



Effect of 17 Alpha-Hydroxyprogesterone Caproate on Preterm Labor Prevention in Pregnant Women with a History of Preterm Labor

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Received 2019 February 05; Revised 2019 May 01; Accepted 2019 May 11.

Abstract

Background: The risk of preterm labor is significantly higher in women with a history of preterm delivery.

Objectives: The current study aimed at investigating the effect of 17 α -hydroxyprogesterone caproate (17-OHPC) on preterm labor prevention in pregnant women with a history of preterm labor.

Methods: In the current randomized control trial, 100 pregnant women with a history of preterm labor were divided in two groups. The 17-OHPC 250 mg was prescribed to the case group from the week 20 of gestation weekly. Sampling was done randomly. The gestational age at birth was measured up and compared with that of previous labor. Data were analyzed using *t*-test.

Results: In the current study, the mean gestational age of previous and present labor were respectively 28.5 ± 5.9 and 33.6 ± 5.2 weeks in the case group ($P = 0.001$). In the control group, the mean gestational age of previous and present labor were 33.3 ± 2.7 and 35.3 ± 2.3 weeks, respectively ($P = 0.001$). The difference between the previous and present gestational age in the case and control groups were 5.1 ± 4.0 and 3.3 ± 1.4 weeks, respectively ($P = 0.228$). The birth weight in the case and control groups were 2.4 ± 0.1 and 2.7 ± 0.7 kg, respectively ($P = 0.256$). The 1-minute Apgar score in the case and control groups were 7.3 ± 2.3 and 7.8 ± 1.7 , respectively ($P = 0.494$). Also, the 5-minute Apgar score in the case and control groups were 8.6 ± 2.2 and 9.1 ± 1.4 , respectively ($P = 0.393$). In the current study, the number of infants requiring admission to the neonatal intensive care unit in the case and control groups were 16 (32%) and 14 (28%) respectively, although the difference was not statistically significant ($P = 0.711$).

Conclusions: The results of the study indicated that although gestational age at birth was higher in the case group than in the control group, the difference was not statistically significant.

Keywords: 17 Alpha-Hydroxyprogesterone Caproate, Preterm Labor, Prenatal Care, Proluton

1. Background

Preterm labor is defined as the birth before 37 weeks of gestation, with a prevalence of 6% - 12% in the developed countries and higher prevalence in the developing countries. Preterm labor is considered as one of the main causes of prenatal and neonatal mortality (1-3). The chance of survival among premature neonates increases with increasing gestational age at birth. In addition to the death issue, the premature baby is also at risk for physical and mental disorders, and there is a great problem of expenses to take care of such babies in the intensive care units (4-6). One of the most important risk factors is the history of preterm delivery, which increases the risk of next preterm labor (7). A lot of researches are performed on prevention of early onset of labor pain. Progesterone is thought to be involved in maintaining the zero stage of labor. Progesterone can

increase the oxytocin breakdown and prevent increase of oxytocin receptors in myometrium. It seems that estrogen and progesterone act as components of a biomolecular system that completes zero stage of labor (8). Progesterone, as one of the hormones secreted by the placenta, is essential for pregnancy. Today, support of luteal phase in ovulation induction cycles and intrauterine insemination is mostly done by progesterone products that increase pregnancy chance and reduce the risk of abortion (9). Progesterone can be administered intramuscularly or vaginally (10). However, there is a controversy about the best type of progesterone in various studies (11). Some suggests a long-term progesterone as an alternative. The 17 alpha-hydroxyprogesterone caproate (17-OHPC) is a progesterone derivative that caproic acid has prolonged its effect (12). This combination is suggested for the treatment of recurrent abortions and prevention from preterm delivery with-

out teratogenic effects (13, 14).

Treatment with 17-OHPC reduces the risk of preterm labor up to 30% in singleton pregnancies. Although this treatment is not effective in twin and triplet pregnancies (15), some studies also report similar results (16, 17). In a study, the preterm labor rate decreased significantly using 17-OHPC (16). Similarly, in another study, the risk of preterm labor significantly reduced in 142 pregnant women who were at risk for preterm labor following the vaginal administration of 100 mg progesterone daily (17). The American College of Obstetricians and Gynecologists has also suggested the use of 17-OHPC to prevent preterm labor (18). Some older studies show controversial results in evaluating the effect of 17-OHPC on preterm delivery prevention (19).

2. Objectives

Because of the different effects of 17-OHPC on the prevention of preterm labor and few studies in this regard from Iran, the current study aimed at evaluating the effect of 17-OHPC on the prevention of preterm labor.

3. Methods

The current randomized clinical trial was performed on 100 pregnant women (reference 21) of gravida \geq II with a history of preterm labor referring to the Perinatology Clinic of Ali ibn Abitalib Hospital in Zahedan, Iran. The present study protocol was approved by the Ethics Committee of Zahedan University of Medical Sciences; all patients were provided with adequate explanations and informed consent was also obtained from them before entering the study.

The inclusion criteria of the study were: lack of symptoms of amniotic fluid leakage, uterine contractions, preeclampsia, vaginal bleeding, and fetal anomalies, no history of cardiovascular disease, diabetes, and uterine abnormalities, and no smoking.

The study was performed by the unpredictable (accessible) method. Based on the literature review (reference of 21), 100 subjects were needed for the study. Each group consisted of 50 subjects enrolled randomly. At first, demographic information of the patients was recorded in checklist. All the subjects signed the informed consent form before entering the research. The 17-OHPC has no side effects on pregnancy. Pregnant women with a history of preterm labor referring to the Perinatology Clinic of Ali ibn Abitalib Hospital were randomly assigned to two groups (random allocation method). Bothe the groups were matched for the conditions of pregnant women.

For 50 pregnant women in the case group, from the 20th week of gestation, 250 mg of 17-OHPC was injected weekly; the muscular injections were performed up to the end of the 36 weeks of gestation, or until delivery. For 50 patients in the control group, pregnant women were followed up without 17-OHPC injection until the end of 36 weeks of gestation. After the completion of follow-up, the gestational age at birth, the birth weight of infants, and their need for NICU (the neonatal intensive care unit) admission in the two groups were compared. These comparisons were performed using SPSS software version 16. To express the quantitative data, the central indicators (mean, etc.) and dispersion (standard deviation, etc.) were used. The percentages were used to describe the qualitative variables. Tables and charts were used to provide better results. In case of normal distribution of data, independent samples *t*-test was used to compare the quantitative variables between the two groups. The normal distribution of data was measured by the Kolmogorov-Smirnov test. Chi-square test was used to compare the qualitative variables of the two groups. The significance level was considered less than 0.05 in all cases.

4. Results

The mean age of the patients in the case and control groups were 27.7 ± 4.1 and 28.1 ± 4.4 years, respectively ($P = 0.531$). Gravidity in the case and control groups were 3.6 ± 1.2 and 1.4 ± 2.1 , respectively ($P = 0.334$) (Table 1).

In the current study, the mean gestational age in previous and present labors were 28.5 ± 5.9 and 33.6 ± 5.2 weeks respectively in the case group, which was significantly different ($P = 0.001$). In the control group, the mean gestational age in previous and present labor were 33.3 ± 2.7 and 35.6 ± 3.2 weeks respectively, which was significantly different ($P = 0.001$). Also, the differences in gestational age at birth in the case and control groups were 1.5 ± 4.4 and 3.3 ± 4.1 weeks respectively; although gestational age at birth was higher in the case group receiving 17-OHPC than in the control group, the difference was not statistically significant ($P = 0.238$) (Tables 2 and 3). In the current study, the birth weight of the newborns in the case and control groups were 2.4 ± 0.1 and 2.7 ± 0.7 kg respectively, which was not significantly different ($P = 0.256$) (Table 4).

Table 1. Comparison of the Mean Age of Subjects in the Two Groups Using *t*-Test

	Case	Report	P Value
Age, y	4.1 ± 27.7	4.4 ± 28.1	0.513
Gravida	1.2 ± 3.7	1.2 ± 4.1	0.334

Table 2. Comparison of the Gestational Age Increase Between the Two Groups, Using Paired Samples *t*-Test

Gestational Age	Previous Pregnancy	Present Pregnancy	P Value
Case	5.9 ± 28.5	5.2 ± 33.6	0.001
Report	2.7 ± 33.3	3.2 ± 35.6	0.001

Table 3. Comparison of Gestational Age Differences in the Recent and Previous Pregnancies Between the Study Groups Using *t*-Test

	Case	Control	P Value
The difference in gestational age between recent and previous gestation	4.0 ± 5.1	4.1 ± 3.3	0.238

Table 4. Effect of 17-OHPC on Preterm Labor Prevention in Terms of Birth Weight in the Study Groups Using *t*-Test

	Case	Control	P Value
Birth weight	1.0 ± 2.4	0.7 ± 2.7	0.152

In the study, the 1-minute Apgar score was 7.23 ± 2.3 in case group and 7.8 ± 1.7 in the control group. There was no statistically significant difference between the two groups ($P = 0.494$). Also, the 5-minute Apgar score was 8.6 ± 2.2 in the case group and 9.1 ± 1.4 in the control group; there was no statistically significant difference between the two groups (Table 5). In the current study, the number of infants requiring NICU admission in the case and control groups were 16 (32%) and 14 (28%) respectively, and the difference was not statistically significant ($P = 0.711$) (Table 5).

5. Discussion

In the current study, from the 20th week of gestation, 250 mg of 17-OHPC was weekly administered intramuscularly to the subjects in the case group. Progesterone can increase the oxytocin breakdown and prevent increase of oxytocin receptors in myometrium. The results of the study showed that the increase in gestational age at birth in the 17-OHPC group was higher than in the control group, but the difference was not statistically significant. In the study by Winer et al., from France, the effect of 17-OHPC was studied on 105 women in both the case and control groups; the results showed that 17-OHPC could not prolong the duration of pregnancy in the singleton pregnant women who were at high risk for preterm labor (20). In the study by Awwad et al., from Lebanon, there was no significant difference in the gestational age at birth between the two groups, which is consistent with the results of the current study, but the birth weight was higher in the case group; therefore, the number of infants with low birth weight in the case group was significantly lower than in the control

group (7.6% vs. 14.3%) (21). In the current study, contrary to the study by Awwad et al., there was no significant difference in birth weight between the two groups. In the study by Caritis et al., from the United States, a sample of 315 women with the history of preterm labor between 25 - 28 weeks of gestation was assessed; women with lower 17-OHPC levels were significantly at higher risk for spontaneous preterm labor compared to the ones with a high 17-OHPC level. As a result, lower plasma levels of 17-OHPC were associated with increased risk of spontaneous preterm labor (22).

According to the study by Nigar et al., the prevalence of preterm delivery was 6.9% in India; the mean gestational age at birth in the 17-OHPC receivers and controls were 36 weeks and 33 weeks plus five days respectively; the gestational age at birth was significantly higher in the case group than in the control group, (23) which is inconsistent with the current study results.

In a study by Timofeev et al., spontaneous preterm labor in black and white women receiving 17-OHPC was reviewed in the United States. Repeated spontaneous preterm labor was less on 34 weeks of gestational age in black women in comparison with whites. In both racial groups, the highest risk factor of repeated preterm labor was cervical length less than 25 mm before the 27th week of gestation (24).

In the study by Safavi et al., on the effect of 17-OHPC on the prevention of preterm labor, the mean gestational age was 36 weeks in the progesterone group and 32 weeks in the control group, and the birth weight of the newborns in the progesterone group was higher than that of the control group (24, 25).

In general, treatment with 17-OHPC could increase the gestational age at birth in women with a history of preterm labor. The study limitations were the small sample size and the study duration; therefore, further researches are needed in this regard.

5.1. Conclusions

The current study findings suggest that although the increase in gestational age in the 17-OHPC group was higher than that of the control group, the difference was not statistically significant.

Acknowledgments

The paper was derived from a Ph.D. dissertation approved by the Ethics Committee of Zahedan University of Medical Sciences in 2014 (ethical code: IR.ZAUMS.REC.1393.6184). The authors hereby acknowledge their gratitude to all the professors, colleagues, and patients who helped them with the project.

Table 5. The Effect of 17-OHPC on Preterm Labor Prevention Based on the Need for NICU Admission in the Two Groups Using Chi-Square Test

NICU Admission	Group			P Value
	Case	Control	Total	
+	16 (32)	14 (28)	30 (30)	0.711
-	34 (65)	36 (72)	70 (70)	
Total	50 (100)	50 (100)	100 (100)	

^aValues are expressed as No. (%).

Footnotes

Authors' Contribution: Designing of the study, developing the theory, performing the examination, verifying the analytical methods, and supervising the findings: Farahnaz Farzaneh and Maryam Razavi. Both authors discussed the results and contributed to the writing of the manuscript.

Conflict of Interests: The authors declared no conflict of interest.

Ethical Approval: IR.ZAUMS.REC.1393.6184.

Funding/Support: The current study was granted by Zahedan University of Medical Science.

References

- Gonzalez R. Parental administration of progesterone for preventing preterm birth: RHL commentary. *The WHO reproductive Health Library*. Geneva: World Health Organization; 2008.
- Kramer MS, Demissie K, Yang H, Platt RW, Sauve R, Liston R. The contribution of mild and moderate preterm birth to infant mortality. Fetal and Infant Health Study Group of the Canadian Perinatal Surveillance System. *JAMA*. 2000;**284**(7):843-9. doi: [10.1001/jama.284.7.843](https://doi.org/10.1001/jama.284.7.843). [PubMed: [10938173](https://pubmed.ncbi.nlm.nih.gov/10938173/)].
- Wood NS, Marlow N, Costeloe K, Gibson AT, Wilkinson AR. Neurologic and developmental disability after extremely preterm birth. EPIcure Study Group. *N Engl J Med*. 2000;**343**(6):378-84. doi: [10.1056/NEJM200008103430601](https://doi.org/10.1056/NEJM200008103430601). [PubMed: [10933736](https://pubmed.ncbi.nlm.nih.gov/10933736/)].
- Petrini JR, Callaghan WM, Klebanoff M, Green NS, Lackritz EM, Howse JL, et al. Estimated effect of 17 alpha-hydroxyprogesterone caproate on preterm birth in the United States. *Obstet Gynecol*. 2005;**105**(2):267-72. doi: [10.1097/O1.AOG.0000150560.24297.4f](https://doi.org/10.1097/O1.AOG.0000150560.24297.4f). [PubMed: [15684150](https://pubmed.ncbi.nlm.nih.gov/15684150/)].
- Spong CY, Meis PJ, Thom EA, Sibai B, Dombrowski MP, Moawad AH, et al. Progesterone for prevention of recurrent preterm birth: Impact of gestational age at previous delivery. *Am J Obstet Gynecol*. 2005;**193**(3 Pt 2):1127-31. doi: [10.1016/j.ajog.2005.05.077](https://doi.org/10.1016/j.ajog.2005.05.077). [PubMed: [16157124](https://pubmed.ncbi.nlm.nih.gov/16157124/)].
- Gilbert WM, Nesbitt TS, Danielsen B. The cost of prematurity: Quantification by gestational age and birth weight. *Obstet Gynecol*. 2003;**102**(3):488-92. [PubMed: [12962929](https://pubmed.ncbi.nlm.nih.gov/12962929/)].
- Petrou S, Mehta Z, Hockley C, Cook-Mozaffari P, Henderson J, Goldacre M. The impact of preterm birth on hospital inpatient admissions and costs during the first 5 years of life. *Pediatrics*. 2003;**112**(6 Pt 1):1290-7. doi: [10.1542/peds.112.6.1290](https://doi.org/10.1542/peds.112.6.1290). [PubMed: [14654599](https://pubmed.ncbi.nlm.nih.gov/14654599/)].
- Odibo AO, Stamilio DM, Nelson DB, Sehdev HM, Macones GA. A cost-effectiveness analysis of prenatal screening strategies for Down syndrome. *Obstet Gynecol*. 2005;**106**(3):562-8. doi: [10.1097/O1.AOG.0000174581.24338.6f](https://doi.org/10.1097/O1.AOG.0000174581.24338.6f). [PubMed: [16135588](https://pubmed.ncbi.nlm.nih.gov/16135588/)].
- Licciardi FL, Kwiatkowski A, Noyes NL, Berkeley AS, Krey LL, Grifo JA. Oral versus intramuscular progesterone for in vitro fertilization: A prospective randomized study. *Fertility and Sterility*. 1999;**71**(4):614-8. doi: [10.1016/S0015-0282\(98\)00515-9](https://doi.org/10.1016/S0015-0282(98)00515-9).
- Miles RA, Paulson RJ, Lobo RA, Press MF, Dahmouh L, Sauer MV. Pharmacokinetics and endometrial tissue levels of progesterone after administration by intramuscular and vaginal routes: A comparative study. *Fertil Steril*. 1994;**62**(3):485-90. doi: [10.1016/S0015-0282\(16\)56935-0](https://doi.org/10.1016/S0015-0282(16)56935-0). [PubMed: [8062942](https://pubmed.ncbi.nlm.nih.gov/8062942/)].
- Schmidt KL, Ziebe S, Popovic B, Lindhard A, Loft A, Andersen AN. Progesterone supplementation during early gestation after in vitro fertilization has no effect on the delivery rate. *Fertil Steril*. 2001;**75**(2):337-41. doi: [10.1016/S0015-0282\(00\)01709-x](https://doi.org/10.1016/S0015-0282(00)01709-x). [PubMed: [11172836](https://pubmed.ncbi.nlm.nih.gov/11172836/)].
- Shearman RP, Garrett WJ. Double-blind study of effect of 17-hydroxyprogesterone caproate on abortion rate. *Br Med J*. 1963;**1**(5326):292-5. doi: [10.1136/bmj.1.5326.292](https://doi.org/10.1136/bmj.1.5326.292). [PubMed: [13977012](https://pubmed.ncbi.nlm.nih.gov/13977012/)]. [PubMed Central: [PMC2123785](https://pubmed.ncbi.nlm.nih.gov/PMC2123785/)].
- Johnson JWC, Austin KL, Jones GS, Davis GH, King TM. Efficacy of 17 α -hydroxyprogesterone caproate in the prevention of premature labor. *New Engl J Med*. 1975;**293**(14):675-80. doi: [10.1056/nejm197510022931401](https://doi.org/10.1056/nejm197510022931401).
- Hendrickx AG, Korte R, Leuschner F, Neumann BW, Poggel A, Binkerd P, et al. Embryotoxicity of sex steroidal hormones in nonhuman primates: II. Hydroxyprogesterone caproate, estradiol valerate. *Teratology*. 1987;**35**(1):129-36. doi: [10.1002/tera.1420350116](https://doi.org/10.1002/tera.1420350116). [PubMed: [3563931](https://pubmed.ncbi.nlm.nih.gov/3563931/)].
- Caritis SN, Rouse DJ, Peaceman AM, Sciscione A, Momirova V, Spong CY, et al. Prevention of preterm birth in triplets using 17 alpha-hydroxyprogesterone caproate: A randomized controlled trial. *Obstet Gynecol*. 2009;**113**(2 Pt 1):285-92. doi: [10.1097/AOG.0b013e318193c677](https://doi.org/10.1097/AOG.0b013e318193c677). [PubMed: [19155896](https://pubmed.ncbi.nlm.nih.gov/19155896/)]. [PubMed Central: [PMC2790283](https://pubmed.ncbi.nlm.nih.gov/PMC2790283/)].
- Meis PJ, Klebanoff M, Thom E, Dombrowski MP, Sibai B, Moawad AH, et al. Prevention of recurrent preterm delivery by 17 alpha-hydroxyprogesterone caproate. *N Engl J Med*. 2003;**348**(24):2379-85. doi: [10.1056/NEJMoa035140](https://doi.org/10.1056/NEJMoa035140). [PubMed: [12802023](https://pubmed.ncbi.nlm.nih.gov/12802023/)].
- da Fonseca EB, Bittar RE, Carvalho MH, Zugaib M. Prophylactic administration of progesterone by vaginal suppository to reduce the incidence of spontaneous preterm birth in women at increased risk: A randomized placebo-controlled double-blind study. *Am J Obstet Gynecol*. 2003;**188**(2):419-24. doi: [10.1067/mob.2003.41](https://doi.org/10.1067/mob.2003.41). [PubMed: [12592250](https://pubmed.ncbi.nlm.nih.gov/12592250/)].
- American College of Obstetricians and Gynecologists. ACOG Committee Opinion. Use of progesterone to reduce preterm birth. *Obstet Gynecol*. 2003;**102**(5 Pt 1):1115-6. [PubMed: [14672496](https://pubmed.ncbi.nlm.nih.gov/14672496/)].
- Keirse MJ. Progesterone and preterm: Seventy years of "deja vu" or "still to be seen"? *Birth*. 2004;**31**(3):230-5. doi: [10.1111/j.0730-7659.2004.00315.x](https://doi.org/10.1111/j.0730-7659.2004.00315.x). [PubMed: [15330887](https://pubmed.ncbi.nlm.nih.gov/15330887/)].
- Winer N, Bretelle F, Senat MV, Bohec C, Deruelle P, Perrotin F, et al. 17 alpha-hydroxyprogesterone caproate does not prolong pregnancy or reduce the rate of preterm birth in women at high risk for preterm delivery and a short cervix: A randomized controlled trial. *Am J Obstet Gynecol*. 2015;**212**(4):485 e1-10. doi: [10.1016/j.ajog.2014.10.1097](https://doi.org/10.1016/j.ajog.2014.10.1097). [PubMed: [25448515](https://pubmed.ncbi.nlm.nih.gov/25448515/)].
- Awwad J, Usta IM, Ghazeeri G, Yacoub N, Succar J, Hayek S, et al. A randomised controlled double-blind clinical trial of 17-hydroxyprogesterone caproate for the prevention of preterm birth in twin gestation (PROGESTWIN): Evidence for reduced neonatal

- morbidity. *BJOG*. 2015;**122**(1):71–9. doi: [10.1111/1471-0528.13031](https://doi.org/10.1111/1471-0528.13031). [PubMed: [25163819](https://pubmed.ncbi.nlm.nih.gov/25163819/)].
22. Caritis SN, Venkataramanan R, Thom E, Harper M, Klebanoff MA, Sorokin Y, et al. Relationship between 17-alpha hydroxyprogesterone caproate concentration and spontaneous preterm birth. *Am J Obstet Gynecol*. 2014;**210**(2):128 e1–6. doi: [10.1016/j.ajog.2013.10.008](https://doi.org/10.1016/j.ajog.2013.10.008). [PubMed: [24113254](https://pubmed.ncbi.nlm.nih.gov/24113254/)]. [PubMed Central: [PMC3926421](https://pubmed.ncbi.nlm.nih.gov/PMC3926421/)].
 23. Nigar A, Hakim S, Mohsin Z. Role of 17 alpha hydroxy progesterone caproate (17OHP) in the prevention of preterm labor. *J Obstet Gynaecol India*. 2012;**62**(4):398–400. doi: [10.1007/s13224-012-0290-1](https://doi.org/10.1007/s13224-012-0290-1). [PubMed: [23904697](https://pubmed.ncbi.nlm.nih.gov/23904697/)]. [PubMed Central: [PMC3500942](https://pubmed.ncbi.nlm.nih.gov/PMC3500942/)].
 24. Timofeev J, Singh J, Istwan N, Rhea D, Driggers RW. Spontaneous preterm birth in African-American and Caucasian women receiving 17alpha-hydroxyprogesterone caproate. *Am J Perinatol*. 2014;**31**(1):55–60. doi: [10.1055/s-0033-1334452](https://doi.org/10.1055/s-0033-1334452). [PubMed: [23456908](https://pubmed.ncbi.nlm.nih.gov/23456908/)].
 25. Omani-Samani R, Sepidarkish M, Safiri S, Esmailzadeh A, Vesali S, Farzaneh F, et al. Impact of gestational weight gain on cesarean delivery risk, perinatal birth weight and gestational age in women with normal pre-pregnancy BMI. *J Obstet Gynaecol India*. 2018;**68**(4):258–63. doi: [10.1007/s13224-017-1023-2](https://doi.org/10.1007/s13224-017-1023-2). [PubMed: [30065539](https://pubmed.ncbi.nlm.nih.gov/30065539/)]. [PubMed Central: [PMC6046671](https://pubmed.ncbi.nlm.nih.gov/PMC6046671/)].