SMFM Statement: Use of 17-alpha hydroxyprogesterone caproate for prevention of recurrent preterm birth

Society for Maternal-Fetal Medicine (SMFM) Publications Committee

Recurrent spontaneous preterm birth (PTB) is a major public health problem. The strongest predictor of PTB is a prior spontaneous preterm birth (sPTB). Spontaneous PTB recurs in up to 50% of women, tends to recur at similar gestational ages, and is more likely to recur with an increased number of prior sPTBs (1, 2). Given the significant adverse outcomes associated with PTB, strategies have been developed to attempt to reduce the risk of recurrence. One of the most commonly employed strategies is the use of supplemental progestogens, including intramuscular (IM) 17-alpha hydroxyprogesterone caproate (17-OHPC), which was approved by the US Food and Drug Administration in 2011 to reduce the risk of PTB in women with a singleton pregnancy who have a history of singleton sPTB.

The potential effectiveness of 17-OHPC for the prevention of recurrent sPTB was evaluated by Meis et al. in a multicenter, double-masked, randomized controlled trial of 17-OHPC or placebo in 463 US women with singleton gestations at risk for recurrent sPTB, published in 2003 (3). They found a 34% reduction in the incidence of recurrent PTB at <37 weeks of gestation with 17-OHPC treatment (from 54.9% to 36.3%, adjusted relative risk [RR] 0.66, 95% confidence interval [CI], 0.54-0.81). The study also demonstrated significant reductions in PTB at <35 and <32 weeks of gestation, in addition to significant reductions in some neonatal complications (intraventricular hemorrhage, necrotizing enterocolitis, and a need for supplemental oxygen) in those receiving 17-OHPC. The study was stopped early based on prespecified criteria after demonstration of efficacy at the second interim analysis; 70% of the planned sample was analyzed.

The data regarding the benefit of 17-OHPC are otherwise relatively limited. A recent meta-analysis of 17-OHPC vs placebo or no treatment for prevention of recurrent PTB identified four randomized clinical trials, including Meis, as well as three smaller studies. This meta-analysis reported a 29% (RR 0.71; 95% CI, 0.53–0.96; P=0.001), 26% (RR 0.74; 95% CI, 0.58–0.96;

P=0.021), and 40% (RR 0.60; 95% CI, 0.42–0.85; P=0.004) reduction in recurrent PTB at <37, <35, and <32 weeks, respectively, in the 17-OHPC group compared with placebo or no treatment (4). In contrast, a recent historical cohort identified no decrease in rates of PTB since the introduction of 17-OHPC. Although these data are mixed, they generally support a benefit of 17-OHPC in the reduction of PTB.

Following the Meis publication, initial guidance from the American College of Obstetricians and Gynecologists and the Society for Maternal-Fetal Medicine (SMFM) recommended treatment with either 17-OHPC or vaginal progesterone to prevent recurrent PTB for women with a prior sPTB (5). Most recently, in 2017, SMFM reaffirmed its recommendation that women with a singleton gestation and a history of prior sPTB between 20 and 36 6/7 weeks of gestation receive 17-OHPC 250 mg IM weekly from 16 to 20 weeks of gestation until 36 weeks of gestation or delivery (6).

The Progestin's Role in Optimizing Neonatal Gestation (PROLONG) trial was a double-blind, placebo-controlled, international trial conducted from 2009–2018 to attempt to confirm that weekly IM injection of 250 mg of 17-OHPC from 16 to 36 weeks of gestation decreases recurrent PTB and neonatal morbidity in women with a prior sPTB in a singleton gestation. This trial enrolled women from 93 sites in 9 countries, with approximately 25% of women from the United States. The co-primary outcomes were PTB at <35 weeks of gestation and composite neonatal morbidity or mortality. PROLONG enrolled over 1700 women and was powered to detect a 30% reduction in PTB at <35 weeks of gestation with a baseline assumption of 30% recurrent PTB rate among women in the placebo arm (7).

The results of the PROLONG trial found no benefit of 17-OHPC compared with placebo in reaching either of the co-primary outcomes. The rate of PTB at <35 weeks of gestation did not differ between the progesterone and placebo arms and was notably much lower than anticipated (11% vs 11.5%, RR 0.95, 95% CI, 0.71-1.26; p=0.7). The neonatal composite outcome also did not differ between groups (5.4% vs 5.2%, RR 1.05, 95% CI, 0.68-1.61; p=0.8). Of note, the rate of PTB at <37 weeks of gestation (which was the primary outcome of the Meis trial) was 23.1% and 21.9% for the 17-OHPC and placebo groups, respectively (RR 1.06, 95% CI, 0.88-1.28).

In comparing the discordant results of the PROLONG and Meis trials, one consideration is the different populations studied, especially with respect to the baseline risk for PTB. These differences include characteristics of the prior PTB(s), as well as additional demographic and reproductive characteristics. Approximately 90% of the PROLONG patients were white and 7% were black; 90% were married; and substance use was infrequent, with about 8% reporting smoking tobacco in pregnancy. In contrast, the Meis trial included 59% black women, of whom approximately 50% percent were married, and over 20% reported smoking. In the Meis trial, 32% of women had >1 prior PTB compared with only 12% in the PROLONG trial, and 91% of women had at least one additional risk factor for PTB (aside from the prior PTB) compared with 48% in PROLONG. These substantial differences in population are reflected in the significantly different baseline rates of PTB in the two trials, with 54.9% recurrent PTB at <37 weeks of gestation in the placebo group in Meis vs 21.9% in PROLONG. Of note, the Meis trial has been criticized because more patients in the placebo arm had >1 prior PTB compared with the 17-OHPC arm (41.2% vs 27.7%; p=0.004). However, analysis with adjustment for this difference did not change the primary findings (3).

Preterm birth is a complex disorder with heterogeneous etiologies and associated underlying mechanisms in different women (8-10). Therefore, substantial differences in the populations studied likely account for the different baseline rates of recurrent PTB and potentially explain some of the contrasting results observed in the Meis and PROLONG trials. Other observational studies of "real world" use of 17-OHPC have also reported that the rate of recurrent PTB and response to treatment is dependent on the population and context (11). However, while differences in the populations enrolled may have contributed to the different outcomes in these two studies, population differences do not completely explain the discrepancy. Specifically, while black race is a known risk factor for PTB and more women in the Meis trial were black, studies have demonstrated an association between nonresponse to 17-OHPC and black race, thus contradicting this argument (12). Another factor possibly associated with the disparate outcomes include the potential for bias in the Meis trial introduced by the higher rate of multiple prior PTBs in the placebo compared with the study arm, although again, the benefit of 17-OHPC remained after adjustment for this difference.

Results of both the Meis and PROLONG trials indicate that 17-OHPC appears to be safe, at least in the short term, with no increase in congenital anomalies or evidence of teratogenic effects seen in either of these studies or suggested in other reports (13, 14). Long-term outcomes are unknown, although long-term adverse effects have not been reported. The PROLONG study plans a two year follow up study of the childhood outcomes.

In summary, differences in study populations between the Meis and PROLONG trials likely contribute to different baseline levels of risk of PTB and may partially explain the differences in response to 17-OHPC. While some women have a higher risk of recurrent sPTB, and factors such as race, number of prior PTBs, and gestational age at prior PTB are associated with recurrence, specific criteria for quantifying risk, interactions between risk factors, and optimal management of at-risk women are not well understood. Further, patient-level criteria for determining potential response to 17-OHPC have yet to be confirmed.

Based on the evidence of effectiveness in the Meis study, which is the trial with the largest number of US patients, and given the lack of demonstrated safety concerns, SMFM believes that it is reasonable for providers to use 17-OHPC in women with a profile more representative of the very high-risk population reported in the Meis trial. For all women at risk of recurrent sPTB, the risk/benefit discussion should incorporate a shared decision-making approach, taking into account the lack of short-term safety concerns but uncertainty regarding benefit. It is important to consider that 17-OHPC is associated with substantial health care costs, injection-site pain, and extra patient visits (15, 16) and that long-term potential maternal and neonatal effects are unknown. The lack of benefit from 17-OHPC seen in the PROLONG trial raises questions regarding the efficacy of 17-OHPC, and additional studies are needed to identify populations in which administration of 17-OHPC may provide needed benefit in the reduction of recurrent sPTB. SMFM will continue to closely follow advances in this area to assure optimal care for women and to provide guidance for maternal-fetal medicine subspecialists.

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From the Society for Maternal-Fetal Medicine, Washington, DC

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