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

SMFM Publications Committee

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The Society for Maternal-Fetal Medicine (SMFM) continues to recommend that all women with a history of a previous spontaneous preterm birth (PTB) of a singleton pregnancy be offered 17-alpha hydroxyprogesterone caproate (17-OHPC) therapy in a subsequent pregnancy with a singleton gestation. Data from several sources suggest that despite these recommendations, there remains continued underutilization of 17-OHPC for eligible patients. 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 and colleagues reported the results of a multi-center double-masked randomized controlled trial (RCT) involving 463 women with a singleton pregnancy and prior spontaneous PTB who received 17-OHPC or placebo. They found a 34% reduction in the incidence of recurrent PTB < 37 weeks of gestation with 17-OHPC treatment (from 54.9% to 36.3%). The study was stopped early based on pre-specified criteria due to findings at the second interim analysis (70% of planned sample were analyzed). The RCT demonstrated significant reductions in both overall PTB and PTB <32 and <35 weeks of gestation, as well as significant reductions in infant complications (IVH, NEC, and need for supplemental oxygen) in those receiving 17-OHPC. In the same year, da Fonseca and colleagues 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 < 37 weeks of gestation (28.5% to 13.8%, p=0.03) and < 34 weeks of gestation (18.6% to 2.7%, p=0.002).

Initial guidance from the American College of Obstetricians and Gynecologist (ACOG) and SMFM recommended treatment with either 17-OHPC or vaginal progesterone for women with a previous spontaneous PTB to prevent recurrent PTB (2003, 2008). In addition, both prior to and after FDA approval of 17OHPC, due to issues with access (e.g. cost, availability, insurance coverage), some experts argued for preferred use of vaginal progesterone and many clinicians had no other options for their patients. In 2012, SMFM revised its recommendations in the clinical guideline entitled *Progesterone and preterm birth prevention: translating clinical trials data into clinical practice* by stating the following: “In singleton gestations with prior SPTB 20-
36 6/7 weeks, 17P 250mg IM weekly preferably starting at 16-20 weeks of gestation until 36 weeks of gestation is recommended." \(^\text{1}\)

The rationale for the change was based on findings from multiple RCT’s. In 2007, O’Brien and colleagues published the findings of a double-masked RCT involving 659 women with singleton pregnancy and prior spontaneous PTB who received either 90 mg vaginal progesterone per day or matching placebo. \(^\text{10}\) This study reported no differences in PTB < 32 weeks of gestation (10.0% vs. 11.3%, OR 0.9, 95% CI 0.52-1.56) or PTB < 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 and colleagues published the findings of their RCT comparing vaginal progesterone to placebo in women with a singleton pregnancy and sonographic short cervix (10-20 mm). \(^\text{11}\) In women without a history of prior PTB (84% of the population), vaginal progesterone was associated with a lower rate of PTB < 33 weeks of gestation (7.6% vs. 15.3%; RR 0.50; 95% CI 0.27–0.90, p=0.02). However, in women with a history of prior PTB between 20-35 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=0.60). Similarly in the RCT published in 2007 by Fonseca and colleagues that compared vaginal progesterone to placebo in women with cervical length < 15 mm, in those women with a history of prior PTB, there were no statistically significant difference in the rate of spontaneous PTB < 34 weeks of gestations. \(^\text{12}\) Moreover, data from the OPPTIMUM Study published in 2016 by Norman and colleagues are consistent with these other trials and support the rationale for the change in SMFM guidance. The OPPTIMUM study was a large (N= 1,228) multi-center double-masked RCT comparing 200 mg vaginal progesterone per day vs. placebo in women at high-risk for PTB. \(^\text{13}\) In subgroup of women a history of prior spontaneous PTB (n=903), there were no differences in the rate of PTB 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 reported a decrease in PTB < 34 weeks of gestation or fetal death (pooled RR 0.66, 95% CI 0.52-0.83)) with vaginal progesterone vs. placebo for women with a sonographically short cervix < 25 mm. However, they did not report outcomes for the subgroup of women with a history of prior spontaneous PTB. In summary, the reasoning that vaginal progesterone has not been adequately proven to decrease recurrent PTB in women with a
history of prior spontaneous PTB is based on the consistency of lack of benefit across multiple RCT’s despite heterogeneity of patient populations, clinical criteria, and progesterone dosing. However, SMFM continues to affirm the use of vaginal progesterone to prevent preterm birth in women with sonographically short cervix ≤ 20mm without a history of prior spontaneous PTB.\(^1\)

Owen and colleagues performed an RCT involving cervical cerclage in women with a prior spontaneous PTB < 34 weeks of gestation, and noted that approximately 69% of those with serial cervical length screening had cervical length that remained > 25 mm.\(^14\) A secondary analysis of this same RCT did not demonstrate any additional benefit of 17-OHPC in women who received a cerclage for cervical shortening. In women with a prior spontaneous PTB who start 17-OHPC 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 prior spontaneous PTB, we recommend continuation of 17-OHPC therapy in women with history of prior spontaneous PTB throughout the pregnancy despite the development of cervical shortening (with or without cervical cerclage placement).

Few studies directly compare 17-OHPC and vaginal progesterone in women with a history of prior spontaneous PTB.\(^16\)\(^-\)\(^18\) A recent meta-analysis reported outcomes for three trials that included a total of 680 women.\(^19\) The largest study to directly compare 17-OHPC and vaginal progesterone was conducted in Saudi Arabia and published in 2013 (this study accounts for 74% subjects in the meta-analysis).\(^18\) In this study, 520 women with a history of one or more mid-trimester PTB or history of cervical cerclage in a prior pregnancy were randomized to receive either 17-OHPC or vaginal progesterone; women receiving vaginal progesterone were less likely to deliver < 34 weeks of gestation than those receiving 17-OHPC (16.6% vs. 25.7%, OR 0.58, 95% CI 0.37-0.89, p=0.02) but not < 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 mid-trimester preterm birth or cerclage), rather than the typical candidate for 17-OHPC in the US. Given the significant differences in study population, eligibility criteria and study protocol, we believe this RCT is not generalizable to women with a prior spontaneous PTB in the US.
Given the available data, this SMFM statement reaffirms its current recommendations: In women with singleton gestation and a history of prior spontaneous PTB between 20 weeks of gestation and 36 6/7 weeks of gestation, we recommend 17-OHPC at 250 mg IM 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 17-OHPC in these patients.
References


