



Editorial

Progesterone and Preterm Delivery are we coming a full circle?

In spite of the myriad advances in perinatal medicine, preterm labor remains difficult to screen for, predict, prevent and treat ¹. Preterm delivery is more common among the poor, the unmarried, cigarette smokers, underweight women, women with multiple gestations, women with uterine anomalies, women with a history of previous preterm delivery, and women without prenatal care. A minority of preterm deliveries are “indicated” deliveries that result from obstetric interventions to end pregnancies whose continuation is perceived as placing the fetus or the mother in jeopardy. The majority of preterm deliveries, however, are spontaneous and result primarily from premature labor, with or without premature rupture of the membranes. The growing number of such deliveries and the rising burden of care has been a stimulus for work on preventing preterm birth.

Although the perinatal mortality rate due to prematurity has decreased dramatically during the past three decades, this reduction has resulted from improvements in neonatal care for premature babies. There has been little contribution of note from obstetricians in this regard except for the administration of antenatal corticosteroids to promote lung maturity. Efforts to screen for “high-risk” women and provide early care, universal provision of care, or enhanced prenatal services have generally failed to improve perinatal outcomes². Physiological measures (the monitoring of uterine contractions), anatomical measures (the ultrasonographic measurement of cervical length), and biochemical measures (the assessment of fetal fibronectin in cervicovaginal secretions) are also poorly predictive of the risk of preterm delivery ³. Efforts to treat women with tocolytic agents for premature labor after it has been diagnosed have had minimal success and have not resulted in improved perinatal outcomes ⁴.

In this somewhat bleak scenario, an old drug is making a comeback. 17 alpha-hydroxyprogesterone caproate (17P) is a weakly active, naturally occurring progesterone that has been isolated from both adrenal glands and corpora lutea. The synthetic caproate ester is virtually inactive when given by mouth but works as a long-acting progestin when administered intramuscularly. The drug was one of the empiric therapies used a few decades ago for threatened miscarriage. It was meant to treat luteal phase defects. However, the relation between luteal phase defects and miscarriage is purely speculative today and treatment with progesterone in threatened miscarriage or in women with a history of recurrent miscarriages has not shown to be useful ⁵.

From animal experiments, we know that progesterone is chiefly responsible for maintaining uterine quiescence during pregnancy; a drop in progesterone level, either in absolute terms or relative to the estrogen level, is integral to the normal initiation of parturition at term. There is evidence that local changes in the progesterone level or the ratio of progesterone to estrogen in the placenta, decidua, or fetal membranes may be important in the initiation of labor in humans. The mechanisms of action of 17P in prolonging gestation are not entirely known. The actions of progesterone on the pregnant myometrium include relaxation of myometrial smooth muscle, blocking of the action of oxytocin, and inhibition of the formation of gap junctions ⁶. There is substantial evidence, however, that preterm labor is not simply the early initiation of otherwise normal through these same physiological mechanisms. Data suggest that preterm labor and preterm rupture of the membranes before labor frequently result from an inflammatory response, with generation of cytokines and matrix metalloproteinases. These mediators appear to incite a paracrine cascade, resulting pathologic labor ⁷.

Whether progesterone treatment suppresses the final common pathway to labor remains an area of debate.

A large randomized trial by Meis et al studied 17P therapy in a group of women with a history of a previous preterm delivery⁸. The mean gestational age at delivery in these 459 women was 30 weeks. These women were at a high risk for preterm delivery in the current pregnancy. They were randomized between 16 and 20 weeks to receive weekly intramuscular injections of 17P (n = 306) or placebo (n = 153). The group of women receiving 17P had significantly fewer preterm deliveries earlier than 37 weeks (36.3% v/s 54.9%; p = 0.001) and 32 weeks (11.4% v/s 19.6%; p = 0.018). Infants of mothers treated with 17P had significantly lower rates of necrotizing enterocolitis, intraventricular haemorrhage and supplemental oxygen.

17P therapy for women with multiple pregnancy has not shown the encouraging results seen in women with singletons. There was not reduction in the risk of preterm birth⁹. The efficacy of 17P in another high risk group with short cervical length on ultrasound is under study¹⁰. Vaginal progesterone has also been studied in similar settings and a systematic review of literature concludes that progesterone therapy may have beneficial effects in well selected patient groups¹¹.

Besides local side effects related to the injection site, a concern in women being treated with 17P is the risk of developing gestational diabetes mellitus¹². Early screening for this may be appropriate in such women. It is reassuring that progesterone treatment did not increase the incidence either maternal chorioamnionitis or neonatal sepsis. Although exposure to 17P during the first trimester was avoided, the experience of late sequelae exposure to the potent sex steroid diethylstilbestrol utero casts a long shadow. Could there be long-term consequences of this treatment would not be obvious during the brief follow-period reported in this trial? Longer-term follow-up of this cohort would help to provide reassurance in this regard.

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