Ohio Perinatal Quality Collaborative Advisory Statement on FDA Review of Progesterone

First posted December 16, 2019. Updated December 31, 2019 to include ACOG Practice Advisory.*

**(ACOG = American College of Obstetricians & Gynecologists)*

The US Food & Drug Administration (FDA) recently convened a Panel to review findings of the PROLONG study, a large international trial that compared pregnancy outcomes in women with a previous preterm birth who were randomly assigned to receive weekly injections of Makena® (17-OHPC) or Placebo. Unlike a previous study that found reduced rates of recurrent preterm birth in women treated with 17-OHPC, the rates of recurrent premature birth in the PROLONG trial were not different, nor were there any differences in neonatal outcomes, compared to placebo. There were also no differences in adverse outcomes or side effects.

The FDA is reviewing the Panel's recommendation that Makena be withdrawn from the market, along with comments submitted by the American College of Obstetricians & Gynecologists (ACOG) and others supporting continued FDA approval until additional studies are done. ACOG based this recommendation on differences in the populations enrolled into the two studies. Makena will remain available until a final decision by FDA is announced.

Participants in OPQC's Progesterone Promotion Project are advised to continue to identify women with increased risk of preterm birth as soon as possible and to complete the electronic Pregnancy Risk Assessment Form 2.0 (PRAF 2.0) to enable continuation of all Medicaid services throughout the pregnancy. OPQC will work closely with the Ohio Department of Medicaid as additional information is provided and the recommendations from FDA and ACOG evolve. ***OPQC encourages providers to follow current ACOG/SMFM recommendations and continue to prescribe 17P until the ACOG recommendations are revised.***

Update as of December 31, 2019. ***Please find the most recent ACOG Statement below (online here):***

Practice Advisory: Clinical guidance for integration of the findings of the PROLONG study: Progestin's Role in Optimizing Neonatal Gestation. ***(Published in Obstetrics & Gynecology October 2019; Volume 134, Issue 4, p 885)***

A trial comparing the efficacy of 17-alpha-hydroxyprogesterone caproate (17-OHPC) 250 mg intramuscular injection weekly compared with placebo on both preterm birth and neonatal morbidity among women with a singleton pregnancy and prior spontaneous preterm birth was published in the American Journal of Perinatology on October 25, 2019 (1). The study was a large international multicenter, randomized, controlled, double blind trial conducted from November 2009 to October 2018 that evaluated 1,877 eligible women, of which 1,740 provided informed consent and underwent randomization. The trial was conducted at 93 facilities across 9 countries associated with a hospital that had access to a Level 3 or greater Neonatal Intensive Care Unit. Twenty-three percent of women were enrolled from the United States. Women were randomized between 16 0/7 to 20 6/7 weeks of gestation with greater than 91% of participants adhering to the assigned protocol, with no differences in the number of study medication injections between those receiving 17-OHPC or placebo (both groups with a median of 18, range 1-22).

This study demonstrated no statistical difference in the co-primary outcome of preterm birth less than 35 0/7 weeks of gestation (17-OHPC 11.0% versus 11.5%; Relative Risk [RR] 0.95 [95% CI 0.71-1.26]; $P = 0.72$) and neonatal composite index (17-OHPC 5.6% versus 5.0%; RR 1.12 [95% CI 0.70-1.66]; $P = 0.73$). Similarly, the rate

of preterm birth less than 37 weeks and less than 32 weeks were not different. No other differences in perinatal or maternal outcomes were detected. However, despite having the same eligibility criteria and study protocol as the trial by Meis et al in 2003 that provided randomized trial evidence for 17-0HPC for the prevention of recurrent preterm birth (2), the patient populations had divergent sociodemographic characteristics and a substantially lower preterm birth rate when compared with the prior study (1, 2). Based on these results, the authors suggest that the PROLONG trial was underpowered to assess treatment efficacy related to preterm birth and neonatal outcomes in this population. Further, due to guidance published in 2008, a possible unintentional selection bias may have occurred in women enrolled in the United States that resulted in women with a higher risk for recurrent preterm birth not being offered or agreeing to participate in the PROLONG study in order to avoid the risk of not receiving active 17OPHC treatment.

Current guidelines in the United States recommend the use of progesterone supplementation in women with prior spontaneous preterm birth (3). Consideration for offering 17-OHPC to women at risk of recurrent preterm birth should continue to take into account the body of evidence for progesterone supplementation, the values and preferences of the pregnant woman, the resources available, and the setting in which the intervention will be implemented. Additional information from planned meta-analysis and secondary analyses will need to be evaluated to assess the impact this intervention has on women at risk of recurrent preterm birth in the United States. ACOG is not changing our clinical recommendations at this time and continues to recommend offering hydroxyprogesterone caproate as outlined in Practice Bulletin # 130, Prediction and Prevention of Preterm Birth (3).

ACOG will be reviewing subsequent forthcoming analyses and will issue updated clinical guidance as appropriate.

This Practice Advisory was developed by the American College of Obstetricians and Gynecologists' Committee on Practice Bulletins—Obstetrics in collaboration with Mark Turrentine, MD, Anjali Kaimal, MD, MAS, Hyagriv Simhan, MD, and Aaron B. Caughey, MD, PhD.

References

1. Blackwell SC, Gyamfi-Bannerman C, Biggio JR Jr, Chauhan SP, Hughes BL, Louis JM, et al. 17-OHPC to prevent recurrent preterm birth in singleton gestations (PROLONG study): a multicenter, international, randomized double-blind trial [published ahead of print]. Am J Perinatol 2019;DOI: 10.1055/,3400227.

2. Meis PJ, Klebanoff M, Thom E, Dombrowski MP, Sibai B, Moawad AH, et al. Prevention of recurrent preterm delivery by 17 alpha-hydroxyprogesterone caproate [published erratum appears in N Engl J Med 2003;349:1299]. N Engl J Med 2003;348:2379-85.

3. Prediction and prevention of preterm birth. Practice Bulletin No. 130. American College of Obstetricians and Gynecologists. Obstet Gynecol 2012;120:964-73.

Additional Resources

Practice Bulletin 130 Prediction and Prevention of Preterm Birth