Published in final edited form as:

Obstet Gynecol. 2009 February ; 113(2 Pt 1): 285–292. doi:10.1097/AOG.0b013e318193c677.

Prevention of Preterm Birth in Triplets: An Evaluation of 17 Alpha-Hydroxyprogesterone Caproate

Steve N. Caritis, MD,

Departments of Obstetrics and Gynecology, University of Pittsburgh, Pittsburgh, PA

Dwight J. Rouse, MD,

Center for Women's Reproductive Health, University of Alabama at Birmingham, Birmingham, AL

Alan M. Peaceman, MD,

Northwestern University, Chicago, IL

Anthony Sciscione, MD,

Drexel University, Philadelphia, PA

Valerija Momirova, MS,

The George Washington University Biostatistics Center, Washington, DC

Catherine Y. Spong, MD,

Eunice Kennedy Shriver National Institute of Child Health and Human Development, Bethesda, MD

Jay D. Iams, MD,

Ohio State University, Columbus, OH

Ronald J. Wapner, MD,

Columbia University, New York, NY

Michael Varner, MD,

University of Utah, Salt Lake City, UT

Marshall Carpenter, MD,

Brown University, Providence, RI

Julie Lo, MD,

University of Texas Southwestern Medical Center, Dallas, TX

John Thorp, MD,

University of North Carolina, Chapel Hill, NC

Brian M. Mercer, MD,

Case Western University, Cleveland, OH

Yoram Sorokin, MD,

Wayne State University, Detroit, MI

Margaret Harper, MD,

Wake Forest University, Winston-Salem, NC

Susan Ramin, MD, and

Corresponding Author: Steve N. Caritis, 300 Halket Street, Room 2229, Pittsburgh, PA 15213, 412-641-4874, 412-641-1133 (fax), scaritis@mail.magee.edu.

Financial Disclosure: The authors have no potential conflicts of interest to disclose.

Clinical Trial Registration: ClinicalTrials.gov, www.clinicaltrials.gov, NCT00099164.

University of Texas at Houston, Houston, TX

Garland Anderson, MD

The University of Texas Medical Branch, Galveston, TX

for the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) Maternal-Fetal Medicine Units Network (MFMU)

Abstract

Objective—To assess whether 17 alpha-hydroxyprogesterone caproate reduces the rate of preterm birth in women carrying triplets.

Methods—We performed this randomized, double blinded, placebo controlled trial in 14 centers. Healthy women with triplets were randomized to weekly intramuscular injections of either 250 mg of 17 alpha-hydroxyprogesterone caproate or matching placebo, starting at 16-20 weeks and ending at delivery or 35 weeks of gestation. The primary study outcome was delivery or fetal loss prior to 35 weeks.

Results—One hundred thirty-four women were randomized, 71 to 17 alpha-hydroxyprogesterone caproate and 63 to placebo; none were lost to followup. Baseline demographic data were similar in the two groups. The proportion of women experiencing the primary outcome (a composite of delivery or fetal loss prior to 35 0/7 weeks) was similar in the two treatment groups : 83% of pregnancies in the 17 alpha-hydroxyprogesterone caproate group and 84% in the placebo group, relative risk (RR) 1.0, 95% confidence interval (CI) 0.9 to 1.1. The lack of benefit of 17 alpha-hydroxyprogesterone caproate was evident regardless of the conception method or whether a gestational age cut off for delivery was set at 32 or 28 weeks.

Conclusion—Treatment with 17 alpha-hydroxyprogesterone caproate did not reduce the rate of preterm birth in women with triplet gestation.

Introduction

Infants delivered prior to term account for the vast majority of perinatal mortality and morbidity. Among triplets, 45% deliver prior to 32 weeks' gestation and perinatal mortality is 59/1000 compared with 4/1000 live births among singleton gestations delivered at term(1,2). Thus, the societal burden of prematurity and its attendant complications are high among fetuses from multifetal gestation. This high risk group is one where interventions to reduce the rate of prematurity have met with little success. Treatment with 17 alpha-hydroxyprogesterone caproate (17-OHPC) reduced the risk of recurrent preterm birth in singleton gestations by one third.³ This treatment, however, proved ineffective in women with twin gestation(4). The current trial assesses the value of this therapy in a group of women at extremely high risk of preterm birth, those with triplet gestation.

Materials and Methods

This placebo controlled, double blinded, randomized clinical trial was undertaken at 14 sites and targeted women with triplet gestation. Recruitment began in April 2004 and was completed in September 2006. Pregnant women with triplets were eligible if their gestational age was at least 16 weeks, and no more than 20 weeks. Exclusion criteria were: serious fetal anomalies, two or more fetuses in one amniotic sac, suspected twin to twin transfusion syndrome, marked ultrasonographic growth discordance (at least three weeks estimated gestational age difference between any two fetuses), planned non-study progesterone therapy after 16 weeks, in-place or planned cerclage, major uterine anomaly (e.g., bicornuate uterus), unfractionated heparin therapy greater than 10,000 units/day, low molecular weight heparin therapy at any dose, and major chronic medical diseases (e.g., insulin-requiring diabetes mellitus or pharmacologically-

treated hypertension). Triplet gestations that were the result of intentional fetal reduction from a quadruplet pregnancy were not excluded but reductions from a higher order gestation were excluded.

An ultrasonographic examination between 12 weeks and 20 weeks 6 days of gestation was performed to screen for major fetal anomalies and to establish gestational age. For spontaneous conceptions, the duration of gestation at the time of randomization was determined according to a previously described algorithm on the basis of the last menstrual period and the results of ultrasonographic measurement of the largest fetus at the earliest ultrasound.(5) For conceptions following assisted reproductive technologies, the duration of gestation was calculated based on the date of embryo transfer and the age of the embryos when transferred. The study was approved by the institutional review board of each clinical site and of the data coordinating center. Consent was given by all subjects before enrollment into the study. The trial is registered at ClinicalTrials.gov (NCT00099164).

Eligible, consenting women were given a trial intramuscular injection of the placebo and returned for a randomization visit not later than 20 weeks 6 days of gestation. At that visit, women who remained eligible were assigned to receive identically appearing active (250 mg 17-OHPC in 1 mL castor oil) or placebo (1 mL castor oil) injections prepared by a research pharmacy. The simple urn method of randomization (6) with stratification according to clinical center was used to create a randomization sequence for each center, and the boxes of 17-OHPC and placebo were packaged for each center according to the randomization sequences. The participating women, their caregivers, and the research personnel were not aware of the study group assignment. After entering the study, women returned for weekly injections through the end of the 34th week of gestation or until delivery, whichever occurred first. At each visit, they underwent systematic assessment for side effects. The usual clinical care provided to women in the study was not otherwise perturbed.

After delivery, study personnel reviewed delivery, newborn, and postpartum records, and documented the date of delivery, birth weight of the infant, and neonatal course, as well as the occurrence of complications of pregnancy and obstetrical interventions. Infants were followed until discharge from the hospital of birth, or, if transferred, from the transfer hospital.

The primary study outcome was a composite of delivery or fetal loss prior to 35 completed weeks' gestation (245 days). Fetal loss included miscarriage, termination, or stillbirth occurring anytime after randomization. Secondary outcomes included selected individual maternal and neonatal outcomes and a composite of serious adverse neonatal outcomes. The composite of serious adverse neonatal outcomes included: neonatal death, respiratory distress syndrome, culture proven sepsis, necrotizing enterocolitis – stage II or III, bronchopulmonary dysplasia, intra-ventricular hemorrhage – grade III or IV, or periventricular leukomalacia or severe retinopathy of prematurity stage III or higher.

Statistical analysis was performed according to the intention-to-treat principle. For the primary outcome, the unit of analysis was the pregnancy, thus if any of the three fetuses died or was born prior to 35 weeks, the pregnancy was considered to have met the outcome. The proportions of women in each study group remaining pregnant with three live fetuses were compared using survival analysis adjusted for gestational age at entry.(7) For baseline data, maternal outcomes and for the primary outcome where the pregnancy was the unit of analysis, continuous variables were compared using the Wilcoxon rank-sum test, and categorical variables with the chi-square or Fisher's exact test as appropriate.

For neonatal binary outcomes, the unit of analysis was the neonate, with robust variance estimation used to account for the clustering of neonates within pregnancies. Log binomial regression was used to calculate relative risks. In cases with rare outcomes, the neonatal data

were analyzed using the worst-per-pregnancy outcome. For birth weight, the Wei-Lachin generalization of the Wilcoxon test⁽⁸⁾ was used, again to account for correlation between the fetuses/neonates within a pregnancy. Where the baseline variables differed between the two groups, covariate adjustment was performed by stratified analysis.

On the basis of data from the US Natality report for 2000 and data from one of the participating institutions, we estimated conservatively that in the placebo group, 80% of triplet gestations would deliver before 35 completed weeks gestation.⁽⁸⁾ Thus, a total sample size of 120 was deemed sufficient to detect a 33 percent reduction in the rate of delivery or loss before 35 weeks, under the assumptions of a type I error (two-sided) of 5 percent and power of greater than 80 percent.

Before the study started, the group sequential method of Lan and Demets with the modified O'Brien-Fleming spending function was chosen for adjustment of the significance level in interim analyses.⁽¹⁰⁾ Three interim analyses were performed and in the final analysis of the primary outcome, two-tailed p-values of less than 0.03 would be considered significant; however, 95% confidence intervals are reported. For all other outcomes, a nominal p-value of $p < 0.05$ was considered significant, and no adjustments were made for multiple comparisons. An independent Data and Safety Monitoring Committee monitored the trial and reviewed the interim results.

Results

We identified 241 eligible women of whom 149 gave consent, and 134 (55.6 % of those eligible) were randomized - 71 to the 17-OHPC group and 63 to the placebo group (Figure 1). Outcome data were available for 100% of the randomized women, and for all of the 402 fetuses (Figure 1). The baseline characteristics of the two study groups were similar (Table 1). There were no significant differences in any of the variables listed except race ($p = 0.03$).

Compliance with the intervention was defined as the ratio of the number of injections received to the number expected per protocol (number of whole weeks from randomization to delivery, or to 34 weeks 6 days gestation, whichever was first). Compliance was 95.6 %, in the 17-OHPC group and 97.0 % in the placebo group ($p = 0.08$).

The rate of the primary outcome (delivery or fetal death prior to 35 weeks) did not differ between groups occurring in 83% (59/71) of pregnancies in the 17-OHPC group, and in 84% (53/63) in the placebo group, relative risk (RR) 1.0, 95% confidence interval (CI) 0.9 to 1.1 (Table 2). Results were similar when adjusted by race. Mean gestational age at delivery did not differ between groups, nor did the proportion of deliveries occurring prior to 32 or 28 weeks. Table 2 also compares each of the components of the primary outcome in the two treatment groups. The rates of spontaneous (48 and 43%) and indicated (35 and 41%) preterm births were similar in the 17-OHPC and in the placebo groups, respectively. There were seven fetal losses from the time of randomization to 34 6/7 weeks, 1 in the 17-OHPC group and 6 in the placebo group. There were no fetal losses after 35 weeks. The fetal death in the 17-OHPC group was associated with multiple malformations. The six fetal losses in the placebo group occurred in three pregnancies; in one, delivery occurred at 23 weeks secondary to preeclampsia and preterm labor and all three babies died during labor; in the other two pregnancies, the deaths were unexplained and the remaining fetuses survived. Figure 2 depicts the proportion of randomized subjects who remained undelivered and with three living fetuses according to the gestational age and treatment group. The two groups were similar ($p = 0.743$). Table 3 summarizes selected maternal outcomes and interventions; there were no significant differences between the two groups.

The rate of the serious adverse composite neonatal outcome (neonatal death, severe retinopathy of prematurity, respiratory distress syndrome, early onset neonatal culture proven sepsis, necrotizing enterocolitis stage II or III, bronchopulmonary dysplasia, intraventricular hemorrhage grade III or IV, or periventricular leukomalacia) was 37% in the 17-OHPC group, versus 34% in the placebo group, RR 1.1, 95% CI 0.7 to 1.7 (Table 4). Table 4 also summarizes selected neonatal outcomes according to treatment group. There were 5 neonatal deaths among four of the pregnancies treated with 17-OHPC. These babies were delivered at 24 (two infants), 25, 30, and 32 weeks. All died due to complications of prematurity. The pregnancy delivered at 24 weeks was the same pregnancy with the fetal demise associated with multiple anomalies. There were two neonatal deaths in the placebo group in two separate pregnancies. Both infants were delivered at 25 weeks and died of complications of prematurity. Likewise, the rates of individual outcomes were similar in the two treatment groups (Table 4). There was a greater proportion of infants in the 17-OHPC group with a birth weight <1500 grams: the difference was statistically different (43% versus 25%, RR 1.7, 95% CI 1.1 to 2.7). However, there was no overall difference in birth weight (as a continuous variable, $p=0.142$) or in the proportion of babies with a birth weight of <2500 grams (RR 0.9, 95% CI 0.9 to 1.0).

Side effects were common in both groups (69% and 65 % in the 17-OHPC and placebo group, respectively, RR 1.1, 95% CI 0.8 to 1.3), but were generally mild and, in the majority (64%) of women who experienced them were limited to pain, swelling, bruising, itching, or redness at the the injection site. Three women (two in the 17-OHPC group and one in the placebo, $p = 0.55$) experienced side effects so severe that the injections were not continued. These side effects included constitutional symptoms and elevated liver enzymes (placebo subject) and intense injection site reactions (two 17-OHPC subjects).

Discussion

This randomized placebo controlled trial has demonstrated that 17-OHPC does not reduce the rate of preterm birth in women with triplet gestation. This lack of benefit occurred regardless of conception method. Combined with our companion study with twins(4), the findings of this study help to further clarify those conditions where 17-OHPC should be considered. Although, 17-OHPC reduces the rate of preterm birth in women with a singleton gestation who had a prior preterm birth, this treatment is ineffective in reducing the rate of prematurity in multifetal gestation. The mechanism of action of 17-OHPC in reducing preterm birth rates in singleton gestation is unclear. Consequently, explanations for why this therapy proved ineffective in multifetal gestations must remain speculative. We undertook this study because we hypothesized that 17-OHPC might impact upon a proposed mechanism for preterm parturition in multiples, that of uterine stretch. The degree of uterine stretch is greater in multiple than in singleton gestation and it is well documented that uterine stretch induces transcription of several Contraction Associated Proteins.(11) These proteins, including oxytocin receptors, gap junctions (Connexin-43) and cyclooxygenase (COX) characterize an activated myometrium. Progesterone inhibits formation of these Contraction Associated Proteins(12). Older studies in humans and animals suggest that 17-OHPC is more potent and has a longer lasting progestational effect than progesterone. (13,14) This led us to postulate that 17-OHPC might suppress expression of those Contraction Associated Proteins better than endogenous progesterone and therefore might reduce the rate of preterm delivery among women with multifetal gestation.

The lack of benefit in multifetal gestation may be due to an inadequate dose of 17-OHPC. For this study and our study in twins, we administered 250 mg intramuscularly weekly; a dose identical to that used in our study of singletons (3). We chose to use this dose because the therapeutic concentration of 17-OHPC was and is still not known. The dose selected for the study of Meis et al in singletons was based on prior studies(15) and a metaanalysis which

suggested that 250 mg 17-OHPC might be effective in reducing preterm birth rates in high risk women.(16) If the 250 mg weekly dose achieves “therapeutic” levels in only a portion of women with singleton gestation, that might explain why the success rate in a study of Meis et al was only 33%. In the same vein, if the dose of 250 mg 17-OHPC weekly does not achieve therapeutic levels in a substantial percentage of women with singletons, it is conceivable that concentrations in women with multifetal gestation are even lower given the physiological changes that occur in pregnancy which generally enhance drug metabolism or elimination. Analysis of the relationship of 17-OHPC concentration and preterm birth rates is currently under investigation in both the women with triplet or twin gestation. This exploration should address those issues related to 17-OHPC dosing and success.

Another plausible explanation for the failure of 17-OHPC to reduce the rates of preterm birth in multifetal gestation may be that myometrial stretch, the proposed mechanism of preterm birth in multiples, is not altered by 17-OHPC. To our knowledge the effect of 17-OHPC on stretch regulated Contraction Associated Proteins (CAPS) has not been evaluated.

Clearly any attempt to define the basis of failure of 17-OHPC in reducing preterm birth rates in multiples or in any other group of patients at increased risk of preterm birth is severely constrained by our lack of understanding of how this treatment works. We have defined the pharmacokinetics of 17-OHPC in multifetal gestation and have shown that the drug has a half life of nearly 9 days. (17) The long half life likely represents slow release from the depot injection site. The mechanism of action of 17-OHPC however has remained elusive. The drug is no better than progesterone in activating progesterone responsive genes through the classic hormone-hormone receptor pathway. (18) 17-OHPC injection does not appear to significantly alter plasma progesterone or 17-hydroxyprogesterone concentrations.(19) Thus, the beneficial effect of 17-OHPC is not likely mediated by an effect on any of these hormones. Clearly, more research is required to define the mechanism of action of this drug.

The results of our study and our companion study in twins provide information on fetal safety of 17-OHPC in pregnancy. In reviewing a recent New Drug Application for 17-OHPC the FDA raised concern about fetal safety because in the study of Meis et al a nonsignificant increase in fetal deaths (RR 1.5, 95% CI 0.3 to 7.3) was seen in the 17-OHPC group.(20) In our study of twins, fetal deaths were more common in the 17-OHPC group but those differences were not statistically different than the placebo treated group (RR 1.4, 95% CI 0.6 to 3.2). In our triplet study, only one fetal death was seen in the 17-OHPC group from the time of enrollment to the study endpoint of 35 weeks and the baby had multiple malformations. Six fetal deaths were seen in the placebo group. Our studies in twins and triplets collectively therefore provide a measure of reassurance that 17-OHPC therapy does not increase the risk of fetal demise. Furthermore, we found similar rates of small for gestational age (SGA) infants in our current study among the two treatment groups.

Another issue about 17-OHPC treatment raised by the study of Meis et al is addressed with the current study and our companion study in twins – the effect of castor oil on preterm birth rates.(20) It has been suggested that the use of castor oil in the placebo group and as a diluent for 17-OHPC might confound findings of 17-OHPC trials by actually increasing uterine contractility through the smooth muscle effects of castor oil.(21) Castor oil is a gastrointestinal stimulant only when taken orally and not likely to have any impact on smooth muscle when given intramuscularly since ricinoleic acid, the active ingredient, is formed by hydrolysis in the gut.(22) Furthermore, the mean gestational ages at delivery in the 17-OHPC and placebo groups were consistent with the gestational age at delivery of triplets reported in the U.S. Natality report of 2005.(23) Similar findings were seen in our study with twins.

Side effects were common in this study and overwhelmingly associated with injection site symptoms such as pain, itching and bruising. These findings were similar to those we reported in our study of twins and singletons.(3,4) We also tracked serious adverse side effects, including outcomes such as maternal death, unplanned hospitalization, and neonatal deaths. There were no maternal deaths reported among our study of triplets or twins. Likewise, the rates of other serious adverse outcomes in these studies were similar in the 17-OHPC and placebo groups.

The application of 17-OHPC therapy to women at risk of preterm birth is supported by our trial in singletons(3) and the meta-analysis of Keirse(16) which summarized the literature on the use of 17-OHPC to prevent preterm birth in earlier studies. This treatment unfortunately has been expanded to other groups of women deemed to be high risk for preterm birth with the expectation that the treatment will work in all high risk group (23). The present study and our companion study in twins clearly point out that such expectations are unfounded and that prospective randomized trials are needed before expanding use of 17-OHPC to other at-risk groups.

In summary, we have shown that 17-OHPC, as prescribed in this trial, does not reduce the rate of preterm birth in triplets and our companion study demonstrated a lack of benefit in twins. Women with multifetal gestation should therefore not be treated with 17-OHPC as a preventative for preterm birth unless new information emerges to alter that recommendation. Treatment with 17-OHPC appears to be safe for the mother and her fetus.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Supported by grants from the National Institute of Child Health and Human Development (HD21410; HD27869; HD40512; HD27915; HD40485; HD34208; HD40500; HD34116; HD40560; HD40544; HD27917; HD27860; HD40545; HD53097; HD36801; HD34136).

The authors thank subcommittee members Elizabeth Thom, PhD, for protocol/data management and statistical analysis, and Allison Northen RN, and Margaret Cotroneo, RN, for protocol development and coordination between clinical research centers. The authors also thank Joyce A. Martin, M.P.H., National Center for Health Statistics, who supplied U.S. natality and infant mortality data.

References

1. Alexander, GR.; Salihu, HM. Perinatal outcomes of singleton and multiple births in the United States, 1995-98. In: Blickstein, I.; Keith, G., editors. Multiple Pregnancy. Taylor and Francis; London and New York: 2005. p. 3-10.
2. Mathews, TJ.; MacDorman, MF. National vital statistics reports. Vol. 54. Hyattsville, MD: National Center for Health Statistics; 2006. Infant mortality statistics from the 2003 period linked birth/infant death data set.
3. Meis PJ, Klebanoff M, Thom E, et al. Prevention of Recurrent Preterm Delivery by 17 Alpha-Hydroxyprogesterone Caproate. N Engl J Med 2003;348:2379-85. [PubMed: 12802023]
4. Rouse DJ, Caritis SN, Peaceman AM, et al. A trial of 17 alpha-hydroxyprogesterone caproate to prevent prematurity in twins. N Engl J Med 2007;357:454-61. [PubMed: 17671253]
5. Carey JC, Klebanoff MA, Hauth JC, et al. Metronidazole to prevent preterm delivery in pregnant women with asymptomatic bacterial vaginosis. N Engl J Med 2000;342:534-540. [PubMed: 10684911]
6. Wei LJ, Lachin JM. Properties of the urn randomization in clinical trials. Control Clin Trials 1988;9:345-64. [PubMed: 3203525]

7. Cnaan A, Ryan L. Survival analysis in natural history studies of disease. *Statistics in Medicine* 1989;8:1255–68. [PubMed: 2814073]
8. Wei LJ, Lachin JM. Two-sample asymptotically distribution-free tests for incomplete multivariate observations. *JASA* 1984;79(387):653–661.
9. Martin, JA.; Hamilton, BE.; Sutton, PD., et al. National vital statistics reports. Vol. 55. Hyattsville, MD: National Center for Health Statistics; 2006. Births: Final data for 2004.
10. Lan KKG, DeMets DL. Discrete sequential boundaries for clinical trials. *Biometrika* 1983;70:659–63.
11. Ouc W, Orsino A, Lye S. Expression of connexin-43 and connexin-26 in the rat myometrium during pregnancy and labor is differentially regulated by mechanical and hormonal signals. *Endocrinology* 1997;138:5398–5407. [PubMed: 9389525]
12. Shynlova O, Mitchell JA, Tsampalieros A, Langille BL, Lye SJ. Progesterone and gravidity differentially regulate expression of extracellular matrix components in the pregnant rat myometrium. *Biol Reprod* 2004;70:986–992. [PubMed: 14645109]
13. Davis ME, Wied G. 17-Alpha-hydroxyprogesterone-caproate: a new substance with prolonged progestational activity. A comparison with chemically pure progesterone. *J Clin Endocrinol Metab* 1995;15(8):923–930.
14. Reifenshtein EC. Introduction of marked as well as prolonged biologic activity by esterification. *Fertil & Steril* 1957;8(1):50–79. [PubMed: 13405048]
15. Johnson J, Austin K, Jones G, Davis G, King T. Efficacy of 17 α -hydroxyprogesterone caproate in the prevention of premature labor. *N Engl J Med* 1975;293:675–680. [PubMed: 1099445]
16. Keirse M. Progestogen administration in pregnancy may prevent preterm delivery. *Br J Obstet Gynecol* 1990;97:149–154.
17. Caritis, S.; Venkataramanan, R. Pharmacokinetics of 17-alpha hydroxyprogesterone caproate (17-OHPC) in women with twin gestation. Abstract # 294; Annual Meeting Society for Gynecologic Investigation; Reno NV. 2007.
18. Attardi BJ, Zeleznik A, Simhan HN, Chiao JP, Mattison DR, Caritis SN. Comparison of progesterone and glucocorticoid receptor binding and stimulation of gene expression by progesterone, 17-alpha hydroxyprogesterone caproate (17-OHPC), and related progestins. *Am J Obstet Gynecol* 2007;197(6):599–e1-7. [PubMed: 18060946]
19. Reijnders F, Thomas C, Doesburg W, Rolland R, Eskes T. Endocrine effects of 17 alpha-hydroxyprogesterone caproate during early pregnancy: a double-blind clinical trial. *Br J Obstet Gynecol* 1998;95:462–468.
20. www.fda.gov/ohrms/dockets/ac/06/slides/2006-4227S1-02-03-FDA_Wesley.ppt
21. Brancazio LR, Murtha AP, Heine RP. Prevention of recurrent preterm delivery by 17 alpha-hydroxyprogesterone caproate. *N Engl J Med* 2003;348(24):2379–85. [PubMed: 12802023]
22. Thiery, M.; Baines, CJ.; Keirse, MJNC. The development of methods for inducing labour. In: Chalmers, I.; Enkin, M.; Keirse, MJNC., editors. *Effective Care in Pregnancy and Childbirth*. Oxford: Oxford University Press; 1989. p. 969-980.
23. Martin JA, Hamilton BE, Sutton PD, Ventura SJ, Menacker F, Kirmeyer S. Births: final data for 2004. *Nat Vital Stat Reports* September 29;2006 55(1)
24. Rittenberg C, Sullivan S, Istwan N, Rhea D, Stanziano G, Newman R. Clinical characteristics of women prescribed 17 alpha-hydroxyprogesterone caproate in the community setting. *Am J Obstet Gynecol* 2007;197(3):252–e1-4.

Figure 1.
Randomization, treatment, and follow-up of participants and their offspring.

Figure 2.

The proportion of randomized subjects who remained undelivered and with three living fetuses according to the gestational age and treatment group.

Table 1**Baseline Characteristics of the Study Subjects**

Characteristic	17-OHPC Group n = 71 (%)	Placebo Group n = 63 (%)
Maternal age (y)	30 [28,35]	32 [28, 35]
Gestational age at randomization (wk)	19 [18, 20]	19 [18, 20]
Pre-pregnancy BMI	24.1 [22.0, 31.0]	25.1 [22.1, 28.7]
Race**		
African American	6 (8)	5 (8)
Caucasian	53 (75)	56 (89)
Hispanic	12 (17)	2 (3)
Marital status		
Married/living with partner	60 (85)	59 (94)
Living alone	11 (15)	4 (6)
Years of school	16 [12, 16]	16 [14, 16]
Nulliparous	45 (63)	33 (52)
Conception		
Spontaneous	21 (30)	18 (29)
Assisted Reproductive Technology (ART)	50 (70)	45 (71)
Prior preterm delivery	0	2 (3)
Chorionicity		
Trichorionic	49 (69)	42 (70)
Dichorionic	13 (18)	14 (23)
Unknown	9 (13)	4 (7)
Smoking during pregnancy	2 (3)	4 (6)
Alcohol during pregnancy	3 (4)	3 (5)
Substance use during pregnancy	1 (1)	0

Data are presented as median [25th %tile, 75th %tile] or number (%)

BMI = Body mass index (kg/m²)

* Race/ethnicity was defined as: AA, all other were classified Caucasian and the Caucasian who self-declared Hispanic were placed in the Hispanic group

Table 2**Primary and Selected Secondary Outcomes According to Treatment Assignment**

Outcome	17-OHPC Group n = 71 (%)	Placebo Group n = 63 (%)	RR (95% CI)
Delivery or fetal loss <35 weeks	59 (83.1)	53 (84.1)	1.0 (0.9,1.1)
Gestational age at delivery* (wks)	32.4 [30.0, 34.4]	33.0 [31.6, 34.3]	p = 0.527
Delivery (%) or fetal loss before: 32 weeks gestation	29 (41)	19 (30)	1.4 (0.8,2.2)
28 weeks gestation	7 (10)	7 (11)	0.9 (0.3,2.4)
Delivery or fetal loss (%) < 35 weeks Spontaneous Conception	18/21	16/18	1.0 (0.8,1.1)
Assisted Reproductive Technology	41/50	37/45	
Delivery < 35 weeks Spontaneous	34 (48)	27 (43)	1.1 (0.8,1.6)
Indicated	25 (35)	26 (41)	0.9 (0.6,1.3)
Pregnancy with fetal loss < 35 weeks	1	3	0.3 (0.0 - 2.9)
≥ 35 weeks	0	0	

Data are presented as median [25th %tile, 75th %tile] or number (%)

RR= relative risk, CI = confidence interval

Table 3

Selected Maternal Outcomes According to Treatment Outcome

	17-OHPC Group n = 71 (%)	Placebo Group n = 63 (%)	RR(95% CI)
Tocolytic therapy	33 (47)	28 (44)	1.0(0.7,1.5)
Corticosteroids for fetal maturation	39 (55)	32 (51)	1.1(0.8,1.5)
Cerclage placement	3 (4)	2 (3)	1.3(0.2,13.3)
Preterm PROM	6 (8.5)	7 (11)	0.8(0.3,2.1)
Preeclampsia/gestational hypertension	15 (21)	18 (29)	0.7(0.4,1.3)
Clinical Chorioamnionitis	1 (1)	0	
Cesarean delivery	71 (100)	62 (98)	1.0 (1.0,1.1)

RR= relative risk, CI = confidence interval

Table 4**Selected Neonatal Outcomes Among Liveborns According To Treatment Group**

Outcome	17-OHPC Group n = 212 (%)	Placebo Group n = 183 (%)	RR (95% CI) [†]
Composite Adverse Outcome	78 (37)	65 (34)	1.1 (0.7, 1.7)
Neonatal death [*]	5 (2)	2 (1)	2.2 (0.4, 12.4)
Retinopathy of prematurity (severe) [*]	0	0	-
Respiratory distress syndrome [*]	65 (31)	50 (27)	1.1 (0.7, 1.8)
Culture proven sepsis [*]	20 (9)	13 (7)	1.3 (0.6, 3.0)
Necrotizing enterocolitis (stage II and III) [*]	2 (0.9)	5 (3)	0.3 (0.0, 3.1)
Bronchopulmonary dysplasia [*]	15 (7)	17 (9)	0.8 (0.3, 2.0)
IVH Grade III/IV [*]	2 (0.9)	4 (2)	0.4 (0.0, 3.8)
Periventricular leukomalacia ^{* ○}	0	1 (0.5)	0 (0.0, 12.8)
Birthweight (mean±SD) [†]	1650 ± 554	1754 ± 494	
< 2500 gm	191 (91)	175 (96)	0.9 (0.9, 1.0)
< 1500 gm	91 (43)	46 (25)	1.7 (1.1, 2.7)
SGA (<10 percentile)	48 (23)	30 (16)	1.4 (0.9, 2.2)
5-minute Apgar < 7	10 (5)	10 (6)	0.9 (0.3, 2.4)
Patent ductus arteriosus	34 (16)	16 (9)	1.8 (0.8, 4.1)
Pneumonia	4 (2)	1 (0.5)	3.5 (0.4, 30.1)
Mechanical ventilation	70 (33)	57 (31)	1.0 (0.7, 1.6)
Seizures	1 (0.5)	0	-

RR= relative risk, CI = confidence interval

Complications were diagnosed based on clinical diagnoses in the medical record.

IVH = Intraventricular hemorrhage

^{*} Component of the serious adverse outcome composite

[†] Wei-Lachin, p=0.142

[○] The RR is based on worse-per-pregnancy outcome because of small sample