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SMFM Statement

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The choice of progestogen for the prevention of preterm birth in women with singleton pregnancy and prior preterm birth

Society for Maternal-Fetal Medicine (SMFM) Publications Committee

The practice of medicine continues to evolve, and individual circumstances will vary. This publication reflects information available at the time of its submission for publication and is neither designed nor intended to establish an exclusive standard of perinatal care. This publication is not expected to reflect the opinions of all members of the Society for Maternal-Fetal Medicine.

The Society for Maternal-Fetal Medicine (SMFM) continues to recommend that all women with a prior spontaneous preterm birth (PTB) of a singleton pregnancy be offered 17-alpha hydroxyprogesterone caproate (17OHP-C) therapy in a subsequent pregnancy with a singleton gestation.[1] Data from several sources suggest that despite these recommendations, there remains continued underutilization of 17OHP-C for eligible patients.[2-5] The purpose of this statement is to reaffirm the choice of progestogen for women with a singleton gestation and a prior spontaneous PTB.

In 2003, Meis et al[6] reported the results of a multicenter, double-masked, randomized controlled trial (RCT) involving 463 women with a singleton pregnancy and prior spontaneous PTB who received 17OHP-C or placebo. They found a 34% reduction in the incidence of recurrent PTB at <37 weeks of gestation with 17OHP-C treatment (from 54.9% to 36.3%).

The study was stopped early based on prespecified criteria because of findings at the second interim analysis (70% of the planned sample was analyzed). The RCT demonstrated significant reductions in both overall PTB and PTB at <32 and <35 weeks of gestation as well as significant reductions in infant complications (intraventricular hemorrhage, necrotizing enterocolitis, and a need for supplemental oxygen) in those receiving 17OHP-C.

In the same year, da Fonseca et al[7] reported the findings of a double-masked RCT of 142 women at high risk for PTB (94% had a prior PTB) who received either 100 mg vaginal progesterone per day or placebo. This study reported a reduction in the incidence of PTB at <37 weeks of gestation (28.5% to 13.8%, $P = .03$) and <34 weeks of gestation (18.6% to 2.7%, $P = .002$).

Initial guidance from the American College of Obstetricians and Gynecologist and SMFM recommended treatment with either 17OHP-C or vaginal progesterone for women with a prior spontaneous PTB to prevent recurrent PTB (2003, 2008).[8] In addition, both prior to and after Food and Drug Administration approval of 17OHP-C because of issues with access (eg, cost, availability, insurance coverage), some experts argued for preferred use of vaginal progesterone, and many clinicians had no other options for their patients.[9]

In 2012, SMFM revised its recommendations by stating the following: "In singleton gestations with prior SPTB [spontaneous PTB] 20–36 6/7 weeks, 17P [17OHP-C] 250 mg IM [intramuscularly] weekly preferably starting at 16–20 weeks of gestation until 36 weeks of gestation is recommended."[1]

The rationale for the change was based on findings from multiple RCTs. In 2007, O'Brien et al[10] published the findings of a double-masked RCT involving 659 women with a singleton pregnancy and prior spontaneous PTB who received either 90 mg vaginal progesterone per day or matching placebo. This study reported no differences in PTB at <32 weeks of gestation (10.0% vs 11.3%; odds ratio [OR], 0.9; 95% confidence interval [CI], 0.52–1.56) or PTB at <37 weeks of gestation (41.7% vs 40.7%; OR, 1.08; 95% CI, 0.76–1.52) between those receiving vaginal progesterone vs placebo.

In 2011, Hassan et al[11] published the findings of their RCT comparing vaginal progesterone with placebo in women with a singleton pregnancy and sonographic short cervix (10–20 mm). In women without a history of a prior PTB (84% of the population), vaginal progesterone was associated with a lower rate of PTB at <33 weeks of gestation (7.6% vs 15.3%; risk ratio [RR], 0.50; 95% CI, 0.27–0.90, $P = .02$). However, in women with a history of a prior PTB between 20 and 35 weeks of gestation, there was not a statistically significant difference (15.8% vs 20.6%; RR, 0.77; 95% CI, 0.29–2.06, $P = .60$).

Similarly, in the RCT published in 2007 by Fonseca et al[12] comparing vaginal progesterone with placebo in women

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with cervical length of <15 mm, those women with a history of a prior PTB had no statistically significant difference in the rate of a spontaneous PTB at <34 weeks of gestation. Moreover, data from the Does progesterone prophylaxis to prevent preterm labour improve outcome? (OPPTIMUM) study published in 2016 by Norman et al[13] are consistent with these other trials and provide further support for the change in SMFM guidance.

The OPPTIMUM study was a large (n = 1228), multicenter, double-masked RCT comparing 200 mg of vaginal progesterone per day to placebo in women at high-risk for spontaneous PTB.[13] In a subgroup of women with a history of a prior spontaneous PTB (n = 903), there were no significant differences in the rate of PTB at <34 weeks of gestation between those receiving vaginal progesterone and placebo (15.9% vs 18.8%).

A systematic review and meta-analysis published by Romero and colleagues in 2016 that included data from the OPPTIMUM study reported a decrease in PTB at <34 weeks of gestation or fetal death with vaginal progesterone vs placebo for women with a sonographically short cervix of <25 mm (pooled RR, 0.66; 95% CI, 0.52-0.83). However, the authors did not report outcomes for the subgroup of women with a history of a prior spontaneous PTB.

In summary, vaginal progesterone has not been adequately proven to decrease recurrent PTB in women with a history of a prior spontaneous PTB in multiple RCTs despite heterogeneity of patient populations, clinical criteria, and progesterone dosing. However, SMFM continues to affirm the use of vaginal progesterone to prevent PTB in women with a sonographically short cervix of ≤20 mm without a history of a prior spontaneous PTB.[1]

Owen et al[14] performed an RCT involving cervical cerclage in women with a prior spontaneous PTB at <34 weeks of gestation and noted that approximately 69% of those with serial cervical length screening had a cervical length that remained at >25 mm. A secondary analysis of this same RCT did not demonstrate any additional benefit of 17OHP-C in women who received a cerclage for cervical shortening.

In women with a prior spontaneous PTB who start 17OHP-C therapy and then develop cervical shortening, it remains unknown whether there is any benefit to change progestogen choice to vaginal progesterone (with or without cervical cerclage placement).[15] Based on available data regarding the lack of benefit of vaginal progesterone in women with a history of a prior spontaneous PTB, we recommend the continuation of 17OHP-C therapy in women with a history of a prior spontaneous PTB throughout the pregnancy despite the development of cervical shortening (with or without cervical cerclage placement).

Few studies directly compare 17OHP-C and vaginal progesterone in women with a history of a prior spontaneous PTB.[16-18] A recent meta-analysis reported outcomes for 3 trials that included a total of 680 women.[19] The largest study to directly compare 17OHP-C and vaginal progesterone was conducted in Saudi Arabia and published in 2013 (this study accounts for 74% of subjects in the meta-analysis).[18]

In this Saudi Arabian study, 520 women with a history of 1 or more midtrimester PTBs or a history of cervical cerclage in a prior pregnancy were randomized to receive either 17OHP-C or vaginal progesterone; women receiving vaginal progesterone were less likely to deliver at <34 weeks of gestation than those receiving 17OHP-C (16.6% vs 25.7%; OR, 0.58; 95% CI, 0.37−0.89; $P = .02$) but not at <37 weeks of gestation (32.8% vs 35.3%). Enrollment in this study focused on a heterogeneous group of women with a cervical insufficiency phenotype (prior midtrimester preterm birth or cerclage), rather than the typical candidate for 17OHP-C in the United States. Given the significant differences in the study population, eligibility criteria, and study protocol, we believe this RCT is not generalizable to women with a prior spontaneous PTB in the United States.

Given the available data, this SMFM statement reaffirms its current recommendations: in women with a singleton gestation and a history of prior spontaneous PTB between 20 and 36 6/7 weeks of gestation, we recommend 17OHP-C at 250 mg intramuscularly weekly, starting at 16−20 weeks of gestation until 36 weeks of gestation or delivery, and vaginal progesterone should not be considered a substitute for 17OHP-C in these patients. ■

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