

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. ≤ 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 ≥ 24 wks, then individualize care. Consider MFM consult

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NB: Here is a ‘Writer’s Embellishment’ with several FAQs

PROGESTERONE TO PREVENT SPONTANEOUS PRETERM BIRTH (SPTB)

By David E. Abel, MFM, August 2015

CURRENT SINGLETON PREGNANCY WITH HX OF SPTB OF TWINS

The data are lacking. If the twin delivery was < 32 weeks, the patient is at risk of a singleton SPTB in the next pregnancy. Options include a) no progesterone OR b) consider progesterone (vaginal) for cervix < 25 mm. The hx of SPTB would warrant transvaginal cervical lengths every two weeks from 16-24 weeks, weekly if the cervix is < 30 mm.

CURRENT TWIN PREGNANCY AND HX OF SPTB

I would recommend following just like a singleton that has a hx of SPTB. Thus, offer 17-P injections OR vaginal progesterone (100 mg). The hx of SPTB would warrant transvaginal cervical lengths every two weeks from 16-24 weeks, weekly if the cervix is < 30 mm.

CURRENT TWIN PREGNANCY, NO HX OF SPTB There is no data to support the use of progesterone in this setting.

CURRENT TWIN PREGNANCY, NO HX OF SPTB AND SHORT CERVIX There is no data to support progesterone in this setting.

IN THE PATIENT WITH A HX OF SPTB, CAN VAGINAL PROGESTERONE BE USED INSTEAD OF 17-P INJECTIONS? Yes, data exists to support either 17-P or vaginal progesterone to reduce the risk of recurrent SPTB in the patient with a history of a SPTB. A vaginal suppository dose of **100 mg** can be used.

IN A NULLIPAROUS PATIENT WITH A CERVIX <20 MM, CAN 17-P INJECTIONS BE USED INSTEAD OF VAGINAL PROGESTERONE? No, there is no data to support 17-P injections. In this case the recommended dose of vaginal progesterone is **200 mg**.

IF A PATIENT IS RECEIVING WEEKLY 17-P INJECTIONS FOR A HX OF SPTB AND HER CERVIX SHORTENS TO <20-25 MM, SHOULD YOU SWITCH TO VAGINAL PROGESTERONE? The current recommendation is NOT to switch, and continue the 17-P injections.

HOW LATE CAN WEEKLY 17-P INJECTIONS BE INITIATED? The best evidence is to start 17-P <21 weeks, however there is some data it can be beneficial if started by ≤ 27 weeks.

HOW LATE CAN VAGINAL PROGESTERONE BE INITIATED IN THE PATIENT WITH A SHORT CERVIX AND NO HX OF SPTB? There is no good data on this. I think 24 weeks or less would be reasonable, but this is just my own opinion.