Society for Maternal-Fetal Medicine
High-risk pregnancy experts

Society for Maternal-Fetal Medicine Statement: Response to EPPPIC and considerations for the use of progestogens for the prevention of preterm birth
3.30.21

An individual participant data (IPD) meta-analysis, *"Evaluating Progestogens for Preventing Preterm birth International Collaborative (EPPPIC): meta-analysis of individual participant data from randomized controlled trials,"* was published in *The Lancet* on March 27, 2021.[1] Including 31 trials with data from 11,644 women and 16,185 offspring, the IPD meta-analysis compared vaginal progesterone, injectable 17-alpha hydroxyprogesterone caproate (17-OHPC), and oral progesterone with no treatment, or with each other, in asymptomatic women at risk of preterm birth (PTB). Data from the Progestin's Role in Optimizing Neonatal Gestation (PROLONG) trial were included in this meta-analysis. Outcomes included PTB (<37 weeks of gestation), early PTB (<34 weeks of gestation), and mid-trimester birth (<28 weeks of gestation). Adverse neonatal outcomes associated with PTB and adverse maternal outcomes were investigated as a composite and individually.

The results showed that compared with those who received no treatment, women with singleton pregnancies at high risk for PTB due to prior spontaneous PTB (sPTB) or short cervix who received 17-OHPC or vaginal progesterone were less likely to deliver before 34 weeks of gestation (17-OHPC five trials, 3053 women; relative risk [RR] 0.83, 95% CI, 0.68–1.01] and vaginal progesterone (nine trials, 3769 women; RR 0.78, 95% CI, 0.68–0.90]). In comparing 17-OHPC and no treatment, the confidence interval crossed equivalence, although the directionality of effect was favorable towards 17-OHPC. Due to the lack of a significant interaction between the type of treatment and effect on preterm birth, the study authors concluded that there was a benefit to both 17-OHPC and vaginal progesterone in reducing the risk of preterm birth. In singleton pregnancies at high-risk for PTB due to prior sPTB or short cervix, both 17-OHPC and vaginal progesterone reduced the risk of PTB before 34 weeks of gestation and improved other birth and neonatal outcomes. However, there was no clear evidence to support one intervention's effectiveness over the other in reducing PTB before 34 weeks of gestation, serious neonatal complication, overall maternal complications, or perinatal death.

Supplementary analyses were conducted using the data from those studies that included cervical length measurement. There was a consistent benefit shown for the use of either 17-OHPC or vaginal progesterone for cervical lengths less than 25 mm. At cervical lengths greater than 30 mm, treatment benefit was not apparent for either vaginal progesterone or 17-OHPC, even in women with a history of prior sPTB. There was no indication that the relative treatment effect for either vaginal progesterone or 17-OHPC varied between women with a shorter cervix (≤25 mm) and those with a longer cervix (>25 mm). The study authors noted that because the underlying risk of preterm birth is greater at shorter cervical lengths, absolute risk reductions are greater for women with a shorter cervix, and treatment might be most useful for this subpopulation.

The study also analyzed trials with multifetal pregnancies with no additional risk factors and found no evidence that 17-OHPC (twins or triplets, eight trials, 2253 women; RR 1.04, 95% CI, 0.92–1.18) or vaginal progesterone (twins, eight trials, 2046 women; RR 1.01, 95% CI, 0.84–1.20) reduced PTB before 34 weeks of gestation. The findings do not support the use of progestogens in unselected multiple gestation pregnancies. In multifetal pregnancies, compared with controls, 17-OHPC increased the risk of preterm premature rupture of membranes (rupture <34 weeks; RR 1.59, 95% CI 1.15–2.22), while vaginal progesterone did not increase this risk (rupture <34 weeks; RR 0.92, 95% CI 0.62–1.35).

Compared with placebo, a possible increase in composite maternal complications was observed for 17-OHPC (RR 1.17, 95% CI, 0.97–1.42) and vaginal progesterone (RR 1.14, 95% CI, 0.93–1.40), primarily due to gestational hypertension and maternal infection events, although individual outcomes were uncertain. There were no maternal deaths in any trials. These findings are based on limited data, as only four of nine vaginal progesterone trials and four of five 17-OHPC trials contributed maternal complication data. In addition, the confidence intervals for these effect sizes crossed equivalence.

These data reaffirm The Society for Maternal-Fetal Medicine's (SMFM) current guidelines that women with a singleton pregnancy and a short cervix (<25 mm) without a history of a prior sPTB be offered treatment with vaginal progesterone. Although the results of this study suggest that either 17-OHPC or vaginal progesterone appear to offer a benefit to women with a singleton gestation and either short cervix or prior sPTB, the certainty regarding the benefit, both maternal and neonatal, is greatest for vaginal progesterone. Current SMFM guidelines recommend the consideration of the use of 17-OHPC in women with a singleton gestation and a history of prior sPTB between 20 and 36 6/7 weeks of gestation. For singleton pregnancies in women with prior sPTB or short cervical length, prescription of progestogen treatment should follow a process of shared decision-making with a discussion of the benefits, potential risks, patient values, cost, limitations of the data, and logistics (eg, choice of progestogen) to maximize patient compliance and optimize pregnancy outcomes.[2] In multifetal gestations, there is insufficient evidence to recommend the use of progestogens outside clinical trials regardless of history of PTB or cervical length. SMFM will continue to review the recent and evolving evidence on the use of progestogens for the prevention of preterm birth and is currently reviewing clinical recommendations to provide additional evidence-based guidance for maternal-fetal medicine subspecialists.

References

1. EPPPIC Group. Evaluating Progestogens for Preventing Preterm birth International Collaborative (EPPPIC): meta-analysis of individual participant data from randomised controlled trials. Lancet. 2021 Mar 27;397(10280):1183-1194.

2.Society for Maternal-Fetal Medicine (SMFM) Publications Committee. SMFM Statement: Use of 17-alpha hydroxyprogesterone caproate for prevention of recurrent preterm birth. Am J Obstet Gynecol. 2020 Jul;223(1):B16-B18.

Click here to access the ACOG Practice Advisory, Clinical Guidance for the Integration of the Findings of the EPPPIC Meta-Analysis: Evaluating Progestogens for Preventing Preterm Birth International Collaborative.

All authors and committee members have filed a disclosure of interests delineating personal, professional, business, or other relevant financial or nonfinancial interests in relation to this publication. Any substantial conflicts of interest have been addressed through a process approved by the Society for Maternal-Fetal Medicine (SMFM) Board of Directors. SMFM has neither solicited nor accepted any commercial involvement in the specific content development of this publication.

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