Published in final edited form as:

Am J Obstet Gynecol. 2009 October ; 201(4): . doi:10.1016/j.ajog.2009.07.009.

The effect of treatment with 17 alpha-hydroxyprogesterone caproate on changes in cervical length over time

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Abstract

Objective—To examine whether women treated with 17 alpha hydroxyprogesterone caproate (17OHPC) to prevent recurrent preterm birth (PTB) experienced a change in cervical shortening over time as compared to women who were not treated.

Study Design—A retrospective exposure cohort study of women, enrolled in a prematurity prevention clinic from 1999–2008, with a singleton pregnancy, one prior spontaneous PTB (<37 weeks) who underwent at least 2 cervical length (CL) measurements by endovaginal ultrasound were included.

Results—Of 200 women, 105 received and 95 did not receive treatment with 17OHPC. Women treated with 17OHPC were more likely to have experienced an earlier prior PTB (26.0 vs 27.8 wks, $p=0.01$) than those not treated with 17OHPC. There was no difference in the average weekly change in cervical length among women treated with 17OHPC compared with those who did not receive treatment after adjustment for covariates [0.79 mm/week, 95% CI: (–1.18, 2.76)].

Conclusion—There was no difference in the average weekly change in cervical length measurements over time in women receiving 17OHPC treatment compared with those who were not treated.

Keywords

cervical length; preterm birth; 17 OHPC; progesterone

Background and Objective

The role of sonographically measured cervical length as a predictor of spontaneous preterm birth has been well established^{1–4}. In women with a history of prior preterm birth, a short cervix denotes an increased risk for recurrent preterm delivery^{2,5–8}. The gestational age at delivery and the number of prior preterm births are also risk factors for recurrent preterm delivery^{9–14}.

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The National Institute of Child Health and Human Development (NICHD) Maternal-Fetal Medicine Units Network reported a significant reduction in the rate of recurrent preterm delivery in women with a prior preterm birth who received weekly injections of 17 alpha-hydroxyprogesterone (17-OHPC)¹⁵. A similar reduction in the rate of preterm delivery before 34 weeks gestation was seen in women at high risk for preterm birth using daily prophylactic vaginal progesterone¹⁶.

A recent randomized trial found that treatment with vaginal progesterone significantly reduced the rate of spontaneous preterm delivery before 34 weeks in asymptomatic women with a short cervix at 20–25 weeks¹⁷. The mechanism by which treatment with 17-OPHC acts to reduce the incidence of preterm birth is unclear; however it is plausible that progesterone treatment may alter the progression of cervical shortening, thereby providing a clinical parameter that could be measured during treatment. In a recent study, women hospitalized for preterm labor treated with twice weekly injections of 17-OHPC were less likely to experience cervical shortening at one and three weeks after therapy compared with women who did not receive 17-OHPC treatment¹⁸. To date, there have been no published reports on whether 17-OHPC is related to changes in cervical length measurements in women treated to prevent recurrent preterm birth. The purpose of our study was to determine whether treatment with 17-OHPC is related to cervical length trajectory in women with a history of prior preterm birth.

Materials and Methods

With institutional review board approval, we performed a retrospective exposure cohort study among a stratified sample of 200 women with a history of prior preterm birth enrolled in The Ohio State University Prematurity Prevention Clinic between 1999–2008 inclusive. Women with a history of one or more prior preterm births between 18⁰ and 36⁶ weeks who were currently pregnant with a singleton gestation and who underwent at least two cervical length measurements during the index pregnancy were included in the analysis. The cervical length trajectory of women treated with 17-OPHC was compared to women who did not receive this medication. Women with multiple gestations, known uterine anomalies, prior cervical surgery and cervical cerclage were not studied. Individual chart review was performed to confirm a history of spontaneous preterm birth, the number of prior spontaneous preterm births and the gestational age at each delivery. Clinical characteristics collected include: gestational age at enrollment, number of visits to clinic, maternal age, race, maternal pre-pregnant body mass index, insurance status, smoking status during pregnancy, and gestational age of earliest and most recent preterm birth. For women receiving 17 -OHPC, gestational age at initiation of treatment was recorded. Use of 17-OHPC was introduced in 2003 in our prematurity clinic. The choice to initiate treatment with 17-OHPC was made individually by the treating physicians with the consent of each woman. Treatment with 17-OHPC was offered to all women with a prior preterm birth, but was specifically recommended to women with a history of early and/or repeated preterm birth, as these risk factors were common in the NICHD Network trial participants¹⁵. The prematurity clinic had a 98% acceptance rate for 17-OHPC treatment during the study period. Once 17-OHPC prophylaxis was initiated, treatment was continued until 36 weeks or delivery unless the patient declined further injections. Cervical length measurements did not influence the decision to initiate or discontinue treatment with 17-OHPC.

Endovaginal sonography was used to measure cervical length in millimeters during visits to the clinic. Transvaginal cervical length was obtained in a standardized manner⁵. The cervix was measured three times, and the shortest measurement of the cervical image that met standard criteria was recorded⁵. Pre-pregnant body mass index (BMI) was categorized according to the National Heart Lung and Blood Institute standard cutoffs¹⁹. The

distributions of variables were compared using chi-square tests, t-tests, Wilcoxon rank sum tests, and Kruskal-Wallis tests as appropriate.

To establish each woman's cervical length trajectory over time, we used all of the available cervical measurements for each patient and obtained estimates of the slopes of these trajectories by regressing cervical length on measurement time. These estimates were then used as the outcome of interest in a linear regression model with 17-OHPC being the primary exposure of interest. Covariates were retained in the final model as confounders if their inclusion resulted in a $\pm 10\%$ change in the estimated effect of 17-OHPC treatment status. All statistical analyses were performed using Stata (StataCorp. 2007. Stata Statistical Software: Release 10. College Station, TX).

Results

Among the 200 patients studied, 105 received 17-OHPC and 95 did not. Maternal clinical and pregnancy characteristics of women by 17-OHPC treatment status are shown in Table 1. Women who received 17-OHPC were more likely to be older, have private payer insurance, have an earlier prior PTB and were enrolled at an earlier gestational age than those not treated. Four women (3.8%) in the 17-OHPC group were non compliant with the weekly regimen of injections, thus receiving only partial treatment. Among the women who received 17-OHPC, the mean gestational age at treatment initiation was 17.6 weeks (range=14.3–24.0). Mean gestational age of first cervical length was 16.6 weeks (range=10.0–27.1). Mean cervical length at first measurement was 34.1mm (range=17.0–58.0). Mean gestational age of last cervical length was 29.9 weeks (range 17.6–33.6). The mean number of cervical length measurements was 6.8 (range=2.0–16.0). The rate of birth before 37 weeks did not differ in women treated versus not treated with 17-OHPC (42.9% vs. 35.8%, respectively ($p=0.31$)).

Women who were treated with 17-OHPC experienced a statistically significant increased rate of cervical shortening of 1.1 mm/week ($SD=1.2$) compared with women who did not receive treatment in whom cervical length decreased by 0.7 mm/week ($SD=0.7$), $p=0.02$. However, after adjustment for covariates, this relationship was no longer present. In fact, a trend suggesting a protective effect of 17-OHPC against cervical shortening over time [0.79 mm/week, 95% confidence interval (CI) = (−1.18, 2.76)] as compared to no treatment (Table 2) appeared, but the effect was not statistically significant. After adjustment, we found a statistically significant increase in average weekly cervical shortening in non-Hispanic black women [−0.42 mm/week, 95% CI = (−0.70, −0.15)] compared with white women. A history of previous fullterm delivery was found to be protective against cervical shortening [0.39 mm/week, 95% CI = (0.05, 0.74) for one previous full-term birth and 0.48 mm/week, 95% CI = (0.08, 0.88) for two or more previous full-term births].

Figure 1 presents the unadjusted mean cervical length by gestational age and 17-OHPC treatment status. As shown in the graph, women for whom 17-OHPC treatment was initiated two or more weeks after the first cervical length measurement (later treatment) appeared to experience more rapid cervical shortening over time. The mean age at which treatment was initiated in the treatment groups was not statistically different (17.7 weeks for those with early treatment versus 17.5 for those receiving later treatment, $p=0.72$); however, the mean gestational age at earliest preterm birth was significantly earlier in the later treatment group (23.7 weeks) versus the early and no treatment groups (26.7 weeks and 27.8 weeks respectively, $p<0.01$).

Comment

We observed similar weekly changes in cervical length shortening over time in women receiving 17-OHPC treatment compared with those who received no treatment, after controlling for confounding factors. In our study population, women receiving 17-OHPC had an earlier prior preterm birth, an established risk factor for recurrent early preterm birth¹². Spong et al found a significantly greater prolongation of pregnancy in women treated with 17-OHPC whose qualifying prior preterm birth was early, before 34 weeks²⁰.

The majority of women (86.3 %) who did not receive 17-OHPC were enrolled prior to the 2002 NICHD report of a reduction in recurrent preterm birth with 17-OHPC treatment¹⁵. Thirteen women declined 17-OHPC prophylaxis after we began to offer it routinely. Although women treated with 17-OHPC entered care at a significantly earlier gestational age than those not treated, all women were initially evaluated within the gestational age window in which 17-OHPC could be initiated, and received a similar number of visits and cervical length measurements during the pregnancy. As noted previously, 17-OHPC prophylaxis was encouraged for women with a history of early and/or multiple prior preterm births..

Although non-Hispanic black women experienced a statistically significant greater decrease in cervical length per week compared with white women regardless of 17-OHPC treatment status, this was not related to timing of 17 OHPC administration and did not result in a higher rate of preterm birth (data not shown). Women with a history of a previous full term delivery experienced significantly less cervical shortening throughout pregnancy. This protective effect became stronger as the number of full term deliveries increased. These findings are consistent with previous studies^{22,23} demonstrating a decrease in risk of recurrent preterm birth in women who have had at least one prior full term delivery.

We did not find an association between 17 OHPC administration and a decrease in cervical length shortening in this observational study of asymptomatic outpatients. Our study differs from the report by Facchinetti¹⁸ in the study population, dose and frequency of 17-OHPC treatment. Facchinetti gave 341 mg of 17-OHPC twice weekly to women treated after successful tocolysis for an acute episode of preterm labor, few of whom (5%) had a history of prior preterm birth.

In our analysis, timing of treatment initiation was found to be a major confounder of the OHPC and cervical length trajectory relation. Women who received later treatment relative to their first cervical length measurement experienced more rapid cervical shortening over time, but it is not clear whether this is related to their *a priori* risk status, to the gestational age at initiation or to the duration of treatment.

The strengths of this study include the number of cervical length measurements collected in a standardized manner among patients over time, and a two-stage regression modeling strategy that uses all of the data to calculate an individual slope for each woman as opposed to using a last measurement minus first measurement approach. The main weakness in our study is that we calculated an average trajectory for each woman over time, which did not allow us to fully examine the effect of timing of treatment initiation on cervical length trajectory, given that women received treatment at varying times. Future analyses should use a more flexible statistical model to investigate the possibility of a change in cervical length trajectory once treatment is commenced.

In conclusion, we did not find a statistically significant decrease in cervical shortening over time. Non-Hispanic black race/ethnicity conferred an independent increased risk of cervical

shortening even after adjusting for treatment status and other covariates. The effect of race/ethnicity on cervical length trajectory over time is a finding that warrants further study.

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Figure 1.
Mean cervical length by gestational age and treatment status

Table 1

Maternal clinical and pregnancy characteristics by 17 alpha hydroxyprogesterone caproate administration (17-OHPC) status

	17-OHPC (n=105)	No 17-OHPC (n=95)	p-value
Race (%)			0.42
Non-black	45.7	40.0	
Black	54.3	60.0	
Age (years) [†]	26.5 ± 4.6	23.5 ± 3.7	<0.01
Insurance status (%)			0.01
Government	59.1	79.0	
Private	35.2	17.9	
Self-pay	5.7	3.2	
Body mass index (kg/m ²)			0.11
Underweight	9.5	5.3	
Normal	37.1	42.1	
Overweight	20.0	30.5	
Obese	33.3	22.1	
Smoked – index pregnancy (%)	41.9	36.8	0.47
Gravidity [†]	4.0 ± 2.0	3.8 ± 1.8	0.61
Number of prior PTB [†]	1.4 ± 0.5	1.4 ± 0.5	0.40
Gestational age at earliest PTB (weeks) [†]	26.0 ± 5.1	27.8 ± 5.0	0.01
Gestational age at most recent PTB (weeks) [†]	28.6 ± 6.2	30.2 ± 5.7	0.06
Gestational age at first visit (weeks) [†]	15.0 ± 4.1	16.3 ± 3.5	0.02
Gestational age at first cervical length [†]	16.5 ± 2.9	16.6 ± 3.3	0.91
Cervical length at first measurement (mm) [†]	34.3 ± 7.9	34.0 ± 7.1	0.74
Number of cervical length measurements [†]	6.9 ± 2.4	6.8 ± 2.5	0.71
Medically indicated delivery (%)	14.3	6.3	0.07
Average change in cervical length/week (mm) [†]	-1.1 ± 1.2	-0.7 ± 0.7	0.02
Preterm birth – index pregnancy (%)	42.9	35.8	0.31

[†] mean ± standard deviation

Table 2

Adjusted mean weekly change in cervical length (mm) by 17 alpha hydroxyprogesterone caproate (17-OHPC) treatment status

	Adjusted estimate (95% confidence interval)	p-value
17-OHPC treatment		0.43
No	Referent	
Yes	0.79 (−1.18, 2.76)	
Timing of 17-OHPC treatment		0.31
No treatment	Referent	
Treatment before first measurement	−0.93 (−2.98, 1.12)	
Treatment at first measurement	−0.97 (−2.96, 1.02)	
Treatment within 2 weeks after first measurement	−0.97 (−2.91, 0.97)	
Treatment more than 2 weeks after first measurement	−1.11 (−3.04, 0.82)	
Race and ethnicity		<0.01
White	Referent	
Non-Hispanic black	−0.42 (−0.70, −0.15)	
Gestational age at earliest preterm birth	0.02 (−0.01, 0.05)	
Number of prior full-term births		<0.01
None	Referent	
One	0.39 (0.05, 0.74)	
Two or more	0.48 (0.08, 0.88)	
Prepregnant body mass index		0.95
Healthy weight	Referent	
Underweight	−0.07 (−0.61, 0.46)	
Overweight	0.22 (−0.12, 0.56)	
Obese	−0.17 (−0.52, 0.17)	