

## Progesterone for the Prevention of Spontaneous Preterm Birth

### A. 17 alpha hydroxyprogesterone caproate

The incidence of preterm birth has risen progressively over the last decade from 9% to 12% of all births in the United States. Preterm birth is the second leading cause of infant mortality in this country and a significant proportion of survivors have residual disabilities. Despite multiple trials of tocolytics, antibiotics, and other preventive strategies, no effective method of preventing preterm birth has been found.

Recently, prophylactic treatment of high risk women with a history of one or more prior spontaneous preterm births with progestational compounds have demonstrated efficacy (1, 2). A prior meta-analysis (3) has also demonstrated a significant reduction in the rate of preterm delivery with the use of 17 alpha hydroxyprogesterone caproate (17P). The American College of Obstetrics and Gynecology (ACOG) has recommended that when progesterone is used, it be restricted to women with a documented history of a previous spontaneous birth at less than 37 weeks of gestation (4). Extensive experience with progesterone has shown it not to be a teratogen (5), and its use in this protocol will not involve administering it during organogenesis in the first trimester.

As a referral center, ANMC renders care to a large number of women who have experienced preterm birth, and an effective preventive treatment would be most advantageous to this population. The preterm birth rate for Alaska Native is higher than the national average, at 13.8%. Referral of these women and/or their infants to Providence Alaska Medical Center for delivery and prolonged level III newborn intensive care generates significant expenditures for the institution that could be avoided by prevention of the problem.

#### Eligible Patients:

- 1) Asymptomatic women with a documented history of one or more prior spontaneous preterm births (less than 37 weeks gestation).
- 2) Spontaneous preterm birth may have been due to idiopathic preterm labor, preterm premature rupture of membranes, cervical insufficiency, or abruption, not associated with hypertensive disease or recreational drug use or other indicated preterm birth.
- 3) Women are ideally identified prior to 20 weeks gestation, and have been dated by ultrasound prior to 20 weeks, and agree to return for weekly injections from 16 weeks to 36 weeks of pregnancy.
- 4) Recent evidence shows that beginning administration of 17P before 27 weeks has a beneficial effect.
- 5) Women who stop 17P therapy, and then resume it later in pregnancy, also experience a beneficial effect despite the hiatus in therapy.

#### Ineligible Patients:

- 1) Women with a history of prior preterm birth due to a known cause such as a uterine malformation or drug-associated abruption.
- 2) Women who present with symptoms of preterm labor (symptomatic uterine contractions, uterine bleeding, ruptured membranes) after 20 weeks gestation.

- 3) Women with a multi-fetal gestation.
- 4) Women with a known fetal anomaly.
- 5) Women with a prior indicated preterm birth (as a result of severe preeclampsia, placenta previa, fetal demise, or threatening maternal medical illness).

Drug Treatment Protocol:

- 1) Weekly intramuscular injection of 17-hydroxyprogesterone caproate (17P) 250 mg\* from 16 through 36 weeks of gestation.
- 2) If the 17P patient develops a short cervix, then continue 17P
- 3) If 17P is not available, then use vaginal 100 mg progesterone suppository

## B. Vaginal Progesterone Therapy for Women with a Short Cervix

There is some newer evidence that progesterone 200 mg vaginal suppositories daily may be of benefit in preventing preterm birth in women found to have a short cervix (less than 2.0 cm, with or without funneling) on ultrasound. These studies have included women with multiple gestation (for whom both cerclage and 17P have not been found to be beneficial), and those with a history of cervical insufficiency.

For example if a transvaginal cervical length at 24 weeks is:

- a.  $>2.0$  cm, no MFM consult needed
- b.  $\leq 2.0$  cm, may be vaginal progesterone candidate. Consult MFM.

While routine transvaginal cervical length at 24 weeks is not currently recommended, if, at any gestational age, a routine US done for other reason detects a short cervix, then discussion with Maternal Fetal Medicine is suggested. This can include further evaluate the patient for treatment with vaginal progesterone, or, if prior to 24 weeks, cervical cerclage.

Short cervix < 24 weeks

- Offer cerclage
- Offer vaginal progesterone

History of cervical insufficiency with a cerclage in current pregnancy

- If patient develops a short cervix, then offer vaginal progesterone

**NB:** Women with symptomatic uterine contractions are **not** candidates for this therapy.

The dose of vaginal progesterone is 200 mg vaginal suppository nightly from discovery of the short cervix until 36 weeks.

If  $\geq 24$  wks, then individualize care. Consider MFM consult

References:

- 1) Prediction and prevention of preterm birth. Practice Bulletin No. 130. American College of Obstetricians and Gynecologists. Obstet Gynecol 2012;120:964–73. (Reaffirmed 2018)
- 2) Management of preterm labor. Practice Bulletin No. 171. American College of Obstetricians and Gynecologists. Obstet Gynecol 2016;128:e155–64. (Reaffirmed 2018)

- 3) 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, 14651858, Issue 7. 2013. (Accessed 10/15/19)
- 4) Society of Obstetricians and Gynaecologists of Canada. The Use of Progesterone for Prevention of Preterm Birth. *J Obstet Gynaecol Can* 2008;30(1):67–71
- 5) Meis PJ, et al. Prevention of recurrent preterm delivery by 17 alpha hydroxyprogesterone caproate. *N Engl J Med* 2003; 348:2379-85.
- 6) Da Fonseca EB, et al. 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; 188:419-24.
- 7) Keirse MJ. Progesterone administration in pregnancy may prevent preterm delivery. *Brit J Obstet Gynaecol* 1990; 97:149-57.
- 8) Fonseca EB, et al. Progesterone and the risk of preterm birth among women with a short cervix. *N Eng J Med* 2007; 357: 462-9.
- 9) Hassan SS, et al. Vaginal progesterone reduces the rate of preterm birth in women with a sonographic short cervix: a multicenter, randomized, double blind, placebo controlled trial. *Ultrasound Obstet Gynecol* 2011; 38:18-31.
- 10) Society for Maternal-Fetal Medicine Publications Committee, with assistance of Vincenzo Berghella. Progesterone and preterm birth prevention: translating clinical trials data into clinical practice. *Am J Obstet Gynecol*. 2012 May;206(5):376-86
- 11) How HY1, Barton JR, Istwan NB, Rhea DJ, Stanziano GJ. Prophylaxis with 17 alpha-hydroxyprogesterone caproate for prevention of recurrent preterm delivery: does gestational age at initiation of treatment matter? *Am J Obstet Gynecol*. 2007 Sep;197(3):260.e1-4.
- 12) Iams JD. Identification of candidates for progesterone: why, who, how, and when? *Obstet Gynecol*. 2014 Jun;123(6):1317-26.

Revised 10/15/19njm  
Reviewed 12/9/17njm  
Revised 10/6/15njm  
Reviewed 8/14/13njm  
Approved 9/21/11njm