

Medical Policy



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

Professional

Original Effective Date: June 15, 2007
 Revision Date(s): October 6, 2011;
 February 14, 2012; March 31, 2014;
 November 9, 2016; July 11, 2017;
 January 1, 2018; November 7, 2018
 Current Effective Date: November 7, 2018

Institutional

Original Effective Date: October 6, 2011
 Revision Date(s): February 14, 2012;
 March 31, 2014; November 9, 2016;
 July 11, 2017; January 1, 2018;
 November 7, 2018
 Current Effective Date: November 7, 2018

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Populations	Interventions	Comparators	Outcomes
Individuals: • With a singleton pregnancy and prior spontaneous preterm birth before 37 weeks of gestation	Interventions of interest are: • Intramuscular injections of progesterone • Vaginal progesterone	Comparators of interest are: • No progesterone therapy	Relevant outcomes include: • Overall survival • Morbid events • Treatment-related morbidity
Individuals: • With a singleton pregnancy and a short cervix (<20 mm)	Interventions of interest are: • Intramuscular injections of progesterone	Comparators of interest are: • No progesterone therapy	Relevant outcomes include: • Overall survival • Morbid events • Treatment-related morbidity
Individuals: • With a singleton pregnancy and a short cervix (<20 mm)	Interventions of interest are: • Vaginal progesterone	Comparators of interest are: • No progesterone therapy	Relevant outcomes include: • Overall survival • Morbid events • Treatment-related morbidity

Populations	Interventions	Comparators	Outcomes
Individuals: • Who are pregnant with twins	Interventions of interest are: • Intramuscular injections of progesterone • Vaginal progesterone	Comparators of interest are: • No progesterone therapy	Relevant outcomes include: • Overall survival • Morbid events • Treatment-related morbidity
Individuals: • Who are pregnant with triplets	Interventions of interest are: • Intramuscular injections of progesterone • Vaginal progesterone	Comparators of interest are: • No progesterone therapy	Relevant outcomes include: • Overall survival • Morbid events • Treatment-related morbidity
Individuals: • With a singleton pregnancy and preterm premature rupture of the membranes	Interventions of interest are: • Intramuscular injections of progesterone • Vaginal progesterone	Comparators of interest are: • No progesterone therapy	Relevant outcomes include: • Overall survival • Morbid events • Treatment-related morbidity
Individuals: • With a singleton pregnancy and prior episode of preterm labor in the current pregnancy	Interventions of interest are: • Intramuscular injections of progesterone • Vaginal progesterone	Comparators of interest are: • No progesterone therapy	Relevant outcomes include: • Overall survival • Morbid events • Treatment-related morbidity

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.

Objective

The objective of this evidence review is to determine whether the use of progesterone therapy to prevent preterm birth improves the net health outcome in high-risk singleton, twin, and triplet pregnancies.

Background

PRETERM LABOR AND DELIVERY

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 rate of preterm delivery.

Treatment

Delalutin® (hydroxyprogesterone caproate) injection was approved in 1956 for a variety of gynecologic and obstetric conditions including the treatment or prevention of threatened spontaneous abortion and habitual abortion. The original approval was based

on safety as defined by existing U.S. Food and Drug Administration (FDA) regulations. In 1971, an additional review under the Drug Efficacy Implementation program determined that the drug was probably effective for those indications. In 1973, FDA modified the effectiveness finding and, along with a review of recent data on the potential association of prenatal hormone exposure and fetal cardiac malformations, withdrew labeled indications for progestin use in pregnancy. In 2010, after a series of interactions between Bristol Myers Squibb (the sponsor of the original new drug application) and FDA, the Administration announced that the manufacturer's removal of the product from the market was not due to safety and efficacy reasons.¹ Progesterone in compounded form continued to be used for pregnancy-related second and third-trimester indications.

Regulatory Status

In 2007, the synthetic progestin, hydroxyprogesterone caproate, was granted an orphan designation. In February 2011, Makena®, an injectable formulation of 17 α -progesterone caproate, was granted a new drug approval by FDA to reduce the risk for preterm birth in singleton pregnancies in women with a history of previous singleton preterm birth. Both intramuscular and subcutaneous injections of Makena® have since been approved by FDA. In 2018, FDA approved a generic version of hydroxyprogesterone caproate (American Regent).

In June 2017, the current manufacturer (AMAG Pharmaceuticals) announced FDA had accepted a supplemental new drug approval for a Makena® subcutaneous autoinjector for review.

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 17 α -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 gestations
 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. in conjunction with or following 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 anatomy and growth survey ultrasound during pregnancy. The ultrasound takes place between 19 weeks, 0 days and 23 weeks, 6 days of gestation.

RATIONALE

This evidence review has been updated with searches of the MEDLINE database. The most recent literature update was performed through June 7, 2018.

Evidence reviews assess the clinical evidence to determine whether the use of a technology improves the net health outcome. Broadly defined, health outcomes are length of life, quality of life, and ability to function—including benefits and harms. Every clinical condition has specific outcomes that are important to patients and to managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of a technology, 2 domains are examined: the relevance and the quality and credibility. To be relevant, studies must represent one or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial (RCT) is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. RCTs are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

PROGESTERONE THERAPY FOR A SINGLETON PREGNANCY AND PRIOR SPONTANEOUS PRETERM BIRTH BEFORE 37 WEEKS OF GESTATION

Clinical Context and Test Purpose

The purpose of progesterone therapy in women who have a singleton pregnancy and prior spontaneous preterm birth before 37 weeks of gestation is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The question addressed in this evidence review is: Does progesterone therapy improve the net health outcome in women with a singleton pregnancy and prior spontaneous preterm birth before 37 weeks of gestation?

The following PICOTS were used to select literature to inform this review.

Patients

The relevant population of interest is women with a singleton pregnancy and prior spontaneous preterm birth before 37 weeks of gestation.

Interventions

The therapy being considered is intramuscular (IM) injections of progesterone or vaginal progesterone.

Comparators

The following comparators are currently being used to make decisions about managing singleton pregnancies with a prior spontaneous preterm birth before 37 weeks: standard of care without progesterone.

Outcomes

The general outcomes of interest are overall survival (eg, neonatal death), morbid events (eg, postnatal respiratory distress), and treatment-related morbidity (eg, neonatal intensive care).

Timing

The timing of interest ranges from preterm labor onset to delivery. Neonatal outcomes up to 2 years after delivery may be of interest.

Setting

Patients are actively managed by obstetricians in an outpatient setting.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess longer term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Systematic Reviews

Oler et al (2017) published a meta-analysis of 3 RCTs (total N=680 patients) that compared IM progesterone with vaginal progesterone in women who had a previous spontaneous preterm delivery.² The mean gestational age at randomization was 16 weeks. Compared with those who received IM progesterone (n=332), women who received vaginal progesterone (n=348) had fewer incidents of spontaneous preterm delivery before 34 weeks of gestation (relative risk [RR], 0.71; 95% confidence interval [CI], 0.53 to 0.95). There was no statistically significant difference between the 2 groups in the rates of spontaneous preterm deliveries before 37 months of gestation. The incidences of respiratory distress syndrome and neonatal intensive care admission did not vary significantly between the groups. The meta-analysis was limited by variability between the RCTs, as well as lack of information on outcomes such as neonatal mortality.

A meta-analysis by Ahn et al (2017) focused on the outcome of neonatal mortality.³ Twenty-two RCTs, which included pregnant women with a history of preterm labor, treated with progesterone, and who reported a 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 vs placebo. For example, for women with singleton pregnancies treated with IM progesterone vs placebo (6 studies), the RR of neonatal death was 0.60 (95% CI, 0.33 to 1.09).

A Cochrane review by Dodd et al (2013) identified 11 trials on women with a previous spontaneous preterm birth; 4 used IM progesterone, 5 used vaginal progesterone, and 2 used oral progesterone.⁴ In a pooled analysis of data from 5 studies, 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 one 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 of 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).

Several systematic reviews and meta-analyses summarizing data on progesterone therapy to reduce preterm birth in high-risk pregnancies have been published.^{5,6} Sotiriadis et al (2012) conducted a meta-analysis of RCTs comparing progesterone with 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.⁵ 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 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 vs placebo (RR=0.49; 95% 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.

Randomized Controlled Trials

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

IM Progesterone

Meis et al (2003) published findings for 463 women randomized to weekly IM injections of 17 α -hydroxyprogesterone caproate (17P) or a placebo injection.⁷ (This is the trial on which the 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 ($p < 0.02$).

Follow-up data on children born during the Meis et al (2003) trial of 17P were reported by Northen et al (2007).⁸ Of the 429 infants discharged alive after birth, 278 (65%) were enrolled. Follow-up attrition 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 trial, resulting in the follow-up of 194 children from the 17P group and 84 from the control group. At an average 48 months of follow-up (range, <36-60 months), no difference was found in physical measures, diagnoses given by health professionals, or in caregivers' assessments of child health.

Vaginal Progesterone

A number of randomized trials have evaluated vaginal progesterone for women with singleton pregnancies in which at least 90% of the population had a previous preterm birth. Crowther et al (2017) published findings on the PROGRESS trial, a multicenter, randomized, placebo-controlled trial of women with a history of a previous spontaneous preterm birth.⁹ Both singleton ($n=775$) and twin ($n=12$) pregnancies were included in this trial; women were randomized to vaginal progesterone ($n=398$) or placebo ($n=389$). No statistically significant difference was seen between the active and control groups in delivery before 37 weeks of gestational age, respiratory distress syndrome, neonatal respiratory disease, or other adverse infant outcomes. Treatment was stopped in 9.9% of the progesterone group and in 7.3% of the placebo group due to side effects (adjusted RR=1.35; 95% CI, 0.85 to 2.15; $p=0.204$). A trial limitation was poor patient compliance, with nearly 9% participants failing to start or appropriately use the medication; the progesterone dosage used (100 mg) was also significantly lower than used in other trials (eg, the OPPTIMUM trial, discussed next).

An additional RCT with a population with mixed risk factors for preterm birth known as the OPPTIMUM study was published by Norman et al (2016).¹⁰ This large multicenter, double-blind trial, which evaluated outcomes in women pregnant with singleton pregnancies who had one of the risk factors for preterm birth. The trial enrolled 1228 women randomized to vaginal progesterone 200 mg daily ($n=618$) or placebo ($n=610$). Risk factors included a history of

preterm birth, a cervical length of 25 mm or less at any time between 18 weeks and 24 weeks of gestation, preterm premature fetal membrane rupture (PPROM), and/or history of a cervical procedure to treat abnormal smears. The trial 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 in 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, the rate of preterm delivery before 37 or 34 weeks (the primary outcome in many other RCTs) was not the sole outcome of this trial.

Majhi et al (2009) in India published the results of a trial of 100 women with singleton pregnancies and a history of spontaneous preterm birth.¹¹ Women were randomized to 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 might have been underpowered.

A large multinational study (including sites in the United States) was published by O'Brien et al (2007).¹² The trial 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 holds for the other maternal or neonatal outcome measures. Compliance and adverse events were similar for both groups.

Da Fonseca et al (2003) in Brazil reported on the results of a trial that randomized 157 women with singleton pregnancies considered at high risk for preterm delivery to daily progesterone or placebo suppositories.¹³ Inclusion criteria were a prior spontaneous preterm birth or other risk factors. A total of 142 (90%) of 157 patients completed the trial. 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 ($p<0.002$).

IM Progesterone vs Vaginal Progesterone

Several RCTs have compared the safety and efficacy of IM and vaginal progesterone for reducing the preterm birth rate in singleton pregnancies. For example, a trial by Elimian et al (2016) included 174 women with singleton pregnancies between 16 and 20 weeks 6 days of gestation with a history of preterm delivery.¹⁴ Patients were randomized to weekly IM injections of 17P 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 trial. Among trial 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 by Mahar et al (2013), 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.¹⁵ The trial was conducted at a single center in Saudi Arabia. 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 IM progesterone (n=256) or vaginal progesterone gel (n=262). Sixteen 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, 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 systematic reviews and RCTs that both IM and vaginal progesterone have demonstrated effectiveness but there are differences in outcomes by route of administration and product used when the varying etiologies for risk of preterm birth are considered.

PROGESTERONE THERAPY FOR A SINGLETON PREGNANCY AND SHORT CERVIX (<20 MM)

Clinical Context and Test Purpose

The purpose of progesterone therapy administered by IM injection or vaginal delivery in women who have a singleton pregnancy and short cervical length is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The question addressed in this evidence review is: Does progesterone therapy improve the net health outcome in women with a singleton pregnancy short cervical length?

The following PICOTS were used to select literature to inform this review.

Patients

The relevant population of interest is women with a singleton pregnancy and a short cervix (<20 mm).

Interventions

The therapy being considered is IM injections of progesterone or vaginal progesterone.

Comparators

The following comparator is currently being used to make decisions about managing singleton pregnancies with a short cervix: standard of care without progesterone.

Outcomes

The general outcomes of interest are overall survival (eg, neonatal death), morbid events (eg, postnatal respiratory distress), and treatment-related morbidity (eg, neonatal intensive care).

Timing

The timing of interest ranges from preterm labor onset to delivery. Neonatal outcomes up to 2 years after delivery may be of interest.

Setting

Patients are actively managed by obstetricians in an outpatient setting.

Study Selection Criteria

The principles followed to select methodologically credible studies for this section are outlined in the first indication above.

IM Progesterone

A double-blind RCT by Grobman et al (2012) 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).¹⁶ The trial 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 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 events, 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 assessed vaginal progesterone for singleton pregnancy and short cervix have been published.

Systematic Reviews

Romero et al (2018) conducted a meta-analysis of individual patient data on the use of vaginal progesterone in women with short cervical length (≤ 25 mm).¹⁷ Five studies were included (total N=974 women) with patients assigned to treatment with vaginal progesterone (n=498) or placebo (n=476). For spontaneous preterm birth prior to 33 weeks of gestation, vaginal

progesterone showed a significant reduction in risk compared with placebo (RR=0.62; 95% CI, 0.47 to 0.81; $p<0.001$). Rates of preterm birth were also significantly lower in the group receiving vaginal progesterone than receiving placebo at less than 36, 35, 34, 32, and 28 weeks of gestation. There were fewer instances of neonatal death for patients treated with vaginal progesterone compared with placebo (1.4% vs 3.2%; RR=0.44; 95% CI, 0.18 to 1.07; $p=0.07$). Review limitations included inconsistently reported or missing data across relevant studies, leading to heterogeneity. Additionally, a small number of patients in subgroup analyses limited the statistical power to estimate treatment effects.

Romero et al (2012) 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.¹⁸ Five RCTs were included in the meta-analysis. Two of the trials, Hassan et al (2011)¹⁹ and Fonseca et al (2007),²⁰ 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 trials 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). This 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 than receiving 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).

Randomized Controlled Trials

A small, placebo-controlled randomized trial on 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.²¹ In this trial by van Os et al (2015), the RR 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 might have been underpowered; enrollment was stopped early due to an unexpectedly low number of women with a short cervix.

IM Progesterone vs Vaginal Progesterone

Bafgni et al (2015) published an RCT that included 78 women with singleton pregnancies who had either a short cervix (<25 mm) (N=45) or a history of preterm delivery (N=33).²² Randomization was done separately for the subgroups. Women were assigned to weekly IM injections of 17P 250 mg or vaginal progesterone 200 mg daily. The primary outcomes were the 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 for

either primary outcome measure. In the overall trial population, the rate of preterm delivery was 33.3% in the vaginal progesterone group and 30.7% in the IM progesterone group ($p=0.088$). Mean gestational age at delivery was 37.1 weeks in the vaginal progesterone group and 36.8 weeks in the IM progesterone group ($p=0.765$). In an analysis of the subgroup with a short cervix, mean gestational age at delivery was 38.0 weeks in the vaginal progesterone group and 37.6 weeks in the IM progesterone group. The difference between groups was not statistically significant. However, the trial was not powered to find differences at the subgroup level, which limits conclusions about the choice use of progesterone for women with a short cervix.

Section Summary: Singleton Pregnancy and Short Cervical Length

IM Progesterone

One placebo-controlled randomized trial that assessed whether injectable progesterone is effective for preventing preterm birth in women with short cervical length was unpowered. Another RCT, which compared injectable with vaginal progesterone, was also not sufficiently powered to detect differences in the subgroup of patients with a short cervix. Thus, conclusions cannot be drawn about the IM progesterone as a treatment for singleton pregnancies and short cervical length.

Vaginal Progesterone

Two meta-analyses found that vaginal progesterone significantly reduced the rate of preterm delivery in women with a short cervical length. In addition, there was a benefit in the subgroup of women with singleton pregnancies and no prior preterm birth. Several RCTs have evaluated vaginal progesterone for preventing preterm birth in women with short cervical length. These trials have tended to be underreported.

PROGESTERONE THERAPY FOR A TWIN GESTATION

Clinical Context and Test Purpose

The purpose of progesterone therapy in women who have a twin gestation is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The question addressed in this evidence review is: Does progesterone therapy improve the net health outcome in women with a twin gestation?

The following PICOTS were used to select literature to inform this review.

Patients

The relevant population of interest is women with a twin gestation.

Interventions

The therapy being considered is intramuscular injections of progesterone or vaginal progesterone.

Comparators

The following comparator is currently being used to make decisions about twin gestations: standard of care without progesterone.

Outcomes

The general outcomes of interest are overall survival (eg, neonatal death), morbid events (eg, postnatal respiratory distress), and treatment-related morbidity (eg, neonatal intensive care).

Timing

The timing of interest ranges from preterm labor onset to delivery. Neonatal outcomes up to 2 years after delivery may be of interest.

Setting

Patients are actively managed by obstetricians in an outpatient setting.

Study Selection Criteria

The principles followed to select methodologically credible studies for this section are outlined in the first indication above.

Systematic Reviews

A Cochrane systematic review and meta-analysis by Dodd et al (2017) evaluated women with multiple pregnancies who were treated with vaginal or IM progesterone.²³ Of the 17 RCTs included (total N=4773 patients), 3 trials included women with triplet pregnancies; the remainder were restricted to women with twin pregnancies. Nine studies compared IM progesterone with placebo or no treatment, and pooled analysis of the results found few differences among the treatment groups for most maternal and infant outcomes. Pooled analysis of 2 studies (n=399) showed a higher incidence of preterm delivery prior to 34 weeks gestation in the IM progesterone group than in groups receiving placebo or no treatment (RR=1.54; 95% CI, 1.06 to 2.26). Pooled analysis of 6 studies (n=3089) showed that perinatal death was also increased in the IM progesterone group, compared with control (RR=1.45; 95% CI, 0.60 to 3.51); heterogeneity of treatment was high ($I^2=71\%$). Both of these findings were attributed to low-quality evidence. Vaginal progesterone was compared with placebo or no treatment in 8 studies. Pooled analyses of 3 showed that perinatal death occurred more often in vaginal progesterone groups than in control groups (RR=1.23; 95% CI, 0.74 to 2.06). No clear group difference was noted between the active and control groups for preterm delivery prior to 34 weeks of gestation. While all but 6 of the included studies were deemed to have low risk of bias (4 studies were not graded) based on issues with blinding, loss to follow-up, or reporting issues, variations among studies in inclusion criteria, and timing, route of administration, and dosage were present.

Schuit et al (2015) published an individual patient data meta-analysis evaluating the effectiveness of progesterone for improving perinatal outcomes in twin pregnancies.²⁴ Reviewers identified 13 trials (n=3668 women; n=7536 infants); 7 trials used vaginal progesterone and 6 used IM 17P. Twelve studies were placebo-controlled, and the 13th 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 (19%) of 2178 children in the 17P group and 318 (17%) of 1888 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 (12%) of 1834 children in the active treatment group and 201 (12) of 1636 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 Cochrane review by Dodd et al (2013), previously described, 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).⁴ Moreover, a pooled analysis of 7 trials (6 were limited to twins, one 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).

Other systematic reviews and meta-analyses of RCTs have also not found that progesterone administration significantly reduces the rate of preterm birth or improves other health outcomes in patients with twin pregnancies.⁵

Randomized Controlled Trials

A trial by El-refaie et al (2016) 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.²⁵ The trial included 322 women randomized to vaginal progesterone 400 mg daily (n=125) or 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 reviewers 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 other studies. Additional studies in this population, including at least one using a high dose of vaginal progesterone, are underway.

Several other RCTs also found that progesterone did not reduce the rate of preterm birth in twin gestations. A study by Awwad et al (2015) included 293 women and used IM progesterone,²⁶ and the study by Brizot et al (2015) enrolled 390 women and used vaginal progesterone.²⁷ A trial by Winer et al (2015) used IM progesterone but was stopped early after enrolling 105 women because interim analysis demonstrated lack of efficacy of progesterone at prolonging pregnancy.²⁸

One of the larger RCT on twin pregnancies, and with the longest follow-up, is the PREDICT trial by Rode et al (2011).²⁹ It was conducted in Denmark and Austria. A total of 667 pregnant women with twins were randomized to 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 (odds ratio, 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, birth weight, 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.

Section Summary: Twin Gestations

Numerous RCTs and several systematic reviews 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 (2) confirming the optimal dose of vaginal progesterone are needed.

PROGESTERONE THERAPY FOR A TRIPLET GESTATION

Clinical Context and Test Purpose

The purpose of progesterone therapy in women who have a triplet gestation is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The question addressed in this evidence review is: Does progesterone therapy improve the net health outcome in women with a triplet gestation?

The following PICOTS were used to select literature to inform this review.

Patients

The relevant population of interest is women with triplet gestation.

Interventions

The therapy being considered is IM injections of progesterone or vaginal progesterone.

Comparators

The following practice is currently being used to make decisions about managing triplet gestations: standard of care without progesterone.

Outcomes

The general outcomes of interest are overall survival (eg, neonatal death), morbid events (eg, postnatal respiratory distress), and treatment-related morbidity (eg, neonatal intensive care).

Timing

The timing of interest ranges from preterm labor onset to delivery. Neonatal outcomes up to 2 years after delivery may be of interest.

Setting

Patients are actively managed by obstetricians in an outpatient setting.

Study Selection Criteria

The principles followed to select methodologically credible studies for this section are outlined in the first indication above.

Systematic Reviews

Triplet pregnancies are discussed in the Cochrane review by Dodd et al (2017), discussed above, and were evaluated considered in 4 included studies; however, outcomes were underrepresented in the review as several studies did not distinguish between twin and triplet gestations.²³

The meta-analysis by Sotiriadis et al (2012) identified 2 trials on progesterone in women with triplet gestations.⁵ Pooled analyses of data from those 2 studies did not find any statistically significant differences in outcomes between women receiving progesterone or placebo.

Randomized Controlled Trials

Both trials evaluated IM injections of 17P. Combs et al (2010), in this RCT evaluating 81 women, randomized 56 to IM injections of 17P and 25 to placebo.³⁰ 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 ($p<0.02$). In the other trial, Caritis et al (2009) randomized healthy women expecting triplets to weekly IM injections of 17P or placebo starting at 16 to 20 weeks and ending at delivery or 35 weeks of gestation.³¹ The primary trial 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 was similar in both treatment groups (83% of pregnancies in the 17P group vs 84% in the placebo group; $RR=1.0$).

Section Summary: Triplet Gestation

A Cochrane review, 2 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.

PROGESTERONE THERAPY FOR A SINGLETON PREGNANCY AND PRETERM PREMATURE FETAL MEMBRANE RUPTURE

Clinical Context and Test Purpose

The purpose of progesterone therapy in women who have a singleton pregnancy and PPRM is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The question addressed in this evidence review is: Does progesterone therapy improve the net health outcome in women with a singleton pregnancy and PPRM?

The following PICOTS were used to select literature to inform this review.

Patients

The relevant population of interest is women with a singleton pregnancy and PPRM before 37 weeks of gestation.

Interventions

The therapy being considered is IM injections of progesterone or vaginal progesterone.

Comparators

The following practice is currently being used to make decisions about managing singleton pregnancies with PPRM: standard of care without progesterone.

Outcomes

The general outcomes of interest are overall survival (eg, neonatal death), morbid events (eg, postnatal respiratory distress), and treatment-related morbidity (eg, neonatal intensive care).

Timing

The timing of interest ranges from preterm labor onset to delivery. Neonatal outcomes up to 2 years after delivery may be of interest.

Setting

Patients are actively managed by obstetricians in an outpatient setting.

Study Selection Criteria

The principles followed to select methodologically credible studies for this section are outlined in the first indication above.

Systematic Reviews

Quist-Nelson et al (2018) published a systematic review and meta-analysis of 6 RCTs (total N=545 patients) evaluating IM progesterone (4 studies) or rectal progesterone (2 studies) compared with placebo or no treatment in women with singleton pregnancies and PPROM.³² No significant differences were noted between patients receiving IM progesterone and placebo in rates of preterm birth at the following time points: less than 37, 34, 32, or 28 weeks of gestation.

Randomized Controlled Trials

Briery et al (2011) published an RCT assessing women with singleton pregnancies diagnosed with PPROM at 20 to 30 weeks of gestation.³³ Women were randomized to weekly injections of 17P (n=33) or placebo (n=36). Two women did not finish the trial, 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.

Section Summary: Singleton Pregnancy and PPROM

A 2018 systematic review identified 6 RCTs that compared IM progesterone with placebo or no treatment; no significant differences between the groups were found. The sole published RCT identified did not find improved neonatal outcomes in women with singleton pregnancies experiencing PPROM who received progesterone vs placebo.

PROGESTERONE THERAPY FOR A SINGLETON PREGNANCY AND PRIOR EPISODE OF preterm labor in current pregnancy

Clinical Context and Test Purpose

The purpose of progesterone therapy in women who have a singleton pregnancy and a prior episode of preterm labor in the current pregnancy is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The question addressed in this evidence review is: Does progesterone therapy improve the net health outcome in women with a singleton pregnancy and a prior episode of preterm labor in the current pregnancy?

The following PICOTS were used to select literature to inform this review.

Patients

The relevant population of interest is women with a singleton pregnancy and a prior episode of preterm labor in the current pregnancy.

Interventions

The therapy being considered is IM injections of progesterone or vaginal progesterone.

Comparators

The following practice is currently being used to make decisions about managing singleton pregnancies with a prior episode of preterm labor in the current pregnancy: standard of care without progesterone.

Outcomes

The general outcomes of interest are overall survival (eg, neonatal death), morbid events (eg, postnatal respiratory distress), and treatment-related morbidity (eg, neonatal intensive care).

Timing

The timing of interest ranges from preterm labor onset to delivery. Neonatal outcomes up to 2 years after delivery may be of interest.

Setting

Patients are actively managed by obstetricians in an outpatient setting.

Study Selection Criteria

The principles followed to select methodologically credible studies for this section are outlined in the first indication above.

IM Progesterone

A systematic review and meta-analysis by Saccone et al (2015) 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.³⁴ 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 birth weight 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

Systematic Reviews

A systematic review and meta-analysis by Suhag et al (2015) 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.³⁵ Five RCTs (total N=441 women) met the inclusion criteria; 3 trials used a no-treatment control and 2

used a placebo. All trials were conducted outside of the United States. A meta-analysis of data from 3 trials (n=298 women) found a statistically significant difference between groups in the primary outcome (preterm birth before 37 weeks). Pooled rates were 42% in the progesterone group and 58% in the control group (RR=0.71; 95% CI, 0.57 to 0.90). 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. Reviewers noted the generally poor quality of the trials (eg, lack of blinding).

After the Suhag systematic review search date, Martinez de Tejada et al (2015) published a multicenter, double-blind, placebo-controlled randomized trial on prevention of preterm delivery in women with a prior episode of preterm labor in the current pregnancy.³⁶ 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 between groups.

Randomized Controlled Trials

Wood et al (2017) reported on an RCT of 41 women with arrested premature labor, randomized to treatment with vaginal progesterone (n=19) or placebo (n=22).³⁷ No statistically significant difference was seen between the active and control group in median gestational age at delivery. Trial limitations included early trial termination, prior to meeting recruitment goals. This trial also included a meta-analysis of 15 trials (N=801) evaluating progesterone in women with arrested preterm labor, which found no statistically significant risk reduction for preterm delivery before 37 weeks of gestation after treatment with vaginal or IM progesterone. The meta-analysis was limited by variability in study quality.

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 used as maintenance tocolysis reduces the rate of preterm birth or improves other outcomes. RCTs have reported mixed findings and had methodologic limitations (eg, lack of blinding).

Summary of Evidence

For individuals who have a singleton pregnancy and prior spontaneous preterm birth before 37 weeks of gestation who receive IM 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. Pooled analyses of RCT data have found statistically significant reductions in term birth rates with progesterone compared with placebo. Findings have been similar in studies that used injectable or vaginal progesterone, but there are differing clinical opinions on the preferred agent for this indication. The evidence is sufficient to determine 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 IM injections of progesterone, the evidence includes 2 RCTs. Relevant outcomes are overall survival, morbid events, and treatment-related morbidity. A placebo-controlled randomized trial did not find that IM progesterone significantly decreased the rate of preterm birth. An RCT comparing IM with 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 that the technology results in a meaningful improvement in the net health outcome.

For individuals who are pregnant with twins who receive IM 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 IM 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 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 IM injections of progesterone or vaginal progesterone, the evidence includes an 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, birth weight, neonatal mortality) in women treated with progesterone vs 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 IM 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 IM progesterone did not report 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 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 might 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) randomized trial was not published at the time clinical input was obtained.¹⁹ The input did not specify the 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, 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 while this policy was under review in 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 suggested there was a difference, commented that the Meis et al (2003)⁷ and da Fonseca et al (2003)¹³ 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 input also raised questions about the clinical applications for cervical length measurement.

Practice Guidelines and Position Statements

American College of Obstetricians and Gynecologists

The American College of Obstetricians and Gynecologists (2016) updated and replaced its practice bulletin on multifetal gestations that included the following statement on progesterone therapy³⁸:

"Progesterone treatment does not reduce the incidence of spontaneous preterm birth in unselected women with twin or triplet gestations and, therefore, is not recommended as an intervention to prevent preterm birth in women with multiple gestations."

Previously, the American College of Obstetricians and Gynecologists (2012; reaffirmed 2014) published a Practice Bulletin on prediction and prevention of preterm birth.³⁹ The bulletin included the following (level A evidence) recommendations 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, regardless of transvaginal ultrasound cervical length, 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

The clinical guidelines by the Society for Maternal-Fetal Medicine (2012) included the following conclusions and recommendations on the use of progesterone to prevent preterm labor⁴⁰:

"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 [randomized controlled trials] 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 [intramuscular] weekly preferably starting at 16-20 weeks until 36 weeks is recommended. In these women, if the TVU CL shortens to 25 mm 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."

The Society (2017) published a position statement on the choice of progestogen.⁴¹ The Society continued to recommend the use of 17 α -hydroxyprogesterone caproate therapy for prevention of preterm birth with singleton pregnancy and prior preterm birth and, in this statement, confirmed that this formulation is the product of choice.

U.S. Preventive Services Task Force Recommendations

Not applicable.

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

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT01050647	Progesterone for the Management of Preterm, Premature Rupture of the Membranes: A Randomized Controlled Trial.	21	Oct 2018
NCT01004029 ^a	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	1710	Nov 2018
Unpublished			
NCT02697331	Evaluation of the Role of Vaginal Progesterone in Prevention of Preterm Labor in Twin Gestation With Short Cervix: Randomised Controlled Trial	120	Oct 2016 (unknown)
NCT02304237 ^a	Vaginal Compared With Intramuscular Progesterone for Prevention of Preterm Birth in High Risk Pregnant Women	360	Dec 2016 (unknown)
NCT02329535	Comparing Double Dose of Vaginal Progesterone to no Treatment for Prevention of Preterm Birth in Twins and Short Cervix	15	Aug 2017 (terminated)

NCT: national clinical trial.

^a Denotes industry-sponsored or cosponsored trial.

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
- J1726 Injection, hydroxyprogesterone caproate (Makena), 10 mg
- J1729 Injection, hydroxyprogesterone caproate, not otherwise specified, 10 mg
- 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)
 - There are specific codes for hydroxyprogesterone caproate injection
 - There is no specific code for progesterone vaginal suppository

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
- O34.42 Maternal care for other abnormalities of cervix, second trimester
- O34.43 Maternal care for other abnormalities of cervix, 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: <ul style="list-style-type: none"> ▪ 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
	Rationale section updated
	In Coding section: <ul style="list-style-type: none"> ▪ Removed HCPCS Code: Q2042 ▪ Revised nomenclature for HCPCS Code: S9208 ▪ Added ICD-10 Diagnoses codes
	References updated
11-09-2016	Description section updated
	In Policy section: <ul style="list-style-type: none"> ▪ In Item C 1 added "twin or" to read "twin or multiple gestation" ▪ In Items A, B, and C header changes "women" to "individuals" ▪ Updated Policy guidelines
	Rationale section updated
	References updated
07-11-2017	In Coding section: <ul style="list-style-type: none"> ▪ Added HCPCS Codes: Q9985, Q9986
01-01-2018	In Coding section: <ul style="list-style-type: none"> ▪ Removed HCPCS Codes: Q9985, Q9986 (Termed 12-31-2017) ▪ Added HCPCS Codes: J1726, J1729 (Effective 01-01-2018) (Note: J1726 replaced Q9986 and J1729 replaced Q9985 with no changes in nomenclature.)
11-07-2018	Description section updated
	In Policy section: <ul style="list-style-type: none"> ▪ In C 4 added "in conjunction with or following" to read "in conjunction with or following cervical cerclage" ▪ Policy Guidelines updated
	Rationale section updated
	In Coding section <ul style="list-style-type: none"> ▪ Removed HCPCS Code: J1725 (Termed on 01-01-2018) ▪ Added ICD-10 Codes: O34.42, O34.43 ▪ Coding notations updated
	References updated

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