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What We Have Learned About the Role of 17-alpha-hydroxyprogesterone Caproate in the Prevention of Preterm Birth

Steve N. Caritis, MD¹, Maisa N. Feghali, MD¹, William A. Grobman, MD, MBA², and Dwight J. Rouse, MD³ for the Eunice Kennedy Shriver National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network

¹Department of Obstetrics, Gynecology and Reproductive Sciences, Magee-Womens Research Institute, University of Pittsburgh School of Medicine ²Department of Obstetrics and Gynecology, Feinberg School of Medicine, Northwestern University, Chicago, Illinois ³Department of Obstetrics and Gynecology, Alpert Medical School of Brown University, Women & Infants Hospital of Rhode Island

Abstract

Despite major advances in neonatal care, the burden of preterm birth remains high. This is not unexpected since strategies to identify and treat risk factors in early pregnancy have not been very effective in reducing the preterm birth rate. Initial studies suggested a potential benefit for 17-alpha-hydroxyprogesterone caproate (17-OHPC) in decreasing the risk of recurrent preterm birth women with a singleton gestation. However, the use of 17-OHPC has not conferred benefit for other categories of women at high-risk for preterm delivery (twins, triplets, short cervical length). The increasing body of evidence suggests that preterm birth is a complex condition with variable mechanisms of disease and significant individual heterogeneity. This review will examine the plausibility of 17-OHPC in preventing preterm birth and the investigation of its clinical efficacy. We will also highlight factors to explain variations in clinical trial outcomes and outline the trajectory needed for future investigations.

Keywords

Preterm birth; Prevention; 17-alpha-hydroxyprogesterone caproate

Preterm birth is the leading cause of neonatal death in the United States and is the most frequent cause of mortality under five years of age worldwide ^{1, 2}. In addition, the immaturity of organ systems increases the risk for short- and long-term complications in

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neonates born before 37 weeks. Preterm infants often require intensive care unit admission and have longer stays compared to their term counterparts. Prematurity also leads to numerous long-term health impairments and has been linked to adult-onset diseases such as hypertension, obesity, and diabetes³⁻⁵. These outcomes come at a significant annual cost that exceeds \$26 billion to cover labor and delivery care for the mother, early intervention services, and special education, in addition to neonatal care, which is responsible for the majority (\$16.9 billion) of the costs⁶. The majority of preterm birth occurs spontaneously in women with singleton pregnancies. However, certain risk factors have been closely linked with an increased risk for prematurity including prior preterm birth, multifetal gestation, short cervical length, and genitourinary infection⁷. These various risk factors underline the different pathways that can lead to preterm delivery. Clinically, risk-based strategies have been developed to identify and treat women at higher risk for preterm delivery. The recent decrease in the rate of preterm birth to 11.4% has been mostly attributed to preventive measures including the use of 17- alpha-hydroxyprogesterone caproate (17-OHPC)⁸. In a randomized study that altered clinical practice, Meis et. al demonstrated a significant reduction in recurrent preterm birth in women treated with 17-OHPC vs. placebo⁹. Since that landmark study, the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Maternal-Fetal Medicine Units (MFMU) Network has conducted numerous investigations on the efficacy of 17-OHPC in other high-risk groups. This review will focus on the findings from the MFMU trials focused on the use 17-OHPC in women with multifetal gestations and in those with a short cervix.

Progesterone's role in parturition

Progesterone, which is the main progestogen in humans, are a group of hormones named for the primary role in supporting gestation and inhibiting uterine activity. Csapo championed the concept of a progesterone block in pregnant rabbits¹⁰. His work formed the basis for the role of progesterone in the onset of labor and set the stage for studies on progesterone supplementation. Numerous animal studies then followed focused on the importance of progesterone in regulating the onset of labor¹⁰⁻¹². In many mammalian species, progesterone plays a direct role in uterine quiescence, and the onset of labor is preceded by a decrease in progesterone and increase in estrogen plasma concentrations. The role of progesterone in the onset of human labor has been less evident. Some studies suggest that local changes in progesterone concentration, the progesterone-to-estrogen ratio, or progesterone receptor type in the placenta, decidua, or fetal membranes may be significant for the initiation of labor^{13, 14}. In the absence of other mechanisms explaining human parturition, and with direct evidence of anti-progestins leading to increased myometrial contractions, progesterone withdrawal has remained a leading hypothesis for human parturition and by extension, preterm birth.

Progesterone vs. 17-OHPC

Progesterone and its naturally occurring metabolite 17- alpha-hydroxyprogesterone (17-OHP) are produced in large amounts in human pregnancy. On the other hand, 17-OHPC does not occur naturally and is synthesized through the acetylation of 17-alpha-hydroxyprogesterone with caproic acid in the presence of toluene sulfonic acid¹⁵. The

structures of progesterone, 17-OHP and 17-OHPC are depicted in Figure 1. This distinction between natural progestins and 17-OHPC is important because of variation in pharmacologic activity and clinical efficacy¹⁶. 17-OHPC is a lipophilic drug and is highly protein-bound in blood. The addition of the caproate moiety is meant to significantly prolong the compound's half-life. In humans, it is primarily metabolized in the liver by the cytochrome P450 (CYP) enzymes, primarily CYP3A4 and to a lesser extent CYP3A5. Metabolites of 17-OHPC have been identified and differ from 17- α -hydroxyprogesterone or progesterone. The caproic acid moiety of 17-OHPC is not removed during metabolism; rather the steroid rings are primarily hydroxylated. After intramuscular administration, elimination of metabolites occurs primarily through feces (~50%) and urine (~30%). 17-OHPC initially gained Federal Drug Administration (FDA) approval in 1956 (NDA 10-347) and was marketed under the trade name Delalutin as a treatment for menstrual disorders (such as dysmenorrhea, pre-menstrual tension, cyclomastopathies, adenosis, and mastodynia), threatened miscarriage and uterine cancer. Along with other progesterone preparations, 17-OHPC was evaluated in preventing preterm birth. In 1990, a meta-analysis demonstrated a pooled odds ratio of 0.50 (95% CI: 0.30–0.85) for preterm birth in women treated with 17-OHPC¹⁷. Subsequently, the MFMU Network performed a double-blind, placebo-controlled trial of in 463 women with singleton gestations and a history of spontaneous preterm birth (Table 1)⁹. Women were enrolled at 16–20 weeks and randomized to weekly 17-OHPC intramuscular injections or an inert oil placebo. Treatment with 17-OHPC was associated with a decreased incidence of delivery before 37 weeks [36.3 vs 54.9%, RR 0.66 (95% CI 0.54–0.81)]. There also was a significant reduction in the rate of deliveries before 32 and 35 weeks. However, the findings of the study were met with concerns. Keirse questioned the reported efficacy of 17-OHPC because of the unexpectedly high frequency of preterm birth in the placebo group (54.9%)¹⁸. In addition, the rate of preterm delivery in the intervention group (36.3%) was comparable to the reported baseline rate of preterm birth for a similar population¹⁹. Nevertheless, these concerns were dismissed by many, as the frequency of preterm birth in the study could be readily explained by a study population that was at particularly high risk of preterm birth given their frequency of multiple early preterm births. Such a group is commonly characterized by inflammation-driven preterm birth, which may have maximized the anti-inflammatory effects of 17-OHPC²⁰.

Still, the drug's efficacy (33% reduction in preterm birth rates), despite a high-risk treatment group, remained puzzling. Treatment response variation may be partially explained by differences in individual pharmacology. In women with a singleton gestation who received the standard dose of 17-OHPC (250 mg weekly) there was a large variation in the maternal plasma concentrations of 17-OHPC (median 15.2 ng/mL, range 3.2–64.6 ng/mL)²¹. The half-life of 17-OHPC was noted to be 16 days ($\pm$ 6 days)²¹. This prolonged half-life likely resulted from a slow release of 17-OHPC from the castor oil depot and/or the maternal adipose tissue. Variation in 17-OHPC levels was further exacerbated by maternal BMI²¹. The large variation in plasma concentrations appear to impact efficacy. The highest preterm birth rates were noted in women with 17-OHPC concentrations at 25–28 weeks in the lowest quartile²². Collectively, these data suggest the benefit for a dose-finding study to better elucidate the therapeutic dosing of 17-OHPC. Adding to the pharmacokinetic effects that

may impact 17-OHPC response are variations in the progesterone receptor (PR). Recent studies by the MFMU Network demonstrated an association between PR gene promoter single nucleotide polymorphisms and the risk of preterm birth^{23,24}. PR polymorphisms appear to have an effect on 17-OHPC efficacy in preventing recurrent preterm birth. Manuck *et al.* identified a specific polymorphism that was linked to an increased risk for preterm birth in Caucasian and Hispanic women who were treated with 17-OHPC²⁵. Conversely, other polymorphisms were linked to an increased risk of preterm birth in women who received the placebo and a significant reduction in recurrent preterm birth in women exposed to 17-OHPC²⁵. These findings add a potential role for a woman's genetic background in explaining the variation in risk for preterm birth and response to 17-OHPC treatment.

17-OHPC in Multifetal Gestation

The incidence of multifetal births in the United States has increased since the 1970s with the rate of twin gestation in 2013 reaching 33.7 per 1000 births and the rate of triplet and higher order multiple gestations reaching 119.5 per 100,000 births⁸. These rates are amplified by the circumstance that 56% of twin gestations and 93% of triplet gestations deliver before 37 weeks⁸. It follows that preterm birth prevention strategies would target multifetal gestations. Given the findings demonstrated by reduced preterm birth rates in singleton gestations with the use of 17-OHPC, two randomized, double-blinded, placebo-controlled trials of the use of 17-OHPC in women with multi-fetal gestations were undertaken by the MFMU between 2004 and 2006 (Table 1)^{26,27}. Both trials were conducted at 14 different centers across the United States. Eligible women underwent randomization to receive either weekly intramuscular injections of 250 mg of 17-OHPC or placebo starting between 16 weeks and 20 weeks. Weekly injections were continued through the end of the 34th week of gestation, or until delivery, whichever occurred first. The first trial focused on women carrying a twin gestation where 325 received 17-OHPC and 330 received placebo. Demographic data between the two groups were similar. The primary outcome, a composite of delivery or fetal death between 35 completed weeks did not differ between the two groups (17-OHPC: 41.5% vs. 37.3%, RR 1.1 with CI of 0.9–1.3)²⁶. The second study was performed in women with a triplet gestation. Using the same study design and primary outcome, the investigators found no statistically significant difference between the preterm birth rate between those who used weekly intramuscular injections of 17-OHPC versus placebo (84% vs. 83%, RR 1.0 with CI 0.8–1.1)²⁷. In both cases, the authors concluded that 17-OHPC was ineffective in reducing the rate of prematurity in multifetal gestation. The studies also showed no differences in the rate of spontaneous and indicated preterm birth, and also that the lack of benefit occurred regardless of conception method (spontaneous vs. assisted reproductive techniques). Subsequent studies found a similar lack of benefit for the use of 17-OHPC to prevent birth, prolong pregnancy, or decrease neonatal morbidity in women with twin and triplet gestations^{28–30}. The MFMU twin study noted a non-significant difference of composite neonatal outcome of serious adverse events in neonates exposed to 17-OHPC compared to placebo (20.2 vs. 18.0%, RR 1.1, 95% CI 0.9–1.5). A secondary pharmacodynamic study of the same group of subjects demonstrated an inverse relationship between 17-OHPC concentration and length of gestation³¹. Most recently, an individual participant data meta-analysis evaluated the effectiveness of progestogens in improving perinatal outcomes in

women with twin gestations³². Combined data from 6 trials failed to demonstrate any benefit of 17-OHPC use in twin pregnancies in reducing adverse perinatal outcomes (RR 1.1, 95% CI 0.97–1.4)³². In fact, in one subset of subjects with a cervical length > 25 mm, perinatal outcome was worse in 17-OHPC treated subjects³².

The lack of 17-OHPC benefit in multifetal gestation may be related to several factors. Preterm birth may follow a different path in women with multifetal gestation prohibiting a direct extension of beneficial strategies from their counterparts with singleton pregnancies. In fact, participants in the MFMU multifetal gestation studies differed significantly from those in the Meis et al. study. They had very low rates of prior preterm delivery in both treatment and placebo groups (6 and 9% in the twin study and 0 and 3% in the triplet study, respectively). The inverse relationship between 17-OHPC concentration and gestational at delivery in twin gestations was further illustrated in a randomized controlled trial of asymptomatic women with a twin gestation and short cervical length (<25mm). In that study, women who used 17-OHPC 500 mg intramuscularly twice weekly noted an increase in preterm delivery before 32 weeks compared to women who did not receive any 17-OHPC (29 vs. 12%, $p=0.007$)³³. Collectively, the findings suggest that 17-OHPC should not be used in multifetal gestation.

17-OHPC in women with a short cervical length

Detection of a short cervical length early in pregnancy is a significant risk factor for preterm delivery^{34–37}. Hence, women with a midtrimester short cervix have been targeted with strategies to prevent preterm deliveries. Vaginal progesterone administration in asymptomatic women with a short cervix (< 20 mm) decreased the rate of preterm birth before 33 weeks of gestation and improved neonatal morbidity^{38–41}. This led to a double-blinded, randomized placebo-controlled MFMU trial to evaluate the utility of 17-OHPC to prolong pregnancy in nulliparous women with a cervical length <30 mm (Table 1)⁴². Eligible women were randomized to weekly intramuscular injections of 250 mg of 17-OHPC ($n=327$) or placebo ($n=330$) starting between 16 3/7 weeks and 22 6/7 weeks. These injections were continued through the end of the 36th week or delivery, whichever occurred first. The primary outcome of preterm birth before 37 weeks did not differ between study groups (25.1% vs 24.2%, RR 1.03, 95% CI 0.79–1.35)⁴². There were several differences between this study's findings and those in which vaginal progesterone was used. Prior trials with vaginal progesterone recruited women with notably shorter cervical length and may have represented a different preterm birth pathway that is more responsive to progestogen therapy. Previously, two retrospective studies did not identify an effect of 17-OHPC treatment of cervical length^{43,44}. While the relationship between plasma concentrations of 17-OHPC and preterm delivery has been evaluated, concentrations of the drug at the level of the cervix have not been assessed. It follows that the lack of benefit of 17-OHPC in women with a short cervical length may be related to limited drug concentrations at the level of the cervix. Several studies utilized higher doses of 17-OHPC but despite this higher dose, 17-OHPC was ineffective in reducing preterm birth rates.

Winer *et al.* randomized women with a singleton pregnancy, cervical length less than 25 mm, and a history of preterm delivery or cervical surgery to treatment with 17-OHPC 500

mg weekly or no treatment⁴⁵. The primary outcome, time from randomization to delivery, did not differ between study arms. In addition, the rate of preterm delivery before 37 weeks was similar in the 17-OHPC arm and the control group (45 vs 44%, $p>0.99$)⁴⁵. The trial had several limitations including the timing of the initiation of 17-OHPC at a median gestational age of 24 weeks and 6 days. This is significantly later than the time period for treatment initiation in the Meis study⁹. While two observational studies noted similar rates of preterm delivery in women who started 17-OHPC early (16–20.9 weeks) or later (21–26.9 weeks) in pregnancy, a later start contradicts the suggested prophylactic mechanism of action of the drug^{46, 47}. In addition, the authors highlighted the possible confounding effect of cerclage use prior to randomization, which occurred in 45% of the 17-OHPC group and 38% of the control group⁴⁵. A similar strategy, albeit with a higher dose of 17-OHPC 500 mg intramuscular injections twice weekly, was evaluated in twin gestations with a short cervical length (<25 mm)³³. Within that trial, 17-OHPC did not improve the primary outcome of time from randomization to delivery compared to no treatment³³.

The contradictory findings and investigations noting a lack of benefit have been crucial in advancing our understanding of preterm birth. While gestational age is directly linked to neonatal outcomes and cost of care, using a gestational age cut-off to define the complex syndrome of preterm birth is not appropriate. Spontaneous preterm birth is now understood to be a multifactorial condition with numerous causes and a likely interaction between genetics, maternal characteristics and the environment surrounding each pregnancy^{48–50}. The variation in the outcomes of clinical trials is a reflection of the heterogeneity of the mechanisms that lead to premature delivery. This heterogeneity was best demonstrated by Esplin *et al.* who performed a cluster analysis of women who had a spontaneous preterm birth before 34 weeks⁵¹. They identified five major clusters representing different phenotypes of preterm birth that were characterized by maternal stress, premature rupture of membranes, familial factors, maternal comorbidities, and a multifactorial cluster that included infection, decidua hemorrhage and placental dysfunction⁵¹. This novel approach has furthered our understanding of common pathways that may lead to preterm birth and can help provide a phenotyping guide for future clinical trial design.

Preterm birth is a complex syndrome with significant morbidity and few successful pre-delivery interventions. In women with a singleton gestation, weekly 17-OHPC injections was demonstrated to decrease the rates of recurrent preterm birth. However, the use of 17-OHPC in other high risk categories (twins, triplets, and short cervical length) has no clear benefit. The variation in outcomes likely lies in the heterogeneity of pathways and mechanisms that lead to premature birth. Further studies are needed to develop interventions that can decrease the burden of preterm birth. To maximize the success of interventions for preterm birth prevention, future investigations should be designed to account for pharmacologic, genetic, and environmental factors that can significantly affect progesterone's efficacy.

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Figure 1.
Chemical structure of progesterone, 17- alpha-hydroxyprogesterone and 17-OHPC

Table 1

Summary of MEMU 17-OHPC trials

Study	Interventions	Design	Inclusion	Exclusion	Primary Outcome	Findings
Meis ⁹ (2003)	Weekly 17-OHPC IM injections (250 mg) vs. castor oil Start: 16–20 weeks 6 days End: 36 weeks or delivery (if occurred sooner)	Randomized double-blind placebo-controlled trial Intention to treat 19 centers N= 310 progesterone N= 153 placebo	Prior spontaneous preterm birth of a singleton pregnancy between 20- and 36 completed weeks	Multifetal gestation Fetal anomalies Progesterone therapy during pregnancy Heparin use during pregnancy Cervical cerclage Antihypertensive medication use Seizure disorder	Spontaneous preterm birth before 37 weeks	Spontaneous preterm birth less than 37 weeks: 17-OHPC group (36.3%) Vs. placebo (54.9%) RR: 0.66 (95% CI 0.54–0.81) Spontaneous preterm birth less than 35 weeks: 17-OHPC group (20.6%) Vs. placebo (30.7%), p=0.02 Spontaneous preterm birth less than 32 weeks: 17-OHPC group (11.4%) Vs. placebo (19.6%), p=0.02
Rouse ²⁶ (2007)	Weekly 17-OHPC IM injections (250 mg) vs. castor oil Start: 16–20 weeks 6 days End: 34 weeks or delivery (if occurred sooner)	Randomized double-blind placebo-controlled trial Intention to treat 14 centers N= 325 progesterone N= 330 placebo	Twin gestation	Fetal anomalies Monochorionic monoamniotic twins Suspected twin- to-twin transfusion syndrome Marked growth discordance between fetuses Fetal death after 12 weeks Progesterone therapy during pregnancy Cervical cerclage Uterine anomalies Heparin use during pregnancy Antihypertensive medication use	Composite: delivery or fetal death before 35 completed weeks	Delivery or fetal death before 35 weeks: 17- OHPC group (41.5%) Vs. placebo (37.3%) RR: 1.1 (95% CI 0.9–1.3) Gestational age at delivery: 17-OHPC group (34.6 weeks) Vs. placebo (34.9 weeks), p=0.527
Caritis ²⁷ (2009)	Weekly 17-OHPC IM injections (250 mg) vs. castor oil Start: 16–20 weeks 6 days End: 34 weeks or delivery (if occurred sooner)	Randomized double-blind placebo-controlled trial Intention to treat 14 centers N= 71 progesterone N= 63 placebo	Triplet gestation	Fetal anomalies Monoamniotic pair Suspected twin- to-twin transfusion syndrome Marked growth discordance between fetuses Fetal death after 12 weeks Progesterone therapy during pregnancy Cervical cerclage Uterine anomalies Heparin use during pregnancy Antihypertensive medication use	Composite: delivery or fetal death before 35 completed weeks	Delivery or fetal death before 35 weeks: 17- OHPC group (83%) Vs. placebo (84%) RR: 1.0 (95% CI 0.9–1.1) Gestational age at delivery: 17-OHPC group (32.4 weeks) Vs. placebo (33.0 weeks), p=0.527
Grobman ⁴² (2012)	Weekly 17-OHPC IM injections (250 mg) vs. castor oil Start: 16–20 weeks 6 days End: 36 weeks or delivery (if occurred sooner)	Randomized double-blind placebo-controlled trial Intention to treat 14 centers N= 327 progesterone N= 330 placebo	Nulliparous women with singleton gestation and cervical length <30 mm between 16 weeks 0 days and 22 weeks 3 days	Multifetal gestation Fetal anomalies Progesterone therapy during pregnancy Heavy vaginal bleeding Premature rupture of membranes Cervical cerclage Antihypertensive medication use Prior cervical surgery	Preterm birth before 37 weeks	Preterm birth before 37 weeks: 17-OHPC group (25.1%) Vs. placebo (24.2%) RR: 1.03 (95% CI 0.79–1.35) Gestational age at delivery: 17-OHPC group (38.9 weeks) Vs. placebo (38.9 weeks), p=0.93

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Study	Interventions	Design	Inclusion	Exclusion	Planned preterm delivery	Primary Outcome	Findings
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