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Updated Clinical Guidance for the Use of Progestogen Supplementation for the Prevention of Recurrent Preterm Birth

Practice Advisory | April 2023

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This Practice Advisory was developed by the American College of Obstetricians and Gynecologists with the assistance of Hyagriv N. Simhan, MD, MS; Allison Bryant, MD, MPH; Manisha Gandhi, MD; and Mark Turrentine, MD.

This Practice Advisory serves as an update to Practice Bulletin No. 234, *Prediction and Prevention of Spontaneous Preterm Birth*, originally published in 2021 [1].

This Practice Advisory is provided to address the April 6, 2023, decision by the U.S. Food and Drug Administration (FDA) to withdraw approval of Makena and its generics (17-alpha hydroxyprogesterone caproate [17-OHPC]) [2]. Additionally, this Practice Advisory serves to update the current evidence and recommendations for the use of progestogen for the prevention of recurrent preterm birth.

This Practice Advisory has been updated to remove a link to the accompanying FAQs, which have been withdrawn, and to incorporate information about compounding.

The American College of Obstetricians and Gynecologists (ACOG) guidance regarding the use of progestogen for the prevention of preterm birth is included in ACOG Practice Bulletin No. 234, "Prediction and Prevention of Spontaneous Preterm Birth" [1]. Updated recommendations are:

- Vaginal progesterone may be considered as a treatment option for patients with a history of preterm birth, singleton gestation, and a shortened cervix. However, vaginal progesterone has not been proven effective in the absence of a shortened cervix and should not be considered as an alternative to 17-OHPC.
- Intramuscular 17-OHPC is not recommended for the primary prevention of preterm birth in patients with a history of spontaneous preterm birth.
- Dependent upon cervical length measurement, prior pregnancy history, and past treatment, a discussion of the range of interventions available to prevent a recurrent preterm birth should occur and a collaborative action plan should be developed.

With regard to the use of prophylactic 17-OHPC specifically for the prevention of recurrent preterm birth, the FDA's assessment of the current body of evidence concluded that there were not sufficient data to indicate that this was an effective treatment in the broad population it was originally approved for—all pregnant people with a prior spontaneous preterm birth between 20 and 37 weeks of gestation. Whether this intervention would be useful in a subset of people requires future study. The FDA does not seem to base its decision on safety concerns. Although compounding remains an option, the FDA's decision to withdraw approval of Makena will significantly impact access to and availability of 17-OHPC for the prevention of preterm birth. Compounded drugs, including those containing hydroxyprogesterone caproate, do not undergo FDA premarket review for safety, effectiveness, or quality. Regulatory concerns in some states or potential limited coverage by medical insurance carriers may result in limited access to compounded medications in some regions of the country.

Another important update to the evidence pertains to the use of vaginal progesterone for prevention of recurrent preterm birth in asymptomatic people. The results of a meta-analysis and an additional recently published study evaluating vaginal progesterone to prevent recurrent preterm birth found that vaginal progesterone was not associated with a reduction in recurrent preterm birth **3** **4** . As a result, ACOG's guidance is updated via this Practice Advisory to recommend that in the setting of a singleton pregnancy with a history of prior spontaneous preterm birth, and in the absence of a shortened cervix, vaginal progesterone should not be offered as a prevention option. The table from the Practice Bulletin is updated and is included in this Practice Advisory **Table 1** .

In summary, at this time, the body of evidence is equivocal regarding the effectiveness of 17-OHPC, and the referenced FDA action will limit access to 17-OHPC for patients. Furthermore, the body of evidence does not indicate that vaginal progesterone is effective for the prevention of recurrent preterm birth in singleton pregnancies with a prior preterm birth between 20 and 37 weeks of gestation in the absence of a shortened cervix **3** **4** . As described in Practice Bulletin No. 234, patients with a singleton pregnancy and prior spontaneous preterm birth should be assessed with serial endovaginal ultrasound cervical length measurement **1** . Dependent upon cervical length measurement, prior pregnancy history, and past treatment, a discussion of the range of interventions available to prevent a recurrent preterm birth should occur and a collaborative action plan should be developed **Table 1** .

Preterm birth remains a significant public health issue and more evidence for effective interventions is urgently needed. The American College of Obstetricians and Gynecologists will continue to monitor the evidence as it evolves and advocate for prevention strategies for preterm birth that are effective and accessible to all patients.

Table 1. Screening and Interventions for Prevention of Preterm Birth

Cervical length ultrasound	IM 17-OHPC	Vaginal progesterone	Ultrasound-indicated cerclage	Physical-examination-indicated cerclage	Cervical pessary
Singleton pregnancy, no prior preterm birth					
Cervix should be visualized at the time of the 18 0/7-22 6/7 weeks of gestation anatomy assessment	Not indicated	Recommended for cervical length equal to or less than 25 mm	Insufficient data: possibly of benefit if the cervical length is less than 10 mm	Consider	Not indicated
Singleton pregnancy, prior spontaneous preterm birth					
Serial (every 1-4 weeks) endovaginal ultrasound measurement of cervical length beginning at 16 0/7 and repeated until 24 0/7 weeks of gestation	Insufficient data	Consider with a cervical length less than 25 mm (versus cerclage)	Consider with a cervical length less than 25 mm (versus vaginal progesterone if not already on progesterone supplementation)	Consider	Not indicated
Multiple gestation					
Cervix should be visualized at the time of the 18 0/7 - 22 6/7 weeks of gestation anatomy assessment	Not indicated	Insufficient data	Insufficient data	Consider	Not indicated

Abbreviations: IM, intramuscular; 17-OHPC, 17-alpha-hydroxyprogesterone caproate

Updated from Table 1 in Prediction and prevention of spontaneous preterm birth. ACOG Practice Bulletin No. 234. American College of Obstetricians and Gynecologists. Obstet Gynecol 2021;138:e65–90.

Access the Society for Maternal-Fetal Medicine statement.

Please contact clinical@acog.org with any questions.

References

1. Prediction and prevention of spontaneous preterm birth. ACOG Practice Bulletin No. 234. American College of Obstetricians and Gynecologists. Obstet Gynecol 2021;138:e65-90. doi: 10.1097/AOG.0000000000004479
   Article Locations:

2. . U.S. Food and Drug Administration. FDA Commissioner and Chief Scientist announce decision to withdraw approval of Makena. FDA; 2023. Accessed April 6, 2023. Available at: https://www.fda.gov/news-events/press-announcements/fda-commissioner-and-chief-scientist-announce-decision-withdraw-approval-makena
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3. Conde-Agudelo A, Romero R. Vaginal progesterone does not prevent recurrent preterm birth in women with a singleton gestation, a history of spontaneous preterm birth, and a midtrimester cervical length >25 mm. Am J Obstet Gynecol 2022;227:923-6. doi: 10.1016/j.ajog.2022.07.054
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4. Nelson DB, Lafferty A, Venkatraman C, McDonald JG, Eckert KM, McIntire DD, et al. Association of vaginal progesterone treatment with prevention of recurrent preterm birth. JAMA Netw Open 2022;5:e2237600. doi: 10.1001/jamanetworkopen.2022.37600
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Topics

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