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Role of 17-Hydroxyprogesterone Caproate as an Adjuvant Therapy in Women With Cervical Cerclage for Prevention of Preterm Delivery: A Retrospective Matched Controlled Study

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Abstract

Background: We aimed to evaluate the role of 17-hydroxyprogesterone caproate (17-OHP) as an adjuvant therapy with cervical cerclage for prevention of preterm delivery.

Methods: We conducted a retrospective case-control study from July 2010 to December 2014 on patients who received 17-OHP with cervical cerclage (group 1). This group was compared to matched control patients who had cervical cerclage only (group 2). The maternal and fetal outcomes were compared between the two groups. All data were collected using SPSS® Mac version 23.

Results: A total of 122 singleton pregnant women with cervical cerclage were observed; among them, 64 patients used 17-OHP with cerclage, and 58 patients received cerclage only. Our analysis demonstrated that there was no significant difference in the outcome between the two groups. Characteristics compared in both groups such as cervical length, miscarriage rates, gestational age at time of delivery, mode of delivery, and other variables did not meet any statistical significance. Preterm outcome at 37, above 37, and below 37 weeks, was similar in both groups. In fetal outcome, the only statistical difference was the Apgar score of neonates at 1 min that was better in group 1 (P = 0.04), but at 5 min, the Apgar score did not show any difference (P = 0.7).

Conclusions: In our study, we found no additional benefits of adjuvant 17-OHP on maternal, fetal outcome, or preterm delivery outcome in comparison to cervical cerclage alone. More prospective randomized studies are recommended to further investigate this matter.

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Introduction

Preterm labor (PL) and prematurity are common problems that affect approximately 5-18% of pregnancies [1]. Prematurity is associated with early and late neonatal complications such as respiratory distress syndrome, sepsis, intra-ventricular hemorrhage, necrotizing enterocolitis, cerebral palsy and neuro-developmental delay [2].

Mothers may experience post-partum depression and anxiety [3]. All these are associated with increased health care costs, and are still challenging tasks to healthcare providers [4].

Different treatment modalities have been used to decrease the rate preterm labor, notably cervical cerclage that has been proven to decrease the incidence of preterm birth.

In a meta-analysis of five randomized clinical trials of women diagnosed with a short cervix < 2.5 cm prior to 24 weeks of gestation, cervical cerclage was compared to expectant management, and researchers concluded that preterm birth < 35 weeks was lower in women who received cervical cerclage in comparison to non-cerclage group [1].

Various forms of progesterone such as injection 17-hydroxyprogesterone caproate (17-OHP), and micronized vaginal progesterone (cyclogest pessary), were studied. They were used alone or as an adjunct to cerclage to further decrease preterm labor incidence in women with prior history of preterm birth or sonographic short cervix [5-8].

In a large randomized clinical trial that compared progesterone vs. placebo without cervical cerclage, progesterone was proved to decrease the risk of spontaneous preterm delivery before 34 weeks [9].

There are few studies with no agreement in the literature about the role of adjuvant 17-OHP compared to cervical cerclage only [10].

In a retrospective study that included 123 patients, the incidence of PL was significantly less in those who received adjuvant 17-OHP in comparison to cerclage alone [11]. Another study of 58 women who received 17-OHP with ultrasound-

Table 1. Demographic Data

Characteristics	Group 1: cerclage plus 17-OHP, n = 64 (%)	Group 2: cerclage only, n = 58 (%)
Age (mean ± SD)	31 ± 4.1	30 ± 5
Gravida, mean (range)	4.13 (1 - 11)	3.95 (1 - 10)
Para, mean (range)	1.3 (0 - 7)	1.45 (0 - 5)
Previous second trimester miscarriage		
No	32 (50%)	27 (47%)
Yes	32 (50%)	31 (53%)
Previous preterm		
No	31 (48%)	32 (55%)
Yes	33 (52%)	26 (45%)
Previous still birth		
No	60 (94%)	57 (98%)
Yes	4 (6%)	1 (2%)
Previous neonatal death		
No	52 (81%)	48 (83%)
Yes	12 (19%)	10 (17%)
Previous cerclage		
No	33 (52%)	28 (48%)
Yes	31 (48%)	30 (52%)
Cervical length before cerclage		
< 2.5 cm	16 (25%)	16 (28%)
≥ 2.5 cm	48 (75%)	42 (72%)
Vaginal infection		
No	44 (69%)	37 (64%)
Yes	20 (31%)	21 (36%)

indicated cerclage, however, did not show any advantageous effect of progesterone in the presence of cerclage [12]. This study aimed to investigate more about the role of 17-OHP with cervical cerclage on maternal and fetal outcome in prevention of PL below 37 weeks' gestation.

Materials and Methods

After institutional board approval, we conducted a retrospective case-control study from July 2010 to December 2014 on patients who received 17-OHP with cervical cerclage (group 1). This group was compared to matched control patients who had cervical cerclage only (group 2).

The inclusion criteria for cervical cerclage were singleton pregnant patients with cervical cerclage who had previous history of spontaneous onset PL or history of spontaneous second trimester miscarriage and asymptomatic women with singleton pregnancy, who have sonographic short cervix < 2.5 cm.

Exclusion criteria included pregnancy with congenital anomalies, history of previous induced preterm delivery, second trimester missed miscarriage, multiple pregnancy, placenta previa, threatened miscarriage, history of any cervical procedures like cone biopsy or loop electrosurgical excision procedure (LEEP), or radical trachelectomy.

For the purpose of this study, second trimester miscarriage was defined as any viable pregnancy that ended in miscarriage spontaneously after 12 weeks of gestation and before the viability of fetus (< 24 weeks). Preterm labor was defined as spontaneous onset of labor, which is determined by cervical changes before 37 completed weeks.

Pre-operative evaluation

Routine high vaginal swab (HVS) culture was done at 12 - 14 weeks' gestation. Transvaginal ultrasound was done for serial cervical length starting from 11th week, and then biweekly till cerclage placement. Patients with cervical funneling, with short cervix which is less than 2.5 cm on transvaginal scan, with history of one or more spontaneous second trimester miscarriages or PL had undergone either therapeutic or pro-

phylactic cervical cerclage within 25 weeks. Gestational age was confirmed by standard sonographic measurements at < 20 weeks' gestation.

Operative procedure

Under general anesthesia, transvaginal cervical cerclage was done using the standard McDonald method with Mersilene tape. Knots were placed anteriorly or posteriorly according to surgeon's choice. Cervical dilatation was rechecked again after each procedure. Patients were hospitalized for 24 h for observation. None of the patients were treated with any tocolysis or analgesics before procedure.

Patients were counseled for 17-OHP and those who agreed were given 250 mg intra-muscular weekly till 36 weeks.

Post-operative follow-up

All patients had routine regular antenatal follow-up. Elective cerclage removal was done at 37 weeks' gestation.

In our study, we tried to measure the maternal, fetal parameters and preterm outcomes comparing both groups.

Statistical analysis

All data were collected using SPSS® Mac version 23. Quantitative data with normal distribution were presented as mean ± SD, otherwise median and range were used. Qualitative data were expressed as frequency and percentage. Chi-square (cross-tabulation) test was used for the analysis. P value < 0.05 (two-sided) was considered as statistically significant.

Results

Of 70 patients in group one, 64 had complete files that were eligible for review. This group was compared to a matched group of 58 patients in the second group.

The mean age in groups 1 and 2 was 30 ± 5 and 31 ± 4.1 years, respectively. Parity, past obstetric history, previous preterm delivery, still birth, previous cervical cerclage and other demographics are shown in Table 1.

For maternal outcome, no difference was noticed between the two groups in terms of emergency cerclage removal, miscarriage rate, spontaneous vaginal delivery or cesarean section rate (Table 2). The miscarriage rate was higher in group 1, 80% compared to 20% in group 2, but the difference was not statistically significant. For premature rupture of membrane, emergency cerclage removal was done for 46% and 54% in group 1 and group 2, respectively.

In terms of fetal outcome, still birth and miscarriage rate in group 1 was 67% and in group 2 was 33%, which also did not show any statistical significance (0.4). Regarding NICU admission, although the admission rate was higher in group 1 (63%) than in group 2 (37%), it was statistically insignificant (P = 0.2).

There was no statistical difference in fetal outcome (Table 2) except in Apgar score at 1 min which was lower in group 1 (P = 0.04). However, there was no difference in Apgar score at 5 min between the two groups.

Preterm outcome below 37 weeks in both groups was similar, at 50% in each group (P = 0.7). About 43.8% women with cerclage plus 17-OHP delivered at 37 weeks' gestation, whereas 56.3% patients in cerclage group, which also did not make for any statistical significance (P = 0.4). Delivery above 37 weeks' gestation also did not show any difference (P = 0.4) (Table 3).

Discussion

High-risk pregnancy for PL women is defined as having either a previous preterm birth, mid trimester loss due to cervical incompetence or having a sonographic short cervix less than 2.5 cm. These pregnancies have a 15-20% risk of recurrent PL before 28 weeks of gestation, 25-30% before 32 weeks, and 50-60% before 37 weeks [13].

We aimed in our study to investigate the role of adjuvant 17-OHP with cervical cerclage in prevention of PL and its maternal and fetal outcomes.

Cervical cerclage has been accepted as the most effective method used in high-risk patients who had spontaneous PL or mid trimester pregnancy loss. It has been proven that cerclage alone decreases the rate of preterm birth [1]. Obstetricians rely on incorporating other adjunct therapies with cerclage, which has proved to be effective to prevent preterm birth [14].

To further improve the maternal and fetal outcome, intramuscular 17-OHP was tried as an adjunct to cerclage till 36 weeks of gestation but its role in reducing preterm birth with cerclage has not been proved yet.

Our results are in accordance with what was reported by Rafael et al on 58 patients. In their study, 15 (25.9%) patients received 17-OHP, and 43 (74.1%) with cervical cerclage only. Use of 17-OHP did not show any significant effect on preterm outcomes among women with a prior spontaneous PL and ultrasound indicated cerclage for cervical length < 2.5 cm in current pregnancy [12].

On the other hand, 17-OHP was reported as effective when used with cerclage on 123 patients in another study by Temming et al [11].

Except for Apgar score at 1 min which was statistically better in the adjuvant group (P = 0.04), all other parameters including Apgar score at 5 min did not show any difference in the two groups (P = 0.7).

The mechanism of action of progesterone for prevention of preterm birth is not well understood. Past studies have proven a variety of actions that support gestation and inhibit uterine activity. This may include activities that relax smooth muscle in the pregnant uterus, prevent formation of the myometrium gap junction and oxytocin receptors, block the impact of oxytocin on the myometrium, and/or have immunosuppressive activity against the activation of T lymphocytes [15]. Drop in progesterone activity or progesterone withdrawal is a key to

Table 2. Maternal and Fetal Outcomes

Outcome	Group 1: cerclage plus 17-OHP, n = 64 (%)	Group 2: cerclage only, n = 58 (%)	P value
Emergency cerclage removal			0.8
No	46 (53%)	41 (47%)	
Threatened preterm	14 (54%)	12 (46%)	
Premature rupture of membrane	4 (44%)	5 (56%)	
Miscarriage			0.2
No	60 (51%)	57 (49%)	
Yes	4 (80%)	1 (20%)	
Spontaneous vaginal delivery			0.1
No	19 (63%)	11 (37%)	
Yes	45 (49%)	47 (51%)	
LSCS			0.3
No	49 (51%)	48 (49%)	
Yes	15 (60%)	10 (40%)	
Fetal outcome			0.4
Alive	60 (52%)	56 (48%)	
Still birth and miscarriage	4 (67%)	2 (33%)	
Fetal weight			0.4
< 2.5 kg	17 (47%)	19 (53%)	
At 2.5 kg	5 (7%)	2 (29%)	
> 2.5 kg	42 (53%)	37 (47%)	
Apgar score at 1 min			0.04
8 - 10	42 (46%)	49 (54%)	
5 - 7	10 (77%)	3 (23%)	
< 5	12 (67%)	6 (33%)	
Apgar score at 5 min			0.7
8 - 10	57 (51%)	54 (49%)	
5 - 7	2 (67%)	1 (33%)	
< 5	5 (63%)	3 (37%)	
NICU admission			0.2
No	47 (49%)	48 (51%)	
Yes	17 (63%)	10 (37%)	

the control system for cervical ripening. The exact systems by which a blockade of progesterone activity may prompt cervical changes are intricate and inadequately interpreted. A decrease in progesterone activity most likely causes cervical changes by the action of inflammatory mediators [16].

In a systematic review, De Franco et al found that available published studies have not observed additive improvement in the prevention of the incidence of preterm birth with the combination of progesterone and cerclage. So they recommended avoiding routine implementations of progesterone in addition to cerclage [14].

On the contrary, Maternal-Fetal Medicine Publications Committee recommended a regular 17-OHP progesterone regimen until 36 weeks after cervical cerclage placement for short cervix less than 2.5 cm [17].

Subsequently, more investigations are warranted to evaluate the role of 17-OHP progesterone as an adjunct with cervical cerclage.

The retrospective analysis is one of our study limitations. However as can be noticed in Table 1, the demographic criteria in both groups are balanced and matched. This may consolidate our results as a matched control study.

In our study, we found no additional benefits of adjuvant 17-OHP on maternal, fetal outcome and preterm delivery below 37 weeks' gestation in comparison to cervical cerclage alone. More prospective randomized studies are recommended

Table 3. Delivery Outcome Data

Outcome (gestation in weeks)	Group 1: cerclage plus 17-OH P, n = 64 (%)	Group 2: cerclage only, n = 58 (%)	P value
Below 37			
No	48 (53%)	42 (47%)	0.7
Yes	16 (50%)	16 (50%)	
At 37			
No	57 (54%)	49 (46%)	0.4
Yes	7 (44%)	9 (56%)	
Above 37			
No	23 (48%)	25 (52%)	0.4
Yes	41 (55%)	33 (45%)	

to further investigate this matter.

Conflicts of Interest

None.

Source(s) of Support

None.

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