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SMFM Statement

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Society for Maternal-Fetal Medicine Statement: Response to the Food and Drug Administration's withdrawal of 17-alpha hydroxyprogesterone caproate

Society for Maternal-Fetal Medicine (SMFM); SMFM Publications Committee

On April 5, 2023, the US Food and Drug Administration withdrew the approval of 17-alpha hydroxyprogesterone caproate, effective immediately, because of the lack of evidence that it reduces the risk of recurrent spontaneous preterm birth. This decision withdraws approval for all formulations of 17-alpha hydroxyprogesterone caproate (both intramuscular and subcutaneous) and applies to both brand name (Makena) and generic versions of the medication. We agree with the Food and Drug Administration determination and discourage continued prescribing of 17-alpha hydroxyprogesterone caproate, including through compounding pharmacies. We do not recommend changing indications for cerclage, indications for vaginal progesterone in patients with a short cervix, or recommendations against activity restriction based on the Food and Drug Administration withdrawal of 17-alpha hydroxyprogesterone caproate from the market. We recommend that discussion of the use of vaginal progesterone for primary prevention of recurrent preterm birth without input of cervical length or in those with a cervical length of $\geq$25 mm includes a shared decision-making process, especially if a progesterone formulation for preterm birth prevention was received in a previous pregnancy. The Food and Drug Administration determined that it would be inappropriate to delay the effective date of the withdrawal to allow patients currently receiving 17-alpha hydroxyprogesterone caproate to finish treatment. We agree with the Food and Drug Administration that there is no evidence of benefit with continued treatment. Patients currently receiving 17-alpha hydroxyprogesterone caproate can be counseled that the Food and Drug Administration's Center for Drug Evaluation and Research has not identified evidence of harm from discontinuation before 37 weeks of gestation.

Key words: 17-alpha hydroxyprogesterone caproate, cerclage, Food and Drug Administration, preterm birth, vaginal progesterone

Introduction

In 2011, the US Food and Drug Administration (FDA) approved intramuscular 17-alpha hydroxyprogesterone caproate (17-OHPC; marketed as Makena) for the sole indication of reduction of recurrent spontaneous preterm birth (PTB) in pregnant people with a singleton pregnancy who had a previous singleton spontaneous PTB. Under typical FDA drug approval processes, at least 2 appropriately designed clinical trials must demonstrate efficacy for a medication to receive approval. Because of the public health burden of PTB and the lack of other effective interventions at the time, the FDA granted 17-OHPC accelerated approval,[1] largely based on the positive findings of the Maternal-Fetal Medicine Units (MFMU) Network study conducted by Meis et al,[2] with the requirement that a second confirmatory study be conducted.

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The Progestin's Role in Optimizing Neonatal Gestation (PROLONG) study, a multicenter, multinational study conducted largely outside of the United States, was conducted from 2009 to 2018 to meet this requirement.[3] The study had 2 coprimary outcomes: PTB at $<$35 weeks of gestation and composite neonatal morbidity and mortality. Except for the primary outcomes and recruitment locations, study investigators designed the PROLONG study to mimic the original MFMU study protocol as much as possible.[4] Despite this, the PROLONG study failed to demonstrate either reduction in spontaneous PTB or improvement in neonatal outcomes among participants treated with 17-OHPC compared with participants treated with placebo.

Food and Drug Administration review since the publication of Progestin's Role in Optimizing Neonatal Gestation

After the publication of the PROLONG study in 2020, the FDA's Center for Drug Evaluation and Research (CDER)

recommended the withdrawal of 17-OHPC's approval as the postmarketing study failed to verify the clinical benefit and the available evidence did not support the efficacy of 17-OHPC for its approved clinical use. In December 2020, the manufacturer of 17-OHPC requested a hearing to appeal the recommendation, which was approved in August 2021 and held in October 2022.

As part of the hearing process, the FDA's Obstetrics, Reproductive, and Urologic Drugs Advisory Committee (the Committee) reviewed the scientific evidence and heard presentations from research scientists, clinicians, and the public regarding 17-OHPC. The FDA Committee was charged with answering the 3 following questions[5,6]:

1. Do the findings from the confirmatory study verify the clinical benefit of 17-OHPC on neonatal morbidity and mortality from complications of PTB?

FDA Committee response: The rate of the composite neonatal outcome was similar in those treated with 17-OHPC and those who received a placebo (5.4% vs 5.2%; relative risk [RR], 1.05; 95% confidence interval [CI], 0.68−1.61). Based on these data, the Committee voted that the findings of the confirmatory study do not verify the clinical benefit of 17-OHPC on neonatal outcomes.

2. Does the available evidence demonstrate that 17-OHPC is effective for its approved indication of reducing the risk of PTB in women with a singleton pregnancy who have a history of singleton spontaneous PTB?

FDA Committee response: The results of the PROLONG study contributed to answering this question, but other scientific publications were also considered. The rate of PTB at <35 and <37 weeks of gestation was not reduced in those treated with 17-OHPC compared with those treated with placebo (11.0% vs 11.5% [RR, 0.95; 95% CI, 0.71−1.26] and 23.1% vs 21.9% [RR, 1.06; 95% CI, 0.88−1.28], respectively). Although the results from the MFMU trial demonstrated benefit, other observational studies and smaller randomized trials failed to consistently demonstrate benefit with 17-OHPC treatment.[7−14] In addition, the Committee reviewed data on treatment effects by population subgroups and concluded that the population differences did not account for the discrepancies between trials. Based on the information reviewed, the Committee voted that the evidence does not demonstrate that 17-OHPC is effective for its approved indication.

3. Should the FDA allow 17-OHPC to remain on the market while an appropriate confirmatory study is designed and conducted?

FDA Committee response: The FDA's CDER stated that only a randomized, double-blind, placebo-controlled trial could verify clinical benefit and advocated that allowing 17-OHPC to remain on the market while another study was conducted would not only hamper recruitment for the study in the United States but also could slow research into other potentially effective therapies. Based on the lack of demonstrated efficacy and per FDA policy on accelerated approval, the Committee voted that 17-OHPC should not be allowed to remain on the market.

Following the original recommendations of the CDER and the recent recommendations of the FDA Committee, on April 5, 2023, the FDA issued a final decision removing approval of 17-OHPC and required its withdrawal from the market, effective immediately.[15] This withdrawal affects all formulations of 17-OHPC, including brand and generic intramuscular 17-OHPC and the subcutaneous autoinjector formulations. In addition to the decision, the FDA issued a frequently asked questions resource for patients and providers.[16]

The FDA acknowledged that a limited supply of 17-OHPC has already been distributed to physicians' offices and pharmacies[16] and recognized that some providers might continue to administer it. At the time of the withdrawal notice, the FDA deferred to CDER to determine whether continued use of this inventory will be permitted.[15] The FDA decision stressed that the unfavorable risk-benefit profile of 17-OHPC should guide decisions about the use of the remaining inventory.[15,16] We agree with the FDA that there is no evidence of benefit with continued treatment for patients currently receiving 17-OHPC and recommend that patients who are currently on 17-OHPC be counseled that the FDA has withdrawn this drug from the market because of a lack of efficacy or benefit. Patients currently receiving 17-OHPC can be counseled that CDER has not identified evidence of harm from discontinuation before 37 weeks of gestation.[17] For those practitioners and patients who wish to switch from 17-OHPC to vaginal progesterone for the remainder of the pregnancy, a shared decision-making process should occur.

Current state

PTB remains a major public health challenge and the most common cause of neonatal morbidity and mortality in the United States. The rate of PTB in Black pregnant people is markedly higher than in White or Hispanic pregnant people in the United States. In 2021, 14.8% of births to Black pregnant people were before term compared with 9.5% and 10.2% of birth to White and Hispanic pregnancy patients.[18] This disproportionate share drives health inequities and disparities in the neonatal period and extends into long-term effects in childhood, adolescence, and adulthood. The etiologies, risk factors, and phenotypes of PTB are heterogeneous and complex, contributing to difficulty in predicting PTB and developing effective prevention strategies. The strongest predictor of spontaneous PTB is a history of previous spontaneous PTB with up to 50% of pregnant people experiencing a recurrent spontaneous PTB.[19] Given the societal burden, it is imperative that evidence-based interventions proven to be effective at reducing the

likelihood of PTB and improving neonatal outcomes be offered to patients at risk of recurrent PTB.

Previous guidance after the publication of PROLONG considered continued use of 17-OHPC in patients with a high-risk profile similar to patients in the MFMU study after shared decision-making with the patient.[20] FDA withdrawal of 17-OHPC from the market removes the option of prescribing on a case-by-case basis, and some clinicians may contemplate obtaining the drug from a compounding pharmacy as was done before FDA approval. Although compounding pharmacies that follow United States Pharmacopeia (USP) standards may offer a reasonable alternative for access to formulations of medications that are administered orally, vaginally, or topically, there has been a historical concern about the safety and sterility of injectable formulations obtained from compounding pharmacies. The FDA decision deferred to CDER to address compounded 17-OHPC.[15,16] With the evolution of the data regarding the lack of overall efficacy of 17-OHPC and discontinued availability, we discourage prescribing 17-OHPC through compounding pharmacies.[16]

Vaginal progesterone

The efficacy of vaginal progesterone for the prevention of recurrent PTB was summarized in the "Evaluating Progestogens for Preventing Preterm Birth International Collaborative (EPPPIC): meta-analysis of individual participant data from randomised controlled trials" study.[14] EPPPIC used individual patient data from 9 trials of vaginal progesterone in 3769 patients with singleton pregnancies at high risk of PTB because of a short cervix or previous spontaneous PTB. Patients who received vaginal progesterone because of a previous spontaneous PTB or a short cervix had a 22% reduction in the likelihood of PTB (RR, 0.78; 95% CI, 0.68−0.90). Moreover, EPPPIC investigators studied the effect modification from a short cervical length using data from the 4 studies of vaginal progesterone that had cervical length data available. In those with a cervical length of ≤30 mm, vaginal progesterone reduced the likelihood of PTB among pregnant patients with (RR, 0.67; 95% CI, 0.48−0.93; n=528) and without (RR, 0.65; 95% CI, 0.45−0.95; n=479) a history of spontaneous PTB. In addition, the investigators examined a smaller group of pregnant people (n=353) with a cervical length of ≤25 mm and noted similar trends among individuals with a history of PTB (RR, 0.71; 95% CI, 0.49−1.03). An aggregate data meta-analysis by Conde-Agudelo and Romero demonstrated a substantial difference in the effect of vaginal progesterone in large studies vs small studies.[21] In sensitivity analyses, when small studies were excluded from the meta-analysis, the reduction in PTB was no longer significant. After adjusting for small study effects, they found that, in asymptomatic pregnant patients, vaginal progesterone did not reduce recurrent PTB at <37 (RR, 0.86; 95% CI, 0.68−1.10) or <34 (RR, 0.92; 95% CI, 0.60−1.42) weeks of gestation and concluded that findings from earlier meta-analyses were largely driven by the larger treatment effects from small studies that were more prone to bias and limited by grouping patients with heterogenous etiologies for PTB (personal history, short cervix, uterine anomalies, etc.). Although this systematic review and meta-analysis did not evaluate effects inclusive of cervical length, it highlights the uncertainty of a beneficial effect of vaginal progesterone in all pregnant people with a history of spontaneous PTB vs only in some subgroups, such as those with a short cervix.

Consistent with other guidance, individuals with a short cervical length of ≤25 mm at <24 weeks of gestation and a history of PTB should be offered treatment with vaginal progesterone, based on the available evidence. The EPPPIC meta-analysis suggests that there may be a benefit to treatment with vaginal progesterone in the subgroup of patients with a cervical length of 25 to 30 mm; however, the data to recommend treatment for this subgroup are limited, and an additional analysis of the meta-analysis by Conde-Agudelo and Romero did not find a benefit of vaginal progesterone in pregnant patients with a history of spontaneous PTB and a cervical length of >25 mm.[22] A discussion of the use of vaginal progesterone for the primary prevention of recurrent PTB without input of cervical length or in those with a cervical length of ≥25 mm should include a shared decision-making process, especially if a progesterone formulation for PTB prevention was received in a previous pregnancy. Factors that should be discussed as part of shared decision-making include the following:

- Gestational age of previous spontaneous PTB
- Use of progesterone in a previous pregnancy
- Number of previous spontaneous PTBs
- Number of term births
- Outcome of most recent pregnancy (ie, preterm vs term)

Cerclage

Ultrasound monitoring of cervical length beginning at approximately 16 weeks of gestation is recommended for all patients with a history of previous PTB to identify those with cervical shortening. We do not recommend changing indications for cerclage or recommendations against activity restriction[23] based on the FDA withdrawal of 17-OHPC from the market. Data from several randomized trials provide strong evidence that placement of cerclage in patients with a cervical length of <25 mm before 24 weeks of gestation is associated with a reduction in the rate of PTB before 35 weeks of gestation (28.0% vs 41.0%; RR, 0.70; 95% CI, 0.55−0.89) and composite neonatal morbidity (15.6% vs 24.8%; RR, 0.64; 95% CI, 0.45−0.91).[24] Although the data are consistent regarding the benefit of cerclage in the setting of a short cervix among patients with a previous PTB, there is a lack of data directly comparing cerclage to vaginal progesterone and a lack of data as to whether the beneficial effects are additive. A meta-analysis that included randomized trials of vaginal progesterone vs placebo and cerclage vs no cerclage in patients with a previous PTB and

a short cervix found a similar magnitude of reduction in PTB at <35 weeks of gestation with either cerclage or vaginal progesterone (RR: 0.68 [95% CI, 0.50−0.93] and 0.70 [95% CI, 0.55−0.89], respectively).[25] Based on the currently available evidence, it is reasonable to offer either cerclage or vaginal progesterone to patients who have a history of PTB and are diagnosed with a short cervix before 24 weeks of gestation. For patients who receive a cerclage, the benefit of adding vaginal progesterone to the treatment regimen is unknown. Similarly, for patients started on vaginal progesterone, the value of continued cervical length surveillance is unproven, and the benefit of cerclage placement if further cervical shortening occurs is unclear.

Future research

Continued research into the development of effective treatments for the prevention of PTB is needed. The manufacturer of 17-OHPC has stated its intent to perform a study that is designed to recruit patients with a high-risk profile to better evaluate the efficacy of 17-OHPC. We support this study and all studies that aim to develop interventions that improve maternal and neonatal outcomes. We will continue to follow advances in this area to assure optimal care for all people who experience pregnancy and to provide up-to-date guidance for maternal-fetal medicine subspecialists.

Summary

- We agree with the FDA determination that 17-OHPC is ineffective for the prevention of PTB and should not be prescribed.
- We agree with the FDA that there is no evidence that patients currently receiving 17-OHPC will benefit from continued treatment. Patients currently receiving 17-OHPC can be counseled that CDER has not identified evidence of harm from discontinuation before 37 weeks of gestation.
- We discourage prescribing 17-OHPC through compounding pharmacies.
- We recommend that discussion of the use of vaginal progesterone for primary prevention of recurrent PTB without input of cervical length or in those with a cervical length of ≥25 mm include a shared decision-making process, especially if a progesterone formulation for PTB prevention was received in a previous pregnancy.
- We do not recommend changing indications for cerclage or recommendations against activity restriction based on the FDA withdrawal of 17-OHPC from the market.
- We do not recommend changing indications for vaginal progesterone in patients with a short cervix based on the FDA withdrawal of 17-OHPC from the market.

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The SMFM recognizes that obstetrical patients have diverse gender identities and is striving to use gender-inclusive language in all of its publications. The SMFM will be using terms such as “pregnant person or persons” or “pregnant individual or individuals” instead of “pregnant woman or women” and will use the singular pronoun “they.” When describing the study populations used in research, the SMFM will use the gender terminology reported by the study investigators.

Reprints will not be available.

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