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Medical Policy

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

Professional	Institutional
Original Effective Date: June 15, 2007	Original Effective Date: October 6, 2011
Revision Date(s): October 6, 2011; February 14, 2012; March 31, 2014; November 9, 2016; July 11, 2017; January 1, 2018; November 7, 2018; September 25, 2019; May 23, 2021; November 5, 2021; October 28, 2022	Revision Date(s): February 14, 2012; March 31, 2014; November 9, 2016; July 11, 2017; January 1, 2018; November 7, 2018; September 25, 2019; May 23, 2021; November 5, 2021; October 28, 2022
Current Effective Date: May 23, 2021	Current Effective Date: May 23, 2021

Archived Date: April 25, 2023 **Archived Date: April 25, 2023**

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

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Populations	Interventions	Comparators	Outcomes
preterm premature rupture of the membranes	• Intramuscular injections of progesterone • Vaginal progesterone	• No progesterone therapy	• 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 pregnancies.

BACKGROUND

Preterm Labor and Delivery

Preterm labor and delivery are major determinants of neonatal morbidity and mortality. In the United States (U.S.), the rate of preterm birth is approximately 10% according to the Centers for Disease Control and Prevention. Social determinants of health and systemic racism in obstetrical healthcare is a challenge in the U.S.; there has been increasing evidence supporting early health deterioration among Black individuals compared to White individuals regarding reproductive health outcomes.[1,] This can put Black women at a higher risk for poorer obstetrical outcomes, and it has been reported that Black women are more than 4 times more likely to die from pregnancy-related complications than White women.

Treatment

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,

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none of these therapies has made a significant demonstrable impact on the incidence of preterm delivery.

Progesterone-dependent regulation of myometrial contractility and local inflammatory responses are thought to be the physiologic basis for the therapeutic use of progesterone and progestins to prevent preterm labor and birth. Progesterone and progestins can be administered by intramuscular (IM) or subcutaneous injection. Compounded vaginal suppositories or intravaginal administration of other formulations such as gels or tablets are also in use.

REGULATORY STATUS

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 Safety Implementation (DESI) program determined that the drug was probably effective for those indications. In 1973, the 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 the FDA, the Administration announced that the manufacturer's removal of the product from the market was not due to safety and efficacy reasons.[2,]

Progesterone in compounded form as a vaginal suppository continued to be used for pregnancy-related second and third-trimester indications.

In 2007, the synthetic progestin, hydroxyprogesterone caproate, was granted an orphan designation. In February 2011, Makena®, an injectable formulation of 17α-progesterone caproate, was granted approval by the FDA to reduce the risk for preterm birth in singleton pregnancies in women with a history of previous singleton preterm birth under its Accelerated Approval Program. The product also has an Orphan Drug Designation. The accelerated approval was based on results of an RCT[3,] that reported that Makena® significantly reduced the risk of preterm birth before 37 weeks of gestational age. The study was not planned or conducted for drug approval and was not powered for neonatal morbidity or mortality outcomes. A confirmatory trial to assess efficacy and safety was required. In 2019, the FDA Bone, Reproductive and Urologic Drugs Advisory Committee (BRUDAC) considered the results of the post-approval study (NCT01004029, Progestin's Role in Optimizing Neonatal Gestation study [PROLONG]). In PROLONG[4,] , Makena® did not significantly reduce the risk of preterm birth or neonatal mortality or morbidity. BRUDAC briefing materials prepared by AMAG Pharmaceuticals, Makena 's

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manufacturer, are publicly available,[5,] as are minutes from this meeting.[6,] The BRUDAC voted 9 to 7 in favor of recommending that FDA withdraw its conditional approval of Makena.[7,] On October 5, 2020, the FDA Center for Drug Evaluation and Research (CDER) proposed that Makena (hydroxyprogesterone caproate injection) be withdrawn from the market.[8,] On October 14, 2020, AMAG Pharmaceuticals, Inc and Covis Pharma Group, requested a public hearing regarding this matter.[9,]On December 14, 2020, the manufacturer submitted supporting documentation detailing the basis for Makena remaining available for use in women who are at risk for preterm birth, including clinical study results that highlight the evidence of the effectiveness of Makena among minority women. In August 2021, the FDA announced that a public hearing would be held in 2022 to address the administration's decision. While the FDA reviews the submission of supporting documentation, Makena remains available.

In 2018, the FDA approved the first generic version of hydroxyprogesterone caproate as well as the Makena (hydroxyprogesterone caproate injection) Subcutaneous Auto-Injector.

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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, 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 (i.e., 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

A. Appropriate training of ultrasonographers with ongoing quality assurance programs are considered critical to the accurate measurement of cervical length in the second trimester.

B. Ultrasonographers 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.

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.

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RATIONALE

This evidence review has been updated regularly with searches of the PubMed database. The most recent literature update was performed through July 26, 2022.

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 1 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. Randomized controlled trials 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.

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

Clinical Context and Therapy Purpose

The purpose of intramuscular (IM) 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 IM 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 PICO was used to select literature to inform this review.

Patients

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The relevant population of interest is women with a singleton pregnancy and prior spontaneous preterm birth before 37 weeks of gestation. A short cervix, a history of multiple prior preterm births, no term pregnancy between a previous spontaneous preterm birth and the current pregnancy, and cigarette smoking are known risk factors. The primary population of interest is women with a singleton pregnancy and prior spontaneous preterm birth before 37 weeks of gestation and predominantly without cervical shortening.

Interventions
The therapy being considered is IM injections of progesterone.

Comparators
For women with a history of spontaneous preterm birth, progesterone supplementation has become the standard of care for managing the risk of recurrent preterm birth. Thus, the primary comparator of interest is vaginal progesterone.

Outcomes
The outcomes of interest are direct clinical benefits including overall survival (OS) (e.g., neonatal death), morbid events (e.g., postnatal respiratory distress, neonatal intensive care, child functional impairment), and treatment-related morbidity (e.g., maternal adverse drug reactions). Gestational outcomes (e.g., gestational age, preterm birth <32, 35, or 37 weeks) are considered surrogate outcomes expected to predict clinical benefit.

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 long-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.

REVIEW OF EVIDENCE

COMPARISON TO PLACEBO

Systematic Reviews
Kuon et al (2021) published a systematic review with meta-analysis evaluating the efficacy of 17-hydroxyprogesterone caproate (17P) for the prevention of preterm birth in women with singleton pregnancies and prior preterm birth.[10,] Only 2 pivotal placebo-controlled RCTs were included in

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the meta-analysis, both of which are summarized in more detail in the section below (Meis et al [2003] and Blackwell et al [2020]). The analysis demonstrated nonsignificant trends of benefit for 17P for preterm birth <37 weeks (relative risk [RR], 0.74; 95% confidence interval [CI], 0.47 to 1.16), <35 weeks (RR, 0.79; 95% CI, 0.53 to 1.18), and <32 weeks (RR, 0.81; 95% CI, 0.57 to 1.14) of gestation, and the risk of necrotizing enterocolitis, (RR, 0.22; 95% CI, 0.02 to 1.95). An increased risk of fetal death (antepartum or intrapartum) seen with 17P also did not reach statistical significance (RR, 1.82; 95% CI, 0.68 to 4.87).

The Evaluating Progestogens for Preventing Preterm Birth International Collaborative (EPPPIC) Group (2021) conducted a meta-analysis that included participant-level data from 31 studies of asymptomatic pregnant women at risk of preterm birth who received IM, vaginal, or oral progesterone therapy (N=11,664 women and 16,185 offspring).[11,] A total of 14 trials compared vaginal progesterone with control (13 vs. placebo, 2 vs. standard care; 6 in singleton pregnancies, 5 in multifetal pregnancies, 3 with mixed populations) and 13 trials compared 17P with control (11 vs. placebo, 2 vs. standard care; 5 in singleton pregnancies, 8 in multifetal pregnancies). Vaginal progesterone was directly compared with 17P in 2 studies of women with singleton pregnancies. Outcomes included preterm birth before 37, 34, and 28 weeks of gestation, as well as adverse neonatal and maternal outcomes. Pooled data from 5 trials comparing 17P with control in singleton pregnancies (n=3053) demonstrated nonsignificant trends of benefit for 17P for preterm birth <37 weeks (RR, 0.94; 95% CI, 0.78 to 1.13), <34 weeks (RR, 0.83; 95% CI, 0.68 to 1.01), and <28 weeks (RR, 0.73; 95% CI, 0.53 to 1.02) of gestation. Similarly, the RR of maternal complications (1.18; 95% CI, 0.97 to 1.31), serious neonatal complications (0.81; 95% CI, 0.60 to 1.09), and fetal death/stillbirth (1.04; 95% CI, 0.60 to 1.83) did not reach statistical significance. A notable relevancy limitation of this review is that the meta-analyses pooled data from RCTs representative of mixed indication populations; including women with various cervical lengths and/or additional risk factors.

Baradwan et al (2021) conducted a systematic review and meta-analysis evaluating 17P compared to placebo for prevention of recurrent preterm birth.[12,] Six RCTs were included (N=1578), and the analysis did not report any statistically significant reductions in preterm birth risk following 17P use compared to placebo at <32 weeks (RR, 0.61; 95% CI, 0.13 to 2.77), <35weeks (RR, 0.60; 95% CI, 0.10 to 3.67), or <37 weeks (RR, 0.68; 95% CI, 0.46 to 1).

Randomized Controlled Trials

Two multicenter, placebo-controlled, double-blind RCTs have been published that evaluated weekly IM injections of 17P for recurrent preterm birth prevention in women with singleton pregnancies and prior preterm birth. Characteristics of these RCTs are summarized in Table 1. Meis et al (2003) is the RCT conducted by the National Institute of Child Health and Human Development (NICHD) Maternal-Fetal Medicine Units (MFMU) Network.[3,] Notable baseline characteristics of enrolled women include that they were 59% Black and that 32% had more than

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1 previous preterm birth. The primary outcome was preterm delivery before 37 weeks of gestation and the study was the basis for the 2011 accelerated approval of 17P.

Blackwell et al (2020) is the post-approval confirmatory RCT required by the U.S. Food and Drug Administration (FDA).[4,] The FDA required that at least 10% of the study participants be enrolled from North American trial sites. Notable baseline characteristics of enrolled women include that they were 7% Black and that 13% had more than 1 previous preterm birth. The majority of women were from countries other than the US (77%). Co-primary outcomes were preterm birth before 35 weeks and a neonatal morbidity composite index. The neonatal composite index included any of the following outcomes: neonatal death, grade 3 or 4 intraventricular hemorrhage, respiratory distress syndrome, bronchopulmonary dysplasia, necrotizing enterocolitis, or proven sepsis. The primary safety outcome was fetal or early infant death. Maternal complications were also evaluated including maternal gestational diabetes mellitus, hypertensive syndromes (gestational hypertension, preeclampsia, eclampsia), chorioamnionitis, and placental abnormalities (abruption and previa).

Table 1. Summary of Key RCT Characteristics in Women With Prior Preterm Birth

Study; Trial	Countries	Sites	Dates	Participants	Interventions	
					Weekly IM injections of 17α-hydroxyprogesterone caproate	**Placebo**
Meis et al (2003)[3,]	US	19	1998-1999	Women with a current singleton pregnancy at 15 to 20 weeks and a previous spontaneous preterm birth	250 mg; n=310	n=153
Blackwell et al (2020)[4,] PROLONG	US, Russia, Ukraine, Hungary, Spain, Bulgaria, Canada, Czech Republic, Italy	93	2009-2018	Women aged ≥ 18 years with a current singleton pregnancy at 16 to 20 weeks and a previous spontaneous preterm birth	250 mg; n=1130	n=578

IM: Intramuscular; PROLONG: Progestin's Role in Optimizing Neonatal Gestation; RCT: randomized controlled trial; US: United States.

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Table 2 provides a summary of key RCT results. Meis et al (2003) reported that IM progesterone significantly reduced the risk of preterm birth before 37 weeks as well as 32 weeks and 35 weeks of gestational age. Infants of women treated with 17P had significantly lower rates of necrotizing enterocolitis, intraventricular hemorrhage, and need for supplemental oxygen. There were no differences in any other neonatal mortality or morbidity outcomes. There were no significant differences between the 2 groups for maternal health-related complications such as the rates of hospital visits for preterm labor, tocolytic drug or corticosteroid use, cesarean delivery, or chorioamnionitis.

Northen et al (2007) published results from a follow-up study of functional outcomes in children born during the Meis et al (2003) trial. [13,] 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 of 48 months of follow-up (range, <36 to 60 months), no difference was found in physical measures, diagnoses given by health professionals, or in caregivers' assessments of child health.

Blackwell et al (2020)[4,] reported no significant differences between IM progesterone and placebo on any preterm birth, neonatal mortality or morbidity, or maternal outcomes. Exploratory subgroup analyses based on the gestational age of the qualifying prior preterm birth, number of prior preterm births, cervical length, geographic regions, race, body mass index, and substance use during pregnancy also failed to demonstrate a significant treatment benefit for IM progesterone for preterm birth outcomes. This included an analysis of the US subgroup (n=391, 23%), which found nonsignificant trends of benefit for IM progesterone on preterm birth outcomes at <35 weeks and <32 weeks, but not at <37 weeks. A follow-up study of childhood functional outcomes of children born during the Blackwell et al (2020) RCT is in progress (NCT01146990).

Table 2. Summary of Key RCT Results

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Outcome	N in analysis	Weekly IM injections of 17α-hydroxyprogesterone caproate, n (%)	Placebo, n (%)	Effect Size (95% Confidence Interval)
Preterm Birth (Gestation <35 weeks)[a]				
Meis et al (2003)[3,]	459	63 (20.6%)	47 (30.7%)	RR, 0.67 (0.48 to 0.93)
Blackwell et al (2020)[4,] PROLONG	1708	93 (8.4%)	51 (8.9%)	RR, 0.93 (0.67 to 1.30)
Preterm Birth (Gestation <37 weeks)[b]				
Meis et al (2003)[3,]	463	111 (36.3%)	84 (54.9%)	RR, 0.66 (0.54 to 0.81)
Blackwell et al (2020)[4,] PROLONG	1708	257 (23.1%)	125 (21.9%)	RR, 1.06 (0.88 to 1.28)
NICU Admission				
Meis et al (2003)[3,]	N/A	NR	NR	NR
Blackwell et al (2020)[4,] PROLONG	1652	137 (12.5%)	58 (10.4%)	RR, 1.21 (0.90 to 1.62)
Respiratory Distress Syndrome				
Meis et al (2003)[3,]	463	29 (9.5%)	23 (15.2%)	RR, 0.63 (0.38 to 1.05)
Blackwell et al (2020)[4,] PROLONG	1652	54 (4.9%)	26 (4.7%)	RR, 1.06 (0.67 to 1.68)
Neonatal Death				
Meis et al (2003)[3,]	463	8 (2.6%)	9 (5.9%)	RR, 0.44 (0.17 to 1.13)
Blackwell et al (2020)[4,] PROLONG	1652	6 (0.5%)	3 (0.5%)	RR, 0.98 (0.24 to 3.91)
Neonatal Morbidity Composite Outcome				
Meis et al (2003)[3,]	N/A	N/A	N/A	N/A
Blackwell et al (2020)[c4,] PROLONG	1652	61 (5.6%)	28 (5.0%)	RR, 1.12 (0.72 to 1.72)

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[a] <35 weeks of gestation is primary outcome for Blackwell, [b] <37 weeks of gestation is primary outcome for Meis, [c]Co-primary endpoint defined as "neonatal death, grade 3 or 4 intraventricular hemorrhage, respiratory distress syndrome, bronchopulmonary dysplasia, necrotizing enterocolitis, or proven sepsis"
IM: Intramuscular; N/A: Not Applicable; NICU: Neonatal Intensive Care Unit; NR: Not Reported; PROLONG: Progestin's Role in Optimizing Neonatal Gestation; RCT: Randomized Controlled Trial; RR: Relative Risk.

Tables 3 and 4 summarize the relevance and conduct limitations of the 2 RCTs. In Meis et al (2003), there was a significantly higher proportion of women in the placebo group with ≥ 1 prior preterm birth at baseline. The significant benefit for IM progesterone in risk of preterm birth <37 weeks remained after adjustment for the number of prior preterm births, (RR=0.70; 95% CI, 0.57 to 0.85). Other potential unmeasured confounding, such as pharmacogenetic factors, may exist. The high baseline risk of preterm birth may limit the relevance of findings from this RCT to a very high-risk US population.

In Blackwell et al (2020), a major conduct limitation is that it was underpowered to assess its planned outcomes. This is due to event rates being much lower than expected (e.g., 8% instead of 30% for preterm birth <35 weeks). This is demonstrated by the upper and lower bounds of the 95% CIs for effect estimates including both clinically meaningful increases and decreases in risk. This limitation precludes drawing conclusions based on these findings. Another important limitation to comparability to the Meis et al study population is the low rate of participants with more than 1 prior preterm birth as well as participants with a short cervix. The majority of participant enrollments were from international sites (i.e., 60% from Russia and Ukraine). There was limited participation of US academic medical centers and members of the MFMU Network. This potentially reflects the availability and common use of 17P as a standard of care during the study period for highest-risk patients and their exclusion from the PROLONG trial. These characteristics may limit the relevance to high-risk US women.

Table 3. RCT - Study Relevance Limitations

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Follow-Up[e]
Meis et al (2003)[3,]	1,4. Very high-risk population: 59% black women (known risk factor for PTB); baseline risk of recurrent PTB in placebo group of 54.9%				

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Blackwell et al (2020)[4,] PROLONG	1,4. Lower than expected proportion of women with a short cervix (2%); lower than expected rate of women with more than 1 prior PTB (13%); small US cohort (23% of total participants)				

PROLONG: Progestin's Role in Optimizing Neonatal Gestation; PTB: preterm birth; RCT: Randomized Controlled Trial; US: United States
The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
[a] Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.
[b] Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4.Not the intervention of interest.
[c] Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively.
[d] Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. No CONSORT reporting of harms; 4. Not establish and validated measurements; 5. Clinical significant difference not prespecified; 6. Clinical significant difference not supported.
[e] Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms.

Table 4. RCT - Study Design and Conduct Limitations

Study	Allocation[a]	Blinding[b]	Selective Reporting[c]	Data Completeness[d]	Power[e]	Statistical[f]
Meis et al (2003)[3,]	4. Significantly higher proportion of women in placebo group had >1 prior PTB (41.2% vs. 27.7%; p=.004)					

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Blackwell et al (2020)[4,] PROLONG					4. Due to much lower than expected PTB event rates, study is underpowered	

PROLONG: Progestin's Role in Optimizing Neonatal Gestation; PTB: Preterm birth; RCT: randomized controlled trial. The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
[a] Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias.
[b] Blinding key: 1. Not blinded to treatment assignment; 2. Not blinded outcome assessment; 3. Outcome assessed by treating physician. 4. Blinding unclear.
[c] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.
[d] Data Completeness key: 1. High loss to follow-up or missing data; 2. Inadequate handling of missing data; 3. High number of crossovers; 4. Inadequate handling of crossovers; 5. Inappropriate exclusions; 6. Not intent to treat analysis (per protocol for noninferiority trials).
[e] Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference; 4. Study did not meet conditions of power calculations.
[f] Statistical key: 1. Analysis is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Analysis is not appropriate for multiple observations per patient; 3. Confidence intervals and/or p values not reported; 4. Comparative treatment effects not calculated.

COMPARISON TO VAGINAL PROGESTERONE

Systematic Reviews

Several RCTs have been published that compare IM progesterone with vaginal progesterone and include women with a prior preterm birth. Systematic reviews have summarized these RCTs. Characteristics of the systematic reviews are shown in Table 5. Table 6 provides a crosswalk of the trials included in the systematic reviews.

A relevant meta-analysis from the EPPPIC Group (2021) was summarized above.[11,] Vaginal and IM progesterone were compared in a meta-analysis of data from 2 RCTs. A notable relevancy limitation of this meta-analysis is the inclusion of data from an RCT that included women with a short cervix (<25 mm). Oler et al (2017) conducted a systematic review of 3 RCTs published between 2013 and 2016.[14,] A total of 680 women with prior preterm birth(s) were analyzed. This excludes a subgroup of 45 women with a short cervix and no history of preterm birth from the RCT by Bafghi et al (2015). The RCTs varied in the formulation of vaginal progesterone used, length of pregnancy at treatment initiation, and duration of treatment. The primary outcome measure was preterm birth before 34 weeks of pregnancy. Risk ratios were calculated using a fixed-effects model. The risk of major biases in the individual studies included in the meta-analysis was assessed by 2 researchers using Cochrane Collaboration standards.

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Choi et al (2020) conducted a systematic review of 6 RCTs published between 2013 and 2019.[15,] A total of 1369 women with a prior preterm birth (n=908, 66%), a short cervix (n=445, n=33%), or both (n=16, 1%) were analyzed. The RCTs varied in their inclusion of women with a short cervix and no previous preterm birth (range, 0% to 100%), the formulation of vaginal progesterone used, the length of pregnancy at treatment initiation, and duration of treatment. The primary outcomes of the meta-analysis were preterm birth before 37, 34, and 28 weeks. Risk ratios were calculated using a fixed-effects model. The risk of major biases in the individual studies included in the meta-analysis was not assessed.

Table 5. SR & M-A Characteristics

Study	Search Dates	Trials	Participants	N (Range)	Design	Duration
EPPPIC Group (2021)[11,]	Inception to June 30, 2019	31 total; 16 studies included women with singleton pregnancies	Asymptomatic women with singleton or multifetal pregnancies at risk of PTB; 2 studies evaluated VP vs. 17P in women with singleton pregnancies	224 (78-146)	RCT	Progesterone was started between 16 and 21 weeks of gestation.
Oler et al (2017)[14,]	Inception to Nov 2016	3	Singleton pregnancies irrespective of cervical length	680 (33-502)	RCT	From 14 to 20 weeks of gestation *until* 36 weeks of gestation, delivery, or PPROM or until delivery.
Choi et al (2020)[15,]	Inception to Feb 2020	6	Singleton pregnant women with a history of PTB or short cervix	1369 (78-502)	RCT	From 14 to 24 weeks of gestation *until* 36 weeks of gestation, delivery, or PPROM or until delivery.

17P: 17-hydroxyprogesterone caproate; EPPPIC: Evaluating Progestogens for Preventing Preterm Birth International Collaborative; PPROM: Preterm premature rupture of the membranes; PTB: Preterm birth; RCT: randomized controlled trial; VP: vaginal progesterone.

Table 6. Comparison of Trials Included in SR & M-A

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Study	N	Participants	IM progesterone	Vaginal progesterone	Length of pregnancy at treatment initiation (weeks)	Treatment completion	Country	Oler et al (2017)[14]	Choi et al (2020)[15]	EPPPIC Group (2021)[11]
Maher et al (2013)[16]	518	Prior preterm birth; excluded short cervix	250 mg weekly	Gel, 90 mg daily	14 to 18	36 weeks of gestation, delivery, or PPROM	Saudi Arabia	•	•	
Bafghi et al (2015)[17]	78	Prior preterm birth (n=33, 42%) or short cervix (<25 mm) (n=45, 58%)	250 mg weekly	Cyclogest suppository, 200 mg daily	16 to 20	Delivery	Iran	•	•	•
Elmian et al (2016)[18]	145	Prior preterm birth or PPROM; cervical length was not routinely measured	250 mg weekly	Micronized suppository, 100 mg daily	16 to 20	36 weeks plus 6 days gestation or delivery	United States	•	•	•
Pirjani et al (2017)[19]	304	Short cervix (<5 mm)	250 mg weekly	Suppository, 400 mg daily	16 to 24	36 weeks of gestation	Iran		•	

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Study	N	Participants	IM progesterone	Vaginal progesterone	Length of pregnancy at treatment initiation (weeks)	Treatment completion	Country	Oler et al (2017)[14,]	Choi et al (2020)[15,]	EPPPIC Group (2021)[11,]
						or delivery				
Shambhavi et al (2018)[20,]	100	Prior preterm birth	250 mg weekly	Micronized effervescent tablet, 200 mg daily	16 to 24	37 weeks of gestation or delivery	India		•	
Choi et al (2020)[15,]	266	Either prior preterm birth (n=128, 52%) or short cervix (<25 mm) (n=103, 42%), or both (n=16, 6%)	250 mg weekly	Utrogestan, micronized natural capsule, 200 mg	16 to 22	36 weeks of gestation or delivery or PPROM	South Korea		•	

EPPPIC: Evaluating Progestogens for Preventing Preterm Birth International Collaborative; IM: intramuscular; PPROM: Preterm premature rupture of the membranes.

Results of the systematic reviews are shown in Table 7. Results from a meta-analysis by the EPPPIC Group favored vaginal progesterone over 17P for the reduction in preterm birth before 37, 34, and 28 weeks of gestation, maternal complications (odds ratio [OR], 2.15; 95% CI, 0.66 to 6.99), perinatal death (OR, 1.77; 95% CI, 0.59 to 5.30), and serious neonatal complications (OR, 1.68; 95% CI, 0.62 to 4.59), but statistical significance was not reached in any of these analyses.[11,]The review by Oler et al (2017)[14,] found significantly lower rates of the primary

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outcome of preterm birth before 34 weeks of gestation with vaginal progesterone, but no significant differences at <28 or <37 weeks of gestation. The difference in preterm birth before 34 weeks was largely based on data from a single RCT by Maher et al (2013)[16,] that represented 82% of the overall sample. The formulation of vaginal progesterone used in this RCT was a gel, administered at 90 mg daily. Oler et al (2017) did not analyze neonatal mortality or morbidity outcomes due to insufficient data. There were no significant differences in respiratory distress syndrome and NICU admission. Only 1 RCT reported adverse treatment reactions, which were lower among the IM progesterone group (12.3% vs. 17.4%; RR, 0.53; 95% CI, 0.31 to 0.91).

In the review by Choi et al (2020),[15,] there were no significant differences between IM and vaginal progesterone in risk of preterm birth before 37, 34, or 28 weeks of gestation. No other outcomes were reported. A notable relevance limitation of this review is that 34% of women in the pooled study population had a short cervix and no history of prior preterm birth, which is not representative of the target population of women with prior preterm births.

Table 7. SR & M-A Results for Intramuscular versus Vaginal Progesterone

Study	Risk of PTB <37 weeks	Risk of PTB <34 weeks	Risk of PTB <28 weeks
Oler et al (2017)[14,]			
Total N	680	680	1182
RR (95% CI)	0.92 (0.75 to 1.12)	0.71 (0.53 to 0.95)	0.93 (0.54 to 1.60)
I^2 (p)	*0%*	*0%*	*0%*
Range of N	33 to 502	33 to 502	502 to 680
Range of effect sizes	0.86 to 0.94	0.65 to 0.90	0.87 to 0.95
Choi et al (2020)[15,]			
Total N	1367	1289	1142
RR (95% CI)	0.91 (0.77 to 1.08)	0.80 (0.61 to 1.04)	1.09 (0.62 to 1.90)
I^2 (p)	*0%*	*26%*	*0%*
Range of N	78 to 502	100 to 502	100 to 502
Range of effect sizes	0.78 to 1.08	0.48 to 1.56	0.32 to 2.15
EPPPIC Group (2021)[11,]			
Total events	NR	NR	NR

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RR (95% CI)	1.15 (0.82 to 1.61)	1.18 (0.69 to 2.03)	1.06 (0.41 to 2.78)
I^2 (p)	NR	NR	NR
Range of N	NR	NR	NR
Range of effect sizes	NR	NR	NR

17P: 17-hydroxyprogesterone caproate; CI: confidence interval; EPPPIC: Evaluating Progestogens for Preventing Preterm Birth International Collaborative; M-A: mete-analysis; NR: not reported; PTB: preterm birth; RR: relative risk; SR: systematic review; VP: vaginal progesterone.

Randomized Controlled Trials

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

Boelig et al (2022) published results from an RCT that included 205 women from 5 U.S centers with singleton pregnancies at <24 weeks of gestation who had a previous spontaneous preterm birth.[21,] Patients were randomized to receive either 200 mg vaginal progesterone nightly (n=94) or 250 mg IM 17P weekly (n=94) from 16 to 36 weeks of gestation. There was no significant difference in preterm birth between the vaginal or IM progesterone groups at <37 weeks (31% vs. 38%; p=.28; RR, 0.81; 95% CI, 0.54 to 1.20), at <34 weeks (9.6% vs. 14.9%; p=.26; RR, 0.64; 95% CI, 0.29 to 1.41), or at <28 weeks (1.1% vs. 4.3%; p=.37; RR, 0.25; 95% CI, 0.03 to 2.20).

Choi et al (2020) published the 'Vaginal Compared with Intramuscular Progestogen for Preventing Preterm Birth in High-Risk Pregnant Women' (VICTORIA) study that compared 200 mg of vaginal micronized progesterone daily (n=131) with weekly IM injections of 17P 250 mg (n=135). This RCT was a multicenter, open-label, equivalence trial of 266 pregnant women with a history of spontaneous preterm birth or short cervical length (<25 mm).[15,] Women were enrolled from tertiary referral hospitals in South Korea. The study population consisted of 52% with a preterm birth history, 42% with a short cervix, and 6% with both a preterm birth history and a short cervix. In the subgroup of women with a preterm birth history (n=128), there were no statistically significant differences between the vaginal and IM progesterone groups in risk of preterm birth before 37 weeks of gestation (23.8% [15/63] vs. 27.7% [18/65]; RR=0.86; 95% CI, 0.48 to 1.55). There were also no differences between groups in the overall study population on secondary outcomes including maternal and neonatal morbidities, adverse events, and patient satisfaction. A notable relevance limitation of the secondary outcome findings is that they included data from the 34% of women with a short cervix and no prior preterm birth. Secondary outcomes were not separately provided for the subgroup with previous preterm birth.

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Shambhavi et al (2018) published results from a randomized, non-controlled trial, that compared the effectiveness of micronized progesterone in effervescent vaginal tablet form (200 mg daily) to IM 17P (250 mg weekly) in preventing recurrent preterm birth.[20,] One hundred participants with singleton pregnancies between 16 and 24 weeks of gestation and at least 1 prior spontaneous preterm birth were randomly allocated to receive either the vaginal (n=50) or IM (n=50) progesterone until 37 weeks' gestation or delivery. Similar rates of preterm birth before 37 weeks of gestation were found for the 2 interventions (20% for the vaginal tablet group and 20.8% for the 17P group, p=.918). The preterm birth rate at <34 weeks (p=.319) or <28 weeks (p=.490) were also similar. Comparable means of gestation at delivery were found as well, with the vaginal progesterone group delivering at 37.4 weeks (standard deviation = 1.67) and the 17P at 37.0 (2.78). All neonates were live-born, and the outcomes were similar between the 2 groups. Overall, the study found no statistically significant difference between the 2 interventions in preventing recurrent preterm birth.

Elimian et al (2016) published results of a trial that included 174 women with singleton pregnancies between 16 and 20 weeks 6 days of gestation with a history of preterm delivery.[18,] 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=.50). Moreover, there were no statistically significant differences in secondary outcomes (e.g., the proportion of women who delivered before 34 weeks or before 28 weeks).

Mahar et al (2013) published results of an unblinded RCT, published by Mahar et al (2013), that 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.[16,] 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 (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 NICU, which was significantly higher in the IM progesterone group (n=64 [26%]) than in the vaginal progesterone group (n=39 [15%]; p=.006). A significantly higher rate of adverse effects was also reported by

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patients in the IM progesterone group (n=35 [14%]) than in the vaginal progesterone group (n=19 [8%]; p=.017).

Section Summary: Intramuscular Injections of Progesterone for a Singleton Pregnancy and Prior Spontaneous Preterm Birth Before 37 Weeks of Gestation
Two RCTs have compared IM progesterone to placebo in individuals who have a singleton pregnancy and prior spontaneous preterm birth. In the RCT by Meis et al (2003), used to support FDA accelerated approval, IM progesterone significantly reduced the risk of the primary outcome of preterm delivery at <37 weeks of gestation as well as <35 and <32 weeks' gestation. Infants of women treated with 17P had significantly lower rates of necrotizing enterocolitis, intraventricular hemorrhage, and need for supplemental oxygen. There were no differences in any other neonatal mortality or morbidity outcomes. There were no significant differences between the 2 groups for maternal health-related complications such as the rates of hospital visits for preterm labor, use of tocolytics or corticosteroids, cesarean delivery, or chorioamnionitis. The study was not planned or conducted for drug approval and was not powered for all neonatal morbidity or mortality outcomes. Gestational outcomes are considered surrogate outcomes expected to predict clinical benefit. The confirmatory RCT by Blackwell et al (2020, PROLONG) found no significant benefit for IM progesterone for the primary outcome of preterm birth <35 weeks as well as a defined neonatal composite outcome. The preterm birth rate in PROLONG was approximately 50% lower than that in the Meis trial despite using a similar design, and therefore, the study was underpowered to assess the primary outcomes. Additionally, PROLONG included a high proportion of patients enrolled from non-US regions further limiting the clinical relevancy of the overall findings to US high-risk women. In the planned prespecified subgroup analysis of the treatment effects for the US subgroup versus non-US subgroups, there were nonsignificant trends of benefit for IM progesterone efficacy for preterm birth before 32 and 35 weeks of gestation, but not before 37 weeks of gestation. One systematic review pooled findings from the 2 key RCTs, and similarly concluded that 17P did not lead to significant reductions in preterm birth rates before 37, 35, and 32 weeks of gestation or fetal death. Another systematic review that used participant-level data from 13 studies likewise did not find significant reductions in preterm birth rates before 37, 34, or 28 weeks of gestation or fetal death with 17P versus control (placebo or standard of care).

Several RCTs have been published that compare IM progesterone with vaginal progesterone and include women with a prior preterm birth. The RCTs varied in the formulation of vaginal progesterone used, length of pregnancy at treatment initiation, and duration of treatment. Three systematic reviews summarized findings from these RCTs, as well as additional RCTs that varied in their inclusion of women with a short cervix and no previous preterm birth (range, 0% to 100%). The 2017 review that exclusively included women with prior preterm birth and no other risk factors found significantly lower rates of preterm birth before 34 weeks of gestation with vaginal progesterone, but no other differences. Two reviews published in 2020 and 2021 did not

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find a difference in preterm birth before 37, 34, or 28 weeks of gestation. The 2020 review pooled study population included 34% of women with short cervices and no prior preterm birth, which is not representative of the target population. This limitation precludes drawing conclusions based on the 2020 review. In the 2021 review, there was heterogeneity in baseline risk of preterm birth amongst included study populations. The 2021 review pooled data on neonatal mortality and morbidity outcomes, demonstrating no statistically significant differences between routes of administration in the risk of serious neonatal complications or perinatal death. However, results trended in favor of vaginal progesterone. These RCTs and reviews demonstrate that differences exist by type of vaginal product used and by varying etiologies for risk of preterm birth.

The RCT with a population most relevant to US women demonstrated a benefit for IM progesterone versus placebo on the surrogate outcomes of preterm birth before 37, 35, and 32 weeks of gestation. Conducting a new confirmatory placebo-controlled trial would be ideal, but is unlikely because IM progesterone has been widely used for many years and continues to be guideline-recommended.

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

Clinical Context and Therapy Purpose

The purpose of vaginal progesterone therapy administered 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 vaginal 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 PICO was used to select literature to inform this review.

Populations

The relevant population of interest is women with a singleton pregnancy and prior spontaneous preterm birth before 37 weeks of gestation and predominantly without cervical shortening. Transvaginal ultrasound cervical length screening for women with a singleton pregnancy and a history of prior spontaneous preterm birth is common. Identification of a shortened cervix suggests an additive risk and may dictate additional treatment, such as cervical cerclage. Other known factors that increase the risk of recurrent preterm birth in women with a prior spontaneous preterm birth are a history of multiple preterm births and no term pregnancy between the previous spontaneous preterm birth and the current pregnancy.

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Interventions
The therapy being considered is vaginal progesterone.

Comparators
For women with a history of spontaneous preterm birth, progesterone supplementation has become the standard of care for managing the risk of recurrent preterm birth. Thus, the primary comparator of interest is IM progesterone.

Outcomes
The general outcomes of most interest are direct clinical benefits including OS, (e.g., neonatal death), morbid events (e.g., postnatal respiratory distress, neonatal intensive care, child functional impairment), and treatment-related morbidity (e.g., maternal adverse drug reactions). Gestational outcomes (e.g., gestational age, preterm birth <32, 35, or 37 weeks) are considered surrogate outcomes expected to predict clinical benefit.

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 long-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.

REVIEW OF EVIDENCE

Systematic Reviews
Several RCTs have been published that compare vaginal progesterone with placebo and include women with a prior preterm birth. These RCTs are heterogenous in the proportion of women with prior preterm births (range, 79% to 100%), the presence of other risk factors (e.g., short cervix, pregnancies of multiples), the formulation (e.g., tablet, capsule, gel, pessary), dose and duration of vaginal progesterone used, and the control treatment (e.g., placebo, no treatment). Five systematic reviews[22,23,] have combined data from these RCTs. Table 8 provides a crosswalk of the trials included in the systematic reviews.

Conde-Agudelo et al (2022) published a systematic review and meta-analysis assessing the efficacy and safety of vaginal progesterone to prevent recurrent preterm birth in singleton pregnancies in women with a history of spontaneous preterm birth. [24,] Data from 10 studies were

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included (N=2958) and results demonstrated that vaginal progesterone significantly decreased the risk of preterm birth <37 weeks (RR, 0.64; 95% CI, 0.50 to 0.81) and <34 weeks (RR, 0.62; 95% CI, 0.42 to 0.92), but there was no significant differences between vaginal progesterone versus placebo in other adverse maternal or perinatal outcomes.

A relevant meta-analysis from the EPPPIC Group (2021) was summarized above. Nine trials compared vaginal progesterone with control (placebo or standard of care) in singleton pregnancies in women at risk of preterm birth (N=3769).[11,] Three of the 9 trials of vaginal progesterone included a mixed population of women with singleton and multifetal pregnancies. Results demonstrated that vaginal progesterone significantly reduced the risk of preterm birth before 34 weeks of gestation (RR, 0.78; 95% CI, 0.68 to 0.90); statistical significance was not reached at <37 weeks (RR, 0.92; 95% CI, 0.84 to 1.00) or < 28 weeks (RR, 0.81; 95% CI, 0.62 to 1.06) of gestation. The increased risk of maternal complications (RR, 1.14; 95% CI, 0.93 to 1.40) and decreased risk of serious neonatal complications (RR, 0.82; 95% CI, 0.65 to 1.04) and fetal death/stillbirth (RR, 0.94; 95% CI, 0.53 to 1.65) observed with vaginal progesterone also did not reach statistical significance.

Phung et al (2021) published a meta-analysis evaluating whether vaginal progesterone reduces spontaneous preterm birth before 37 weeks of gestation in asymptomatic high-risk women with a singleton pregnancy and normal mid-gestation cervical length.[25,] Data from 3 studies (N=1127) were analyzed. Results demonstrated that vaginal progesterone did not significantly reduce spontaneous preterm birth before 37 weeks (RR, 0.76; 95% CI, 0.37 to 1.55) or before 34 weeks (RR, 0.51; 95% CI, 0.12 to 2.13) of gestation. No additional outcomes were explored in this review.

The National Institute for Health and Care Excellence (NICE) (2019) published an evidence review on the clinical effectiveness of prophylactic progesterone in preventing preterm labor to inform their guideline NG25.[26,] The target population was pregnant women (singleton or multiple gestations) at risk of preterm labor and birth due to any of several possible risk factors: a history of spontaneous preterm birth, a history of preterm pre-labor rupture of membranes, a history of mid-trimester loss, mid-trimester bleeding, a history of cervical trauma, a short cervix that has been identified on scan and/or bulging membranes in the current pregnancy, and a positive fetal fibronectin test. Comparators of interest were 1 intervention compared to another, placebo, or no treatment. Prespecified 'critical outcomes' were preterm birth before 34 weeks of gestation, stillbirth, and infant mortality prior to discharge. Other 'important outcomes' were gestational age at birth, early onset of neonatal sepsis, maternal satisfaction/quality of life, and neurodevelopmental outcomes at 18 months or greater. The NICE review included the 5 RCTs identified below, as well as the Cochrane review by Dodd et at (2013), and further RCTs and an individual patient data meta-analysis including populations with a wider range of risk factors (e.g., twins, short cervix) and/or comparators (e.g., no treatment). De novo pooled analyses

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were conducted using data from the original articles, rather than extracting estimates from the Cochrane review by Dodd et al (2013). Subgroup analyses were performed on the studies including women with a history of spontaneous preterm birth. Results from the subgroup analyses found that vaginal progesterone significantly reduced the risk of preterm birth before 34 weeks of gestation (5 RCTs, n=507; RR, 0.27; 95% CI, 0.15 to 0.49), but not stillbirth (2 RCTs; n=1410; RR, 0.97; 95% CI, 0.39 to 2.44), or infant mortality (2 RCTs; n=1551; RR, 0.53; 95% CI, 0.25 to 1.12). Among the other pooled 'important outcomes', the only significant difference was a significant benefit for progesterone in reducing the risk of neonatal sepsis (3 RCTs; n=1031; RR, 0.14; 95% CI, 0.03 to 0.79).

A meta-analysis by Ahn et al (2017) focused on the outcome of neonatal mortality.[22,] Twenty-two RCTs, which included pregnant women with various risk factors for preterm birth (e.g., prior preterm birth, short cervix, multiple gestations), 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 versus placebo. For example, for women with singleton pregnancies treated with IM progesterone versus 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 in women with a previous spontaneous preterm birth; 4 used IM progesterone, 5 used vaginal progesterone, and 2 used oral progesterone.[23,] The 5 RCTs of vaginal progesterone were heterogenous in their population (i.e., singletons and twins) and their comparators (i.e., placebo or no treatment). In a pooled analysis of data from the 5 studies, vaginal progesterone significantly reduced the rate of preterm birth before 37 weeks of gestation (n=1065, RR, 0.52; 95% CI, 0.29 to 0.92).

A notable relevancy limitation of all 5 reviews is that their meta-analyses pooled data from RCTs representative of the intended population and comparators with those that are not, due to their inclusion of women with a variety of additional risk factors. This relevancy limitation precludes drawing conclusions about the applicability of the review findings to the intended population.

Table 8. Comparison of Placebo-Controlled Trials of Vaginal Progesterone Included in SR & M-A

Primary Study (Year)	**Conde-Agudelo (2022)[24,]**	**Phung et al (2021)[25,]**	**EPPPIC Group (2021)[11,]**	NICE (2019)[26,]	**Ahn et al (2017)[22,]**	**Dodd et al (2013)[23,]**

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Crowther et al (2017)[27,]	●		●	●		
Norman et al (2016, 2018)[28,29,]	●	●	●	●		
Azargoon et al (2016)[30,]	●		●			
Van os et al (2015)[31,]		●	●			
Aboulghar et al (2012)[32,]			●			
Cetingoz et al (2011)[33,]	●					
Hassan et al (2011)[34,]			●			
Majhi et al (2009)[35,]	●		●	●		●
O'Brien et al (2007)[36,]	●	●	●	●	●	●
Da Fonseca et al (2003)[37,]	●		●	●		●

EPPPIC: Evaluating Progestogens for Preventing Preterm Birth International Collaborative; M-A: Meta-Analysis; NICE: National Institute for Health and Care Excellence; SR: Systematic Review.

Randomized Controlled Trials

Crowther et al (2017) published results from the vaginal progesterone pessaries for pregnant women with a previous preterm birth to prevent neonatal respiratory distress syndrome trial, a multicenter, randomized, placebo-controlled trial of women with a history of a previous spontaneous preterm birth.[27,] 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=.204). A trial limitation was poor patient compliance, with nearly 9% of participants failing to start or appropriately use the medication; the progesterone dosage used (100 mg) was also significantly lower than used in other trials (e.g., the OPPTIMUM trial, discussed next).

Norman et al (2016, 2018) published results from the 'dOes Progesterone Prophylaxis To prevent preterm labour IMprove oUtcoMe?' (OPPTIMUM) RCT.[28,29,] This large multicenter, double-blind trial evaluated outcomes in women pregnant with singleton pregnancies who had 1 of several possible risk factors for preterm birth. The trial enrolled 1228 women randomized to vaginal progesterone tablets 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

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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. Sixteen percent (96/600) of women in the treatment group and 18% (108/597) in the placebo group experienced fetal death or delivery before 34 weeks, the primary obstetric outcome (OR, 0.86; 95% CI, 0.61 to 1.22). Eight percent (46/589) of babies born to women in the treatment group and 11% (62/587) of those born to women in the placebo group experienced the primary neonatal outcome (OR, 0.72; 95% CI, 0.44 to 1.17). The mean Bayley-III cognitive score of the 2-year-old children whose mothers were in the treatment group was 97.3 points (standard deviation=17.9 points; n=430) and 97.7 points for the children of the placebo group (standard deviation=17.5 points; n=439; difference in means=-0.48; 95% CI, -2.77 to 1.81). Overall compliance with the assigned intervention was 69%. The authors concluded that progesterone had no statistically significant beneficial or harmful effects on any of the primary outcomes.

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.[35,] 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 of gestation; this difference was statistically significant (p=.003). The difference in the rates of preterm birth before 34 weeks of gestation (2 [4%] in the progesterone group and 3 [6%] in the control group) was not statistically significant (p=.64), but this analysis might have been underpowered.

O'Brien et al (2007) published a large multinational study (including sites in the U.S.).[36,] 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 of gestation (42% vs. 41%), <32 weeks of gestation (10% vs. 11%), or mean gestational age at delivery (36.6 weeks vs. 36.6 weeks), 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 published 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.[37,] 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 of gestation was 13.8% in the intervention group and 28.5% in the control group; this difference was statistically significant (p<.03). The rate of delivery before 34 weeks of

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gestation 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<.002).

Section Summary: Vaginal Progesterone for a Singleton Pregnancy and Prior Spontaneous Preterm Birth Before 37 Weeks of Gestation
A number of placebo-controlled RCTs and systematic reviews have evaluated vaginal progesterone for women with singleton pregnancies. These RCTs are heterogenous in the proportion of women with prior preterm births (range, 79% to 100%), the presence of other risk factors (e.g., short cervix, pregnancies of multiples), the formulation (e.g., tablet, capsule, gel, pessary), dose and duration of vaginal progesterone used, and the control treatment (e.g., placebo, no treatment). The RCTs demonstrate that differences in the effects of vaginal progesterone exist based on these sources of heterogeneity. Identification of specific subpopulations of women who may benefit most and/or optimal vaginal progesterone regimens is still needed. The 2 most comprehensively performed systematic reviews with meta-analyses (EPPPIC group [2021] and NICE [2019]) found decreased preterm birth rates at <34 weeks of gestation with vaginal progesterone.

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

Clinical Context and Therapy Purpose
The purpose of progesterone therapy administered by IM injection 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 administered by IM injection improve the net health outcome in women with a singleton pregnancy and short cervical length?

The following PICO was used to select literature to inform this review.

Populations
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.

Comparators

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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 outcomes of most interest are direct clinical benefits including OS (e.g., neonatal death), morbid events (e.g., postnatal respiratory distress, neonatal intensive care, child functional impairment), and treatment-related morbidity (e.g., maternal adverse drug reactions). Gestational outcomes (e.g., gestational age, preterm birth <32, 35, or 37 weeks) are considered surrogate outcomes expected to predict clinical benefit.

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 long-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.

REVIEW OF EVIDENCE

Randomized Controlled Trial

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 (i.e., participants did not have a history of preterm birth).[38,] The trial was conducted at 14 centers in the U.S. 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 of gestation) 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 an interim analysis by an independent data and safety monitoring board determined there was an extremely low probability of finding a significant difference between groups if enrollment continued. Therefore, the trial was halted early.

Additional RCTs comparing IM progesterone to vaginal progesterone in women with short cervical length were identified and are discussed in the vaginal progesterone section below.

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Section Summary: Intramuscular Progesterone Therapy for Singleton Pregnancy and Short Cervix
One placebo-controlled RCT (which was halted early based on interim analysis) was identified that assessed the efficacy of IM progesterone. The study found a low probability of statistical significance between the 2 groups.

Vaginal Progesterone Therapy for a Singleton Pregnancy and Short Cervix (< 20 mm)
Clinical Context and Therapy Purpose
The purpose of vaginal progesterone therapy administered 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 vaginal progesterone therapy improve the net health outcome in women with a singleton pregnancy and short cervical length?

The following PICO was used to select literature to inform this review.

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

Interventions
The therapy being considered is 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 or the use of IM progesterone.

Outcomes
The outcomes of most interest are direct clinical benefits including OS (e.g., neonatal death), morbid events (e.g., postnatal respiratory distress, neonatal intensive care, child functional impairment), and treatment-related morbidity (e.g., maternal adverse drug reactions). Gestational outcomes (e.g., gestational age, preterm birth <32, 35, or 37 weeks) are considered surrogate outcomes expected to predict clinical benefit.

Study Selection Criteria
Methodologically credible studies were selected using the following principles:

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- 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 long-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.

REVIEW OF EVIDENCE

SYSTEMATIC REVIEWS

Comparison to Placebo

The National Institute for Health and Care Excellence (NICE) (2019) published an evidence review on the clinical effectiveness of prophylactic progesterone in preventing preterm labor to inform their guideline NG25.[26,] The target population was pregnant women (singleton or multiple gestations) at risk of preterm labor and birth due to any of several possible risk factors: a history of spontaneous preterm birth, a history of preterm pre-labor rupture of membranes, a history of mid-trimester loss, mid-trimester bleeding, a history of cervical trauma, a short cervix that has been identified on scan and/or bulging membranes in the current pregnancy, and a positive fetal fibronectin test. Comparators of interest were 1 intervention compared to another, placebo, or no treatment. Prespecified 'critical outcomes' were preterm birth before 34 weeks of gestation, stillbirth, and infant mortality prior to discharge. Other 'important outcomes' were gestational age at birth, early onset of neonatal sepsis, maternal satisfaction/quality of life, and neurodevelopmental outcomes at 18 months or greater. The NICE review included the placebo-controlled RCT by van Os et al (2015) identified below, as well as the Cochrane review by Dodd et at (2013), the individual patient data meta-analysis by Romero et al (2018), and further RCTs of populations other than the intended population, with additional risk factors (e.g., history of preterm birth) or cervical lengths other than the intended <20 mm (e.g., <15 mm or <30 mm). De novo pooled analyses were conducted using data from the original articles, rather than extracting estimates from the Cochrane review by Dodd et al (2013). Subgroup analyses were performed on the studies including women with a short cervical length (<15 mm to <30 mm). Results from the subgroup analyses found that vaginal progesterone significantly reduced the risk of preterm birth before 34 weeks of gestation (3 RCTs, N=357; RR, 0.58; 95% CI, 0.40 to 0.86), but not infant mortality (3 RCTs; N=812; RR=0.42; 95% CI, 0.16 to 1.08). There were no significant differences in other outcomes. A notable relevancy limitation of this review is that the meta-analyses pooled data from RCTs representative of the intended population with those that are not, due to the inclusion of women with various cervical lengths and/or additional risk factors. This relevancy limitation precludes drawing conclusions about the applicability of the review findings to the intended population.

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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).[39,] Five studies were included (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<.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=.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.[40,] Five RCTs were included in the meta-analysis. Two of the trials, Hassan et al (2011)[34,] and Fonseca et al (2007),[41,] limited enrollment to women with a short cervix (defined as ≤15 mm in 1 study and 10 to 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 pregnancy and no history of preterm birth, there remained a significant benefit of progesterone treatment to reduce the rate of preterm birth before 33 weeks of gestation (RR, 0.60; 95% CI, 0.39 to 0.92). This 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 a 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).

Intramuscular Progesterone versus Vaginal Progesterone

A relevant meta-analysis from the EPPPIC Group (2021) was summarized above.[11,] Intramuscular progesterone was compared to vaginal progesterone in an analysis of data from women with

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singleton pregnancies and cervical length ≤25 mm. Cervical length was not recorded in all studies, so analyses were based on 65% to 70% of women (approximately 1454 women). Results favored vaginal progesterone for a reduction in preterm birth before 37 (OR, 1.17; 95% CI, 0.53 to 2.65), 34 (OR, 1.25; 95% CI, 0.48 to 3.03), and 28 (OR, 1.06; 95% CI, 0.29 to 4.21) weeks of gestation, perinatal death (OR, 1.06; 95% CI, 0.20 to 5.91), and serious neonatal complications (OR, 1.14; 95% CI, 0.33 to 4.10), but statistical significance was not reached in any of these analyses. There was also a nonsignificant statistical trend of benefit for a reduction in maternal complications with IM progesterone (OR, 0.74; 95% CI, 0.09 to 4.67). A notable relevancy limitation of this review is that the meta-analysis pooled data from RCTs representative of the intended population with those that are not, due to the inclusion of women with a short cervical length that was >20 mm and additional risk factors.

RANDOMIZED CONTROLLED TRIALS

Comparison to Placebo

van Os et al (2015) conducted a small, placebo-controlled randomized trial on women with a short cervical length (≤30 mm) and no prior preterm birth.[31,] In this trial, the RR of preterm birth before 32 weeks of gestation 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 since enrollment was stopped early due to an unexpectedly low number of women with a short cervix.

Intramuscular Progesterone versus Vaginal Progesterone

Choi et al (2020) published the South Korean VICTORIA RCT that compared 200 mg of vaginal micronized progesterone daily (n=131) with weekly IM injections of 17P 250 mg (n=135) in a multicenter, open, equivalence trial of 266 pregnant women at high-risk of a preterm birth in the current pregnancy.[15,] VICTORIA enrolled women with either a history of preterm birth (52%), a short cervix (<25 mm) (42%), or both (6%). In the subgroup of women with a short cervix (n=103), there was no statistically significant difference between the vaginal progesterone and 17P groups in the risk of preterm birth before 37 weeks of gestation (18.8% [9/48] vs. 18.2% [10/55]; RR, 1.03; 95% CI, 0.46 to 2.33). A key limitation of this subgroup analysis is imprecision. The RCT was not powered to detect differences in preterm birth and neonatal outcomes in the short cervix subgroup. As the upper and lower bounds of the 95% CI for the RR of preterm birth <37 weeks of gestation include both clinically meaningful increases and decreases in risk, no conclusions can be reached based on this finding. No differences were reported between groups overall on secondary outcomes including maternal and neonatal morbidities, adverse events, and patient satisfaction. A notable relevance limitation of the secondary outcome findings is the inclusion of data from the 52% of women with a prior preterm birth and without a short cervix. Secondary outcomes were not separately provided for the subgroup with a short cervix.

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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).[17,] 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=.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=.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 of progesterone for women with a short cervix.

Section Summary: Vaginal Progesterone Therapy for Singleton Pregnancy and Short Cervical Length

Several RCTs have evaluated vaginal progesterone compared to placebo or IM progesterone for preventing preterm birth in women with short cervical length. These trials have tended to be underpowered for meaningful clinical outcomes. Multiple meta-analyses have found that vaginal progesterone significantly reduced the rate of preterm delivery in women with a short cervical length. In addition, there was benefit in a subgroup of women with singleton pregnancies and no prior preterm birth. One meta-analysis compared IM and vaginal progesterone in women with singleton pregnancies and cervical length ≤25 mm. There was a nonsignificant statistical trend of benefit for vaginal progesterone for the reduction in preterm birth, perinatal death, and serious neonatal complications, and a nonsignificant statistical trend of benefit for IM progesterone for the reduction in maternal complications. The inclusion of women with a short cervical length that was >20 mm and additional risk factors for preterm birth is a limitation of this review as it relates to the comparison of IM and vaginal progesterone in the intended population.

PROGESTERONE THERAPY FOR A TWIN GESTATION

Clinical Context and Therapy Purpose

The purpose of progesterone therapy in women who have 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 twin gestation?

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The following PICO was used to select literature to inform this review.

Populations
The relevant population of interest is women with twin gestation. Multifetal pregnancies are at risk of preterm labor and preterm birth.

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 twin gestations: standard of care without progesterone .

Outcomes
The outcomes of most interest are direct clinical benefits including OS (e.g., neonatal death), morbid events (e.g., postnatal respiratory distress, neonatal intensive care, child functional impairment), and treatment-related morbidity (e.g., maternal adverse drug reactions). Gestational outcomes (e.g., gestational age, preterm birth <32, 35, or 37 weeks) are considered surrogate outcomes expected to predict clinical benefit.

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 long-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.

REVIEW OF EVIDENCE

Systematic Reviews
Three systematic reviews with meta-analyses have evaluated women with multiple pregnancies who were treated with vaginal or IM progesterone.[42,11,43,] A crosswalk of relevant trials included in the systematic reviews is provided in Table 9. Characteristics of these systematic reviews are provided in Table 10.

Table 9. Comparison of Trials/Studies Included in SR & M-A

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Study	D'Antonio et al (2021)[42,]	EPPPIC Group (2021)[11,]	Dodd et al (2019)[44,]
Rehal et al (2020)[45,]	●		
Dang et al (2019)[46,]	●		
Crowther et al (2017)[27,]		●	
El-Refaie et al (2016)[47,]	●*		
Awwad et al (2015)[48,]	●	●	●
Brizot et al (2015)[49,]	●	●	●
Senat et al (2013)[50,]	●	●	●
Serra et al (2013)[51,]	●	●	●
Wood et al (2012)[52,]	●	●	●
Aboulghar et al (2012)[32,]	●	●	●
Combs et al (2011)[53,]	●	●	●
Lim et al (2011)[54,]	●	●	●
Rode et al (2011)[55,]	●	●	●
Klein et al (2011)[56,]	●		
Cetingoz et al (2011)[33,]	●		●
Combs et al (2010)[57,]		●	●
Durnwald et al (2010)[58,]	●		
Briery et al (2009)[59,]	●	●	●
Caritis et al (2009)[60,]		●	●
Norman et al (2009)[61,]	●	●	●
Rouse et al (2007)[62,]	●	●	●
Fonseca et al (2007)[41,]	●	●	
Hartikainen-Sorri et al (1980)[63,]			●

*This study was retracted on July 27, 2021.[64,] The authors did not obtain approval from a research ethics committee before conducting this trial. Furthermore, concerns about the data reported in the article are under investigation. Waleed El-Refaie stated on behalf of all co-authors that they do not agree with this retraction.
EPPPIC: Evaluating Progestogens for Preventing Preterm Birth International Collaborative; M-A: meta-analysis; SR: systematic review.

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Table 10. SR & M-A Characteristics

Study	Dates	Trials	Participants	N (Range)	Design	Duration
D'Antonio et al (2021)[42,]	Through March 2021	26 total trials; 18 studies (5821 pregnancies) compared VP (11 studies) or 17P (7 studies) compared to control.	Women with twin pregnancies	3595 (24 to 1169)	RCTs	Not explicitly specified; across studies, progesterone was started between 11 and 24 weeks of gestation
EPPPIC Group (2021)[11,]	Through July 2019	31 trials total; 16 trials included women with multifetal pregnancies (8 studies each evaluated VP and 17P).	Asymptomatic women at risk of preterm birth; 9 studies exclusively included women with twin pregnancies, 3 studies included women with singleton and twin pregnancies, and 1 study each included women with a twin or triplet pregnancy, triplet pregnancy, triplet or quad pregnancy, or twin, triplet, or quad pregnancy.	VP studies in multifetal pregnancies: 2046 (4 to 341); 17P studies in multifetal pregnancies: 2253 (14 to 336)	RCTs	Not explicitly specified; across studies that included multifetal pregnancies, progesterone was started between 16 and 24 weeks of gestation
Dodd et al (2019)[44,]	Through November 2016	16 trials (7 trials evaluated VP and 9 trials	Women with multifetal pregnancies; 12 studies exclusively	4548 (30 to 677)	RCTs	Not explicitly specified; across studies that included multifetal

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Study	Dates	Trials	Participants	N (Range)	Design	Duration
		evaluated 17P).	included women with twin pregnancies; 3 studies included women with twin or triplet pregnancy, and 1 study included women with a triplet pregnancy.			pregnancies, progesterone was started between 16 and 24 weeks of gestation

17P: 17-hydroxyprogesterone caproate; EPPPIC: Evaluating Progestogens for Preventing Preterm Birth International Collaborative; M-A: meta-analysis; PTB: preterm birth; RCT: randomized-controlled trial; SR: systematic review; VP: vaginal progesterone.

Results from the meta-analyses are summarized in Table 11. Preterm birth before 34 weeks of gestation was a key outcome in all 3 meta-analyses. In the meta-analysis by D'Antonio et al (2021), when compared to control (standard of care without progesterone), neither vaginal progesterone nor 17P significantly reduced the risk of preterm birth before 34 weeks of gestation or perinatal death.[42,] It is important to note that this meta-analysis included data from a retracted RCT by El-Refaie et al (2016).[64,] Furthermore, the analysis included 4 studies of women with twin pregnancies and a short cervix (<10 to 30 mm). Outcomes were not separately provided for the subgroup with twin pregnancy without a short cervix. A relevant meta-analysis from the EPPPIC Group (2021) was introduced above.[11,] In women with multifetal pregnancies, neither vaginal progesterone nor 17P significantly reduced the risk of preterm birth before 34 weeks of gestation, perinatal death, or maternal complications versus control. In this analysis, data from all studies with multifetal pregnancies (twin, triplet, quadruplet) were pooled together, and outcomes were not separately provided for the subgroup with twin pregnancy only. In an updated Cochrane review by Dodd et al (2019), 17P significantly increased the risk of preterm birth before 34 weeks of gestation compared to control; this increased risk was not seen with vaginal progesterone.[44,] The risk of perinatal death did not significantly differ between vaginal progesterone or 17P and control.

A notable relevancy limitation of all 3 reviews is that their meta-analyses pooled data from RCTs representative of the intended population with those that are not, due to their inclusion of women with a variety of additional risk factors (e.g., short cervical length, prior preterm birth).

Table 11. SR & M-A Results

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Study	PTB <34 weeks of gestation	Perinatal death	Maternal complications
D'Antonio et al (2021)[42,]			
VP vs. control			
No. of RCTs (N)	6 (2672 pregnancies)	7 (5198 pregnancies)	
Pooled effect (95% CI)	RR, 1.04 (0.84 to 1.30)	RR, 1.19 (0.83 to 1.70)	
I^2 (p)	38% (.6)	0% (.4)	
Range of N	NR	NR	
Range of effect sizes	NR	NR	
17P vs. control			
No. of RCTs (N)	3 (923 pregnancies)	5 (3782 pregnancies)	
Pooled effect (95% CI)	RR, 1.09 (0.74 to 1.60)	RR, 0.81 (0.42 to 1.58)	
I^2 (p)	39% (.7)	65% (.5)	
Range of N	NR	NR	
Range of effect sizes	NR	NR	
VP vs. 17P			
No. of RCTs (N)	9 (3695 pregnancies)		
Pooled effect (95% CI)	RR, 1.14 (0.70 to 1.85)		
I^2 (p)	I^2 not provided (.6)		
EPPPIC Group (2021)[11,]			
VP vs. control			
N	8 (2046)	4103	1938
Pooled effect (95% CI)	RR, 1.01 (0.84 to 1.20)	RR, 1.19 (0.67 to 2.10)	RR, 0.93 (0.73 to 1.17)

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Study	PTB <34 weeks of gestation	Perinatal death	Maternal complications
I^2 (p)	NR	NR	NR
Range of N	4 to 334	NR	NR
Range of effect sizes	0.64 to 1.31	NR	NR
17P vs. control			
N	2253	4744	2095
Pooled effect (95% CI)	RR, 1.04 (0.92 to 1.18)	RR, 1.00 (0.67 to 1.50)	RR, 1.09 (0.94 to 1.27)
I^2 (p)	NR	NR	NR
Range of N	14 to 336	NR	NR
Range of effect sizes	0.66 to 1.67	NR	NR
Dodd et al (2019)[44,]			
VP vs. control			
No. of RCTs (N)	5 (1503)	3 (2287)	
Pooled effect (95% CI)	RR, 0.9 (0.66 to 1.23)	RR, 1.23 (0.74 to 2.06)	
I^2 (p)	36.27% (.18)	0% (.89)	
Range of N	39 to 341	85 to 664	
Range of effect sizes	0.69 to 1.35	1.11 to 1.98	
17P vs. control			
No. of RCTs (N)	2 (399)	6 (3089)	
Pooled effect (95% CI)	RR, 1.54 (1.06 to 2.26)	RR, 1.45 (0.6 to 3.51)	
I^2 (p)	0% (.62)	70.54% (0)	
Range of N	78 to 160	75 to 660	

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Study	PTB <34 weeks of gestation	Perinatal death	Maternal complications
Range of effect sizes	1.37 to 1.67	0.07 to 4.24	

17P: 17-hydroxyprogesterone caproate; CI: confidence interval; EPPPIC: Evaluating Progestogens for Preventing Preterm Birth International Collaborative; MA: meta-analysis; NE: not estimable; NR: not reported; PTB: preterm birth; RCT: randomized-controlled trial; RR: relative risk; SR: systematic review; VP: vaginal progesterone.

Randomized Controlled Trials

Numerous RCTs have evaluated the effectiveness of progesterone for improving perinatal outcomes in twin pregnancies. As the majority of RCTs have been previously evaluated by the above-described systematic reviews, they will not be comprehensively described here. However, a sampling of RCTs with noteworthy characteristics (i.e., exceptional size/duration, uncommon treatment regimen, important subpopulations) are highlighted in Table 12. Of note, a 2016 RCT published by El-Refaie et al was retracted and therefore removed from this summary of evidence.

Table 12. Summary of Key RCT Characteristics

Study; Trial	Countries	Sites	Dates	Participants	Interventions	
					Active	Comparator
Rode et al (2011)[55,]	Denmark and Austria	17	June 2006 to October 2008	667 pregnant women with twins	Vaginal progesterone 200 mg initiated between 20 and 24 weeks of gestation and continued until either 34 weeks of gestation, ROM, or delivery (n=334)	Placebo (n=343)
Rehal et al (2021)[45,]EVENTS	England, Spain, Bulgaria, Italy, Belgium, and France	22	May 2017 to April 2019	1194	Vaginal progesterone 600 mg initiated between 11 and 14 weeks	Placebo (n=598)

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					of gestation and continued, until either 34 weeks of gestation, ROM, or delivery (n=596)	

RCT: randomized controlled trial; ROM: rupture of the membranes.

Table 14 summarizes results from the 2 RCTs. In Rode et al (2011), the incidence of the primary outcome (delivery before 34 weeks of gestation) did not differ significantly between groups.[55,] 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 (e.g., birth weight, neonatal death, perinatal complications) also did not differ significantly between groups. The investigators conducted follow-up 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. In Rehal et al (2021), the incidence of the primary outcome (spontaneous birth between 24 and 33 weeks of gestation) also did not differ significantly between groups.[45,] However, subgroup analyses based on cervical length found that while progesterone had no significant effect on preterm birth in women with cervical length <30 mm (OR, 0.56; 95% CI, 0.20 to 1.60), progesterone may increase risk of preterm birth in women with cervical length of ≥30 mm (OR, 1.61; 95% CI, 1.01 to 2.59). Progesterone and placebo had similar treatment effects on other secondary outcomes, including stillbirth or neonatal death, neonatal complications, neonatal therapy, and poor fetal growth. An important conduct limitation of this RCT is that because the event rates were lower than anticipated, it is underpowered to detect differences in both primary and secondary outcomes. Additional study relevance limitations and study design and conduct limitations are summarized in Tables 14 and 15.

Table 13. Summary of Key RCT Results

Study	PTB <34 weeks of gestation[a]	Spontaneous birth between 24^{+0} and 33^{+6} weeks of gestation[a]	Infant death
Rode et al (2011)[55,]			
Vaginal progesterone, n/N (%)	51/343 (15.3%)		9/664 (1.4)
Placebo, n/N (%)	63/341 (18.5)		8/678 (1.2)

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OR (95% CI)	0.8 (0.5 to 1.2)		1.2 (0.3 to 4.0)
Rehal et al (2021)[45,]			
Vaginal progesterone, n/N (%)	97/582 (16.7)	56/541 (10.4)	15/1164 (1.3)
Placebo, n/N (%)	93/587 (15.8)	44/538 (8.2)	10/1174 (0.9)
OR (95% CI)	1.10 (0.80 to 1.51)	1.35 (0.88 to 2.05)	1.57 (0.70 to 3.53)

a:Preterm birth <34 weeks of gestation was the primary outcome in the study by Rode et al (2011) and spontaneous birth between 24^{+0} and 33^{+6} weeks of gestation was the primary outcome in the study by Rehal et al (2021).
CI: confidence interval; OR: odds ratio; PTB: preterm birth; RCT: randomized controlled trial.

Table 14. Study Relevance Limitations

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Duration of Follow-up[e]
Rode et al (2011)[55,]	4. International study				
Rehal et al (2021)[45,]					2. Not sufficient duration for harms; only 1 month follow up after completion of treatment.

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
[a] Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.
[b] Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4.Not the intervention of interest.
[c] Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively.
[d] Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. No CONSORT reporting of harms; 4. Not establish and validated measurements; 5. Clinical significant difference not prespecified; 6. Clinical significant difference not supported.
[e] Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms.

Table 15. Study Design and Conduct Limitations

Study	Allocation[a]	Blinding[b]	Selective Reporting[c]	Data Completeness[d]	Power[e]	Statistical[f]
Rode et al (2011)[55,]	1. The proportion of monochorionic					

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	gestations was slightly higher in the placebo group					
Rehal et al (2021)[45,]					2:Underpowered to detect differences in both primary and secondary outcomes	

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
[a] Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias.
[b] Blinding key: 1. Not blinded to treatment assignment; 2. Not blinded outcome assessment; 3. Outcome assessed by treating physician.
[c] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.
[d] Data Completeness key: 1. High loss to follow-up or missing data; 2. Inadequate handling of missing data; 3. High number of crossovers; 4. Inadequate handling of crossovers; 5. Inappropriate exclusions; 6. Not intent to treat analysis (per protocol for noninferiority trials).
[e] Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference.
[f] Statistical key: 1. Analysis is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Analysis is not appropriate for multiple observations per patient; 3. Confidence intervals and/or p values not reported; 4. Comparative treatment effects not calculated.

Section Summary: Twin Gestations

Numerous RCTs and several systematic reviews have consistently found that progesterone (IM or vaginal) is not associated with decreased rates of preterm delivery and other perinatal outcomes (e.g., perinatal death) in women pregnant with twins. A 2021 RCT that used a dose of 600 mg, started early at 11 to 14 weeks, did not find a significant benefit for progesterone in reducing preterm birth between 24 to 36 weeks of gestation. Intramuscular and vaginal progesterone were compared to each other in 1 meta-analysis, but a significant trend of benefit was not seen for either formulation. Additional studies are needed to determine the optimal route and dose of vaginal progesterone.

PROGESTERONE THERAPY FOR A TRIPLET GESTATION

Clinical Context and Therapy 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.

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

The following PICO was used to select literature to inform this review.

Populations
The relevant population of interest is women with triplet gestation. Multifetal pregnancies are at risk of preterm labor and preterm birth.

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 outcomes of most interest are direct clinical benefits including OS (e.g., neonatal death), morbid events (e.g., postnatal respiratory distress, neonatal intensive care, child functional impairment), and treatment-related morbidity (e.g., maternal adverse drug reactions). Gestational outcomes (e.g., gestational age, preterm birth <32, 35, or 37 weeks) are considered surrogate outcomes expected to predict clinical benefit.

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 long-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.

REVIEW OF EVIDENCE

Systematic Reviews
Triplet pregnancies are discussed in the Cochrane review by Dodd et al (2017) and 2021 meta-analysis by the EPPPIC group, discussed above, and were evaluated in 4 included studies; however, outcomes were underrepresented in the reviews as several studies did not distinguish between twin and triplet gestations.[43,11,] The 2021 meta-analysis combined twin and triplet data

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when evaluating outcomes.[11,] Since only 4 of the 16 trials of multifetal pregnancies included triplet gestations, data from this meta-analysis are summarized in the section on twin gestation.

The meta-analysis by Sotiriadis et al (2012)[65,] pooled data on the 2 trials on progesterone in women with triplet gestations described below.[57,60,] 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

Combs et al (2010) reported an RCT evaluating 81 women randomized 56 to IM injections of 17P and 25 to placebo.[57,] 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=.36). However, there were 13 mid-trimester fetal losses in the 17P group and none in the placebo group (p<.02).

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.[60,] 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 Therapy Purpose

The purpose of progesterone therapy in women who have a singleton pregnancy and premature premature rupture of membranes (PPROM) 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 PPROM?

The following PICO was used to select literature to inform this review.

Populations

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The relevant population of interest is women with a singleton pregnancy and PPROM 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 PPROM: standard of care without progesterone. This commonly includes administration of a course of corticosteroids and prophylactic antibiotic therapy.

Outcomes
The outcomes of most interest are direct clinical benefits including OS (e.g., neonatal death), morbid events (e.g., postnatal respiratory distress, neonatal intensive care, child functional impairment), and treatment-related morbidity (e.g., maternal adverse drug reactions). Gestational outcomes (e.g., gestational age, preterm birth <32, 35, or 37 weeks) are considered surrogate outcomes expected to predict clinical benefit.

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 long-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.

REVIEW OF EVIDENCE

Systematic Reviews
Quist-Nelson et al (2018) published a systematic review and meta-analysis of 6 RCTs (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.[66,] No significant differences were noted between patients receiving IM progesterone and placebo in rates of preterm birth at the following time points: <37, 34, 32, or 28 weeks of gestation.

Randomized Controlled Trials
A double-blind, placebo-controlled RCT by Langen et al (2018) assessed outcomes for women with PPROM who received weekly injections of 17P to delay delivery.[67,] The multicenter trial

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enrolled 21 women with singleton pregnancies, clinically confirmed PPROM, and no evidence of active infection or major fetal malformation and who were between 24 and 32 weeks' gestation. The study was closed prematurely due to low enrollment. The active intervention group (n=10) received weekly 17P injections until 34 weeks of gestation or delivery, and the control group (n=11) received placebo injections. The primary outcome was reaching 34 weeks of gestation. None of the participants remained pregnant until 34 weeks; the mean gestational age at delivery for the placebo group was 28.3 weeks (95% CI, 27.2 to 30.3) and 29.5 weeks for the active treatment group (95% CI, 27.7 to 31.5; p=.44). The mean number of days between starting the injections and delivery was 8 for the placebo group (95% CI, 5.3 to 13.4) and 14.5 for the treatment group (95% CI, 8.9 to 29.1; p=.14). Maternal and neonatal outcomes were similar between the groups. No benefit from the administration of 17P was identified.

Briery et al (2011) published an RCT assessing women with singleton pregnancies diagnosed with PPROM at 20 to 30 weeks of gestation.[59,] 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=.15). Neonatal outcomes, including birth weight, length of stay in the NICU, 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 in singleton pregnancies with PPROM; no significant differences between the groups were found. Two RCTs did not find improved pregnancy and neonatal outcomes in women who received progesterone versus placebo.

PROGESTERONE THERAPY FOR A SINGLETON PREGNANCY AND PRIOR EPISODE OF PRETERM LABOR IN CURRENT PREGNANCY

Clinical Context and Therapy 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 PICO was used to select literature to inform this review.

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

Interventions
Upon initial presentation of women with threatened or active preterm labor, common primary tocolytics to slow or stop contractions include magnesium sulfate, indomethacin, and nifedipine. Primary tocolysis is successful in stopping preterm labor in many women. However, since the risk of preterm labor remains high in these women, maintenance tocolysis can be used after arrested preterm labor to prevent recurring preterm labor and subsequent preterm birth. The maintenance tocolytic 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 outcomes of most interest are direct clinical benefits including OS (e.g., neonatal death), morbid events (e.g., postnatal respiratory distress, neonatal intensive care, child functional impairment), and treatment-related morbidity (e.g., maternal adverse drug reactions). Gestational outcomes (e.g., gestational age, preterm birth <32, 35, or 37 weeks) are considered surrogate outcomes expected to predict clinical benefit.

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 long-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.

REVIEW OF EVIDENCE

INTRAMUSCULAR PROGESTERONE

Systematic Reviews

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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.[68,] Five RCTs (N=426 women) met the inclusion criteria; 4 trials used a no-treatment control and 1 used a placebo. Only one trial was conducted in the U.S. 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 of gestation). 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 later gestational age at delivery. Secondary outcomes with similar rates between groups included the incidence of recurrent preterm labor, neonatal death, and neonatal sepsis.

Randomized Controlled Trials

An additional RCT by Shaamash et al (2020)[69,] published subsequent to the systematic review and meta-analysis by Saccone et al (2015) described above has explored a clinical scenario where tocolysis followed by IM progesterone may be used in the presence of placenta previa. This open, single-center RCT recruited women with placenta previa between 24 and 28 weeks who were treated at a University-affiliated obstetric outpatient clinic in Assiut, Egypt. A total of 114 women were randomized to IM progesterone 250 mg (n=57) or no progesterone (n=57) administered weekly through 37 weeks' gestation. The preterm delivery rate (<37 weeks) was significantly lower in the IM progesterone group (37% vs. 63.5%; p=.004). Neonatal intensive care unit admissions were also lower in the IM progesterone group (31.4% vs. 78.8%; P=.000). Other benefits of IM progesterone included fewer bleeding attacks and higher mean birth weight. While encouraging, important reporting limitations preclude the conclusive interpretation of these findings. Although some patients in both groups were described as having threatened preterm labor (37% vs. 40%) and tocolysis with magnesium sulfate or nifedipine was reportedly considered, no data were provided on overall rates of tocolysis administered for each group, which tocolytic agents were used, at what dosage, and for how long. Therefore, the applicability of the tocolytic protocol to the current U.S. standard of care and comparability between groups cannot be determined.

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.[70,] Five RCTs (N=441 women) met the inclusion criteria; 3 trials used a no-treatment control and 2 used

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a placebo. All trials were conducted outside of the U.S. 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 of gestation). 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 of gestation (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 (e.g., lack of blinding).

Randomized Controlled Trials

Additional RCTs have been published subsequent to the systematic review and meta-analysis by Suhag et al (2015) described above. These have also reported mixed findings which are summarized below.

Martinez de Tejada et al (2015) published a multicenter, double-blind, placebo-controlled randomized trial on the prevention of preterm delivery in women with a prior episode of preterm labor in the current pregnancy.[71,] 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=.20). Secondary outcomes, including delivery before 34 weeks, delivery before 32 weeks, and neonatal outcomes, were also similar between groups.

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).[52,] No statistically significant difference was seen between the active and control group in the 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.

Hyett et al (2020) reported on a double-blind, placebo-controlled RCT of the effectiveness of vaginal progesterone 400 mg used as maintenance tocolytic therapy following arrested preterm labor.[72,] Between December 2014 and February 2015, this trial randomized 85 women who presented to the obstetric services of 2 hospitals affiliated with Shiraz University of Medical Sciences in Shiraz, Iran with threatened preterm labor at 24 to 34 weeks of gestation. Participants were randomized to either daily vaginal progesterone (n=45) or placebo (n=40). Maintenance tocolytic therapy was started after preterm labor was successfully arrested following administration of a standard protocol of IV magnesium sulfate and IM betamethasone. Although the proportion of preterm births before a prespecified gestation time was not reported as in

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previous RCTs, mean gestational age at delivery was significantly longer in the progesterone group (37.5 vs. 34.2 weeks; p=.0001). There were mixed findings across various neonatal outcomes. For example, while NICU admissions were fewer in the progesterone group (22% vs. 45.5%; p=.03), there were no differences in neonatal deaths (2.4% vs. 6.1%; p=.43) or respiratory distress syndrome (12.2% vs. 24.2%; p=.17). An important conduct limitation of this RCT is the reliance on a per-protocol analysis that excluded a higher proportion of patients in the placebo group (9% vs. 17%). Other limitations include no assessment of treatment compliance or adverse effects that may have impacted compliance.

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

Meta-analyses of RCTs have not definitively found that IM or vaginal progesterone used as maintenance tocolysis reduces the rate of preterm birth or improves other outcomes. These RCTs demonstrated inconsistent benefits for progesterone. Heterogeneity in preterm birth outcome definitions (e.g., birth at < 32, 34, or 37 weeks of gestation or mean/median gestational age) and methodologic limitations (e.g., lack of blinding, inadequate handling of missing data) make it difficult to draw conclusions about the source of the variation.

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 17P, the evidence includes several RCTs and meta-analyses. Relevant outcomes are OS, morbid events, and treatment-related morbidity. The RCTs varied in baseline risk for preterm birth, the formulation of vaginal progesterone comparator used, the gestational age length of pregnancy at treatment initiation, and the duration of treatment. Two RCTs have compared IM progesterone to placebo in individuals who have a singleton pregnancy and prior spontaneous preterm birth. The RCT with a population most relevant to U.S. women demonstrated a benefit for IM progesterone versus placebo for a reduction in the risk of the primary outcome of preterm delivery at <37 weeks of gestation, as well as <35 and <32 weeks of gestation. The RCT was used to support FDA accelerated approval. Gestational outcomes are considered surrogate outcomes expected to predict clinical benefit. Infants of women treated with 17P had significantly lower rates of necrotizing enterocolitis, intraventricular hemorrhage, and need for supplemental oxygen. There were no differences in any other neonatal mortality or morbidity outcomes. There were no significant differences between the 2 groups for maternal health-related complications such as the rates of hospital visits for preterm labor, use of tocolytics or corticosteroids, cesarean delivery, or chorioamnionitis. The study was not planned or conducted for drug approval and was not powered for all neonatal morbidity or mortality outcomes. The confirmatory RCT (Progestin's Role in Optimizing Neonatal Gestation study [PROLONG]) found no significant benefit for IM progesterone for the primary outcome of preterm birth <35 weeks of gestation, as well as a defined neonatal composite outcome. However, a lower than predicted event rate resulted in the

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study being underpowered to assess the primary outcomes. A high proportion of patients enrolled from non-U.S. regions further limited the clinical relevancy of the overall findings to U.S. high-risk women. In the planned prespecified subgroup analysis of the treatment effects for the U.S. subgroup versus non-U.S. subgroups, there were nonsignificant trends of benefit for IM progesterone efficacy for preterm birth before 32 and 35 weeks of gestation, but not before 37 weeks of gestation. Two meta-analyses similarly demonstrated that IM progesterone did not lead to statistically significant reductions in preterm birth rates before 37, 35, 34, 32, and 28 weeks of gestation or fetal death. A meta-analysis with the most relevant pooled population found significantly lower rates of preterm birth <34 weeks of gestation with vaginal versus IM progesterone, but no differences at <28 or <37 weeks of gestation. In contrast, a larger meta-analysis that included a heterogeneous population of women at risk of preterm birth did not find a statistically significant difference in the risk of preterm birth before 37, 34, or 28 weeks of gestation with vaginal versus IM progesterone, but the results trended in favor of vaginal progesterone. This meta-analysis also reviewed neonatal mortality or morbidity outcomes, and demonstrated no statistically significant differences between routes in the risk of serious neonatal complications or perinatal death; trends were again in favor of vaginal progesterone. Conducting a new confirmatory placebo-controlled trial would be ideal but is unlikely because IM progesterone has been widely used for many years and continues to be guideline-recommended. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have a singleton pregnancy and prior spontaneous preterm birth before 37 weeks of gestation who receive vaginal progesterone, the evidence includes several RCTs and systematic reviews. Relevant outcomes are OS, morbid events, and treatment-related morbidity. Placebo-controlled RCTs are heterogeneous in baseline risk, the formulation of vaginal progesterone used, and the control treatment (e.g., placebo, no treatment). Statistically significant reductions in preterm delivery rates varied across RCTs for vaginal progesterone based on these sources of heterogeneity. Pooled analyses of RCT data have found statistically significant reductions in preterm birth rates with progesterone compared with placebo, but interpretation of their findings is limited by their inclusion of study populations with a wider range of risk factors than the intended population. The evidence is sufficient to determine that the technology results in an 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 1 RCT. Relevant outcomes are OS, morbid events, and treatment-related morbidity. The placebo-controlled RCT (which was halted early based on interim analysis) did not find that IM progesterone significantly decreased the rate of preterm birth. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

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For individuals who have a singleton pregnancy and a short cervix (<20 mm) who receive vaginal progesterone, the evidence includes RCTs and meta-analyses. Relevant outcomes are OS, morbid events, and treatment-related morbidity. Several RCTs have evaluated vaginal progesterone compared to placebo and compared to IM progesterone for preventing preterm birth in women with short cervical length. These trials have tended to be underpowered for meaningful clinical outcomes. Multiple 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 a subgroup of women with singleton pregnancies and no prior preterm birth. One meta-analysis compared IM and vaginal progesterone in women with singleton pregnancies and cervical length ≤25 mm. There was a nonsignificant statistical trend of benefit for vaginal progesterone for the reduction in preterm birth, perinatal death, and serious neonatal complications, and a nonsignificant statistical trend of benefit for IM progesterone for the reduction in maternal complications. However, the inclusion of women with a short cervical length that was >20 mm and additional risk factors is a limitation of this meta-analysis as it relates to the comparison of IM and vaginal progesterone in the intended population. The evidence is sufficient to determine that the technology results in an 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 OS, morbid events, and treatment-related morbidity. The RCTs and several meta-analyses of these studies have consistently found that progesterone (IM or vaginal) is not significantly associated with decreased rates of preterm delivery or other perinatal outcomes in pregnant women with twins. One RCT that used a dose of 600 mg, started early at 11 to 14 weeks, did not find a significant benefit for progesterone in reducing preterm birth between 24 to 36 weeks of gestation. Intramuscular and vaginal progesterone were compared to each other in 1 meta-analysis, but a significant trend of benefit was not seen for either formulation. However, the inclusion of women with a short cervical length is a limitation of this meta-analysis as it relates to the comparison of IM and vaginal progesterone in the intended population. Additional studies in this population are needed to identify the optimal route and dose of progesterone. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who are pregnant with triplets who receive IM injections of progesterone or vaginal progesterone, the evidence includes RCTs and a meta-analyses. Relevant outcomes are OS, 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 that the technology results in an improvement in the net health outcome.

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For individuals with a singleton pregnancy and PPROM who receive IM injections of progesterone or vaginal progesterone, the evidence includes 2 RCTs and a systematic review of 6 RCTs. Relevant outcomes are OS, morbid events, and treatment-related morbidity. The 2 RCTs did not find improved pregnancy and neonatal outcomes in women who received progesterone versus placebo. A 2018 systematic review identified 6 RCTs that compared IM progesterone with placebo or no treatment in singleton pregnancies with PPROM; no significant differences between the groups were found. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with a singleton pregnancy following successful tocolysis of a 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 OS, morbid events, and treatment-related morbidity. These RCTs demonstrated inconsistent benefits for progesterone. Heterogeneity in preterm birth outcome definitions (e.g., birth at <32, 34, or 37 weeks of gestation or mean/median gestational age) and methodologic limitations (e.g., lack of blinding, inadequate handling of missing data) make it difficult to draw conclusions about the source of the variation. 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. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

SUPPLEMENTAL INFORMATION

The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the evidence review conclusions.

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

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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.[34,] 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)[3,] and da Fonseca et al (2003)[37,] 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
Guidelines or position statements will be considered for inclusion in 'Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

American College of Obstetricians and Gynecologists
The American College of Obstetricians and Gynecologists (ACOG) (2021) published an updated Practice Bulletin (#234) on the prediction and prevention of preterm birth.[73,] The Bulletin includes the following level A evidence recommendations related to progesterone therapy:

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- "Vaginal progesterone is recommended for asymptomatic individuals without a history of preterm birth with a singleton pregnancy and a short cervix."
- "Intramuscular 17-OHPC is not recommended for prevention of preterm birth in patients who do not have a history of spontaneous preterm delivery."
- "Patients with a singleton pregnancy and a prior spontaneous preterm birth should be offered progesterone supplementation (either vaginal or intramuscular) in the context of a shared decision-making process incorporating the available evidence and the patient's preferences."

The Bulletin includes the following level B evidence recommendations related to progesterone therapy:

- "Intramuscular 17-OHPC is not recommended for prevention of preterm birth based solely on the indication of multiple gestation."
- "Routine prophylactic use of vaginal progesterone to prevent preterm birth in twin pregnancies is not recommended."

The Bulletin includes the following level C evidence recommendations related to progesterone therapy:

- "Patients with a singleton gestation, a prior spontaneous preterm birth, and a short cervix in the second trimester who are not on progesterone supplementation should be informed of their increased risk of preterm birth, the two treatment options available (vaginal progesterone and cerclage), and the uncertainty about which management course is best in the context of a shared decision-making process."
- "Patients with a singleton gestation, prior spontaneous preterm birth, and a short second-trimester cervix who are on progesterone supplementation should be informed of their increased risk of preterm birth, and cerclage may be offered in addition to continuation of progesterone."

ACOG (2021) updated and replaced its practice bulletin on multifetal gestations (previously Practice Bulletin #169).[74,] The updated Practice Bulletin (#231) on multifetal gestations includes the following level A evidence recommendation related to 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."

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 labor[75,]:

"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]."

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"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."

In follow-up to their 2012 statement, the Society published a position statement in 2017 on the choice of progestogen.[76,] The Society continued to recommend the use of 17α-hydroxyprogesterone caproate therapy for prevention of preterm birth with a singleton pregnancy and prior preterm birth and, in this statement, confirmed that this formulation is the product of choice.

In response to the PROLONG trial results,[4,], the Society published the following updated statement: "The Society for Maternal-Fetal Medicine believes that the differences in these results [PROLONG] from the earlier Meis, et al trial, which did show a benefit of 17-OHPC in reducing the rate of spontaneous PTB (sPTB), may be at least partially explained by differences in study populations. SMFM concludes that it is reasonable for providers to use 17-OHPC in women with a profile more representative of the very-high-risk population reported in the Meis trial. For all

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women at risk of recurrent sPTB, the risk/benefit discussion should incorporate a shared decision-making approach, taking into account the lack of short-term safety concerns but uncertainty regarding benefit."[77,]

In response to the systematic review and meta-analysis by the EPPPIC group, the Society published the following statement regarding the reviews findings: "These data reaffirm The Society for Maternal-Fetal Medicine's (SMFM) current guidelines that women with a singleton pregnancy and a short cervix (<25 mm) without a history of a prior sPTB be offered treatment with vaginal progesterone. Although the results of this study suggest that either 17-OHPC or vaginal progesterone appear to offer a benefit to women with a singleton gestation and either short cervix or prior sPTB, the certainty regarding the benefit, both maternal and neonatal, is greatest for vaginal progesterone."[78,] The statement goes on to state: "In multifetal gestations, there is insufficient evidence to recommend the use of progestogens outside clinical trials regardless of history of PTB or cervical length."

Cochrane Collaboration

Medley et al (2018) published a systematic review of international clinical guidelines addressing screening, medications or surgery, and other interventions for prevention and management of preterm birth.[79,] Their search strategy included all clinical practice guidelines current from June 2013 to May 2017. Quality assessment was based on the adherence of guidelines to 4 of 13 Institute of Medicine (IOM) Standards for a Trustworthy Guideline: (1) publicly accessible development and funding process; (2) addressing evidence gaps and summarization of evidence for benefits and harms related to each recommendation; (3) based on a systematic review; (4) development by a multidisciplinary panel including clinical experts and patient or other health consumers. The review included 56 articles produced by 16 guideline developers, including ACOG. Quality assessment indicated that "included guidelines were overwhelmingly based on good-quality methods." The only area of international consensus related to progesterone was "vaginal progesterone in asymptomatic women without history of preterm birth who have cervical length of <20 mm before or at 24 weeks' gestation."

National Institute for Health and Care Excellence

The National Institute for Health and Care Excellence (2015) published guidance on the care of women at increased risk of preterm labor and birth (NG25).[26,] This guidance was last updated on June 10, 2022 , and includes the following recommendations regarding the use of prophylactic vaginal progesterone:

- "Offer a choice of prophylactic vaginal progesterone OR prophylactic cervical cerclage to women who have both a history of spontaneous preterm birth (up to 34^{+0} weeks of pregnancy) or mid-trimester loss (from 16^{+0} weeks of pregnancy onwards) and results from a transvaginal ultrasound scan carried out between 16^{+0} and 24^{+0} weeks of pregnancy that show a cervical length of 25 mm or less. Discuss the risks and benefits of

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both options with the woman, and make a shared decision on which treatment is most suitable."

- "Consider prophylactic vaginal progesterone for women who have either a history of spontaneous preterm birth (up to 34^{+0} weeks of pregnancy) or mid-trimester loss (from 16^{+0} weeks of pregnancy onwards) or results from a transvaginal ultrasound scan carried out between 16^{+0} and 24^{+0} weeks of pregnancy that show a cervical length of 25 mm or less."
- "When using vaginal progesterone, start treatment between 16^{+0} and 24^{+0} weeks of pregnancy and continue until at least 34 weeks."

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

Ongoing and Unpublished Clinical Trials
Some ongoing and currently unpublished trials that might influence this review are listed in Table 16.

Table 16. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT03428685	Prediction and Prevention of Twin Premature Birth	1714	Jan 2023
Unpublished			
NCT01146990	A Prospective, Noninterventional Follow-Up Study of Children Aged 23 to 25 Months, Born to Mothers Who Received Hydroxyprogesterone Caproate Injection, 250 mg/mL, or Vehicle for Prevention of Preterm Birth	584	Nov 2020
NCT02913495	Vaginal Versus Intramuscular Progesterone for the Prevention of Recurrent Preterm Birth	224	Dec 2020
NCT04807543	Effect of Progesterone on Latent Phase Prolongation in Patients With PretermPremature Rupture of Membrane	100	Dec 2020
NCT02697331	Evaluation of the Role of Vaginal Progesterone in Prevention of Preterm Labor in Twin Gestation With Short Cervix: Randomized Controlled Trial	144	Dec 2019

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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.

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CODING

The following codes for treatment and procedures applicable to this policy are included below for informational purposes. This may not be a comprehensive list of procedure codes applicable to this policy.

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.

The code(s) listed below are medically necessary ONLY if the procedure is performed according to the "Policy" section of this document.

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)

ICD-10 DIAGNOSES	
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:

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REVISIONS	
	▪ 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: ▪ 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: ▪ 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: ▪ Added HCPCS Codes: Q9985, Q9986
01-01-2018	In Coding section: ▪ 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: ▪ 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 ▪ Removed HCPCS Code: J1725 (Termed on 01-01-2018) ▪ Added ICD-10 Codes: O34.42, O34.43 ▪ Coding notations updated
	References updated
09-25-2019	Description section updated
	Rationale section updated
	References updated
05-23-2021	Description section updated
	In Policy section • Removed "performed in the office setting" from Item A.1

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REVISIONS	
	• Replaced "Centers" with "Ultrasonographers" in Policy Guidelines #2
	Rationale section updated
	References updated
11-5-2021	Updated Description Section
	Updated Rationale Section
	Updated References Section
10-28-2022	Updated Description Section
	Updated Policy Guideline Section ▪ Section A: Removed reference "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"
	Updated Rationale Section
	Updated References Section
04-25-2023	Archived

REFERENCES

1. Greenberg MB, Gandhi M, Davidson C, et al. Society for Maternal-Fetal Medicine Consult Series #62: Best practices in equitable care delivery-Addressing systemic racism and other social determinants of health as causes of obstetrical disparities. Am J Obstet Gynecol. Aug 2022; 227(2): B44-B59. PMID 35378098
2. Beitz J, Office of Drug Evaluation III. Office Director Memo FDA Center for Drug Evaluation and Research. Application Number: 21945Orig1s000 [Approval Action for NDA 021945: Makena]. 2011; https://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/021945Orig1s000ODMemo.pdf. Accessed July 26, 2021.
3. Meis PJ, Klebanoff M, Thom E, et al. Prevention of recurrent preterm delivery by 17 alpha-hydroxyprogesterone caproate. N Engl J Med. Jun 12 2003; 348(24): 2379-85. PMID 12802023
4. Blackwell SC, Gyamfi-Bannerman C, Biggio JR, et al. 17-OHPC to Prevent Recurrent Preterm Birth in Singleton Gestations (PROLONG Study): A Multicenter, International, Randomized Double-Blind Trial. Am J Perinatol. Jan 2020; 37(2): 127-136. PMID 31652479
5. AMAG Pharmaceuticals. Makena Advisory Committee Briefing Materials. https://www.fda.gov/media/132004/download. 2019. Accessed July 27, 2021.
6. Food and Drug Administration Center for Drug Evaluation and Research. Summary Minutes of the Bone, Reproductive and Urologic Drugs Advisory Committee Meeting October 29, 2019. https://www.fda.gov/media/136107/download. Published 2019. Accessed September 1, 2022

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Blue Cross and Blue Shield of Kansas will continue to monitor published literature for any updated information. If there are questions about coverage of this service, please contact Blue Cross and Blue Shield of Kansas customer service, or your professional / institutional relations representative.

7. AMAG Pharmaceuticals. Press Release: AMAG reports on FDA advisory committee meeting for Makena (hydroxyprogesterone caproate injection). https://www.amagpharma.com/news/amag-reports-on-fda-advisory-committee-meeting-for-makena-hydroxyprogesterone-caproate-injection/ November 1, 2019. Accessed July 25, 2021.
8. Food and Drug Administration. CDER proposes withdrawal of approval for Makena. October 5, 2020. Accessed July 26, 2021. https://www.fda.gov/drugs/drug-safety-and-availability/cder-proposes-withdrawal-approval-makena
9. AMAG Pharmaceuticals. AMAG Pharmaceuticals files submission in response to the Food And Drug Administrations Notice of Opportunity for a Hearing and proposal to withdraw approval of Makena (hydroxyprogesterone caproate injection). December 14, 2020. Accessed July 26, 2021. https://ir.amagpharma.com/news-releases/news-release-details/amag-pharmaceuticals-files-submission-response-food-and-drug
10. Kuon RJ, Berger R, Rath W. 17-Hydroxyprogesterone Caproate for the Prevention of Recurrent Preterm Birth - A Systematic Review and Meta-analysis Taking into Account the PROLONG Trial. Geburtshilfe Frauenheilkd. Jan 2021; 81(1): 61-69. PMID 33487666
11. Stewart LA, Simmonds M, Duley L, et al. Evaluating Progestogens for Preventing Preterm birth International Collaborative (EPPPIC): meta-analysis of individual participant data from randomized controlled trials. Lancet. Mar 27 2021; 397(10280): 1183-1194. PMID 33773630
12. Baradwan S, Abdulghani SH, Abuzaid M, et al. 17-alpha hydroxyprogesterone caproate for the prevention of recurrent preterm birth among singleton pregnant women with a prior history of preterm birth: a systematic review and meta-analysis of six randomized controlled trials. Obstet Gynecol Sci. Nov 2021; 64(6): 484-495. PMID 34670064
13. Northen AT, Norman GS, Anderson K, et al. Follow-up of children exposed in utero to 17 alpha-hydroxyprogesterone caproate compared with placebo. Obstet Gynecol. Oct 2007; 110(4): 865-72. PMID 17906021
14. Oler E, Eke AC, Hesson A. Meta-analysis of randomized controlled trials comparing 17-hydroxyprogesterone caproate and vaginal progesterone for the prevention of recurrent spontaneous preterm delivery. Int J Gynaecol Obstet. Jul 2017; 138(1): 12-16. PMID 28369874
15. Choi SJ, Kwak DW, Kil K, et al. Vaginal compared with intramuscular progestogen for preventing preterm birth in high-risk pregnant women (VICTORIA study): a multicentre, open-label randomised trial and meta-analysis. BJOG. Dec 2020; 127(13): 1646-1654. PMID 32536019
16. Maher MA, Abdelaziz A, Ellaithy M, et al. Prevention of preterm birth: a randomized trial of vaginal compared with intramuscular progesterone. Acta Obstet Gynecol Scand. Feb 2013; 92(2): 215-22. PMID 23016508

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Blue Cross and Blue Shield of Kansas will continue to monitor published literature for any updated information. If there are questions about coverage of this service, please contact Blue Cross and Blue Shield of Kansas customer service, or your professional / institutional relations representative.

17. Bafghi AS, Bahrami E, Sekhavat L. Comparative Study of Vaginal versus Intramuscular Progesterone in the Prevention of Preterm Delivery: A Randomized Clinical Trial. Electron Physician. Oct 2015; 7(6): 1301-9. PMID 26516434
18. Elimian A, Smith K, Williams M, et al. A randomized controlled trial of intramuscular versus vaginal progesterone for the prevention of recurrent preterm birth. Int J Gynaecol Obstet. Aug 2016; 134(2): 169-72. PMID 27168167
19. Pirjani R, Heidari R, Rahimi-Foroushani A, et al. 17-alpha-hydroxyprogesterone caproate versus vaginal progesterone suppository for the prevention of preterm birth in women with a sonographically short cervix: A randomized controlled trial. J Obstet Gynaecol Res. Jan 2017; 43(1): 57-64. PMID 27775195
20. Shambhavi S, Bagga R, Bansal P, et al. A randomised trial to compare 200 mg micronized progesterone effervescent vaginal tablet daily with 250 mg intramuscular 17 alpha hydroxy progesterone caproate weekly for prevention of recurrent preterm birth. J Obstet Gynaecol. Aug 2018; 38(6): 800-806. PMID 29557230
21. Boelig RC, Schoen CN, Frey H, et al. Vaginal progesterone vs intramuscular 17-hydroxyprogesterone caproate for prevention of recurrent preterm birth: a randomized controlled trial. Am J Obstet Gynecol. May 2022; 226(5): 722.e1-722.e12. PMID 35189093
22. Ahn KH, Bae NY, Hong SC, et al. The safety of progestogen in the prevention of preterm birth: meta-analysis of neonatal mortality. J Perinat Med. Jan 01 2017; 45(1): 11-20. PMID 27124668
23. Dodd JM, Jones L, Flenady V, et al. Prenatal administration of progesterone for preventing preterm birth in women considered to be at risk of preterm birth. Cochrane Database Syst Rev. Jul 31 2013; (7): CD004947. PMID 23903965
24. Conde-Agudelo A, Romero R. Does vaginal progesterone prevent recurrent preterm birth in women with a singleton gestation and a history of spontaneous preterm birth? Evidence from a systematic review and meta-analysis. Am J Obstet Gynecol. Apr 20 2022. PMID 35460628
25. Phung J, Williams KP, McAullife L, et al. Vaginal progesterone for prevention of preterm birth in asymptomatic high-risk women with a normal cervical length: a systematic review and meta-analysis. J Matern Fetal Neonatal Med. Jul 01 2021: 1-9. PMID 34210207
26. National Institute for Health and Care Excellence (NICE). Preterm labour and birth: Evidence review for clinical effectiveness of prophylactic progesterone in preventing preterm labour. https://www.nice.org.uk/guidance/ng25/evidence/clinical-effectiveness-of-prophylactic-progesterone-in-preventing-preterm-labour-pdf-6847804765 Published August 2019. Accessed September 1, 2022.
27. Crowther CA, Ashwood P, McPhee AJ, et al. Vaginal progesterone pessaries for pregnant women with a previous preterm birth to prevent neonatal respiratory distress syndrome (the PROGRESS Study): A multicentre, randomised, placebo-controlled trial. PLoS Med. Sep 2017; 14(9): e1002390. PMID 28949973

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Blue Cross and Blue Shield of Kansas will continue to monitor published literature for any updated information. If there are questions about coverage of this service, please contact Blue Cross and Blue Shield of Kansas customer service, or your professional / institutional relations representative.

28. Norman JE, Marlow N, Messow CM, et al. Vaginal progesterone prophylaxis for preterm birth (the OPPTIMUM study): a multicentre, randomised, double-blind trial. Lancet. May 21 2016; 387(10033): 2106-2116. PMID 26921136
29. Norman JE, Marlow N, Messow CM, et al. Does progesterone prophylaxis to prevent preterm labour improve outcome? A randomised double-blind placebo-controlled trial (OPPTIMUM). Health Technol Assess. Jun 2018; 22(35): 1-304. PMID 29945711
30. Azargoon A, Ghorbani R, Aslebahar F. Vaginal progesterone on the prevention of preterm birth and neonatal complications in high risk women: A randomized placebo-controlled double-blind study. Int J Reprod Biomed. May 2016; 14(5): 309-16. PMID 27326415
31. van Os MA, van der Ven AJ, Kleinrouweler CE, et al. Preventing Preterm Birth with Progesterone in Women with a Short Cervical Length from a Low-Risk Population: A Multicenter Double-Blind Placebo-Controlled Randomized Trial. Am J Perinatol. Aug 2015; 32(10): 993-1000. PMID 25738790
32. Aboulghar MM, Aboulghar MA, Amin YM, et al. The use of vaginal natural progesterone for prevention of preterm birth in IVF/ICSI pregnancies. Reprod Biomed Online. Aug 2012; 25(2): 133-8. PMID 22695310
33. Cetingoz E, Cam C, Sakalli M, et al. Progesterone effects on preterm birth in high-risk pregnancies: a randomized placebo-controlled trial. Arch Gynecol Obstet. Mar 2011; 283(3): 423-9. PMID 20091317
34. Hassan SS, Romero R, Vidyadhari D, et al. Vaginal progesterone reduces the rate of preterm birth in women with a sonographic short cervix: a multicenter, randomized, double-blind, placebo-controlled trial. Ultrasound Obstet Gynecol. Jul 2011; 38(1): 18-31. PMID 21472815
35. Majhi P, Bagga R, Kalra J, et al. Intravaginal use of natural micronised progesterone to prevent pre-term birth: a randomised trial in India. J Obstet Gynaecol. Aug 2009; 29(6): 493-8. PMID 19697195
36. O'Brien JM, Adair CD, Lewis DF, et al. Progesterone vaginal gel for the reduction of recurrent preterm birth: primary results from a randomized, double-blind, placebo-controlled trial. Ultrasound Obstet Gynecol. Oct 2007; 30(5): 687-96. PMID 17899572
37. da Fonseca EB, Bittar RE, Carvalho MH, et al. Prophylactic administration of progesterone by vaginal suppository to reduce the incidence of spontaneous preterm birth in women at increased risk: a randomized placebo-controlled double-blind study. Am J Obstet Gynecol. Feb 2003; 188(2): 419-24. PMID 12592250
38. Grobman WA, Thom EA, Spong CY, et al. 17 alpha-hydroxyprogesterone caproate to prevent prematurity in nulliparas with cervical length less than 30 mm. Am J Obstet Gynecol. Nov 2012; 207(5): 390.e1-8. PMID 23010094
39. Romero R, Conde-Agudelo A, Da Fonseca E, et al. Vaginal progesterone for preventing preterm birth and adverse perinatal outcomes in singleton gestations with a short cervix: a meta-analysis of individual patient data. Am J Obstet Gynecol. Feb 2018; 218(2): 161-180. PMID 29157866

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Blue Cross and Blue Shield of Kansas will continue to monitor published literature for any updated information. If there are questions about coverage of this service, please contact Blue Cross and Blue Shield of Kansas customer service, or your professional / institutional relations representative.

40. Romero R, Nicolaides K, Conde-Agudelo A, et al. Vaginal progesterone in women with an asymptomatic sonographic short cervix in the midtrimester decreases preterm delivery and neonatal morbidity: a systematic review and metaanalysis of individual patient data. Am J Obstet Gynecol. Feb 2012; 206(2): 124.e1-19. PMID 22284156
41. Fonseca EB, Celik E, Parra M, et al. Progesterone and the risk of preterm birth among women with a short cervix. N Engl J Med. Aug 02 2007; 357(5): 462-9. PMID 17671254
42. D'Antonio F, Berghella V, Di Mascio D, et al. Role of progesterone, cerclage and pessary in preventing preterm birth in twin pregnancies: A systematic review and network meta-analysis. Eur J Obstet Gynecol Reprod Biol. Jun 2021; 261: 166-177. PMID 33946019
43. Dodd JM, Grivell RM, OBrien CM, et al. Prenatal administration of progestogens for preventing spontaneous preterm birth in women with a multiple pregnancy. Cochrane Database Syst Rev. Oct 31 2017; 10: CD012024. PMID 29086920
44. Dodd JM, Grivell RM, OBrien CM, et al. Prenatal administration of progestogens for preventing spontaneous preterm birth in women with a multiple pregnancy. Cochrane Database Syst Rev. Nov 20 2019; 2019(11). PMID 31745984
45. Rehal A, Benko Z, De Paco Matallana C, et al. Early vaginal progesterone versus placebo in twin pregnancies for the prevention of spontaneous preterm birth: a randomized, double-blind trial. Am J Obstet Gynecol. Jan 2021; 224(1): 86.e1-86.e19. PMID 32598909
46. Dang VQ, Nguyen LK, Pham TD, et al. Pessary Compared With Vaginal Progesterone for the Prevention of Preterm Birth in Women With Twin Pregnancies and Cervical Length Less Than 38 mm: A Randomized Controlled Trial. Obstet Gynecol. Mar 2019; 133(3): 459-467. PMID 30741812
47. El-Refaie W, Abdelhafez MS, Badawy A. Vaginal progesterone for prevention of preterm labor in asymptomatic twin pregnancies with sonographic short cervix: a randomized clinical trial of efficacy and safety. Arch Gynecol Obstet. Jan 2016; 293(1): 61-67. PMID 26044148
48. Awwad J, Usta IM, Ghazeeri G, et al. A randomised controlled double-blind clinical trial of 17-hydroxyprogesterone caproate for the prevention of preterm birth in twin gestation (PROGESTWIN): evidence for reduced neonatal morbidity. BJOG. Jan 2015; 122(1): 71-9. PMID 25163819
49. Brizot ML, Hernandez W, Liao AW, et al. Vaginal progesterone for the prevention of preterm birth in twin gestations: a randomized placebo-controlled double-blind study. Am J Obstet Gynecol. Jul 2015; 213(1): 82.e1-82.e9. PMID 25731690
50. Senat MV, Porcher R, Winer N, et al. Prevention of preterm delivery by 17 alpha-hydroxyprogesterone caproate in asymptomatic twin pregnancies with a short cervix: a randomized controlled trial. Am J Obstet Gynecol. Mar 2013; 208(3): 194.e1-8. PMID 23433324
51. Serra V, Perales A, Meseguer J, et al. Increased doses of vaginal progesterone for the prevention of preterm birth in twin pregnancies: a randomised controlled double-blind multicentre trial. BJOG. Jan 2013; 120(1): 50-7. PMID 22882759

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52. Wood S, Rabi Y, Tang S, et al. Progesterone in women with arrested premature labor, a report of a randomised clinical trial and updated meta-analysis. BMC Pregnancy Childbirth. Aug 02 2017; 17(1): 258. PMID 28768474
53. Combs CA, Garite T, Maurel K, et al. 17-hydroxyprogesterone caproate for twin pregnancy: a double-blind, randomized clinical trial. Am J Obstet Gynecol. Mar 2011; 204(3): 221.e1-8. PMID 21376161
54. Lim AC, Schuit E, Bloemenkamp K, et al. 17-hydroxyprogesterone caproate for the prevention of adverse neonatal outcome in multiple pregnancies: a randomized controlled trial. Obstet Gynecol. Sep 2011; 118(3): 513-520. PMID 21860279
55. Rode L, Klein K, Nicolaides KH, et al. Prevention of preterm delivery in twin gestations (PREDICT): a multicenter, randomized, placebo-controlled trial on the effect of vaginal micronized progesterone. Ultrasound Obstet Gynecol. Sep 2011; 38(3): 272-80. PMID 21739497
56. Klein K, Rode L, Nicolaides KH, et al. Vaginal micronized progesterone and risk of preterm delivery in high-risk twin pregnancies: secondary analysis of a placebo-controlled randomized trial and meta-analysis. Ultrasound Obstet Gynecol. Sep 2011; 38(3): 281-7. PMID 21739499
57. Combs CA, Garite T, Maurel K, et al. Failure of 17-hydroxyprogesterone to reduce neonatal morbidity or prolong triplet pregnancy: a double-blind, randomized clinical trial. Am J Obstet Gynecol. Sep 2010; 203(3): 248.e1-9. PMID 20816146
58. Durnwald CP, Momirova V, Rouse DJ, et al. Second trimester cervical length and risk of preterm birth in women with twin gestations treated with 17- hydroxyprogesterone caproate. J Matern Fetal Neonatal Med. Dec 2010; 23(12): 1360-4. PMID 20441408
59. Briery CM, Veillon EW, Klauser CK, et al. Women with preterm premature rupture of the membranes do not benefit from weekly progesterone. Am J Obstet Gynecol. Jan 2011; 204(1): 54.e1-5. PMID 20869038
60. Caritis SN, Rouse DJ, Peaceman AM, et al. Prevention of preterm birth in triplets using 17 alpha-hydroxyprogesterone caproate: a randomized controlled trial. Obstet Gynecol. Feb 2009; 113(2 Pt 1): 285-92. PMID 19155896
61. Norman JE, Mackenzie F, Owen P, et al. Progesterone for the prevention of preterm birth in twin pregnancy (STOPPIT): a randomised, double-blind, placebo-controlled study and meta-analysis. Lancet. Jun 13 2009; 373(9680): 2034-40. PMID 19523680
62. Rouse DJ, Caritis SN, Peaceman AM, et al. A trial of 17 alpha-hydroxyprogesterone caproate to prevent prematurity in twins. N Engl J Med. Aug 02 2007; 357(5): 454-61. PMID 17671253
63. Hartikainen-Sorri AL, Kauppila A, Tuimala R. Inefficacy of 17 alpha-hydroxyprogesterone caproate in the prevention of prematurity in twin pregnancy. Obstet Gynecol. Dec 1980; 56(6): 692-5. PMID 7443111
64. Retraction Note: Vaginal progesterone for prevention of preterm labor in asymptomatic twin pregnancies with sonographic short cervix: a randomized clinical trial of efficacy and

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safety. https://link.springer.com/article/10.1007%2Fs00404-021-06152-1. Published July 27, 2021. Accessed August 4, 2021.
65. Sotiriadis A, Papatheodorou S, Makrydimas G. Perinatal outcome in women treated with progesterone for the prevention of preterm birth: a meta-analysis. Ultrasound Obstet Gynecol. Sep 2012; 40(3): 257-66. PMID 22611023
66. Quist-Nelson J, Parker P, Mokhtari N, et al. Progestogens in singleton gestations with preterm prelabor rupture of membranes: a systematic review and metaanalysis of randomized controlled trials. Am J Obstet Gynecol. Oct 2018; 219(4): 346-355.e2. PMID 29614278
67. Langen ES, Sit A, Sherwin K, Lyell DJ, Blumenfeld YJ, El-Sayed YY. A double-blind, randomized, placebo-controlled trial of 17 alpha-hydroxyprogesterone caproate in the management of preterm premature rupture of membranes. Amer J Perinatol. 2018;(35(08):779-784. DOI: 10.1055/s-0037-1617428
68. Saccone G, Suhag A, Berghella V. 17-alpha-hydroxyprogesterone caproate for maintenance tocolysis: a systematic review and metaanalysis of randomized trials. Am J Obstet Gynecol. Jul 2015; 213(1): 16-22. PMID 25659469
69. Shaamash AH, Ali MK, Attyia KM. Intramuscular 17-hydroxyprogesterone caproate to decrease preterm delivery in women with placenta praevia: a randomised controlled trial. J Obstet Gynaecol. Jul 2020; 40(5): 633-638. PMID 31670998
70. Suhag A, Saccone G, Berghella V. Vaginal progesterone for maintenance tocolysis: a systematic review and metaanalysis of randomized trials. Am J Obstet Gynecol. Oct 2015; 213(4): 479-87. PMID 25797233
71. Martinez de Tejada B, Karolinski A, Ocampo MC, et al. Prevention of preterm delivery with vaginal progesterone in women with preterm labour (4P): randomised double-blind placebo-controlled trial. BJOG. Jan 2015; 122(1): 80-91. PMID 25209926
72. Hyett J, Asadi N, Zare Khafri M, et al. The use of vaginal progesterone as a maintenance therapy in women with arrested preterm labor: a double-blind placebo-randomized controlled trial. J Matern Fetal Neonatal Med. Mar 2022; 35(6): 1134-1140. PMID 32216490
73. The American College of Obstetricians and Gynecologists. Practice Bulletin No. 234. Prediction and Prevention of Preterm Birth. https://journals.lww.com/greenjournal/Fulltext/2021/08000/Prediction_and_Prevention_of_Spontaneous_Preterm.35.aspx. August 2021. Accessed July 26, 2021.
74. The American College of Obstetricians and Gynecologists. Practice Bulletin No. 231. Multifetal Gestations: Twin, Triplet, and Higher-Order Multifetal Pregnancies. https://www.acog.org/clinical/clinical-guidance/practice-bulletin/articles/2021/06/multifetal-gestations-twin-triplet-and-higher-order-multifetal-pregnancies. June 2021. Accessed July 28, 2021.

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75. Berghella V, Blackwell S, Anderson B, et al. Progesterone and preterm birth prevention: translating clinical trials data into clinical practice. Am J Obstet Gynecol. May 2012; 206(5): 376-86. PMID 22542113
76. Society for Maternal-Fetal Medicine (SMFM) Publications Committee. The choice of progestogen for the prevention of preterm birth in women with singleton pregnancy and prior preterm birth. Am J Obstet Gynecol. Mar 2017; 216(3): B11-B13. PMID 28126367
77. Society for Maternal-Fetal Medicine (SMFM) Publications Committee. SMFM Statement: Use of 17-alpha hydroxyprogesterone caproate for prevention of recurrent preterm birth. Am J Obstet Gynecol. 2020 Jul;223(1):B16-B18.
78. Society for Maternal-Fetal Medicine (SMFM) Publications Committee. Society for Maternal-Fetal Medicine Statement: Response to EPPPIC and considerations for the use of progestogens for the prevention of preterm birth. Published March 30, 2021. Accessed July 28, 2021. https://www.smfm.org/publications/383-smfm-statement-response-to-epppic-and-considerations-of-the-use-of-progestogens-for-the-prevention-of-preterm-birth
79. Medley N, Poljak B, Mammarella S, et al. Clinical guidelines for prevention and management of preterm birth: a systematic review. BJOG. Oct 2018; 125(11): 1361-1369. PMID 29460323

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