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What we have learned about the role of 17-alpha-hydroxyprogesterone caproate in the prevention of preterm birth

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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, and 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.

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Preterm birth is the leading cause of neonatal death in the United States and is the most frequent cause of mortality under 5 years of age worldwide.[1,2] In addition, the immaturity of organ systems increases the risk for short-term and long-term complications in 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 diabetes.[3–5] These results 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 costs.[6] 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 infection.[7] 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. placebo.[9] 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 that 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, is 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 rabbits.[10] 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 labor.[10–12] 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 antiprogestins 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 acid.[15] The structures of progesterone, 17-OHP, and 17-OHPC are depicted in Figure. This distinction between natural progestins and 17-OHPC is important because of variation in pharmacologic activity and clinical efficacy.[16] 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-alpha-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

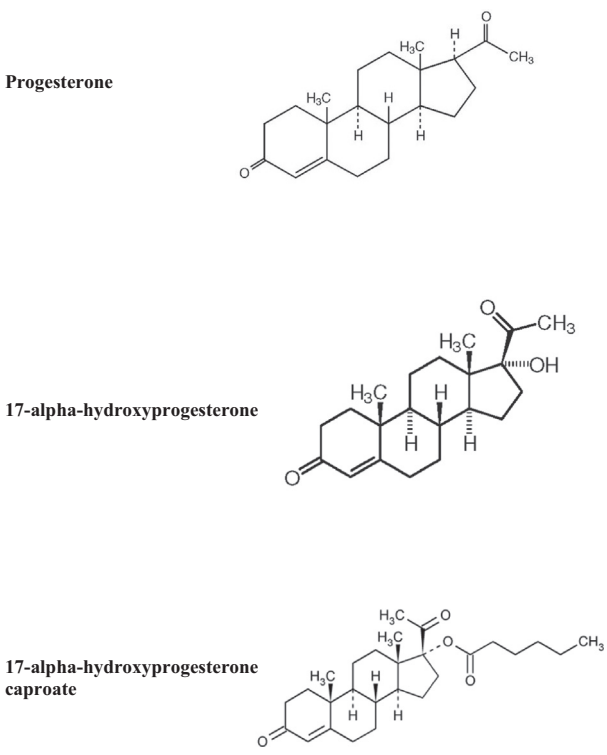

Fig. – Chemical structure of progesterone, 17-alpha-hydroxyprogesterone, and 17-OHPC.