International Journal of Gynecology and Obstetrics 86 (2004) 358–364

International Journal of GYNECOLOGY & OBSTETRICS

www.elsevier.com/locate/ijgo

Article

Beta-human chorionic gonadotropin in cervicovaginal secretions and preterm delivery

A. Garshasbi[a,*], T. Ghazanfari[b], S. Faghih Zadeh[c]

[a]*Department of Obstetrics and Gynecology, Shahed University, Faculty of Medicine, Tehran, Iran*
[b]*Department of Immunology, Shahed University, Faculty of Medicine, Tehran, Iran*
[c]*Department of Bio Statistics, Tarbiat Modaress University, Faculty of Medical Sciences, Tehran, Iran*

Received 7 January 2004; received in revised form 5 May 2004; accepted 11 May 2004

Abstract

Objectives: To determine whether concentrations of β-HCG in cervicovaginal secretions could predict spontaneous preterm birth (SPB) in asymptomatic high risk pregnancies. *Methods:* A cohort study was undertaken with cervicovaginal samples collected from 540 pregnant women between 20 to 28 weeks of gestation. Levels of β-HCG were measured by ELISA test. *Results:* There was 3.2-fold increase in cervicovaginal β-HCG concentrations among patients with SPB vs. term delivery. A single cervicovaginal β-HCG >77.8mIU/ml, between 20 and 28 weeks' gestation, identified patients with subsequent SPB vs. term delivery with sensitivity of 87.5% (95% CI: 47.4–97.9) and a specificity of 97% (95% CI: 86.5–99.4) with positive and negative predictive values of 88.5% and 98%, respectively. Multiple logistic regression indicates that cervicovaginal β-HCG level >77.8mIU/ml was an independent predictor of SPB (adjusted odds ratio 19.97, 95% CI: 10.65–37.45). *Conclusions:* Cervicovaginal β-HCG is a sensitive and specific predictor of patients with subsequent preterm delivery.

Keywords: Beta-human chorionic gonadotropin; Preterm delivery; Preterm labor

1. Introduction

Spontaneous preterm birth (SPB) occurs in 7–11% pregnancies before 37 weeks' gestation [1] and in 3–4% of pregnancies before 34 weeks' gestation [2]. Most neonatal deaths of normal infants occur when they are born before 34 weeks' gestation. Recent advances in prenatal health care have not altered the incidence of SPB, but there is effective management to reduce the associated complications. Antenatal steroids significantly reduce morbidity and mortality [3]. Timely instigation 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 [4–6].

Appearance of human chorionic gonadotropin (HCG), in both maternal serum and amniotic fluid is probably the result of direct HCG diffusion from

*Corresponding author. Tel.: +98-2188-30160; fax: +98-2188-29142.

0020-7292/04/$30.00
doi:10.1016/j.ijgo.2004.05.006

Table 1
Demographic and obstetric characteristics of patients with spontaneous preterm delivery vs. term delivery

	Spontaneous preterm delivery group ($n=153$)	Term delivery group ($n=387$)	Significance
Maternal age (years)	24.7 ± 6.3	26.9 ± 5.9	NS[a]
Parity			
Nulliparous (n, %)	40 (26.1%)	132 (34.1%)	0.002
Multiparous (n, %)	113 (73.8%)	255 (65.8%)	0.002
Indication for enrollment			
History of previous preterm delivery (n, %)	82 (53.5%)	286 (73.9)	0.000
History of second trimester abortion (n, %)	54 (35.2%)	78 (20.1%)	NS
Incompetent cervix (n, %)	11 (7.1%)	19 (4.9%)	NS
Uterine malformation (n, %)	6 (3.9%)	4 (1.03%)	NS
Gestational age at delivery (weeks ± S.D.)	32.1 ± 2.1	38 ± 1.5	0.000
Birth weight (g ± mean S.D.)	1789.3 ± 463.3	3188 ± 454.2	0.000

[a] Non-significant.

the placenta [7]. HCG, like fibronectin, could be found in cervicovaginal secretions [8]. It has been suggested that the HCG level in vaginal fluid is a useful marker of premature rupture of membranes (PROM) [9]. Bernstein et al. have reported that the sensitivity of cervicovaginal β-HCG was not as high as that of fetal fibronectin, however, its specificity, positive and negative predictive values showed same figures in the prediction of preterm delivery [10]. Guvenal et al. have showed that cervicovaginal β-HCG in patients with preterm labor might be used as a predictive test [11].

The objective of this study is to evaluate whether β-HCG concentration in cervicovaginal secretions of asymptomatic pregnant women considered high risk for preterm delivery would be associated with preterm delivery.

2. Materials and methods

2.1. Study design, sample collection, and population

The study was approved by Shahed University. A cohort study was undertaken with cervicovaginal samples collected from pregnant women who have at least one risk factor for preterm delivery. All women were followed at the obstetrics clinic of Hazrat Zaynab hospital between April 2002 and October 2003. Risk factors were designed such as: history of SPB in previous pregnancies, a history of second trimester abortion, a history of incompetent cervix and uterine malformation. Criteria for exclusion from the study were: fetal congenital anomalies, placenta previa, vaginal bleeding, pregnancy induced hypertension or pre-eclampsia, fetal growth restriction, fetal distress, preterm rupture of membranes, and all conditions that could have an impact on β-HCG concentration such as erythroblastosis and multiple pregnancy.

Each subject was enrolled between 20 and 28 complete weeks of pregnancy. Gestational age was based on the last menstruation if the last menstrual period and the earliest ultrasound biparietal diameter did not differ by more than 10 days. If not, the biparietal diameter was used to define gestational age. After the initial examination at 20 and 28 weeks of gestation, patients were examined at 2-week intervals. The primary outcome was defined as a SPB (after preterm rupture of mem-

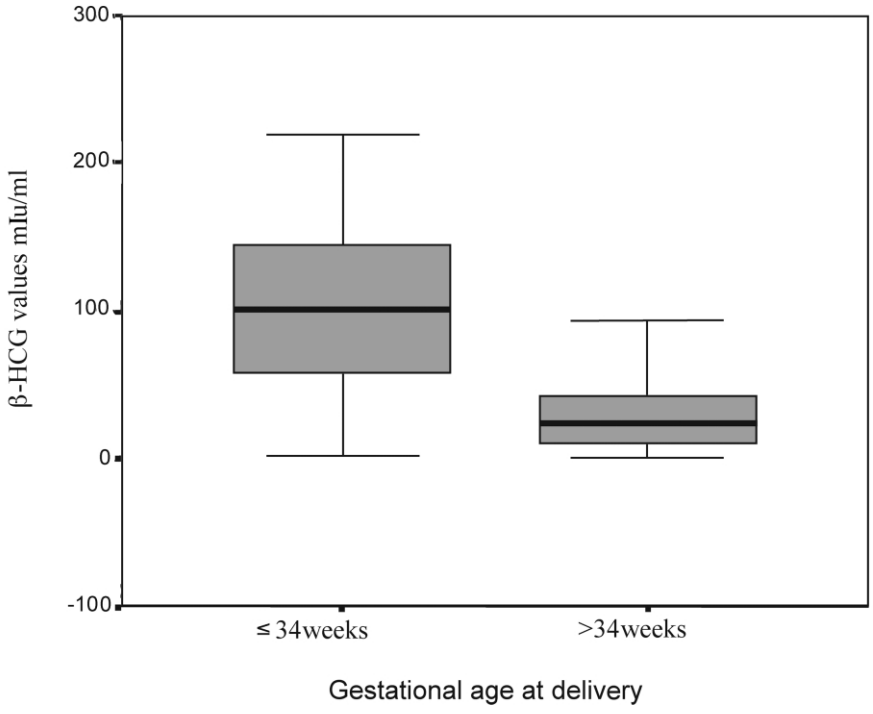

Fig. 1. Cervicovaginal β-HCG values in the group with spontaneous preterm birth vs. a group with delivery at term ($P=0.000$).

branes or spontaneous labor) at ≤34 weeks of gestation. The protocol was approved by the local ethics committee, and written consent was obtained after detailed information was given to every patient selected for the study.

Samples of cervicovaginal secretions were obtained during speculum examination. A cotton tip swab was placed first into endocervical canal and then into the posterior fornix of the vagina, each for 30 s. It was then placed in a dry tube for transportation to the laboratory.

Demographic, obstetric and outcome data were collected for all patients enrolled. The patients and their providers of obstetric care were blinded to the results of the β-HCG assays.

The study group consisted of patients with singleton gestations undergoing SPB before ≤34 weeks' gestation. The control group consisted of pregnant women with singleton gestations delivered at term.

2.2. Immunoassay

Samples were refrigerated and assayed within 72 h. The assay process began with addition of 0.75 ml saline solution to the tube containing the swab. The resulting solution was quantitatively tested for presence of β-HCG. The β-HCG level was measured by ELISA method using a commercial kit (Equipar, Italy). Results are reported in mIU/ml. Assay sensitivity was determined as 0.7 mIU/ml by the manufacturer.

2.3. Data analysis

Statistical analysis was performed with SPSS software.

A χ^2 or Fisher's exact test, Student's *t*-test or Wilcoxon rank sum test was performed as indicated. Multiple logistic regression was utilized to ascertain whether β-HCG was an independent

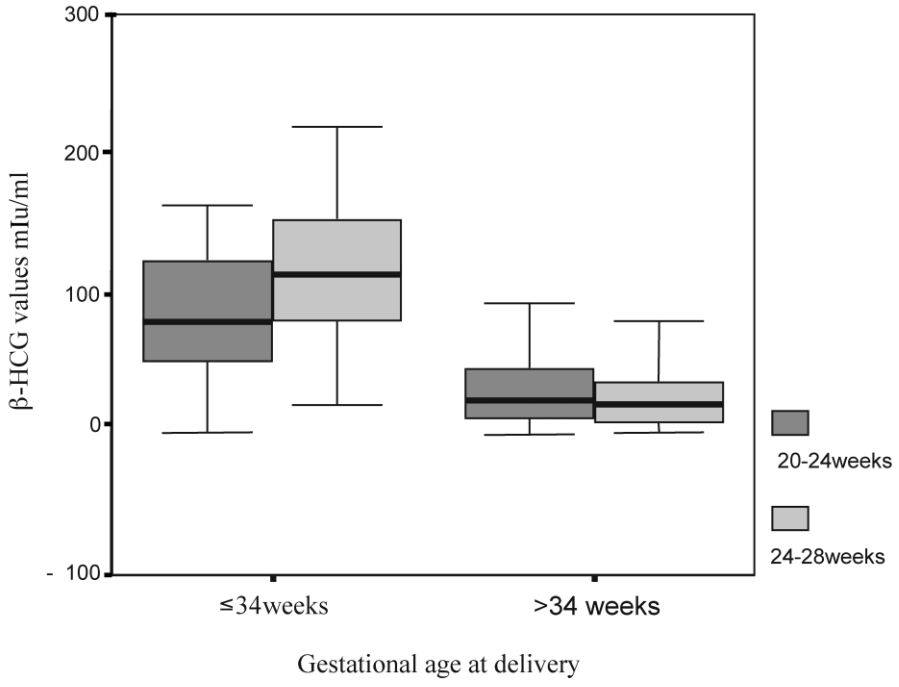

Fig. 2. Cervicovaginal β-HCG values obtained at 20–24 and 24–28 weeks' gestation in the group with spontaneous preterm birth vs. a group delivered at term.

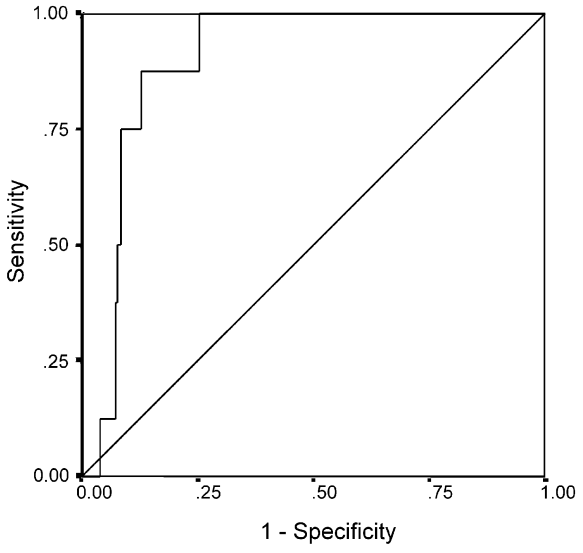

Fig. 3. ROC curve for β-HCG for spontaneous preterm birth. The area under curve is 0.898 (84.3–95.2%;95% CI).

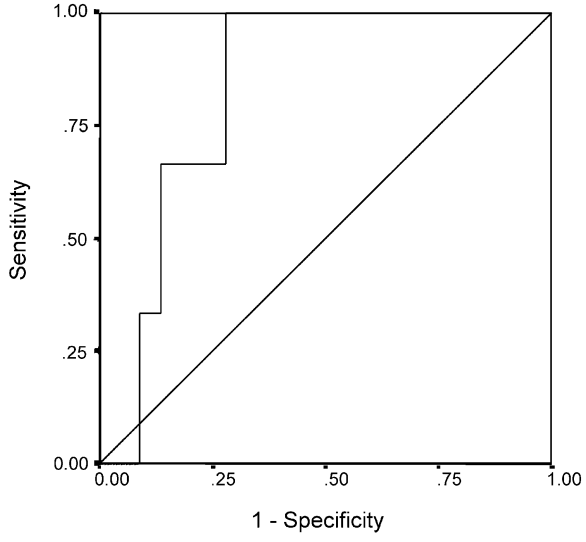

Fig. 4. ROC curve for β-HCG obtained at 20–24 weeks' gestation for detection of spontaneous preterm birth. The area under curve is 0.833 (72.1–94.5%; 95% CI).

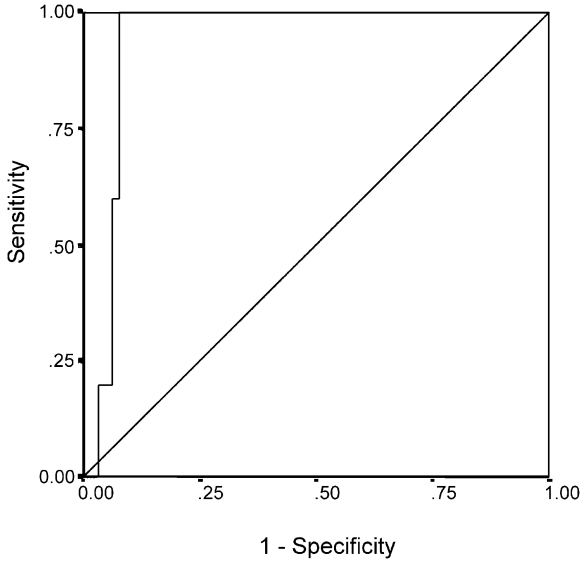

Fig. 5. ROC curve for β-HCG obtained at 24–28 weeks' gestation for detection of spontaneous preterm birth. The area under curve is 0.938 (89.5–98%; 95% CI).

predictor of preterm delivery. Receiver–operator characteristic (ROC) curve analysis was used to establish the cut-off values for cervicovaginal β-HCG, which optimized the prediction of SPB. Sensitivity, specificity, positive and negative predictive values with their 95% confidence intervals were also calculated. A value of $P<0.05$ was considered significant.

3. Results

Among 540 pregnant women considered at high risk for SPB 153 (28.6%) delivered before 34 weeks' gestation.

Table 1 presents the maternal, obstetric, and neonatal characteristics of women who had a SPB in comparison with those delivered at term. Mean maternal age (±S.D.) for the study cohort was 24.7±5.9, and 31.8% of them were nulliparas. Of the study cohort, 68.1% had a history of preterm delivery, 24.2% a second trimester abortion, 5.5% an incompetent cervix, and 1.8% uterine malformations.

Fig. 1 shows β-HCG values obtained from cervicovaginal secretion in women delivered term or preterm. The mean (±S.D.) β-HCG value in the preterm group was significantly higher in comparison with the term group (106.4±58.7 mIU/ml vs. 32.3±31.6 mIU/ml, $P<0.000$).

Fig. 2 shows the early β-HCG values obtained in 20–24 weeks in comparison to values at 24–28 weeks and the relations of values with SPB and term delivery. In SPB group mean (±S.D.) β-HCG values obtained at 24–28 weeks were significantly higher than at 20–24 weeks (116.7±58.9 mIU/ml vs. 85.6±55.7 mIU/ml, $P<0.000$). In the term group mean (±SD) β-HCG values obtained at 20–24 weeks were significantly higher than at 24–28 weeks (37.1±37.5 mIU/ml vs. 28.1±25 mIU/ml, $P<0.001$).

Reciver–operating characteristic (ROC) curve analysis was used to establish the optimal cut-off values the β-HCG levels of cervical secretions in order to predict preterm delivery (Fig. 3). A value of 77.8 mIU/ml had a sensitivity of 87.5% (47.7–97.9; 95% CI) and specificity of 97% (86.5–99.4; 95% CI) with positive and negative predictive values of 88.5% and 98%.

ROC curve analysis was used to establish the optimal cut-off values for β-HCG levels obtained at 20–24 and 24–28 weeks in order to predict preterm delivery (Figs. 4 and 5).

Table 2
Sensitivity, specificity, positive and negative predictive values of cervicovaginal β-HCG at 20–24 and 24–28 weeks' gestation for prediction of spontaneous preterm birth

No. weeks' gestation	β-HCG value (mIU/ml)	Sensitivity	Specificity	Positive PV[a]	Negative PV[a]
20–24	77.8	66.7%	86.5%	33%	94%
24–28	90.9	80%	92.2%	63%	74%

[a] Predictive value.

Table 2 presents the sensitivity, specificity, positive and negative predictive values of β-HCG cut-off that was obtained at different intervals.

Moreover, after the risk factors in Table 1 were entered into a multiple logistic regression model, cervicovaginal β-HCG >77.8 mIU/ml obtained at 20–28 weeks proved to be independently associated with SPB (adjusted odds ratio 19.97, 95% CI 10.65–37.45).

4. Discussion

In the present study, we evaluated the diagnostic value of β-HCG in cervicovaginal secretions to predict SPB. The results indicate that cervicovaginal β-HCG measured between 20 and 28 weeks were significantly higher in patients delivered preterm than in those delivered at term. Cervicovaginal β-HCG levels >77.8 mIU/ml were associated with subsequent preterm deliveries in about 87% of cases. Conversely, 97% of patients who delivered at term had cervicovaginal β-HCG ≤77.8 mIU/ml. Cervicovaginal β-HCG proved to be a better predictor of SPB than demographic and obstetric risk factors.

Bernstein et al. observed a rise in median β-HCG values in cervicovaginal secretions until approximately 10–15 weeks' gestation to a peak of 44 mIU/ml and a decline to 5.6 mIU/ml between 20 and 25 weeks of gestation. The median concentration of β-HCG in cervicovaginal secretions subsequently remained at this level for the ongoing of pregnancy [9]. In women with elevated levels of β-HCG in cervicovaginal secretions, the likely sources of hormone are either the maternal serum or the amniotic fluid. β-HCG may leak selectively across fetal membranes or as a result of an inflammatory process that can precede the onset of preterm labor, when β-HCG may escape from the maternal serum into the cervical secretions.

Bernstein et al. reported the cut-off value β-HCG of cervicovaginal secretions obtained in 24–28 weeks' gestation of pregnant women who had risk factors for SPB. According to the cut-off value of >50 mIU/ml sensitivity, specificity, and positive and negative predictive values for predicting delivery before 34 weeks' gestation were 50%, 87%, 33%, and 93%, respectively.

Guvenal et al. found that cervicovaginal β-HCG levels obtained in 24–36 weeks' gestation were significantly higher in women with SPB compared with women who delivered at term ($P=0.031$) [10]. The optimal cut-off value for β-HCG (27.1 mIU/ml) had a sensitivity of 87.5%, a specificity of 65.4%, and positive and negative predictive values of 28% and 97%, respectively.

The cut-off value of cervicovaginal β-HCG of our study calculated by ROC was 77.8 mIU/ml between 20 and 28 weeks. This cut-off value had a sensitivity, specificity, and positive and negative predictive value of 87%, 97%, 88.5%, 98%, respectively, for SPB. The sensitivity reported in this study is similar to the values of Guvenal et al., but higher than those reported by Bernstein et al. (87% vs. 87%, 50%). The specificity is higher than previously reported by Bernstein et al. or Guvenal (97% vs. 87%, 65%). An explanation for this discrepancy would be the differences in the study populations and cut-off time's data.

Our study indicates that a value of cervicovaginal β-HCG >77.8 mIU/ml, between 20 and 28 weeks' gestation, can identify approximately 87% of women who will deliver before 34 weeks' gestation. The results of this study suggest that a single cervicovaginal β-HCG measurement in pregnant women between 20 and 28 weeks' gestation might be used to predict SPB.

References

[1] Maternal and Child Health Consortium. Confidental enquiries into stillbirths and deaths in infancy (CESDI): 6th annual report. London: Stationery Office, 1999.
[2] Peters KD, Kochanek KD, Murphy SL. Deaths: final data for 1996. Natl Vital Stat Rep 1998;47:1–100.
[3] Crowley P. Prophylactic corticosteroids for preterm birth. Cochrance Database Syst Rev 2000;2:CD000065.
[4] McLean M, Bistis A, Davis J, Walters W, Hackshaw A, De Voss K, 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;181:207–215.
[5] Pateroster DM, Stella A, Gerace P, Manganelli F, Plebani M, Snijders D, Nicolini U. Biochemical markers for the prediction of spontaneous preterm birth. Int J Gynecol Obstet 2002;79(2):123–129.

[6] 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;165:858–866.

[7] Iams JD, Casal D, McGregor JA, Goodwin TM, Kreaden US, Lowensohn R, et al. Fetal fibronectin improves the accuracy of diagnosis of preterm labor. Am J Obstet Gynecol 1995;173:141–145.

[8] Kleytzky OA, Rossman F, Betrolli SI, Olatt LD, Mishell DR Jr. Dynamics of human chorionic gonadotropin, prolactin, and growth hormone in serum and amniotic fluid throughout normal human pregnancy. Am J Obstet Gynecol 1985;151:878–884.

[9] Anai T, Tanaka Y, Hirota Y, Miyakawa I. Vaginal fluid HCG levels for detecting premature rupture of membranes. Obstet Gynecol 1997;2:261–264.

[10] Bernstein PS, Stern R, Line N, Furgiuele J, Karmen A, Comerford-Freda M, et al. Beta-human chorionic gonadotropin in cervicovaginal secretion as a predictor of preterm delivery. Am J Obstet Gynecol 1998;179:870–873.

[11] Guvenal T, Kantas E, Erselcan T, Culhaoglu Y, Cetin A. Beta-human chorionic gonadotropin and prolactin assays in cervicovaginal secretions as a predictor of preterm delivery. Int J Gynecol Obstet 2001;75:229–234.