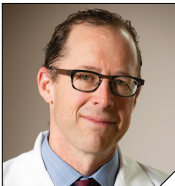


ILLUSTRATION: KIMBERLY MARTENS FOR OBG MANAGEMENT

Progesterone supplementation does not PROLONG pregnancy in women at risk for preterm birth: What do we do now?

What is the future for 17P now that a required trial for the drug's efficacy showed that its use did not reduce preterm birth, neonatal morbidity, or fetal/early infant deaths—and an FDA advisory committee recommended withdrawal of the drug's approval?



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Preterm birth (PTB) remains a significant public health concern and a major cause of newborn morbidity and mortality. In the United States, 1 in 10 babies are born preterm (< 37 weeks), and this rate has changed little in 30 years.¹

In 2011, the US Food and Drug Administration (FDA) approved progesterone supplementation—specifically, 17 α -hydroxyprogesterone caproate (17P) injection (Makena)—to prevent recurrent PTB in women with a singleton pregnancy at high risk by virtue of a prior spontaneous PTB.² This was the first-ever FDA-approved drug for PTB prevention, and it was the first drug approved by the FDA for use in pregnancy in more than 15 years. The approval of 17P utilized the FDA's Subpart H Accelerated Approval Pathway, which applies to therapies that: 1) treat serious conditions with unmet need, and 2) demonstrate safety and efficacy on surrogate end points reasonably likely to predict clinical benefit.³

The authors report no financial relationships relevant to this article.

By voting their approval of 17P in 2011, the FDA affirmed that PTB was a serious condition with unmet need, that birth < 37 weeks was an accepted surrogate end point, and that there was compelling evidence of safety and benefit. The compelling evidence presented was a single, randomized, vehicle-controlled clinical trial conducted by the Maternal-Fetal Medicine Units (MFMU) Network, which showed significant reduction in recurrent PTB < 37 weeks (from 54.9% in the placebo group to 36.3% in the 17P group; $P < .001$; relative risk [RR], 0.66; 95% confidence interval [CI], 0.54–0.81).⁴

In 2017, the Society for Maternal-Fetal Medicine (SMFM) reaffirmed the use of 17P to prevent recurrent PTB and, that same year, it was estimated that 75% of eligible patients received 17P.^{5,6} Importantly, Subpart H approval *requires* one or more follow-up clinical trials confirming safety and efficacy. And the FDA has the right—the responsibility—to revisit approval if such trials are either not performed or are unfavorable.

The recently published PROLONG study by Blackwell and colleagues is this required postapproval confirmatory trial conducted to verify the clinical benefit of 17P supplementation.⁷

Study design, and stunning results

PROLONG (Progestin's Role in Optimizing Neonatal Gestation) was a randomized (2:1), double-blind, vehicle-controlled, multicenter international trial (2009–2018) conducted to assess the safety and efficacy of 17P injection in 1,708 women with a singleton pregnancy and one or more prior spontaneous PTBs.⁷ Women in the active treatment group ($n = 1,130$) received weekly intramuscular injections of 17P, while those in the control group ($n = 578$) received weekly injections of inert oil vehicle.

Results of the trial showed no significant reduction in the coprimary end points, which were PTB < 35 weeks (11.0% in the 17P group vs 11.5% in the placebo group; RR, 0.95;

95% CI, 0.71–1.26) and neonatal morbidity index (5.6% in the 17P group vs 5.0% in the placebo group; RR, 1.12; 95% CI, 0.68–1.61). There was no evidence of benefit for any subpopulation (geographic region, race, or other PTB risk factor). Maternal outcomes also were similar between the groups. No significant safety concerns were identified.

Important differences between MFMU and PROLONG trials

Strengths of the PROLONG trial include its randomized, placebo-controlled design, excellent follow-up rate, and use of a protocol that mirrored that of the MFMU trial. The primary limitation of PROLONG is that participants experienced a lower rate of PTB compared with those in the MFMU trial. The rate of PTB < 37 weeks was 54.9% in the control group of the MFMU trial compared with 21.9% in PROLONG.

Given the low rate of PTB in PROLONG, the study was underpowered for the co-primary outcomes. In addition, lower rates of PTB in PROLONG compared with in the MFMU trial likely reflected different patient populations.⁸ Moreover, PROLONG was an international trial. Of the 1,708

participants, most were recruited in Russia (36%) and Ukraine (25%); only 23% were from the United States. By contrast, participants in the MFMU trial were recruited from US academic medical centers. Also, participants in the MFMU trial were significantly more likely to have a short cervix, to have a history of more than one PTB, and to be African American.

Discrepant trial results create clinical quandary

In October 2019, the FDA's Bone, Reproductive and Urologic Drugs Advisory Committee voted 9-7 to withdraw approval for 17P. Committee members struggled with the conflicting data between the 2 trials and hesitated to remove a medication whose use has become standard practice. Ultimately, however, it was lack of substantial evidence of effectiveness of 17P that swayed the committee's vote. While the FDA generally follows the recommendation of an advisory committee, it is not bound to do so.

Societies' perspectives

So what are physicians and patients to do? It is possible that a small subgroup of women at extremely high

risk for early PTB may benefit from 17P administration. SMFM stated: "... it is reasonable for providers to use 17-OHPC [17P] in women with a profile more representative of the very high-risk population reported in the Meis [MFMU] trial."⁸ Further, the American College of Obstetricians and Gynecologists (ACOG) stated in a Practice Advisory dated October 25, 2019, that "ACOG is not changing our clinical recommendations at this time... [We] will be reviewing subsequent forthcoming analyses and will issue updated clinical guidance as appropriate."⁹

Where we stand on 17P use going forward

17P should be available to women who previously may have benefited from its use. However, 17P should not be recommended routinely to prevent recurrent spontaneous PTB in women with one prior PTB and no other risk factors. Of note, the PROLONG trial does not change recommendations for cervical length screening. Women with a history of a prior spontaneous PTB should undergo cervical length screening to identify those individuals who may benefit from an ultrasound-indicated cerclage. ●

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