OBG MANAGEMENT

Preterm birth affects one of every eight infants born in the United States and is the leading cause of neonatal mortality. At least five strong meta-analyses have demonstrated that progesterone significantly reduces the incidence of recurrent preterm birth. Evidence is less compelling in other settings.

Can progesterone prevent prematurity—dependably?

Here's what we know, after 30 years of study, about the usefulness of progesterone in 4 settings: recurrent preterm birth, multiple gestation, a short cervix, and preterm labor

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CASE

Patient worries about recurrent preterm birth

Ms. Jones is 13 weeks into her fourth pregnancy when she arrives at your office for her first prenatal visit. Her obstetric history is significant. In 2003, her first pregnancy was complicated by preterm labor at 25 weeks, preterm premature rupture of membranes at 26 weeks, and spontaneous vaginal delivery at 27 weeks. The infant experienced respiratory distress syndrome, bronchopulmonary dysplasia, necrotizing enterocolitis, and grade III intraventricular hemorrhage, and she was given a diagnosis of mild cerebral palsy at age 3.

Two years later, the patient's second pregnancy was complicated by preterm labor at 22 weeks and spontaneous vaginal delivery at 23 weeks, with an Apgar score of 3, 1, and 0. The infant did not survive.

In 2007, Ms. Jones was given a diagnosis of missed abortion at 8 weeks' gestation and underwent dilation and curettage.

Today, she asks what you plan to do to optimize the outcome of her current pregnancy. Her risk of preterm birth is significantly higher than that of the general population, which is 12.7%.

What can you offer to her?

Progesterone supplementation is the best option for Ms. Jones. Data accumulating over the past 30 years suggest that progesterone reduces the likelihood of preterm birth in women who have a history of spontaneous preterm birth. In fact, a cumulative

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Why it's vital to reduce preterm birth

Despite decades of research, initiative, and medical advances, the rate of preterm birth continues to rise, affecting one of every eight infants born in the United States—more than 500,000 babies each year. The impact of preterm birth is enormous, with implications that span from the immediate to the long-term.

In 2001, preterm birth surpassed birth defects as the leading cause of neonatal mortality. It is also the leading cause of infant mortality among African Americans and the second leading overall cause of all infant mortality.

The outlook for babies who survive preterm birth is concerning, as well. One of every five children who have mental retardation was born preterm, as was one of every three children who have vision impairment, and roughly one of every two children who have cerebral palsy. Low-birth-weight babies are commonly born preterm and face an increased risk of cardiovascular disease (including myocardial infarction, stroke, and hypertension), diabetes, and, possibly, cancer as adults.

Preterm birth not only affects the health of the baby and the family, but has long-term health and economic implications for society, costing at least $26 billion a year.[26]

meta-analysis noted that evidence of progesterone's benefit is striking enough that "statistical uncertainty" is not a valid reason for forgoing its use.[1]

This article describes what's been learned about progesterone supplementation to reduce preterm birth—specifically, the patients likely to benefit, the various formulations available, and the data on long-term outcomes—with an eye toward helping you weigh its utility in your practice.

The article focuses on four vulnerable populations:

- **Women who have a history of preterm birth.** Data suggest these patients are likely to benefit from progesterone.
- **Women carrying a multiple gestation.** Progesterone does not appear to prevent preterm birth in this group.
- **Women who have a short cervix.** Some data are promising. Further study is needed.
- **Women who experience preterm labor.** Data are promising, but preliminary.

Progesterone supplementation in high-risk women is one opportunity for prevention—but clearly not the complete answer. Despite progesterone administration, some women continue to deliver preterm. We have work ahead of us tailoring the therapy to the underlying mechanism, and the heterogeneity of preterm labor and delivery remains a limiting factor.

POPULATION 1

Women who have a history of preterm birth

Women who have already delivered preterm face an elevated risk of doing so in any subsequent pregnancy (**TABLE 1**). Three recent double-blind, randomized, controlled trials explored the efficacy of progesterone in the prevention of recurrent preterm birth.[2–4] All three trials enrolled women at high risk of preterm birth; two included only women who had a history of spontaneous preterm birth, and 90% of the participants of the third trial had such a history as their risk factor.

The trials involved three different formulations of progesterone:

- intramuscular injection of 250 mg of 17α-hydroxyprogesterone caproate
- 100-mg vaginal suppository of progesterone
- 90 mg of vaginal progesterone gel (Prochieve 8% / Crinone 8%).

Two of the trials found a significantly lower rate of preterm birth among women randomized to progesterone. The third found no difference between the progesterone and placebo groups.

Meta-analyses of all studies, including these three, found that the risk of recurrent preterm birth can be reduced by as much as 40% to 55% and low birth weight by 50% using progesterone.[5,6]

Details of the trials

Meis and colleagues conducted a multicenter trial of 463 pregnant women who had a documented history of spontaneous preterm delivery.[2] Starting between 16 and 20 weeks' gestation, participants were randomized in a 2:1 ratio to weekly injection of 250 mg of 17α-hydroxyprogesterone caproate or

TABLE 1 A woman who gives birth prematurely once likely will the next time

Source	Gestational age at first delivery	Relative risk of recurrent preterm birth (95% confidence interval)
Maternal–Fetal Medicine Units Network[30]	<37 weeks	2.5 (1.9–3.2)
Missouri database, 1989–1997[31]	<35 weeks	3.6 (3.2–4.0)
University of Texas Southwestern Medical Center, 1988–1999[32]	<35 weeks	5.9 (4.5–7.0)
Denmark, 1982–1987[33]	32–36 weeks	4.8 (3.9–6.0)
Denmark, 1982–1987,[33] Maternal–Fetal Medicine Units Network[30]	<32 weeks	6.0 (4.1–8.8)
Maternal–Fetal Medicine Units Network[30]	<28 weeks	10.6 (2.9–38.3)

an inert oil placebo, with injections continuing until delivery or 36 weeks' gestation.

Among the findings:

- Treatment with progesterone significantly reduced the risk of delivery at less than 37 weeks' gestation, with an incidence of 36.3% in the progesterone group versus 54.9% in the placebo group (relative risk [RR], 0.66; 95% confidence interval [CI], 0.54–0.81).
- Progesterone reduced the risk of delivery at less than 35 weeks' gestation, with an incidence of 20.6% in the progesterone group versus 30.7% in the placebo group (RR, 0.67; 95% CI, 0.48–0.93).
- Progesterone reduced the risk of delivery at less than 32 weeks' gestation, with an incidence of 11.4% in the progesterone group versus 19.6% in the placebo group (RR, 0.58; 95% CI, 0.37–0.91).
- Progesterone was effective in African Americans and non–African Americans.
- Infants of women treated with progesterone had significantly lower rates of necrotizing enterocolitis and intraventricular hemorrhage and less need for supplemental oxygen.

In a trial by da Fonseca and colleagues, 142 high-risk women who were pregnant with a singleton fetus were given a 100-mg vaginal suppository of progesterone or placebo daily (at night) between 24 and 34 weeks of gestation.[3] Preterm birth occurred in 13.8% of the women treated with progesterone versus 28.5% of women in the placebo group ($P<.05$). More women were delivered before 34 weeks' gestation in the placebo group (18.5%) than in the progesterone group (2.7%).

O'Brien and associates studied 659 pregnant women who had a history of spontaneous preterm birth.[4] Participants were randomly assigned to receive daily treatment with progesterone vaginal gel or placebo, starting between 18 and 22.9 weeks' gestation and continuing until delivery, 37 weeks' gestation, or premature rupture of membranes. The gel was administered in the morning.

In this trial, progesterone did not decrease the rate of preterm birth at 32 weeks' gestation or less (10% in the progesterone group versus 11.3% in the placebo group; odds ratio, 0.9; 95% CI, 0.52–1.56).

It is unclear whether the formulation, timing, or dosage was responsible for the different outcomes in these trials (**TABLE 2**, page 56).

In this population, the number needed to treat is low

At least five strong meta-analyses have explored the prevention of recurrent preterm birth.[1,7–10] These analyses demonstrate that progesterone supplementation significantly reduces the incidence of low birth weight and preterm birth. In some cases, it also reduces the rate of respiratory distress syndrome and intraventricular hemorrhage.

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Infants of women treated with progesterone had significantly lower rates of necrotizing enterocolitis and intravenous hemorrhage and less need for supplemental oxygen

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TABLE 2 5 progesterone formulations have been tested for the prevention of preterm birth

Formulation	Dosage	Administration	Dosing schedule	Gestational age at initiation	Gestational age at completion
17α-Hydroxyprogesterone caproate[2]	250 mg	Intramuscular	Weekly	16.0–20.0 weeks	36.9 weeks
Progesterone[3]	100 mg	Vaginal suppository	Daily at bedtime	24 weeks	34 weeks
Progesterone[14]	200 mg	Vaginal suppository	Daily at bedtime	24 weeks	34 weeks
Prochieve 8%/Crinone 8%[4]	90 mg	Vaginal suppository bioadhesive formulation/gel	Every morning	18.0–22.9 weeks	37 weeks
Progesterone[19]	400 mg	Vaginal suppository	Daily	After arrest of preterm labor	Delivery

FAST TRACK

Preterm birth likely arises from different causes in women with a previous preterm birth and women carrying a multiple gestation

Based on these data, Petrini and associates calculated that, if all pregnant women who had a history of spontaneous preterm birth had been offered progesterone in 2002, 10,000 preterm births could have been prevented.[11]

The number needed to treat (NNT) to avoid one preterm birth was eight for 17α-hydroxyprogesterone caproate and 10 using another progesterone formulation. The NNT to prevent low birth weight was 12.

To put these figures in context, consider the use of low-dose aspirin to prevent stroke, which has a NNT of 102, and the use of a β-blocker to prevent cardiac death in patients who have suffered a myocardial infarction, which carries a NNT of 42.

POPULATION 2

Women who are carrying a multiple gestation

Given the success of progesterone in preventing recurrent preterm birth, it was a matter of time before investigators began to consider its use in another high-risk group: women carrying a multiple gestation. In two double-blind, placebo-controlled trials—one from the United States and the other from the United Kingdom—17α-hydroxyprogesterone caproate or placebo was given, starting between 16 and 20 weeks' gestation in women who were carrying a twin or triplet gestation.[12,13] Neither trial demonstrated a benefit for the use of progesterone in this population.

The etiology of preterm birth is likely different in women with a previous preterm birth than it is in women carrying a multiple gestation. The former are more likely to have an inflammatory, immunologic, or infectious process that leads to recurrent preterm birth, whereas women carrying multiples are thought to be at risk of preterm birth by virtue of the "stretch hypothesis"—the theory that the uterus is stretched excessively, leading to an earlier trigger of labor. Women who had a history of preterm birth and who were carrying a multiple gestation were eligible for these trials.

In the US trial, progesterone failed to reduce the rate of preterm birth in women who were carrying twins or triplets.[13] This lack of benefit was seen regardless of whether conception was spontaneous or the result of assisted reproductive technologies, whether placentation was dichorionic or monochorionic, and regardless of the cutoff for gestational age. On average, the women in this trial delivered at 34.8 weeks, compared with a national average of 35.2 weeks for women carrying twins.[13]

Similar findings were reported from the UK trial, which enrolled 500 women carrying a twin gestation who were randomized to daily vaginal progesterone gel (90 mg) or placebo from 24 to 34 weeks' gestation.[12]

A meta-analysis of the three trials that included multiple gestation[12–14] found progesterone to have no benefit in women car-

How progesterone might inhibit preterm birth

Progesterone is a familiar player in the ObGyn specialty. In its natural form, the steroid hormone is produced by the corpus luteum to promote pregnancy.

In target cells, progesterone binds to its receptor and forms a transcription factor. It also can be active independent of nuclear receptors, which may explain why it remains effective even when circulating concentrations are high, suggesting that its action may be local and not systemic.

Progesterone exerts biologic effects on the myometrium, chorioamniotic membranes, and cervix.

Myometrial effects include:

- a decrease in the conduction of contractions
- a reduction of spontaneous muscle activity
- a decrease in the number of oxytocin receptors
- prevention of the formation of gap junctions
- a rise in the threshold for stimulation.

Progesterone decreases myometrial estrogen responsiveness by inhibiting estrogen-receptor expression and appears to maintain uterine quiescence by limiting the production of prostaglandins and inhibiting the expression of contraction-associated protein genes, including gap junctions, ion channels, oxytocin, and prostaglandin receptors within the myometrium.[27] Some investigators have suggested that progesterone prevents preterm birth predominantly by virtue of its anti-inflammatory properties[28] and ability to prevent cervical ripening.[29]

The 17α-hydroxyprogesterone form of the hormone also affects salivary concentrations of estriol. In a secondary analysis, the ratio of salivary estriol to progesterone increased as pregnancy progressed among women who received placebo, but remained flat among women treated with 17α-hydroxyprogesterone.[2] One theory is that labor may be triggered by an increase in the activity of estriol, compared with progesterone.

It also is notable that estriol concentrations in the mother's blood and saliva derive mainly from the fetus and placenta (from the fetus' production of cortisol), suggesting that the action of 17α-hydroxyprogesterone acetate may also affect the feto-placental unit.

rying twins. The pooled odds ratio of the effect of progesterone on preterm delivery or intrauterine death before 34 weeks' gestation was 1.16 (95% CI, 0.89–1.51).[12]

POPULATION 3

Women who have a short cervix

Because women who have a short cervix have a heightened risk of spontaneous preterm delivery, the utility of progesterone in prolonging gestation was explored in this population—with less than definitive results. An editorial accompanying the main study of this issue concluded that it is too early to recommend use of progesterone in women who have a short cervix.[15]

Progesterone was effective overall, but not in subgroup analysis

Iams and associates expertly delineated the risk of spontaneous preterm birth in the setting of a shortened cervix at 24 weeks' gestation. They found a cervical length of about 12 mm to be at the first centile, with a relative risk of preterm birth of 14.[16] (Compare this with the average cervical length of 36 to 44 mm at 24 weeks.)

Fonseca and colleagues then explored the benefit of progesterone therapy in preventing preterm birth in women who had a shortened cervical length between 20 and 25 weeks' gestation.[14] They screened more than 24,000 women and found 413 who had a cervical length of less than 15 mm. Of these women, 250 were randomized to micronized progesterone (200 mg in a vaginal suppository), starting at 24 weeks. This was twice the dosage given in the Brazilian trial involving women who had a history of preterm birth,[3] but the authors thought that women who had a short cervix were at higher risk of preterm birth and, therefore, needed a higher dosage of progesterone. Although all women in this trial had a short cervix, the population overall was more heterogeneous than in other trials, including women who had a history of preterm birth (30% of participants) and women carrying a multiple gestation (19% of participants).

Progesterone reduced the risk of preterm birth in the overall cohort, with 19% of the women who received progesterone delivering preterm, versus 34% of those who received placebo (odd ratio [OR], 0.56; 95% CI, 0.36–0.86). Progesterone did not reduce the rate of perinatal mortality or neonatal morbidity. A subgroup analysis of only the nulliparous women was conducted, given that 30% of the study population had a history of preterm

birth. That analysis showed no benefit.

DeFranco and associates[17] published a secondary analysis of 46 women from a large randomized trial[4] who had a cervical length of less than 28 mm. Of these women, 19 received progesterone and 27 received placebo. Of the 19 who received progesterone, 15 had a history of preterm birth. Of the 27 who received placebo, 22 had such a history. The authors found that progesterone significantly reduced preterm birth at less than 37, 35, and 32 weeks. However, again because of the small sample size and the inclusion of women with a history of preterm birth, these findings are not definitive.

Randomized trials designed to test the effect of progesterone in women who have a short cervix are called for. Numerous studies are underway.[15]

POPULATION 4

Women who experience preterm labor

Two recent trials explored the use of progesterone in this context. In one, progesterone was administered during the episode of preterm labor; in the other, it was given after successful tocolysis.

In the first trial, Facchinetti and colleagues studied 60 women who were pregnant with a singleton fetus and who were in active preterm labor.[18] These women were randomly assigned to 341 mg of intramuscular 17α-hydroxyprogesterone caproate or placebo twice weekly, with cervical length monitored weekly. Women in the progesterone group were less likely to deliver by 7 or 21 days, and their cervical length was longer at both time points.

Borna and Sahabi evaluated use of progesterone as maintenance therapy after successful tocolysis.[19] Seventy women were randomly assigned to progesterone (400-mg suppository) or no treatment. Women who received progesterone had a longer latency period (36 versus 24 days; *P*=.03), less respiratory distress (11% versus 36%), and a lower rate of low birth weight (27% versus 52%) than did women receiving no treatment.

What are the long-term effects of progesterone exposure?

Therapeutic interventions during pregnancy affect two people—one of them during a period of intense development that can have a lifelong impact. Although studies of progesterone to prevent preterm birth involve administration of the hormone after 16 weeks—well beyond the major period of organogenesis—concerns about potential teratogenic and other long-term effects have been raised. It is notable that progesterone has been widely used for decades during the first trimester—the period of organogenesis—in women who have a poor pregnancy history and early loss, to treat the "luteal phase defect."

A Cochrane review of 14 studies of progesterone in the prevention of stillbirth and miscarriage[20] and a systematic review of 14 cohort and case-control studies[21] involving first-trimester exposure found no harm related to progesterone use. These findings are consistent with those of a meta-analysis by Coomarasamy and colleagues, which also found no harm related to the use of progesterone.[1]

Numerous studies have explored the long-term effects of progesterone on offspring, including a review of outcomes of pregnancies treated before 1990[22] and data from animal studies.[23] Children from a trial by Meis[22] were followed up at around 4 years of age to assess any differences in physical health and the achievement of developmental milestones between children who were exposed to progesterone and those who were not.[24] Investigators used the Ages and Stages Questionnaire score, assessment of developmental milestones, and physical exams to evaluate the 348 children. No differences were seen in height, weight, and head-circumference percentiles; achievement of developmental milestones; gender roles; and physical health.

Serving up The Big Picture

In a systematic review of 11 trials (2,425 women and 3,187 infants) involving the use of progesterone to prevent preterm birth in

FAST TRACK

A Cochrane review found no harm related to use of progesterone

high-risk women—including those who had a history of preterm birth, those carrying a multiple gestation, and those with a short cervix—Dodd and colleagues found mixed results.[10] Progesterone reduced the rate of preterm birth before 34 weeks' gestation in women who had a history of preterm birth, as well as in those who had a short cervix, but no improvement was seen in women carrying a multiple gestation.

A cumulative meta-analysis by Coomarasamy and colleagues found that progestogens significantly reduce the rate of preterm birth, a benefit that was evident beginning in 1975.[1]

The most recent Committee Opinion from the American College of Obstetricians and Gynecologists[25] concludes that "it is important to offer progesterone for pregnancy prolongation to only women with a documented history of a previous spontaneous birth at less than 37 weeks of gestation." The opinion also takes into account the findings of the Fonseca trial in regard to women who have a short cervix,[14] and concludes that "progesterone supplementation may be considered for use in asymptomatic women with a short cervix."

Trials of other high-risk groups, including women who have a positive fibronectin test, bleeding, or iatrogenic preterm labor, are needed. The fact that progesterone supplementation is not universally effective in women who have a history of preterm birth suggests that not all pathways leading to preterm birth are ameliorated by progesterone therapy. Given the many similarities between women who have a history of preterm birth and women who have a short cervix, evidence may ultimately be available to support the benefits of progesterone in both situations. However, the lack of a benefit in women carrying a multiple gestation likely reflects the different underlying mechanism in that group.

CASE: RESOLVED

You discuss with Ms. Jones the options available to reduce the likelihood of recurrent preterm birth. She opts for progesterone

supplementation, which is initiated at 16 weeks' gestation, with no restrictions on activity. A sonogram at 18 weeks reveals normal anatomy and a cervical length of 4 cm.

At 22 weeks' gestation, Ms. Jones visits the labor and delivery unit complaining of leaking fluid. You perform a sterile speculum exam, which is negative, monitor her for several hours, and send her home.

At 26 weeks, the patient experiences contractions and is again evaluated. An examination reveals the cervix to be long and closed. After prolonged monitoring, Ms. Jones is again sent home.

At 37 weeks' gestation, the patient reports another episode of leaking fluid. This time, a sterile speculum exam is positive, and you begin induction of labor.

Labor proceeds smoothly, and Ms. Jones delivers a 3,100-g infant. The newborn has an Apgar score of 8 and 9 at 1 and 5 minutes, respectively.

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