

Is there enough evidence to support the use of 17 Alpha-Hydroxyprogesterone Caproate in preventing preterm labor in healthy women who have had a prior preterm delivery?

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Citation

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Abstract

INTRODUCTION

Preterm birth is defined as spontaneous or medically induced labor prior to the onset of 37 weeks. Currently, preterm birth is the number one cause of neonate mortality and can lead to morbidities such as cerebral palsy, heart defects, chronic lung diseases, and neurological deficits. Currently, it is unknown why some women experience preterm labor while others are unaffected. It is clear through numerous studies that many factors can contribute to preterm birth such as race, socioeconomic factors, uterine infections, and uterine abnormalities. There have been trials conducted to see if giving 17 Alpha-Hydroxyprogesterone Caproate (17P) will decrease the incidence of preterm births. It is thought that since 17P is an active metabolite of progesterone that it will have the same properties as progesterone such as relaxing smooth muscle, blocking the action of oxytocin, and inhibiting formation of gap junctions resulting in prevention of preterm birth. Therefore, it is important to researchers and physicians to find out how to prevent preterm births to decrease the mortality, morbidities, and costs associated with caring for preterm infants.

BACKGROUND

Preterm labor is defined as the spontaneous or induced delivery of a fetus prior to reaching 37 weeks gestation. In the United States statistics from 2004 show that 1 in 8 babies were born prematurely; this means that each year approximately 530,000 infants are born prior to 37 weeks.¹ The most recent data demonstrates these numbers steadily rising with increases in 2005 at 12.7%.² Preterm birth is the leading cause of death in the first month of life and is the leading cause of neonate morbidity and mortality in the

United States.³ It is estimated that the cost of caring for a premature infant averages about \$3500/day and can reach 1 million dollars in cases where the neonate has a prolonged hospital stay. Additionally, preterm births are associated with serious medical conditions such as cerebral palsy, neurosensory disabilities, patent ductus arteriosus, hearing deficits, blindness, and bronchopulmonary dysplasia.^{2,3}

There are many markers available that can help predict preterm labor such as fibronectin, estradiol, interleukin-6, or progesterone, and estriol. Currently, fibronectin has shown to have the highest specificity and sensitivity in predicting preterm labor. The test is deemed positive if >50 ng/ml are found in vaginal or cervical secretions after the 20th week of pregnancy. If positive this indicates that the mucous membrane lining of the uterus is separating and parturition is imminent. Preterm births are more common among women that have had a prior preterm delivery, in women that are below their desired weight, women that smoke cigarettes, black women, women lacking prenatal care, and women with uterine abnormalities.^{4,7} In the past, tocolytics have been utilized to stop the progression of preterm births, specifically brethine, magnesium sulfate and procordia. Additionally, the use of cerclage, bed rest, and prompt treatment of vaginal infections with antibiotic therapy has also been used to prolong pregnancy. Unfortunately, as of yet, none of the methods have demonstrated continued success leaving physicians and researchers with no real answers on how to prevent preterm births.

In order to halt the process of labor we must better understand the cascade of events that result in the onset of parturition. Some of the steps that move the uterus from a

state of relaxation to a state of regular, constant activity are well known while others still remain an enigma. The uterus maintains a relaxed non-contractile state throughout pregnancy through the mechanisms of nitric oxide, corticotrophin releasing hormone, progesterone, parathyroid hormone, relaxin, prostacyclin and various other peptides. After a series of steps involving proteins and ion channels, the uterus becomes stimulated and begins to rhythmically contract through the actions of prostaglandins and oxytocin. What is not fully understood is how exactly the fetus sends a signal to the uterine muscle causing the contractions to change from an irregular to regular pattern resulting in the onset of labor.^{4,7}

Progesterone is a hormone produced by the corpus luteum (yellow body), placenta, and adrenal cortex. In the early stages, progesterone causes changes in the uterus allowing it to become a more desirable environment for a fertilized ovum to implant. During pregnancy progesterone causes the smooth muscles of the uterus to relax, prevents oxytocin from exerting its effects on the uterine muscle, and most importantly prevents communication between cells of the uterine muscle, thereby preventing the onset of labor. With this understanding, it is understandable why researchers would research progesterone and its metabolites in inhibiting preterm labor.³ Several trials involving goats, sheep, and humans have been performed to determine what, if any, role progesterone can play in preventing preterm births. In these studies, it was noted that as serum levels of progesterone began to decrease and levels of estrogen began to increase, the onset of labor ensued.³ Additionally, there is evidence that these same changes in hormone levels may also play a fundamental role in the onset of labor in humans.²

The first known trials using progesterone date back to 1953 when progesterone was given prophylactically to determine if it could prevent spontaneous abortions in women with a prior history. Later studies began using IM injections of 17 Alpha Hydroxyprogesterone Caproate; a natural metabolite of progesterone that is derived from the corpus luteum and the adrenal gland.⁸ This metabolite is almost completely inactive when given orally, but when given by IM injection, it has long lasting effects. Currently, there is no data available that is able to completely explain the mechanism of this drug. The fact that it is a metabolite of progesterone leads researches to question whether it also has similar mechanisms of action like progesterone which involves relaxing smooth muscle, blocking the action of oxytocin and

inhibiting formation of gap junctions. These later studies changed the focus from preventing spontaneous abortions to preventing preterm births. In preventing preterm births, these studies have shown great promise and encouraged more research in this area.³

Many steps can be undertaken by the patient and the managing physician to decrease preterm labor incidences such as continual management of any underlying chronic comorbidities of the mother throughout the pregnancy, maintenance of adequate weight gain especially in teenage mothers, ample exercise, checking folic acid levels, discussing stress and the negative effects on outcome of the pregnancy, education on the harmful effects of drugs and alcohol on the fetus, and treating infections promptly and adequately. Ideally, it is best to undertake these discussions prior to becoming pregnant, but this is not always possible.

METHODS

A search was conducted using the Academic Search Premier (EBSCO), MEDLINE with full text, CINAHL with full text, and PUBMED using “progesterone, singleton, AND preterm” as keywords. The advanced search only permitted “full free text”. In narrowing the search under the advanced search section the words singleton and 17 Alpha Hydroxyprogesterone Caproate were used. When beginning this search only articles in the last 5 years were considered, but when looking at animal research and the limited studies of preterm births with only one prior singleton preterm birth, reviews from 8 years ago were included.

This etiology question is best answered by level I/A evidence, such as a randomized double blind control study. In these studies much concern was and still is raised in regard to giving painful injections to women weekly with a placebo (castor oil), knowing this would provide no benefit at all.

DISCUSSION

STUDY 1

The first study reviewed was a double blind placebo controlled trial that studied the relationship between 17 Alpha-Hydroxyprogesterone Caproate and preterm births entitled, “Prevention of Recurrent Preterm Delivery by 17 Alpha-Hydroxyprogesterone Caproate”, written by Paul J. Weiss.² The purpose of this study was to determine if the metabolite of progesterone, 17 Alpha-Hydroxyprogesterone (17P), would help reduce the incidence of preterm deliveries

in women who had a prior spontaneous preterm delivery. Researches were interested in this study as many previous trials involving progesterone compounds had shown conflicting evidence regarding outcomes. Women enrolled in the study were followed throughout their pregnancy; all records obtained from their prenatal period through their postpartum period were reviewed. The infants were also followed until the time of discharge or transfer to another facility. In this study, preterm delivery was defined as delivery prior to 37 weeks. Women were enrolled in the study if they had a previous singleton spontaneous preterm delivery and were between 15-20 weeks gestation in the current pregnancy. Excluded from the study were women who had known fetal anomalies, seizure disorders, history of cerclage, received progesterone prior to study, currently on heparin or hypertensive medications, and those scheduled to deliver at another birthing center. All participants that met the criteria were given a full explanation of the study and consents were obtained. Initially, the trial ran from April 1998” until February 1999”; however it was stopped due to a recall by the FDA which stated poor documentation and quality control during the study. The study was later restarted when a new company supplied the drug and placebo. It should be noted that the most recent study did not contain any data previously obtained; old data was discarded and only new information obtained was used. The same criteria were used for the study, which ran from September 1999” until February 2002”. Once all records were reviewed, 1039 women were deemed eligible to participate. Only 463 women would give consent to participate; randomization of the groups resulted in 310 women in the progesterone group and 153 in the placebo group.

Statistical analysis was performed using the Wilcoxon rank-sum test which compared the median of a single column of numbers against a hypothetical median which was entered by this study. In instances where the value was <5 in any single column, this test would always produce a P value greater than 0.05. In these instances, the Fischer’s exact test was used because it is best in analyzing sample sizes that are small, by exactly calculating the significance of the deviation from the null hypothesis.

The two groups were chosen based on a random assignment to either the control or placebo group. The groups were similar in length of pregnancy, education level, race, smoking and/or substance abuse, and body habitus. The only difference noted between the groups was an increased

incidence of prior preterm deliveries in the placebo group. The women receiving the placebo had a mean of 1.6 versus the progesterone group which was 1.4. The control group received weekly IM injections of 250mg of 17P and the placebo group received weekly IM injections of castor oil; injections continued until 36 weeks gestation. The control group was larger as researchers felt it unjustified to give the placebo group weekly injections fully aware they would not be beneficial.

Compliance in this study was not allowing more than 10 days to lapse between receiving weekly injections. Of all the participants involved in the study, 91.5% were deemed compliant. The outcome of this study showed that 111 women in the control group and 84 women in the placebo group delivered prior to 37 weeks. Fetal outcomes showed that infants delivered in the control group were less likely to weigh less than 2500 grams; 27.2% control group versus 41.1% placebo group. Additionally, infants born to the women in the control group had less intraventricular hemorrhage, necrotizing enterocolitis, and less need for oxygen after birth.

Fault in this study lies in deviating from the initial criteria which was a history of a single spontaneous preterm delivery. It was discovered that the placebo group had more previous preterm deliveries than the control group, placing these women in the high risk category which ultimately may have skewed the results. This study should have been halted based on these findings as this results in inequality between the groups. In addition, when the initial drug was recalled, the study should have been totally discarded and a completely new study should have ensued do to the fact there is always a possibility that some of the prior info may have made its way into the second study.

As realized by the researchers, this study should be evaluated with apprehension due to the fact that high risk women were enrolled in this study. More studies need to be performed that will aid in the prolongation of pregnancies where either there is no prior history of preterm birth or only a singleton birth. Another consideration is the fact that some researchers and clinicians believe that castor oil may actually stimulate uterine contractions; this was disputed by the researchers conducting this trial.

STUDY 2

The second study reviewed was a randomized double blind placebo controlled trial that studied the incidence of preterm

birth in twin gestations in women that were receiving weekly injections of 250mg of 17P and was entitled, “A Trial of 17 Alpha-Hydroxyprogesterone Caproate to Prevent Prematurity in Twins” written by Dwight J. Rouse.⁶ The researchers in this study were inspired by the results of prior studies using 17P, but they were concerned that it would be difficult to find a decent size sampling of women who had only one prior spontaneous preterm delivery. The reason they chose to include twins in the study was for the above stated reason and also to determine if additional risk factors would change the effectiveness of the 17P. Since twin births are becoming a more common occurrence it was decided they would study this population of women. The outcomes to be measured were a delivery of twins prior to 35 weeks gestation or fetal death. Data was analyzed based on the intention-to-treat principle which can be used in research trials when participants may not adhere or are withdrawn from the study if poor outcomes occur.⁷ The pregnancy was analyzed in this study and the outcome was met if delivery prior to 35 weeks gestation involved the fetus and not other outside influences. This study was carried out in 14 satellite sites from April 2004 through February 2006; no other information was available as to geographic or affiliation to main testing site. To be included in the study, participants had to be carrying twins with a gestation of at least 16 weeks but not more than 20 weeks and three days. Exclusion criteria for this study was a prior spontaneous fetal death after 12 weeks, an obvious inconsistency between gestational age of the fetuses, single placenta, fetal anomalies, twin to twin transfusion syndrome, progesterone therapy not planned in study, cerclage, significant uterine anomalies, current heparin therapy, insulin dependent diabetes, and hypertension. This study was approved by the review board and the data coordinating center and consent was obtained from all eligible participants.

Data from the MFM network estimated that prior to 35 weeks 35% of twins in this study would be born; therefore, they believed that a study group of 600 women would detect a 33% reduction in deliveries prior to 35 weeks and yield 80% power. In this study, initially 661 women were included in the study, but only the outcomes of 655 records were available. Outcomes were based on 325 women in control group receiving 250mg IM injections of 17P and 330 women receiving IM injections of the placebo (castor oil) beginning at 20 weeks gestation. Participants were randomized according to the standards set by the George Washington University. The women presented to the center weekly for

injections up until 34 weeks gestation or delivery.

Compliance was determined as receiving the injection every seven days until the actual delivery; compliance was 94.5% in the control group and 95% in the placebo group. It was noted that preterm birth or fetal death prior to 35 weeks was not very different between the two groups; in the 17P group it was 135 out of 325 (41.5%) and 123 out of 330 or 37.3% in the placebo group with a 95% confidence interval. Additionally, outcomes such as RDS (respiratory distress syndrome), necrotizing enterocolitis, intraventricular hemorrhage, and retinopathy of prematurity were almost equal at 20.2% in the control group versus 18% in placebo the group. This study did not demonstrate decreases in preterm births, better fetal outcomes, or longer gestation periods in the women receiving 17P.

This study is important because it was looking to answer the same question of whether 17P would aid in decreasing the incidence of preterm deliveries; the main differences being twin gestations and history of a documented preterm birth was not required. In the summary researchers discussed how their results did not support using 17P to reduce incidence of preterm birth in twin pregnancies. The researchers further stated they couldn't understand why 17P was beneficial in the singleton pregnancies with a history of a preterm birth but not in their study. In this study it was noted that only 10% of the women enrolled had a prior preterm birth; had the researchers included more women with a history of a preterm birth they would have a better comparison to the first study. Another important question to be answered in future studies involving twin gestations is whether or not the dose of 17P was adequate for twin gestations; some consideration may include doubling the amount of 17P given. It is known that in twin gestations, the blood volume is much greater than in singleton pregnancies; as much as 20%. In light of this information, researchers in this study should have considered the ramifications of using the same dose as in the prior study with singleton gestations.

This study was used because currently there are very few studies available to review that show the effects of 17P in healthy pregnant women with few problems and a history of a prior preterm birth. Therefore, this study was chosen because the exclusion criteria for this study seemed adequate in ruling out other factors that may contribute to preterm birth. Additionally, there were a small percentage of women who had a previous preterm birth. So in some ways it was comparable to the first study and in other ways very

different. Based on the results this study showed that 17P did not increase nor decrease the incidence of preterm births; not enough evidence from this one study is enough to support or refute the use of 17P in preventing preterm births.

CONCLUSION

The use of progesterone in women with preterm labor has resulted in many different outcomes. Clearly there is some compelling evidence that there is a benefit to giving progesterone to pregnant women with a history of preterm labor but the evidence is not clear when it comes to multiple gestations. Studies have failed to provide any substantial evidence to suggest that it would be detrimental to the mother or fetus if progesterone were given prophylactically. As noted in the second study, the incidence of respiratory distress syndrome, necrotizing enterocolitis, intraventricular hemorrhage, and retinopathy of prematurity were not more prevalent in the group receiving the 17P injections.⁶ Therefore; at this point it appears that it may be beneficial to some populations to administer 17P as an aid in preventing preterm births.

In spite of all of the past and current research regarding preterm births, the signaling of labor by the fetus still remains a mystery that has yet to be solved. In order to truly decrease the incidence of preterm labor, further research is warranted in this area. It is paramount that we understand all the mechanisms involved in the cascade of events that change irregular contractions to regular contractions.

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