ACOG Statement: Clinical Guidance for Integration of the Findings of the PROLONG Study: Progestin's Role in Optimizing Neonatal Gestation

Practice Advisory | October 2019

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.

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.

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References

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