Impact of prior gestational age at preterm delivery on effectiveness of 17-alpha-hydroxyprogesterone caproate in practice

Victor H. González-Quintero, MD, MPH; Lesley de la Torre, DO; Debbie J. Rhea, MPH; Carmen M. Tudela, MD; Enrique Vazquez-Vera, MD; Cheryl Desch, RN, MS; Niki B. Istwan, RN

OBJECTIVE: We sought to examine if 17-alpha-hydroxyprogesterone caproate (17OHPC) effectiveness is dependent on the earliest gestational age (GA) at prior spontaneous preterm birth (SPTB) when administered in the clinical setting.

STUDY DESIGN: Women enrolled for outpatient services with current singleton gestation and ≥1 prior SPTB between 20-36.9 weeks were identified. Data were divided into 3 groups according to earliest GA of prior SPTB (20-27.9, 28-33.9, and 34-36.9 weeks). We compared GA at delivery of current pregnancy and incidence of recurrent SPTB between women enrolled in outpatient 17OHPC administration program (n = 2978) and women receiving other outpatient services without 17OHPC (n = 1260).

RESULTS: Rates of recurrent SPTB for those with and without 17OHPC prophylaxis, respectively, according to GA at earliest SPTB were: 20-27.9 weeks at earliest SPTB, 32.2% vs 40.7%, $P = .025$; 28-33.9 weeks at earliest SPTB, 34.1% vs 45.5%, $P < .001$; and 34-36.9 weeks at earliest SPTB, 29.3% vs 38.8%, $P < .001$.

CONCLUSION: 17OHPC given to prevent recurrent SPTB is effective regardless of GA at earliest SPTB.

Key words: 17-alpha-hydroxyprogesterone caproate, gestational age at delivery, spontaneous preterm birth

Cite this article as: González-Quintero VH, de la Torre L, Rhea DJ, et al. Impact of prior gestational age at preterm delivery on effectiveness of 17-alpha-hydroxyprogesterone caproate in practice. Am J Obstet Gynecol 2010;203:257.e1-5.

Despite ongoing prevention efforts, preterm birth (PTB) rates continue to rise in the United States with 12.8% of all births in 2006 considered preterm or <37 completed weeks of gestation.[1] Women who have experienced a spontaneous PTB (SPTB) are at increased risk of delivering preterm in a subsequent pregnancy.[2] The use of 17-alpha-hydroxyprogesterone caproate (17OHPC) has been shown to be effective in reducing the incidence of recurrent PTB in women with a current singleton pregnancy and a documented history of an SPTB.[3]

A secondary analysis of women with a previous SPTB enrolled in a randomized placebo-controlled trial evaluating prophylactic use of 17OHPC vs placebo for the prevention of recurrent PTB questioned if the effectiveness of 17OHPC was dependent on the gestational age (GA) at the earliest prior PTB. Spong et al[4] concluded that 17OHPC is associated with a prolongation of pregnancy overall but especially for those women whose previous SPTB occurred at <34 weeks. In their study, statistical significance was not reached for patients with and without 17OHPC prophylaxis whose earliest prior SPTB had occurred at 34-36.9 weeks' gestation. The purpose of the present study is to examine if 17OHPC effectiveness is dependent on the earliest GA at prior SPTB when administered in the clinical setting.

Materials and Methods

We conducted a retrospective analysis of deidentified clinical data collected from high-risk pregnant women enrolled in outpatient perinatal services provided by Alere, formerly Matria Healthcare. The Women's and Children's Health Division of Alere provides physician-prescribed comprehensive home-based services to pregnant women throughout the United States who have medical or pregnancy-related problems that could harm their pregnancies including preterm labor, gestational diabetes, hypertensive conditions, coagulation disorders, and nausea and vomiting in pregnancy.

Clinical data were prospectively collected from the patient and her physician throughout provision of outpatient services and at conclusion of the pregnancy, and maintained in a relational database. All data were collected using standardized operating procedures, forms, and customized proprietary computer software. All women provided written consent for outpatient services and allowed for the use of their deidentified protected health information for research and reporting purposes.

Records from women with a current singleton gestation, a history of at least 1 SPTB with a documented GA between 20-36.9 weeks, and a documented pregnancy outcome of the current pregnancy were identified. Each record was labeled

From the Division of Maternal-Fetal Medicine, Department of Obstetrics and Gynecology, University of Miami School of Medicine, Miami, FL (Drs González-Quintero, de la Torre, Tudela, and Vazquez-Vera); and the Department of Clinical Research, Alere Women's and Children's Health, Atlanta, GA (Ms Rhea, Ms Desch, and Ms Istwan).

Presented as a poster at the 30th Annual Meeting of the Society for Maternal-Fetal Medicine, Chicago, IL, Feb. 1-6, 2010.

Received March 1, 2010; revised April 22, 2010; accepted June 7, 2010.

Reprints not available from the authors.

0002-9378/$36.00

doi: 10.1016/j.ajog.2010.06.020

TABLE 1
Maternal characteristics according to earliest gestational age of prior spontaneous preterm birth

Characteristic	20-27.9 wk (n = 896)	28-33.9 wk (n = 1493)	34-36.9 wk (n = 1849)	*P* value
No. of women receiving 17OHPC	692 (77.2%)	1148 (76.9%)	1138 (61.5%)	< .001
Mean GA at 17OHPC start, wk	18.7 ± 2.4	18.7 ± 2.5	18.8 ± 2.5	.900
	17.9 (15.7, 24.9)	17.9 (14.6, 24.9)	18 (15.6, 24.9)	
Maternal age, y	29.9 ± 5.7	30.5 ± 5.5	30.5 ± 5.2	.010
	30 (17, 49)	31 (16, 45)	31 (17, 46)	
Black race	338 (37.7%)	335 (22.4%)	263 (14.2%)	< .001
Smoking	51 (5.7%)	102 (6.8%)	88 (4.8%)	.037
>1 PPTB	273 (30.5%)	427 (28.6%)	347 (18.8%)	< .001
Not married	362 (40.4%)	465 (31.1%)	424 (22.9%)	< .001

Data presented as mean ± SD, median (minimum, maximum), or n (%) as indicated.
17OHPC, 17-alpha-hydroxyprogesterone caproate; *GA*, gestational age; *PPTB*, previous preterm birth.
González-Quintero. Gestational age at earliest spontaneous preterm birth. Am J Obstet Gynecol 2010.

as to if weekly 17OHPC injections or other progestational agents were prescribed during the current pregnancy. Excluded were women reporting use of progestational agents other than 17OHPC in the current pregnancy, or who initiated 17OHPC at ≥25 weeks' gestation. All decisions regarding use or nonuse of progestational agents were made by each patient's individual health care provider. Pregnancy outcomes were compared between 2978 women who received 17OHPC and 1260 women with a history of SPTB receiving other outpatient services but no 17OHPC prophylaxis.

At the start of outpatient services, all women received an initial in-home patient education session with an experienced perinatal nurse. Verbal instruction and written patient education materials were provided to each patient related to pregnancy and the specific condition that placed their pregnancy at risk. In addition, women enrolled in the 17OHPC administration program received weekly skilled perinatal nursing visits for maternal assessment and administration of 250-mg intramuscular injections of 17OHPC given via the Z-track method until 36 completed weeks or preterm delivery. The 17OHPC was compounded at a qualified pharmacy using US Pharmacopeia Reference standards in an International Organization Standardization class 5 clean room with adequate quality control procedures and documentation to ensure sterility and potency of each vial. Arrangements were made for home delivery of unit dose, preservative-free vials of 17OHPC using the specifications and formulation of the 17OHPC used in the Meis et al[3] network study including the vehicle (castor oil). A nurse and pharmacist were available by telephone for questions and concerns 24 hours a day, 7 days a week. Perinatal nurses provided clinical communication and care coordination with the patient's physician and case manager as needed.

For this study, records were divided into 3 groups according to their earliest GA of prior SPTB (20-27.9, 28-33.9, and 34-36.9 weeks). The GAs and reasons for all past deliveries were captured during the enrollment process and were patient reported. If the woman was unsure, the space for that information was left blank. Within each group, we compared the GA at delivery of the current pregnancy and incidence of recurrent SPTB between the study group of women who received 17OHPC and controls who did not receive 17OHPC. Comparisons were made using Pearson χ^2, Kruskal-Wallis H, and Mann-Whitney *U* test statistics. Logistic regression models were used to test relative associations for significant univariate factors within each of the 3 GAs at earliest SPTB groups. All *P* values reported were 2-sided and considered statistically significant if < .05.

Results

A total of 4238 records were included in the analysis. Maternal characteristics according to the earliest GA of prior SPTB subgroups are reported in Table 1. Overall, 2978 (70.3%) women received weekly prophylactic 17OHPC injections in the current pregnancy: 692 in the 20-27.9 weeks' subgroup, 1148 in the 28-33.9 weeks' subgroup, and 1138 in the 34-36.9 weeks' subgroup. The 1260 women not receiving 17OHPC were enrolled for daily outpatient perinatal nursing surveillance: 957 (75.9%) received twice-daily uterine monitoring and telephonic assessment of subjective signs and symptoms of preterm labor, 180 (14.3%) received outpatient treatment for nausea and vomiting of pregnancy, and 123 (9.8%) received services related to diabetes, hypertension, or anticoagulation. Tocolytic use was more common in women not receiving 17OHPC than those prescribed 17OHPC (75.0% vs 13.9%, respectively; $P < .001$).

GA at delivery for women receiving 17OHPC was significantly greater compared to women not receiving 17OHPC although this difference in GA at delivery was <1 week within each subgroup (Figure 1). In the 20-27.9 weeks at earliest prior SPTB subgroup, the mean GA at delivery was 36.0 ± 3.6 weeks for women receiving 17OHPC compared to 35.7 ± 3.0 weeks for women not receiving

17OHPC ($P = .025$). In the 28-33.9 weeks group, the mean GA at delivery was 36.4 ± 2.8 weeks for women receiving 17OHPC compared to 35.6 ± 2.9 weeks for women not receiving 17OHPC ($P < .001$). In the 34-36.9 weeks' group, the mean GA at delivery was 37.0 ± 2.2 weeks for women receiving 17OHPC compared to 36.3 ± 2.2 for women not receiving 17OHPC ($P < .001$).

Rates of recurrent SPTB are presented in Figure 2. Women who received 17OHPC were less likely to experience a recurrent preterm delivery compared to women who did not receive 17OHPC. In the group with the earliest prior SPTB at 20-27.9 weeks, 32.2% of women receiving 17OHPC delivered preterm compared to 40.7% of women not receiving 17OHPC ($P = .025$; odds ratio [OR], 0.693; 95% confidence interval [CI], 0.503–0.956) with a 59% power for observed difference. In the 28-33.9 weeks' group, 34.1% of women receiving 17OHPC delivered preterm compared to 45.5% of women not receiving 17OHPC ($P < .001$; OR, 0.618; 95% CI, 0.484–0.790) with a 96% power. In the 34-36.9 weeks' group, 29.3% of women receiving 17OHPC delivered preterm compared to 38.8% of women not receiving 17OHPC ($P < .001$; OR, 0.652; 95% CI, 0.535–0.794) with a 98% power.

Within each subgroup a logistic regression analysis was performed to control for maternal characteristics of black race, smoking, maternal age, unmarried status, and history of >1 SPTB (Table 2). A significant effect of 17OHPC treatment was observed in all 3 subgroups.

TABLE 2
Logistic regression for preterm delivery <37 weeks within each gestational age category

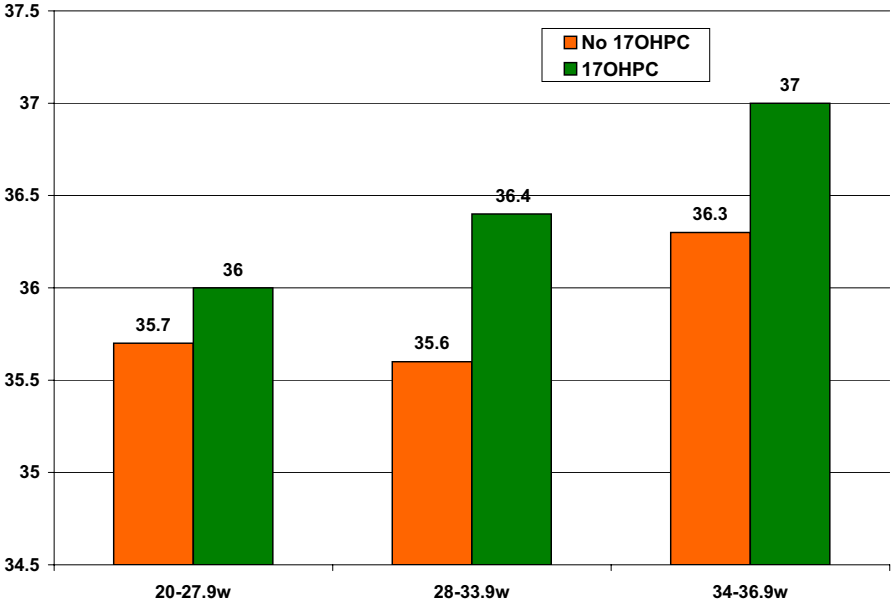
Earliest prior SPTB, wk	OR (95% CI) for 17OHPC	*P* value
20-27.9	0.675 (0.487–0.936)	.018
28-33.9	0.595 (0.463–0.765)	< .001
34-36.9	0.647 (0.528–0.792)	< .001

Controlling for black race, maternal age, smoking, unmarried status, and >1 prior preterm birth.
17OHPC, 17-alpha-hydroxyprogesterone caproate; *CI*, confidence interval; *OR*, odds ratio; *SPTB*, spontaneous preterm birth.
González-Quintero. Gestational age at earliest spontaneous preterm birth. Am J Obstet Gynecol 2010.

Comment

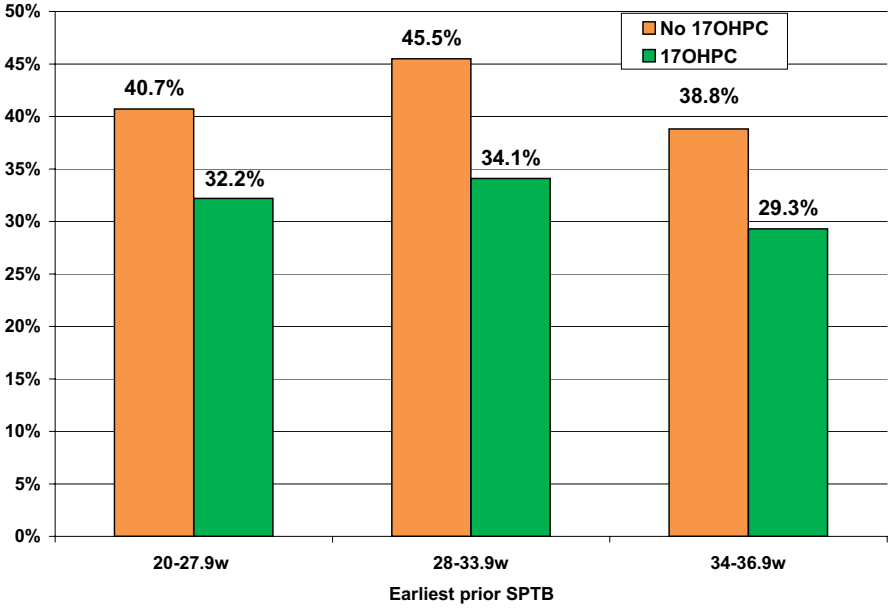
Although 17OHPC prophylaxis is widely recommended for women with a history of SPTB, there are still many unanswered questions regarding its use and performance in the community setting. In the present study of 4238 women of which 2978 received 17OHPC, we have shown that prophylactic administration of 17OHPC given to prevent recurrent SPTB is effective regardless of GA at earliest prior SPTB. The results of the present study differ from an earlier study by Spong et al.[4] In the secondary analysis of 459 women with a previous SPTB enrolled in a randomized placebo-controlled trial evaluating prophylactic use of 17OHPC vs placebo, Spong et al[4] reported that 17OHPC was associated with a prolongation of pregnancy overall but especially for those women whose previous SPTB occurred at <34 weeks. If the woman's earliest SPTB occurred between 34-36.9 weeks the reduction in rates of PTB in the current pregnancy with the use of 17OHPC was not significant (OR, 0.62; 95% CI, 0.29–1.32). The results of the secondary analysis could make a clinician less confident in the decision to prescribe 17OHPC for women with a history of late PTB, although these authors cautioned clinicians that their analysis lacked power to fully address efficacy in this subgroup of patients with an earliest PTB between 34-36.9 weeks and that larger numbers of patients needed to be examined. Spong et al[4] reported rates of recurrent SPTB for women receiving 17OHPC and an earliest prior SPTB between 20-27.9, 28-33.9, and 34-36.9 weeks of 42%, 34%, and 33%, respectively. In the present study we found rates of recurrent SPTB for women receiving 17OHPC in the community setting and an earliest prior SPTB between 20-27.9, 28-33.9, and 34-36.9 weeks of 32.2%, 34.1%, and 29.3%, respectively. For those women receiving placebo, Spong et al[4] found rates of recurrent SPTB of 63%, 56%, and 47% for

FIGURE 1
Gestational age at delivery



17OHPC, 17-alpha-hydroxyprogesterone caproate.
González-Quintero. Gestational age at earliest spontaneous preterm birth. Am J Obstet Gynecol 2010.

FIGURE 2
Rates of recurrent spontaneous preterm birth (SPTB)



17OHPC, 17-alpha-hydroxyprogesterone caproate.

González-Quintero. Gestational age at earliest spontaneous preterm birth. Am J Obstet Gynecol 2010.

women with an earliest SPTB between 20-27.9, 28-33.9, and 34-36.9 weeks, respectively. These rates of recurrent SPTB are considerably higher than the rates of recurrent SPTB in the present study for women who did not receive 17OHPC but were recipients of daily outpatient perinatal nursing services. In the present study rates of recurrent SPTB for those not receiving 17OHPC were 40.7%, 45.5%, and 38.8% for women with an earliest SPTB between 20-27.9, 28-33.9, and 34-36.9 weeks, respectively. Impressive differences in overall GA at delivery between treated and untreated patients were not found in either study.

Evidence from randomized controlled trials regarding the efficacy and use of 17OHPC is limited to 1 study in the contemporary literature.[3] Clinicians are challenged as to how best to incorporate the treatment in community practice as questions remain as to how 17OHPC will perform in patients who may not have met the original study inclusion criteria. In the study of Meis et al[3] enrollment was limited to women with a GA of 16-20.9 weeks. Two prior investigations examined the effect of late initiation of 17OHPC, showing benefit with initiation of treatment even if the patient is found to be a candidate after the 20th week of gestation.[5,6] González-Quintero et al[5] compared rates of recurrent PTB in women starting treatment with 17OHPC at 16-20 and 21-26.9 weeks. Rates of PTB were similar in both groups regardless of GA at initiation of 17OHPC prophylaxis. How et al[6] confirmed these findings by demonstrating no difference in rates of PTB if 17OHPC was started >20 weeks' gestation. This type of information assists physicians in the treatment of patients with a previous PTB who present late to prenatal care.

In the trial of Meis et al[3] women received weekly 17OHPC injections until the 36th week of gestation or delivery (whichever came first). In the community setting both patients and physicians may question the necessity of continuing treatment until the 36th week. Rebarber et al[7] studied the effect of early cessation of 17OHPC on the incidence of spontaneous recurrent preterm delivery. The study group was compromised of patients who were electively terminating 17OHPC at <32 weeks. The women with early cessation of 17OHPC were significantly more likely to have spontaneous recurrent PTB at <37, <35, and <32 weeks. The results of the study by Rebarber et al[7] support continuation of 17OHPC until 36 completed weeks of gestation as in the protocol of Meis et al.[3] GA of the patients earliest PTB was not evaluated in this study.

Our study has weaknesses that should be examined as they may have confounded our results. Limitations of the study are those inherent to retrospective research. The patients were not randomized and we do not know why some women, seemingly eligible for 17OHPC due to history of preterm delivery, were not prescribed 17OHPC. Although the sample size is large and represents women from throughout the United States we cannot ensure that all women received the same level of care or counseling information from their providers. While all women in the study received outpatient nursing services and had telephonic access to obstetric nurses and pharmacists for questions and concerns 24 hours a day, 7 days a week, the intensity of outpatient surveillance received was not identical between those women receiving 17OHPC and those not receiving 17OHPC. Depending on the outpatient services prescribed, women may have received weekly nursing visits or daily telephonic assessment. A prior study by Rittenberg et al[8] that examined pregnancy outcomes in women receiving prophylactic 17OHPC vs prophylactic daily perinatal nursing services with uterine monitoring showed no differences in rates of SPTB at <37, <35, or <32 weeks between the groups. Patients were matched by maternal race, marital status, tobacco use, and number of prior preterm deliveries, although GA at prior PTB was not available for comparison. As the majority of women not receiving 17OHPC in the present study had daily outpatient surveillance with uterine monitoring and many received continuous subcutaneous tocolysis they may have been at higher risk for preterm delivery than those women receiving 17OHPC. An additional weakness of the present study is that we do not know if similar results would be found in women receiving 17OHPC through means other than weekly home nursing visits.

Currently, the only tool available in the prevention of PTB in women with history of a PTB is 17OHPC prophylaxis. Further studies are needed to better identify which patients are most likely to benefit from prophylactic treatment with 17OHPC. This present study including outcomes of almost 3000 women receiving 17OHPC offers strong evidence of the importance of utilizing 17OHPC for women with a history of PTB even if their earliest PTB occurred in the late preterm period. In summary, women with history of a PTB benefit from 17OHPC prophylaxis regardless of the GA at previous spontaneous PTB. ■

REFERENCES

1. Martin JA, Hamilton BE, Sutton PD, et al. Births: final data for 2006. Natl Vital Stat Rep 2009;57:1-104.

2. Mercer BM, Goldenberg RL, Moawad AH, et al. The preterm prediction study: effect of gestational age and cause of preterm birth on subsequent obstetric outcome. Am J Obstet Gynecol 1999;181:1216-21.

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.

4. Spong CY, Meis PJ, Thom EA, et al. Progesterone for prevention of recurrent preterm birth: impact of gestational age at previous delivery. Am J Obstet Gynecol 2005;193:1127-31.

5. González-Quintero VH, Istwan NB, Rhea DJ, Smarkusky L, Hoffman MC, Stanziano GJ. Gestational age at initiation of 17α-hydroxyprogesterone caproate (17P) and recurrent preterm delivery. J Matern Fetal Neonatal Med 2007; 20:249-52.

6. How HY, Barton JR, Istwan NB, Rhea DJ, Stanziano GJ. Prophylaxis with 17-alpha-hydroxyprogesterone caproate for prevention of recurrent preterm delivery: does gestational age at initiation of treatment matter? Am J Obstet Gynecol 2007;197:260.e1-4.

7. Rebarber A, Ferrara LA, Hanley ML, et al. Increased recurrence of preterm delivery with early cessation of 17-alpha-hydroxyprogesterone caproate. Am J Obstet Gynecol 2007; 196:224.e1-4.

8. Rittenberg C, Newman RB, Istwan NB, Rhea DJ, Stanziano GJ. Preterm birth prevention by 17 alpha-hydroxyprogesterone caproate vs daily nursing surveillance. J Reprod Med 2009;54:47-52.