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Does hydroxyprogesterone caproate injection alter second trimester screening markers and neonatal outcomes?

Hidroksiprogesteron kaproat enjeksiyonu, ikinci trimester tarama belirteçlerini ve yenidoğan sonuçlarını değiştirir mi?

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Abstract

Aim: In the second trimester, biochemically evaluating maternal serum markers such as alpha-fetoprotein (AFP), unconjugated estriol (uE3), and human chorionic gonadotropin (hCG) may be performed as prenatal screening for neural tube defects (NTDs) and fetal aneuploidy and anomalies. We evaluated whether supplementation of 17-hydroxyprogesteronecaproate (17OHPC) in the second trimester can effect these markers. In addition, we evaluated pregnancy outcomes in pregnant women using 17OHPC.

Methods: This case control study included 1275 pregnant women between December 2014 and March 2018. The progesterone (study) group included women with a previous preterm birth and cervical length >25 mm. The control group included healthy pregnant women with a cervical length >25 mm and no previous preterm birth. Maternal age, body mass index (BMI) at the time of screening, gestational age at the time of screening, levels of maternal serum AFP, uE3, and hCG, fetal sex, fetal birth weight, Apgar score 5th minute <7, and admission to the neonatal intensive care unit (NICU) were evaluated.

Results: There was no statistically significant difference for maternal age, BMI, gestational age, fetal sex, fetal birth weight, Apgar score 5th minute <7, and admission to the NICU. The mean maternal serum uE3 and AFP levels were significantly less in the study group than in control group (P=0.008 and P=0.046, respectively). However, the mean maternal serum hCG levels were significantly higher in the study (P=0.033).

Conclusions: Second trimester screening tests for fetal aneuploidy and NTDs can give incorrect results in pregnant women using 17OHPC. These incorrect results may cause misdiagnosis and over-management. New threshold values for these markers in pregnant women using 17OHPC should be identified.

Keywords: 17-hydroxyprogesterone caproate, Prenatal screening tests, Progesterone therapy, Preterm delivery

Öz

Amaç: İkinci trimesterde, alfa-fetoprotein (AFP), konjuge olmayan estriol (uE3) ve insan koryonik gonadotropin (hCG) gibi maternal serum markırlarını biyokimyasal olarak değerlendirerek; nöral tüp defekti (NTD) ve bazı fetal anöploidi taraması yapılabilmektedir. İkinci trimesterde düşük tedavisi için 17-hidroksiprogesteron kaproat (17OHPC) takviyesinin bu markerleri etkileyip etkilemediğini değerlendirmek. Ayrıca, gebelerde 17OHPC kullanımının gebelik sonuçlarına etkisini değerlendirmektir.

Yöntemler: Bu retrospektif çalışma Aralık 2014 ile Mart 2018 arasında 1275 gebe içermekteydi. Annelik yaşı, tarama sırasındaki vücut kitle indeksi (VKİ), tarama sırasındaki gebelik yaşı, maternal serum AFP, uE3 ve hCG düzeyleri, fetal cinsiyet, fetal doğum ağırlığı, Apgar skoru 5. dakika <7 ve yenidoğan yoğun bakım ünitesine (NICU) giriş değerlendirildi.

Bulgular: Anne yaşı, VKİ, gebelik yaşı, fetal cinsiyet, fetal doğum ağırlığı, Apgar skoru 5. dakika <7 ve NICU'ya kabul edilmesinde istatistiksel olarak anlamlı bir fark yoktu. Ortalama maternal serum uE3 ve AFP düzeyleri progesteron grubunda kontrol grubuna göre anlamlı derecede düşüktü (sırasıyla p=0,008, p=0,046). Bununla birlikte, ortalama maternal serum hCG düzeyleri progesteron grubunda kontrol grubundan anlamlı derecede yüksekti (p=0,033).

Sonuçlar: Fetal anöploidi ve NTD'ler için yapılan ikinci trimester tarama testleri, 17OHPC kullanan hamile kadınlarda yanlış sonuçlar verebilir. Bu yanlış sonuçlar yanlış tanı ve aşırı yönetime neden olabilir. 17OHPC kullanan gebelerde bu belirteçler için yeni eşik değerleri tanımlanmalıdır.

Anahtar kelimeler: 17-hidroksiprogesteron-kaproat, Doğum öncesi tarama testleri, Progesteron tedavisi, Erken doğum

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Introduction

Preterm birth, which is defined as delivery prior to 37 weeks of gestation, accounts for over 85 percent of all perinatal morbidity and mortality. It is unsuccessful to postpone acute preterm labor, so protective strategies such as progesterone therapy are used by many clinics. Progesterone has an important role in maintaining pregnancy by protecting fetal membrane explants from apoptosis. Hence, progesterone therapy may decrease the rate of preterm birth or premature membrane rupture [1,2]. In addition, it maintains uterine serenity in the second and third trimesters [3].

The Food and Drug Administration (FDA, USA) approved 17-hydroxyprogesterone caproate (17OHPC) to reduce the risk of recurrent preterm birth in women with a singleton pregnancy and a history of prior spontaneous preterm delivery [4]. According to recent randomized trials, 17OHPC should start in the second trimester and continue until 37 weeks of gestation for maximum effect [5,6].

In the second trimester, biochemically evaluating maternal serum markers such as alpha-fetoprotein (AFP), unconjugated estriol (uE3), and human chorionic gonadotropin (hCG) may be performed as prenatal screening for neural tube defects (NTDs) [7] and some fetal aneuploidy and anomalies [8]. For example, elevated maternal serum AFP levels may indicate a fetal abnormality such as NTDs, abdominal wall defects, congenital nephrosis, or some tumors related to elevated AFP [9].

We evaluated whether supplementation of 17OHPC in the second trimester can affect the serum markers AFP, uE3, and hCG. In addition, we evaluated pregnancy outcomes in pregnant women using 17OHPC.

Materials and methods

This case control study, which was approved by the Institutional Ethics Committee, was performed in the Health Sciences University Kayseri Training and Research Hospital between December 2014 and March 2018. In total, 1275 pregnant Caucasian women were included in the study. Demographic characteristics such as maternal age, body mass index (BMI), gestational age, fetal birth weight, Apgar score 5th minute <7 and fetal gender were obtained from the hospital database. In addition, admission to the neonatal intensive care unit (NICU) and levels of maternal serum AFP, uE3, and hCG were evaluated.

All pregnant women included in this study were examined in our hospital from the first visit to delivery. All participants received a second trimester triple test for fetal aneuploidy and NTDs between the 16th and 19th weeks of gestation. Women with high-risk pregnancy factors such as multiple pregnancy, hypertension, body mass index >30 kg/m^2, diabetes mellitus, fetal growth retardation, miscarriages, fetal aneuploidy, endocrine diseases, chronic liver disease, using other medications, and tobacco were excluded from this study. All patients used folic acid, iron, or multivitamin preparations.

For measurement of hCG, AFP and uE3 levels in maternal serum samples, ImmuliteOne® system kits (Siemens Medical Solutions Diagnostics Limited, United Kingdom), which are based on the chemiluminescence method, were used with the Immulite 2000 device (Diagnostic Products Corporation, ABD). The values were recorded as the multiple of the median (MoM). Values were adjusted for age, weight, and gestational week. The second trimester triple test was calculated using the PRISCA 4.0 (Prenatal Risk Calculator, TYPOLOG Software/GmBH, Hamburg, Germany).

The progesterone (study) group included women with a previous preterm birth and cervical length >25 mm [5,6]. In our clinic, we apply 250 mg 17OHPC intramuscularly after the 16th week of gestation and continue weekly until the 37th week of gestation [6]. Patients with a cervical length ≤25 mm were excluded from this study because we use natural progesterone vaginally [5]. The control group included healthy pregnant women with a cervical length >25 mm and no previous preterm birth.

Statistical analysis

The Kolmogorov-Smirnov test was used for testing the normality of the data, and the variance homogeneity was assessed with the Levene test. Values were stated as mean ± standard deviation or median (25th percentile–75th percentile). Parametric comparisons were performed using a t-test, and nonparametric comparisons were performed using the Mann–Whitney U test. Minitab 16 (Minitab Inc.; State College, PA, USA) was used for all comparisons, and results were considered statistically significant when the P value was less than 0.05.

Results

This study consisted of 1275 pregnant women with 1115 in the control group and 160 in the progesterone group. Comparisons of maternal characteristics are shown in Table 1. There was no statistically significant difference between groups in terms of maternal characteristics such as age, gravidity, BMI, and gestational week at the examination time. Comparisons of biochemical parameters are shown in Table 2.

Table 1: Comparisons of maternal characteristics

	Progesterone group (n: 160)	Control group (n: 1115)	p
Maternal Age (years)	26.31 ± 6.14	26.73 ± 6.00	0.453
Maternal BMI (kg/m^2)	24.7 (23.7-28.9)	24.9 (23.5-28.6)	0.513
Gravidity	2 (2-3)	2 (2-3)	0.841
Gestational week at screening	17 (16-17)	16 (16-17)	0.278

Values are expressed as mean ± standard deviation or median (25th percentile–75th percentile). BMI: body mass index

Table 2: Comparison of biochemical parameters

	Progesterone group (n: 160)	Control group (n: 1115)	p
uE3 (ng/ml)	0.57 ± 0.26	0.72 ± 0.36	0.008
uE3 MoM	0.71 (0.55-0.92)	0.77 (0.62-0.98)	0.216
AFP(lU/ml)	31.0 ± 12.0	36.3 ± 23.5	0.046
AFP MoM	0.82 (0.61-1.08)	0.90 (0.69-1.12)	0.435
hCG (mlU/ml)	23698 (16733-31766)	18993 (13073-26303)	0.033
hCG MoM	0.98 (0.81 -1.29)	0.84 (0.60-1.11)	0.029

Values are expressed as mean ± standard deviation or median (25th percentile–75th percentile). uE3: unconjugated estriol, AFP: alpha-fetoprotein, hCG: human chorionic gonadotropin, MoM: multiple of the median

The mean maternal serum uE3 and AFP levels were significantly less in the progesterone group than in the control group (p=0.008 and p=0.046, respectively). However, the mean maternal serum hCG levels were significantly higher in the progesterone group than the control group. In addition, the MoM values of these biochemical parameters were evaluated. The median (25th percentile–75th percentile) uE3 MoM value was 0.71 (0.55-0.92) in the progesterone group whereas it was 0.77 (0.62-0.98) in the control group (p=0.216). The median (25th

percentile–75th percentile) AFP MoM value was 0.82 (0.61-1.08) in the progesterone group and 0.90 (0.69-1.12) in the control group (p=0.435). However, the median (25th percentile–75th percentile) hCG MoM value was statistically higher in the progesterone group than the control group [the median (25th percentile–75th percentile) values were 0.98 (0.81-1.29) and 0.84 (0.60-1.11), respectively, p=0.029].

Neonatal outcome and fetal characteristics were evaluated (Table 3). No significant differences for fetal birth weight, fetal gender, Apgar score 5th minute <7, and admission to the NICU were found.

Table 3: Comparison of fetal characteristics and neonatal outcomes

	Progesterone group (n: 160)	Control group (n: 1115)	p
Fetal gender	Male: 78 (48.7%)	Male: 555 (49.8%)	NS
	Female: 82 (51.2%)	Female: 560 (50.2%)	NS
Fetal birth-weight (g)	3120 ± 440	3130 ± 380	0.919
Apgar 5th minute <7	5 (3.1%)	31 (2.7%)	0.761
Admission to NICU	7 (4.5%)	47 (4.2%)	0.401

Values are expressed as mean ± standard deviation or n (%). NS: not significant, NICU: neonatal intensive care unit

Discussion

Maternal serum AFP, uE3, and hCG are markers of second trimester screening tests for fetal aneuploidy and NTDs. In this study, we evaluated whether using 17OHPC affected these markers. In order to increase the power of the study, homogeneous groups were selected. For maternal characteristics such as maternal age, BMI, gravidity, and gestational weeks at the time of screening, there was no significant difference between groups.

hCG, which is synthesized from trophoblasts, is a glycoprotein hormone. The secretion amount is proportional to the amount of trophoblastic tissue [10]. In the present study, we found that 17OHPC could increase maternal serum hCG levels. Both serum hCG levels and hCG MoM values were higher in the progesterone group than control group. Progesterone may increase placental volume [11]. Hence, increased trophoblastic tissue can increase production of hCG. Seventy percent of hCG is metabolized in the liver and 30% of hCG is metabolized in the kidneys [12]. However, progesterone may slow the metabolism of hCG in the liver. The effect of 17OHPC on hCG levels may be important for clinical use of hCG as a biochemical marker. Increased serum hCG levels may unfavorably affect second trimester screening tests for fetal aneuploidy. There is no similar study evaluating the effect of 17OHPC on maternal serum hCG level in the literature.

AFP, which is synthesized from the yolk sac, gastrointestinal tract, and fetal liver, is a glycoprotein macromolecule. It binds the estradiol hormone in the normal fetus. The AFP level rises until the 32nd gestational week, and then falls rapidly towards birth. The level increases in multiple pregnancies, open neural tube defects, and abdominal wall defects. The levels of AFP can fall in pregnant women with Down syndrome and trisomy 18 [7]. It can also be used as a tumor marker in adults. Although high-quality second-trimester fetal anatomy ultrasonography is suggested, maternal serum AFP should be performed to improve detection of NTDs when optimal images of the fetal spine or intracranial anatomy cannot be acquired (e.g. absence of high-quality ultrasound device, fetal position, or maternal obesity) [13]. In this study, we found serum AFP levels were lower in the progesterone group than in the control group. No similar studies evaluate the effect of 17OHPC on maternal serum AFP. 17OHPC may decrease production of AFP in the fetal liver. The effect of 17OHPC on AFP levels may be important for the clinical use of AFP as a biochemical marker. Decreased serum AFP levels may unfavorably affect the success of second trimester screening tests for NTD and fetal aneuploidy.

uE3 is one of the three major estrogens produced in the human body. Because uE3 production occurs in the placenta and fetus, levels increase significantly in pregnancy. Non-pregnant women, post-menopausal women, and men have similar levels. The fetal adrenal cortex-derived dehydroepiandrostenedione-sulfate (DHEA-S) is converted to 16-hydroxydehydroepiandrostenedione-sulfate (16α-OH-DHEA-S) in the fetal liver. DHEA-S and 16α-OH-DHEA-S are converted into estradiol-17α (E2) and estriol (E3) in the placenta. Shortly after E3 is produced, it is metabolized to the conjugate form in the maternal liver [14]. The active form of unconjugated estriol (uE3) accounts for 9% of total E3 in circulation. A decrease in the level of uE3 may indicate problems with fetal development. In this study, we found that serum uE3 levels were lower in the progesterone group than in the control group. Effect of 17OHPC on uE3 levels may be important for clinical use of uE3 as a biochemical marker. Decreased serum uE3 levels may unfavorably affect the success of second trimester screening tests for fetal aneuploidy. 17OHPC may negatively affect production of estriol in the fetal adrenal gland and liver as well as the placenta. Another study assessed the effect of 17OHPC on maternal salivary E3 levels. Klebanoff et al. [15] found significantly less salivary E3 levels in the progesterone group than in the control group.

We also investigated whether there was a difference in pregnancy outcomes. We did not find any positive or negative impact of 17OHPC use on neonatal outcomes such as fetal birth weight, Apgar score 5th minute <7, and admission to the NICU between study groups.

17OHPC, which is used to reduce the risk of recurrent preterm birth in women with a singleton pregnancy and a history of prior spontaneous preterm delivery, considerably alters serum markers such as AFP, uE3, and hCG. There was no previous study evaluating whether supplementation of 17OHPC in the second trimester affects these maternal serum markers in the literature. Hence, this is the first study. The limitation of this study is the nature of the retrospective. Another limitation is that we cannot evaluate long term effect of 17HPC on neonates.

Conclusion

We suggest that second trimester screening tests for fetal aneuploidy and NTDs might give incorrect results in pregnant women using 17OHPC. These incorrect results may cause misdiagnosis and over-management. Further research is needed and new threshold values for these markers in pregnant women using 17OHPC should be identified.

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