

Use of Progesterone to Reduce Preterm Birth

Committee on Obstetric Practice

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ABSTRACT: Preterm birth affects 12% of all births in the United States. Recent studies support the hypothesis that progesterone supplementation reduces preterm birth in a select group of women. Despite the apparent benefits of progesterone, the ideal progesterone formulation is unknown. The American College of Obstetricians and Gynecologists' Committee on Obstetric Practice and the Society for Maternal Fetal Medicine believe that further studies are needed to evaluate the optimal preparation, dosage, route of administration, and other indications for the use of progesterone for the prevention of preterm delivery. Based on current knowledge, 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.

Preterm birth affects 12% of all births in the United States. This statistic has led multiple investigators to identify those women at greatest risk (eg, those with prior preterm delivery, multiple gestation, short cervical length, maternal weight less than 50 kg, bleeding, and those of African American race). Recent randomized trials comparing progesterone with placebo have been conducted using several groups at high risk and low risk for preterm delivery. The purpose of this Committee Opinion is to review these results.

A large randomized placebo-controlled trial investigating the use of 17α -hydroxyprogesterone caproate ("17P") therapy (250 mg administered intramuscularly) for the prevention of preterm birth in a select, high-risk group of women (with a documented history of a previous spontaneous singleton preterm birth at less than 37 weeks of gestation) was conducted for the National Institute of Child Health and Human Development (NICHD) Maternal-Fetal Medicine Units Network (1). A total of 459 women with a history of previous spontaneous singleton births at less than 37 weeks of gestation were enrolled between 16 weeks and 20 weeks of gestation. Of note, the mean gestational age of their previous preterm deliveries was 30.7 weeks. They were ran-

domly assigned to receive weekly intramuscular injections of 17α -hydroxyprogesterone caproate ($n = 306$) or placebo ($n = 153$) from enrollment to 37 weeks of gestation or delivery. The study was stopped early when results showed a significant protection against recurrent preterm birth for all races of women who received 17α -hydroxyprogesterone caproate. This study demonstrated significant reductions in preterm and early preterm birth, low birth-weight, as well as significant reductions in infant complications (intraventricular hemorrhage, necrotizing enterocolitis, neonatal intensive care unit admissions, and the need for supplemental oxygen therapy) with progesterone therapy (Table 1). Four-year follow-up found no adverse health outcomes of surviving children (2).

In a randomized placebo-controlled trial of supplemental vaginal progesterone (100 mg daily) in 142 women at high risk for preterm birth (more than 90% of whom had a previous spontaneous singleton preterm birth) the authors found that for delivery at less than 34 weeks of gestation, the preterm birth rate was significantly lower among women receiving progesterone than among those receiving placebo (2.7% versus 18.6%) (3). The results of this study and the NICHD trial support the hypothesis that proges-



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Table 1. Rates of Preterm Labor With Progesterone Therapy or Placebo

Gestation	Placebo Group (n = 153)	Progesterone Group (n = 306)	Relative Risk	Confidence Interval	P
Less than 37 weeks	54.9%	36.3%	0.66	0.54–0.81	.001
Less than 35 weeks	30.7%	20.6%	0.67	0.48–0.93	.0165
Less than 32 weeks	19.6%	11.4%	0.58	0.37–0.91	.0180

Data from Meis PJ, Klebanoff M, Thom E, Dombrowski MP, Sibai B, Moawad AH, et al. Prevention of recurrent preterm delivery by 17 alpha-hydroxyprogesterone caproate. *N Engl J Med* 2003;348:2379–85.

terone supplementation reduces preterm birth in women at risk for preterm birth, with a prior preterm birth.

The effectiveness of progesterone supplementation has been evaluated in several other high-risk groups for preterm delivery, with conflicting results. A randomized trial of 17 α -hydroxyprogesterone caproate in 661 women with twin gestations found no benefit of progesterone supplementation for the prevention of preterm delivery (4). A randomized trial of 659 women with a history of spontaneous preterm delivery randomized and treated between 18 weeks and 23 weeks of gestation with 90 mg of natural progesterone vaginal gel or placebo found no improvement in preterm birth at less than 37 weeks, less than 35 weeks or less than 32 weeks of gestation. (5). Another randomized trial evaluated asymptomatic women with a short cervix and singleton and twin gestations. Of 24,620 women screened with endovaginal ultrasonography between 20 weeks and 25 weeks of gestation, 413 women had a cervical length less than 15 mm (1.5%) and of those women, 250 were randomized (1:1) to daily vaginal progesterone (200 mg micronized progesterone capsules) or placebo from 24 weeks to 34 weeks of gestation. Of note, 15% of the study population had a history of a prior preterm delivery and 10% of the study population had a twin gestation. Overall, progesterone therapy significantly reduced the rate of spontaneous preterm birth at less than 34 weeks of gestation (19.2% versus 34.3%) [6].

Despite the apparent benefits of progesterone in some situations, the ideal formulation is unknown. The 17 α -hydroxyprogesterone caproate used in the NICHD trial was specially formulated for the trial and is not currently commercially available. Although the initial trial (3) used 100 mg vaginal suppositories and demonstrated pregnancy prolongation with treatment, vaginal progesterone gel was not beneficial in reducing preterm birth in women with a history of spontaneous preterm delivery randomized and treated between 18 weeks and 23 weeks of gestation (5). Micronized progesterone capsules (200 mg vaginally daily) were used in the trial of progesterone for asymptomatic women with a very short cervix (less than 15 mm), and appeared to be effective for this indication (6). Whether the differences seen in efficacy of the recently studied vaginal preparations reflects differences in dosages (100 mg versus 200 mg), variation in absorp-

tion and bioavailability with different preparations (gel versus capsule versus suppository), or differences in study populations remain to be elucidated. Progesterone has not been studied as a supplemental treatment to cervical cerclage for suspected cervical insufficiency, as a preventive agent for asymptomatic women with a positive cervicovaginal fetal fibronectin screen result, as a tocolytic agent, or as a therapeutic agent after tocolysis, and it should not be used at this time for these indications alone.

Progesterone supplementation for the prevention of recurrent preterm birth should be offered to women with a singleton pregnancy and a prior spontaneous preterm birth due to spontaneous preterm labor or premature rupture of membranes. Current evidence does not support the routine use of progesterone in women with multiple gestations. Progesterone supplementation for asymptomatic women with an incidentally identified very short cervical length (less than 15 mm) may be considered; however, routine cervical length screening is not recommended. The American College of Obstetricians and Gynecologists' Committee on Obstetric Practice and the Society for Maternal Fetal Medicine believe that further studies are needed to determine if there are other indications for progesterone therapy for the prevention of preterm delivery.

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