Boston Medical Center Maternity Care Guideline
Guideline: Prevention of Recurrent Spontaneous Preterm Birth
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Background Information

Introduction

Progesterone administration has been shown to decrease the risk of subsequent preterm birth in women with a history of a prior spontaneous preterm birth.

Spontaneous preterm birth for is defined as birth from **16w0d– 36w6d** gestation that results from *spontaneous* onset of contractions and includes PPROM. A delivery will be considered a spontaneous preterm birth even if labor was subsequently augmented or cesarean delivery was required, as long as spontaneous contractions proceeded these interventions. In addition, for the purposes of this guideline, deliveries due to preterm prelabor rupture of membranes (PPROM) or suspected abruptions will also be considered spontaneous preterm births.

Patients with a spontaneous pregnancy loss in the second trimester have a 10.8% risk for either another second trimester loss or preterm birth in a subsequent pregnancy. Based on this data, Markham et al included women with a prior pregnancy loss starting at 16 weeks gestation in their study looking at preterm birth prevention on a population level using progestins. This study using this criteria found a decrease in preterm birth with progesterone therapy.

Diagnosis

- A thorough obstetrical history should be taken at the initial prenatal visit and documented in the appropriate portion of the electronic medical record.
    - If preterm birth discovered, provider should clarify if it was iatrogenic or spontaneous. Key examples:
        - IOL at 34/36+6 for PPROM qualifies as spontaneous preterm birth (SPTB)
        - SAB >15 weeks GA DOES qualify
        - CS for bleeding previa preterm does NOT qualify
        - IOL for bleeding, NRFHT, preeclampsia preterm does NOT qualify

- A separate problem of “History of Preterm birth” should be added to the problem list and the plan of care should be documented there

Treatment/Management

1. <u>Progesterone therapy</u>

Women with a history of a prior spontaneous birth should be offered progesterone treatment to decrease the risk of a subsequent preterm birth.

- **Injection:** The preferred treatment is 17-OH progesterone caproate (17-OHP) 250 mg intramuscular or 17-OHP 275mg subcutaneous qweek starting at 16-20 weeks until 36 weeks.
- **Vaginal Suppository:** Only **if** 17-OHP is not available, has unacceptable side effects, or declined by the patient, vaginal progesterone will be offered, 200 gm nightly from 16 -36 weeks. This conversation should happen in the context of an MFM consult.
    - Allergy alert: (Abbott Laboratories, Abbott Park, IL), is a capsule approved for oral use but may be used as a vaginal suppository. **The capsule contains peanut oil so all patients need to be screen for peanut allergies prior to administration**. In addition, compounded suppositories may also be used if available.
- A note on Oral Progesterone: Oral progesterone is the least studied route for the prevention of recurrent preterm and *neither ACOG nor SMFM endorses the use of oral progesterone for the prevention of recurrent preterm birth*. BMC MFM will not be recommending oral progesterone.

2. <u>Cervical ultrasound</u>

- In those patients with a preterm birth prior to 35 weeks, we recommend vaginal cervical length every two weeks, starting at 16 weeks through 23 weeks.
    - Referral to ATU should always indicate all relevant history. If h/o spontaneous preterm birth is indicated the patient will be booked automatically.
- If the cervical length is less than 25 mm, cerclage will be offered by MFM and care transferred to MFM
    - *If a patient is on 17-OH PG due to a prior preterm birth and develops a short cervical length, there is **no data** to suggest she should change to vaginal progesterone. She should continue taking 17-OH PG weekly*

3. <u>Cerclage</u>

If the cervical length is less than 25 mm, cerclage will be offered

NB: Cerclage placement has only been demonstrated to be beneficial in pregnancies with a cervical length less than 2.5 cm in the setting of a prior preterm birth less than 34 weeks. However, since documentation is lacking regarding prior preterm births in a significant number of our patients, we elected to include weeks 34 and 35 in this surveillance group.

Logistical Practice for BMC and CHC providers

A. Referral for history of spontaneous preterm birth

1. Provider reviews obstetric history and identifies spontaneous preterm birth
2. Provider places referral for MFM consult in EPIC – indicate h/o spontaneous preterm birth
    a. It is reasonable to order Makena at this point if the provider is comfortable with the history and the patient agrees. If prenatal provider orders the Makena at a CHC, they will follow their own workflow and be responsible for the prior auth
3. Patient will be booked for a telemedicine consult with MFM to discuss recommendations and engage in shared decision making.

B. Logistics of implementing recommendations

1. **Makena** - If Makena is recommended and the patient gets care at BMC or any CHC *other than East Boston* the MFM will place the order for Makena.
    a. Care at YACC – IM Makena
        i. MFM will place a therapy plan so the patient can have the nurse administer the weekly injection at YACC
        ii. MFM will message ASR to book patient for RN visits at YACC for weekly injections
    b. Care at YACC – SC Makena (home auto-injector)
        i. If the patient prefers home injections, the MFM will order the sc 275mg formulation to dispense 5 per time for total of 20
            1. Mail order pharmacy preferred
                a. Send Rx to the BMC Cornerstone pharmacy
                b. Indicate in free text that patient is a CHC patient:
                c. Indicate to mail to home or CHC
            2. Pick up from pharmacy preferred
                a. MFM will send Rx to the BMC Yawkey pharmacy
                b. Indicate in free text that patient is a CHC patient
            3. Do not send to alternate pharmacy unless there is an independent plan to complete the prior authorization paperwork.
        ii. MFM will message ASR to book patient for an RN visit at YACC to teach her how to self-inject
    c. Care at CHC (*Not EB*) –

    If CHC provider would like to start the process of ordering Makena prior to the MFM consultation, that CHC team will be responsible for filling out the Prior Auth etc. If a provider would like to wait for the MFM visit, the MFM can follow the workflow below

        i. IM Makena
            1. Clarify if patient wants Makena mailed to her home address or

CHC address or if she wants to pick it up at BMC every month

2. MFM will order Makena 250mg IM syringes to dispense 5 per time for total of 20
    a. Mail order pharmacy preferred
        i. Send Rx to the BMC Cornerstone pharmacy
        ii. Indicate in free text that patient is a CHC patient:
        iii. Indicate to mail to home or CHC
    b. Pick up from pharmacy preferred
        i. MFM will send Rx to the BMC Yawkey pharmacy
        ii. Indicate in free text that patient is a CHC patient
    c. Do not send to alternate pharmacy unless there is an independent plan to complete the prior authorization paperwork.
3. Patient receives at home/CHC and brings to their CHC for weekly injections

ii. SC Makena (home autoinjector)
1. If patient opts for home injections, the MFM will order Makena 275mg sc to dispense 5 per time for total of 20
    a. Mail order pharmacy preferred
        i. Send Rx to the BMC Cornerstone pharmacy
        ii. Indicate in free text that patient is a CHC patient:
        iii. Indicate to mail to home or CHC
    b. Pick up from pharmacy preferred
        i. Send Rx to the BMC Yawkey pharmacy
        ii. Indicate in free text that patient is a CHC patient
    c. Do not send to alternate pharmacy unless there is an independent plan to complete the prior authorization paperwork.
2. MFM will message ASR to book patient for an RN visit at YACC to teach her how to self inject with either first autoinjector device or demo device

iii. MFM will EPIC message referring provider to communicate plan for Makena acquisition

iv. At cervical lengths, MFM will do chart review/check with patient to ensure getting Makena

2. **Cerclage** – surgery will be arranged by MFM
    a. Prophylactic cerclage: arranged by MFM during consult; case dependent.
        i. Patient may return to care at original site but needs to be cared for or comanaged by OB/Gyn MD.

    b. US indicated cerclage: Determined at ATU visit, real time consultation with MFM.
        i. If a patient is ultimately found to have a short cervix and gets a cerclage, their care should be transferred to MFM.

Patient Education/Helpful links

https://www.marchofdimes.org/complications/progesterone-treatment-to-help-prevent-premature-birth.aspx - Single sheet handout in English and Spanish from March of Dimes

http://mombaby.org – Printable booklet in English and Spanish from UNC

Appendix

- Tables/diagrams

Comment on literature review:

Since the release of **The Progestin's Role in Optimizing Neonatal Gestation** (**PROLONG**) trial, there has been many questions regarding the role of 17-hydroxy progesterone caproate (17-OHPC) use to prevent recurrent preterm birth. This study enrolled over 1700 women from 93 sites in 9 countries (about 25% from the US). This study found no benefit of 17-OHPC.

There are some differences between the PROLONG trial and the Meis trial (which is the basis our current recommendations for the use of 17-OHPC in women with a prior preterm birth). Important for our population, the Meis trial included 59% of black women compared to the PROLONG trial of 7%. The risk of preterm birth in the controls in the Meis trial was 55% compared to 23% in the PROLONG trial.

Based on the available data which suggests that the patient population may partially explain some of the differences in outcomes between the Meis original study and the recent PROLONG study, SMFM suggests: *"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. For all women at risk of recurrent sPTB, the risk/benefit discussion should incorporate a shared decision-making approach, taking into account the lack of short-term safety concerns but uncertainty regarding benefit."* (See Appendix 2)

Since our BMC population is similar to the Meis study, we recommend that 17-OHPC offered to all of our patients with a prior preterm birth, however, a discussion regarding recent data refuting this benefit is appropriate.

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Appendix 1 – ACOG Practice Advisory

Practice Advisory: Clinical guidance for integration of the findings of the PROLONG study: Progestin's Role in Optimizing Neonatal Gestation

A trial comparing the efficacy of 17-alpha-hydroxyprogesterone caproate (17-OHPC) 250 mg intramuscular injection weekly compared with placebo on both preterm birth and neonatal morbidity among women with a singleton pregnancy and prior spontaneous preterm birth was published in the American Journal of Perinatology on October 25, 2019 (1). The study was a large international multicenter, randomized, controlled, double blind trial conducted from November 2009 to October 2018 that evaluated 1,877 eligible women, of which 1,740 provided informed consent and underwent randomization. The trial was conducted at 93 facilities across 9 countries associated with a hospital that had access to a Level 3 or greater Neonatal Intensive Care Unit. Twenty-three percent of women were enrolled from the United States. Women were randomized between 16 0/7 to 20 6/7 weeks of gestation with greater than 91% of participants adhering to the assigned protocol, with no differences in the number of study medication injections between those receiving 17-OHPC or placebo (both groups with a median of 18, range 1-22).

This study demonstrated no statistical difference in the co-primary outcome of preterm birth less than 35 0/7 weeks of gestation (17-OHPC 11.0% versus 11.5%; Relative Risk [RR] 0.95 [95% CI 0.71-1.26]; *P* = 0.72) and neonatal composite index (17-OHPC 5.6% versus 5.0%; RR 1.12 [95% CI 0.70-1.66]; *P* = 0.73). Similarly, the rate of preterm birth less than 37 weeks and less than 32 weeks were not different. No other differences in perinatal or maternal outcomes were detected. However, despite having the same eligibility criteria and study protocol as the trial by Meis et al in 2003 that provided randomized trial evidence for 17-0HPC for the prevention of recurrent preterm birth (2), the patient populations had divergent sociodemographic characteristics and a substantially lower preterm birth rate when compared with the prior study (1, 2). Based on these results, the authors suggest that the PROLONG trial was underpowered to assess treatment efficacy related to preterm birth and neonatal outcomes in this population. Further, due to guidance published in 2008, a possible unintentional selection bias may have occurred in women enrolled in the United States that resulted in women with a higher risk for recurrent preterm birth not being offered or agreeing to participate in the PROLONG study in order to avoid the risk of not receiving active 17OPHC treatment.

Current guidelines in the United States recommend the use of progesterone supplementation in women with prior spontaneous preterm birth (3). 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. Additional information from planned meta-analysis and secondary analyses will need to be evaluated to assess the impact this intervention has on women at risk of recurrent preterm birth in the United States. ACOG is not changing our clinical recommendations at this time and continues to recommend offering hydroxyprogesterone caproate as outlined in Practice Bulletin # 130, Prediction and Prevention of Preterm Birth (3).

ACOG will be reviewing subsequent forthcoming analyses and will issue updated clinical guidance as appropriate.

This Practice Advisory was developed by the American College of Obstetricians and Gynecologists' Committee on Practice Bulletins—Obstetrics in collaboration with Mark Turrentine, MD, Anjali Kaimal, MD, MAS, Hyagriv Simhan, MD, and Aaron B. Caughey, MD, PhD.

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3. Prediction and prevention of preterm birth. Practice Bulletin No. 130. American College of Obstetricians and Gynecologists. Obstet Gynecol 2012;120:964-73.

Additional Resources

Practice Bulletin 130 Prediction and Prevention of Preterm Birth
Practice Bulletin 171 Management of Preterm Labor
Committee Opinion 713 Antenatal Corticosteroid Therapy for Fetal Maturation
Committee Opinion 652 Magnesium Sulfate Use in Obstetrics
Obstetric Care Consensus 6 Periviable Birt

Appendix 2: **SMFM Statement: Use of 17-alpha hydroxyprogesterone caproate for prevention of recurrent preterm birth Society for Maternal-Fetal Medicine (SMFM) Publications Committee**

Recurrent spontaneous preterm birth (PTB) is a major public health problem. The strongest predictor of PTB is a prior spontaneous preterm birth (sPTB). Spontaneous PTB recurs in up to 50% of women, tends to recur at similar gestational ages, and is more likely to recur with an increased number of prior sPTBs (1, 2). Given the significant adverse outcomes associated with PTB, strategies have been developed to attempt to reduce the risk of recurrence. One of the most commonly employed strategies is the use of supplemental progestogens, including intramuscular (IM) 17-alpha hydroxyprogesterone caproate (17-OHPC), which was approved by the US Food and Drug Administration in 2011 to reduce the risk of PTB in women with a singleton pregnancy who have a history of singleton sPTB.

The potential effectiveness of 17-OHPC for the prevention of recurrent sPTB was evaluated by Meis et al. in a multicenter, double-masked, randomized controlled trial of 17-OHPC or placebo in 463 US women with singleton gestations at risk for recurrent sPTB, published in 2003 (3). They found a 34% reduction in the incidence of recurrent PTB at <37 weeks of gestation with 17-OHPC treatment (from 54.9% to 36.3%, adjusted relative risk [RR] 0.66, 95% confidence interval [CI], 0.54-0.81). The study also demonstrated significant reductions in PTB at <35 and <32 weeks of gestation, in addition to significant reductions in some neonatal complications (intraventricular hemorrhage, necrotizing enterocolitis, and a need for supplemental oxygen) in those receiving 17-OHPC. The study was stopped early based on prespecified criteria after demonstration of efficacy at the second interim analysis; 70% of the planned sample was analyzed.

The data regarding the benefit of 17-OHPC are otherwise relatively limited. A recent meta-analysis of 17-OHPC vs placebo or no treatment for prevention of recurrent PTB identified four randomized clinical trials, including Meis, as well as three smaller studies. This meta-analysis reported a 29% (RR 0.71; 95% CI, 0.53–0.96; P=0.001), 26% (RR 0.74; 95% CI, 0.58–0.96; P=0.021), and 40% (RR 0.60; 95% CI, 0.42–0.85; P=0.004) reduction in recurrent PTB at <37, <35, and <32 weeks, respectively, in the 17-OHPC group compared with placebo or no treatment (4). In contrast, a recent historical cohort identified no decrease in rates of PTB since the introduction of 17-OHPC. Although these data are mixed, they generally support a benefit of 17-OHPC in the reduction of PTB.

Following the Meis publication, initial guidance from the American College of Obstetricians and Gynecologists and the Society for Maternal-Fetal Medicine (SMFM) recommended treatment with either 17-OHPC or vaginal progesterone to prevent recurrent PTB for women with a prior sPTB (5). Most recently, in 2017, SMFM reaffirmed its recommendation that women with a singleton gestation and a history of prior sPTB between 20 and 36 6/7 weeks of gestation receive 17-OHPC 250 mg IM weekly from 16 to 20 weeks of gestation until 36 weeks of gestation or delivery (6).

The Progestin's Role in Optimizing Neonatal Gestation (PROLONG) trial was a double-blind, placebo-controlled, international trial conducted from 2009–2018 to attempt to confirm that weekly IM injection of 250 mg of 17-OHPC from 16 to 36 weeks of gestation decreases recurrent PTB and neonatal morbidity in women with a prior sPTB in a singleton gestation. This trial enrolled women from 93 sites in 9 countries, with approximately 25% of women from the United States. The co-primary outcomes were PTB at <35 weeks of gestation and composite neonatal morbidity or mortality. PROLONG enrolled over 1700 women and was powered to detect a 30% reduction in PTB at <35 weeks of gestation with a baseline assumption of 30% recurrent PTB rate among women in the placebo arm (7).

The results of the PROLONG trial found no benefit of 17-OHPC compared with placebo in reaching either of the co-primary outcomes. The rate of PTB at <35 weeks of gestation did not differ between the progesterone and placebo arms and was notably much lower than anticipated (11% vs 11.5%, RR 0.95, 95% CI, 0.71-1.26; p=0.7). The neonatal composite outcome also did not differ between groups (5.4% vs 5.2%, RR 1.05, 95% CI, 0.68-1.61; p=0.8). Of note, the rate of PTB at <37 weeks of gestation (which was the primary outcome of the Meis trial) was 23.1% and 21.9% for the 17-OHPC and placebo groups, respectively (RR 1.06, 95% CI, 0.88-1.28). 3

P=0.021), and 40% (RR 0.60; 95% CI, 0.42–0.85; P=0.004) reduction in recurrent PTB at <37, <35, and <32 weeks, respectively, in the 17-OHPC group compared with placebo or no treatment (4). In contrast, a recent historical cohort identified no decrease in rates of PTB since the introduction of 17-OHPC. Although these data are mixed, they generally support a benefit of 17-OHPC in the reduction of PTB.

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In comparing the discordant results of the PROLONG and Meis trials, one consideration is the different populations studied, especially with respect to the baseline risk for PTB. These differences include characteristics of the prior PTB(s), as well as additional demographic and reproductive characteristics. Approximately 90% of the PROLONG patients were white and 7% were black; 90% were married; and substance use was infrequent, with about 8% reporting smoking tobacco in pregnancy. In contrast, the Meis trial included 59% black women, of whom approximately 50% percent were married, and over 20% reported smoking. In the Meis trial, 32% of women had >1 prior PTB compared with only 12% in the PROLONG trial, and 91% of women had at least one additional risk factor for PTB (aside from the prior PTB) compared with 48% in PROLONG. These substantial differences in population are reflected in the significantly different baseline rates of PTB in the two trials, with 54.9% recurrent PTB at <37 weeks of gestation in the placebo group in Meis vs 21.9% in PROLONG. Of note, the Meis trial has been criticized because more patients in the placebo arm had >1 prior PTB compared with the 17-OHPC arm (41.2% vs 27.7%; p=0.004). However, analysis with adjustment for this difference did not change the primary findings (3).

Preterm birth is a complex disorder with heterogeneous etiologies and associated underlying mechanisms in different women (8-10). Therefore, substantial differences in the populations studied likely account for the different baseline rates of recurrent PTB and potentially explain some of the contrasting results observed in the Meis and PROLONG trials. Other observational studies of “real world” use of 17-OHPC have also reported that the rate of recurrent PTB and response to treatment is dependent on the population and context (11). However, while differences in the populations enrolled may have contributed to the different outcomes in these two studies, population differences do not completely explain the discrepancy. Specifically, while black race is a known risk factor for PTB and more women in the Meis trial were black, studies have demonstrated an association between nonresponse to 17-OHPC and black race, thus contradicting this argument (12). Another factor possibly associated with the disparate outcomes include the potential for bias in the Meis trial introduced by the higher rate of multiple prior PTBs in the placebo compared with the study arm, although again, the benefit of 17-OHPC remained after adjustment for this difference. 4

Results of both the Meis and PROLONG trials indicate that 17-OHPC appears to be safe, at least in the short term, with no increase in congenital anomalies or evidence of teratogenic effects seen in either of these studies or suggested in other reports (13, 14). Long-term outcomes are unknown, although long-term adverse effects have not been reported. The PROLONG study plans a two year follow up study of the childhood outcomes.

In summary, differences in study populations between the Meis and PROLONG trials likely contribute to different baseline levels of risk of PTB and may partially explain the differences in response to 17-OHPC. While some women have a higher risk of recurrent sPTB, and factors such as race, number of prior PTBs, and gestational age at prior PTB are associated with recurrence, specific criteria for quantifying risk, interactions between risk factors, and optimal management of at-risk women are not well understood. Further, patient-level criteria for determining potential response to 17-OHPC have yet to be confirmed.

Based on the evidence of effectiveness in the Meis study, which is the trial with the largest number of US patients, and given the lack of demonstrated safety concerns, 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. For all women at risk of recurrent sPTB, the risk/benefit discussion should incorporate a shared decision-making approach, taking into account the lack of short-term safety concerns but uncertainty regarding benefit. It is important to consider that 17-OHPC is associated with substantial health care costs, injection-site pain, and extra patient visits (15, 16) and that long-term potential maternal and neonatal effects are unknown. The lack of benefit from 17-OHPC seen in the PROLONG trial raises questions regarding the efficacy of 17-OHPC, and additional studies are needed to identify populations in which administration of 17-OHPC may provide needed benefit in the reduction of recurrent sPTB. SMFM will continue to closely follow advances in this area to assure optimal care for women and to provide guidance for maternal-fetal medicine subspecialists. 5

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From the Society for Maternal-Fetal Medicine, Washington, DC
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