancy, they have not demonstrated a beneficial effect on neonatal morbidity.

Dosing recommendations for nifedipine are a 30 mg loading dose, followed by 10 to 20 mg every 4 to 6 hours.³¹ Maternal side effects may include flushing, headache, nausea, dizziness, and transient hypotension. Neonatal side effects have not been documented. Nifedipine should not be used in conjunction with magnesium sulfate because the combination has resulted in cardiac collapse (LOE: 3).³²

Beta-agonists marginally useful

Beta-agonists increase cyclic AMP, thereby causing smooth muscle relaxation. Betamimetics are widely used as tocolytic agents. Although they have been shown to prolong pregnancy by 24 to 48

TABLE 3

Evaluation of proposed treatments for preterm labor

Treatment	Comment	NNT	LOE	References
Calcium channel blockers	Reduce preterm delivery, decrease neonatal morbidity, well-tolerated	11	1	26, 27
Beta-agonists	Prolong pregnancy but no beneficial effect on neonatal morbidity; maternal side effects often lead to discontinuation	N/A	1	33, 34
Magnesium sulfate	Does not prolong pregnancy; maternal side effects often lead to discontinuation	N/A	1	33, 40
Prostaglandin inhibitors	Prolong pregnancy but no beneficial effect on neonatal morbidity; increase risk of postpartum hemorrhage	N/A	1 2	33 43
Antibiotics	No evidence to support use	N/A	1	44
Corticosteroids	Strongly recommended; decrease neonatal morbidity, well-tolerated	U	1	46

NNT, number needed to treat; LOE, level of evidence; N/A, not applicable; U, unavailable data.

hours, they have not decreased adverse perinatal or neonatal outcomes (LOE: 1).^{33,34} In addition, they have been associated with maternal side effects of palpitations, arrhythmias, nausea, tremor, chorioamnionitis, hyperglycemia, hypokalemia, and pulmonary edema. The risk of pulmonary edema increases if beta-agonists are used with magnesium sulfate.^{33,35} Fetal and neonatal side effects may include tachycardia, hyperinsulinemia, and hyperglycemia.^{14,35}

Terbutaline is the preferred beta-agonist for preterm labor due to low cost and multiple dose forms. It may be administered subcutaneously, 0.25 mg every 30 minutes up to 1 mg in 4 hours, or by intravenous infusion, 2.5 to 10 µg per minute up to an effective maximum dose of no more than 30 µg per minute. Once stabilized, the patient is often maintained on oral terbutaline, 2.5 to 5 µg by mouth every 4 to 6 hours until term. This practice, however, has not been shown to significantly prolong pregnancy (LOE: 1).³⁶

The major benefit of terbutaline may be in the management of preterm uterine contractions without cervical changes. Among patients with premature contractions at 20 to 34 weeks, who were randomized to hydration or observation or a single subcutaneous dose of 0.25 mg of terbutaline, the shortest length of stay in triage was for the women who received the terbutaline (LOE: 1).³⁷

Magnesium sulfate:

No good rationale for use

Magnesium sulfate in the management of preterm labor is controversial. Although widely used in North America, it is generally avoided in Europe, Australia, and the United Kingdom^{38,39} due to the absence of clear evidence showing efficacy in the face of its adverse effect profile. Data from systematic reviews indicate it does not delay or prevent preterm birth (LOE: 1).^{33,40} In addition, maternal side effects may require discontinuation of treatment. Side effects include flushing, nausea,

headache, ileus, and hypocalcemia. Pulmonary edema is a serious maternal side effect and is increased when magnesium is co-administered with other tocolytic agents. Cardiac arrest is rare.^{14,33} Not only does evidence suggest magnesium sulfate does not delay or prevent preterm birth, but one study suggests its use may increase infant mortality (LOE: 2).⁴¹

In one trial of 1062 women, magnesium sulfate or placebo was given at 30 weeks' gestation. Two years following birth, children of mothers who received magnesium sulfate exhibited less gross motor dysfunction than those born to mothers who received placebo, 18% vs 34% respectively (LOE: 1).⁴² However, the rate of pediatric mortality and cerebral palsy, the primary endpoints of the study, did not differ between the groups. Further studies are necessary before magnesium sulfate can be recommended for neuroprotection.

Prostaglandin inhibitors may be preferred for hydramnios

Indomethacin is the prostaglandin synthetase inhibitor most studied in preterm labor, though the numbers of patients in these studies was generally small.³³ Indomethacin reduced the rate of preterm delivery within 7 days of treatment and before 37 weeks gestation. However, it did not decrease the rate of neonatal morbidity. Importantly, indomethacin was associated with an increased risk of postpartum hemorrhage (LOE: 1).³³ A retrospective review demonstrated an increase in incidence and severity of postnatal patent ductus arteriosus in neonates whose mothers were treated with indomethacin (LOE: 2).⁴³ Most prospective studies, however, have not found this complication. Prostaglandin inhibitors may be the preferred choice of tocolytics if hydramnios is suspected in conjunction with preterm labor.

Antibiotics: one indication only

It is hypothesized that women who experience preterm labor have infections of the upper genital tract, and that infection or inflammation leads to contractions. A meta-analysis of 11 randomized

trials with 7428 women in preterm labor and intact membranes demonstrated that, although prophylactic antibiotics decreased the incidence of maternal infection, there was no benefit in neonatal outcomes (LOE: 1).⁴⁴ Although it did not reach statistical significance, there was a trend towards an increase in neonatal deaths in the antibiotic group, raising concerns about their use. Therefore, administration of prophylactic antibiotics in this patient population is not recommended. Conversely, antibiotic prophylaxis is recommended for all women colonized with group B streptococcus, unless a cesarean delivery is planned, to prevent perinatal disease.⁴⁵

Corticosteroids beneficial for preterm infants

Antenatal corticosteroids reduce mortality, incidence and severity of respiratory distress syndrome, and intraventricular hemorrhage in preterm infants (LOE: 1).⁴⁶ Women at risk for preterm delivery between 24 and 34 weeks of gestation should be given betamethasone 12 mg IM, two doses 24 hours apart, or dexamethasone 6 mg IM, two doses 12 hours apart. There are no significant maternal or neonatal adverse effects with these regimens. Administration of tocolytic drugs may be necessary to prolong gestation and provide time for steroids to act.

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