

Do progestational compounds reduce preterm delivery in high-risk gravidas?

Meis PJ, Klebanoff M, Thom E, et al, for the National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network. Prevention of recurrent preterm delivery by 17 alpha-hydroxyprogesterone caproate. *New Engl J Med.* 2003;348:2379-2385.

OBJECTIVE To determine whether weekly injections of 17 alpha-hydroxyprogesterone caproate (17P) reduce the risk of preterm delivery in women with a documented history of spontaneous preterm delivery.

METHODS AND RESULTS In this double-blind, placebo-controlled trial, researchers randomly assigned 463 patients at high risk for preterm delivery to receive weekly intramuscular injections of 17P (250 mg) or placebo from 16 to 20 weeks of gestation through 36 weeks. Outcome data were available for 459 women (99.1%).

Treatment with 17P significantly reduced the risk of delivery at less than 37 weeks' gestation: Incidence was 36.3% in the progesterone group versus 54.9% in the placebo group (relative risk, 0.66; 95% confidence interval, 0.54 to 0.81). It also reduced the risk of delivery at less than 35 weeks and less than 32 weeks. Infants of women treated with the compound had significantly lower rates of necrotizing enterocolitis, intraventricular hemorrhage, and need for supplemental oxygen. There was no significant difference in miscarriage or stillbirth rates.

WHO MAY BE AFFECTED BY THESE FINDINGS? Gravidas at high risk for preterm delivery.

EXPERT COMMENTARY Although we have improved our ability to identify women at risk, we have not been successful at preventing preterm birth—indeed, its incidence is

actually rising, due primarily to increased use of assisted reproductive technology. Preterm birth complicates approximately 12% of deliveries, but accounts for more than 85% of perinatal morbidity and mortality.^{1,2}

The study by Meis and colleagues is a well-designed and well-executed randomized, double-blind, placebo-controlled, multicenter trial. Compliance with designated therapy was reported as 91.5%. The preterm delivery rate of 54.9% in the control group confirms that this cohort is indeed at high risk of preterm birth (see "Why progesterone?" page 16).

I have only 1 minor criticism: The authors chose to deliver the drug via weekly intramuscular injections, which may not be a desirable route of administration for many women. Half of the women (231 of 463) reported at least 1 adverse effect, though most of these were minor local reactions at the injection site.

The authors found no evidence of teratogenicity—of note, no virilization of female offspring, which was a theoretic concern.

Findings apply only to high-risk gravidas. More study is required to determine whether progesterone supplementation can reduce preterm birth in low-risk women. This is important because most preterm births occur in patients with no identifiable risk factors.

The results of this study are consistent with prior publications.^{8,9} In a similar recent trial carried out in Brazil, 142 women at high risk for preterm birth were randomized to receive daily supplementation with progesterone vaginal suppositories (100 mg) or placebo from 24 through 34 weeks of gestation.⁹ The preterm delivery rate was significantly lower in the progesterone group, as was the rate of delivery before 34 weeks. By monitoring

Why progesterone?

Progesterone receptor antagonists readily induce abortion if given before 7 weeks of gestation. Similarly, surgical removal of the corpus luteum, the source of progesterone, before 7 weeks results in spontaneous pregnancy loss. These data suggest that adequate production of progesterone by the corpus luteum is critical to maintaining pregnancy until the placenta assumes this function at 7 to 9 weeks' gestation.

The role of progesterone in later pregnancy is less clear. It has been proposed that progesterone may be important in maintaining uterine quiescence in the latter half of pregnancy by limiting production of stimulatory prostaglandins and inhibiting expression of contraction-associated protein genes (ion channels, oxytocin and prostaglandin receptors, and gap junctions) within the myometrium.^{3,4}

Circulating progesterone levels during labor are similar to levels measured 1 week prior to labor,⁵ suggesting that progesterone withdrawal is not a prerequisite for labor in humans. This is in contrast to most laboratory animals, in which progesterone withdrawal is an essential component of parturition. However, circulating hormone levels do not necessarily reflect tissue levels; thus, it is still possible that the onset of labor in women may follow a withdrawal of progesterone activity at the level of the uterus.⁶ In support of this hypothesis, administration of the progesterone receptor antagonist RU486 at term leads to increased uterine activity and induction of labor.⁷

The promise of 17P. The results of several small clinical trials suggested that antenatal supplementation with 17P, a progesterone metabolite, may reduce the rate of preterm birth in high-risk women by 15% to 70%, though it was not clear whether this translated into a reduction in perinatal mortality or morbidity.⁸ No decrease in spontaneous abortion was observed. For this reason, 17P was chosen for the current study. It is possible that other progesterone metabolites may be equally or more effective in preventing preterm delivery. Further studies are awaited.

patients with an external tocodynamometer once a week for 60 minutes, researchers also were able to demonstrate a significant difference in spontaneous uterine contractions between the groups, suggesting that progesterone supplementation may exert its effect by maintaining uterine quiescence in the latter half of pregnancy.

BOTTOM LINE Progesterone supplementation to prevent preterm birth remains investigational. Further studies are needed to evaluate its effectiveness in decreasing preterm delivery rates in high- and low-risk populations and to better understand its mechanism of action.

Given the absence of proven alternatives, however, it may be appropriate to offer such treatment to patients at highest risk for early preterm birth, such as those with higher-order multifetal pregnancies or a history of recurrent preterm deliveries. Evidence is insufficient to recommend progesterone treatment for women presenting in acute preterm labor. ■

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