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17 alpha-hydroxyprogesterone caproate for the prevention of preterm birth in women with prior preterm birth and a short cervical length

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Abstract

Objective—To evaluate 17-alpha hydroxyprogesterone caproate (17P) for prevention of preterm birth (PTB) in women with prior spontaneous PTB (SPTB) and cervical length (CL) <25mm.

Study Design—Planned secondary analysis of the NICHD-sponsored randomized trial evaluating cerclage for women with singleton gestations, prior SPTB (17-33 6/7weeks), and CL<25mm between 16-22 6/7weeks. Women were stratified at randomization to intent to use or

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not use 17P. The effect of 17P was analyzed separately for cerclage and no cerclage groups. Primary outcome was PTB<35weeks.

Results—In 300 women, 17P had no effect on PTB<35weeks in either cerclage (p=0.64) or no cerclage (p=0.51) groups. Only PTB<24weeks (OR=0.08) and perinatal death (OR=0.14) were significantly lower for those with 17P in the no cerclage group.

Conclusions—17P had no additional benefit for prevention of PTB in women who have prior spontaneous PTB and get ultrasound-indicated cerclage for CL<25mm. In women who do not get cerclage, 17P reduced previable birth and perinatal mortality.

Keywords

progesterone; short cervical length; cerclage; preterm birth

Background and Objective

A short cervical length (CL) on second trimester transvaginal ultrasound (TVU) is currently the best method to predict spontaneous preterm birth (SPTB). (1) Prior SPTB is perhaps the strongest historic risk factor for recurrent SPTB (2). Cerclage (3-8) and progesterone (9,10) supplementation have been the two interventions proposed most often to prevent PTB once the short TVU CL has been detected or in women with prior SPTB.

It has now been shown in a large randomized trial that cerclage reduces the incidence of recurrent PTB <24 and <37 weeks, as well as perinatal mortality, in women with both a prior spontaneous PTB 17-33 6/7 weeks and also a short CL < 25 mm, identified between 16-22 6/7 weeks (3). This confirmed results from a meta-analysis (8) of prior trials (4-7). In one trial (9) and one systematic review and meta-analysis (10), 17 alpha-hydroxyprogesterone caproate (17P) has been associated with a reduction of recurrent SPTB. It is unclear if the effects of 17P (for prior SPTB) and cerclage (for short CL) are additive in women with both risk factors. Moreover, it is unclear if 17P is beneficial in women with a prior PTB and a short CL who do not undergo ultrasound-indicated cerclage.

Our objective was to estimate the effect of 17P for the prevention of PTB in women with prior SPTB, and a short CL, with and without ultrasound-indicated cerclage.

Materials and Methods

This is a planned secondary analysis of the NICHD-sponsored randomized trial evaluating cerclage for women with singleton gestations, prior SPTB (17-33 6/7 wks), and short CL < 25 mm measured between 16 and 22 6/7 weeks. This randomized controlled trial was performed by 15 U.S. Clinical Centers between January, 2003 and November, 2007. (3) Each center obtained Institutional Review Board approval. Exclusion criteria were fetal anomaly, planned history-indicated cerclage, and clinically significant maternal-fetal complications (3). Gestational age was always confirmed by standard sonographic biometric measurements at less than 20 weeks' gestation. Sonologists underwent a uniform certification process by a single investigator (J.O.) to ensure uniformity in sonographic measurements of TVU CL screening. (3,11).

Women with prior SPTB were screened with TVU CL starting at 16 0/7 – 21 6/7 weeks, then every 2 weeks until 22 6/7 weeks unless the CL was observed to be 25-29 mm, after which the scan frequency was increased to every week. Women who were detected by TVU screening to have a short CL <25mm at 16-22 6/7 weeks were randomized after informed consent to cerclage or no cerclage.

Very early in the trial (May, 2003), after the first 10 women were randomized, the results of a randomized trial of 17P became available (9). In response to this report the steering committee and an independent data and safety monitoring board recommended that women eligible for the cerclage trial be counseled regarding the use of progesterone for preterm birth prevention, and an additional randomization stratum, reflecting the patient's stated intent to use progesterone, was added. The suggested 17P dose was 250mg IM starting at 16 weeks and continued weekly until 36 weeks. Subsequent use of 17P was recorded and actual use was utilized for these analyses.

Study nurses contacted patients weekly to record medication use. To determine if the reported use on the study data forms reflected actual use of 17P, medical records were reviewed for study patients at the center with the largest number of recruited study patients. Of the 23 patients at this center with a reported dose, 20 (91%) received at least one recorded dose of 17P. There was 85% agreement between the reported 17P and the administered 17P (kappa=0.85). Therefore we concluded that the reported 17P on the study data forms was an accurate reflection of actual 17P use. We then defined actual use of 17P for our analyses as at least one reported dose on the study data forms.

The effect of 17P use was analyzed separately for the cerclage and no cerclage groups. Randomization to cerclage/no-cerclage (intent to treat) was used in the primary analysis. (3) We also planned to analyze data by actual cerclage/no-cerclage placement groups. In this latter analysis, women were allocated to the cerclage group if they actually received a cerclage, and to the 'no cerclage' group if they did not receive cerclage.

The primary outcome of this secondary analysis as well as that of the primary analysis (3) was PTB < 35 weeks. Secondary outcomes included birth < 7 days from randomization, PTB < 24, < 28, < 32, and < 37 weeks, and perinatal death. Perinatal death was defined as either a stillbirth or a post natal death prior to hospital discharge. Maternal age, race, smoking, drug use, shortest CL, gestational age of the qualifying preterm birth, prior induced abortion, number of sonograms, and gestational age at randomization were considered as possible confounders.

The primary study outcome and other categorical variables were compared with chi-square tests and, where appropriate, Fisher's exact test. Continuous variables were analyzed using the t-test and Wilcoxon rank-sum test where appropriate. Differences in time to birth were assessed with Kaplan-Meier curves and the log-rank test. Multivariable logistic regression and Cox proportional hazard models considered possible confounders for the outcomes of preterm birth < 35 weeks and time to birth respectively. We selected an alpha level of < 0.05 to represent statistical significance.

Results

Of 1014 women with prior SPTB who were screened with TVU CL at 16-22 6/7 weeks, 318 had a CL <25mm, of which 302 agreed to randomization. Of these, 300 were available for this analysis, because one woman was lost to follow up and one woman was excluded because she received vaginal progesterone, not 17P. Of these 300, 148 were randomized to cerclage and 152 were randomized to no-cerclage.

Of the 148 women with a prior SPTB, a short CL<25mm, and who were randomized to receive cerclage, characteristics were similar except for race/ethnicity ($p < 0.01$), smoking ($p = 0.036$), and total number of vaginal sonograms ($p = 0.03$) between the 47 women who used progesterone, and the 101 who did not use 17P (table 1). 17P had no effect on PTB < 35 weeks (p=0.64), or on other outcomes (table 2).

Of the 152 women with a prior SPTB, a short CL<25mm, and who were randomized to *not* receive cerclage, significant disparities were found only for prior induced abortion (p = 0.003) and years of education (p = 0.001) between the 52 women who used, and the 100 did not use 17P (table 3). While 17P had no effect on PTB < 35 weeks (p=0.51), the odds of PTB <24 weeks (OR=0.08, p=0.0022) and perinatal death (OR=0.14, p=0.0029) were significantly lower for those with 17P in the no cerclage group (table 4).

In multivariable logistic regression models, the odds of PTB < 35 weeks were lower for increasing CL at randomization (OR = 0.91; 95% CI: 0.85 – 0.98; p = 0.012) for women randomized to cerclage. For women randomized to no-cerclage, the odds of PTB < 35 weeks were higher for black women (OR = 4.23; 95% CI: 1.31 - 13.62; p = 0.016) and lower for longer CL at randomization (OR = 0.39; 95% CI: 0.77 - 0.92; p < 0.0001). Similar results of shortest CL were seen in Cox models for time to delivery, where women randomized to cerclage (HR = 0.94; 95% CI: 0.90 – 0.97; p = 0.0003) and women randomized to no cerclage (HR = 0.97; 95% CI: 0.94 – 1.00; p = 0.077) were less likely to deliver for larger values of CL at randomization.

The shortest CL was a significant predictor in both the cerclage and no cerclage multiple logistic regression models for PTB < 35 weeks. Therefore, we considered the effect of 17P among those women with CL <15 mm at randomization versus those with CL 15-24 mm at randomization. (12,13) Analyses of the interaction between CL sub-groups and 17P use were not significant for any outcome when stratified by cerclage randomization groups. However, after considering all randomized women and controlling for randomization group, we found that progesterone use did have a statistically significant effect on reducing the odds of both previable birth (OR = 0.11; 95% CI: 0.15 - 0.88; p = 0.0371) and perinatal death (OR = 0.18; 95% CI: 0.04 - 0.81; p = 0.026) for those women with CL 15-24 mm. These effects were not significant for the women with CL < 15 mm. In the Cox proportional hazards models stratified by randomization group there was no effect of 17P use on time to delivery for either group of women.

Differences in the time-to-delivery for women who did and did not use 17P were assessed with Kaplan-Meier curves. We again considered women assigned to cerclage (n=148) and to nocerclage (n=152) separately. We found no statistically significant difference in time-to-delivery between 17P use and non-use for any cerclage subpopulation. The significance levels are: randomized to cerclage, p=0.639 (figure 1); randomized to no-cerclage, p=0.694 (figure 2). Note that we did see a large separation between the 17P users and non-users at early gestational age for women assigned to no-cerclage and women who received cerclage. Notably, at 24 weeks the proportion of women yet to deliver is much higher for those taking progesterone than for those not taking progesterone in the no-cerclage group (figure 2).

Of the 148 women assigned to receive cerclage, 10 did not undergo surgery. Of the 152 women assigned to the no-cerclage group, 14 received a post-randomization stitch. Thus, 152 women actually received cerclage and 148 did not. We observed similar results when considering actual cerclage placement and non-placement (data not shown). For example, 17P was associated with a non significant OR of 0.70 (95% CI 0.23, 2.09) for perinatal death in the cerclage group.

Comment

17P in women with a prior SPTB and a cerclage for short CL < 25 mm at 16-22 6/7 weeks was not associated with an effect on PTB < 35 weeks. Several trials (9,10) have demonstrated that 17P prevents SPTB in women with prior PTB, and this is now recommended (14). A meta-analysis (8) of randomized trials, and individual trial (5) and,

more importantly, one large individual trial (3) have shown that cerclage prevents SPTB in women with a prior SPTB if they develop a short CL<25mm. Our data do not support the hypothesis that these two interventions (17P and cerclage) are cumulative in their benefit in this highly selected patient population.

In the absence of cerclage, 17P was associated with a reduction in previable birth and perinatal mortality in women with a prior SPTB and a CL <25 mm. Our results are in agreement with the benefit shown of 17P in women with prior SPTB in general (9). The effect of 17P for asymptomatic women with a short CL has not yet been reported, but is under much current investigation. Vaginal progesterone has also been associated with prevention of preterm birth in women with a short CL (13,15), but the effect of cerclage was not evaluated in these two trials.

The possible relationship between 17P and ultrasound-indicated cerclage has not been studied before, so this is a strength of our study. A prior study (16) reported the effect of 17P in women with cerclage, but could not distinguish between cerclage placed for history- or ultrasound- or even physical exam-indications. Another strength is the use of 17P was actually confirmed with measure of compliance. While the clinical trial was not powered for this secondary analysis, we did plan for it near the inception of the primary study. Because the sample size was predetermined by the results of the clinical trial, this study may have had insufficient power to detect a clinically significant effect of 17P at other preterm gestational age cutoffs. 17P was associated with lower incidences of the primary and secondary outcomes, but rarely were the analyses significant. If one examines Tables 2 and 4, the rates of early PTB at 28 and 32 weeks show that for women with no cerclage and no 17P, the rates of PTB are 25% and 34%, respectively; if one performs cerclage those rates drop to 17% and 25%; if one does not perform cerclage but starts 17P the rates also drop and are similar at 15% and 21%; and then finally if one does both cerclage and 17-OHP the rates appear the lowest at 9% and 17%. The OR for benefit from 17P is about 0.5 for both sets of patients with and without cerclage. It's true that the OR for these effects were not statistically significant, with upper limits of the OR varying between 1.14 and 1.51, but this may be due to Beta error. Post-hoc analysis reveals that, to detect a change in the rate of PTB<35weeks from 34% to 30%, 2134 women are needed in each 17P and non-17P group (for the cerclage arm) to have 80% power. Similarly, for 80% power, to detect a change in the rate of PTB<32weeks from 25% to 17%, 406 women are needed in each arm, and for a difference in the rate of PTB<28weeks from 17% to 9%, 276 women are needed in each arm. In a larger study, these observed effects may be significant; the observed OR effects are consistent in both groups and are therefore suggestive of possible benefit of both therapies together. A more definitive study of this would be a 4-armed randomized factorial trial of placebo-no-cerclage, cerclage-no-17P, 17P-no-cerclage, and cerclage plus 17P.

Only one trial has compared the effect on SPTB of ultrasound-indicated cerclage versus 17P in women with a short CL<25mm (17). The cumulative effect of cerclage with 17P could therefore not be evaluated. No differences in effect were noted between 17P and cerclage groups, but the trial did not recruit the planned sample size because it was felt 'impractical, unethical and unreasonable' to withhold 17P from women (in the cerclage group) with prior SPTB. Cerclage was more effective at preventing SPTB compared to 17P in women with CL<15mm. This is in agreement with our results, showing that 17P is effective at 15-24mm, but may not be as effective at shorter cervical lengths.

It is yet unclear if progesterone prevents a cervix from shortening. In asymptomatic women with prior PTB, 17P prophylaxis was not associated with an effect on cervical length shortening in one study (18), while in another, it was associated with significant preservation of cervical length (19). In women with preterm labor, 17P injections instead prevented

further cervical shortening (20). If 17P prevented cervical shortening from occurring, then women who responded best to 17P may never have developed a CL < 25mm and therefore this study may have inadvertently "selected" for women who are not "responders" to 17P. In them, this would obviate the need for ultrasound-indicated cerclage, and justify using both approaches (17P for prior SPTB, and cerclage for short CL) for prevention of preterm birth in women with a prior SPTB.

Several questions remain for use of progesterone and cerclage for prevention of preterm birth. Many factors may dictate management, such as prior obstetrical/gynecological history and risk factor for preterm birth, number of fetuses, degree of cervical shortening and gestational age at detection, etc. For example, cerclage may be better for shorter CL (3,17), while progesterone may be more efficacious for women with lesser degrees of cervical shortening. (13) It is important to highlight that in our study women were screened serially by ultrasound for a short CL, and studies who screen only once may have different results. Better understanding of the mechanisms of 17P and of cerclage will help the clinician understand further how these two interventions are best employed. The fact that cerclage may have more of a mechanical mechanism while 17P may work more by its anti-inflammatory properties might make their effect cumulative. The role of inflammation (21), infection, genetic markers, enzymes (e.g. sialidases, collagenases), FFN, and other factors will play a larger role in selection of these therapies for the woman with a short CL in the near future. (22,23) More research is also needed to look at interactions of several possible therapies for short CL, such as cerclage, progesterone, indomethacin, antibiotics, and others. Several trials and studies are currently ongoing and will soon provide more evidence to be able to answer these questions and guide clinical care.

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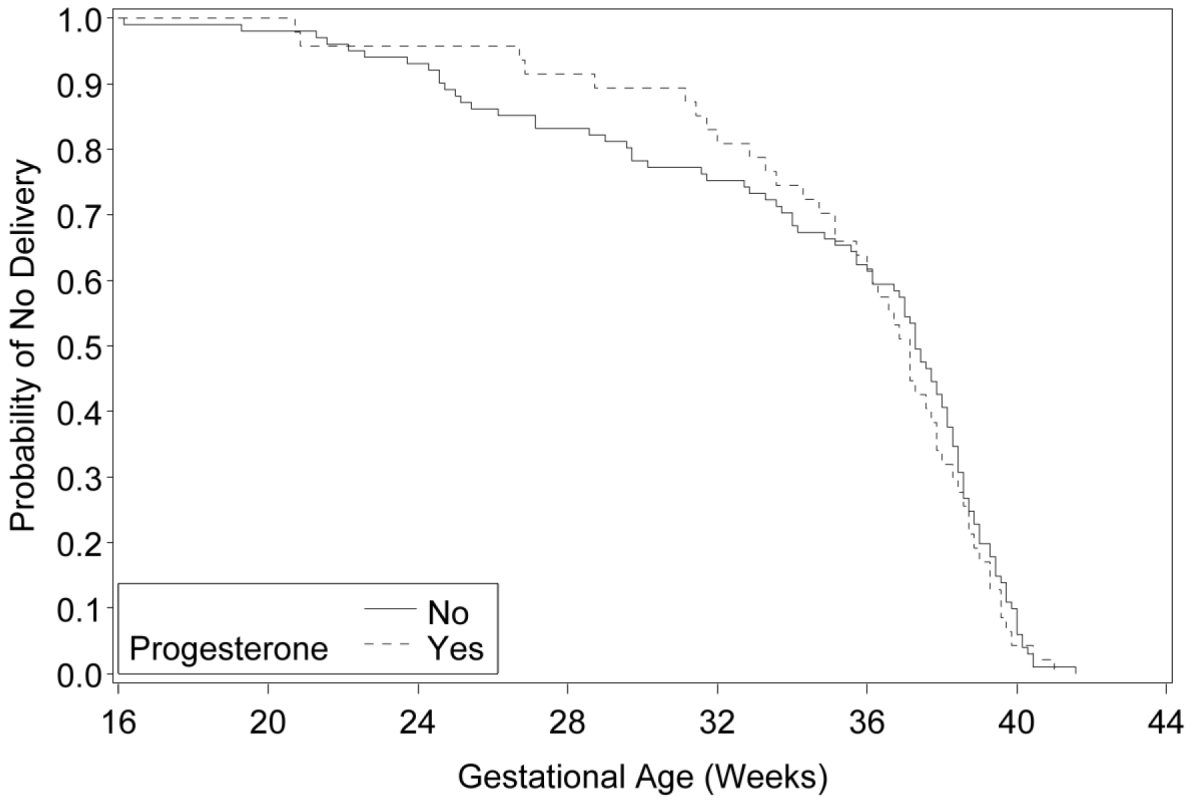

Figure 1.
Time to delivery for women with and without progesterone use, randomized to **cerclage** (p=0.639).

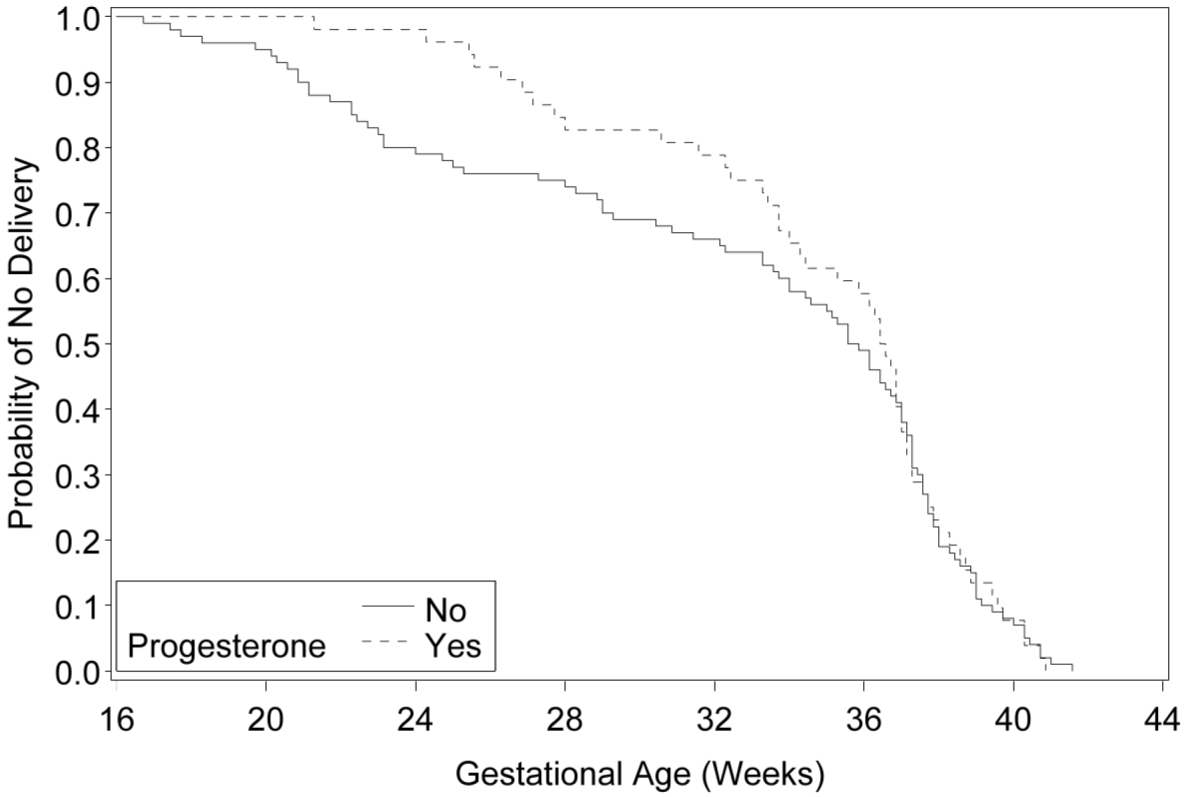

Figure 2.
Time to delivery for women with and without progesterone use, randomized to **no cerclage** (p=0.694)

Table 1

Baseline characteristics by actual progesterone use for 148 women with prior SPTB, short CL <25mm at 16-22 6/7weeks, and randomized to **cerclage** placement.

	17P (n = 47)	No 17P (n = 101)	P value
Maternal age (y)	26.9 (6.3)	26.1 (5.1)	0.38
Race/ethnicity*			<0.01
Black (non-Hispanic)	26 (55)	54 (53)	
White (non-Hispanic)	13 (28)	12 (12)	
Hispanic	2 (4.3)	25 (25)	
Other	6 (13)	10 (10)	
Cigarette use	12 (26)	12 (12)	0.036
Any drug abuse	3 (6)	2 (2)	0.33**
One or more prior induced abortion	7 (15)	18 (18)	0.66
Years of education	12.5 (2.1)	11.8 (3.0)	0.15
Gestational age of qualifying birth (weeks)	23.2 (4.8)	24.7 (4.8)	0.08
Gestational age at randomization (weeks)	18.9 (1.9)	19.6 (1.9)	0.054
Cervical length at randomization (mm)	19.0 (5.5)	18.5 (6.6)	0.64
Total number of vaginal sonograms	2 (1, 4)†	2 (1, 4)†	0.03

Data presented as mean± 1 SD, or n (%).

*Race and ethnic group are self-reported

**Fisher's exact test

†Median and interdecile range

Table 2

Perinatal outcomes and actual progesterone use for 148 women randomized to **cerclage**.

	17P (n = 47)	No 17P (n = 101)	P value	OR (95% CI)
Preterm birth < 35 weeks	14 (30)	34 (34)	0.64	0.84 (0.40, 1.77)
Birth < 7 days from randomization	0 (0)	4 (4)	0.31*	0.23 (0.01, 4.32)
Previable birth < 24 weeks	2 (4)	7 (7)	0.72*	0.60 (0.12, 2.99)
Preterm birth < 28 weeks	4 (9)	17 (17)	0.18	0.46 (0.16, 1.45)
Preterm birth < 32 weeks	8 (17)	25 (25)	0.29	0.62 (0.26, 1.51)
Preterm birth < 37 weeks	23 (49)	43 (43)	0.47	1.29 (0.65, 2.59)
Perinatal death	3 (6)	10 (10)	0.76*	0.62 (0.16, 2.37)

Data presented as n (%).

* Fisher's exact test

Table 3

Baseline characteristics by actual progesterone use for 152 women with prior SPTB, short CL <25mm at 16-22 6/7 weeks, randomized to **no cerclage**.

	17P (n = 52)	N0 17P (n = 100)	P value
Maternal age (y)	26.3 (4.5)	26.8 (5.3)	0.56
Race/ethnicity*			0.25
Black (non-Hispanic)	32 (62)	60 (60)	
White (non-Hispanic)	13 (25)	15 (15)	
Hispanic	4 (7.7)	13 (13)	
Other	3 (5.8)	12 (12)	
Cigarette use	12 (23)	17 (17)	0.37
Any drug abuse	6 (11.5)	4 (4)	0.09**
One or more prior induced abortion	15 (29)	10 (10)	0.0029
Years of education	12.8 (1.8)	11.5 (2.6)	0.0011
Gestational age of qualifying birth (weeks)	24.0 (5.0)	24.7 (4.6)	0.36
Gestational at randomization (weeks)	19.6 (2.0)	19.4 (2.1)	0.56
Cervical length at randomization (mm)	19.5 (5.0)	19.4 (5.5)	0.87
Total number of vaginal sonograms	3 (1, 4)†	2 (1, 4)†	0.21

Data presented as mean± 1 SD, or n (%).

*Race and ethnic group are self-reported

**Fisher's exact test

†Median and interdecile range

Table 4

Perinatal outcomes by actual progesterone use for 152 women randomized to **no cerclage**.

	17P (n = 52)	No 17P (n = 100)	P value	OR (95% CI)
Preterm birth < 35 weeks	20 (39)	44 (44)	0.51	0.80 (0.40, 1.58)
Birth < 7 days from randomization	0 (0)	3 (3)	0.55*	0.27 (0.01, 5.23)
Previable birth < 24 weeks	1 (2)	20 (20)	0.0022	0.08 (0.01, 0.60)
Preterm birth < 28 weeks	8 (15)	25 (25)	0.17	0.55 (0.23, 1.31)
Preterm birth < 32 weeks	11 (21)	34 (34)	0.10	0.52 (0.23, 1.14)
Preterm birth < 37 weeks	31 (60)	59 (59)	0.94	1.03 (0.52, 2.03)
Perinatal death	2 (4)	23 (23)	0.0029	0.14 (0.03, 0.61)

Data presented as n (%).

*Fisher's exact test