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Effectiveness and Harms of 17-α Hydroxyprogesterone Caproate (Makena) to Prevent Preterm Birth

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Overview

Preterm birth (PTB), defined as delivery at a gestational age of less than 37 weeks, contributes to short- and long-term health outcomes for offspring. The causes of PTB are varied and complex; thus, effective interventions likely need to be multifaceted. A weekly injection, 17α-hydroxyprogesterone caproate (17P; brand name Makena), is approved by the U.S. Food and Drug Administration (FDA) to treat PTB in women with singleton pregnancies and a prior spontaneous preterm birth (sPTB). Because of this indication, Medicaid administrators are interested in the effectiveness and safety of 17P. In this report, Center for Evidence-based Policy (Center) researchers synthesize evidence from 7 eligible randomized controlled trials (RCTs).

Key Findings

Clinical Evidence

- Few U.S.-based RCTs of good methodological quality have been published evaluating the effectiveness and harms of 17P in women with singleton pregnancies and a prior sPTB. There was 1 large, good-methodological-quality RCT (PROLONG) comparing 17P to a placebo in more than 100 sites in 9 countries, including the United States.

Effectiveness

- Among 3 fair-methodological-quality RCTs eligible for this report, findings suggest that 17P is not significantly more effective at preventing recurrent PTB or increasing gestational age than vaginal progesterone.
- We identified 4 eligible RCTs that compared 17P with a placebo or routine care. Results from 2 good-methodological-quality RCTs did not support a treatment benefit of 17P for preventing sPTB or for any other maternal or neonatal outcomes. The 2 poor-methodological-quality studies reported that exposure to 17P reduced the risk of recurrent PTB.

Harms

- No significant risk of maternal or neonatal harms were identified for singleton pregnancies exposed to 17P in the 7 RCTs and one 4-year 17P trial follow-up included in this report.

Ongoing Trials

- Four ongoing RCTs are: evaluating increased dosage of 17P for women who weigh more than 165 pounds before pregnancy; comparing 17P with a higher dosage of vaginal progesterone than has been used in previous trials; and conducting a 2-year safety follow-up for a large confirmatory trial of 17P versus placebo.

Background

Approximately 1 in 10 live births in the U.S. occurs before 37 weeks gestation,[1] and Medicaid programs paid for 49% of all PTBs from 2010 to 2014.[2] The incidence of PTB for women with singleton pregnancies increased for the fourth year in a row in 2018 to 8.1%,[3] and PTB is associated with greater infant morbidity and mortality compared to full-term births (i.e., ≥ 39 and < 41 weeks of gestation).[4]

Pregnant women with a prior sPTB are at a higher risk of preterm delivery than women with a first pregnancy or a previous full-term delivery.[5] Analysis of U.S. birth certificate data found that 133,000 women with a prior sPTB delivered in 2002, and about 22.5% (n = 29,910) of these women had a recurrent sPTB.[6] Approximately 22.5% to 31.6% of women with 1 prior sPTB are expected to have another PTB in a subsequent pregnancy,[5-7] and this risk increases for each additional prior PTB.[5] Other risk factors associated with sPTB include short interpregnancy interval (i.e., less than 18 months), smoking, drug use, obesity, undernutrition, young maternal age, high levels of stress, and maternal race/ethnicity.[8-10] Regardless of socioeconomic position, non-Hispanic black women are more likely to have an sPTB than non-Hispanic white women.[11]

The American College of Obstetricians and Gynecologists published an opinion in 2008 supporting the use of 17P for patients with singleton pregnancy and a prior sPTB.[12] This was followed by guidelines promoting the use of intramuscular and vaginal progesterone to prevent sPTB from the Society for Maternal-Fetal Medicine in 2012.[13] Guidelines suggest that providers prescribe 17P between 16 and 20 weeks of gestation for singleton pregnancies with a prior singleton sPTB, continuing weekly injections until the end of the 36th week of gestation or delivery, whichever is first.[13] Before 2011, 17P was available from compounding pharmacies at a relatively low cost: a single dose was priced from $10 to $20.[14] In February 2011, the FDA approved 17P under the brand name Makena, which was first priced at $1,440 per dose and subsequently reduced to $690 per dose.[15] At that time, the FDA also released a statement explaining that the drug owner of Makena had obtained 7 years of exclusivity under the Orphan Drug Act, but that the FDA did not intend to take enforcement action against compounding pharmacies producing 17P under the appropriate safety and legal standards.[16] An FDA statement in July 2012 superseded its previous guidance, stating that compounding pharmacies cannot compound drugs that are "essentially copies" of Makena and that the FDA intended to take appropriate action against pharmacies found to be in violation.[17] The FDA has since approved 4 generic compounds of 17P for pregnant women.[18]

The incidence of PTB, related racial/ethnic disparities, associated infant health outcomes, and financial costs are cause for significant concern among medical and public health officials. Interventions to reduce or prevent PTB are limited. State Medicaid program administrators are interested in understanding the effectiveness and harms of 17P to prevent PTB.

PICO

Population: women with a singleton pregnancy and a history of sPTB (before 37 weeks of gestation)

Intervention: 17P

Comparators: active comparators (e.g., vaginal progesterone); no treatment; placebo

Outcomes: PTB (before 37 weeks of gestation), gestational age at delivery, birth weight, adverse events (e.g., respiratory distress syndrome), serious adverse events (e.g., neonatal mortality)

Key Questions

1. What is the effectiveness of 17P for preventing PTB?
2. What are the harms of 17P for preventing PTB?
3. What are the ongoing RCTs testing the effectiveness of 17P for women with a singleton pregnancy and a history of singleton sPTB?

Methods

We searched Medicaid Evidence-based Decisions Project (MED) clinical evidence sources (e.g., Ovid MEDLINE, Cochrane library, Clinical Trials Registry) for RCTs, controlled clinical trials, and systematic reviews of the effectiveness and harms of 17P to prevent sPTB. Publication in English within the last 20 years was an additional eligibility criterion. One Center researcher assessed the methodological quality of the studies included in this report and a senior researcher reviewed these ratings. See Appendix A for more information about search strategies, inclusion and exclusion criteria, and how quality assessment was performed. When sufficient information was reported, we calculated risk ratios and noted these calculations with this symbol: ‡.

Findings

Effectiveness

We identified 7 eligible RCTs with peer-reviewed publications: 2 trials were based in the U.S.[19,20]; 1 multinational trial included sites within the U.S.[21]; and 4 other international trials were based in Egypt,[22] Iran,[23] India,[24] and Saudi Arabia[25] (Table 1). Three trials[19,24,25] compared 17P to vaginal progesterone, and 4 trials[20-23] evaluated the effectiveness of 17P compared to a placebo or routine care. Each study included women with singleton pregnancies and a history of sPTB, and excluded women with other clinical risk factors, such as premature rupture of membranes and arrested preterm labor at the time of trial entry. The primary outcomes of interest for this report were sPTB (defined as before 37 weeks of gestation), birth weight, adverse events (e.g., respiratory distress syndrome), and serious adverse events (e.g., neonatal death). We will first describe findings from eligible U.S. trials and then describe non-U.S. trials.

Table 1. Study Characteristics of Eligible RCTs for 17P

Author, Year, Country	Number	Outcomes	Methodological Quality
17P vs. Vaginal Progesterone			
Elimian et al., 2016,[19] U.S.	N = 174 17P n = 82 100 mg vaginal progesterone n = 92	• sPTB < 37 weeks • sPTB < 28 and < 34 weeks • Gestational age • Birth weight • Neonatal death	Fair • Investigators and participants were aware of treatment condition (open-label study), and it is unclear whether researchers were able to influence which treatment participants received.
Maher et al., 2013,[25] Saudi Arabia	N = 518 17P n = 256 90 mg vaginal progesterone n = 262	• sPTB < 34 weeks • sPTB > 32 and < 37 weeks • Birth weight • Neonatal death • NICU admission	Fair • Investigators and participants were aware of treatment condition (open-label study), and it is unclear whether researchers were able to influence which treatment participants received.
Shambhavi et al., 2018,[24] India	N = 100 17P n = 50 200 mg vaginal progesterone n = 50	• sPTB < 37 weeks • sPTB < 34 weeks • NICU admission • Respiratory distress syndrome • Neonatal sepsis • Neonatal death	Fair • Investigators and participants were aware of treatment condition (open-label study), and it is unclear whether the researchers were able to influence which treatment participants received, and the source of funding for this study was not declared.
17P vs. Placebo or Routine Care			
Meis et al., 2003,[20] U.S.	N = 463 17P n = 310 Castor oil placebo n = 153	• sPTB < 37 weeks • sPTB < 35 weeks • sPTB < 32 weeks • Birth weight • Respiratory distress syndrome • Neonatal sepsis • Neonatal death	Poor • Baseline characteristics of average number or prior PTBs were not evenly distributed between the groups, and one study site recruited a disproportionate number of participants.
Blackwell et al., 2019,[21] U.S. and 8 other countries	N = 1,708 17P n = 1,130 Castor oil placebo n = 578	• sPTB < 35 weeks • Neonatal mortality and morbidity • sPTB < 37 weeks • sPTB < 32 weeks • Birth weight	Good

Author, Year, Country	Number	Outcomes	Methodological Quality
Saghafi et al., 2011,[23] Iran	N = 100 17P n = 50 Routine care n = 50	• sPTB < 37 weeks • Gestational age • Birth weight	Poor • Researchers might have been able to influence the assignment of participants to one group or another; unclear study design and analytic plan and differences in baseline characteristics between the treatment and control groups might have biased the results.
Ibrahim et al., 2010,[22] Egypt	N = 50 17P n = 25 Saline placebo n = 25	• sPTB < 37 weeks • NICU admission • Respiratory distress syndrome • Neonatal sepsis • Neonatal death	Good

Abbreviations. 17P: 17α-hydroxyprogesterone caproate; NICU: neonatal intensive care unit; sPTB: spontaneous preterm birth.

17P vs. Vaginal Progesterone

Elimian et al.[19] conducted a fair-methodological-quality RCT that enrolled pregnant women seeking care at the University of Oklahoma Medical Center from 2007 to 2010. We rated the methodological quality as fair because the health care providers, participants, and researchers knew which treatment the participants were receiving throughout the trial and analysis and might have been able to influence which treatment participants received, which might have biased the findings.

Researchers recruited and randomly assigned 174 women with singleton pregnancies and a prior sPTB to either a group that received weekly 17P injections (250 mg; n = 66) or a group that self-administered daily vaginal progesterone gel through an applicator (90 mg; n = 79).[19] Although the trial lost 29 participants to follow-up (16.6%), the authors reported that the women who dropped out did not significantly differ on baseline characteristics from the women who completed the trial.[19]

The main outcome for this study was recurrent sPTB, but there were no statistically significant differences in sPTB for women who received 17P and women who used vaginal progesterone (Table 3).[19] The number of women who delivered at or before 28 weeks (P = .99) and 34 weeks (P = .83) did not differ by group.[19] Additionally, infants in both groups were similar in birth weight, gestational age at delivery, and experience of adverse events such as sepsis, respiratory distress syndrome, or neonatal death (Table 2).[19] Similar to the Meis et al.[20] trial in the next section of this report, the incidence of sPTB in both treatment groups was higher than would be expected in the population of women with a prior singleton sPTB (Table 2).

Table 2. Trials of 17P vs. Vaginal Progesterone

Outcome	Analysis N	17P	Vaginal Progesterone	Effect Size; 95% Confidence Interval
Gestation < 37 Weeks, n (%)				
Elimian et al., 2016[19]	145	29 (43.9%)	30 (38.0%)	RR, 1.16; 0.78 to 1.71‡; *P* = .50
Maher et al., 2013[25]	502	88 (35.3%)	84 (33.2%)	RR, 1.06; 0.83 to 1.36‡; *P* = .61
Shambhavi et al., 2018[24]	98	10 (20.0%)	10 (20.8%)	RR, 1.04; 0.47 to 2.30‡; *P* > .05
Birth Weight in Grams, Mean (Standard Deviation)				
Elimian et al., 2016[19]	145	2,703.2 (851)	2,777.6 (1,131)	Test for difference in means NR, *P* = .66
Maher et al., 2013[25]	502	2,562.2 (780.7)	2,637.0 (737.2)	Test for difference in means NR, *P* = .08
Shambhavi et al., 2018[24]	98	2,620.0 (661)	2,766.0 (558)	Test for difference in means NR, *P* = .24
Sepsis, n (%)				
Elimian et al., 2016[19]	145	3 (4.5%)	1 (1.3%)	RR, 3.64; 0.39 to 34.14†; *P* > .05
Maher et al., 2013[25]	502	4 (2.0%)	5 (2.0%)	RR, 0.81; 0.22 to 2.99; *P* > .05
Shambhavi et al., 2018[24]	98	2 (4%)	1 (2%)	RR, 2.08; 0.20 to 22.23‡; *P* > .05
Respiratory Distress Syndrome, n (%)				
Elimian et al., 2016[19]	145	5 (7.6%)	9 (11.4%)	RR, 0.67; 0.23 to 1.89‡; *P* > .05
Maher et al., 2013[25]	502	26 (10.4%)	19 (7.5%)	RR, 1.39; 0.79 to 2.45; *P* > .05
Shambhavi et al., 2018[24]	98	4 (8%)	2 (4%)	RR, 2.08; 0.40 to 10.85‡; *P* > .05
Neonatal Death, n (%)				
Elimian et al., 2016[19]	145	7 (10.6%)	5 (6.3%)	RR, 1.68; 0.56 to 5.03‡; *P* > .05
Maher et al., 2013[25]	502	10 (4.0%)	6 (2.4%)	RR, 1.69; 0.63 to 4.59; *P* > .05
Shambhavi et al., 2018[24]	98	1 (2%)	0 (0%)	RR, 3.06; 0.13 to 73.35‡; *P* > .05

Notes. ‡Calculated by Center staff. Abbreviations. NR: not reported; RR: risk ratio.

Non-U.S. RCTs for 17P vs. Progesterone

Maher et al.[25] conducted a fair-methodological-quality RCT in Saudi Arabia between 2009 and 2011 in which 518 women with a prior sPTB were randomly assigned to either a group that received weekly 17P injections (250 mg; n = 256) or a group that self-administered daily vaginal micronized progesterone suppositories (100 mg; n = 262). We rated the methodological quality of the study as fair because all participants, health care providers, and researchers were aware of which treatment participants received and might have been able to influence which treatment participants received, possibly biasing the results.

The 2 groups were similar in age, parity, gestational age at randomization, compliance, history of sPTB, and cervical length.[25] Only 16 women (3%) were lost to follow-up, and although attrition did not differ significantly by treatment, the authors did not test whether women who dropped out of the study were different from women who remained in the study in terms of baseline characteristics.[25] The primary outcome for this study was sPTB, but there was no significant difference in risk of sPTB between the group of women who received weekly 17P injections and the group who used daily vaginal progesterone (Table 2).[25]

Although there was not a significant difference between the groups in the proportion of recurrent PTB before 37 weeks gestation, women who used vaginal progesterone were less likely to deliver before 34 weeks (*P* = .02), 32 weeks (*P* = .04), and 28 weeks (*P* = .04) than women receiving 17P injections.[25] In other words, women exposed to 17P were at a higher risk for delivery before 34 weeks of gestation (risk ratio [RR], 1.55; 95% confidence interval [CI], 1.09 to 2.19; *P* = .01‡). Neonates born to women who had received 17P had a higher risk of being admitted to the neonatal intensive care unit (RR, 1.67; 95% CI, 1.16 to 2.38; *P* = .005‡) The infants from the 2 groups did not significantly differ by average birth weight or by adverse events such as sepsis, respiratory distress syndrome, or neonatal death (Table 2).[25]. The findings from this study favored exposure to vaginal progesterone over 17P for increasing gestational age at delivery, which was likely related to the increased risk of admission to the neonatal intensive care unit in the infants exposed to 17P.

Shambhavi et al.[24] conducted a fair-methodological-quality RCT with 100 women in India who had at least one prior sPTB, and randomly assigned women to receive either weekly 17P injections (250 mg) or daily vaginal tablets of micronized progesterone (200 mg).[24] We rated the methodological quality rating of this trial as fair because providers, researchers, and participants all knew which treatment the participants received, researchers might have been able to influence which treatment participants received, and the authors did not declare the source of funding for this study. Each of these elements might have biased the findings.

The 2 groups were similar on maternal characteristics, such as age, parity, cervical length, and prior sPTB. In contrast to the other studies described in this report, Shambhavi et al.[24] reported the number of women who had a prior abortion in addition to previous sPTB, although the proportions did not differ significantly between groups.[24] About one-third of the sample had a previous first trimester abortion (n = 32), and 12% had a prior second trimester abortion.[24] Two women in the 17P group were excluded from analysis because of medically indicated PTB during the trial.[24] Similar to the Elimian et al.[19] and Maher et al.[25] studies, there were no significant differences in risk of sPTB for women in the 17P group and the vaginal progesterone group.[24]

The infants were not significantly different by average birth weight, or by adverse events such as sepsis, respiratory distress syndrome, or neonatal death between the 2 groups (Table 2).[24] In contrast to the other trials described in this report, the incidence of sPTB in the Shambhavi et al.[24] trial was low (20.4%; n = 20) for the whole sample.

17P vs. Placebo

In the RCT performed by the National Institute of Child Health and Human Development (NICHD) Maternal-Fetal Medicine Unit Network, researchers randomly assigned 463 participants to receive 17P or a castor oil placebo with a 2:1 ratio.[20] The Meis et al.[20] article that presented the main results from the trial also included information about the protocol and the history of the trial. We rated the methodological quality of this trial as poor because the 2 groups were not balanced on all baseline characteristics that are highly related to risk of recurrent sPTB (Table 1), and because 25% of the sample was from one academic center.[26] The authors reported a statistically significant reduction in the risk of delivering before 37 weeks of gestation for women who received weekly 250 mg 17P injections (RR, 0.70; 95% CI, 0.57 to 0.85; $P < .05$; Table 3).[20] Risk reduction appeared to be similar for non-Hispanic black women (RR, 0.68; 95% CI, 0.51 to 0.90; $P < .05$) vs. women of other races/ethnicities (RR, 0.64; 0.47 to 0.87; $P < .05$).[20] The authors also reported that exposure to 17P was associated with reduced risk of delivery before 35 weeks (RR, 0.67; 95% CI, 0.48 to 0.93; $P < .05$) and 32 weeks (RR, 0.58; 95% CI, 0.37 to 0.91; $P < .05$). Infants delivered by women who had received 17P injections had reduced risk of birth weight under 2,500 grams (RR, 0.66; 95% CI, 0.51 to 0.87; $P = .003$).[20]

Women in the placebo group had a statistically significantly higher average of prior PTBs than the women receiving 17P,[20] which indicated that the 2 groups of women did not have the same baseline risk for having a sPTB. In a secondary analysis of data from this trial, Meis et al.[27] reported that women in the placebo group with 2 or more sPTBs had higher odds of having an sPTB during the trial than women in the placebo group with 1 prior sPTB (odds ratio [OR], 3.38; 95% CI, 1.36 to 8.40; $P = .009$).[27] However, another secondary analysis, using the Meis et al.[20] trial data and controlling for this imbalance indicated that women with a very early prior sPTB (at 20 to 30 weeks gestation) might have had longer pregnancies on average when treated with 17P, even if that did not result in a term or full-term delivery (≥ 37 and < 41 weeks of gestation).[28] All women had higher odds of having an sPTB during the trial if their penultimate pregnancy was preterm, whether they received 17P (OR, 2.81; 95% CI, 1.36 to 5.82; $P = .005$) or the placebo (OR, 3.07; 95% CI, 1.03 to 9.13; $P = .04$).[27] According to another secondary analysis, the average qualifying sPTB for women in the Meis et al.[20] trial occurred at about 30 weeks of gestation, which is considered very early preterm.[28] Therefore, this sample might have included more very-high-risk pregnancies than would be expected in the general population of women with a prior sPTB, which could limit the generalizability of the findings.[28]

Compared to state population studies of women with a prior singleton sPTB and a current singleton pregnancy, the proportion of women receiving placebo injections who delivered before 37 weeks of gestation was higher than expected in the Meis et al.[20] trial. For example, the NICHD Consecutive Pregnancies Study retrospectively analyzed the pregnancies of 51,086 women in Utah from 2002 to 2010 and reported that 31.6% of women with a prior singleton sPTB delivered before 37 weeks of gestation in a subsequent singleton pregnancy.[5] Retrospective analysis of natality data from 2002 in New Jersey and Missouri indicated that

22.5% of women with a singleton pregnancy and a prior singleton sPTB delivered before 37 weeks.[6] Natality data for women with first and second singleton pregnancies from 1980 to 1995 in Georgia indicated that among women whose first pregnancy resulted in sPTB, 19.9% of white women and 26.0% of black women delivered before 37 weeks of gestation in their second pregnancy.[29]

Trial participants are not a random sample of the population of women at risk for sPTB, so we would not expect the incidence of sPTB in a trial to be exactly the same as the prevalence of sPTB in the population of women at risk for sPTB due to a prior sPTB. However, the difference between these estimates and the trial incidence is striking. Several researchers not involved in the trial published critiques of the generalizability of the conclusions of articles from the Meis et al.[20] trial because of the unexpectedly high number of women in the placebo group who delivered before 37 weeks of gestation.[30-34]

The results of the Meis et al.[20] study should be interpreted with caution because the 17P and placebo groups did not have a similar average number of prior sPTBs, the whole sample was higher risk than the general population of eligible pregnancies, and a large concentration of participants was from one study site. The high proportion of recurrent PTB in the placebo group related to higher average risk was likely the driver behind significantly different outcomes between the 2 groups, rather than a treatment effect of 17P for reducing the risk of PTB.

Confirmatory Trial

Blackwell et al.[21] completed a large-scale replication of the Meis et al.[20] study (N = 1,708). This multicenter, multinational, placebo-controlled RCT (Progestin's Role in Optimizing Neonatal Gestation [PROLONG]; NCT01004029) launched in October 2009 and concluded in December 2018.[35] We rated this as a good-methodological-quality study. The PROLONG trial was a confirmatory trial required by the FDA during the accelerated approval process by which Makena (trade name for 17P) received approval. This confirmatory trial was designed to address known limitations of the Meis et al. trial, including limiting the proportion of the sample that could be enrolled at each study location. The FDA also required that at least 10% of the final sample live in the United States or Canada. Additional information was gathered on the enrolled women, including cervical length, so that the investigators could stratify by and analyze different risks.

In the trial, 1,130 women received 17P and 578 women received a placebo; the two groups had similar baseline characteristics.[21] The difference between spontaneous PTB at less than 35 weeks of gestation was not statistically significantly different between groups (RR, 0.93; 95% CI, 0.67 to 1.30; $P = .72$). Similarly, no significant difference was found between the two groups for sPTB at less than 37 weeks of gestation (RR, 1.06; 95% CI, 0.88 to 1.28; $P > .05$; Table 3), or less than 32 weeks of gestation (RR, 0.88; 95% CI, 0.52 to 1.48; $P > .05$).[21] Although the sample had lower risk for a recurrent PTB on average when compared to the sample in the Meis et al.[20] study, there was no meaningful relationship between any risk factor and receipt of 17P that would support a clinical benefit of using 17P in a particular subpopulation.[26] The study investigators and biostatisticians at the FDA conducted exploratory analyses by various subgroups of the study sample. These analyses included subgroups defined by gestational age of the qualifying prior preterm birth, number of PTBs, cervical length, geographic region (i.e., U.S.

versus non-U.S.), race, body mass index, and substance use during pregnancy. None of these subgroup analyses demonstrated a treatment benefit for 17P.[21,26]

Further, infants exposed to 17P compared to a placebo did not have a statistically significantly different neonatal morbidity and mortality composite index (5.4% vs. 5.2%; *P* = .84).[21,26,36] This trial was powered to detect a difference between the groups for neonatal death, but no difference was found (RR, 0.87; 0.4 to 1.81; *P* > .05).[26] Respiratory distress syndrome was the primary condition driving the morbidity index, and infants in the 17P group did not have significantly lower risk for this condition (RR, 1.06; 95% CI, 0.67 to 1.68; *P* > .05).[26] Birth weight was not significantly different for infants in the 17P group (mean = 3,076; standard deviation = 630.0) and the placebo group (mean = 3,080.1; standard deviation = 609.2).[26]

Table 3. Trials of 17P vs. Placebo or Routine Care

Outcome	Analysis N	17P	Placebo	Effect Size; 95% Confidence Interval
Gestation < 37 Weeks, n (%)				
Meis et al., 2003[20]	463	111 (36.3%)	84 (54.9%)	RR, 0.70; 0.57 to 0.85; *P* < .05
Blackwell et al., 2019[21]	1,708	257 (23.1%)	125 (21.9%)	RR, 1.06; 0.88 to 1.28; *P* > .05
Saghafi et al., 2011[23]	100	16 (32%)	30 (60%)	RR, 0.55; 0.35 to 0.86‡; *P* = .008
Ibrahim et al., 2010[22]	50	8 (32%)	13 (52%)	RR, 0.62; 0.28 to 1.35‡; *P* > .05
Birth Weight < 2,500 grams, n (%)				
Meis et al., 2003[20]	463	82 (27.2%)	62 (41.1%)	RR, 0.66; 0.51 to 0.87†; *P* < .05
Blackwell et al., 2019[21]		NR	NR	NR
Saghafi et al., 2011[23]	100	26 (52%)	14 (28%)	RR, 1.86; 1.11 to 3.12‡; *P* = .02
Ibrahim et al., 2010[22]	50	5 (20%)	10 (40%)	RR, 0.50; 0.20 to 1.25‡; *P* > .05
Sepsis, n (%)				
Meis et al., 2003[20]	463	9 (3.0%)	4 (2.6%)	RR, 1.12; 0.35 to 3.58†; *P* > .05
Blackwell et al., 2019[21]	1,708	5 (0.5%)	3 (0.5%)	RR, 0.84; 0.20 to 3.56; *P* > .05
Saghafi et al., 2011[23]		NR	NR	NR
Ibrahim et al., 2010[22]		NR	NR	NR
Respiratory Distress Syndrome, n (%)				
Meis et al., 2003[20]	463	29 (9.5%)	23 (15.2%)	RR, 0.63; 0.38 to 1.05†; *P* > .05
Blackwell et al., 2019[21]	1,652	54 (4.9%)	26 (4.7%)	RR, 1.06; 0.67 to 1.68; *P* > .05
Saghafi et al., 2011[23]		NR	NR	NR
Ibrahim et al., 2010[22]		NR	NR	NR
Admission to Neonatal Intensive Care, n (%)				
Meis et al., 2003[20]		NR	NR	NR
Blackwell et al., 2019[21]	1,652	137 (12.5%)	58 (10.4%)	RR, 1.21; 0.90 to 1.62; *P* > .05
Saghafi et al., 2011[23]		NR	NR	NR
Ibrahim et al., 2010[22]	50	3 (12%)	9 (36%)	RR, 0.33; 0.10 to 1.09‡; *P* > .05

Outcome	Analysis N	17P	Placebo	Effect Size; 95% Confidence Interval
Neonatal Death, n (%)				
Meis et al., 2003[20]	463	8 (2.6%)	9 (5.9%)	RR, 0.44; 0.17 to 1.13†; *P* > .05
Blackwell et al., 2019[21]	1,706	6 (0.5%)	3 (0.5%)	RR, 0.98; 0.24 to 3.91; *P* > .05
Saghafi et al., 2011[23]		NR	NR	NR
Ibrahim et al., 2010[22]	50	1 (4%)	4 (16%)	RR, 0.25; 0.03 to 2.08; *P* > .05

Notes. †Risk ratio and confidence interval estimates not adjusted for baseline difference in the number of prior preterm births between the 17P and placebo groups. ‡Calculated by Center staff. Abbreviations. NR: not reported; RR: risk ratio.

Non-U.S. RCTs for 17P vs. Placebo or Routine Care

Saghafi et al.[23] conducted a poor-methodological-quality RCT (N = 100) in Iran between 2007 and 2008. The authors reportedly randomly divided participants to receive 17P or routine care, likely in a 1:1 ratio. We rated the methodological quality as poor because the authors failed to clearly report how participants were assigned to groups, all individuals involved in the trial knew group assignment of participants, and the analytic approach was only vaguely described. The 2 groups were similar in maternal characteristics, including number of previous miscarriages, preterm deliveries, and gestational age at prior sPTB, but it was unclear how the authors tested potential differences and used information about baseline characteristics in the analyses.[23]

Similar to the Meis et al.[20] study, women in this trial had an average of more than 1 prior sPTB. Additionally, the focal pregnancy in this trial was most often a third or higher order pregnancy.[23] Compared to women who received routine care, women who received 17P had reduced risk of sPTB (RR, 0.53; 95% CI, 0.34 to 0.85; *P* = .008‡).[23] Infants in the 17P group had a significantly higher average gestational age (mean =36.94 weeks) than infants in the routine care group (mean = 35.1 weeks; *P* = .01).[23] Although the average birth weight for infants in the 17P group was significantly higher (17P mean =2,695 grams [g] vs. routine care mean =2,399 g; *P* =.02), there were significantly fewer low birth weight infants (< 2,500 g) in the routine care group (Table 3).[23]

Ibrahim et al.[22] conducted a good-methodological-quality RCT in Egypt between 2006 and 2008, in which 50 women with prior sPTB were randomly assigned to receive 17P or a saline placebo in a 1:1 ratio, and the participants and researchers did not know the assignment. Most of the pregnancies in this trial were fourth or higher order pregnancies.[22] Although more women in the 17P group gave birth at term compared to the placebo group, the finding was not statistically significant (Table 3).[22] Average gestational age at delivery was significantly higher for infants in the 17P group (mean =37.47 weeks) than for infants in the placebo group (mean =34.71 weeks; *P* < .01), but there was no significant difference between the 2 groups for low birth weight (Table 3).[22]

Safety

We reviewed all of the RCTs described above for reported information about maternal and neonatal adverse events. We identified 1 publication[37] that presented follow-up data for

surviving children from the Meis et al. study,[20] collected when the children were about 4 years old.

Maternal Safety

About half of the women (n = 231) in the Meis et al.[20] trial reported at least 1 adverse effect. Injection site reactions, such as soreness (n = 158), swelling (n = 65), and bruising (n = 31) were the most common adverse effects reported by 17P and placebo recipients. Although women from both groups reported these adverse reactions, 17P recipients were significantly more likely to have swelling (n = 53 vs. n = 12; *P* = .007) or a lump (n = 17 vs. n = 2) at the injection site.[20] Similarly, more 17P recipients in the Maher et al.[25] trial reported adverse effects than women who used vaginal progesterone (n = 35 vs. n = 19; *P* = .02). Women who received 17P reported pain, swelling, and headache (n = 35; 14.1%), and women using vaginal progesterone reported bloating, nausea, and vaginal soreness (n = 19; 7.5%).[25] In the Shambhavi et al.[24] trial, 20% (n = 10) of participants using vaginal progesterone had vaginal discharge not related to an infection, and 29.2% (n = 14) of 17P recipients had mild pain at the injection site. No other maternal harms were documented in the trials reviewed in this report.

Neonatal Safety

Because 19-norprogesterone has caused some masculinization of the female fetus in the past, researchers expressed concern that the development of sexual organs might be affected in the fetuses of mothers who received any progesterone intervention. To evaluate this for participants in the Meis et al.[20] trial, Northern et al.[37] collected physical examination data through medical records and the Ages and Stages Questionnaires for 278 children from the Meis et al. trial,[20] equivalent to 80% of the original study population. Of this sample, 194 were children of women who received 17P injections, and 84 were children of women who received placebo injections.[37] Women in the 17P group began injections between 16 and 20 weeks gestation during the trial, with a median start date at around 19 weeks of gestation.[37] The median number of injections received was 16 (range, 1 to 21).[37] The authors found no evidence that any women in the placebo group received 17P at any time during the trial.[37]

The fetuses in this trial were only exposed to 17P after embryological genital development was complete (16 weeks of gestation and later).[37] The authors reported no significant difference in genital or reproductive tract abnormalities between children whose mothers received 17P (n = 194) and children whose mothers received the placebo (n = 84).[37] Four children (2%) in the 17P group had anomalies, including micropenises, an undescended testicle, and early puberty for 1 female child (0.5%).[37] One child (1%) in the placebo group had pubic hair at the time of the examination.[37]

Children from the 2 groups were similar in overall health, height and weight percentile, blood pressure, required medications, operations, and impairments limiting daily childhood activities.[37] The authors did not find any significant differences between children in the 2 groups for medical diagnoses from a health professional, including asthma, ear infections, allergies, eczema, migraines, diabetes, sickle cell anemia, and cerebral palsy.[37]

Results from the Ages and Stages Questionnaires and the Preschool Activities Inventory indicated that at an average of 48 months after delivery, surviving children from the 2 groups did

not differ in communication, gross or fine motor skills, problem solving, personal-social skills, or gender role behavior.[37] Additionally, there were no differences in diagnoses by a health professional for communication problems, attention or learning problems, developmental delay, autism, or activity and coordination problems.[37]

Ongoing Studies

We identified 3 ongoing studies in which 17P is the treatment or comparator for the prevention of PTB in women with singleton pregnancies and a history of PTB, and 1 ongoing follow-up study for the PROLONG study (Table 4).

Table 4. Ongoing Studies of 17P for Women with a Singleton Pregnancy and Prior sPTB

NCT Number, Location, Enrollment	Treatment	Comparator	Outcomes	Estimated Completion Date
NCT02913495, U.S., N = 224	200 mg micronized progesterone vaginally daily until 36 weeks plus 6 days or delivery	250 mg 17P once weekly until 36 and 6 days or delivery	• Preterm birth • Gestational age • Birth weight • Adverse effects	August 2019
NCT03433040, U.S., N = 63	500 mg 17P once weekly until 36 weeks or delivery	250 mg 17P once weekly until 36 weeks or delivery	• Preterm birth for pregnant women who are obese	August 2020
NCT03292731, U.S., N = 300	500 mg 17P once weekly until 36 weeks or delivery	250 mg 17P once weekly until 36 weeks or delivery	• Preterm birth • Plasma concentration of 17-OHPC	December 2020
NCT01146990, PROLONG Follow-up, U.S. and international sites, N = 584	250 mg 17P once weekly until 36 weeks or delivery	Castor oil placebo	• Safety follow-up between 23 to 25 months, after gestational adjustment • Ages and Stages Questionnaire • Bayley III • Neurologic exam	October 2020

Note. Trials of 17P for indications other than prior sPTB were excluded. Source. Information adapted from the U.S. National Library of Medicine Clinical Trials Registry for trials without a published protocol.

Discussion

PTB is a complex condition with a multifaceted etiology making it unlikely that a single intervention will be a panacea. Three fair-methodological-quality RCTs found no difference for maternal or neonatal outcomes between groups receiving 17P or vaginal progesterone. Two poor-methodological-quality RCTs reported that pregnant women with a prior PTB exposed to 17P had lower risk of delivering before 37 weeks gestation and having a baby with low birth weight compared to women exposed to a placebo. However, 2 good-methodological-quality

RCTs found that there was no difference in risk of PTB, neonatal morbidity or mortality between groups exposed to 17P or a placebo. One of these good-methodological-quality RCTs was the largest RCT in this report, addressed potential biases of the trial this RCT was replicating, and included exploratory analyses to consider whether subpopulations might benefit from receiving 17P. None of the planned or exploratory analyses found any significant differences in maternal or neonatal outcomes between women randomized to receive 17P or a placebo.

There was little difference in sPTB outcomes between women receiving 17P, a placebo, routine care, or vaginal progesterone. In head-to-head trials, 17P was not significantly better at reducing risk of sPTB than vaginal progesterone. However, each of the 3 trials with vaginal progesterone used different concentrations of progesterone (90 mg, 100 mg, and 200 mg), versus the stable amount of 250 mg 17P weekly injections across studies. The different dosage in each study makes it challenging to determine whether there is a difference in clinical benefit between 17P and vaginal progesterone for preventing recurrent PTB in women with a prior PTB.

No serious harms were observed in the trials included in this report for pregnant women or neonates exposed to 17P, and a 4-year follow-up did not identify significant differences in the health or development of surviving children from pregnancies exposed to 17P. A 2-year follow-up of about a third of the liveborn neonates in PROLONG trial is in progress, and will likely result in peer-reviewed publication in 2021. All trials in this report initiated progesterone treatment between 16 and 20 weeks of gestation, and there is no evidence from RCTs to support initiation at earlier or later points during gestation.

Although observational studies were beyond the scope of this report, we found 4 non-randomized studies of pregnant women with a prior PTB that were conducted after the publication of the Meis et al.[20] study. Nelson et al.[38] conducted a prospective cohort study with 430 pregnant women with a prior PTB exposed to 17P, and found that the cohort exposed to 17P had higher risk of sPTB than a historical cohort in the same obstetric population not exposed to 17P. Another prospective study of 224 women in a high-risk population by Sibai et al.[39] found no difference in recurrent PTB between women exposed to 17P and women not exposed to 17P. Ning et al.[40] retrospectively compared 132 women who initiated 17P injections early (before 17 weeks) or later (between 17 and 28 weeks) in pregnancy, and found no statistically significant difference in recurrent PTB. Rebarber et al.[41] found that the proportion of women experiencing recurrent PTB was 29.8% in a retrospective description of 3,139 women who received weekly 17P injections in clinical practices covered by private insurance. This sample had, on average, lower risk than the Meis et al.[20] treatment group, but experienced a similar rate of recurrent PTB.[41] As discussed previously in this report, estimates for recurrent PTB range from about 20% to 32% in statewide populations not exposed to 17P.[5,6,29] We did not rate the methodological quality of these studies, but the findings are consistent with those from the PROLONG study that call into question the effectiveness of 17P to prevent recurrent PTB.

On March 7, 2019, AMAG Pharmaceuticals presented preliminary data from the PROLONG study, which used Makena for the weekly 17P injections for women in the treatment group.[36] The reporting of these data revealed no statistically significant differences and automatically triggered an FDA advisory committee hearing to review the results; this type of hearing occurs when confirmatory trial data are available related to a drug with accelerated approval.[26] The

hearing took place on October 29, 2019, and the committee voted 9 to 7 to revoke approval of Makena for preventing recurrent PTB after unanimously agreeing that the PROLONG trial results did not support a clinical benefit for Makena.[26] The FDA has yet to announce whether they will officially revoke approval of Makena in light of the failure of PROLONG to confirm a clinical benefit of Makena.

Engagement with women to assess their needs immediately after a PTB and continuing into the interpregnancy interval, although challenging to design and implement, might provide more opportunity to prevent adverse prenatal outcomes affected by complex social factors. Expanding partnerships to agencies beyond Medicaid, particularly with Title V, might facilitate successful preventive strategies during the interpregnancy period. This is particularly important in light of recent evidence from PROLONG about the lack of effectiveness of Makena and the likelihood that approval will be revoked.

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Appendix A. Methods

Search Strategy

We searched Medicaid Evidence-based Decisions Project (MED) clinical evidence sources to identify systematic reviews (with and without meta-analyses) and randomized controlled trials (RCTs) using the terms *premature birth*, *preterm birth*, *17-alpha Hydroxyprogesterone Caproate*, *Makena*, and *17P*. We limited searches of core sources to citations published after January 1, 1999 to capture publications from the time the foundational study began to present day.

Evidence Sources Searched

- Agency for Healthcare Research and Quality (AHRQ)
- Evidence-based Practice Centers (EPC) Reports
- Effective Health Care (EHC) Program
- Canadian Agency for Drugs and Technologies in Health (CADTH)
- Cochrane Library (Wiley Interscience)
- National Institute for Health and Care Excellence (NICE), Evidence
- Ovid MEDLINE including In-Process & Other Non-Indexed Citations and Epub Ahead of Print
- Veterans Administration Evidence-based Synthesis Program (ESP)

Ovid MEDLINE Search Strategy

1. ((premature ajd2 birth or preterm) adj2 birth)

2. exp Premature Birth/pc [Prevention & Control]

3. exp 17 alpha-Hydroxyprogesterone Caproate/

4. (MAKENA or 17P).af.

5. 1 or 2

6. 3 or 4

7. 5 and 6

Cochrane Library Search Strategy

1. MeSH descriptor: [Premature Birth] explode all trees

2. MeSH descriptor: [17-alpha-Hydroxyprogesterone] explode all trees

3. #1 and #2

4. #1 or #2

Inclusion Criteria

We included controlled clinical trials of 17P compared with placebo, routine care, and any other intervention used to treat women with singleton pregnancies and a prior singleton sPTB published in English since January 1, 2003.

Exclusion Criteria

We excluded studies if they were published in a language other than English, lacked a randomized controlled trial design, or study participants had multiple pregnancies, premature rupture of membranes, arrested preterm labor, or a short cervix.

Quality Assessment

Methodological Quality of Included Studies

We assessed the methodological quality of the included randomized controlled trials using standard instruments developed and adapted by MED that are modifications of instruments used by several renowned, respected organization.[42] One experienced researcher independently rated the methodological quality of included studies. A second experienced researcher reviewed each assessment. Disagreement was managed by discussion.

Randomized Controlled Trials

Good-quality randomized controlled trials include a clear description of the population, setting, intervention, and comparison groups; a random and concealed allocation of patients to study groups; low dropout rates; and intention-to-treat analyses. Good-quality randomized controlled trials also have low potential for bias from conflicts of interest and funding source(s). Fair-quality randomized controlled trials have incomplete information about methods that might mask important limitations or a meaningful conflict of interest. Poor-quality randomized controlled trials have clear flaws that could introduce significant bias.

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