



**Indian Health Service**  
**National Pharmacy and Therapeutics Committee**  
**Formulary Brief: 17-Hydroxyprogesterone Caproate**  
**for the Prevention of Preterm Birth**



-April 2021-

**Background:**

Preterm Birth (PTB) refers to delivery occurring between 20 and 37 weeks of gestation. In the US, 10% of all deliveries are preterm, the majority being nulliparous. Most PTB is spontaneous (70-80%) and is the leading cause of infant morbidity and mortality in the US and worldwide<sup>1</sup>. A prior PTB increases risk of subsequent PTB 15-30% and up to 60% after two PTBs. Two-thirds of PTB occur in women with no risk factors, however race, age, multiple gestation, prior cervical surgery, and presence of chronic medical conditions (obesity, type II diabetes mellitus (DM), hypertension, renal insufficiency and non-physiologic anemia) modify risk<sup>1</sup>. Studies suggest that women with DM have up to 1.92 times higher odds of having a PTB than women without DM<sup>2</sup>. In American Indian/Alaska Native (AI/AN) populations, the rate of PTB was third highest of any race in the US in 2007<sup>3</sup>. Infant mortality rates for AI/AN populations were nearly twice as high as white populations for the last two decades (8.15 vs. 4.63 in 2018)<sup>4</sup>.

Interventions for PTB are limited and include progesterone supplementation with 17-hydroxyprogesterone caproate (17-OHPC) or vaginal progesterone (not FDA approved in US). Cervical cerclage is a procedure reserved for refractory cases. 17-OHPC is FDA approved for prevention of PTB. Questions from the field regarding recent data about the efficacy of 17-OHPC and an FDA advisory panel which recommended revocation of the FDA approval for 17-OHPC prompted this review. Following the NPTC clinical evaluation, and due to conflicting primary data and a possible change in FDA approval of Makena<sup>®</sup>, this product was **not added to the IHS National Core Formulary**.

**Discussion:**

17-OHPC (Makena<sup>®</sup>) is the only FDA approved treatment for PTB, indicated for pregnant females  $\geq 16$  years of age. Treatment may begin between 16 weeks 0 days and 20 weeks 6 days of gestation with weekly administration until 37 weeks (through 36 weeks, 6 days) gestation or until delivery, whichever comes first<sup>6</sup>.

In 2003, the Maternal Fetal Medicine Unit Network conducted a placebo-controlled randomized controlled trial (RCT) assessing the use of 17-OHPC to prevent PTB. It included 463 women  $>20$  weeks' gestation with a history of PTB, 59% of whom were black, receiving weekly injections of 250mg of 17-OHPC or placebo. The primary outcome was preterm delivery before 37 weeks. Maternal outcomes in placebo versus the treatment group were notable for a relative risk reduction of 0.66 (95% CI: 0.54-0.81) for delivery at 37 weeks with the number needed to treat to prevent one PTB being 5.4. There were also improvements in infant outcomes with improved rates of supplemental O<sub>2</sub>, intraventricular hemorrhage, and necrotizing enterocolitis in the treatment group. There was no difference in fetal or neonatal death, hospital visits for preterm labor, or medically induced preterm labor. Of note, the PTB rate in placebo group was 54.9%, significantly higher than the projected 37%.

Following this publication, use of progesterone increased to prevent PTB in mothers with prior PTB and all 17-OHPC was compounded given the absence of a commercially available product. Subsequently, the American College of Gynecology and Obstetrics (ACOG) and the Society for Maternal Fetal Medicine officially recommended the use of progesterone to reduce the rates of preterm birth limited to patients with prior PTB. Makena<sup>®</sup> was approved by the FDA in 2011 as an orphan drug through the accelerated approval process given concerns that compounded progesterone was of variable potency. The approval was provisional requiring a confirmatory trial to demonstrate efficacy with the approved drug (the 2013 Meis trial did NOT use the Makena<sup>®</sup> product). In 2012, the FDA recommended limiting use of the compounded agents and shortly thereafter a catastrophic outbreak of fungal meningitis was traced back to compounded steroids. No documented cases of patient harm were found related to 17-OHPC. Around the same time, sonographic screening for cervical length became standard practice, and ACOG has recommended therapeutic intervention to prevent PTB in cervical shortening  $\leq 20$  mm in women with no prior spontaneous birth and  $<25$  mm in women with a prior spontaneous preterm birth at  $<34$  weeks of gestation increasing the population of women eligible for treatment with 17-OHPC<sup>14</sup>.

In 2019, the efficacy trial for Makena<sup>®</sup> mandated by the FDA (the PROLONG study) was published. The study population was markedly different from that of Meis et al. with 1,708 women  $>18$  yo with prior documented spontaneous preterm birth (SPTB) who were between 16wks and 20wks (+6 weeks), however 87% were white, 12% with prior SPTB, 89% married/lived with partner<sup>8</sup>. Most of the study population resided in Eastern Europe where 17-OHPC was not standard of care for prior PTB and short cervix. Results were null – there were no significant differences in rates of PTB less than 35 weeks or frequency of fetal/early infant death. In the small US cohort study, the rate of PTB less than 35 weeks was higher but treatment with Makena<sup>®</sup> still did not show a statistically significant difference in prevention of PTB.

The EPPPIC group published a meta-analysis of individual participant data from RCTs in 2021 which found a trend towards prevention of PTB with 17-OHPC but no significant risk reduction and a small relative risk reduction with vaginal progesterone in PTB and low birth weight<sup>9</sup>. In response to the PROLONG study, the FDA convened an advisory committee to review the current FDA approval for Makena<sup>®</sup>. Conclusions were that the PROLONG trial did not provide evidence of efficacy and it was recommended that the FDA remove its approval for Makena<sup>®</sup> for recurrent PTB. As of the writing of this brief, the FDA has not made changes to the approval of Makena<sup>®</sup>.

Additional meta-analysis from the Center for Evidence Based Policy at Oregon Health and Science University published recommendations after analysis of both the Meis and PROLONG trials and determined that neither study supported the efficacy of progesterone for prevention of PTB and recommended that the FDA revoke their approval.

### Findings:

Current guidelines vary between country and drug availability. The ACOG recommends 17-OHPC therapy for patients with prior SPTB and recommends 17-OHPC for women with singleton pregnancies and cervical length <25mm. The Society for Maternal Fetal Medicine recommends that women with singleton gestation and a prior history of SPTB should be treated with 17-OHPC 250mg per week IM starting 16-20 weeks until 36 weeks' gestation and that vaginal progesterone should not be a substitute. The Society of Obstetricians and Gynecologists of Canada recommends treatment with vaginal progesterone in a daily dose of 200mg for a singleton pregnancy and 400mg for a multiple pregnancy for prevention of SPTB in high risk women: previous SPTB, singleton pregnancy and short cervical length, and women with multiple pregnancy. The World Health Organization has no explicit recommendations.

There is limited data on long term outcomes for infants of mothers that received 17-OHPC or vaginal progesterone. A study published in 2016 evaluated 1228 women who received vaginal progesterone and followed the infants to 48 months post-delivery. Using a complex composite score which included health factors, behavioral scale scores and EQ-5D (standardized measure of quality of health) study concluded that there were no measurable differences in neurocognitive development in children whose mothers were treated with vaginal progesterone. A follow-up to the Meis et al. trial showed that at 48 months post-delivery there were no significant difference in developmental exam scores or genital or reproductive anomalies (n=270).

### Conclusions:

PTB is a relatively common outcome of many singleton pregnancies in the U.S. Risk factors for PTB include but are not limited to previous PTB, short cervical length, lower socioeconomic status, maternal comorbidities (obesity, DM). AI/AN women are more likely than white counterparts to have PTB. Long standing use of progesterone has been complicated by safety issue within the supply chain and the cost of the FDA approved medication. Large RCTs examining the effects of progesterone in the prevention of preterm labor exist but outcome data is conflicting. Data for prevention of PTB in women with prior PTB supports use of progesterone. Data for prevention of PTB in nulliparous women with short cervix trends toward reduction of relative risk with 17-OHPC. Limited data suggests that childhood wellness is not affected by maternal progesterone. Multiple professional societies in the U.S. still recommend use of 17-OHPC in the treatment of patients who are high risk for PTB.

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