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ORIGINAL ARTICLE / ÖZGÜN ARAŞTIRMA

Beta-human chorionic gonadotropin concentrations in cervicovaginal secretions as an early marker of preterm delivery

Preterm doğumun erken bir belirteci olarak serviko-vajinal sekresyonlardaki gonadotropin konsantrasyonları

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ABSTRACT

Objectives: To investigate beta-human corionic gonadotropin (β-hCG) levels in cervicovaginal secretions as an early marker for preterm delivery.

Methods: The study included 55 patients at 25-36 of gestational weeks with preterm delivery risk factors including a history of preterm labor in a previous pregnancy or history of second trimester abortion. Beta-human chorionic gonadotropin (β-hCG) levels of cervicovaginal secretions were measured in all patients by the radioimmunoassay method using a commercial kit.

Results: Preterm delivery was observed in 25 patients and 30 patients gave term delivery. No significant differences were found between preterm and term delivery groups in age, gravidity and parity (P>0.05). APGAR scores and anthropometric measurements of newborns were significantly lower in preterm delivery group (P<0.001). Preterm delivery group had significantly higher cervicovaginal β-hCG levels compared with normal controls (94.7±37.7 vs. 35.5±14.8 mIU/ml, respectively, P<0.001). When 75 mIU/ml value of β-hCG level was taken as cut-off value; the sensitivity of the test was found as 76%, specifity 91.6%, positive predictive value 95.0% and negative predictive value as 79.9%.

Conclusion: Concentrations of β-hCG in cervicovaginal secretions may be a useful early biochemical marker to detect preterm. Based on β-hCG levels in cervicovaginal secretions a closer follow-up may decrease some complications of preterm delivery. *J Clin Exp Invest 2010; 1(1): 16-20*

Key words: Preterm delivery, beta-hCG, predictive value, servico-vaginal secretions

ÖZET

Amaç: Preterm doğum erken belirteci olarak serviko-vajinal sekresyonlardaki koriyonik gonadotropin'in rolünü araştırmak.

Yöntemler: Bir önceki doğumu erken doğum veya ikinci trimester düşük öyküsü risk faktörü olan, 25-36 gebelik haftasına sahip 55 gebe çalışmaya alındı. Hastaların tümünde servikovajinal sekresyonlardaki beta-insan koriyonik gonadotropin (β-hCG) düzeyleri radioimmunassay yöntemiyle ticari bir kit kullanılarak ölçüldü.

Bulgular: Gebelerden 25'i preterm, 30'u term doğum yaptı. Term ve preterm doğum yapana gebe grupları arasında yaş, gebelik sayısı ve parite açısından farklılık saptanmadı (P>0.05). Preterm doğum grubunda yenidoğan APGAR skorları ve bebeklerin antropometrik ölçümleri term doğum grubundan anlamlı düşük bulundu (P<0.05). Serviko-vaginal β-hCG düzeyleri; preterm grubunda, term doğum grubuna göre anlamlı yüksek bulundu (sırasıyla 94.7±37.7 mIU/ml ve 35.5±14.8 mIU/ml, P<0.001). Beta-hCG için, 75 mIU/ml cut-off değeri olarak alındığında; duyarlılığı %76, özgüllüğü %91.6, pozitif prediktif değeri %95 ve negatif prediktif değeri %79.9 olarak bulundu.

Sonuç: Preterm doğum açısından yüksek riskli hastalarda servikovajinal sekresyonlardaki β-hCG konsantrasyonu iyi bir biyokimyasal belirteç olabilir. Servikovajinal sıvılardaki β-hCG düzeyine dayanarak preterm doğum geliştireceği öngörülen hastalarda daha yakın takip ile komplikasyonlar azaltılabilir. *Klin Den Ar Derg 2010; 1(1): 16-20*

Anahtar kelimeler: Preterm doğum, beta-hCG, prediktif değer, serviko-vajinal sekresyonlar

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INTRODUCTION

Preterm delivery is the leading cause of perinatal morbidity and mortality throughout the world[1]. Accurate markers to determine whether a pregnant woman is at high risk for premature delivery would potentially allow improved surveillance and more timely intervention to improve the outcome[2-5].

Spontaneous preterm birth (SPB) occurs in 7–11% pregnancies before 37 gestational weeks and in 3–4% of pregnancies before 34 gestational weeks. Most neonatal deaths of healthy infants occur when they are born before 34 gestation weeks[1]. Recent advances in prenatal health care have not altered the incidence of SPB, but there is effective management to reduce the associated complications[6,7]. Antenatal steroids significantly reduce morbidity and mortality[8].

In present study we want to determine whether beta human corionic gonadotropin (β-hCG) concentration in cervicovaginal secretions of pregnant women can be taken as a prognostic risk marker for preterm birth.

Timely initiation of such a treatment in clinical practice depends on accurate prediction of SPB. Many tests have been reported to predict SPB such as cervicovaginal fetal fibronectin and cervical alpha fetoprotein[2-5].

Appearance of β-hCG, in both maternal serum and amniotic fluid is probably the result of direct β-hCG diffusion from the placenta[9]. Beta-hCG, like fibronectin, could be found in cervicovaginal secretions[10-13]. It has been suggested that the β-hCG level in vaginal fluid is a useful marker of premature rupture of membranes[10].

The aim of this study was to evaluate whether β-HCG concentration in cervicovaginal secretions would be a biochemical predictor for preterm delivery in pregnant women with high risk for preterm delivery.

METHODS

Patients

This study was performed at the Obstetrics Clinic of Dicle University Hospital between September-2004 and -2005. Fifty five patients at 25-36 gestational weeks were enrolled into the study. Twenty-five of 55 pregnant women delivered preterm babies and 30 of 55 pregnant women delivered term babies. Risk factors were accepted as having a history of preterm labor in previous pregnancy and/or a history of second trimester abortion.

The protocol was approved by the local ethics committee an informed consent was obtained from all patients. The gestational age was assessed on the basis of the last menstrual period, and confirmed by the ultrasonographic examination in the first trimester. If menstrual history was unreliable, or there was a difference of more than 10 days between menstrual and ultrasonographicly found dates, the ultrasonographic date was used.

Inclusion criteria for the study were singleton gestation, gestational age between 25 and 36 weeks, intact amniotic membranes (i.e. no obvious leakage of amniotic fluid, no pooling and negative ferning test results), absence of other maternal or fetal complications at admission and during pregnancy. Cervical and vaginal secretion sampling and ultrasonographic assessment were performed at admission by the same physician (Dr. M.E.S.).

Criteria for exclusion from the study were fetal congenital anomalies, placenta previa, vaginal bleeding, pregnancy-induced hypertension or preeclampsia, fetal growth restriction, fetal distress, multiple gestation, or preterm rupture of membranes and all conditions that may have an effect on cervicovaginal β-hCG concentration. None of the patients were receiving tocolytic therapy at the time of sampling.

The patients were followed up until delivery. Labors that occur before 37th week (259th day) of pregnancy were defined as preterm delivery.

Obtaining samples and method of β-hCG measurement

Cervicovaginal secretion samples were obtained during speculum examination from all patients. A cotton tipped swab was placed first into the endocervical canal and then into the posterior fornix of vagina, each for 30s. The swab was placed in a tube containing 1 ml of saline solution and the tube was shaken for 1 min before the swab was disposed off. The assay procedure began with centrifugation of the solution at 3500×g for 5 min to remove particulate matter. The remaining solution was quantitatively tested for the presence of β-hCG. The level

of β-hCG was measured by the radioimmunoassay method using a commercial kit (Roche Diagnostics, Mannheim, Germany). The kits were used by a moduler system (Roche E 170). Measurements were done in the Central Biochemistry Laboratory of Dicle University Hospital. Beta-hCG levels below the cut-off value of 0.2 mIU/ml were accepted as the minimum detectable value.

Statistical analysis

Data were expressed as mean±SD. Minumum and maximum values were calculated. Statistical analyses were done by using SPSS 12.0 program (SPSS Inc, Ill, Ca). Student's t-test or Chi-square tests were used in group comparisons in demographic and clinical data, where appropriate. Pearson's correlation analysis was used to assess the relationships between patient and control group. A value of $P<0.05$ was considered significant.

RESULTS

Of 55 patients, 25 cases who delivered at preterm were included in the study group and 30 cases who delivered at term consisted of the control group.

For the study cohort, mean maternal age was 27.6 years, median gravity was 4.3 and parity was 3.1. At the time of delivery mean gestational age that calculated from femur length (FL) was 31.6 weeks (Table 1). There was no history of preterm birth in 72 % of study group, but remained 28% had a history of preterm birth. Proportion of abortion during the second trimester was 8% and having two abortions was 4%.

Table 1. Demographic and obstetric characteristics of patients with preterm delivery vs. term delivery and β-hCG levels of cervicovaginal secretions

	Preterm (n=25)	Term (n=30)	P
Maternal age	27.6±6.9	28.7±7.6	NS
Gravida	4.3±2.7	4.2±3.2	NS
Parity	3.0±2.5	2.5±2.4	NS
Nulliparous, n (%)	6 (24.0)	9 (16.4)	NS
Multiparous, n (%)	19 (76.0)	21 (83.6)	NS
Gestational age at delivery	31.6±5.5	38.0±2.6	<0.001
Birth (g)	1810±614	3265±606	<0.001
β-HCG (mIU/ml)	94.7±37.7	35.5±14.8	<0.001

NS: not significant

The mean maternal age was 28.6 years, median gravity was 4.2 and parity was 2.5 in the control group. At the time of delivery mean gestational age, as calculated from femur length (FL), was 38 weeks. In the control group, 6.7% of women had a history of one preterm birth and 6.7% had history of two preterm births. During the second trimester ratio of cases having an abortion was 10%, ratio of cases having two abortions was 3.3% and ratio of three abortions was 3.3 % in the control group.

Comparing study group with control group, no statistically significant differences were found in age, gravida and parity ($P>0.05$). However, there were statistically significant differences between the study and control groups with regard to birth weight and gestational age ($P<0.05$) (Table 1) Birth weight and gestational age were significantly lower in the preterm group compared with the control group ($P<0.05$) (Table 1).

Table 2. Basic characteristics of the preterm and term groups at delivery.

	Preterms (n=25)	Terms (n=30)	P
Biparietal diameter, cm	31.2±3.3	37.8±1.2	<0.001
Head circ., cm	31.4±3.3	37.8±1.1	<0.001
Abdominal circ. cm	31.6±3.4	37.7±1.2	<0.001
Femur length, cm	31.6±3.3	38.0±1.0	<0.001
APGAR score (1st min)	4.8±1.5	6.9±1.8	<0.001
APGAR score (5th min)	7.2±1.4	8.7±1.2	<0.001

Circ.: circumference

First and 5th minute APGAR scores of infants in the preterm group were significantly lower in comparison with the control group ($P<0.05$) (Table 2). When compared with control group, the preterm group had significantly increased β-hCG concentrations in cervicovaginal secretions (35.5±14.8 mIU/ml vs. 94.7±37.7 mIU/ml , $P<0.001$) (Table 1).

A cut-off value of 77.8 mIU/ml for β-hCG levels in cervicovaginal secretions (at 25 percentile) had a sensitivity of 76% and specificity of 91.6% with positive and negative predictive values of 95% and 79.9%, respectively.

There was no significant correlation of β-hCG with other parameters both in preterm group and the control group ($P>0.05$).

DISCUSSION

Preterm birth continues to be a leading cause of perinatal morbidity and mortality throughout the world[1]. Recent advances in prenatal health care have markers that facilitate more accurate prediction of preterm birth. The use of biological markers to enhance clinical accuracy in predicting preterm birth has been recently proposed[2-5]. These tests have high capacity to identify the patients with high risk. Therefore these patients can be easily followed up and an effective management can be performed to these patients.

Preterm delivery can be prevented and fetal lung maturation can be accelerated by early diagnosis of asymptomatic patients that at risk of preterm birth. If low risk of preterm birth is diagnosed, length of hospital stay and close follow-up visits can be decreased. Additionally, aggressive tocolysis therapy must be avoided.

In the present study our aim was to determine whether human chorionic gonadotropin (hCG) can be a predictor of preterm birth. Beta-hCG is produced by placenta during pregnancy. Therefore it is found in high concentrations in maternal plasma and amniotic fluid. During the early weeks of pregnancy, amniotic fluid β-hCG levels are similar to maternal serum levels, then β-hCG in amniotic fluid decrease to %20 of maternal plasma levels and follow a similar gestational pattern[9]. From the time of conception concentrations in maternal serum and amniotic fluid of hCG rise to a peak between 8 and 12 weeks' gestation and then decline to plateau levels at approximately 18 weeks for the rest of the pregnancy. Recently, beta-hCG levels have also been studied in the cervicovaginal secretions of pregnant women (10-12). Anai et al. were the first to measure hCG levels in vaginal fluid (10). Their original study suggested that quantitative measurement of hCG from vaginal fluid may serve as a useful marker of premature rupture of fetal membranes.

In this study we observed that β-hCG level in cervicovaginal secretions of pregnant women with preterm delivery was three times more than the control group. In women with elevated levels of beta-hCG in the cervicovaginal secretions, the likely sources of the hormone are either the maternal serum or the amniotic fluid. An elevated level of this hormone in the cervicovaginal secretions of patient with preterm labor and intact membranes is more surprising. The possible source of β-hCG in cervicovaginal secretions in patients delivered preterm presumably is the leakage across the damaged membranes. Because of the size of the β-hCG molecule, it may be impossible to suppose that β-hCG is selectively leaking across the fetal membranes without substantial quantities of water and other molecules from the amniotic fluid. An alternative explanation may be that as a result of the inflammatory process that can precede the onset of preterm labor, there is an escape of β-hCG from the maternal serum into the cervical secretions.

Bernstein et al.[11] measured beta-hCG levels from cervicovaginal secretions of patients who had a risk factor for preterm delivery, between 24 and 28 gestational weeks. According to the cut-off value of >50 mIU/ml, sensitivity, specificity, and positive and negative predictive values for predicting preterm delivery were 50%, 87%, 33%, and 93%, respectively[11]. Guvenal et al.[12], utilizing a cut-off value of 28 mIU/ml between 24 and 36 gestational weeks and reported sensitivity, specificity, and positive and negative predictive values for preterm delivery as 87%, 65%, 28% and 97% respectively.

Garshasbi et al.[14] studied β-hCG levels cervicovaginal secretions of patients who had a risk factor for preterm delivery, between 24 and 28 gestational weeks. In their study the cut-off value of cervicovaginal β-hCG was reported to be 77.8 mIU/ml. According to this cut-off value the sensitivity, specificity, and positive and negative predictive values for predicting preterm delivery were 87%, 97%, 88.5% and 98%, respectively.

The cut-off value of cervicovaginal β-hCG of our study was 77.8 mIU/ml between 24 and 36 weeks of gestation. According to this cut-off value the sensitivity, specificity, and positive and negative predictive values for preterm delivery were 76%, 91.6%, 95% and 79.9%, respectively. The sensitivity reported in this study was higher than the values of Berstein et al.[11], but lower than those reported by Garshabi et al.[14] and Guvenal et al.[12].

Our specificity was higher than previously reported by Bernstein et al.[11] or Guvenal et al.[12]. Positive predictive value reported in this study was higher than the findings of all three studies that mentioned above[11,12,14], on the contrary, the negative predictive value was lower than values of those

three studies. An explanation for this discrepancy would be the differences in the study populations and cut-off data.

Garshabi et al.[14] compared history of preterm labor in study group and control group and they found significant difference between two groups. It was reported that ratio of previous preterm delivery in control group has been higher than the ratio in study group. In contrast; ratio of previous preterm labor in the study group was higher than the control group in our study.

In present study mean neonatal birth weight was 1810 g in the preterm group and 3265 g in the control group. Preterm birth increases perinatal morbidity and mortality because of low birth weight and low gestational age and organ immaturity of premature babies.

There were significant differences between two groups in APGAR scores. Mean APGAR score of the preterm group was significantly lower than the score of the control group. According to this data we suggest that there might be increase in neonatal morbidity and mortality as a result of preterm delivery. Preterm birth is a leading cause of perinatal morbidity and mortality in Turkey and throughout the world, and it can be prevented and fetal lung maturation can be accelerated by early diagnosis of asymptomatic patients at risk of preterm birth.

The patient's history, physical examination, and laboratory and ultrasound findings must be thoroughly evaluated to determine management of preterm labor. Additionally fetal lung maturation might be accelerated by administration of corticosteroids[15]. It is better to avoid from aggressive therapies as prophylactic tocolysis because of complications, increased cost and ineffectiveness of therapy[16].

The data derived from this study suggested that cervicovaginal β-hCG concentrations in women with high risk for preterm labor might be used as a biochemical marker. Further investigations are necessary to confirm the benefit of cervicovaginal β-hCG and to determine appropriate management strategies that supported by biochemical and physical findings.

REFERENCES

1.Copper RL, Goldenberg RL, Creasy RK, et al. A multicenter study of preterm birth weight and gestational age-specific neonatal mortality. Am J Obstet Gynecol 1993;168:78-84.

2.McLean M, Bistis A, Davis J, et al. Prediction risk of preterm delivery by second-trimester measurement of maternal plasma corticotropin-releasing hormone and alpha-fetoprotein concentrations. Am J Obstet Gynecol 1999;181:207-15.

3.Pateroster DM, Stella A, Gerace P, Manganelli F, Plebani M, Snijders D. Biochemical markers for the prediction of spontaneous preterm birth. Int J Gynecol Obstet 2002;79 2:123-9.

4.Leitich H, Egarter C, Kaider A, Hohlagschwandtner M, Berghammer P, Husslein P. Cervicovaginal fetal fibronectin as a marker for preterm delivery: a meta-analysis. Am J Obstet Gynecol 1991 ;165:858-66.

5.Iams JD, Casal D, McGregor JA, et al. Fetal fibronectin improves the accuracy of diagnosis of preterm labor. Am J Obstet Gynecol 1995;173:141-5.

6.Brecht G, Creasy RK. Preterm Labor: its diagnosis and management. Am J Obstet Gynecol 1986;3:154-9.

7.Gqzaway CP. Mullinsi L. Prevention of preterm labor and premature rupture of the membranes. Clin Obstet Gynecol 1986;29:835-41.

8.Crowley P. Prophylactic corticosteroids for preterm birth. Cochrance Database Syst Rev 2000;2:, p. CD000065.

9.Kletzky OA, Rossman F, Bertolli SI, Platt LD, Mishell DR. Dynamics of human chorionic gonadotropin, prolactin, and growth hormone in serum and amniotic fluid throughout normal human pregnancy. Am J Obstet Gynecol 1985; 151:878-84.

10.Anai T, Tanaka Y, Hirota Y, Miyakawa I. Vaginal fluid hCG levels for detecting premature rupture of membranes. Obstet Gynecol 1997;2:261-4.

11.Bernstein PS, Stern R, Line N, et al. Beta-human chorionic gonadotropin in cervicovaginal secretion as a predictor of preterm delivery. Am J Obstet Gynecol 1998;179:870-3.

12.Guvenal T, Kantas E, Erselcan T, Culhaoglu Y, Çetin A. Beta-human chorionic gonadotropin and prolactin assays in cervicovaginal secretions as a predictor of preterm delivery. Int J Gynecol Obstet 2001;75:229-34.

13.Creasy RK, Gummer BA, Liggins GC. System for predicting spontaneous preterm birth. Obstet Gynecol 1980; 55:693-9.

14.Garshasbi A, Ghazanfari T, Faghih Zadeh S. Beta-human chorionic gonadotropin in cervicovaginal secretions and preterm delivery. Int J Gynecol Obstet 2004,86:358-64.

15.Crowley P. Prophylactic corticosteroids for preterm birth. CochraneDatabase Syst Rev 2000;2:, p. CD000065.

16.Christopher A. Sullivan C, Morrison JC. Emergent management of the patient in preterm labor. Obstet Gynecol Clin N Am 1995;22:197-202.