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Effect of 17 α-Hydroxyprogesterone Caproate on the Prevention of Preterm Labor: A Randomized Controlled Trial Study

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ABSTRACT

Background & aim: Based on the previous reports, treatment with 17 α-Hydroxyprogesterone caproate (17-OHPC) decreased the risk of preterm labor (PTL). However, some studies indicated contrasting results. This study aimed to investigate the effect of 17-OHPC on the prevention of PTL.

Methods: This randomized controlled trial was performed on singleton pregnant women with a history of PTL referring to Imam Khomeini Hospital, Sari, Iran. The experimental group was subjected to an intramuscular weekly injection of 250 milligrams of 17-OHPC from week 16 to 37 of gestational age (n=50). The control group received routine prenatal care. Data were collected using a self-structured checklist, and analyzed using SPSS software (version 18) through independent T-test, Mann-Whitney U test, and the Chi-square test.

Results: The mean age of the experimental and control groups were 24.4±2.6 and 25±2.38 years, respectively. According to the results, there were no significant differences between the groups regarding the risk of PTL less than 35 and 37 completed weeks (P=0.21, P=0.23). Furthermore, a significant relationship was observed between the use of 17-OHPC and birth weight (P<0.05). The frequency of birth weight less than 2500 g in the experimental group was significantly lower than that in the control group (RR:1.56, 95% CI:1.6-2.29, P=0.023).

Conclusion: The results of the outcome analysis based on the separation of gestational age and birth weight in the case and control groups showed no significant differences between the groups regarding the risk of PTL less than 35 and 37 completed weeks.

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Introduction

Preterm labor (PTL) is defined as labor beginning before 37 weeks of pregnancy with a prevalence rate varied from 6% to 12% in developed countries; moreover, it is more prevalent in developing countries which is counted as one of the major causes of mortality and morbidity (1). In addition to the mortality issue, the preterm neonate has a high risk of exposing to mental and physical disorders, and there is a high cost for the neonate to be cared for and saved at the Neonatal Intensive Care Units (2).

The exact etiology of PTL is unknown; however, several predisposing factors, such as maternal, congenital, and hormonal, as well as infections, mother's lifestyle, and chronic diseases of the mother are effective in this regard (3, 4). The prevention of PTL is unavoidable, and each

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prevention method has its own complications and side effects (5). The medications suppressing the uterus called tocolytics, such as beta-mimetic, magnesium sulfate, calcium channel blockers, anti-prostaglandins (indomethacin), and anti-oxytocin are utilized for the treatment of the acute primary PTL (6). However, there is no evidence supporting the effect of conservative tocolytics' treatment with available medications; furthermore, their utilization has not been suggested in the literature (7).

Progesterone is one of the secreting hormones from the placenta which is crucial for the survival of pregnancy (8). This hormone was considered as a factor for preventing PTL at the beginning of the 1960s (9). Treatment with 17 α-Hydroxyprogesterone caproate (17-OHPC) decreases the risk of PTL by one-third in singleton pregnancies although it is not effective in dual or triplet pregnancies (9, 10). On the other hand, recent studies have shown that the use of progesterone along the second trimester of pregnancy has a very low risk of development of teratogenic complications (6). Meis, Klebanoff (11) reported in a study that the rate of PTL in a group receiving 17-OHPC decreased significantly. In a study performed on 142 pregnant women with the risk of PTL, it was concluded that the risk of PTL decreased significantly in people receiving 100 mg of vaginal progesterone on a daily basis (12).

Therefore, the American College of Obstetricians and Gynecologists established a committee and supported the usage of 17-OHPC in order to prevent PTL (13). Nonetheless, some older studies which investigated the effect of 17-OHPC on the prevention of PTL indicated contrasting results (14, 15). It is reported that vaginal progesterone and 17-OHPC may show different effects and several factors, such as the community under study, the number of embryos, and the cervix length can cause fundamental different results.

The 17-OHPC has shown different results regarding its efficacy and benefits in groups that are subjected to risks; moreover, since it is dependent on the type and dosage of injection, it obligates more studies to clarify these problems. With this background in mind and due to the lack of studies in the north of Iran, this study aimed to investigate the effect of 17-OHPC on the prevention of PTL.

Materials and Methods

This randomized controlled trial was performed on singleton pregnant women with a history of PTL referring to the prenatal clinic of Imam Khomeini Hospital, Sari, Iran, from March to September 2015. Approximately, 260 patients referred to this clinic during this period. The exclusion criteria were: 1) active phase of labor, 2) preterm rupture of membranes, 3) preeclampsia, 4) vaginal bleeding, 5) maternal-fetal diseases in which extending the pregnancy is dangerous, 6) signs of fetal distress and anomalies, 7) dilation more than 3 centimeters and cervical length less than 30 millimeters, 8) contraindication of tocolytics, 9) evidence supporting the infection inside the amnion fluid, 10) obvious signs of pyelonephritis, 11) allergy to progesterone demonstrating as dizziness, migraine, optical disorders, depression, and increase in the blood sugar while using the drug, which is called 'progesterone allergy), and 12) maternal diseases requiring treatment (i.e., hypertension, cancer, seizure, thromboembolic disease, liver disease, patients being treated with oral beta-adrenergic for asthma were also considered). According to a study carried out by Saghafi, Khadem (16) with the prevalence rate of 32% (P1) and 60% (P2) in the case and control groups, respectively, the sample size was estimated at 47 participants in each groups (i.e., case and control) in order to get the power of 80% and accuracy of 95%. However, regarding the sample attrition, 50 people were included in the case and control groups. Subsequently, the patients were randomly assigned into two equal groups using a permuted block randomization method. It should be noted that the samples of each block were selected via systematic randomization.

A checklist including age, body mass index (BMI), gravity, abortion history, and type of previous delivery (i.e., natural or cesarean) was prepared for each patient. The validity of this checklist was confirmed using the revisions of 5 obstetrics and gynecology experts. Following that, the case group was subjected to an intramuscular weekly injection (based on similar studies) of 250 milligrams of 17-OHPC (Bayer, Germany) during weeks 16-37 of

pregnancy. On the other hand, the control group received routine prenatal care without any special interventions. Eventually, the mean gestational age according to the first day of the last menstruation period or the pregnancy's first-trimester sonography, the prevalence of PTL, average neonatal birth weight, and the weight frequency distribution were recorded in this study.

The study protocol was approved by the Ethics Committee of Mazandaran University of Medical Sciences, Sari, Iran (IR.MAZUMS.REC.95.115) and registered in the Iranian Clinical Trial registry (IRCT20190309042978N2). The patients were informed of the research objectives and procedures. Moreover, they were assured of the voluntary participation and the confidentiality of their information. Written informed consent was obtained from all participants.

The data were analyzed using SPSS software (version 18.0) (SPSS Inc., Chicago, Illinois) through descriptive statistics (i.e., frequencies, mean, and standard deviation for socio-demographic variables of the participants). Furthermore, independent sample T-test and Mann-Whitney U test were utilized to compare the quantitative variables between the case and control groups. Additionally, qualitative variables were compared using the Chi-square test. Regarding the maternal and neonatal outcomes, the relative risk (RR) at a 95% confidence interval (CI) and P-value were calculated. A P-value less than 0.05 was considered statistically significant.

Results

A total of 100 pregnant women were included in this study and assigned into two groups of case and control (50 women per group). The mean ages in the group receiving 17-OHPC and the control group were 24.4±2.6 and 25±2.38 years, respectively.

Table 1. Demographic characteristics of the participants

Variable	Total	Case group (n=50)	Control group (n=50)	P-value
Age*	2.48±24.87	2.6±24.4	2.38±25	**0.60** [a]
Body mass index*	4.47±23.87	3.06±24.32	0.74±24.03	**0.62** [a]
Previous preterm gestational age*	2.15±31.8	2.12±31.92	2.18±31.68	**0.63** [b]
Birth weight of previous delivery*	380±1790	360±1820	410±1770	**0.66** [a]
Type of previous delivery*				
Vaginal		28 (56)	32 (64)	**0.41**[c]
Cesarean section		22 (44)	18 (36)	
Gravidity**				
Twice		4 (80)	37 (74)	**0.63** [c]
More than three times		10 (20)	13 (26)	
Abortion**	13 (13)	6 (12)	7 (14)	**0.36** [c]

* Data are presented as mean±standard deviation ** Data are presented as frequency (percentage)

[a] Student's t-test [b] Mann-Whitney U [c] $\chi^2 test$

Moreover, the mean BMI in all cases was 23.87±4.47. The majority of the women had more than two gravidities, and 13 mothers had abortions. The obtained results from this study revealed no significant difference between the case and control groups regarding age, BMI, gravidity, abortion, gestational age, and birth weight of previous preterm delivery (P>0.05) (Table 1).

As shown in Table 2, the mean birth weights in the 17-OHPC recipient group and the control group are 2702 and 2528 g, respectively. In general, with respect to the comparison of birth weights in two groups, a significant difference was observed between the two groups in this regard (P<0.05).

The outcome analysis was performed based on the separation of gestational age and birth

weight in the case and control groups in this study. Regarding the comparison of the effects of 17-OHPC on preventing PTL among pregnant women in the case group, the results showed that 21 (42%) and 16 (32%) women had PTL before the 37th and 35th weeks of pregnancy, respectively. Moreover, 27 (54%) and 22 (44%) women in the control group obtained the corresponding figures, respectively.

Table 2. Comparison of case and control groups regarding gestational age and weight

Variable	Case group	Control group	P-value
Birth weight	354.98±2702	496.43±2528	**0.04**[a]
Gestational age	1.21±35.90	2.06±35.3	**0.26**[b]

* Data are presented as mean±standard deviation, [a] Student's t-test [b] Mann-Whitney U

These differences showed the preventive effect of 17-OHPC on the prevention of PTL. There were no significant differences between the groups regarding the risk of PTL less than 37 completed weeks (RR: 1.2, 95% CI: 0.85-1.88, P=0.23) and PTL less than 35 completed weeks (RR: 1.6, 95% CI: 0.73-3.77, P=0.21). In addition, the results showed that the frequency of birth weight less than 2500 g in the case group was significantly lower than that in the control group (RR:1.57, 95% CI:1.06-2.29, P=0.023). This represented an improvement of the birth weight in the progesterone group, compared to the control group (Table 3).

Table 3. Maternal outcome based on gestational age and neonatal birth weight in case and control groups

Outcome		Case group	Control group	RR (95% CI)	P-value*
Gestational age	Before 37 weeks	21 (42)	27 (54)	1.2 (0.85-1.88)	0.23
	Before 35 weeks	16 (32)	22 (44)	1.67 (0.73-3.77)	0.21
Birth weight	Between 3000-3500 g	11 (22)	10 (20)	0.94 (0.57-1.54)	0.8
	between 2500-3000 g	25 (50)	15 (30)	0.64 (0.4-101)	0.04
	less than 2500 g	14 (28)	25 (50)	1.56 (1.6-2.29)	0.023

Data are presented as frequency (percentage). *χ^2 test

Discussion

This study aimed to evaluate the effect of 17-OHPC on the prevention of PTL in patients with a history of PTL referring to Imam Khomeini Hospital, Sari, Iran. Despite extensive clinical trials in PTL and many advances in midwifery, the best treatment is still under discussion. Unfortunately, no progress has been made in the last two decades to reduce preterm birth rates (16). The natural 17-OHPC compound, which is natural progesterone secreted from the placenta, unlike other synthetic progesterone, has no known teratogenic effect and has no specific maternal and placental effects (17). In this study which was performed on 100 pregnant women, the mean age of mothers was 24 years, whereas the mean age of mothers was 28 years in a study conducted by Saghafi in Mashhad (16). The majority of the women had more than two pregnancies, and 13 mothers had miscarriages. In a study conducted by Saghafi et al. (2011), the number of pregnancies in the progesterone recipient group and the control group were 3.66 and in 3.7, respectively, which was similar to the findings in this study (16).

In a study performed by Co et al., 174 women obtained a BMI of less than 25 with a mean of 21.2 kg/m2, and 216 participants had a BMI of 25 and greater than 25 with a mean of 33.5 kg/m2 (18). The mean previous gestational age in a study by Saghafi was 30.67 weeks in the intervention group and 32.76 weeks in the control group (16), which was consistent with the results of the present study. The results of this study showed that 17-OHPC had no significant effect on gestational age, compared to the control group. This result is inconsistent with the findings of a study by Romero (19). Although it was a systematic review and meta-analysis that ultimately reviewed five studies. The results are generally stated and no

adjustments have been made based on the progesterone daily dose received that in present study subjects received 250 mg of 17-OHPC. Saghafi et al. (2011) showed that preterm birth rates were statistically significantly lower than in the control group; although, it was which was not similar to the results of the present study (16). In both studies, mothers with a history of PTL were evaluated, and they were subjected to an intramuscular weekly injection of 250 mg of 17-OHPC, which was similar in both studies.

According to a study conducted by Grobman et al. on US nulliparous women who were under the treatment of intramuscular 17-alpha-hydroxyprogesterone, gestational age was higher in the case than the control group; nevertheless, it was not statistically significant, which was consistent with the results of this study (20). Both studies utilized a dose of 250 mg. The present study investigated women with a history of spontaneous PTL and a cervical length greater than 30 mm; however, the cervical length was less than 30 mm in a study performed on the US nulliparous women (20). Shorter cervical length appears to increase the risk of amniotic fluid infections, and progesterone has less effect on preventing labor-induced infection (21).

Similarly, Razavi et al. investigated the effect of 17-OHPC on PTL prevention among pregnant women with a history of PTL. The results showed that the birth weights were 2.4±1.0 kg and 2.7±0.7 kg in the case and control groups, respectively, which was not different significantly (22). In a study conducted by Shahgheibi et al. in 2016, the results showed that 11 (22%) and 39 (78%) women with PTL had less and more than 37 weeks, respectively; however, in the placebo group, these figures were 29 (58%) and 21 (42%), respectively. This finding showed that 17-OHPC had a preventive effect on PTL in the intervention group (23), which this was not in line with the present study.

In the current study, the mean birth weights were 2702 and 2528 g in the progesterone recipient group and the control group. The overall comparison between the case and control groups regarding birth weight showed a significant difference between these groups in terms of the use of 17-OHPC and birth weight, which was inconsistent with the results of a study conducted by Razavi (22). Furthermore, Romero et al. in 2016 showed that the utilization of vaginal progesterone in women with a cervical length less than 25 mm reduced the birth rate of infants weighing less than 1500 g (19). In the present study, the use of 17-OHPC increased the birth weight of neonates, as well as the number of neonates weighing more than 2500 g in the progesterone-treated group, which was higher than that in the control group. Hassan also obtained the same results (24). In a study carried out by Grobman et al., the birth weight was higher in the case group; however, it was not statistically different from that in this study, and there were no significant differences among infants weighing less than 2500 g. It is worth mentioning that 22% of the infants in the underweight group weighed less than 2500 g (20), which was different from the results obtained from this study.

Following the authority's opinion, no placebo group was included in this study to eliminate the confounding factors. Furthermore, further studies are required to determine the wider generalizability of our findings since this study was performed at one medical institution (i.e., Imam Khomeini Hospital, Sari, Iran). Accordingly, it was impossible to control all factors influencing the outcomes (e.g., social, and emotional). Future studies are suggested to consider these factors.

Conclusion

The results of the outcome analysis based on the separation of gestational age and birth weight in the case and control groups showed no significant differences between the groups regarding the risks of PTL less than 35 and 37 completed weeks. Moreover, the frequency of birth weight less than 2500 g in the case group was significantly lower than that in the control group.

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Conflicts of interest

Authors declared no conflicts of interest.

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