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Prevention of preterm delivery with 17-hydroxyprogesterone caproate: Pharmacologic considerations

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ABSTRACT

Despite advances in neonatal care, the burden of preterm birth remains high. Preterm birth is a multifactorial problem, and strategies to identify and treat medical risk factors in early pregnancy have not been effective in reducing preterm birth rates. In a sentinel clinical trial, prophylactic therapy with 17-hydoxyprogesterone caproate (17-OHPC) reduced the risk of recurrent, spontaneous preterm birth in 34% of women. As a result, clinical practice changed and extensive research on 17-OHPC followed. The increasing body of evidence demonstrated a variable efficacy of the drug. This review will examine the plausibility, pharmacology, clinical efficacy, and safety of 17-OHPC when used in the setting of preterm birth prevention. We will also discuss pharmacokinetic and pharmacodynamics data to highlight drug metabolism and mechanism of action, which will help clarify the variability in clinical outcomes and efficacy.

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Introduction

Premature birth in the United States accounts for 35% of deaths in the first year of life at an estimated annual cost exceeding $26 billion.[2,3] Efforts to identify and prevent preterm birth have led to a modest decrease in the annual rate in the United States from a peak of 12.8% in 2006 to 11.5% in 2012.[4] In addition to mortality, long-term morbidity is a significant risk of preterm birth and both are inversely related to gestational age at birth. The majority of preterm births occur in singleton pregnancies following the spontaneous early onset of the parturition process. However, certain factors are associated with an increased risk for preterm birth: multifetal gestation, shortened cervical length, genitourinary infection, smoking, and a prior preterm birth.

Clinical interventions to decrease the rate of preterm birth have focused on identifying women who are at an increased risk for preterm birth and the use of prophylactic and therapeutic options in such subjects. Unfortunately, despite vigorous efforts at treatment of preterm labor with labor-inhibiting drugs (tocolytics), intensive prenatal care, patient education, and bed rest, rates of preterm birth have not decreased significantly over the past 40 years. One of the very few preventive measures to have shown some promise

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in randomized trials is the use of 17-OHPC, a progestational agent. In a sentinel article that drastically changed clinical practice, Meis et al.[1] demonstrated a 34% reduction in delivery before 37 weeks in women with a prior preterm birth, who received weekly injections of 17-OHPC. Treatment with 17-OHPC has proven effective in reducing the rate of preterm birth in women with a history of spontaneous preterm delivery, but it appears to be ineffective in other high-risk categories such as women with a short cervical length and those with multifetal gestation. This review will focus on the pharmacologic properties of 17-OHPC, which may explain the variability in outcomes noted in clinical trials.

Plausibility of progesterone for preterm birth

Progesterone is thought to act in support of gestation and to inhibit uterine activity. The concept of a "progesterone block" was advanced and championed by Csapo in the 1950s based on his extensive and pioneering experiments in pregnant rabbits.[5] This formed the basis for the study of progesterone supplementation and the role of progesterone in the onset of labor. As such, numerous animal studies support the importance of progesterone in regulating the onset of labor.[5–7] In sheep, goats, and many other mammalian species, a decrease in plasma progesterone (P) and an increase in estrogen (E) preceded the onset of labor. The ability of progesterone to maintain uterine quiescence during pregnancy has been shown in lower mammalian species. In these species, progesterone withdrawal is a necessary step in the events leading to parturition. The role of progesterone and changes in P/E ratio on the onset of labor in human beings and other primates is less well known. Although some investigators have described low progesterone concentrations or low P/E ratios in the plasma of women destined to deliver prematurely, no consistent evidence exists documenting decreases in plasma progesterone or P/E ratio prior to the onset of labor at or before term.[8] Nonetheless, some evidence exists that local changes in progesterone or the P/E ratio in the placenta, decidua, or fetal membranes may be important in the initiation of labor.[9] The progesterone withdrawal theory remains a leading hypothesis because no other mechanism for the onset of human parturition has been definitively established and because synthetic antiprogestins stimulate myometrial contractions.

In light of these findings, progesterone was theorized as an agent to prevent preterm birth. Early studies yielded conflicting results regarding its efficacy in preventing preterm birth. These studies were limited by small sample sizes and inclusion of heterogeneous patient populations. With increasing evidence, it appears that 17-OHPC therapy has condition-specific efficacy in decreasing the risk for preterm birth. A meta-analysis published by Keirse in 1990 included only studies that evaluated the effect of 17-OHPC on a range of outcomes including preterm birth. This meta-analysis found a pooled odds ratio of roughly 0.50 (95% CI: 0.30–0.85) for preterm birth among women treated with 17-OHPC.[10] Since then, various trials have focused on progesterone use for the prevention of preterm birth. In 463 women with singleton gestations and a history of spontaneous preterm birth, weekly 17-OHPC intramuscular injections was associated with a decreased incidence of preterm birth (RR = 0.66, 95% CI: 0.54–0.81) compared to placebo.[1] In women with twin gestation, weekly 17-OHPC injections did not reduce preterm birth or adverse neonatal outcomes compared to placebo.[11–13] In a multicenter randomized controlled trial, weekly 17-OHPC injections did not decrease the risk of preterm delivery in nulliparous women with a singleton gestation and a short cervical length (<30 mm).[14] Furthermore, two randomized controlled trials also demonstrated a lack of benefit for 17-OHPC in triplet gestation.[15,16] Based on these randomized controlled trials, current guidelines recommend the use of 17-OHPC only for the prevention of preterm birth in singleton pregnancies with a history of preterm birth.[17,18] As a tocolytic agent, 17-OHPC has proven unsuccessful.[19–21]

Pharmacokinetic properties of 17-OHPC

Progesterone and its naturally occurring metabolite 17-hydroxyprogesterone are produced in large amounts in human pregnancy. On the other hand, 17-OHPC is not a naturally occurring substance but rather is synthesized through the acetylation of 17-hydroxyprogesterone with caproic acid in the presence of toluene sulfonic acid.[22] The structures of progesterone, 17-OHP and 17-OHPC are depicted in Figure 1. Despite widespread usage of 17-OHPC in the 1950s through 1970s, little information about the pharmacology of this agent is available. It 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,

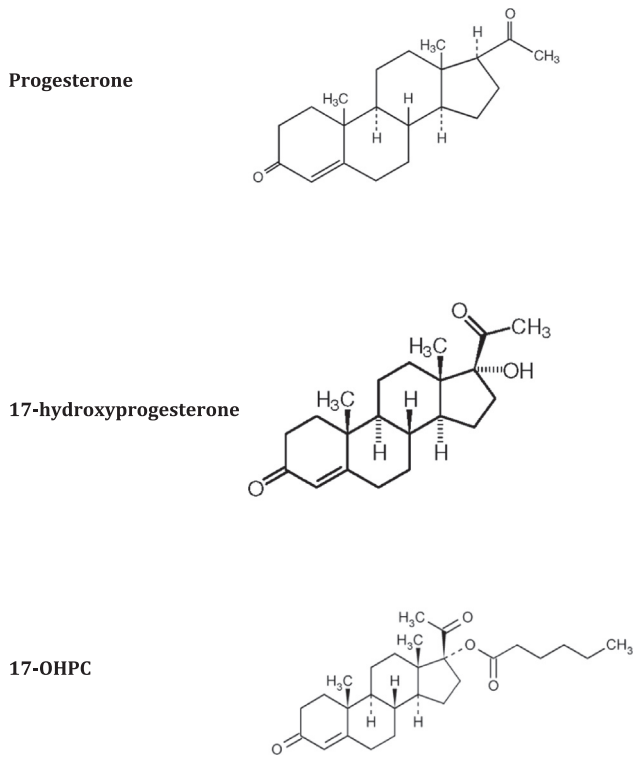

Fig. 1 – Chemical structure of progesterone, 17-hydroxyprogesterone and 17-OHPC.

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