Progesterone supplementation shared decision making

Progesterone may reduce the risk of another preterm birth after a prior preterm birth (20-36&6 weeks) that happened after preterm labor (PTL) or premature preterm rupture of membranes (PPROM). Progesterone can be given in many ways. The most studied form is:

Hydroxyprogesterone caproate 250 mg intramuscular injections weekly from 16-36 weeks (also known as 17-alpha-hydroxyprogesterone caproate or 17OHPC)

What do we know about progesterone and recurrent preterm birth?

In 2003, the Meis trial suggested a 1/3rd reduction in recurrent preterm birth with the use of 17OHPC – it was such a powerful effect that the study was stopped early. 17OHPC was given provisional FDA approval and was universally recommended/ adopted by about 2012. Although the studied name brand drug was expensive (~$10,000 per pregnancy), less expensive compounded alternatives do exist (~$200 per pregnancy) and preterm birth is very expensive in terms of both money and risk to family wellbeing.

In 2019, the PROLONG trial designed to evaluate the FDA's provisional approval saw no benefit of progesterone supplementation in reduction of recurrent preterm birth. The FDA advisory panel voted 9 to 7 to withdraw provisional approval. The FDA has not taken any such action yet.

In response, the leading organizations of obstetrics and high risk obstetrics (ACOG and SMFM) made statements:

ACOG: "Consideration for offering 17-OHPC to women at risk of recurrent preterm birth should continue to take into account the body of evidence for progesterone supplementation, the values and preferences of the pregnant woman, the resources available, and the setting in which the intervention will be implemented."

SMFM: "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."

What were the differences between the two study groups?

The most important difference between the two groups seems to be that the Meis group was much higher risk. What made them higher risk? Many had multiple preterm births, earlier preterm births (<32-35 weeks) and were smokers. Although the Meis study included many more African American women and we know race is a substantial risk factor for preterm birth, subgroup analysis failed to show the strong benefit of 17OHPC for African American women, so it is unclear whether race should be considered an important difference between these two groups.

Is there other data to consider?

In 2018, a study was published looking at preterm birth rates before and after use of progesterone and also found about a 1/3rd reduction in preterm birth. As a possible risk, however, patients getting progesterone had almost twice the risk of gestational diabetes. Otherwise, data supports safety in pregnancy but whether there are long term risks, such as metabolic risks to the child (risk of diabetes, obesity, etc) is unknown. Also, presenting for weekly shots from 16-36 weeks during a pandemic may carry additional risks.

Are there other options to consider to assess or reduce my risk?

Natural or micronized progesterone used vaginally nightly from 16-36 weeks
Preparations include 200mg suppositories (Prometrium), 100mg tablets (Endometrin) and 90mg gel (Crinone)

These may be reasonable alternatives and have been proven beneficial in some patients with short cervix, but data is limited on their impact on recurrent preterm birth risk.

A **transvaginal cervical length** can help assess your risk and **cerclage** is an important intervention for some patients.

OF NOTE: Subcutaneous progesterone HAS NOT been adequately studied and IS NOT recommended as an alternative.

Spong CY, Meis PJ, Thom EA, et al. Progesterone for prevention of recurrent preterm birth: impact of gestational age at previous delivery. Am J Obstet Gynecol 2005; 193:1127.
Blackwell SC, Gyamfi-Bannerman C, Biggio JR Jr, et al. 17-OHPC to Prevent Recurrent PTB in Singletons (PROLONG Study): A Multicenter, International, Randomized Double-Blind Trial. Am J Perinatol 2020; 37:127.
Quist-Nelson J, Parker P, Mokhtari N, et al. Progestogens in singleton gestations with preterm prelabor rupture of membranes: a systematic review and metaanalysis of RCTs. Am J Obstet Gynecol 2018; 219:346.

What should I do?

Have you had more than one preterm birth?

Were your preterm births at <32-35 weeks?

Do you smoke?

Have you previously had a better outcome in a pregnancy while using progesterone?

Would you take comfort in feeling like you were "doing everything you can"?

→ Possibly more likely to benefit

→ Strongly consider progesterone supplementation from 16-36 weeks

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Do you have a history of just one prior preterm delivery closer to 37 weeks?

Do you have a history of term deliveries without progesterone?

Are you a non-smoker?

Was your previous preterm delivery twins?

Do you like to avoid medications if possible?

→ Less likely to benefit

→ Do not initiate progesterone supplementation at 16 weeks

Are you and your family members at higher risk for metabolic problems?
(Obesity, history of diabetes in self or family, etc)

→ Consider the potential risks and benefits to make your decision

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Are you interested in progesterone supplementation but want to avoid injections or the risk of getting the injections during the pandemic?

→ Vaginal progesterone seems to be a reasonable alternative to IM

(SubQ NOT recommended)

Was your prior preterm delivery at <34 weeks?

→ Transvaginal cervical length measurement

→ If your cervix measures <2.5 cm Your doctor will talk to you about cerclage

It is unclear whether progesterone helps if you need a cerclage

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Provider notes on TVCL:
Low risk patients (no prior deliveries before 34w): universal screening around 20w is reasonable – if TVCL <2.5cm at <24w →start vaginal progesterone and refer for high risk consult for reassessment, periviable counseling, etc.
High risk patients (history of PTB at 32-34w for PTL or PPROM): screening indicated, recommend single screen around 20w – if TVCL <3cm → follow-up in 1 week, if TVCL <2.5cm → high risk consult for cerclage
Highest risk patients (history of PTB at <32w for PTL or PPROM): screening indicated, recommend serial screening between 16-22w – if TVCL ≥3cm →reassess in 2-3 weeks, if TVCL <3cm → follow-up in 1 week, if TVCL <2.5cm → high risk consult for cerclage

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