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High-risk pregnancy experts

SMFM Statement

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

Society for Maternal-Fetal Medicine (SMFM) Publications Committee

In late 2019, results from the Progestin's Role in Optimizing Neonatal Gestation (PROLONG) trial were published showing no benefit of weekly injections of 17-alpha hydroxyprogesterone caproate (17-)HPC) from 16-20 weeks of gestation in women with a history of a singleton PTB in reducing the rates of subsequent PTB and neonatal morbidity. The Society for Maternal-Fetal Medicine believes that the differences in these results from the earlier Meis, et al trial, which did show a benefit of 17-OHPC in reducing the rate of spontaneous PTB (sPTB), may be at least partially explained by differences in study populations. SMFM concludes 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.

Recurrent spontaneous preterm birth (PTB) is a major public health problem. The strongest predictor of PTB is a prior spontaneous preterm birth (sPTB). sPTB 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 and with a history of singleton sPTB.

The potential effectiveness of 17-OHPC to prevent recurrent sPTB was evaluated by Meis et al[3] in a multicenter, double-masked, randomized controlled trial of 17-OHPC vs placebo in 463 American women with singleton gestations at risk for recurrent sPTB, published in 2003. 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 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.

Data on 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 4 randomized clinical trials, including Meis, and 3 smaller studies. This meta-analysis reported a 29% (RR, 0.71; 95% CI, 0.53−0.96; P=.001), 26% (RR, 0.74; 95% CI, 0.58−0.96; P=.021), and 40% (RR, 0.60; 95% CI, 0.42−0.85; P=.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 PTB rates since the introduction of 17-OHPC. Although these data are mixed, they generally support a benefit of 17-OHPC in PTB reduction.

After 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 250-mg 17-OHPC IM weekly starting at 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 to 2018 to attempt to confirm that weekly IM injection of 250-mg 17-OHPC from 16 to 36 weeks of gestation decreases recurrent PTB and

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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 coprimary outcomes were PTB at <35 weeks of gestation and composite neonatal morbidity or mortality. PROLONG enrolled more than 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 from the PROLONG trial showed no benefit of 17-OHPC compared with placebo in reaching either of the coprimary 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=.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=.8). Of note, PTB rate 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 from the PROLONG and Meis trials, one consideration is the different study populations, especially with respect to the baseline risk for PTB. These differences include characteristics of prior PTB(s) and additional demographic and reproductive characteristics. Approximately 90% of the patients in the PROLONG trial were white and 7% were black; 90% were married; and substance use was infrequent, with about 8% reporting tobacco smoking during pregnancy. In contrast, the Meis trial included 59% black women, of whom approximately 50% were married, and more than 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 1 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 2 trials, with 54.9% recurrent PTB at <37 weeks of gestation in the placebo group in the Meis trial vs 21.9% in the PROLONG trial. 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=.004). However, analysis with adjustment for this difference did not change the primary findings.[3]

PTB is a complex disorder with heterogeneous etiologies and associated underlying mechanisms in different women.[8–10] Therefore, substantial differences in the study populations likely account for the different baseline rates of recurrent PTB and potentially explain some of the contrasting results observed between 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 are dependent on the population and context.[11] However, although differences in the study populations may have contributed to the different outcomes in these 2 studies, population differences do not completely explain the discrepancy. Specifically, although black race is a known risk factor for PTB and more women in the Meis trial were black, studies have reported 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 from 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 trial plans a 2-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 for PTB and may partially explain the differences in response to 17-OHPC. 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. However, specific criteria for quantifying risk, interactions between risk factors, and optimal management of at-risk women are not well understood. Furthermore, patient-level criteria for determining potential response to 17-OHPC have yet to be confirmed.

On the basis of the evidence of effectiveness in the Meis study, 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 use 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 its efficacy, and additional studies are needed to identify populations in which 17-OHPC administration may provide the 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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