ONLINE EXCLUSIVE

Q/ Should we stop prescribing IM progesterone to women with a history of preterm labor?

Lee Dresang, MD
University of Wisconsin Department of Family Medicine and Community Health, Madison

Lia Vellardita, MA
Ebling Library, University of Wisconsin School of Medicine and Public Health, Madison

DEPUTY EDITOR
Richard Guthmann, MD, MPH
Advocate Illinois Masonic Family Medicine Residency, Chicago

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EVIDENCE-BASED ANSWER

A/ **YES, WE SHOULD STOP THE ROUTINE PRESCRIBING** of IM progesterone to prevent preterm delivery. A 2003 randomized controlled trial (RCT) found that weekly intramuscular (IM) 17 hydroxyprogesterone (17-OHP) for women with a singleton pregnancy and a history of spontaneous preterm delivery decreased the preterm delivery rate by 34% (strength of recommendation [SOR]: **B**, single RCT). However, the follow-up 2020 PROLONG RCT did not find that 17-OHP prevents preterm birth or improves neonatal outcomes. This held true for subgroup analyses (SOR: **B**, single larger RCT). (Notably, though, the PROLONG study had very few Black participants when compared with the 2003 study.)

The US Food and Drug Administration (FDA) has recommended withdrawing 17-OHP from the market. The American College of Obstetricians and Gynecologists (ACOG) and the Society for Maternal-Fetal Medicine (SMFM) have released statements supporting shared decision-making with women regarding the prescribing of 17-OHP for preterm delivery prevention (SOR: **C**, expert opinion).

Evidence summary

Early evidence suggested benefit from IM progesterone

A 2003 RCT compared weekly IM progesterone (n = 310) and placebo (n = 153) injections in women with a history of spontaneous preterm delivery. Participants were at 15w0d to 20w3d of a singleton pregnancy with no fetal abnormality. The 17-OHP group, compared to the placebo group, had significantly fewer deliveries at < 37 weeks (36.3% vs 54.9%; relative risk [RR] = 0.66; 95% CI, 0.54 to 0.81; number needed to treat [NNT] = 6), at < 35 weeks (20.6% vs 30.7%; RR = 0.67; 95% CI, 0.48 to 0.93; NNT = 10), and at < 32 weeks (11.4% vs 19.6%; RR = 0.58; 95% CI, 0.37 to 0.91; NNT = 13).[1] There were significantly lower rates of necrotizing enterocolitis, intraventricular hemorrhage, and need for supplemental oxygen in infants of women in the treatment group.[1] The study was underpowered to detect neonatal morbidity.

A 2013 Cochrane Review (5 studies including the 2003 RCT; 602 women) found that 17-OHP led to a decreased risk of birth at < 34 weeks (RR = 0.31; 95% CI, 0.14-0.69). It also led to a significant reduction in perinatal and neonatal mortality, birth at < 37 weeks, birthweight < 2500 g, use of assisted ventilation, incidence of necrotizing enterocolitis, and admission to the neonatal ICU.[2]

In a large follow-up study, progesterone did not demonstrate benefit

The PROLONG study was a double-blind, placebo-controlled international RCT of women with a previous singleton spontaneous preterm birth. The study involved 93 clinical centers in 9 countries: 41 in the United States and 52 outside the United States. The PROLONG study was much larger than the 2003 study: 1139 active treatment (vs 310) and 578 placebo (vs 153) participants. Women were randomized 2:1 to receive ei-

Our best evidence does not support routine IM progesterone use to prevent preterm delivery.

ther 250 mg 17-OHP or inert oil placebo weekly from 16w0d-20w6d until 36 weeks. The outcome measures were: (1) delivery at < 35 weeks and (2) a neonatal morbidity composite index. This composite index included any of the following: neonatal death, grade 3 or 4 intraventricular hemorrhage, respiratory distress syndrome, bronchopulmonary dysplasia, necrotizing enterocolitis, and proven sepsis.[3]

Progesterone did not improve any of the studied outcomes: there were no significant differences in the frequency of birth at < 35 weeks (17-OHP 11% vs placebo 11.5%; RR = 0.95; 95% CI, 0.71-1.26), in neonatal morbidity index (17-OHP 5.6% vs placebo 5%; RR = 1.12; 95% CI, 0.68-1.61), and in frequency of fetal/early infant death (17-OHP 1.7% vs placebo 1.9%; RR = 0.87; 95% CI, 0.4-1.81).[3] In the United States subgroup (n = 391; 23% of all patients), there was no significant difference in rate of birth at < 35 weeks (17-OHP 15.6% vs placebo 17.6%; RR = 0.88; 95% CI, 0.55-1.40).[3]

However, PROLONG had some limitations. Importantly, the 2003 RCT included 183 (59%) non-Hispanic Black women in the experimental group and 90 (58.5%) in the control group, whereas the 2020 PROLONG study had only 6.6% non-Hispanic Black participants. The neonatal outcome data for the PROLONG study only included 6 Black women in the experimental arm and 3 in the control arm.[3,4] Black women have prematurity rates that are 2 to 3 times higher than those in White women.[5]

Additionally, the PROLONG study had fewer smokers and more women who were married/living with a partner. Compared with prior studies, the PROLONG study had a lower proportion of women with > 1 spontaneous preterm birth and fewer with a shortened cervix (< 2%).[3] As a result of having lower risk participants, PROLONG may have been underpowered to detect improvements in outcome.[3]

A subsequent meta-analysis suggests some benefit for high-risk women

The 2021 Evaluating Progestogens for Preventing Preterm birth International Collaborative (EPPPIC) meta-analysis of individual data from 31 RCTs—involving 11,644 women and 16,185 babies—found that, compared with placebo, 17-OHP for women with a history of preterm delivery or short cervix did not significantly decrease the number of babies born before 34 weeks (5 trials [including the 2003 RCT and PROLONG studies]; 3053 women; RR = 0.83; 95% CI, 0.68–1.01).[6] However, it found that vaginal progesterone significantly decreased birth prior to 34 weeks (9 trials; 3769 women; RR = 0.78, 95% CI, 0.68-0.90).[6] The authors concluded that both IM and vaginal progesterone decreased preterm delivery in high-risk women. The effect was stronger for women with a short cervix than for women with a history of preterm delivery.[6]

Recommendations from others

In 2008, a joint ACOG/SMFM statement said, "Progesterone supplementation for the prevention of recurrent preterm birth should be offered to women with a singleton pregnancy and prior spontaneous preterm birth."[7] A 2012 ACOG Practice Bulletin stated that, "A woman with a singleton gestation and a prior spontaneous preterm singleton birth should be offered progesterone supplementation starting at 16 to 24 weeks of gestation, regardless of transvaginal ultrasound cervical length, to reduce the risk of recurrent spontaneous preterm birth."[8]

In 2011, Makena (hydroxyprogesterone caproate injection) received accelerated approval from the FDA. In October 2020, the FDA Advisory Committee recommended that Makena be withdrawn from the market (9 to 7 vote).[9] On October 5, 2020, the FDA's Center for Drug Evaluation and Research (CDER) proposed that Makena be withdrawn from the market "because the required postmarket study failed to verify clinical benefit and we have concluded that the available evidence does not show Makena is effective for its approved use."[10] A subgroup analysis by CDER did not find benefit for any subgroup, including high-risk women.[10] However, Makena will remain on the market unless its manufacturer withdraws it or the FDA Commissioner mandates its removal.

In response to the FDA's proposal, both ACOG and SMFM recommended that "ob-

stetric health care professionals discuss Makena's benefits, risks, and uncertainties with their patients"[11] as part of "a shared decision-making approach, taking into account the lack of short-term safety concerns but uncertainty regarding benefit."[12] Both organizations reiterated their position on shared decision-making after the EPPPIC meta-analysis was published.[13]

Studies comparing the 2 routes of administration (vaginal and IM) are underway.[13]

Editor's takeaway

Our best evidence does not support routine IM progesterone use to prevent preterm delivery. However, therapeutic inertia, uncertainty, and defensive medicine may slow down adoption of this newer evidence. Shared decision-making can assist treatment decisions, but it is not a substitute for following the best evidence. **JFP**

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