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A randomized trial of cerclage vs. 17 α-hydroxyprogesterone caproate for treatment of short cervix*,**

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Abstract

Objective: To determine pregnancy outcome in patients with short cervix on transvaginal ultrasound between 16 and 24 weeks' gestation treated with McDonald cerclage compared to weekly intramuscular injections of 17 α-hydroxyprogesterone caproate (17OHP-C).

Methods: From November 2003 through December 2006, asymptomatic, singleton pregnancies were screened with transvaginal ultrasound between 16–24 weeks' gestation. Patients with a cervical length (CL) ≤25 mm were offered enrollment. Patients were randomly assigned to treatment with McDonald cerclage or weekly intramuscular injections of 17OHP-C. The primary outcome was spontaneous preterm birth (PTB) prior to 35 weeks' gestation.

Results: Seventy-nine patients met inclusion criteria; 42 were randomly assigned to the cerclage and 37 to 17OHP-C. Spontaneous PTB prior to 35 weeks' gestation occurred in 16/42 (38.1%) of the cerclage group and in 16/37 (43.2%) of the 17OHP-C group (relative risk, 1.14 95% CI, 0.67, 1.93). A post hoc analysis of patients with a prior PTB showed no difference in spontaneous PTB <35 weeks between groups. A similar analysis of patients with a CL≤15 mm showed a reduction in spontaneous PTB <35 weeks in the cerclage group (relative risk 0.48, 0.24–0.97).

Conclusion: Women with CL ≤25 mm in the second-trimester appear to have similar risks of delivering prior to 35 weeks' gestation when treated with 17OHP-C or McDonald cerclage. However, cerclage may be more effective in preventing spontaneous PTB in women with CL≤15 mm.

Keywords: Cervical length; 17 α-hydroxyprogesterone caproate; spontaneous preterm birth; short cervix.

Introduction

The pathophysiology of spontaneous preterm birth (PTB) continues to elude investigators as the rate of premature birth continues to rise in the US [10]. Measurement of cervical length (CL) by transvaginal ultrasound is a powerful tool to predict spontaneous PTB [13, 16]. It enables the clinician to visualize the lower uterine segment being pulled up into the uterine corpus, the unrolling of the endocervical os/sphincter and the excavation of the internal endocervical canal. The short cervix has been extensively studied and described as the anatomical manifestation of a final common pathway in the pathologic syndrome of preterm parturition [18, 20].

The two most common treatments for an ultrasound-diagnosed short cervix in the mid-trimester are cervical cerclage and progesterone supplementation. Cerclage therapy continues to be utilized despite clinical trials challenging its effectiveness [4, 21, 22]. Progesterone supplementation has become a standard treatment to prevent recurrent spontaneous PTB, and most recently has been shown to reduce spontaneous PTB by 44% in women with a short cervix [6, 14]. However, no studies to date have compared the two treatments in a randomized trial.

We hypothesized that patients who received weekly intramuscular injections of 17OHP-C will experience fewer spontaneous PTB prior to 35 weeks' gestation compared to patients treated with cerclage. The purpose of this study was to determine pregnancy outcomes in patients with ultrasound-diagnosed short cervix in the mid-trimester receiving medical therapy with 17OHP-C compared to surgical therapy with McDonald cerclage.

Material and methods

Under an Institutional Review Board approved protocol, singleton pregnancies presenting to the Lehigh Valley Hospital Perinatal Testing Center between November 2003 and December

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2006 with risk factors for spontaneous PTB were screened with serial transvaginal ultrasound beginning at 16 weeks gestation. Risk factors for PTB included history of spontaneous PTB, second-trimester pregnancy loss, previous cervical surgery (conization or loop excision), or documented uterine anomaly. Also low-risk, asymptomatic singleton pregnancies between 16 and 24 weeks' gestation were screened for evidence of cervical shortening with transabdominal ultrasound as part of routine anatomical survey. If the cervix appeared short ($\leq$25 mm) transabdominally, a transvaginal ultrasound was performed. Transvaginal CL measurement was obtained using the standardized technique described by Rust et al. [21].

Patients with ultrasonographic evidence of short cervix, defined as a transvaginal CL $\leq$25 mm, were offered enrollment into study. Exclusion criteria included any known fetal chromosomal or structural anomaly, multiple gestation, known allergy to progesterone, ruptured membranes, vaginal bleeding, evidence of an active intra-amniotic infection (diagnosed clinically or by amniocentesis), prolapse of endocervical membranes beyond the external cervical os, persistent uterine activity accompanied by cervical change, or an obstetrically indicated delivery.

Patients who met the study inclusion criteria and provided informed written consent were enrolled in the study. Management of the study population is detailed in Figure 1. Patients were hospitalized for inpatient bed rest, transabdominal amniocentesis to exclude intra-amniotic infection, a complete blood count, a pelvic examination, cervico-vaginal fetal fibronectin sampling 24 h after the last pelvic exam, urogenital cultures for *Chlamydia trachomatis, Neisseria gonorrhea, Mycoplasma hominis, Ureaplasma urealyticum*, Group B streptococcus, *Gardnerella vaginalis*, and a urine culture. Empiric treatment with indomethacin (100 mg orally followed by 50 mg every 6 h) and clindamycin (900 mg intravenous every 8 h) was initiated for 48–72 h. After this initial treatment, all patients underwent repeat transvaginal ultrasound to exclude rapidly progressing cervical shortening and prolapse of membranes beyond the external cervical os.

Randomization was accomplished by computer generated assignment to McDonald cerclage or 17OHP-C. Assignments were concealed in sequentially numbered opaque envelopes by a co-ordinator not involved in screening, enrollment, or randomization. The randomization sequence was secured by administrative staff until enrollment was terminated. Participants were enrolled by maternal fetal medicine physicians or certified nurse practitioners. Randomization was accomplished by handing out the sequentially numbered opaque envelops. Due to the intrinsic nature of the study design, there was no masking in this trial. Patients were assigned to either McDonald cerclage (active control group) or weekly administration of 17OHP-C (intervention group). The cerclage group received a single stitch McDonald cerclage with 1-0 Prolene (Ethicon, Inc. Somerville, NJ) placed by a maternal-fetal medicine physician under regional anesthesia. If necessary, prolapse of endocervical membranes was reduced by either retrograde filling the bladder with 500 cc of sterile normal saline solution and/or transcervical placement of a 16F Foley catheter.

The 17OHP-C group received weekly intramuscular injections of 250 mg 17 α-hydroxyprogesterone caproate by a registered nurse at the weekly follow-up CL measurements. Compliance was ensured by weekly contact with the patient. Any missed appointment was followed up with perinatal nurse contact and

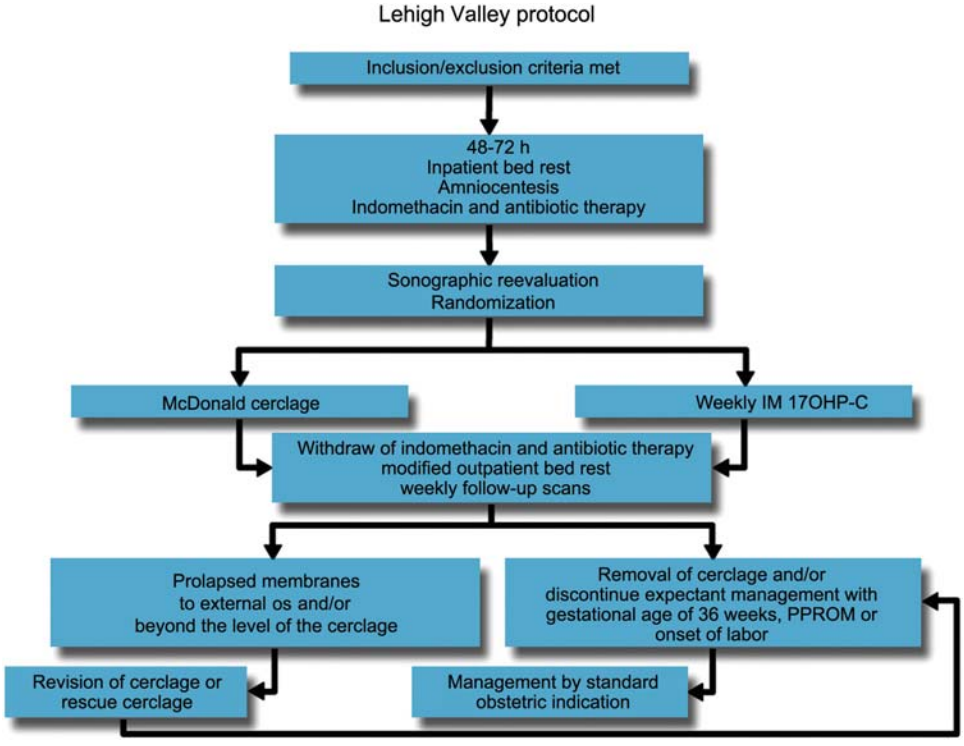

Figure 1 Treatment protocol. PPROM = preterm premature rupture of membranes.

evaluation of access to care. These injections were started upon randomization and administered weekly until 36 weeks' gestation.

Patients were educated to promptly report signs and symptoms of preterm labor, advised to follow modified bed rest, and were scheduled for weekly outpatient follow-up visits with transvaginal ultrasound. At gestational ages prior to 24 weeks, a rescue cerclage was allowed under this protocol if membranes prolapsed beyond the level of the cerclage in the cerclage group or if membranes prolapsed beyond the level of the external os in the 17OHP-C group. Treatment was discontinued at 36 weeks' gestation, including cerclage removal if applicable. Cerclage was removed on an emergent basis for the following clinical scenarios: rupture of membranes, preterm labor placing tension of the cerclage and refractory to tocolytic therapy, preterm labor with contraindications to tocolytic therapy, clinical diagnosis of chorioamnionitis or abruptio placentae. Antepartum, intrapartum, and postpartum care were by standard obstetrical practice. No ultrasound-indicated cerclages were placed outside the study protocol.

The primary outcome was spontaneous PTB prior to 35 weeks' gestation. Secondary outcomes included obstetrical complications and neonatal morbidity and mortality. Obstetric complications included chorioamnionitis, abruptio placentae, preterm premature rupture of membranes (PPROM), need for a rescue procedure, days from study enrollment to delivery, and gestational age at delivery. Neonatal morbidity was stratified as follows: no morbidity was defined as no neonatal intensive care admission and routine newborn care; mild morbidity was defined as neonatal intensive care admission without severe morbidity; severe morbidity was defined as life threatening morbidity including respiratory distress syndrome requiring mechanical ventilation >24 h, intraventricular hemorrhage, neonatal sepsis, or necrotizing enterocolitis. Perinatal death included any stillbirth or neonatal death during the study period. Study group comparisons included maternal age, race, parity, insurance type, and gestational age at study entry. Risk factors for spontaneous PTB analyzed included prior second trimester loss between 16 and 23 weeks' gestation, prior spontaneous PTB between 24 and 36 weeks' gestation, earliest PTB, prior cervical surgery, fetal fibronectin status, positive urogenital culture, müllerian anomaly, digital cervical exam, width and depth of prolapse of fetal membranes into the endocervical canal, distal CL and post-cerclage CL. A post hoc subgroup analysis comparing the effect of cerclage to 17OHP-C on gestational age at delivery in patients with a CL ≤ 15 mm and a previous PTB was performed.

In a previous study, the incidence of PTB in a similar cohort of patients (asymptomatic, short cervix) who received cerclage was $\sim 45\%$ [4]. We calculated to have 80% power to detect a 50% reduction in spontaneous PTB prior to 35 weeks' gestation, 77 patients were required for each study arm with a two-tailed α-0.05. An interim analysis was planned and completed when half the study participants were enrolled and delivered.

Tests of association between the cerclage and 17OHP-C groups were performed using Pearson's χ^2, Fisher's exact, and Student's *t*-test (or non-parametric equivalents) where appropriate. The relative risks of developing specific complications in the cerclage group as compared to the 17OHP-C group were calculated. Cox proportional hazards models was constructed to evaluate for differences between the two treatment groups for delivery prior to 35 weeks. Kaplan-Meier curves were generated to compare gestational age at birth by treatment group. All statistical analysis was performed on an intention-to-treat basis using STATA 9.2 (StataCorp LP, College Station, TX) and used a two-tailed α of 0.05.

Results

Of the 91 consecutive patients who met study inclusion criteria and were offered enrollment into the study protocol, eight declined randomization, two experienced PPROM prior to randomization, and two had evidence of

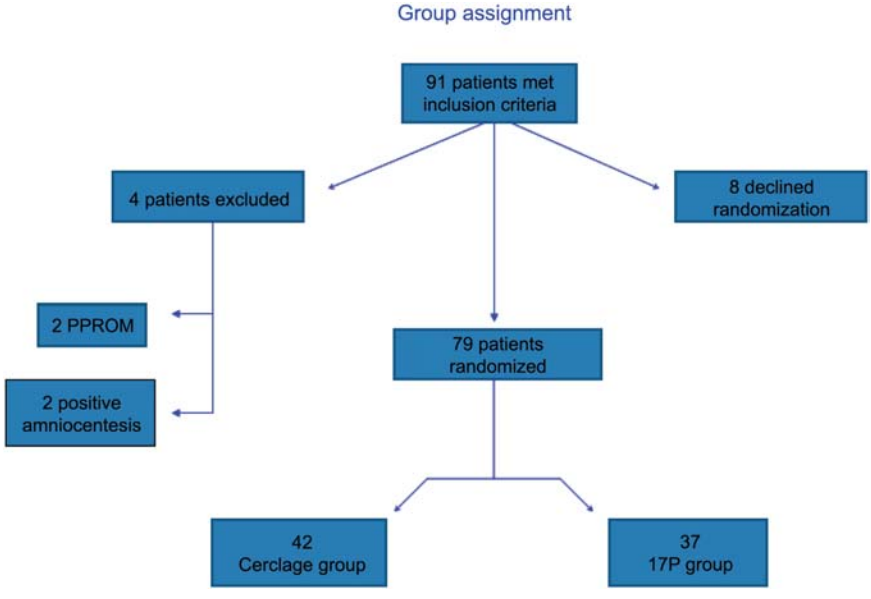

Figure 2 Distribution of study participants.

intra-amniotic infection diagnosed by amniocentesis (positive amniotic fluid culture and intra-amniotic glucose <10 mg/dL). Seventy-nine patients remained: 42 randomized to the cerclage group and 37 randomized to the 17OHP-C group (Figure 2). There were no patients who were lost to follow-up or non-compliant with 17OHP-C therapy. There were no indicated PTB in either study group. There were no complications from amniocentesis or any adverse clinical outcomes to indomethacin or antibiotic therapy. None of the patients in either study group demonstrated rapidly progressing cervical shortening or prolapse of endocervical membranes beyond the external os on repeat transvaginal ultrasound after the initial 48–72 h treatment period.

There were no differences in demographic characteristics of patients in each study group (Table 1). There were no statistically significant differences between the two treatment groups with regard to history of a previous second trimester loss, previous PTB, earliest gestational age of previous PTB, prior cervical surgery (Table 2). Digital pelvic examinations and transvaginal CL measurements at study enrollment were similar between both groups. There was no difference in distal CL or width of endocervical funnel between groups. However, patients in the cerclage group had a more pronounced prolapse of chorio-amniotic membranes (P = 0.02); while patients in the 17OHP-C group were more likely to have bacterial vaginosis (P = 0.04). The mean post-cerclage CL was 35 mm, compared to a 14.5 mm mean pre-cerclage CL. There was no difference in genital culture results between the two study groups.

Analysis of obstetric and neonatal outcome demonstrated no difference between the cerclage group and the 17OHP-C group with respect to chorioamnionitis, abruptio placentae, PPROM, need for rescue procedure, or neonatal morbidity (Table 3). The primary outcome of spontaneous PTB prior to 35 weeks' gestation occurred equally in both study groups (38.1% vs. 43.2%; relative risk, 1.14; 95% CI, 0.67, 1.93). Mean gestational age at delivery was similar in both study groups with the cerclage group and 17OHP-C group delivering at 32.9 ± 6.4 weeks and 33.0 ± 5.9 weeks, respectively (P = 0.96).

Cox regression analysis adjusting for gestational age at trial enrollment demonstrated no significant difference in delivery prior to 35 weeks' gestation (P = 0.75). Kaplan-Meier curve is shown in Figure 3. There was no statistical difference in women with CL ≤25 mm delivering prematurely at gestational ages prior to 24, 28, 32, 35, or 37 weeks, respectively. However, there did appear to be a benefit to cerclage when evaluating those patients with a CL ≤15 mm (n = 37; 22 cerclage and 15 17OHP-C). The cerclage group experienced a significant reduction

Table 1 Demographic characteristics.

Characteristic	Cerclage (n = 42)	17OHP-C (n = 37)
Age (years)	29.6 ± 7.15	27.6 ± 6.58
Race		
Caucasian	18 (42.9)	16 (43.2)
Hispanic	16 (38.1)	11 (29.7)
African American	7 (16.7)	9 (24.3)
Other	1 (2.4)	1 (2.7)
Private insurance	16 (38.1)	15 (40.5)
Multiparity	29 (69.0)	22 (59.5)
Gestational age at entry (week)	20.0 ± 6.41	20.9 ± 5.89

Data are n (%) or mean ± standard deviation.

Table 2 Risk factors for spontaneous preterm birth.

Variable	Cerclage (n = 42)	17OHP-C (n = 37)	P-value
Prior 2nd trimester loss 16–23 weeks	9 (21.4)	6 (16.2)	0.58
Prior preterm birth 24–36 weeks	16 (16)	11 (29.7)	0.48
Earliest preterm birth (week)	25.3 ± 5.9	25.7 ± 5.4	0.83
Distal cervical length (mm)	14.5 ± 6.6	16.8 ± 5.1	0.11
Width of funnel (mm)	13.4 ± 4.9	14.3 ± 7.7	0.56
Depth of funnel (mm)	20.1 ± 11.2	14.2 ± 7.4	0.02
Digital examination			
Dilatation (cm)	<1 cm	<1 cm	0.84
Effacement	25%	37%	0.08
Station	–3	–3	0.48
Prior cervical surgery	12 (28.6)	5 (13.9)	0.17
Müllerian anomaly	0 (0.0)	0 (0.0)	0.99
Bacterial vaginosis	2 (4.8)	8 (21.6)	0.04
U. urealyticum*	23 (54.8)	21 (60.0)	0.64
M. hominis	8 (19.1)	9 (25.7)	0.58
Group B streptococcus**	9 (22.0)	4 (11.8)	0.25
C. trachomatis	0 (0.0)	0 (0.0)	0.99
N. gonorrhea	1 (2.4)	0 (0.0)	0.35
+ Fetal fibronectin***	11 (29.7)	8 (25.0)	0.66

Data are n (%) or mean ± standard deviation. *Data available on 77 out of 79 patients. **Data available on 75 out of 79 patients. ***Data available on 69 out of 79 patients.

Table 3 Primary and secondary outcomes.

Outcome	Cerclage (n = 42)	17OHP-C (n = 37)	RR (95% CI)	P-value
Gestational age at delivery (weeks)	32.9 ± 6.4	33.0 ± 5.9		0.96
Days from enrollment to birth	92.2 ± 40.9	84.8 ± 38.6		0.41
Chorioamnionitis	12 (28.6)	8 (21.6)	0.76 (0.35, 1.65)	
Abruptio placentae	3 (7.5)	6 (17.1)	2.27 (0.61, 8.44)	
PPROM	13 (32.5)	13 (37.1)	1.14 (0.61, 2.12)	
Rescue procedure	4 (9.5)	5 (13.5)	1.42 (0.41, 4.89)	
Preterm birth CL ≤25 mm				
<37 weeks gestation	22 (52.4)	22 (59.4)	1.14 (0.77, 1.68)	
<35 weeks gestation	16 (38.1)	16 (43.2)	1.14 (0.67, 1.93)	
<32 weeks gestation	15 (35.7)	13 (35.1)	0.98 (0.54, 1.79)	
<28 weeks gestation	10 (23.8)	7 (18.9)	0.79 (0.34, 1.88)	
<24 weeks gestation	5 (11.9)	3 (8.1)	0.68 (0.17, 2.66)	
Preterm birth CL ≤15 mm*				
<37 weeks gestation	10 (45.5)	13 (86.7)	0.52 (0.32, 0.86)	
<35 weeks gestation	7 (31.8)	10 (66.7)	0.48 (0.24, 0.97)	
<32 weeks gestation	7 (31.8)	8 (53.3)	0.60 (0.27, 1.29)	
<28 weeks gestation	5 (22.7)	5 (33.3)	0.68 (0.24, 1.95)	
<24 weeks gestation	3 (13.6)	3 (20.0)	0.68 (0.17, 2.75)	
Neonatal morbidity (%)				0.34
None	28 (66.7)	21 (56.8)		
Mild	1 (2.3)	5 (13.5)		
Severe	9 (21.4)	7 (18.9)		
Death	5 (11.9)	4 (10.8)		

Data are n (%) or mean ± standard deviation. PPROM = preterm premature rupture of membranes, CL = cervical length, RR = relative risk, CI = 95% confidence interval. *Cerclage (n = 22); 17OHP-C (n = 15).

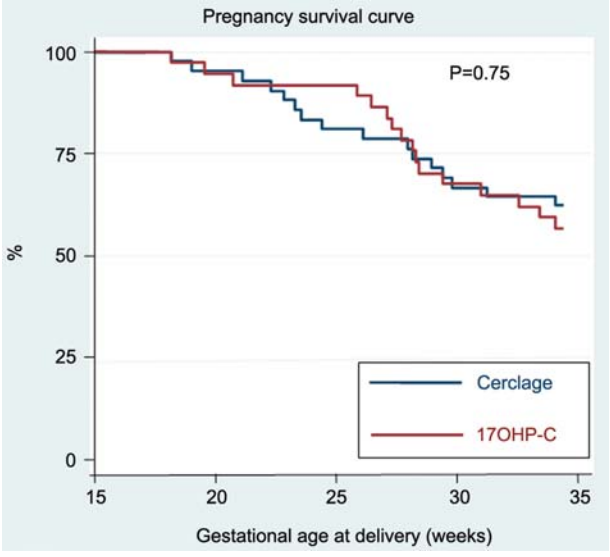

Figure 3 Kaplan-Meier survival curve analysis with respect to gestational age at delivery. Blue line, cerclage; Red line, 17OHP-C.

in spontaneous PTB <35 weeks (31.8%) compared to the 17OHP-C group (66.7%) (Table 3).

Perinatal outcome for the eight patients who declined study enrollment and treated with expectant management with serial transvaginal surveillance were similar to the 17OHP-C and cerclage groups. The four patients receiving a cerclage revision delivered at 21, 24, 24, 31 weeks, respectively. The five patients initially assigned to 17OHP-C who received a rescue cerclage delivered at 28, 35, 37, 38, 39 weeks, respectively. An analysis of the 42 patients with a previous spontaneous PTB showed no difference in primary and secondary pregnancy outcomes between treatment groups.

Discussion

The diagnosis of midtrimester cervical shortening is a puzzle for practicing clinicians. Numerous studies have demonstrated the reliability and reproducibility of CL measurements in providing a risk assessment of spontaneous PTB [2, 11–13, 16]. However, despite its usefulness in identifying those at highest risk of premature birth, the American College of Obstetricians and Gynecologists has cautioned against the routine use of transvaginal ultrasound due to the lack of effective treatment options [1].

However, new data have been published in an attempt to validate progesterone supplementation as an effective treatment for cervical shortening. Fonseca et al. [6] demonstrated a 44% reduction in spontaneous PTB prior to 34 weeks in patients with a CL ≤15 mm using 200 mg intravaginal progesterone daily between 24 and 34 weeks' gestation. Another randomized controlled trial utilized 100 mg of daily intravaginal progesterone sup-

plementation in high-risk singleton pregnancies with a previous PTB, cervical insufficiency or a Müllerian anomaly, showing a 49% reduction of spontaneous PTB in the progesterone group [7].

Our goal was to determine pregnancy outcome in asymptomatic women with short cervix in the mid-trimester who were randomly assigned to treatment with McDonald cerclage compared to weekly intramuscular injections of 17OHP-C. This study did not demonstrate a significant improvement in reducing spontaneous PTB prior to 35 weeks' gestation among participants with a CL $\leq$25 mm who received 17OHP-C as compared to McDonald cerclage. We found no difference in obstetric or neonatal outcomes, including our primary outcome of spontaneous PTB prior to 35 weeks' gestation in our patient population.

There are several possible explanations for our results and analysis of these data should be interpreted with caution. First, we recognize that we are underpowered to detect a 50% reduction in spontaneous PTB between study groups. We anticipated randomizing 160 patients to allow for attrition during the study. However, the trial was stopped early by the authors because after 3 years of recruitment, an interim analysis showed no difference in outcome between treatment groups. With new data being presented regarding the benefits of progesterone supplementation, we felt it was impractical, unethical, and unreasonable to withhold progesterone from one study group to achieve our enrollment goal. Thus, we may be unable to identify a benefit of 17OHP-C compared to cerclage due to type II error. We felt that by publishing these data, it would allow for inclusion in a meta-analysis with other similarly designed clinical trials. Alternatively, weekly supplementation with 250 mg of 17OHP-C may be as effective as cerclage therapy in preventing spontaneous PTB in patients with CL $\leq$25 mm.

There are discrepancies in the literature regarding the optimal dose and formulation of progesterone supplementation in reducing spontaneous PTB. Patient heterogeneity, use of different progestational agents, and route of delivery may account for the diversity in outcomes. We chose the synthetic caproate esther formulation of progesterone (17OHP-C) because it has been shown to reduce spontaneous PTB in high-risk patients with a previous PTB. 17OHP-C differs from natural progesterone in composition and route of administration. Since 17OHP-C is a long acting progestogen that is only structurally related to natural progesterone, it may not convey identical clinical response as natural progesterone. Also, local vaginal absorption of natural progesterone may quell site specific inflammation in the cervico-vaginal microenvironment. A different dose, formulation or route of delivery may have a more beneficial effect on reducing spontaneous PTB.

Although, progesterone has anti-inflammatory effects and plays a key role in uterine quiescence, the precise mechanism of how 17OHP-C prevents premature parturition is poorly understood. Investigators have identified anti-inflammatory properties, prevention of prostaglandin production, altered gene expression, inhibition of oxytocin binding and gap junction formation, as progesterone's contribution of pregnancy maintenance [3, 8, 9, 15]. Progesterone may also contribute to the cervix's ability to act as a guard against the upward passage of potentially harmful agents and to maintain the competence of the lower uterine segment and endocervical sphincter. However, if a subacute upper genital tract infection is present once the cervix is short and funneled, as in our study, 17OHP-C may not be effective in reducing the rate of spontaneous PTB in these patients.

The strength of this study is that it is a randomized trial comparing two treatments for ultrasound-diagnosed short cervix. We compared intervention with 17OHP-C to McDonald cerclage. The Kaplan-Meier survival curve demonstrates no apparent difference in gestational age at delivery or spontaneous PTB prior to 35 weeks' gestation, corresponding well with the perinatal outcomes data between study groups. 17OHP-C appears to be at least as effective as cerclage in treating patients with CL $\leq$25 mm. However, cerclage may be superior to 17OHP-C in reducing premature birth in patients with shorter CL ($\leq$15 mm) due to initiation of uterine myometrial contractions [19].

We caution interpretation of these data as conclusive until a large, adequately powered multi-center trial can be performed to address this clinical question. Although the benefit of cerclage in women with a CL $\leq$15 mm is in agreement with recently published data, our study was conservatively underpowered to show if weekly 17OHP-C was superior to cerclage in reducing spontaneous PTB [17]. Weekly injections of 17OHP-C may be insufficient to extend pregnancy in women with shortened CL in the midtrimester, but daily vaginal progesterone therapy may be a better consideration. These data, coupled with recently published data on this subject [5–7, 17], will hopefully encourage more investigation comparing medical and surgical treatments for short cervix.

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