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A survey of βhCG in Cervicovaginal Secretions as a predictor of Preterm Delivery

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ABSTRACT

The purpose of this study was to evaluate the relationship between the levels of βhCG cervicovaginal secretions and preterm delivery. A cross-sectional analysis was used and cerevicovaginal secretion specimens were obtained from women in their 24th-36th weeks (every 6 days) of pregnancy who presented the pregnancy clinic with preterm labor manifestations. Frozen samples (at -20°C) were assayed with radio immunoassay method in 72 hours, showed the higher mean values of βhCG in cervicovaginal secretions in group 1(preterm labor and delivery) compared with group 2 (preterm labor and term delivery) and group 3 (control). There was a considerable difference in the value of human chorionic gonadotropin among three pregnant groups. Elevated cervicovaginal levels of βhCG (22.5 milli unit per milliliter) is associated with preterm delivery (97% sensivity, 76% specifity, 81% positive predictive value, 96% negative predictive value). The cut-off group 2 and 3 are also reported, which showed the βhCG level could be used as a useful parameter for preterm delivery prediction.

Key words: βhCG, Chorionic gonadotropin, Preterm labor, Preterm delivery.

INTRODUCTION

Preterm delivery is one of the most important issues in reproductive health and it is one of the serious prenatal events [1]. Preterm delivery is responsible for 75- 80 percent of neonatal death to causes other than congenital anomalies [2]. Most neonatal deaths of healthy infants occur when they are born before 34 gestation weeks [3]. The diagnosis of preterm labor is difficult. The traditional method for diagnosis of preterm labor is accompanied by a high false positive rate [4]. The accurate identification of high risk pregnancies is important [6]. A suitable screening test that was affordable, for all pregnant women be useful, non-invasive and is dedicated to the positive is required [7]. Serum markers are associated with preterm labor [8]. Cervical or vaginal fetal fibronectin levels, assessed serially or at specific gestational age, have been shown to be a potential predictor in several studies [9,10]. However, reported sensitivities, specificities, positive and negative predictive values have varied considerably in different studies and are far from optimal in some [9]. One of the studied markers to predict preterm delivery is a glycoprotein, human chorionic gonadotropin (hCG)[11]. Human chorionic gonadotropin in cervicovaginal secretions was found in high concentration until 20 week´s gestation, but after 20 weeks of gestation, it remained at a stable level [12]. The amount of βhCG in the cervicovaginal secretions mirrors the levels in the maternal serum and the amniotic fluid. The elevation of βhCG levels in the cervicovaginal secretions may be due, via the maternal serum, to the inflammatory process that can precede the onset of labor. It may be related to the elevation of βhCG levels in the cervical secretions before active labor [13]. The aim of the current study is to assess the diagnostic accuracy of β-subunit of human chorionic gonadotropin (βhCG) in cervicovaginal secretions, as a biochemical predictor of preterm labor, among both normal pregnant women and those presenting with threatened preterm labor.

MATERIALS AND METHODS

2.1 Study setting and population

A comparative cross-sectional study was performed with cervicovaginal samples collected from pregnant women who have at least one risk factor for preterm delivery. The study population consisted of patients, admitted to 29 Bahman, Azzahra and Taleghany medical hospitals with sign and symptoms suggestive of preterm labor and intact membranes (n=60) and normal pregnancy (n=27). Gestational age of each enrolled subject was between 24 and 36 weeks. Gestational age was estimated on the basis of the first day of menstruation (LMP); it was estimated by ultrasonography if LMP was unreliable. If the estimation difference between LMP and ultrasonography was more than ten days, the reported age on the basis of ultrasonography was considered as the gestational age.

2.2 Inclusion criteria

Symptoms suggestive of preterm labor included regular uterine contractions (at least four in 20 min or eight in 60 min), low abdominal back pain, pelvic pressure, increased vaginal discharge, cervical dilatation<3 cm and intact amniotic membranes (i.e. no obvious leakage of amniotic fluid and negative ferning and nitrazine paper reaction test result).

3.2 Exclusion criteria

Exclusion criteria included confirmed rupture of fetal membranes, gestational age less than 24 weeks or more than 37 weeks, polyhydramnios, multiple pregnancy, abruption placenta, placenta previa, cervical cerclage, amniocentesis, presence of gross blood in the vagina, coitus during 24 past hours, symptoms of intraamniotic infections, presence of systemic diseases, intra uterine fetal growth restriction, prior tocolysis, congenital anomalies, pre-eclampsia, fetal distress, cervical dilation of at least 4 cm and all conditions that could have an impact on βhCG concentration.

4.2 The control group

The control group was include pregnant women matching the study group, with the same inclusion and exclusion criteria without being in threatened preterm labor such women will be recruited from women attending outpatient clinics for routine antenatal care. 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.

5.2 Procedures and method of βhCG measurement

For two groups, before digital examination, cervicovaginal secretions were taken by applying speculum; this method is consistent with conducted researches by Bernstein [13]. At the first step, 1 cc normal saline have been poured into the posterior fornix of vagina and then after 30 seconds, 1 cc of the present secretion were taken by a syringe and poured into a dry test tube for transportation to the library. All samples were taken before administrating tocolytic medications. Levels of βhCG were measured by applying the method of Radio immunoassay. Evaluation sensitivity was less than 1 Iu/cc. Variable intra and inter assay accuracy was less than 7%. All included women of both groups followed up until delivery. Cases of study group were categorized into two groups: women with preterm delivery (before completed 37 weeks gestation, n=31) and women with delivery at term (≥completed 37 weeks gestation, n=29). Demographic, obstetric and outcome data were collected for all enrolled patients.

6.2 Statistical analysis

Statistical analysis performed using statistical package for social sciences (spss) for windows. Continuous variables were analyzed by the analysis of variance and categorical data were analyzed by the chi-square test (x^2). Receiver operator characteristics (ROC) curve analysis was used to find the best cut-off level of βhCG in the cervicovaginal secretion to predict preterm labor. Diagnostic validity will be assessed using the terms of sensitivity, specificity, positive predictive value, negative predictive value. Significance level will be set at 0.05.

RESULTS

Among of the attended patients with preterm labor, 31 cases get preterm delivery and 29 had full term delivery. All of cases in control group had delivery at term. The table 1 shows comparison of demographic characteristics of preterm and term delivery groups. In the tables has been not seen significant relationship between studied groups in terms of mother age, education level, the number of delivery and gestational age when accepted. There was significant difference between gestational age in the time of delivery and sampling interval until delivery (table 1). Demographic and obstetrics data of patients in three groups are listed in Table 1.

Table 1: Demographic and obstetrics characteristics of patients with (1) preterm labor & preterm delivery, (2) preterm labor& term delivery, (3) term delivery

Demographic characteristics	Preterm labor and delivery	Preterm labor and term delivery	Term delivery (control group)	Significant
Maternal age (years)	24.45 ± 4.23	23.31± 4.23	25.92 ± 5	NS
Education level				
Primary school n(%)	11(35.5%)	11(37.9%)	7(25.9%)	NS
High school n(%)	11(35.5%)	10(35.5%)	7(25.9%)	NS
University n(%)	6(19.4%)	5(17.2%)	8(29.6%)	NS
Parity				
Nulliparous (n)	14	18	13	NS
Multiparous (n)	17	11	14	NS
Week of pregnancy at admission (weeks)	31.14 ± 3.64	31.04 ± 3.8	31.4 ±3.80	NS
Delivery (Weeks)	32.1 ± 3.6	39.04 ± 1.38	39.04 ± 1.38	0.0001
Sampling – delivery interval (days)	6.77 ± 6.87	59.76 ± 27.36	59.76 ± 27.36	0.0001
βhCG (mIμ/ml)	34 ± 7.47	17.44 ± 10.64	10.02 ± 7.66	0.0001

Figure 1 shows βhCG values obtained from cervicovaginal secretion in women term or preterm delivery. The mean values of βhCG for preterm labor and delivery were 34 ± 7.47, preterm labor and term delivery 17.44 ± 10.64 and term delivery (control group) 10.02 ± 7.66. As it can be seen from Figure 1, the mean value of cervicovaginal βhCG in preterm delivery is significantly more than term delivery (p≤0.03).

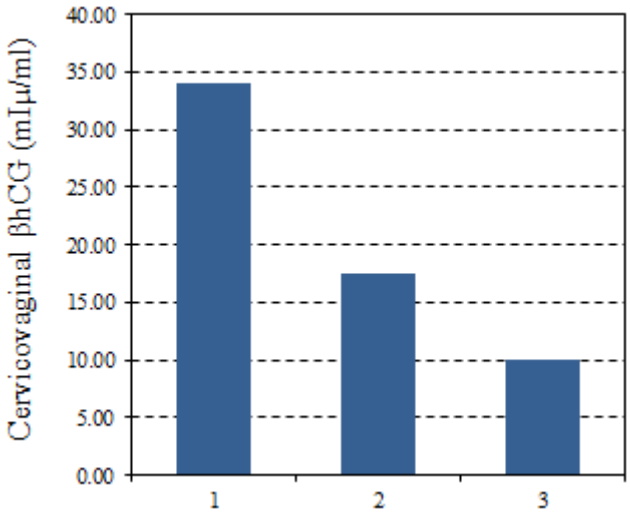

Figure 1: Cericovaginal βhCG levels in (1) preterm labor & preterm delivery, (2) preterm labor& term delivery, (3) term delivery, (P<0.03).

ROC curve is to identify and compare cut-off point of βhCG hormone in three groups. The obtained ROC curves for three groups are shown in Figures 2 to 4 and will be discussed in the next section.

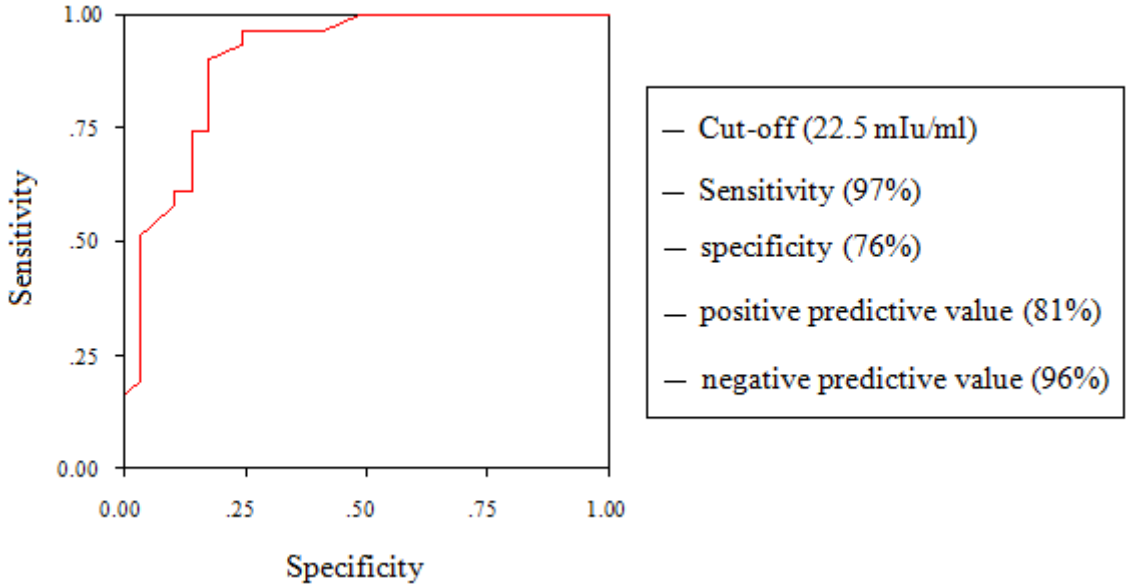

Figure 2: ROC curve for determination of βhCG cut-off and for separation of preterm labor & delivery and preterm labor & term delivery.

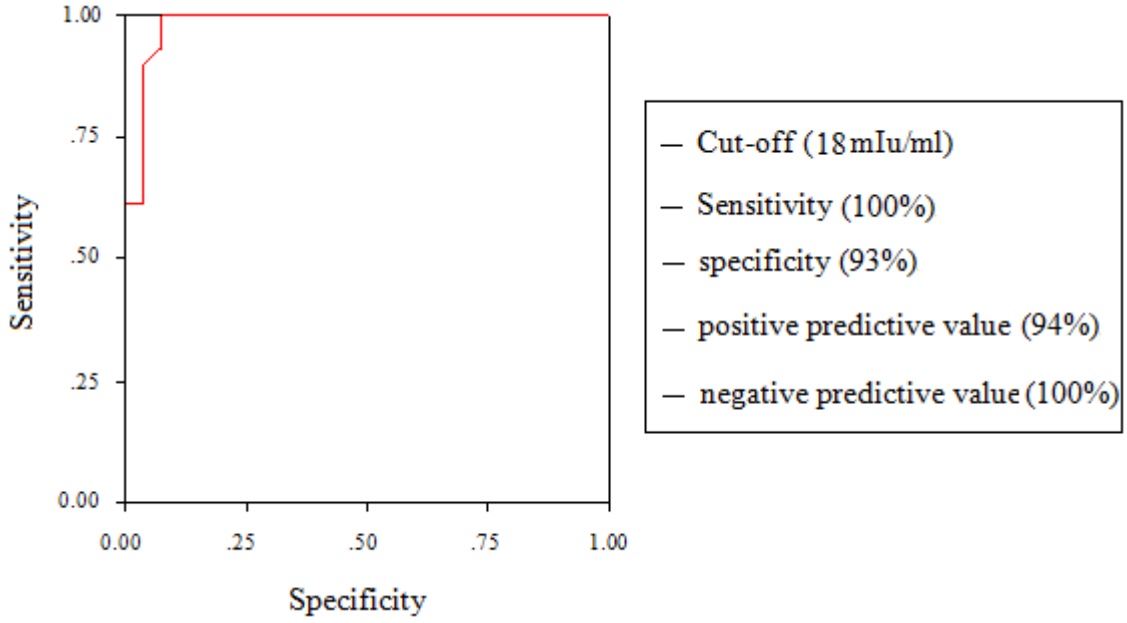

Figure 3: ROC curve for determination of βhCG cut-off and for separation of preterm labor & preterm delivery and term delivery.

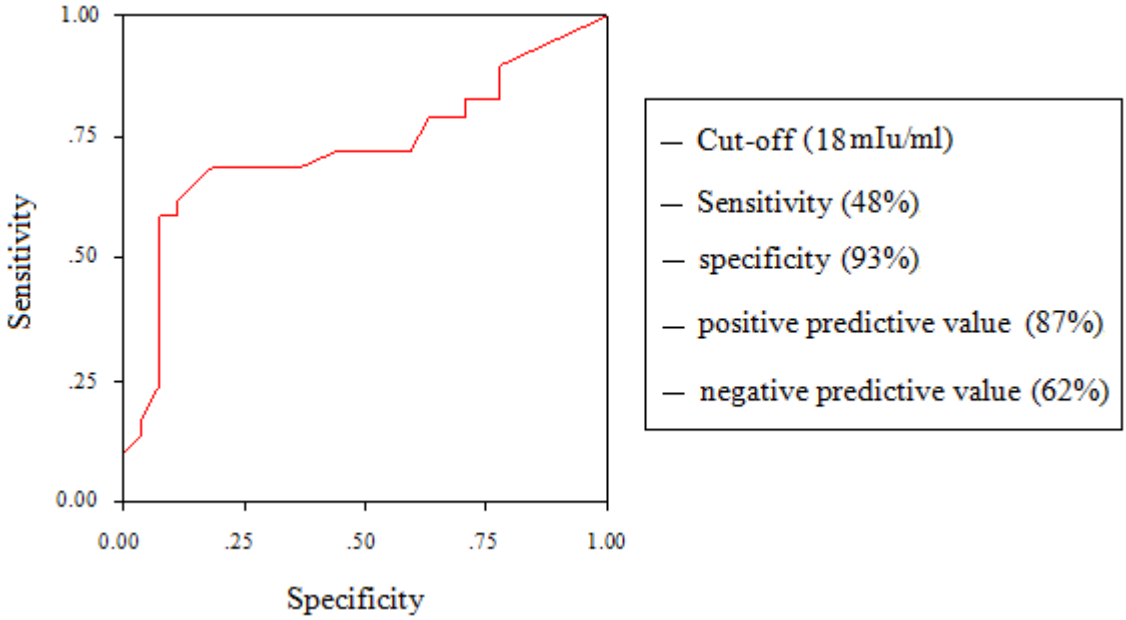

Figure 4: ROC curve for determination of βhCG cut-off and for separation of preterm labor & term delivery and term delivery.

DISCUSSION

Since the treatment of preterm labor and its prevention has had less success, today the investigations has been focused to predict possibility of preterm delivery. For screening high risk pregnancy several tests and markers has been developed. Many of these markers related to embryonic proteins. In the present study, we evaluated and compared one of these diagnostic protein markers, human chorionic gonadotropin, and its association with preterm labor and whether this glycoprotein marker can be used as a marker to predict preterm labor. Preterm delivery can be prevented and fetal lung maturation can be accelerated by early diagnosis of asymptomatic patients that at risk for preterm birth. If risk of preterm birth is low, duration of hospital stay and intervals of follow up visits will be decreased. Moreover, aggressive tocolytic therapy must be avoided. [14]. On the other hand, neonatal intensive care units are present in a few hospitals so this transfer will be a burden of concerns for the families. Human chorionic gonadotropin, which is produced in the placenta, is present in high concentrations in the amniotic fluid and maternal serum during pregnancy. Concentration in the maternal serum and amniotic fluid rise to a peak between 8 and 12 weeks of pregnancy, then decline until approximately the 18th week to plateau for the rest of the pregnancy [15]. Anai et al. were the first to measure hCG level in vaginal fluid. Their original study suggested that quantitative measurement of hCG level from vaginal fluid may serve as a useful marker of premature rupture of fetal membranes [16]. In the report by Bernestein , βhCG concentrations in cervicovaginal secretions were determined every 2 weeks in pregnant patients between 24 and 36 weeks of gestation. The cut off values of 50 mIu/ml for hCG to predict preterm labor before 34 weeks had a sensitivity of 50%, specificity of 87%, PPV of 33% and NPV of 93% [13]. In another study, by Guvenal et.al (2001) conducted on 60 patients, cervicovaginal βhCG and prolactin levels were significantly higher in the preterm group when compared with those of the term delivery group. The optimal cut-off values for βhCG (27.1 mIu/ml) gave a sensitivity level of 87.5% and specificity of 65.4% with positive and negative predictive values of 28% and 97%, respectively [17]. Garshasbi et.al studied βhCG levels of 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 βhCG 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 delivery were 87%, 97%, 88.5% and 98% respectively [18]. These researches have concluded that cervicovaginal βhCG measurement in patients with preterm labor may be used as a predictive test. In present study, according of ROC curves, the cut-off of cervicovaginal βhCG secretions for predicting preterm labor and delivery and preterm labor & term delivery was 22.5 mIu/ml and the rate of sensitivity, specificity, positive and negative predictive value for cut-off were 97%, 76%, 81% and 96%,respectively (Fig. 2); the cut-off value of cervicovaginal βhCG secretions for predicting preterm labor & preterm delivery and term delivery was 18 mIu/ml and the rate of sensitivity, specificity, positive and negative predictive value for cut-off were 100%, 93%, 94% and 100%,respectively (Fig. 3) and the cut-off value of cervicovaginal βhCG secretions for predicting preterm labor & term delivery and term delivery was 18 mIu/ml and the rate of sensitivity, specificity, positive and negative predictive value for cut-off were 48%, 93%, 87% and 62% respectively (Fig. 4). In other conducted studies, as it is seen, the rate of cut-off and βhCG predictive value to distinguish the preterm delivery from term delivery is evaluated that in comparison of the reported data with the present study, it is seen the rate of βhCG cut-off in this study is closer than the reported data from Guvenal study

that is 28 mIu/ml and is related to Turkish, meanwhile, it is different from the reported cut-off by the Bernstein <50 mIu/ml which is related to the European countries. This major difference perhaps is arising from hormones natural differences in different races and geographic areas that for the reason of proximity with the neighborhood countries; this is actually evident in the rate of βhCG cut-off value. In the points of the rates of sensitivity, specificity, positive and negative predictive value, generally, this study is similar to Guvenal study. This proximity may be due to the similarity of the studied cases and the applied methods. Also, the differences of this study results with the Bernestein study may be secondary to the differences between the samples, limiting to the high risk patients for preterm labor. In addition, differences in method and participant characteristics were the other factors of differences in the rates of sensitivity, specificity, positive and negative predictive values.

CONCLUSION

This study showed that the rate of βhCG values in the gestational age of 24-36 weeks with a high confidence can distinguish preterm delivery from term delivery and can be a suitable method for predicting preterm delivery and could be use as a predictor test which is cheap, easy and free of any medical consequence.

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REFERENCES

[1] E Knobil; JD Neil. Encyclopedia of Reproduction, 1rd ed., Academic press, USA, **1998**(3); pp. 1037-1052.
[2] FG Cunnigham; KJ Leveno; SL Bloom; JC Hauth; DJ Rouse; CY Spong. Williams obstetrics, 23rd ed., Mc Graw Hill, USA, **2009**; pp. 804-831.
[3] RL Copper; RL Goldenberg; RK Creasy; et al. *American Journal Obstetrics & Gynecology*, **1993**, 168, 78.
[4] JF King; A Grant; MJ Keirse; I Chalmers.. *British Journal of obstetrics & Gynaecology*, **1988**, 95(3), 211.
[5] L Sanchez-Ramos; C Mentel; R Bertholf; A Kaunitz. I Delke; C Loge. *International Journal of Gynecology obstetrics*, **2003**, 83, 151.
[6] K Gyetvai; ME Hannah; ED Hodnett; A Ohlsason. *Obstetrics & Gynecology*, **1999**, 94, 869.
[7] DL Wong; ShE Perry; MJ Hockenbery; DL Lowdermilk. Maternal child nursing care, 2rd ed, Mosby, USA, **2002**, 2, pp. 410-417.
[8] RK Creasy; R Resnik. Matenal- Fetal medicine, 4rd ed., W.B.Saunders Company, Philadelphia, **2004**, 4, pp.498-525.
[9] H Leitich; C Egarter; A Kaider; M Hohlagschwandtner; P Berghammer; P Husslein. *American Journal Obstetrics & Gynecology*, **1999**, 180, 1169.
[10] JD Imas; D Casal; JAM Gregor; TM Goodwin; US Kreaden; R Lowensohn. *American Journal Obstetrics & Gynecology*, **1995**, 173, 141.
[11] JR Wax; AM Lopes; PA Benn; T Lerer; JD Steinfeld. *Journal of Maternal-Fetal Medicine*, **2002**, 9, 161.
[12] A Gurbuz; A Karateke; M Ozturkmen; C Kabaca. *International Journal of Gynecology & Obstetrics*, **2004**, 85, 132.
[13] PS Bernstein; R Stern; N Lin; J Furgiuele; A Karmen; M Comerford and et al. *American Journal Obstetrics & Gynecology*, **1998**, 179, 870.
[14] ME Sak; S Sak; T Gul. *Journal Of Clinical and Experimental Investigations*, **2010**, 1, 16.
[15] G Braunstein; J Rasor; D Adler; H Danzer; ME Wade. *American Journal Obstetrics & Gynecology*, **1976**, 126, 678.
[16] T Anai; Y Tanka; Y Hirota; I Miyakawa. *Obstetrics and Gynecology*, **1997**, 89, 261.
[17] T Guvenal; E Kantas; T Erselcan; Y Culhaoglu; A Cetin. *International Journal of Gynecology & Obstetrics*, **2001**, 75, 229.
[18] A Garshasbi; T Ghazanfari; S Faghih zadeh. *International Journal of Gynecology & Obstetrics* **2004**, 86, 358.