

# Managing preterm birth in those at risk: Expert strategies

Four experts share what they will do in their practice for pregnant women with a history of preterm birth should the option of using 17  $\alpha$ -hydroxyprogesterone caproate be withdrawn

Obstetricians face the potential practice dilemma of having withdrawn from the market the only drug approved by the US Food and Drug Administration (FDA) for the prevention of preterm birth in women with a singleton pregnancy who have a history of singleton spontaneous preterm birth. In the recently published PROLONG (Progesterone's Role in Optimizing Neonatal Gestation) study by Blackwell and colleagues, the trial results revealed that there were no significant differences in preterm birth between women treated with 17  $\alpha$ -hydroxyprogesterone caproate (17P; Makena) and those who received placebo.<sup>1</sup> For study details and comments, see

“Progesterone supplementation does not PROLONG pregnancy in women at risk for preterm birth: What do we do now?” by Michael House, MD, and Errol Norwitz, MD, PhD, MBA, on page 36. Subsequently, the FDA's Bone, Reproductive and Urologic Drugs Advisory Committee voted 9-7 to recommend pursuit of approval withdrawal for 17P.

To assess how experienced obstetricians would manage women with previous preterm birth if 17P became unavailable, OBG MANAGEMENT conducted an informal survey. Here, 4 experts respond to the question, “What are you going to do in your practice for women with a history of a previous preterm birth if 17P is no longer an option?”

## IN THIS ARTICLE

Dr. Alex Vidaeff  
comments

[page 40](#)

Dr. Michael Ross  
comments

[page 41](#)

Dr. Errol Norwitz  
comments

[page 42](#)

## Not ready to leave behind 17P for recurrent preterm delivery



### Patrick Duff, MD

Professor  
Division of Maternal-Fetal Medicine  
Department of Obstetrics and Gynecology  
University of Florida College of Medicine  
Gainesville, Florida

Preterm delivery is arguably the most important problem in perinatal medicine. It occurs in 10% to 12% of all obstetric patients in the United States, and complications of prematurity account for the

majority of neonatal deaths. A major risk factor for recurrent preterm delivery is a prior history of spontaneous preterm delivery, with or without preterm premature rupture of membranes. Clearly, prevention of recurrence is of paramount importance.

In the Maternal-Fetal Medicine Units (MFMU) Network trial, Meis and colleagues

*The authors report no financial relationships relevant to this article.*

demonstrated a 34% reduction (relative risk [RR], 0.66; 95% confidence interval [CI], 0.54–0.81) in the risk of recurrent preterm delivery in women who received weekly 250-mg injections of 17P (also called 17-OHPC). After publication of that trial, use of 17P became accepted practice in the United States.<sup>2</sup>

The PROLONG study by Blackwell and colleagues questions the value of 17P.<sup>1</sup> In that international trial, which included 1,708 women from 41 centers in the United States and 52 outside the United States, the authors were unable to show any significant difference in the frequency of preterm delivery < 35 weeks (11.0% in the women receiving 17P and 11.5% in women receiving placebo; RR, 0.95; 95% CI, 0.71–1.26). Even when they examined the subset of women treated at US medical centers, they could not demonstrate any significant difference in treatment outcome.

At least 2 major explanations account for the discrepancy between the MFMU and the Blackwell studies. First, the participants in the PROLONG trial were clearly not at the same increased risk for recurrent preterm delivery as those in the MFMU trial. Second, in the PROLONG trial only the minority of

participants were from the United States. In fact, given the relatively low rate of recurrent preterm delivery in the PROLONG trial, the study was underpowered to detect meaningful differences in maternal outcome. Therefore, I am not ready to abandon the use of progesterone supplementation in women at risk for recurrent preterm delivery.

If the FDA removes 17P from the market, my approach with at-risk patients will be as follows:

- I will encourage all at-risk women to eliminate obvious risk factors, such as smoking, illicit drug use, and excessive physical activity.
- I will encourage optimal nutrition and appropriate weight gain.
- I will test all patients for chlamydia, gonorrhea, and bacterial vaginosis and treat women who are infected.
- After the patient completes the first trimester, I will treat her with micronized progesterone, 200 mg daily, intravaginally. I will continue this medication until 36 to 37 weeks.
- I will perform an assessment of cervical length at 16, 20, and 24 weeks' gestation. In patients with demonstrable cervical shortening, I will perform a cerclage.

### FAST TRACK

*Participants in PROLONG were not at the same increased risk for recurrent preterm delivery as those in the MFMU trial, and only a minority of PROLONG participants were from the United States*

## Rational management options for reducing risk of preterm delivery



**Alex C. Vidaeff, MD, MPH**

Professor  
Division of Maternal-Fetal Medicine  
Department of Obstetrics and Gynecology  
Baylor College of Medicine and  
Texas Children's Hospital, Pavilion for Women  
Houston, Texas

**M**ost women who experience a spontaneous preterm delivery (sPTD) do not deliver prematurely in subsequent pregnancies.<sup>3</sup> Two recent systematic reviews, in 2014 and 2017, found an overall risk of recurrent sPTD of 20.2% and 30%, respectively.<sup>4,5</sup> These numbers are closer to the background event rate of 21.9%

in the PROLONG trial, while only a few women have a recurrence risk of more than 50%, as in the Meis MFMU trial.<sup>1,2</sup> A public health recommendation cannot be made for an intervention that is expected to work only in rare cases and fail in a majority of cases. Therefore, 17P is no longer a viable option for preventing recurrence in pregnant

women with a history of sPTD, with only rare possible exceptions.

What evidence-based alternatives can be offered to pregnant women who had a previous sPTD?

Ultrasound assessment of cervical length has emerged as an effective prognosticator for recurrence in women with a prior sPTD, being able to predict 65.4% of sPTDs at a false-positive rate of 5%.<sup>6,7</sup> Furthermore, sonographic cervical length measurements identify high-risk women who may not need any intervention. It has been shown that, among women with prior sPTD who maintain a normal cervical length up to 24 weeks, more than 90% will deliver at 35 weeks or after without intervention.<sup>8</sup>

In the United States, interventions to reduce sPTD, once a short cervix has been identified, include vaginal progesterone supplementation and cerclage. The benefit from vaginal progesterone has been documented by an individual patient data meta-analysis, while the benefit of cerclage has been highlighted in a Cochrane Review.<sup>9,10</sup> The results of an adjusted indirect comparison meta-analysis suggest that both interventions are equally effective.<sup>11</sup> Therefore, the decision

on how best to minimize the risk of recurrent sPTD must be individualized based on historical and clinical circumstances, as well as the woman's informed choice.

Based on current data, the following approach appears rational to me:

- Cervical ultrasound surveillance between 16 and 24 weeks' gestation to identify the subgroup of women at significantly increased risk of sPTD recurrence.
- With cervical length  $\leq$  25 mm, vaginal progesterone supplementation may be considered. Preferential consideration for progesterone may be given when lower genital tract inflammation is suspected, given the possible anti-inflammatory action of progesterone.<sup>12,13</sup>
- If cervical shortening progresses to 15 to 20 mm, cerclage may be considered. Waiting for a cervix  $<$  15 mm may be unadvisable. In conditions of a very short cervix, frequently dilated, with exposure of the fetal membranes, ascending subclinical intra-amniotic infection already may be present, reducing the efficacy of cerclage. Preferential consideration for cerclage also may be given with 2 sPTDs or mid-trimester losses or with a history of a successful cerclage.

### FAST TRACK

*It has been shown that, among women with prior sPTD who maintain a normal cervical length up to 24 weeks, more than 90% will deliver at 35 weeks or after without intervention*

## Screen cervical length early, and use cerclage or vaginal progesterone as appropriate



**Michael G. Ross, MD, MPH**

Distinguished Professor of Obstetrics and Gynecology and Public Health  
Geffen School of Medicine at UCLA and  
Fielding School of Public Health at UCLA  
Los Angeles, California

In patients with a history of a previous preterm birth, if 17P is no longer an option, I would revert to screening for short cervix with transvaginal ultrasound.

Screen all high-risk patients at the first prenatal visit, so as not to miss a short cervix before 16 weeks' gestation. Then, beginning

at 16 weeks, screen every 2 weeks until approximately 24 weeks.

If the cervix shortens to 25 mm or less, offer cerclage or vaginal progesterone. If the cervix shortens to 20 mm or less, I would strongly support cerclage or vaginal progesterone.

CONTINUED ON PAGE 42

# Use of 17P is still an option, for now



**Errol R. Norwitz, MD, PhD, MBA**

Louis E. Phaneuf Professor of Obstetrics and Gynecology  
 Tufts University School of Medicine  
 Chief Scientific Officer  
 Chair, Department of Obstetrics and Gynecology  
 Tufts Medical Center  
 Boston, Massachusetts

**T**he way in which 17P was handled by the FDA is exactly the way the system is designed to work; this should be seen as a success, not a failure.

Given the urgent need for an intervention to prevent preterm birth, the lack of any alternative, and a single, well-designed randomized controlled trial that confirmed safety and suggested some benefit, the FDA approved 17P supplementation in February 2011 for a limited indication only—one or more prior unexplained sPTD—using the expedited review mechanism.<sup>2</sup> Under this mechanism, a follow-up clinical trial is required to confirm efficacy. This was the PROLONG trial, which failed to show any significant benefit of 17P supplementation in terms of either preterm birth prevention or neonatal outcome.<sup>1</sup>

In October 2019, an FDA advisory committee met again to review these and other data. After presentations from a range of stakeholders and a robust discussion, the advisory

committee voted to pursue approval withdrawal of 17P due to the lack of consistent evidence of benefit (it is important to note that this was not because of safety concerns). This is exactly the way the process is designed to work.

Where does this leave physicians and patients? It is clear that progesterone supplementation is not a panacea for preterm birth prevention and is not indicated for all women at high risk, even those with one or more prior unexplained sPTDs. Given that preterm birth is a syndrome and not a single diagnosis, it is still possible that there is a subgroup of women who may benefit from this intervention. For this reason—and because there is no clear alternative and no known downside to the administration of this drug (other than cost)—physicians still may choose to discuss this option with their patients and, after counseling, patients still may choose to accept it. If in doubt, engage the “shared decision-making model”; talk to your patients. ●

## FAST TRACK

*Given that preterm birth is a syndrome and not a single diagnosis, it is still possible that there is a subgroup of women who may benefit from 17P*

### References

- Blackwell SC, Gyamfi-Bannerman C, Biggio JR, et al. 17-OHPC to prevent recurrent preterm birth in singleton gestations (PROLONG study): a multicenter, international, randomized double-blind trial. *Am J Perinatol*. 2019. doi:10.1055/s-0039-3400227.
- Meis PJ, Klebanoff M, Thom E, et al; for the National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network. Prevention of recurrent preterm delivery by 17 alpha-hydroprogesterone caproate. *N Engl J Med*. 2003;348:2379-2385.
- Jams JD, Goldenberg RL, Mercer BM, et al; National Institute of Child Health and Human Development Maternal-Fetal Medicine Units. The Preterm Prediction Study: recurrence of spontaneous preterm birth. *Am J Obstet Gynecol*. 1998;178:1035-1040.
- Kazemier BM, Buijs PE, Mignini L, et al; EBM CONNECT. Impact of obstetric history on the risk of spontaneous preterm birth in singleton and multiple pregnancies: a systematic review. *BJOG*. 2014;121:1197-1208.
- Phillips C, Velji Z, Hanly C, et al. Risk of recurrent spontaneous preterm birth: a systematic review and meta-analysis. *BMJ Open*. 2017;7:e015402.
- Owen J, Yost N, Berghella V, et al; National Institute of Child Health and Human Development Maternal-Fetal Medicine Units. Mid-trimester endovaginal sonography in women at high risk for spontaneous preterm birth. *JAMA*. 2001;286:1340-1348.
- To MS, Skentou CA, Royston P, et al. Prediction of patient-specific risk of early preterm delivery using maternal history and sonographic measurement of cervical length: a population-based prospective study. *Ultrasound Obstet Gynecol*. 2006;27:362-367.
- Berghella V, Seibel-Seamon J. Contemporary use of cervical cerclage. *Clin Obstet Gynecol*. 2007;50:468-477.
- Romero R, Conde-Agudelo A, Da Fonseca E, et al. Vaginal progesterone for preventing preterm birth and adverse perinatal outcomes in singleton gestations with a short cervix: a meta-analysis of individual patient data. *Am J Obstet Gynecol*. 2018;218:161-180.
- Alfirevic Z, Stampalija T, Medley N. Cervical stitch (cerclage) for preventing preterm birth in singleton pregnancy. *Cochrane Database Syst Rev*. 2017;6:CD008991.
- Conde-Agudelo A, Romero R, Da Fonseca E, et al. Vaginal progesterone is as effective as cervical cerclage to prevent preterm birth in women with a singleton gestation, previous spontaneous preterm birth, and a short cervix: updated indirect comparison meta-analysis. *Am J Obstet Gynecol*. 2018;219:10-25.
- Sakai M, Shiozaki A, Tabata M, et al. Evaluation of effectiveness of prophylactic cerclage of a short cervix according to interleukin-8 in cervical mucus. *Am J Obstet Gynecol*. 2006;194:14-19.
- Vidaeff AC, Ramin SM, Gilstrap LC, et al. Impact of progesterone on cytokine-stimulated nuclear factor-kappa B signaling in HeLa cells. *J Matern Fetal Neonatal Med*. 2007;20:23-28.