Indian Health Service

IHS National Pharmacy and Therapeutics Committee

Progesterone Use in Preterm Birth Prevention

October 2013

Background:

The IHS National Pharmacy and Therapeutics Committee (NPTC) reviewed progesterone use in the prevention of preterm birth (PTB) at the August 2013 meeting. The review was conducted in conjunction with Jean Howe, MD, MPH, IHS Chief Clinical Consultant in Obstetrics & Gynecology. This discussion included clinical and utilization data for this medication. Although a formulary modification was not undertaken, NPTC supports the procurement of progesterone for prevention of preterm labor for appropriately selected candidates at sites offering maternity care.

Discussion:

Preterm birth (PTB), or delivery before 37 weeks, occurred in 11.7% of births in the U.S. in 2011 and accounted for 85% of perinatal mortality and morbidity. Acute preterm labor is difficult to treat and pregnancy often cannot be prolonged beyond 48 to 72 hours. Successful PTB prevention has been demonstrated with the use of progesterone prophylaxis in selected high-risk pregnancies.[1] An AHRQ-sponsored comprehensive review found that the use of progesterone decreased the risk of neonatal death by half and the risk of a recurrent PTB by one third.[2]

Identified risk groups for preterm birth include women with a history of spontaneous preterm birth in a prior pregnancy and women with a shortened cervix seen by ultrasound in the current pregnancy. Two key trials have shown benefit using progesterone for recurrent PTB prevention. A trial by Da Fonseca included high-risk women with history of spontaneous singleton PTB, uterine malformation, or cervical cerclage. The women were randomized to placebo or 100mg progesterone suppositories from gestational weeks 24-34. The progesterone group resulted in decreased risk of PTB (3% treated vs. 19% in the placebo group delivered at <34 wks).[3] A second trial by the Maternal Fetal Medicine Units Network included women with a history of a spontaneous singleton PTB. Patients were randomly assigned to either placebo or compounded hydroxyprogesterone caproate 250mg IM weekly beginning at gestational weeks 16–20 and continuing until 36 weeks. The results of this trial showed a significant reduction of the risk of PTB in the progesterone groups (11 vs. 20% at < 32 wks and 21 vs. 31% at < 35 wks).[4]

A meta-analysis of 5 RCTs investigating vaginal progesterone vs. placebo in patients with cervical shortening showed a decrease in PTB at <28, <33, and <35 weeks. This benefit was shown in women with cervical length of 10-20mm, regardless of history of prior PTB and was similar at 90, 100, and 200mg daily doses.[5] In contrast, no significant reduction in PTB was shown in a trial by Grobman in which women with a cervical length <30mm in gestational weeks 16-22 were randomized to 250mg IM 17-hydroxyprogesterone caproate or placebo until week 36.[6] Also, in O'brien et al, the largest randomized trial comparing vaginal progesterone gel (90mg) daily treatment to placebo showed no significant difference in PTB rate. This was initiated between gestation weeks 18 and 23 and continued until week 37.[7]

Large systematic reviews have shown favorable results using progesterone in PTB. A recent Cochrane review concludes that progesterone use in women with previous spontaneous PTB is associated with a decreased risk of perinatal death, PTB, and other fetal risks. In women with cervical shortening diagnosed via ultrasound, progesterone is associated with decreased risk of PTB but an increased risk of urticaria. While progesterone is recommended, the optimal dose, route of administration, and time to initiate therapy for these indications is unclear.[8]

As illustrated above, a variety of agents and routes of administration have been studied. In 2012 ACOG recommended that women with prior spontaneous PTB be offered progesterone supplementation for PTB prevention, regardless of cervical length, beginning at 16-24 gestational weeks and continuing through 36 weeks. For patients with cervical shortening of 20mm or less by 24 weeks of gestation, vaginal progesterone is recommended for PTB prevention in those with a singleton gestation without prior PTB.[9] (For women with both a history of PTB *and* cervical shortening in the current pregnancy, surgical placement of a cervical cerclage is to be considered.) There is unclear evidence regarding the use of progesterone in the following: Prior PTB of twins, current multiple gestation pregnancy, pregnancy associated with assisted reproductive technology (ART), uterine anomaly, preterm premature rupture of membranes, positive fetal fibronectin test, acute preterm labor or after cerclage placement.

In 2011, the FDA approved Makena, a weekly IM progesterone injection ($330 per injection). IM progesterone injections are also available from compounding pharmacies ($22 per dose). Vaginal progesterone requires daily administration and is available as an 8% gel, a micronized tablet, or compounded as a vaginal suppository. Practically, the choice of agent and route may be guided by individual expert consultation, patient and provider preference, and local availability.

Findings:
There is clinical merit to the use of progesterone in appropriate patients and it should be made accessible to patients at IHS sites providing maternity care. Although Progesterone was not added by the NPTC to the National Core Formulary, many clinicians, along with the current ACOG opinion statement, support a strategy of progesterone use to prevent PTB and progesterone agents should be made available based on individual patient criteria. When indicated, the clinical benefits clearly outweigh the risks of treatment for most patients. The NPTC will continue to watch the clinical data, utilization, and procurement data for this class for future consideration.

If you have any questions regarding this document, please contact the NPTC at nptc1@ihs.gov.

References:

1. Norwitz ER. Progesterone supplementation to reduce the risk of spontaneous preterm birth. In: UpToDate, Basow, DS (Ed), UpToDate, Waltham, MA, 2013.
2. Likis FE, Andrews JC, Woodworth AL, et al. Progestogens for Prevention of Preterm Birth. Comparative Effectiveness Review No. 74. (Prepared by the Vanderbilt Evidence-based Practice Center under Contract No. 290-2007-10065-I). AHRQ Publication No. 12-EHC105-EF. Rockville, MD: Agency for Healthcare Research and Quality. September 2012. www.effectivehealthcare.ahrq.gov/reports/final.cfm.
3. Da Fonseca EB, Bittar RE, Carvalho MH, Zugaib M. Prophylactic administration of progesterone by vaginal suppository to reduce the incidence of spontaneous preterm birth in women at increased risk: a randomized placebo-controlled double blind study. *Am J Obstet Gynecol*, 2003; 188: 419-424.
4. 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-hydroxyprogesterone caproate. *N Engl J Med* 2003; 348:2379-85.
5. Romero R, Nicolaides K, Conde-Agudelo A, et al. Vaginal progesterone in women with an asymptomatic short cervix in the midtrimester decreases preterm delivery and neonatal morbidity: a systematic review and meta-analysis of individual patient data. Am J Obstet Gynecol 2012; 206:124.e1-19.
6. Grobman WA, Thom EA, Spong CY, et al. 17 alpha-hydroxyprogesterone caproate to prevent prematurity in nulliparas with cervical length less than 30 mm. *Am J Obstet Gynecol*. 2012;207(5):390.e1-8.doi: 10.1016/j.ajog.2012.09.013.
7. O'brien JM, Adair CD, Hall DR, et al. Progesterone vaginal gel for the reduction of recurrent preterm birth: primary results from a randomized, double-blind, placebo-controlled trial. Ultrasound Obstet Gynecol. 2007:30(5)687.
8. Dodd JM, Jones L, Flenady V, Cincotta R, Crowther CA. Prenatal administration of progesterone for preventing preterm birth in women considered to be at risk of preterm birth. *Cochrane Database of Systematic Reviews* 2013, Issue 7. Art. No.: CD004947. DOI: 10.1002/14651858.CD004947.pub3.
9. American College of Obstetricians and Gynecologists. Prediction and prevention of preterm birth. Practice Bulletin No. 130. *Obstet Gynecol* 2012;120:964-73.