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Single Measurement of Salivary Estriol as a Predictor of Preterm Birth

[1]Khani Soghra, [1]Shahhosseini Zohreh, [1]Abedian Kasgari Kobra and [2]Mahdavi Mohammad Reza
[1]Department of Midwifery, Faculty of Nasibeh Nursing and Midwifery,
Mazandaran University of Medical Sciences, Sari, Iran
[2]Department of Laboratory Sciences, Faculty of Para Medical,
Mazandaran University of Medical Sciences, Sari, Iran

Abstract: One of the major problems in obstetrics and pediatrics is preterm birth. A new method of prediction of preterm birth is by salivary estriol. This study aimed to determine the predictive value of single measurement of salivary estriol and its relationship with preterm birth. In this study, the salivary specimens of 466 pregnant women of 25-34 weeks gestational age were collected and kept in a freezer until delivery. Consequently, the salivary specimens were thawed and estriol levels were measured. The cut-off point for estriol was determined by a receiver operating characteristics curve. Salivary estriol levels equal to or higher than the cut-off point (2.6 ng mL^{-1}) were considered as the estriol (+) group and those lower than 2.6 ng mL^{-1} were considered as the estriol (-) group. Our findings showed that 36 (18.3%) subjects in the estriol (+) group and 22 (8.2%) subjects in the estriol (-) group had preterm deliveries. There was a significant relationship between salivary estriol levels and preterm birth ($\chi^2 = 10.636$, $p = 0.001$). Sensitivity, specificity and predictive values (positive and negative) of estriol were 62, 60, 18.3 and 82%, respectively. Single measurement of salivary estriol at 25-34 weeks of gestation, with its high negative predictive values, could be beneficial to identify women who will not develop preterm labor. This outcome suggests that unnecessary interventions should be avoided to prevent preterm births.

Key words: Preterm birth, predictive values, salivary estriol

INTRODUCTION

Despite numerous developments in the treatment of preterm labor, its prevalence has not diminished in recent decades (Denney *et al*., 2008). Preterm labor may result in several complications, such as intraventricular hemorrhage, cerebral palsy, neurological complications in newborns, increased cesarean rate and increased cost of delivery expenditure (Beck *et al*., 2010; Behrman and Butler, 2007; Moster *et al*., 2008). Preterm labor is the major cause of fetal death within 28 days of life worldwide (Beck *et al*., 2010; Flood and Malone, 2012; Nankabirwa *et al*., 2011). Moreover, the presence of complications associated with preterm delivery, such as multiple pregnancies, placenta previa, amniotic fluid infection, incompetent cervix, fetal anomalies, uterine abnormalities, polyhydramnios and preeclampsia are a major area of concern of maternal and neonatal health (Beck *et al*., 2010; Nankabirwa *et al*., 2011; Brandt *et al*., 2000; Sangkomkamhang *et al*., 2011; Mizrahi *et al*., 1999; Borna *et al*., 2004; Magee *et al*., 2011). It is noteworthy that, with the establishment of preterm labor, there is a low success rate for its prevention (Ali *et al*., 2000; Cunningham *et al*., 2010; Matijevic *et al*., 2006). Therefore, early prediction of preterm delivery is crucial.

Several factors have been discussed as risk factors for preterm delivery, such as socioeconomic factors, employment status and obstetrical history. However, approximately 20% of preterm deliveries are iatrogenic because of medical or obstetrical causes (Beck *et al*., 2010; Sangkomkamhang *et al*., 2011; Ofori *et al*., 2008). Currently, different methods are used to identify women who are at risk for preterm delivery, including risk scoring systems (Crane *et al*., 1999), cervical dilation (How *et al*., 2008), measuring cervical length by ultrasonography (Souka *et al*., 2011), assessment of fetal fibronectin (Bolt *et al*., 2011), assessment of uterine contractions (Grgic *et al*., 2012) and the presence of beta human chorionic gonadotropin in blood and cervicovaginal secretions (Khani *et al*., 2010; Onderoglu and Kabukcu, 1997). However, none of these methods is known to be an accurate predictor of preterm delivery (Cunningham *et al*.,

Corresponding Author: Abedian Kasgari Kobra, Department of Midwifery, Faculty of Nasibeh Nursing and Midwifery, Vesal Street, Amir Mazandarani Boulevard, Sari, P.O. Box 4816715793, Mazandaran Province, Iran
Tel: +98 151 2267342-5 Fax: +98 151 2268915

2010). Recently, serial measurement of salivary estriol (every 1 to 2 weeks) for the prediction of preterm labor has been introduced and approved by the U.S Food and Drug Administration (Ramsey and Andrews, 2003; McGregor *et al*., 1998). Estriol is the most abundant estrogen in late pregnancy, with the estriol levels rising approximately 2-4 weeks before delivery and remaining stable until delivery (Heine *et al*., 2000).

Because available interventions for preventing of preterm birth has some limitations, thus, the use of biochemical markers to identify women at risk for preterm birth will be research tools (Ramsey and Andrews, 2003; Vogel *et al*., 2005). As weekly measurement of salivary estriol to detect premature births increase the cost of health care in the pregnant women and may be with inconvenience for them, this study was conducted to determine the diagnostic value of single measurement of salivary estriol to predict preterm birth.

MATERIALS AND METHODS

This study was conducted in 466 singleton pregnant women at 25-34 weeks of gestation with intact fetal membranes. Subjects who had a history of previous abortion, preterm delivery, congenital malformation, fetal growth restriction, placental abruption and serious maternal disease during pregnancy were excluded. Subjects who used estrogen metabolism inhibitors, such as corticosteroids, phenytoin and tranquilizers were excluded. Gestational age was determined using the first day of the last menstrual period together with ultrasonography in early pregnancy to increase accuracy. Eligible participants completed a demographic and obstetrical questionnaire with the help of a midwife in prenatal care clinics in Sari/Iran from October 2007 to June 2009. Subjects were then referred to a laboratory to have their salivary sample collected. Salivary samples were collected in a special plastic container 1 h after being fasted. Subjects were required to avoid smoking, mouth washing and chewing gum 1 hour prior to sampling. Samples, which had not been contaminated by blood, were frozen at -20°C. Subsequently, the amount of estriol in saliva was determined using the Meditec kit (Lab System Devices, Germany) and the ELISA method. All subjects were followed up by midwives as co-investigators until postpartum.

The collected data were analyzed by the Statistical Package for Social Sciences for Windows version 13.0 (SPSS Inc., Chicago, IL, USA) and a receiver operating characteristics curve was plotted. Subjects with salivary estriol levels = 2.6 ng mL^{-1} (197 cases) were considered as the estriol (+) group and the remaining subjects (269 cases) with salivary estriol levels <2.6 ng mL^{-1} were considered as the estriol (-) group.

Mean and Standard Deviation (SD) were computed and reported. The association between variables was examined by χ^2 and t-test. Relative risk, sensitivity, specificity and positive and negative predictive values were also reported.

Ethical approval was obtained from the ethical committee at Mazandaran University of Medical Sciences. Permission for collected data was obtained from the Health Organization Chief Executive Officers when required. All of the participants were informed of the purpose and design of the study. The participation was voluntary with concern for confidentiality and anonymity and subjects provided written informed consent prior to the study.

RESULTS

The mean age of the total participants was 24.51 years (SD = 1.89). Socio-demographic characteristics of the women, as well as the status of both groups for qualitative variables, such as education level, employment status and Body Mass Index (BMI) are reported in Table 1. Our findings showed there were no significant differences between the two groups regarding neonatal weight, the level of education, occupational status, gravidity, BMI and gestational age at sampling time. Mean±SD time interval between sampling and delivery time in the estriol (+) group was 2.6±1.5 weeks and it was

Table 1: Demographic characteristics of subjects in the estriol (+) and estriol (-) groups

Variables	Estriol (-)	Estriol (+)	p-value
Age (year)*	26.21±5.5	25.64±5.9	0.29
Maternal weight gain during pregnancy (kg)*	11.2±5.2	11.3±4.2	0.84
Neonatal weight (g)*	3199±543	3163±635	0.5
Education**			
Under diploma	131 (48.7)	88 (44.7)	0.58
Diploma	125 (46.5)	101 (51.2)	
Graduated	13 (4.8)	8 (4.1)	
Occupational status**			
Employed	15 (5.6)	12 (6.1)	0.84
Housewife	254 (94.4)	185 (93.9)	
Gravidity**			
1	236 (87.7)	181 (91.9)	0.069
2	27 (10)	9 (4.5)	
≥3	6 (2.3)	7 (3.6)	
BMI**			
<19.8	7 (2.6)	6 (3)	0.6
19.8-24.9	165 (61.4)	109 (55.4)	
25-30	77 (28.6)	63 (32)	
>30	20 (7.4)	19 (9.6)	
Gestational age at sampling time (weeks)*	25.81±2.1	26.3±1.4	0.97
Interval between sampling time and delivery (weeks)*	3.02±1.9	2.6±1.5	0.45

*: Mean±SD, **: Frequency (percent)

Table 2: Distribution of preterm birth in both groups based on the cut-off point of salivary estriol ≥2.6 ng mL^{-1}

	Preterm birth	
Salivary estriol (ng mL^{-1})	Yes	No
2.6	36 (18.3)	161 (81.7)
<2.6	22 (8.2)	247 (91.8)

Values in brackets are percentage

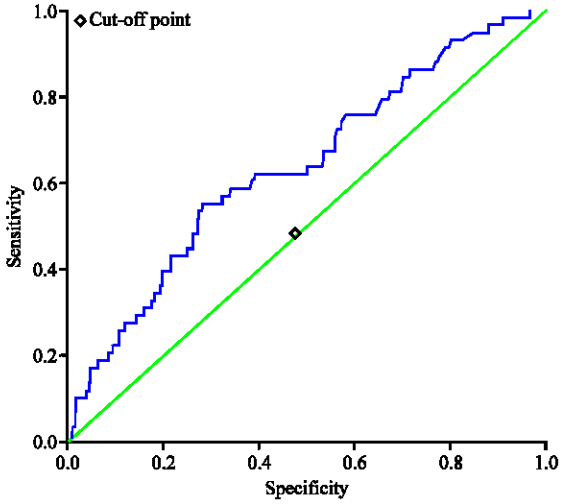

Fig. 1: Cut-off point of salivary estriol to predict preterm delivery

3.02±1.9 weeks in the estriol (-) group, with no significant difference between the groups (Mann-Whitney U-test, p = 0.45).

Among the 197 subjects with salivary estriol (+), 36 (18.3%) had preterm delivery and among 269 mothers in the estriol (-) group, 22 (8.2%) had preterm delivery. There was a relationship between preterm labor and salivary estriol levels (χ^2 = 10.6, p = 0.001) (Table 2). The mean salivary estriol levels in the preterm group were 3.9±2.4 ng mL^{-1} and they were 2.9±2.1 ng mL^{-1} in the non-preterm group. The Student's t-test showed a significant difference between the preterm and non-preterm groups regarding mean salivary estriol levels (t = 3.43, p = 0.001).

The area under the receiver operating characteristics curve was 0.637 and the 95% confidence interval was 0.56-0.715, with a cut-off point of 2.6 ng mL^{-1} (Fig. 1). Sensitivity, specificity and positive and negative predictive values of estriol were 62, 60, 18.3 and 82%, respectively.

DISCUSSION

As targeted obstetric interventions to prevent preterm birth, a major complication of pregnancy, are accomplished with a low success rate, its prediction by chemical biomarkers including; salivary estriol remains largely an interesting issue for research (Ramsey and Andrews, 2003; Vogel *et al*., 2005). The authors engaged in this processes to find if single measurement of salivary estriol is an appropriate test for screening of women deemed at increased risk for preterm birth?

Our findings showed that women with salivary estriol levels ≥2.6 ng mL^{-1} had a 2.2-fold higher risk of preterm delivery (18.3% versus 8.2%). In an observational-analytical study by Tehranian *et al*. (2003) they measured salivary estriol levels once at labor in 43 mothers with preterm delivery and compared them with those in 43 mothers with term delivery. They found that salivary estriol levels in the preterm labor group were 2.8-fold higher than those in women with term delivery (Tehranian *et al*., 2003). However, compared with mentioned study, it seems our study's results have more implications in clinical practice and are more valid findings owing to the method of our study (prospective) and the sampling time, which was during pregnancy. That is, women who screen positive may be at risk for preterm birth and, thus, timely interventions are indicated to prevent preterm birth.

This study showed that the negative predictive value of salivary estriol was much higher than its positive predictive value (82% versus 18.3%). This finding is consistent with other studies (Ramsey and Andrews, 2003; McGregor *et al*., 1998; Heine *et al*., 2000; Vogel *et al*., 2005; Moran *et al*., 1992), but the novelty of our study was a single measurement of salivary estriol levels during pregnancy, as opposed to weekly serial measurements. Validation of our results by future studies could greatly reduce extra costs imposed on society because of protocols for screening mothers who are at risk for preterm delivery (Tehranian *et al*., 2003). The high negative predictive value of salivary estriol could be a valuable test profile for avoiding inappropriate obstetrics interventions for prevention of preterm delivery, such as prolonged bed rest and absence from work, as well as prescribed tocolytics, which in turn can prevent high stress of the mother and other family members.

The low positive predictive value of salivary estriol in our study is in accordance with other studies (Goffinet, 2005). The easy and noninvasive saliva collection technique compared with other predictor tests and easy laboratory techniques for detecting salivary estriol are advantages of this method. In contrast, the short interval between taking a salivary sample and the time of birth, indicated positive salivary estriol test is a late predictor of preterm birth which limiting its clinical use. However, further studies are recommended to confirm the predictive value of single measurement of salivary estriol in pregnant women.

CONCLUSION

In conclusion, the high negative predictive value of salivary estriol can be used to identify women who are at very low risk for preterm labor. In addition, excessive costs for mother and care system as well as unnecessary interventions to prevent preterm labor could be avoided by single measurement of this biomarker at an appropriate gestational age.

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