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The effect of 17α-Hydroxyprogestrone Caproate on prevention of preterm labor in high-risk pregnant women: a clinical trial study

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ABSTRACT

Preterm labor is defined as birth before 37th week of pregnancy. Despite of progressive improvement in gynecological care, the prevalence of preterm labor is growing. The aim of this study was to investigate the effect of 17α-Hydroxyprogestrone Caproate on prevention of preterm labor in high-risk pregnant women. This double-blinded clinical trial study was conducted on 100 pregnant women who admitted to Besat hospital, Sananadj, Iran during 2013-2014. Women were block randomized and divided in two intervention (n=50) and control (n=50) groups. The intervention group was injected 250 mg 17α-Hydroxyprogestrone Caproate intramuscularly during 24th until 34th week on a weekly basis and placebo was given to control group. The results showed that 11 women (22%) with preterm labor on less than 37 week and 39 (78%) on more than 37 week, however, in placebo group these figures were 29 (58%) and 21 (42%), respectively. This finding showed that 17α-Hydroxyprogestrone Caproate had preventive effect on preterm labor in intervention group. The logistic regression also showed that there was a significant difference between two intervention and control groups (p=0.001). It seems that 17α-Hydroxyprogestrone Caproate had preventive effect on preterm labor.

Keywords: 17α-Hydroxyprogestrone Caproate, preterm labor, high-risk pregnancy

INTRODUCTION

Preterm labor is defined as birth before the 37th week of pregnancy [1] and occurs in 12% of all labors. It is the

cause of 65% of neonatal deaths and premature newborns. Despite considerable improvements in obstetrics care and extensive studies, its prevalence is increasing [1, 2].In neonates who survive, there is a high prevalence of acute and long-term complications such as respiratory distress syndrome, body weight at birth less than 2,500 g, a need for mechanical respiration, admission to the NICU and an increased need for supportive oxygen [3].

The survival rate of preterm neonates increases when the duration of pregnancy increases. In addition to mortality and morbidity, preterm neonates are at risk of physical and mental abnormalities and caring for these neonates requires intensive care centers [4,5,6].Studies have shown that mother's history of preterm labor has a direct relationship with the occurrence of another pre- term labor and will be inherited by the next generation [7].

Prevention of preterm labor is inevitable and every one of the prevention methods has its advantages and side effects. Today, for primary treatment of preterm labor, there are various tocolytic drugs, such as beta mimetics, magnesium sulfate and calcium blockers, which inhibit uterine contractions and are used to suppress uterine contractile activities [8].However, there is no evidence supporting the effectiveness of these drugs in preterm labor, and using these medications is not recommended. Prescribing progesterone for prevention of preterm labor has a 30-year history and its use for prevention of spontaneous abortion or supporting the luteal phase goes back to 40 years ago [9].Progesterone is the main human progestin, and has been used also for the treatment of premenstrual syndrome, post-partum depression, repeated abortion, prevention of preterm labor, and in recent years, for supporting the luteal phase for in-vitro fertilization [10,11]. Since 1960, 17α-hydroxyprogesterone caproate has been investigated for its safety and efficacy in prevention of pre-term labor. Recent studies have shown that progesterone complexes, such as 17α-hydroxyprogesterone caproate, administered intramuscularly decreased preterm labor in women with a history of preterm labor [12] .Recent studies also have shown that using progesterone during the second trimester decrease the risk for teratogenicity [13].

Preterm labor risks factors are including; history of preterm labor, premature birth and congenital uterine abnormalities. Considering the contradictory results regarding the use of progesterone for prevention of preterm labor, several meta-analyses have been conducted. Almost in all studies the usefulness of progesterone in decreasing pre-term labor is shown. Meanwhile, all researchers recommend the need for further investigation [1].

In many animal studies, uterine deprivation of the inhibitory hormone, progesterone, plays the main role in the beginning of labor. In humans, prescribing anti-progesterone medications, such as RU486, mifepristone or onapristone increases uterine responsiveness and induces cervical changes in 12 - 48 hours. This result shows that progesterone has a role in preventing the onset of labor [14]. Very limited studies have been carried out in this regard, for instance, in a study by Meis et al. they concluded that weekly injection of 17α-hydroxyprogesterone caproate from the 16th week until the 36th week, in women with history of preterm labor, decreased the rate of preterm labor [15].

Considering the importance of preterm labor and pre-mature birth and also their complications, and the limited number of studies in this regard in Iran, the aim of this study was to investigate the effect of 17α-Hydroxyprogestrone Caproate on preterm labor prevention in high-risk pregnant women.

MATERIALS AND METHODS

In this double-blind clinical trial study 100 pregnant women who were admitted to Besat hospital in sanandaj, Iran during 2013 - 2014 and who met the inclusion criteria were block randomized into two groups: intervention (n =50) and placebo (n = 50) (Fig1) . The two groups were similar in terms of age of pregnancy and preterm labor risk factors. After classification and being given an explanation about the study, written consent was obtained. Information regarding past history, such as a history of preterm labor, cervical shortness, history of cerclage, history of the mother's own premature birth or that of her sister, and acquired and/or congenital uterine abnormalities noticed in sonography were documented. Subjects were followed, and 250 mg 17α-hydroxyprogesterone caproate ampoules were injected intramuscularly on a weekly basis from the 24th until the34th week, and placebo was given to the control group.

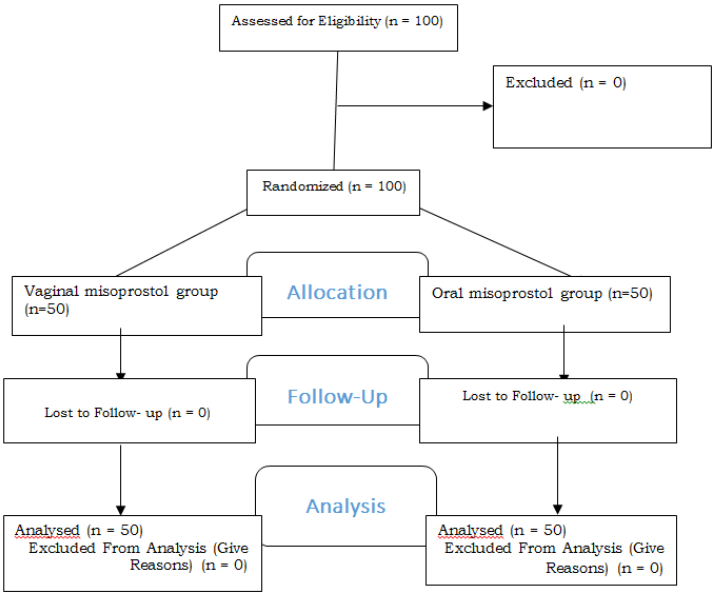

Figure 1. Flow diagram of the progress through the phases of a two-group parallel randomized trial

In this double-blinded study, the drug and the placebo were similar in shape, and the clinician who injected the medication was not aware of the contents of the injection. The participants were instructed to admit themselves in a timely manner to the hospital when they felt regular and rhythmic contractions. In the hospital, contractions were monitored by tocodynamometer, and in the case of real contractions, patients were admitted and treated with tocolytics. For women in whom labor was not stopped, despite treatment with tocolytics, data were documented. At the end of the study, the age of the pregnancy at the time of birth and the preterm labor incidence rates were compared between both groups.

Inclusion criteria for this study included: singleton pregnancy with an accurate age of pregnancy (pregnancy was confirmed with sonography before the 12th week and based on LMP. If LMP was not available, age of pregnancy determined by two sonography studies, two weeks apart); history of preterm labor before the 37th week; history of pre- mature birth; history of premature birth in sister; acquired and/or congenital uterine abnormalities (unicorn uterus, double corn uterus, septated uterus, arcuate uterus and double uterus); and age 18 - 45 years.

The exclusion criteria included: high blood pressure, cancer, seizure, thromboembolic disease or asthma under beta adrenergic treatment; age less than 18 and more than 45 years; intrauterine growth retardation; vaginal bleeding; PROM; cervical dilation more than 2 cm; major known embryonic abnormalities; progesterone sensitivity; non-following the patient; twin or multiple pregnancy; contraindications for tocolysis such as fetal distress, chorioamnionitis, preeclampsia or unstable hemodynamics; uterine contractions; diabetes; history of cerclage; and cervical shortness.

This study was approved by Ethics Committee of Kurdistan University of Medical Sciences, Sanandaj, Iran; it was also registered in Iranian registry for Clinical Trials with the following registration code: IRCT2014101019222N2

RESULTS

The results showed that the mean and standard deviation of age in the intervention group was 25.4 ± 2.58 with a confidence interval of 24.6 - 26.1. In the placebo group, the mean and standard deviation of age was 27.4 ± 2.21 with a confidence interval of 26.6 - 27.8 (Table 1).

Regarding gravidity, the distribution in the intervention group was: 16 women (32%) were in gravida 1, 22 (44%) in gravida 2, 11 (22%) in gravida 3 and 1 (2%) in gravida 4. In the placebo group, 8 women (16%) were in gravida 1, 27 (54%) in gravida 2, 14 (28%) in gravida 3 and 1 (2%) in gravida 4 and there was no significant difference

between the two groups.

Regarding the frequency distribution of previous preterm labor, in the intervention group 20 (42%) women had a history of previous preterm labor and 30 (58%) women had no history of preterm labor. In the placebo group 20 (40%) women had and 30 (60%) women did not hah a previous preterm labor. The chi-square test showed that there was no significant difference between the two groups. In regards to the frequency distribution of a previous premature birth in the intervention group, 4 (8%) women had a history of previous premature birth, and 46 (92%) women had no history of premature birth. In the placebo group, 3 (6%) women had and 47 (94%) women did not have a previous premature birth. The Chi-Square test showed that there was no significant difference between the two groups. In the frequency distribution of previous pre- mature birth in sister, in the intervention group 3 (6%) women had a history of previous premature birth in their sister, and 47 (94%) women had no history of premature birth in their sister, while in the placebo group 3 (6%) women had and 47 (94%) women did not have history of pre-mature birth in their sister. There was no significant difference between the two groups.

In terms of a history of acquired uterine abnormalities, in the intervention group 13 (26%) women had a history of acquired uterine abnormalities and 37 (74%) women had no history of acquired uterine abnormalities. In the placebo group 14 (28%) women had and 36 (72%) women did not have a history of acquired uterine abnormalities. There was also no significant difference between the two groups.

In terms of previous congenital uterine abnormalities, in the intervention group 7 (14%) women had a history of congenital uterine abnormalities, and 43 (86%) women had no history of congenital uterine abnormalities, while in the placebo group, 6 (12%) women had and 44 (88%) women did not have a history of congenital uterine abnormalities. There was no significant difference between the two groups (Table 2).

Table 1. Average (SD) of age in the two Groups

Age	Number	Mean (SD)	Confidence interval
Intervention	50	25.4 (2.58)	24.4 - 26.1
Control	50	27.4 (2.21)	26.6 - 27.8

Table 2. Detailed Information for the two Groups

	Intervention	Control	Chi-Square	P Value
Gravida			2.99	0.39
1	16 (32)	8 (16)		
2	22 (44)	27 (54)		
3	11 (22)	14 (28)		
4	1 (2)	1 (2)		
Para			1.12	0.57
1	25 (71.4)	27 (64.2)		
2	10 (28.6)	14 (33.3)		
3		1 (2.5)		
Previous preterm labor			0	1
Yes	20 (42)	20 (40)		
No	30 (58)	30 (60)		
Previous premature birth			0.15	0.69
Yes	4 (8)	3 (6)		
No	46 (92)	47 (94)		
Previous premature birth in sister			0	1
Yes	3 (6)	3 (6)		
No	47 (94)	47 (94)		
History of acquired uterine abnormality			0.11	0.82
Yes	13 (26)	14 (28)		
No	37 (74)	36 (72)		
History of congenital uterine abnormality			0.11	0.73
Yes	7 (14)	6 (12)		

Table 3. Comparing the Effect of 17α-Hydroxyprogesterone Caproate on Prevention of Preterm Labor in Pregnant Women Aged 18 - 45 Years old

Preterm Labor	Intervention	Control	T	Degree of Freedom (df)	OR (Confidence) Interval)
Before 37th week	11 (22)	29 (58)	-3.91	1	0.69 (0.58 - 0.83)
After 37th week	39 (78)	21 (42)	-3.91	1	0.69 (0.58 - 0.83)

Table 4. Comparing the Effect of 17α-Hydroxyprogesterone Caproate on Prevention of Preterm Labor in Pregnant Women Aged 18 - 45 Years old Based on Different Groups

Variable	OR	Confidence Interval	P value
Intervention- Control	0.19	(0.07 - 0.47)	0.0001
History of congenital uterine abnormality	2.31	(0.64 - 8.3)	0.20
History of acquired uterine abnormality	0.39	(0.29 - 2.08)	0.62
History of preterm labor	0.66	(0.27 - 1.62)	0.37
History of premature birth	0.33	(0.24 - 7.11)	0.74
History of preterm labor in sister	1.65	(0.27 - 9.87)	0.55
History of preterm labor in mother	1.01	(0.19 - 5.37)	0.98
Age group (less than 25 and more than 25 years)	0.65	(0.19 - 2.19)	0.49

Comparing the effect of 17α-hydroxyprogesterone caproate on preventing preterm labor in pregnant women between 18 - 45 years old in the intervention group, 11 (22%) women had preterm labor before the 37th week and 39 (78%) women had preterm labor after the 37th week, meanwhile, in the placebo group these figures were 29 (58%) and 21 (42%), respectively. These differences showed the preventive effect of 17α-hydroxyprogesterone caproate on prevention of preterm labor (Table 3).

The logistic regression analysis showed that there was a significant difference between the intervention and placebo groups, and 17α-hydroxyprogesterone caproate was effective in women with a history of congenital uterine malformation and history of preterm labor (Table 4).

DISCUSSION

Results of the study showed that there was no significant difference between the two groups in terms of gravidity, parity, history of preterm labor, history of premature birth, history of premature birth in sister or history of acquired and congenital uterine abnormalities.

In a study by Meis et al. which conducted on 503 Scottish pregnant women with a proved history of preterm labor, 310 women with a history of preterm labor were given weekly injections of 17α-hydroxyprogesterone caproate from the 16th week until the 36th week. Results showed that treatment with progesterone decreased the rate of pre-term labor before the 37th week. This result is consistent with our findings ($P = 0.02$) [15].

In a study by Pessel et al. in the U.S., 237 pregnant women with similar cervical length were studied. In this study, 184 women were given 17α-hydroxyprogesterone caproate from the 16th week until the 37th week. The age of the pregnancy and history of previous preterm labor were similar in both groups. The results showed that cervical shortness among women with a history of preterm labor occurs similarly, regardless of receiving or not receiving 17α-hydroxyprogesterone caproate ($P = 0.67$) [16] .In another study by Fonseca et al., 413 pregnant women who had cervical shortness(15 mm or less) based on sonography were characterized during routine prenatal care. These women were randomized into two groups. One group was treated with 200 mg progesterone vaginal suppository, and the other was given placebo. Treatment with progesterone caused significant reduction of spontaneous labor before the 34th week ($P < 0.05$) [17].

Progesterone is a natural hormone that is secreted by the corpus luteum and the placenta at the beginning of the pregnancy and its vital role in maintaining pregnancy has been proven. Researchers have used this hormone for preventing preterm labor in late pregnancy. In a study by Fontenot and Fantasia in 2012 in Brazil, it was shown that vaginal progesterone given from the 16th week to the 34th week is effective in preventing preterm labor in women with history of preterm labor [18].

In a study by O'Brien et al., 659 pregnant women with history of preterm labor were randomized into two groups. One group was treated with a progesterone vaginal suppository (90 mg) from the 16th until the 32nd week and the

other with the placebo. There was no significant difference between the two groups in terms of preterm labor rates, and preventive therapy with vaginal progesterone did not decrease pre-term labor recurrence before the 32nd week in women with history of preterm labor [19].

CONCLUSION

Results from the present study showed that 17α-hydroxyprogesterone caproate had a preventive effect on preterm labor. However, further studies with larger sample size are required to assess the role of 17α-hydroxyprogesterone caproate in preventing preterm labor.

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