



APEC Guidelines Prior Spontaneous Preterm Birth

Preterm birth is defined as delivery before 37 weeks gestation. Prematurity is the leading cause of perinatal mortality in the US and is the major reason why we lag behind other developed nations in infant mortality rates. Approximately 70% of neonatal deaths, 36% of infant deaths, and 25-50% of cases of long-term neurologic impairment in children can be attributed to preterm birth.(ACOG, 2012a) The estimated cost of preterm births exceeds \$26.2 billion annually with an average cost of care for a preterm birth ten times greater than that of a full term birth, \$32,325 to \$3,325 respectively. (CDC, 2008) In 2013, preterm birth occurred in 11.4% of 4 million births in the US and 15.1% of 58,000 births in the state of Alabama. ("March of Dimes 2014 Premature Birth Report Card," 2014) Alabama, Louisiana, Mississippi, and Puerto Rico each received a report card grade of "F" from the March of Dimes in 2014 for high preterm birth rates.

Spontaneous preterm birth (sPTB) is defined as delivery before 37 weeks as a result of spontaneous labor or rupture of membranes. Women with a prior sPTB are at high risk for another preterm birth with recurrence rates ranging from 25-50%. This risk is highest in women with a short cervix (<25 mm) with the risk inversely related to the cervical length. Studies have demonstrated the effectiveness of progesterone in the prevention of recurrent preterm birth in singleton pregnancies. (da Fonseca, Bittar, Carvalho, & Zugaib, 2003; Fonseca et al., 2007; Hassan et al., 2011; Meis et al., 2003) In a study by Owen, cerclage was found to delay preterm birth and prevent pre-viable delivery in women with a history of sPTB and a short cervical length <25 mm. (Owen et al., 2009) Current evidence does not support the routine use of progesterone in women with multiple gestations nor does it support placement of cerclage in the setting of a short cervix in multiple gestations as this may increase the risk of preterm birth by up to 50%. (Berghella et al., 2005).

Recommendations

PROGESTERONE:

- All women currently pregnant with a singleton gestation and a prior history of a singleton spontaneous preterm birth less than 37 weeks gestation should be counseled on the beneficial effects of progesterone therapy. (ACOG, 2012b) Treatment should be initiated at 16-20 weeks and continued until 36 weeks of gestation. Given the 35% reduction in recurrent sPTB, therapy should be prescribed rather than offered, using an opt-out rather than an opt-in mentality.

APEC Guidelines Prior Spontaneous Preterm Birth

- 17 α -hydroxyprogesterone caproate (17-P) IM (commercial brand Makena®) is currently the only FDA approved drug therapy available for women with a current singleton pregnancy with a history of singleton sPTB less than 37 weeks of gestation.
- 17-P **has not** demonstrated efficacy in women without a history of preterm birth who have a short cervix nor in women pregnant with multiples; thus, 17-P should **not** be used in these populations. (Caritis, Rouse, Peaceman, & et al., 2009; Combs et al., 2011; Grobman, Thom, Spong, & al., 2012; Rouse et al., 2007)
- Although the preponderance of evidence in support of progesterone for recurrent preterm birth prevention involves the use of 17-P IM, several of the vaginal progesterone trials also included women with prior preterm birth. Therefore, it is unclear whether one route of progesterone administration is more beneficial in women with prior preterm birth. In the setting of a short cervix, the vaginal route is preferred.
- Currently there is no evidence to treatment of patients who had a prior sPTB of twins or patients currently pregnant with twins who had a prior singleton PTB with 17-P prescription. There is insufficient evidence to recommend routine treatment with 17-P in either of these populations.

CERVICAL LENGTH SCREENING:

- Pregnant women with a prior history of sPTB less than 34 weeks gestation should be offered cervical length ultrasound screening at 16-18 weeks and every 2 weeks until 22 weeks of gestation. Those found to have a cervical length <25 mm are candidates for cerclage; the greatest benefit may be in those with a cervical length <15 mm. (Owen et al., 2009)
- Current evidence does not support placement of cerclage in the setting of a short cervix in multiple gestations as this may increase the risk of preterm birth by up to 50%. (Berghella et al., 2005).
- Cervical length can only be accurately assessed with a transvaginal ultrasound examination performed by an individual trained in the proper measurement of the cervical length. While this expertise may be available in some physician offices, in some cases it may be necessary to have the patient evaluated in a radiology suite familiar with this measurement or a Maternal-Fetal Medicine consultation may be considered.
- For women who have had a prior preterm birth and now have a visually abnormal cervix (e.g. cervical laceration, prior large loop excision), consideration should be given to further evaluation by a Maternal-Fetal Medicine specialist for consideration of adjunctive therapies.

APEC Guidelines Prior Spontaneous Preterm Birth

Progesterone formulations

The optimal formulation of progesterone is not known but the following were efficacious in clinical trials:

Indications for Use	Progesterone formulation	Dosage	Trial reference
Prior sPTB	17 α -hydroxyprogesterone caproate*	250mg IM weekly	(Meis et al., 2003)
Prior sPTB or short cervical length (<20 mm)	Vaginal suppositories#	100 mg vaginal suppository every night	(da Fonseca et al., 2003)
Prior sPTB or short cervical length (<20 MM)	Micronized capsules†	200 mg vaginally daily	(Fonseca et al., 2007)
Short cervical length between 10 and 20 mm	8% vaginal progesterone gel	90 mg vaginally daily	(Hassan et al., 2011)

*17-P is available through the Alabama Medicaid Pharmacy Plan as the commercial brand Makena®. For patients who have not yet received Medicaid approval, or who do not qualify for the Alabama Medicaid Maternity Care Program, 17-P can be obtained through the Makena Care Connection patient assistance program 1-800-847-3418. Compounded 17-P is available only with prior approval from Medicaid.

#Progesterone vaginal suppositories are not clinically available but can be obtained from compounding pharmacies for patients desiring that mode of therapy.

†Micronized progesterone capsules are marketed generically and are the same medication as the commercial brand Prometrium. Progesterone gel is marketed as 8% Crinone gel; it is not currently available generically. Neither of these formulations is currently FDA approved for a preterm birth prevention indication. Prometrium is covered by the Alabama Medicaid Pharmacy Plan, Crinone gel is not.

Quality Indicators/Benchmarks

- Progesterone treatment in women with a current singleton pregnancy and a prior singleton sPTB who present for care by 20 weeks of gestation.
- Cervical length ultrasound in women with a prior sPTB <34 weeks of gestation who present for care before 22 weeks.
 - APEC acknowledges that not all providers and patients will have equal access to cervical length screening according to the schedule outlined above. This indicator is being examined in order to identify opportunities to remove barriers to care and enhance resource provision to patients throughout the state.

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This document should not be construed as dictating an exclusive course of treatment or procedure to be followed.

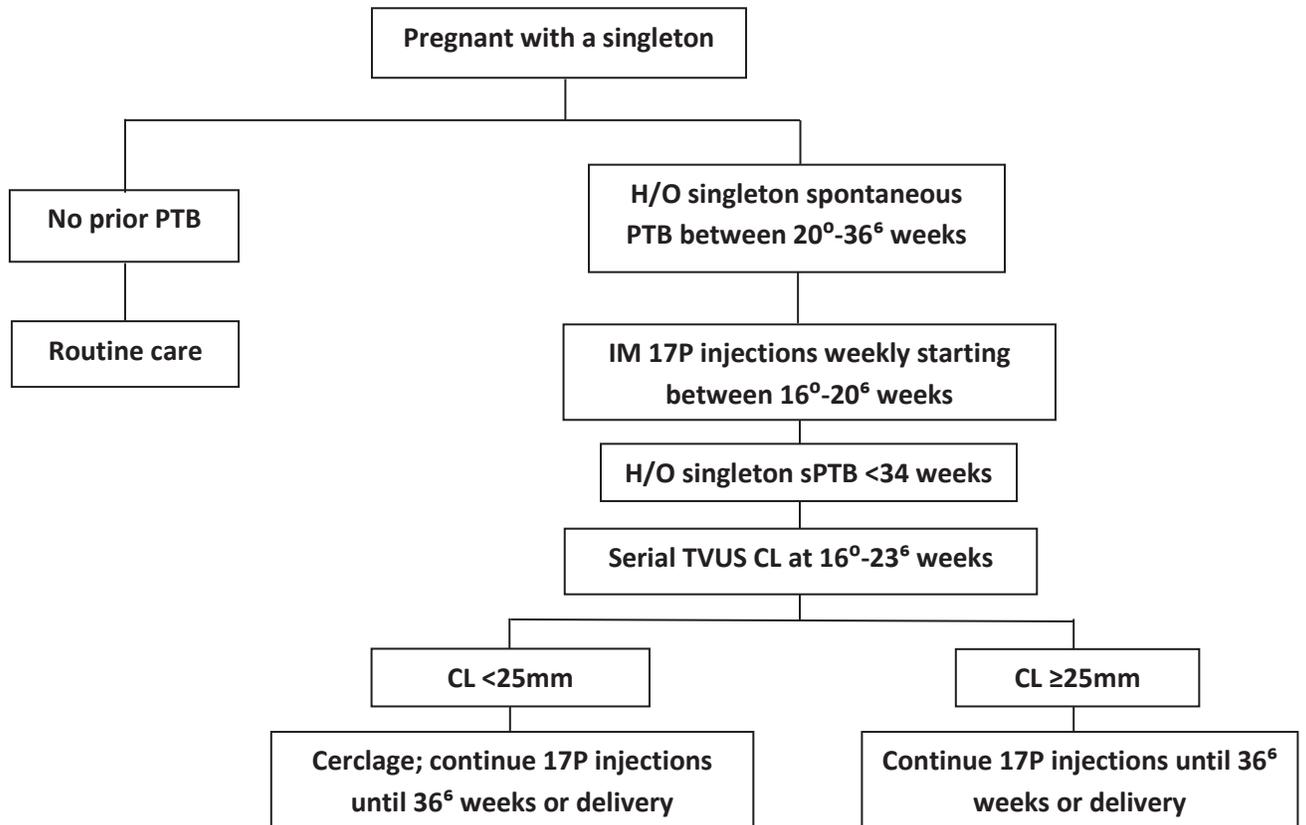
APEC Guidelines Prior Spontaneous Preterm Birth

17 α -hydroxyprogesterone caproate clinical eligibility:

- Singleton pregnancy.
- Prior singleton spontaneous preterm birth <37 weeks of gestation.

Patients must meet the FDA-approved indication for 17-P defined as current singleton pregnancy with a **history of singleton spontaneous preterm birth less than 37 weeks** of gestation.

Risk factor for preterm birth	Injectable HPC	Comments
History of singleton spontaneous preterm birth	✓	IM 17-P has been shown to be effective in women with a history of singleton SPTB <37 weeks.(da Fonseca et al., 2003; Meis et al., 2003; O'Brien, Adair, Lewis, & al., 2007) Once initiated, patients should remain on 17P injections, regardless of detection of short cervical length or use of cerclage.
Short cervix with no history of preterm birth	Not indicated	IM 17-P has not demonstrated efficacy in women without a history of preterm birth who have a short cervix.(Grobman et al., 2012)
Multiples (twins, triplets, etc.)	Not indicated	IM 17-P has not demonstrated efficacy in women pregnant with multiples.(Caritis et al., 2009; Combs et al., 2011; Rouse et al., 2007)
History of preterm birth of multiple gestation	Not indicated	IM 17-P has not demonstrated efficacy in women with a prior preterm birth of multiples.



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APEC Guidelines

Prior Spontaneous Preterm Birth

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