Does weekly progesterone prolong gestation in women who have PPROM?

NO. This randomized trial of 69 women who experienced preterm premature rupture of membranes (PPROM) at 20 to 30 weeks' gestation found no difference in the length of gestation between women given 250 mg of 17-alpha-hydroxyprogesterone (17P) or placebo weekly.

FAST TRACK

Weekly 17-alpha-hydroxyprogesterone did not prolong gestation in women who experienced PPROM at 20 to 30 weeks' gestation

Briery CM, Veillon EW, Klauser CK, et al. Women with preterm premature rupture of the membranes do not benefit from weekly progesterone. Am J Obstet Gynecol. 2011;204(1):54.e1–5.

EXPERT COMMENTARY

Alex C. Vidaeff, MD, MPH, Professor, Division of Maternal-Fetal Medicine, Department of Obstetrics, Gynecology, and Reproductive Sciences, University of Texas Medical School at Houston, Houston, Tex.

Approximately 13 million preterm births occur annually worldwide.[1] Depending on the geographic locale, PPROM is responsible for 16% to 40% of these births.[2]

The clinical approach to PPROM is one of the most contentious issues in obstetrics, with disagreement on virtually every aspect of it. Under debate are the lower and upper limits of the gestational age range at which intervention is warranted, as well as the use of ancillary interventions such as corticosteroids and antibiotics. Briery and colleagues add to the scientific debate now by asking whether 17P would be effective as cotreatment (with antibiotics) to prolong latency after PPROM.

According to their findings, the answer to this question is "No."

Details of the trial

Briery and colleagues conducted a placebo-controlled, double-blind, randomized clinical trial of women with a singleton gestation complicated by PPROM. Excluded from the study were women whose pregnancy involved additional fetal or placental complications.

All women included in the study received antibiotics according to a protocol from the National Institutes of Health; they also were given betamethasone for fetal maturation. Tocolytics were not used. Because randomization did not occur until after each woman was transferred from the labor and delivery unit to the high-risk floor, we can assume that no participants were manifesting uterine contractions.

Women received weekly injections of 17P or placebo until 34 weeks' gestation or delivery. The primary outcome was the interval from study entry to delivery.

One woman had a pregnancy of 23.5 weeks' duration at randomization; the remainder had gestations that were 24 weeks or older. There were no other differences in demographics, cervical dilatation, gestational age at study entry, or reasons for delivery between the two study groups.

Study design may have been unrealistic

The authors calculated that they needed a sample size of 56 patients to detect a 50% increase in latency, based on population data from their institution showing that 80% of patients who have PPROM deliver within 7 days. Such a calculation may have set an unrealistic—albeit logistically convenient—goal, rendering the study underpowered to detect smaller effects. Note, for example, that when antibiotics are given to women who

have PPROM, prolongation of the latency period is only 33% (pooled effect from a recent meta-analysis).[3] Even so, given the findings of Briery and colleagues, latency improvement after 17P administration would appear to be unlikely even in a larger study. There was not even a trend toward a longer interval to delivery (mean of 11.2 days with 17P vs 14.5 days with placebo).

Only secondary prevention of preterm birth is effective

The indications for progesterone supplementation in pregnancy are still evolving as part of a sustained scientific effort to prevent preterm labor and delivery. Strategies to prevent preterm delivery can be categorized as primary, secondary, or tertiary, as can strategies for other public health concerns.

Because any number of variables—known and unknown—may trigger preterm labor, identifying them and providing **primary preventive strategies** in the entire pregnant population remain elusive tasks.

Tertiary prevention—i.e., treatment given to already symptomatic individuals—is also notoriously ineffective. There are no data supporting the use of progesterone as primary prevention (in low-risk women) or tertiary prevention (e.g., tocolytic). ACOG made note of this in 2003, and its conclusions remain valid today.[4] According to a 2010 Cochrane review, there is insufficient evidence to advocate progestational agents as tocolytic agents for women who present with threatened or established preterm labor.[5]

In light of these data, the results reported by Briery and colleagues are hardly surprising. In women who may have already entered the irreversible phase of parturition (manifesting uterine contractions; presenting with advanced, painless cervical dilatation; or after PPROM), progesterone will remain ineffective. The only applicable use of prophylactic progesterone in pregnancy is as **secondary prevention**.[4] In contrast to primary and tertiary prevention, the secondary level of prevention—i.e., an intervention aimed at minimizing the risk of preterm birth in women who are identified as having an elevated risk—is supported by several systematic reviews of randomized, controlled trials.[6,7] According to these reviews, progesterone certainly is effective in high-risk pregnant women who have a short cervix or a history of spontaneous preterm birth. The same cannot be said about women who have PPROM.

WHAT THIS EVIDENCE MEANS FOR PRACTICE

Based on the evidence, including this study by Briery and colleagues, administration of antibiotics appears to be the only intervention available to delay delivery and reduce neonatal morbidity in the setting of PPROM.[8] The use of tocolytics is not supported by the data in the clinical context of PPROM.[9]

››Alex C. Vidaeff, MD, MPH

FAST TRACK

The use of tocolytics in the setting of PPROM is not supported by the data

References

1. Villar J, Abalos E, Carroli G, et al. Heterogeneity of perinatal outcomes in the preterm delivery syndrome. Obstet Gynecol. 2004;104(1):78–87.
2. Simmons LE, Rubens CE, Darmstadt GL, et al. Preventing preterm birth and neonatal mortality: exploring the epidemiology, causes, and interventions. Semin Perinatol. 2010;34(6):408–415.
3. Hutzal CE, Boyle EM, Kenyon SL, et al. Use of antibiotics for the treatment of preterm parturition and prevention of neonatal morbidity: a meta-analysis. Am J Obstet Gynecol. 2008;199(6):620.e1–8.
4. Society for Maternal Fetal Medicine Publications Committee. ACOG Committee Opinion #419. Use of progesterone to reduce preterm birth. Obstet Gynecol. 2008;112(4):963–965.
5. Su L-L, Samuel M, Chong Y-S. Progestational agents for treating threatened or established preterm labor. Cochrane Database Syst Rev. 2010;(1):CD006770. doi: 10.1002/14651858.CD006770.
6. Dodd JM, Crowther CA. The role of progesterone in prevention of preterm birth. Int J Women Health. 2010;1:73–84.
7. Rode L, Langhoff-Roos J, Andersson C, et al. Systematic review of progesterone for the prevention of preterm birth in singleton pregnancies. Acta Obstet Gynecol Scand. 2009;88(11):1180–1189.
8. Kenyon S, Boulvain M, Neilson JP. Antibiotics for preterm rupture of membranes. Cochrane Database Syst Rev. 2003;(2):CD001058. doi: 10.1002/14651858.CD001058.
9. Mercer BM. Is there a role for tocolytic therapy during conservative management of preterm premature rupture of the membranes? Clin Obstet Gynecol. 2007;50(2):487–496.