### Progesterone Therapy as a Technique to Reduce Preterm Birth in High-Risk Pregnancies

#### Populations
- **Individuals:** With a singleton pregnancy and prior spontaneous preterm birth before 37 weeks of gestation

#### Interventions of interest
- Intramuscular injections of progesterone
- Vaginal progesterone

#### Comparators of interest
- A different medication
- No progesterone therapy

#### Relevant outcomes include:
- Overall survival
- Morbid events
- Treatment-related morbidity

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DESCRIPTION

Preterm birth is the leading cause of neonatal morbidity and mortality and effective primary preventive interventions have remained elusive. In recent years, there has been renewed interest in the use of progesterone (injectable and intravaginal formulations) to prevent preterm birth.

Background

Preterm labor and delivery are major determinants of neonatal morbidity and mortality. In the United States, the rate of preterm birth is 12%. A variety of diagnostic and prophylactic measures to prevent preterm labor and delivery have been investigated, including home uterine activity monitoring, subcutaneous terbutaline tocolytic therapy, and routine culture and antibiotic treatment of subclinical bacterial vaginosis. To date, none of these therapies has made a significant demonstrable impact on the incidence of preterm delivery. In the past, intramuscular (IM) injections of hydroxyprogesterone caproate (ie, Delalutin) were used routinely to prevent premature labor. However, the drug has teratogenic properties, and the U.S. Food and Drug Administration (FDA) labeled it category D (ie, studies have demonstrated fetal risk, but use of the drug may outweigh the potential risk). Delalutin was voluntarily withdrawn from the market in 1999.
Recently, there has been renewed research interest in IM injection of 17α-hydroxyprogesterone caproate (17P). 17P is a weakly acting, naturally occurring progesterone metabolite, which when coupled with caproate dextran works as a long-acting progestin when administered intramuscularly. 17P has been manufactured locally by compounding pharmacies. After an extended application process, Makena, another injectable form of 17P was approved by FDA in 2011. Intravaginal progesterone gel and suppositories have also been used.

**Regulatory Status**
On February 3, 2011, Makena® (K-V Pharmaceuticals), an injectable formulation containing 17α-hydroxyprogesterone caproate was approved by the U.S. Food and Drug Administration (FDA) through the premarket approval process. The product is called Makena and is being marketed by K-V Pharmaceuticals. It is indicated to reduce preterm birth in women with a singleton pregnancy who have a history of singleton spontaneous preterm birth. Makena is not intended for women with multiple gestations or women with other risk factors for preterm birth. Injectable hydroxyprogesterone caproate had previously been approved by FDA in 1956 under the brand name Delalutin®. This product was voluntarily withdrawn from the market in 1999.

**POLICY**
A. For individuals with a singleton pregnancy and prior history of spontaneous preterm birth before 37 weeks of gestation, the following may be considered *medically necessary*:
   1. Weekly injections of 17α-hydroxyprogesterone caproate, performed in the office setting, initiated between 16 and 20 weeks of gestation and continued until 36 weeks 6 days
   2. Daily vaginal progesterone between 24 and 34 weeks of gestation

B. For individuals with a singleton pregnancy and a short cervix (< 20 mm), the following may be considered *medically necessary*:
   1. Daily vaginal progesterone initiated between 20 and 23 weeks 6 days of gestation and continued until 36 weeks 6 days

C. Progesterone therapy as a technique to prevent preterm delivery is considered *experimental / investigational* in pregnant individuals with other risk factors for preterm delivery, including but not limited to:
   1. twin or multiple gestation
   2. prior episode of preterm labor in current pregnancy (ie, progesterone therapy in conjunction with tocolysis or following successful tocolysis)
   3. positive test for cervicovaginal fetal fibronectin
   4. cervical cerclage and/or
   5. uterine anomaly
Policy Guidelines
1. Note: Appropriate training of ultrasonographers with ongoing quality assurance programs are considered critical to the accurate measurement of cervical length in the second trimester. In the trial by Hassan et al. (2011), all sonographers involved in measurement of cervical length were required to participate in a training program and to obtain certification.
2. Centers that measure cervical length may need to do an additional ultrasound during pregnancy. The ultrasound takes place between 19 weeks, 0 days and 23 weeks, 6 days of gestation.

RATIONALE
This evidence review was updated with searches of the MEDLINE database. The most recent literature review was performed through June 24, 2016. Following is a summary of the key literature to date.

Overall Effectiveness of Progesterone for Reducing Preterm Birth in High-Risk Pregnancies
Several systematic reviews and meta-analyses summarizing data on progesterone therapy to reduce preterm birth in high-risk pregnancies have been published. In 2012, Sotiriadis et al conducted a meta-analysis of randomized controlled trials (RCTs) comparing progesterone and placebo in women at high risk of preterm birth due to a history of preterm birth, short cervix during the second trimester, or multiple pregnancies. The analysis focused on neonatal and perinatal mortality rates; studies that did not report these outcomes were excluded. Neonatal mortality was defined as the number of deaths from birth to 28 days. Perinatal mortality was defined as deaths that occurred at less than 28 days of age plus fetal deaths that had a stated or presumed period of gestation of 20 weeks or more. Findings were reported separately for singleton, twin, and triplet gestations. Six trials published between 2003 and 2011 provided data for the analysis of singleton pregnancies. Three used systemic progesterone (oral or intramuscular [IM]) and 3 used vaginal progesterone. A pooled analysis of data from the studies on singleton pregnancies found a significantly lower risk of neonatal death in the group receiving progesterone versus placebo (relative risk [RR], 0.49; 95% confidence interval [CI], 0.29 to 0.82). No significant difference between groups was found for the outcome of perinatal death. A significant benefit for progesterone was also found for a composite adverse outcomes variable (RR=0.58; 95% CI, 0.37 to 0.89). The analyses of studies evaluating twin and triplet pregnancies are discussed in the next sections on these topics.

A 2016 meta-analysis by Ahn et al focused on the outcome of neonatal mortality. Twenty-two RCTs that included pregnant women treated with progesterone and that reported neonatal death met eligibility criteria. Neonatal death was defined as mortality within 1 month of delivery. Four pooled analyses were conducted: women with singleton pregnancies treated with vaginal progesterone or IM progesterone and women with multiple pregnancies treated with vaginal progesterone or IM progesterone. None of the meta-analyses found a significantly increased risk of neonatal death associated with progesterone administration versus placebo. For example, for women with singleton pregnancies treated with IM progesterone versus placebo (6 studies), the relative risk of neonatal death was 0.60 (95% CI, 0.33 to 1.09).
In 2016, Norman et al published a large multicenter double-blind RCT (the OPPTIMUM study) evaluating outcomes in women pregnant with singletons who had 1 of a number of risk factors for preterm birth. The study included 1228 women assigned to receive vaginal progesterone 200 mg daily (n=618) or placebo (n=610). Risk factors included history of preterm birth, cervical length of 25 mm or less at any time between 18 and 24 weeks of gestation, preterm premature fetal membrane rupture (PPROM), and/or history of a cervical procedure to treat abnormal smears. The study had 3 primary outcomes: (1) fetal death or delivery before 34 weeks; (2) neonatal morbidity or death; and (3) cognitive score at 22 to 26 months of age, assessed using the Bayley-III instrument. In unadjusted analyses, the progesterone group (7%) had a significantly lower rate of neonatal morbidity or death than the placebo group (10%; p=0.02) and there were no significant between-group differences for the other 2 outcomes. When analyses were adjusted for multiple primary outcomes, none of the 3 outcomes differed significantly between groups. The trial did not find a significant benefit of progesterone on the composite outcome of fetal death or preterm delivery before 34 weeks in this mixed population. However, rate of preterm delivery before 37 or 34 weeks (the primary outcome in many other RCTs) was not the sole outcome in this trial.

Singleton Pregnancy and Prior Spontaneous Preterm Birth
A 2013 Cochrane review by Dodd et al identified 11 trials on women with a previous spontaneous preterm birth; 4 used IM progesterone, 5 used vaginal progesterone, and 2 used oral progesterone. In a pooled analysis of data from 5 studies, the reviewers found that, compared with placebo, progesterone (any route) reduced the rate of preterm birth less than 34 weeks of gestation in women with a history of spontaneous preterm birth (RR=0.31; 95% CI, 0.14 to 0.69). Four of the 5 studies used vaginal progesterone and 1 used an oral formulation. Moreover, when data from 10 studies were pooled, there was a statistically significant difference in the rate of preterm birth less than 37 weeks (RR=0.55; 95% CI, 0.42 to 0.74). For the outcome preterm birth before 37 weeks, progesterone was significantly better than placebo among subsets of studies that used IM injections (n=4) and vaginal preparations (n=5).

Key RCTs focusing on women with singleton pregnancies and a previous preterm birth are described next.

IM Progesterone
In 2003, Meis et al published findings for 463 women randomized to receive weekly IM injections of 17α-hydroxyprogesterone caproate (17P) or a placebo injection. (This is the trial on which Food and Drug Administration based its approval of an injectable formulation of 17P in 2011.) Injections began at 16 to 20 weeks of gestation and continued until 36 weeks of gestation. The frequency of delivery before 37 weeks of gestation (the primary outcome) was 36.3% in the progesterone group compared with 54.9% in the placebo group. While this difference was statistically significant (p<0.001), the rate of preterm delivery in the placebo group (54.9%) was exceptionally high. The frequency of delivery before 35 weeks was 20.6% in the progesterone group and 30.7% in the placebo group; this difference was also statistically significant (p<0.02).

In 2007, follow-up data on children born during the Meis trial of 17P were published. Of the 429 infants discharged alive after birth, 278 (65%) were enrolled. Loss to follow-up occurred due to the loss of centers no longer in the network (n=81) and parents or guardians who could not be contacted (n=55) or who declined to participate (n=15). There was a 2:1 treatment ratio in the original study, resulting in the follow-up of 194 children from the 17P group and 84 from the...
control group. An average 48 months of follow-up (range, <36-60 months) found no difference in physical measures, diagnoses given by health professionals, or in caregivers’ assessments of child health.

**Vaginal Progesterone**

Three randomized trials evaluated vaginal progesterone for women with singleton pregnancies in which at least 90% of the population had a previous preterm birth.

A large multinational study (including sites in the United States) was published in 2007 by O’Brien et al.8 The study randomized 659 women with a singleton pregnancy to once-daily treatment with progesterone vaginal gel or placebo between 18 and 37 weeks of gestation. Results from 611 (93%) women showed no difference between the active and control groups for rates of preterm birth at 37 weeks or less (42% vs 41%), rates of preterm birth at 32 weeks or less (10% vs 11%), or mean gestational age at delivery (36.6 weeks vs 36.6 weeks), —all respectively. The same held for the other maternal or neonatal outcome measures. Compliance and adverse events were similar for the 2 groups.

In 2003, da Fonseca et al in Brazil reported the results of a trial that randomized 157 women with singleton pregnancies considered at high risk for preterm delivery to receive daily progesterone or placebo suppositories.9 Inclusion criteria were a prior spontaneous preterm birth or other risk factors. A total of 142 (90%) of 157 patients completed the study. Of these, 133 (93.7%) had a previous preterm birth, 5 (3.5%) had uterine malformation, and 4 (2.8%) had an incompetent cervix. The mean gestational age of the prior preterm birth was 33 weeks. The rate of delivery before 37 weeks was 13.8% in the intervention group and 28.5% in the control group. This difference was statistically significant (p<0.03). The rate of delivery before 34 weeks was 2.8% in the intervention group and 18.6% in the placebo group; this was also statistically significant in favor of the progesterone treatment group (p<0.002).

In 2009, Majhi et al in India published a trial of 100 women with singleton pregnancies and a history of spontaneous preterm birth.10 Women were randomized to receive micronized natural progesterone intravaginally via capsules (n=50) or no treatment (n=50). All participants were included in the analysis; there was no loss to follow-up. Six (6%) of 50 patients in the progesterone group and 19 (38%) of 50 patients in the control group had a preterm birth before 37 weeks; this difference was statistically significant (p=0.003). The difference in the rates of preterm birth before 34 weeks—2 (4%) in the progesterone group and 3 (6%) in the control group—was not statistically significant (p=0.64), but this analysis may have been underpowered.

An unresolved issue is whether efficacy differs by the type of formulation of the intravaginal progesterone. The O’Brien study, which had negative findings, used vaginal gel while the da Fonseca and Majhi studies, both of which had positive findings, used suppositories or capsules.

**IM Progesterone Versus Vaginal Progesterone**

Several RCTs have compared the safety and efficacy of IM and vaginal progesterone for reducing the preterm birth rate in singleton pregnancies. The trials are described next.

A 2016 trial by Elimian et al included 174 women with singleton pregnancies between 16 and 20 weeks 6 days of gestation with a history of preterm delivery.11 Patients were randomized to weekly IM injections of hydroxyprogesterone caproate 250 mg (n=82) or vaginal micronized
progesterone 100 mg daily (n=92). The study analysis was per protocol; 145 (83%) of 174 women completed the study. Among study completers, the primary outcome (the proportion of women who delivered before 37 weeks) was met by 43.9% in the IM progesterone group and by 37.9% in the vaginal progesterone group (p=0.50). Moreover, there were no statistically significant differences in secondary outcomes (eg, the proportion of women who delivered before 34 weeks or before 28 weeks).

An unblinded RCT, published in 2013 by Mahar et al, compared the safety and efficacy of vaginal and IM progesterone for reducing the rate of preterm birth in women with singleton pregnancies and a prior preterm birth.12 The study was conducted at a single center in Saudi Arabia and no industry support was reported. Participants were at a gestational age between 14 and 18 weeks, and the primary efficacy outcome was delivery before 34 weeks of gestation. A total of 518 women were randomized to receive IM progesterone (n=256) or vaginal progesterone gel (n=262). A total of 16 participants were lost to follow-up. There were 42 (16%) deliveries before 34 weeks in the vaginal progesterone group and 64 (25%) deliveries before 34 weeks in the IM progesterone group. The difference between groups was statistically significant, favoring the vaginal progesterone group (odds ratio [OR], 0.58; 95% CI, 0.37 to 0.89). Secondary maternal outcomes, including admission for threatened preterm labor, premature rupture of membranes, and use of tocolytic therapy, did not differ significantly between groups. Most secondary neonatal outcomes, including rates of neonatal death, respiratory distress syndrome, and sepsis, did not differ significantly between groups. The exception was admission to the neonatal intensive care unit, which was significantly higher in the IM progesterone group (n=64 [26%]) than in the vaginal progesterone group (n=39 [15%]; p=0.006). A significantly higher rate of adverse effects was also reported by patients in the IM progesterone group (n=35 [14%]) than in the vaginal progesterone group (n=19 [8%]; p=0.017).

Section Summary: Singleton Pregnancy and Prior Spontaneous Preterm Birth
A Cochrane review of RCTs found that progesterone (all routes of administration combined) reduced the rate of preterm birth in women with singleton pregnancies and a history of preterm birth. There is evidence from RCTs that both IM and vaginal progesterone are effective and neither route of administration is clearly superior.

Singleton Pregnancy and Short Cervical Length
IM Progesterone
A 2012 double-blind RCT by Grobman et al evaluated the efficacy of IM 17P for preventing preterm birth in women with short cervical length and who were nulliparous (ie, participants did not have a history of preterm birth).13 The study was conducted at 14 centers in the United States. Short cervix was defined as less than 30 mm between 16 weeks 0 days and 22 weeks 3 days. A total of 657 women were randomized to weekly injections of 17P (n=327) or placebo injections (n=330). No participants were lost to follow-up. The primary outcome (preterm birth before 37 weeks) occurred in 82 (25%) women in the 17P group and in 80 (24%) women in the placebo group. The difference between groups was not statistically significant (RR=1.03; 95% CI, 0.79 to 1.35). Other outcomes, including delivery before 35 weeks, gestational age at delivery, hospital visits for preterm labor, and adverse effects, also did not differ significantly between groups. The investigators initially planned to enroll 500 women in each group, but, based on interim analysis by an independent data and safety monitoring board that determined there was an extremely low probability of finding a significant difference between groups if enrollment continued, the trial was halted early.
Vaginal Progesterone
Several RCTs and a systematic review and meta-analysis of RCTs have been published. In 2012, Romero et al published a meta-analysis of individual patient data from RCTs comparing vaginal progesterone with placebo or no treatment in asymptomatic pregnant women with a sonographically confirmed short cervix (≤25 mm) in the mid-trimester.\(^{14}\) Five RCTs were included in the meta-analysis. Two of the trials, Hassan et al (2011)\(^ {15}\) and Fonseca et al (2007),\(^ {16}\) limited enrollment to women with a short cervix (defined as ≤15 mm in 1 study and 10-20 mm in the other) and the remaining studies included women with a wider range of risk factors but reported results separately for women with a short cervix. All studies were double-blind and placebo-controlled. The studies included data on 775 women; 723 (93%) had singleton pregnancies and 52 (7%) had twin pregnancies.

A pooled analysis of data from the 5 studies found that treatment with vaginal progesterone was associated with a statistically significant reduction in the risk of preterm birth before 33 weeks of gestation compared with placebo (12.4% vs 22.0%, respectively; RR=0.58; 95% CI, 0.42 to 0.80). When the analysis was limited to women with a singleton birth and no history of preterm birth, there remained a significant benefit of progesterone treatment to reduce the rate of preterm birth before 33 weeks (RR=0.60; 95% CI, 0.39 to 0.92). The Romero review also examined preterm birth outcomes for other time periods. In the analysis of all available data, rates of preterm birth before 35, 34, 30, and 28 weeks of gestation were significantly lower in the group receiving vaginal progesterone compared with placebo. The outcome of preterm birth before 36 weeks of gestation was marginally significant, and there was no significant difference between groups in the rate of preterm birth before 37 weeks of gestation (37% in the treatment group vs 43% in the placebo group).

A small, placebo-controlled RCT in women with a short cervical length (≤30 mm) and no prior preterm birth did not find a statistically significant benefit for vaginal progesterone in preventing preterm birth.\(^ {17}\) In this 2015 trial by van Os et al, the rate of preterm birth at 32 weeks was 2% in the progesterone group and 8% in the control group (RR=0.33; 95% CI, 0.04 to 3.0) and at 34 weeks it was 7.0% and 10.0%, respectively (RR=1.2; 95% CI, 0.39 to 3.5). The trial may have been underpowered; enrollment was stopped early due to an unexpectedly low number of women with a short cervix.

IM Progesterone Versus Vaginal Progesterone
In 2015, Bafgi et al published an RCT that included 78 women with singleton pregnancies who had either a short cervix (<25 mm) or a history of preterm delivery.\(^ {18}\) Randomization was done separately for the 2 subgroups. Women were assigned to weekly IM injections of 17P 250 mg or vaginal progesterone 200 mg daily. The primary outcomes were rate of preterm delivery (<37 weeks) and mean gestational age at the time of delivery. Follow-up data were available for all participants. There were no significant differences between groups on either of the primary outcome measures. In the overall study population, the rate of preterm delivery was 33.3% in the vaginal progesterone group and 30.7% in the vaginal progesterone group (p=0.088). Mean (SD) gestational age at delivery was 37.1 (2.2) weeks in the vaginal progesterone group and 36.8 (2.8) weeks in the IM progesterone group (p=0.765). In an analysis of the subgroup with a short cervix, mean age at delivery was 38.0 (1.43) years in the vaginal progesterone group and 37.6 (1.6) years in the IM progesterone group. The difference between groups was not statistically significant. However, the study was not powered to find differences at the subgroup level, which limits conclusions about use of IM progesterone in women with a short cervix.
Section Summary: Singleton Pregnancy and Short Cervical Length
Three RCTs have evaluated vaginal progesterone for preventing preterm birth in women with short cervical length. A recent meta-analysis of data from 5 RCTs found that vaginal progesterone significantly reduced the rate of preterm delivery in women with a short cervical length. In addition, there was benefit in the subgroup of women with singleton pregnancies and no prior preterm birth. One placebo-controlled RCT that assessed whether injectable progesterone is effective for preventing preterm birth in women with short cervical length was unpowered. Another RCT that compared injectable and vaginal progesterone and included women with a short cervix was also not powered to detect differences in the short cervix subgroup. Thus conclusions cannot be drawn about the comparability of the 2 delivery systems.

Twin Gestations
Several systematic reviews and meta-analyses of RCTs have not found that progesterone administration significantly reduces the rate of preterm birth or improves other health outcomes in patients with twin pregnancies.1,3,19 In 2015, Schuit et al published an individual patient data meta-analysis evaluating the effectiveness of progesterone for improving perinatal outcomes in twin pregnancies.19 The investigators identified 13 trials (total N=3668 women); 7 trials used vaginal progesterone and 6 used IM 17P. Twelve studies were placebo-controlled and the thirteenth compared progesterone with no treatment. Studies enrolled twin pregnancies at a gestational age of at least 16 weeks but less than 24 weeks of gestation. The primary outcome of the meta-analysis was a composite of perinatal mortality and severe neonatal morbidity. Among the studies on 17P, the primary outcome occurred in 423 (20%) of the children in the 17P group and 318 (17%) in the control group; the difference was not statistically significant (RR=1.2; 95% CI, 0.87 to 1.5). Rates of the primary outcome in studies on vaginal progesterone were 219 (13%) in the active treatment group and 201 (13%) in the control group. As with 17P, rates did not differ significantly between groups (RR=0.96; 95% CI, 0.83 to 1.1).

The 2013 Cochrane review (previously described)3 pooled data from 5 trials of vaginal progesterone and found no significant benefit over placebo on the rate of preterm birth at less than 34 weeks of gestation (RR=0.92; 95% CI, 0.69 to 1.23). Moreover, a pooled analysis of 7 trials (6 were limited to twins and 1 included other multiples) did not find that progesterone significantly reduced the rate of preterm birth less than 37 weeks (RR=1.04; 95% CI, 0.95 to 1.14). There was also no difference in the rate of perinatal death (RR=0.93; 95% CI, 0.45 to 1.94; 7 trials, 5 limited to twin pregnancies).

The largest RCT on twin pregnancies published to date, and with the longest follow-up, was published in 2011 by Rode et al (the PREDICT trial).20 It was conducted in Denmark and Austria. A total of 667 pregnant women with twins were randomized to receive vaginal progesterone or placebo. Treatment was initiated between 20 and 24 weeks of gestation and continued until either 34 weeks of gestation, rupture of the membranes, or delivery. The primary outcome (delivery before 34 weeks of gestation) did not differ significantly between groups. Preterm delivery before 34 weeks occurred in 51 (15.3%) of 334 women in the treatment group and 63 (18.5%) of 341 women in the control group (OR=0.8; 85% CI, 0.5 to 1.2). Similarly, there were no significant differences between groups in the rates of preterm delivery before 22, 28, 32, or 37 weeks of gestation. Rates of neonatal outcomes (eg, birthweight, neonatal death, perinatal complications) also did not differ significantly between groups. The investigators conducted follow-ups at 6 and 18 months after birth. They did not find significant differences between...
groups on children’s scores on the Ages and Stages Questionnaire, a parent-administered instrument.

Several more recent RCTs, published in 2014 and 2015, also found that progesterone did not reduce the rate of preterm birth in twin gestations. A study by Awwad et al included 293 women and used IM progesterone21 and the study by Brizot et al enrolled 390 women and used vaginal progesterone.22 A trial by Winer et al used IM progesterone but was stopped early after enrolling 105 women because interim analysis demonstrated lack of efficacy of progesterone at prolonging pregnancy.23

A 2016 study by El-refaie et al focused on women pregnant with twins who had a short cervix (20-25 mm) and used a higher dose of progesterone (400 mg) than used in previous studies.24 The trial included 322 women randomized to vaginal progesterone 400 mg daily (n=125) or to a no treatment control group (n=125). The rate of preterm labor before 34 weeks was 35.3% in the progesterone group and 52.8% in the control group (p=0.010). (The authors appeared to use the terms preterm labor and preterm birth synonymously.) The rate of preterm labor before 32 weeks also significantly favored the progesterone group, but the rates of preterm labor before 28 weeks were similar in both groups. Mean gestational age at delivery was significantly longer in the progesterone group (34.3 weeks) than in the control group (33.4 weeks; p=0.007). This is the first published RCT evaluating progesterone to prevent preterm birth in women pregnant with twins who have a short cervix and it also used a higher dose of progesterone than previous studies. Additional studies in this population, including at least 1 using a high dose of vaginal progesterone, are underway.

Section Summary: Twin Gestations
Numerous RCTs and several meta-analyses have consistently found that progesterone is not associated with decreased rates of preterm delivery and other perinatal outcomes (eg, perinatal death) in women pregnant with twins. A 2016 RCT found that a high dose of vaginal progesterone was associated with a lower rate of preterm labor than no treatment in patients with twin pregnancies and a short cervix. Additional studies (1) replicating these findings in women with both twin pregnancy and short cervix and (2) confirming the optimal dose of vaginal progesterone are needed.

Triplet Gestations
The 2012 Sotiriadis meta-analysis3 identified 2 trials on progesterone in women with triplet gestations. Pooled analyses of data from these 2 studies did not find any statistically significant differences in outcomes between women receiving progesterone or placebo. Both trials evaluated IM injections of 17P. Caritis et al randomized healthy women with triplets to receive weekly IM injections of 17P or placebo starting at 16 to 20 weeks and ending at delivery or 35 weeks of gestation.25 The primary study outcome was delivery or fetal loss before 35 weeks. A total of 134 women were randomized, with 71 assigned to 17P and 63 to placebo; none were lost to follow-up. The proportion of women experiencing the primary outcome (a composite of delivery or fetal loss before 35 weeks) was similar in the 2 treatment groups: 83% of pregnancies in the 17P group and 84% in the placebo group (RR=1.0). In the other trial, by Combs et al, which included 81 women, 56 were assigned to receive IM injections of 17P and 25 to placebo.26 Treatment started at 16 to 22 weeks of gestational age and continued until 34 weeks. There was no significant difference in the mean gestational age at delivery (31.9 weeks in
the 17P group vs 31.8 weeks in the placebo group, p=0.36). However, there were 13 mid-
trimester fetal losses in the 17P group and none in the placebo group (p<0.02).

**Section Summary: Triplet Gestations**
Two RCTs and a meta-analysis of data from these 2 trials did not find that progesterone is
associated with improved outcomes in women pregnant with triplets.

**Singleton Pregnancy and Preterm Premature Rupture of the Membranes**
In 2011, Briery et al published a study including women with singleton pregnancies diagnosed
with PPROM at 20 to 30 weeks of gestation. They were randomized to receive weekly injections
of 17P (n=33) or placebo (n=36). Two women did not finish the study, though data were
analyzed on an intention-to-treat basis. There was no significant difference between groups in
the gestational age at delivery (mean, 27.3 weeks in the progesterone group vs 29.5 weeks in
the placebo group; p=0.15). Neonatal outcomes, including birth weight, length of stay in the
neonatal intensive care unit, and neonatal morbidity and mortality, also did not differ significantly
between groups. For example, mean birth weight was 1216 grams in the progesterone group and
1396 grams in the placebo group (p=0.15).

**Section Summary: Singleton Pregnancy and Preterm Premature Rupture of the
Membranes**
The single published RCT identified did not find improved outcomes in women with singleton
pregnancies experiencing PPROM who received progesterone versus placebo.

**Singleton Pregnancy and Prior Episode of Preterm Labor in Current Pregnancy
IM Progesterone**
A 2015 systematic review and meta-analysis by Saccone et al selected RCTs that included women
with single gestations who had successfully arrested preterm labor who were assigned to
maintenance tocolysis with IM progesterone or a control intervention. Five RCTs (total N=426
women) met the inclusion criteria; 4 trials used a no treatment control and 1 used placebo. Only
1 trial was conducted in the United States. A meta-analysis of data from 3 trials (n=293 women)
did not find a significant difference between groups in the primary outcome (preterm birth before
37 weeks). Pooled rates were 42% in the progesterone group and 51% in the control group
(RR=0.78; 95% CI, 0.50 to 1.22). Pooled rates of preterm birth before 34 weeks of gestation
also did not differ significantly between groups (RR=0.60; 95% CI, 0.28 to 1.12). Findings on
secondary outcomes were mixed. Several secondary outcomes favored the progesterone group,
including having a higher mean birthweight and a later gestational age at delivery. Secondary
outcomes with similar rates between groups included the incidence of recurrent preterm labor,
neonatal death, and neonatal sepsis.

**Vaginal Progesterone**
A 2015 systematic review and meta-analysis by Suhag et al searched for RCTs that included
women with single gestations who had successfully arrested preterm labor and who were
assigned to maintenance tocolysis with vaginal progesterone or a control intervention. Five
RCTs (total N=441 women) met the inclusion criteria; 3 trials used a no treatment control and 2
used placebo. All trials were conducted outside of the United States. A meta-analysis of data from
3 trials (n=296 women) found a statistically significant difference between groups in the primary
outcome (preterm birth before 37 weeks). Pooled rates were 62% in the progesterone group and
86% in the control group (RR=0.71; 95% CI, 0.57 to 1.90). A meta-analysis of 2 trials did not
find a significant difference in the rates of preterm birth before 34 weeks (RR=0.75; 95% CI, 0.36 to 1.57). Findings were mixed on other secondary outcomes. The authors noted the general poor quality of the trials (eg, lack of blinding).

Subsequent to the systematic review search date, Martinez de Tejada et al published a multicenter, double-blind, placebo-controlled RCT on prevention of preterm delivery in women with a prior episode of preterm labor in the current pregnancy.30 The trial included 385 women successfully treated with acute tocolysis between 24 and 34 weeks of gestation. The primary efficacy outcome (preterm delivery before 37 weeks of gestation) did not differ significantly between groups. Rates were 42.5% in the progesterone group and 35.5% in the placebo group (p=0.20). Secondary outcomes, including delivery before 34 weeks, delivery before 32 weeks, and neonatal outcomes, were also similar in the 2 groups.

**Section Summary: Singleton Pregnancy and Prior Episode of Preterm Labor in Current Pregnancy**

Meta-analyses of RCTs have not definitively found that IM progesterone or vaginal progesterone reduce the rate of preterm birth or improve other outcomes. RCTs had mixed findings and methodologic limitations (eg, lack of blinding).

**Ongoing and Unpublished Clinical Trials**
Some currently unpublished trials that might influence this review are listed in Table 1.

### Table 1. Summary of Key Trials

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCT01050647</td>
<td>Progesterone for the Management of Preterm, Premature Rupture of the Membranes: A Randomized Controlled Trial.</td>
<td>40</td>
<td>Oct 2016</td>
</tr>
<tr>
<td>NCT02697331</td>
<td>Evaluation of the Role of Vaginal Progesterone in Prevention of Preterm Labor in Twin Gestation With Short Cervix: Randomized Controlled Trial</td>
<td>120</td>
<td>Oct 2016</td>
</tr>
<tr>
<td>NCT02304237a</td>
<td>Vaginal Compared With Intramuscular Progesterone for Prevention of Preterm Birth in High Risk Pregnant Women</td>
<td>360</td>
<td>Dec 2016</td>
</tr>
<tr>
<td>NCT02329535</td>
<td>Comparing Double Dose of Vaginal Progesterone to no Treatment for Prevention of Preterm Birth in Twins and Short Cervix</td>
<td>214</td>
<td>Jan 2018</td>
</tr>
<tr>
<td>NCT01004029a</td>
<td>A Phase 3B, Multi-Center, Randomized, Double-Blind Study of Hydroxyprogesterone Caproate Injection, 250 mg/mL, Versus Vehicle for the Prevention of Preterm Birth in Women With a Previous Singleton Spontaneous Preterm Delivery</td>
<td>1707</td>
<td>Nov 2018</td>
</tr>
</tbody>
</table>

NCT: national clinical trial.

a Denotes industry-sponsored or cosponsored trial.

**Summary of Evidence**

For individuals who have a singleton pregnancy and prior spontaneous preterm birth before 37 weeks of gestation who receive intramuscular injections of progesterone or vaginal progesterone, the evidence includes randomized controlled trials (RCTs) and a meta-analysis. Relevant
outcomes are overall survival, morbid events, and treatment-related morbidity. Pooled analyses of RCT data found statistically significant reductions in term birth rates with progesterone compared with placebo. Findings were similar in studies that used injectable or vaginal progesterone. The evidence is sufficient to determine qualitatively that the technology results in a meaningful improvement in the net health outcome.

For individuals who have a singleton pregnancy and a short cervix (<20 mm) who receive intramuscular injections of progesterone, the evidence includes 2 RCTs. Relevant outcomes are overall survival, morbid events, and treatment-related morbidity. A placebo-controlled RCT did not find that intramuscular progesterone significantly decreased the rate of preterm birth. An RCT comparing intramuscular and vaginal progesterone did not find a significant difference in preterm delivery in the subgroup of women with a short cervix; however, the ability to draw conclusions from this trial is limited because it was not powered for a subgroup analysis. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have a singleton pregnancy and a short cervix (<20 mm) who receive vaginal progesterone, the evidence includes several RCTs and a meta-analysis of individual patient data from the RCTs. Relevant outcomes are overall survival, morbid events, and treatment-related morbidity. A meta-analysis of RCTs found that vaginal progesterone significantly reduced the rate of preterm delivery. The evidence is sufficient to determine qualitatively that the technology results in a meaningful improvement in the net health outcome.

For individuals who are pregnant with twins who receive intramuscular injections of progesterone or vaginal progesterone, the evidence includes RCTs and systematic reviews. Relevant outcomes are overall survival, morbid events, and treatment-related morbidity. The RCTs and several meta-analyses of these studies have consistently found that progesterone is not significantly associated with decreased rates of preterm delivery or other perinatal outcomes in pregnant women with twins. One RCT found that a high dose of vaginal progesterone was associated with a lower rate of preterm delivery in women pregnant with twins who also had a short cervix; additional studies in this population are needed to confirm findings and optimal dose of medication. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who are pregnant with triplets who receive intramuscular injections of progesterone or vaginal progesterone, the evidence includes RCTs and a meta-analysis. Relevant outcomes are overall survival, morbid events, and treatment-related morbidity. Two RCTs and a meta-analysis of data from these 2 trials did not find that progesterone was associated with improved outcomes in women pregnant with triplets. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals with a singleton pregnancy and preterm premature rupture of the membranes who receive intramuscular injections of progesterone or vaginal progesterone, the evidence includes 1 RCT. Relevant outcomes are overall survival, morbid events, and treatment-related morbidity. The RCT did not find a lower rate of preterm delivery or neonatal outcomes (eg, birthweight, neonatal mortality) in women treated with progesterone versus placebo. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals with a singleton pregnancy and prior episode of preterm labor in the current pregnancy who receive intramuscular injections of progesterone or vaginal progesterone, the evidence includes RCTs and meta-analyses. Relevant outcomes are overall survival, morbid
events, and treatment-related morbidity. A meta-analysis of RCTs on intramuscular progesterone did not find significantly better outcomes compared with control interventions. A meta-analysis of RCTs on vaginal progesterone had mixed findings. The evidence is insufficient to determine the effects of the technology on health outcomes.

**Clinical Input Received From Physician Specialty Societies and Academic Medical Centers**

While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process, through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted.

**2011 Input**

Responses were received from 1 physician specialty society and 6 academic medical centers while this policy was under review in 2011. There was unanimous agreement among the academic medical center respondents that both weekly injections of progesterone and daily intravaginal progesterone may be considered medically necessary to prevent preterm births in singleton pregnancies when there is a history of spontaneous preterm birth. The physician specialty society respondent referred to the association’s clinical guideline, which stated that progesterone is recommended for women with a prior spontaneous preterm birth and that the optimal formulation is not known. Two physician respondents commented that it may be appropriate to begin vaginal progesterone earlier in pregnancy, similar to intramuscular (IM) progesterone, which is given starting between 16 and 36 weeks of gestation. One respondent commented that, while data supported the use of both IM and vaginal progesterone in women with a history of preterm birth, the data were stronger in support of IM progesterone.

There was near-consensus from academic medical center respondents that progesterone therapy may be considered medically necessary for women with a short cervix. The Hassan et al (2011)15 randomized trial was not published at the time clinical input was obtained. The input did not specify timing of vaginal progesterone in women with a short cervix.

Input was also received from 4 academic medical centers on start and stop dates. All reviewers supported the use of different start and stop dates, rather than a uniform set of dates across all formulations and indications. Most reviewers agreed with all recommended start and stop dates as written in the policy statement. For injectable progesterone, the reviewers agreed with using the U.S. Food and Drug Administration–approved start and stop dates.

**2009 Input**

Responses were received from 2 physician specialty societies and 4 academic medical centers, which responded strongly, agreeing with the policy statements as adopted in October 2009. There was unanimous agreement that injectable progesterone and vaginal progesterone may be considered medically necessary for women with a singleton pregnancy and a history of preterm delivery before 37 weeks of gestation. All but 1 response indicated there was no evidence supporting 1 mode of progesterone administration over another. The single response, from an academic medical center, that said there was a difference, commented that the Meis (2003)6 and da Fonseca (2003)9 studies differed, and thus 1 formulation may be preferred over another for a particular patient. The least amount of agreement was on short cervical length as a risk factor;
however, most providing input agreed with the current policy statement. The clinical input also raised questions about the clinical applications for cervical length measurement.

Practice Guidelines and Position Statements

American College of Obstetricians and Gynecologists
In May 2014, the American College of Obstetricians and Gynecologists (ACOG) published a Practice Bulletin on multifetal gestations that included the following statement on progesterone therapy:

- “Progesterone treatment does not reduce the incidence of spontaneous preterm birth in unselected women with twin or triplet gestations and, therefore, is not recommended.”

Previously, in October 2012, ACOG published a Practice Bulletin on prediction and prevention of preterm birth. The bulletin included the following recommendations (level A evidence) related to progesterone therapy in women with singleton pregnancies:

- “A woman with a singleton gestation and a prior spontaneous singleton birth should be offered progesterone supplementation starting at 16-24 weeks of gestation … to reduce the risk of recurrent spontaneous preterm birth.”
- Vaginal progesterone is recommended as a management option to reduce the risk of preterm birth in asymptomatic women with a singleton gestation without a prior preterm birth with an incidentally identified very short cervical length less than or equal to 20 mm before or at 24 weeks of gestation.

Society for Maternal-Fetal Medicine
A 2012 clinical guideline by the Society for Maternal-Fetal Medicine included the following conclusions and recommendations:

1. There is insufficient evidence to recommend the use of progestogens in singleton gestations with no prior PTB [preterm birth], and unknown CL [cervical length].
2. In women with singleton gestations, no prior SPTB [spontaneous preterm birth], and short TVU [transvaginal ultrasound] CL 20 mm at 24 weeks, vaginal progesterone, either 90-mg gel or 200-mg suppository, is associated with reduction in PTB and perinatal morbidity and mortality, and can be offered in these cases.
3. The issue of universal TVU CL screening of singleton gestations without prior PTB for the prevention of PTB remains an object of debate. CL screening in singleton gestations without prior PTB cannot yet be universally mandated. Nonetheless, implementation of such a screening strategy can be viewed as reasonable, and can be considered by individual practitioners. Given the impact on prenatal care and potential misuse of universal screening, stretching the criteria and management beyond those tested in RCTs should be prevented. Practitioners who decide to implement universal TVU CL screening should follow strict guidelines. Practitioners who choose to screen low-risk singleton gestations may consider offering vaginal progesterone, either 90-mg gel or 200-mg suppositories, for short TVU CL 20 mm at 24 weeks.
4. In singleton gestations with prior SPTB 20-36 6/7 weeks, 17P 250 mg IM weekly preferably starting at 16-20 weeks until 36 weeks is recommended. In these women, if the TVU CL shortens to 25mm at 24 weeks, cervical cerclage may be offered.
5. Progestogens have not been associated with prevention of PTB in multiple gestations, PTL [preterm labor], or PPROM [preterm premature rupture of membranes]. There is insufficient evidence to recommend the use of progestogens in women with any of these risk factors, with or without a short CL. Some experts offer 17P to women with a prior SPTB and a current
multiple gestation, but there are insufficient data to evaluate the risks and benefits of this intervention in this population.”

**U.S. Preventive Services Task Force Recommendations**
Not applicable.

**CODING**
The following codes for treatment and procedures applicable to this policy are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

**CPT/HCPCS**
- 96372 Therapeutic, prophylactic, or diagnostic injection (specify substance or drug); subcutaneous or intramuscular
- 99506 Home visit for intramuscular injections
- J1725 Injection, hydroxyprogesterone caproate, 1 mg
- Q9985 Injection, hydroxyprogesterone caproate, not otherwise specified, 10 mg (Effective July 1, 2017)
- Q9986 Injection, hydroxyprogesterone caproate (Makena), 10 mg (Effective July 1, 2017)
- S9208 Home management of preterm labor, including administrative services, professional pharmacy services, care coordination, and all necessary supplies or equipment (drugs and nursing visits coded separately), per diem (do not use this code with any home infusion per diem code)

**ICD-9 Diagnosis**
- V23.41 Supervision of pregnancy with history of pre-term labor

**ICD-10 Diagnoses (October 1, 2015)**
- O09.212 Supervision of pregnancy with history of pre-term labor, second trimester
- O09.213 Supervision of pregnancy with history of pre-term labor, third trimester

**REVISIONS**
- **10-06-2011** Policy added to the bcbsks.com web site.
- **02-14-2012** In Coding section:
  - Added HCPCS code: J1725 (effective 01-01-2012)
- **03-31-2014** Description section updated
  - In Policy section:
    - In Item C added risk factor, "prior episode of preterm labor in current pregnancy (i.e., progesterone therapy in conjunction with tocolysis or following successful tocolysis)"
    - In Item C 4 added "and" to read, "cervical cerclage and/or"
    - Reformatted Item C
    - Added Policy Guidelines
REFERENCES


