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**Learning Objectives:**
After participating in this educational activity, participants should be better able to:
1. Incorporate strategies for providing optimal clinical management to women at risk for preterm birth, based on established SMFM, ACOG, and ACNM recommendations.
2. Define the historical role of 17-OHPC in the management of preterm birth.
3. Identify clinical trial factors—patient populations, healthcare systems—that can influence the results of a clinical trial.

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# The Clinical Conundrum in Managing Preterm Birth: Balancing Historical Trial Results, Society Guidelines, and Clinical Experience with a Contradictory Trial Outcome

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## INTRODUCTION

Since its approval in 2011, 17-alpha hydroxyprogesterone caproate (17-OHPC, trade name Makena®, AMAG Pharmaceuticals, Inc, Waltham, MA) has been designated the "standard of care " for treating pregnant patients with a history of spontaneous preterm birth (SPTB) by the American College of Obstetricians and Gynecologists (ACOG), the Society for Maternal-Fetal Medicine (SMFM), and the American College of Nurse Midwives (ACNM).[1-3] Several clinical trials and years of clinical experience have demonstrated its safety and efficacy.[4-6]

On March 8, 2019, AMAG Pharmaceuticals announced topline results from the PROLONG (Progestin's Role in Optimizing Neonatal Gestation) trial; a randomized, double-blinded, placebo-controlled clinical trial evaluating 17-OHPC in patients with a history of a prior spontaneous singleton preterm delivery. The PROLONG trial was conducted as part of an approval commitment under the US Food and Drug Administration's (FDA) "Subpart H" accelerated approval process. Results of the trial did not demonstrate a statistically significant difference between the treatment and placebo arms for the co-primary endpoints. The first endpoint was the rate of preterm delivery at <35 weeks; the second endpoint was the percentage

of patients who met criteria for the pre-specified neonatal morbidity and mortality composite index.[7]

On October 29, 2019, the FDA, Bone, Reproductive, and Urologic Drugs Advisory Committee met to better understand and interpret the PROLONG clinical trial. While the committee discussed multiple questions, in a vote on the key question as to whether the FDA should withdraw approval for 17-OHPC, 9 advisory committee members voted to recommend this withdrawal, while 7 committee members voted to leave the product on the market under accelerated approval and required a new confirmatory trial, which is not feasible in the United States. Among the clinicians on the advisory committee, 5 of the 6 who practice obstetrics voted to keep 17-OHPC on the market and generate more data from a prospective observational study.[8]

The question arises as to how Ob/Gyn clinicians translate the results of the PROLONG trial to their practice setting. This is of particular importance given that 17-OHPC was reaffirmed by ACOG and SMFM shortly after the FDA Advisory Committee as the "standard of care" for managing women with a history of spontaneous preterm birth. This CME-designated activity is meant to provide guidance in addressing this question.

## 17-OHPC HISTORICAL TRIAL RESULTS: THE PREPONDERANCE OF EVIDENCE CONFIRMS ITS EFFICACY

In 1956, 17-OHPC received initial FDA approval for the treatment of habitual and recurrent abortion, and threatened miscarriage. Its use as a prophylactic therapy to reduce the risk of preterm birth in the 1960s–1980s was hampered by inconsistent clinical trial results, poor study design—including heterogeneous inclusion criteria—and theoretical concerns regarding safety. However, in 1989, Keirse presented a seminal meta-analysis of 7 clinical trials of 17-OHPC spanning the years 1964–1985.[4] In the Discussion section, Keirse noted:

"Thus, the trials of 17a-hydroxyprogesterone caproate showed a statistically significant reduction in the frequency of preterm labour, preterm birth and low birth-weight. The effects of 17a-hydroxyprogesterone on the frequency of preterm birth were consistent among trials except for the trial of Hartikainen-Sorri et al. (1980), which was the only one not dealing with singleton pregnancies. It is possible that twin pregnancies are different in this respect, and that beneficial effects of 17a-hydroxyprogesterone are confined to singleton pregnancies……The present study indicates that injections of 17a-hydroxyprogesterone caproate may reduce the occurrence of preterm birth among women so treated."

The Keirse meta-analysis served as the basis for evaluating 17-OHPC in a large multicenter trial, which was a research proposal championed by Dr. Paul Meis for the NIH NICHD Maternal-Fetal Medicine Units (MFMU) Network.

## THE MEIS (MFMU NETWORK) TRIAL: THE PIVOTAL TRIAL LEADING TO THE FDA APPROVAL OF 17-OHPC

In 2003, Meis and colleagues published in the *New England Journal of Medicine* a landmark study assessing the efficacy of 17-OHPC in women with a history of spontaneous preterm birth (SPTB).[5] This multicenter, randomized trial conducted by members of the NICHD/NIH MFMU Network included 463 women with prior SPTB who were randomized to receive either 17-OHPC weekly at 16–20 weeks' gestation or a placebo until 37 weeks gestation. The rate of recurrent SPTB <37 weeks gestation was reduced from 55% in the placebo group to 36% in the 17-OHPC group (RR, 0.66;95% CI, 0.54–0.81). In addition, the trial showed a significant reduction in rates of preterm delivery at <35 and 32 weeks, compared with placebo. While not powered to assess neonatal outcomes, a significant reduction of Grade 3 and 4 IVH and necrotizing enterocolitis in the 17-OHPC group was also reported.

Since publication of the Meis trial, a number of studies have further evaluated, and confirmed, the efficacy of 17-OHPC in the prevention of preterm birth. One trial by Mason demonstrated a reduction in deliveries <35 weeks (41.7% in control group and 26.4% in 17-OHPC group).[6] In 2012, a retrospective analysis conducted by Sibai et al of data from women with prior preterm birth enrolled in a Home Health Agency Prematurity Program all of whom received 17-OHPC. reported preterm birth rates at <37 weeks' gestation that were similar to the original NICHD Meis study (34.4% Sibai vs. 36.3% Meis).[9]

## ACOG/SMFM/ACNM: 17-OHPC AS THE STANDARD OF CARE IN THE PREVENTION OF PRETERM BIRTH IN WOMEN WITH A PRIOR HISTORY OF PTB

In 2011, the FDA approved 17-OHPC for the prevention of preterm birth in women with a prior history of preterm birth. As a consequence of this action, the leading Ob/Gyn professional societies—SMFM, ACOG, and ACNM—put forth clinical guidelines to assist the Ob/Gyn clinician in identifying and managing pregnant patients at risk of preterm birth.

These publications included comprehensive reviews of clinical trials and provided detailed recommendations for progestogen treatment in selected high-risk pregnancies.[1-3] Key recommendations included:

- For singleton pregnancies in women with a history of prior SPTB, 17-OHPC is recommended to prevent recurrent preterm birth.
- For singleton pregnancies in women without a history of prior spontaneous preterm birth, vaginal progesterone is recommended to prevent preterm birth in patients diagnosed with a cervical length ≤20 mm by transvaginal ultrasound between 18 and 24 weeks' gestation.

## THE CLINICAL CONUNDRUM: BALANCING HISTORICAL TRIAL RESULTS, SOCIETY GUIDELINES, AND CLINICAL EXPERIENCE WITH A CONTRADICTORY TRIAL OUTCOME

### The PROLONG Trial: No Significant Difference in Rates of Preterm Birth in 17-OHPC Compared to Placebo

On March 8, 2019, AMAG announced topline results from the PROLONG trial, a randomized, double-blinded, placebo-controlled clinical trial evaluating 17-OHPC in patients with a history of a prior spontaneous singleton preterm delivery. Results of the trial did not demonstrate a statistically significant difference between the treatment and placebo arms for the co-primary endpoints. The first endpoint was the rate of preterm delivery at <35 weeks (17-OHPC treated group, 11% vs. placebo, 11.5%; $P = .72$). The second endpoint was the percentage of patients who met criteria for the prespecified neonatal morbidity and mortality composite index (17-OHPC treated group, 5.4% vs. placebo, 5.2%; $P = .84$). The adverse event profile between the 2 arms was comparable. The patient demographics of the trial merit important notice. Of the approximately 1,700 women enrolled in the trial, >75% were enrolled in trial sites outside the United States, with >60% of patients residing in Russia or Ukraine. Because of site selection, the rate of recurrent preterm birth in the placebo arm was substantially lower than expected from the Meis trial (21.9% in PROLONG vs. 54.9% in the Meis).

On October 29, 2019, the FDA Bone, Reproductive, and Urologic Drugs Advisory Committee met to better understand and interpret the PROLONG clinical trial. In a vote on the key question as to whether the FDA should withdraw approval for 17-OHPC, 9 advisory committee members voted to recommend this withdrawal, while 7 committee members voted to leave the product on the market under accelerated approval and required a new confirmatory trial. Five of the 6 members who practice obstetrics voted to keep 17-OHPC on the market and generate more data.[8]

## REAFFIRMING SOCIETY GUIDELINES: SMFM AND ACOG RESPOND TO THE PROLONG TRIAL RESULTS

### ACOG's Response

Following the FDA's Advisory Committee announcement, ACOG issued a Practice Advisory statement, titled "Practice Advisory: Clinical Guidance for Integration of the Findings of the PROLONG Study: Progestin's Role in Optimizing Neonatal Gestation."[8] This guidance summarized the PROLONG trial results and identified some particularly important methodologic differences between the Meis trial and the PROLONG trial. Specifically, it noted that:

Despite the 2 trials having the same eligibility criteria and study protocols, the patient populations had divergent sociodemographic characteristics and a substantially lower preterm birth rate at <35 weeks (10% in PROLONG) when compared with the rate demonstrated in the Meis trial (30%). Based on these results, the PROLONG trial authors suggested that the PROLONG trial was underpowered to assess treatment efficacy related to preterm birth and neonatal outcomes in this population.

In light of the ACOG preterm birth guidance published in 2008, a possible unintentional selection bias may have occurred in women enrolled in the United States; specifically, women with a higher risk for recurrent preterm birth were not being offered or agreeing to participate in the PROLONG study in order to avoid the risk of not receiving active 17-OHPC treatment.

**In concluding its Practice Advisory, ACOG stated:**

"Current guidelines in the United States recommend the use of progesterone supplementation in women with prior spontaneous preterm birth. Consideration for offering 17-OHPC to women at risk of recurrent preterm birth should continue to take into account the body of evidence for progesterone supplementation, the values and preferences of the pregnant woman, the resources available, and the setting in which the intervention will be implemented. Additional information from planned meta-analysis and secondary analyses will need to be evaluated to assess the impact this intervention has on women at risk of recurrent preterm birth in the United States." **ACOG is not changing our clinical recommendations at this time and continues to recommend offering hydroxyprogesterone caproate as outlined in Practice Bulletin #130, Prediction and Prevention of Preterm Birth.** (*Disclaimer: bolded statement is for emphasis by the author, not ACOG.*)

### SMFM's Response

SMFM also responded to the FDA Advisory Committee findings by issuing a statement similar to the one by ACOG. Titled "SMFM Statement: Use of 17-alpha Hydroxyprogesterone Caproate for Prevention of Recurrent Preterm Birth", it presented a comprehensive assessment of the two trials' patient populations and how these differences could have contributed to the discordant results. Specifically, this assessment noted:

"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% 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 2 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.[5] Preterm birth is a complex disorder with heterogeneous etiologies and associated underlying mechanisms in different women.[10-12] 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."

**The SMFM concluded their guidance by stating:**

"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.**

*(Disclaimer: bolded statement is for emphasis by the author, not SMFM.)*

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."[13]

## CONCLUSION

Since its approval by the FDA in 2011, 17-OHPC has been utilized safely and effectively to prevent spontaneous preterm birth in women with such a history. Pre-approval, 17-OHPC demonstrated comparable safety and efficacy in such women for over 40 years. In light of this well-established efficacy and safety record, SMFM, ACOG, and ACNM in 2012 designated 17-OHPC the "standard of care" in women with a prior history of spontaneous preterm birth. Thousands of Ob/Gyn clinicians have utilized 17-OHPC in thousands of at-risk patients with the desired results of prolonging these pregnancies.

ACOG's and SMFM's reaffirmation of their previous clinical guidelines after the announcement of the PROLONG trial results in March 2019 cannot be overemphasized. Their assessments of the differences in patient populations between the PROLONG trial and the MEIS trial, with their recommendations to continue to use 17-OHPC according to the patient criteria defined in their previous guidances, provide a clear clinical path for managing women at high risk of spontaneous preterm delivery in pregnant women with a history of prior preterm birth. Based on all available data, it is important that an FDA-approved drug such as 17-OHPC be available for patients who may benefit from it and for obstetric providers to decide who are the best candidates to offer 17-OHPC.

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