Progesterone for preterm delivery prevention

Three cases explore the questions of yay or nay and appropriate administration routes

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IN THIS ARTICLE

Researchers have been studying the use of exogenous progestins for prevention of preterm delivery (PTD) for almost 60 years, but conflicting results contribute to an ongoing debate. Interpretation of the available data is particularly difficult because different forms and doses of progestins have been used in disparate study populations.

Based on available data, progesterone supplementation is not effective as a primary prevention strategy for PTD in the general low-risk obstetric population. PTD is a complex problem with varied and incompletely elucidated pathogenic pathways, making it unlikely that one interventional approach would be effective for all pregnant women. As a result, emerging indications for the use of progesterone are based on risk factors for PTD (ie, prior PTD and/or short cervix). However, this secondary prevention approach is a limiting factor in itself because 50% of women destined to have a PTD have no identifiable risk factors.[1] In addition, researchers have found that progestins are ineffective at delaying delivery for women with multiple gestation, suggesting that a distinct underlying mechanism of early parturition is present in these women, and that this mechanism is unresponsive to progestins.[2]

The formulations used in the study of progestin supplementation for PTD prevention have been almost exclusively either the synthetic 17 alpha-hydroxyprogesterone caproate (17-OHPC) or natural progesterone administered orally or vaginally. In 2003, the American College of Obstetricians and Gynecologists (ACOG) supported the use of progesterone to reduce the rate of PTD,[3] and in 2011, the US Food and Drug Administration (FDA) approved 17-OHPC for use as prophylaxis against recurrent PTD. As a result, in recent years, the perceived standard of care for a majority of practitioners in the United States had been that all women with a previous preterm birth should be offered 17-OHPC. It may be interesting to note that in other parts of the world, the same enthusiastic adoption did not occur. For example, in Australia and New Zealand in 2007, only 5% of practitioners were using progesterone for this indication.[4] Further, 17-OHPC is not recommended by professional guidelines in the United Kingdom and has remained unavailable in Germany.

The publication in 2019 of the PROLONG trial called into question the use of 17-OHPC for the prevention of PTD.[5] In the December 2019 issue of *OBG Management* ("Managing preterm birth in those at risk: Expert strategies"), I expressed the opinion that with

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only rare exceptions, 17-OHPC is no longer a viable option for recurrent PTD prevention.[6] In light of these developments, what scientific evidence is relevant and applicable to the care of women at risk for PTD?

CASE 1 Previous spontaneous PTD at 31 weeks

MC is an asymptomatic 32-year-old woman with a singleton pregnancy at 13 weeks' gestation. You see her for a maternal-fetal medicine consultation because 2 years ago she had a spontaneous PTD at 31 weeks' gestation. What management recommendations can you make to decrease her risk of recurrent PTD?

Cervical length measurement narrows in on risk

The indication "previous preterm birth" is largely meaningless because of the heterogeneity in preterm birth pathways (preterm birth as a syndrome[7]) and inadequate risk characterization. Among women who experience a spontaneous PTD, 70% to 80% do not deliver prematurely in subsequent pregnancies.[8] To better characterize the risk of PTD recurrence, ultrasound assessment of cervical length should be used. Research has shown that among women with a prior spontaneous PTD who maintain a normal cervical length until 24 weeks' gestation, more than 90% will deliver at 35 weeks or after without intervention.[9] Such an approach not only identifies the subgroup of women at significantly increased risk of recurrence but also eliminates unnecessary interventions.

Cervical ultrasound surveillance should be initiated at 16 weeks' gestation. A short cervix before 16 weeks is not associated with a statistically significant increase in risk for PTD.[10] Shortening of the cervix begins approximately 10 weeks before delivery in any gestational age group.[11] Therefore, ultrasound assessment of the cervix at 28 weeks and after is irrelevant. In addition, after 28 weeks, cervical length varies greatly leading to loss in the predictive power of the cervical measurement.[12] Based on these considerations, cervical surveillance may be extended up to 26 weeks. Although cervical cerclage is not an option in the United States in cases in which a short cervix is detected between 24 and 26 weeks, vaginal progesterone supplementation may still be considered.

CASE 1 Continued

MC was started on ultrasound cervical surveillance at 16 weeks' gestation. Her cervical length was initially normal (> 2.5 cm), but at 18 weeks the measurement was 2.2 cm. What is your recommendation?

The value of vaginal progesterone

There appears to be increasing consensus on the value of vaginal progesterone for women with a midtrimester short cervix on sonography, with or without a history of PTD. An individual patient data meta-analysis demonstrated the benefits of vaginal progesterone.[13] Although there was no evidence of an effect on PTD at less than 37 weeks, the rates of PTD at less than 36 weeks and spontaneous PTD at less than 34 weeks were significantly reduced (by 20% and 28%, respectively). Also, there was a significant reduction in the risk of respiratory distress syndrome (53%) and composite neonatal morbidity and mortality (41%), with no significant impact on infant development up to the second year of life.[13]

The lack of generalizable evidence of benefit on childhood outcomes, combined with considerable uncertainty about the exact role and mechanism of action of exogenous progestins, contribute to the ongoing debate. Vaginal progesterone dosage regimens have been based on extrapolations from experience with progesterone in nonpregnant women, and recent pharmacokinetic studies have revealed how precarious such extrapolations may be. As an example, in nonpregnant women, the bioavailability of oral and vaginal progesterone is similar.[14] In pregnancy, however, while daily oral progesterone doubles a pregnant woman's serum progesterone level,[15] daily vaginal administration of progesterone results in only a modest rise in serum

FAST TRACK

Most (90%) of women with prior PTD who maintain a normal cervical length until 24 weeks will deliver at or after 35 weeks' gestation without intervention

progesterone, with a coefficient of variation among individuals that is double that outside of pregnancy.[16] It is, therefore, considered that vaginal progesterone in pregnancy may have a local action secondary to the uterine first-pass effect. The uterine first-pass effect for vaginal progesterone was described in nonpregnant women and is only assumed to occur in pregnancy as well.[17]

After evaluating the data from the largest available study of vaginal progesterone,[18] the FDA concluded in 2012 that the study did not meet the statistical significance generally expected to support the approval of a new product. However, according to a more comprehensive evidence review developed in 2019 by the National Guideline Alliance in the United Kingdom, women with a history of PTD and women with a short cervix derive an important benefit from the use of vaginal progesterone; thus, this intervention should be offered to them.[19] At this time, a short cervix and PTD prevention are not considered FDA-approved indications for progesterone supplementation in pregnancy. However, vaginal progesterone is FDA approved for use in pregnant women with a history of infertility.

FAST TRACK

Limited observational data seem to suggest that vaginal progesterone plus cerclage have added benefit

CASE 1 Continued

MC initiated treatment with daily vaginal progesterone at 18 weeks' gestation and returned for ultrasound cervical length examination weekly instead of every other week. At 20 weeks' gestation, cervical length was 2.0 cm; the following week it was 1.4 cm. What would you recommend at this point?

When to consider cerclage

If cervical shortening progresses to about 1.5 cm while a woman is being treated with vaginal progesterone, cerclage may be considered. The benefit of cerclage in patients with prior PTD and a short cervix was highlighted in a 2018 Cochrane Review.[20] In this stepwise management approach to a short cervix, waiting for a cervix to be less than 1.5 cm may be unadvisable. Under conditions of a very short cervix that is frequently dilated with exposure of fetal membranes, ascending subclinical intra-amniotic infection may already be present, reducing the efficacy of any preventive measures. Preferential consideration for cerclage from the start over initial vaginal progesterone also may be appropriate when there is a history of 2 spontaneous PTDs or mid-trimester losses, a history of a successful cerclage, or with a very short cervix (< 1.0 cm) at the initial evaluation. As for the latter, a 2018 individual patient data meta-analysis of vaginal progesterone found no benefit when the cervix was less than 1.0 cm.[13]

Progesterone plus cerclage likely to add benefit

The results of an adjusted indirect comparison meta-analysis suggest that both interventions—vaginal progesterone and cerclage—are equally effective.[21] Assuming that there is no clinically meaningful difference in benefit associated with these 2 treatments, the next logical question is whether combining the 2 therapies provides any added benefit; limited observational data seem to suggest that it does. In a retrospective cohort of 86 consecutive singleton pregnancies among women who underwent ultrasound-indicated cerclage, those who used vaginal progesterone after cerclage (n = 45) had a lower rate of PTD.[22] Also, a small (66 cases) case-control study demonstrated the benefit of administration of vaginal progesterone as a rescue intervention in women with cerclage and progressive cervical shortening despite cerclage.[23]

CASE 2 Woman experiences adverse effects from vaginal progesterone

MS is a 25-year-old G2P0101 who was started on vaginal progesterone as prophylaxis for recurrent PTD. She is now at 20 weeks' gestation, with a stable remnant cervical length of 2.0 cm. She is reporting an increasing vaginal burning sensation and vaginal discharge caused by the nightly vaginal progesterone applications, to the point that she is unwilling to continue the treatment. She asks if any alternatives to vaginal progesterone are available to decrease her risk of PTD.

Is oral progesterone an option?

In the 1980s and 1990s, oral micronized progesterone was widely used in France at doses of 900 to 1,200 mg/d for women at risk for PTD. The practice was stopped when secondary hepatic effects, including cholestasis of pregnancy, were reported at a higher rate in treated women.[24] A rise in the serum concentration of progesterone metabolites has been associated with impaired biliary excretion and subsequent accumulation of bile acids.[25] In other reports, elevated serum transaminase activity was found in pregnant women treated with oral micronized progesterone, and withdrawal of treatment frequently has led to improvement in transaminase levels.[26] The synthesis of endogenous progesterone during normal pregnancy is between 250 and 500 mg/d,[26] and experts have expressed concern that exogenous progesterone supplementation may impose an additional load on the hepatic transport of sulfated metabolites. Unlike orally administered progesterone, progestins given by the vaginal route avoid the hepatic first-pass effect. For this reason, they may be associated with less hepatic dysfunction.

Although not recommended by professional guidelines, oral progesterone administration for the prevention of PTD has been used in the United States. A 2015 survey of Wisconsin prenatal care providers found that of those who prescribed any progesterone for PTD prevention, oral progesterone was prescribed by 13.1% of obstetricians, 24.4% of midwives, and 40.7% of family medicine practitioners.[27]

Some limited recent evidence from a meta-analysis of 3 trials investigating oral progesterone versus placebo suggests effectiveness in the prevention of recurrent PTD and reduction in perinatal morbidity and mortality.[15] However, the number of cases included in the meta-analysis (386) was too small to support definitive clinical recommendations. Furthermore, questions have been raised in the literature about the reliability of the largest trial included in that meta-analysis.[28]

CASE 3 Two previous spontaneous PTDs

A 29-year-old G3P0201 presents for her first prenatal appointment at 10 weeks' gestation. With her first pregnancy she had a spontaneous PTD at 23 weeks, and the neonate did not survive. In her second pregnancy, she was treated with 17-OHPC from 16 weeks' gestation. She had a spontaneous PTD at 29 weeks, and that child is developing normally by her report. She believes that 17-OHPC helped her in her last pregnancy and is anxious about the risk for still another PTD. Consistent with the concept of shared decision-making, you inform her of the results of the recent PROLONG trial and statements on the subject released by professional organizations such as ACOG and the Society for Maternal-Fetal Medicine (SMFM). What options does she have?

17-OHPC may be a possibility in very high-risk women

According to a SMFM statement released in the wake of the PROLONG trial publication, ". . . SMFM believes that it is reasonable for providers to use 17-OHPC in women with a profile more representative of the very high-risk population reported in the Meis trial".[29] Only a few women will have a recurrence risk of PTD over 50%, as was the background event rate in the Meis trial.[30] Such a risk level may be suspected, as an example, in women with 2 or more prior early (before 34 weeks) PTDs without intervening term deliveries. Even in those cases, if treatment with 17-OHPC is decided upon, ultrasound cervical surveillance should be added as an additional safety measure. ●

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Progestins given by the vaginal route avoid the hepatic first-pass effect and may be associated with less hepatic dysfunction than orally administered progesterone

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CONTINUED ON PAGE 36

CONTINUED FROM PAGE 35

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