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RESEARCH ARTICLE

SALIVARY PROGESTERONE LEVELS AS A PREDICTOR OF PRETERM BIRTH

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ABSTRACT

Purpose: In our study we aimed to predict preterm delivery using the salivary progesterone levels.
Material and Method: In this follow-up study, we collected salivary samples from 100 pregnant women at 24, 27 and 30 weeks' gestation. Pregnant women with preeclampsia, diabetes, twin pregnancy and intrauterine growth restriction were not included in the study. The salivary progesterone levels were determined by enzyme immunoassay. The patients were followed until delivery.
Findings: Preterm birth occurred in 11 (9.09%) of the 100 patients. The mean progesterone levels of patients that delivered preterm were lower than the levels of the term deliveries. Statistically, the progesterone levels were significant at week 24 and 27 (p=0.031, p=0.018). Although the progesterone levels of the preterm births at week thirty were low, this was not found to be statistically significant (p=0.061). The preterm birth rate in patients with no history of preterm birth was 2.2%, and in patients with a positive history of preterm birth the rate was 27.3% (p=0.004). In the ROC curve, with respect to predicting preterm birth the progesterone levels at week 27 were more significant than the levels at weeks 24 and 30.
Result: Assessing the salivary progesterone level is a non-invasive method with high sensitivity, its assessment between 20-30 weeks of pregnancy is useful for predicting preterm birth. However, it must not be forgotten that preterm birth is a multifactorial process. Considering this, it is important to evaluate the markers and the clinical features togetherto predict and prevent preterm birth instead of using a single marker alone. By doing so, high-risk patients can be identified and the appropriate treatment can be delivered.

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INTRODUCTION

Preterm birth is defined as birth of a baby at less than 20 to 37 weeks of pregnancy. And the birth of a baby before 32 weeks of pregnancy is referred to as early preterm birth. In this period, six or more contractions in one hour, 3 cm cervical dilatation, 80% effacement, membrane rupture and vaginal bleeding are signs of preterm birth and often result with preterm delivery (Hueston wj, 1998 and Macones, 1994). Despite the advances in intensive care facilities that have improved the prognosis of low birth weight babies, it has not been possible to predict preterm birth or to reduce the rates of preterm birth. The preterm birth rate is 10-11% in all pregnancies (Creasy, 1994). In 1961 the World Health Organization included gestational age as a criterion for premature babies and included babies born at 37 weeks of pregnancy and before in this group. Low birth weight (2500 grams or lower) and prematurity (37 or less weeks) have been distinguished (American College of Obstetricians and Gynecologists, 1995).

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Preterm birth is the most important factor that determines the future of a fetus with no anomalies, and it is still the most important cause of perinatal mortality and morbidity. During the last 20 years, the rates of preterm birth have been increasing in industrialized countries. The increase of multiple pregnancies, the increased frequency of obstetric interventions and the increasing use of ultrasound to identify gestational age can be mentioned among the reasons of the increase of preterm birth rates (Gelisen, 2001). The review of the neonatal mortality rates revealed that babies born before completion of 37 weeks' gestation account for 83% of the neonatal deaths (Cooper, 1993 and Kesim *et al.,* 1996). The incidence of birth before 37 weeks' gestation has been reported as 8-10%. This group accounts for 75% of newborn morbidity and mortality. Preterm birth is directly responsible for 75-90% of the neonatal deaths that are not related to fatal congenital anomalies. The nursling, neonatal and postnatal death rates have decreased by approximately 50% in the last 20 years. However, the mortality rates did not decrease in preterm (< 37 weeks) births and low birth weight (LBW < 2500 gr) babies. The rate of preterm births has increased from 9.4% to 11.8% between 1981 and 1999. Of neonatal deaths, 65% occurs in LBW newborns (7.6% of all births), 51% occurs in very low birth weight (VLBW <

1500gr) newborns (1.4% of all births). The IMR (infant mortality rate) is 180.9 in 1000 births in early preterm newborns, and 2.62 in term births. And this is 69 times higher than it is in preterm births. The IMR in preterm newborns born between 32 to 36 weeks' gestation is 9.4 in 1000 births and is 3.5 fold higher in comparison to term newborns (Wright, 2005). The most important problems of babies born early are caused by organ immaturity. With today's advanced technology, only VLBW babies are subject to these dangers. This rate is 25% in the groups that survive with the lowest body weight (450-800 gr). The most important diseases that develop in this group are blindness, deafness, cerebral palsy or mental retardation (Gelisen, 2001). Two very important issues for preterm babies is their survival and their future quality of life. The physical and intellectual development of many preterm babies is delayed in comparison to their peers born at term. Therefore, timely identification of preterm birth and its prevention are two of the most important topics of obstetrics. The most appropriate approach to reduce the rate of preterm births is to identify the risk factors to diagnose preterm birth earlier. Patients under threat of preterm birth are usually administered tocolytics to prevent preterm birth. Randomized studies have shown that tocolytic treatment can delay preterm birth for up to 7 days, however, it does not reduce perinatal mortality or morbidity significantly (Mauricie, 1996 and Panter, 1996). Therefore, it is important to identify pregnant women at high risk for preterm birth in the earlier stages of pregnancy before preterm labor begins. Educating these patients and timely interventions when necessary will reduce the morbidity and mortality caused by preterm birth. Meis and colleagues (al.), attempted to establish the factors that caused preterm birth before 37 weeks of pregnancy in a community-based study they conducted with women with singleton pregnancies within the framework of the Maternal-Fetal Medicine Network of the National Institute of Child Health and Human Development (NICHD). The cause was established in approximately 28% of the preterm births. These were: preeclampsia (43%), fetal distress (27%), fetal growth restriction (10%), abruptio placenta (7%), fetal death (7%). The remaining 72% were caused by spontaneous preterm labor induced or not induced by membrane rupture (Meis *et al*., 1998).

The diagnosis of preterm labor (PTL) is made by detecting cervical changes in the gynecological examination and by identifying the presence of uterine contractions. However, the rate of false-positive diagnosis is substantially high. In these cases, the patient is needlessly admitted to hospital and costs rise. The tocolytic agents itself also poses a risk to the mother and the fetus with its known side effects (Timor-Tritsch, 1996). The Bishop score is used to diagnose PTL by gynecological examination. The fact that these examinations are not objective and that each examination carries the risk of infection restricts is utility and safety. Additionally, some researchers state that determining the cervical dilatation in gynecological examination is also a risk factor for iatrogenic preterm labor and birth (Sener, 1996). Other methods that can be used to evaluate the cervix are transabdominal or transvaginal measurements of the cervical length. With these methods, the cervical length, the presence of funneling, and the length and width of funneling can be examined. Visualizing the cervix with ultrasonography, is considered as an alternative method for the assessment the cervical length and preterm labor, (Timor-Tritsch, 1996; Andersen, 1990; Gomez *et al.,* 1994). Before easily recognizable cervical effacement and dilatation develops, it is difficult to distinguish true and false labor. Uterine contractions alone may be misleading due to Braxton-Hicks contractions. These contractions may be painful or painless, and are irregular with no certain rhythm and they may cause an important confusion during the diagnosis of preterm labor. Not seldom, the uterine activity referred to as Braxton-Hicks contractions emerges in women delivering before term and this leads to theerroneous diagnosis of false labor. The plasma and serum levels of certain substances have been assessed to detect preterm birth beforehand.With this purpose, many studies have been conducted on alkaline phosphatase, AFP (alpha-fetoprotein), CRF (corticotropin-releasing factor), CRP (C-reactive protein), ferritin, IL-6 (interleukin-6), ICAM-1 (intracellular adhesion molecule-1). However, there is no test with an ideal sensitivity and predictive value. In 2009, Lachelin *et al*. identified that low salivary progesterone levels of pregnant women at high risk for preterm birth were associated with spontaneous preterm birth (Lachelin, 2009). In this study we carried out, we aimed to predict spontaneous preterm birth using the salivary progesterone levels measured between 24-30 weeks' gestation. With this purpose, we carried out 3 measurements of progesterone levels starting from 24 weeks of pregnancy onwards with intervals of three weeks.

MATERIALS AND METHODS

Our study was planned as a follow-up study, it included 100 cases that applied to the obstetrics polyclinic of the Celal Bayar University Research and Application Hospital between 15.12.2009 and 15.02.2010. Prior to the study, the patients had given their approval after being provided with necessary information and reading the information form. Pregnant women that were 24 weeks and higher were included in the study. Patients with preeclampsia, diabetes, twin pregnancies and intrauterine growth restriction were not included in the study. Routine medical and obstetric history was obtained and obstetric and physical examination was performed in all of the cases that met the specified criteria among the patients that had applied to our clinic for pregnancy. The routine pregnancy tests were performed. Salivary samples were collected at 24, 27, and 30 weeks' gestation without using any instruments, naturally without any stimulus into clean tubes that did not contain any anticoagulants. The saliva samples were centrifuged, stored at -80^0 and analyzed in one session. All of the data of the cases were recorded on their pregnancy charts. The treatment protocols delivered, the treatment durations and complications were also recorded. The gestational age of the cases included in the study was calculated according to the date of last menses and/or the ultrasounds performed in the first trimester.

The progesterone levels in the salivary samples were assessed using the Progesterone Saliva (DBC-Diagnostics Biochem Canada Inc., London, Ontario, Canada) kit by the enzyme immunoassay method. The intra-assay coefficient of variation (CV) of the kit was calculated as 13.3;2% for the concentration 32.93 pg/ml, as 5.9% for the concentration 78.3 pg/ml and as 7.37% for the concentration 302.67 pg/ml. Inter-assay CV

values for the concentration 30.83 were calculated as %12.7;2, as 7.7% for the concentration 75.03 and as 10.9% for the concentration 241.06 pg/ml. The study data was assessed using the SPSS 10.0 computed statistics software and descriptive statistics (number, percentage, mean and standard deviation) the Mann-Whitney U test, the Chi-square and ROC analyses were used.

RESULTS

In this follow-up study we designed, we obtained saliva samples starting from 24 weeks' gestation until 30 weeks' gestation with intervals of three weeks from 100 patients that applied to our polyclinic and we assessed the progesterone levels particularly to predict spontaneous delivery.

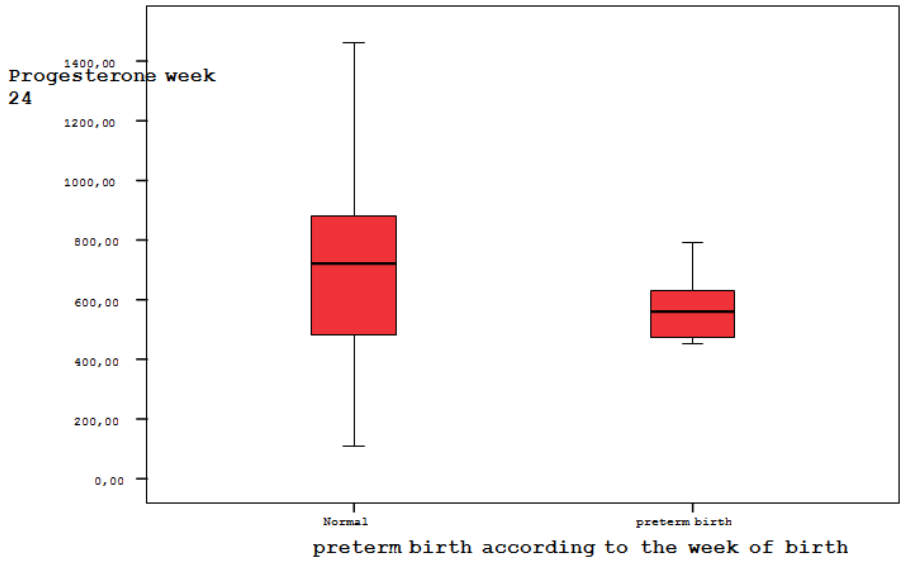
Table 1. Descriptive group statistics

	Preterm birth according to the week of birth	N	Mean	Std. Deviation	Std. Error Mean
Age	Normal	89	27.5955	4.08912	.43345
	preterm birth	11	27.7273	5.33087	1.60732
Gravida	Normal	89	2.0674	.90199	.09561
	preterm birth	11	2.0000	1.18322	.35675
Parity	Normal	89	.7191	.76854	.08147
	preterm birth	11	.7273	1.00905	.30424
Abortus	Normal	89	.3483	.52443	.05559
	preterm birth	11	.3636	.67420	.20328
Living	Normal	89	.6742	.63560	.06737
	preterm birth	11	.7273	1.00905	.30424
Progesterone at week 24	Normal	89	709.3820	305.16853	32.34780
	preterm birth	11	574.6364	116.09675	35.00449
Progesterone at week 27	Normal	89	841.5056	296.33186	31.41111
	preterm birth	11	700.7273	126.93628	38.27273
Progesterone week 30	Normal	89	897.1798	265.00020	28.08996
	preterm birth	11	802.0909	115.90553	34.94683

Table 2. Mann-Whitney U Test

	Gravida	Parity	Abortus	Living	week 24.	week 27.	progesterone week 30
Mann-Whitney U	427.5	456.0	475.0	460.5	320.0	299.0	349.5
Wilcoxon W	493.5	522.0	541.0	526.5	386.0	365.0	415.5
Z	-.733	-.409	-.196	-.357	-1.867	-2.099	-1.542
Asymp. Sig. (2-tailed)	.463	.683	.844	.721	.062	.036	.123

a Group variable: Preterm birth according to the week of birth



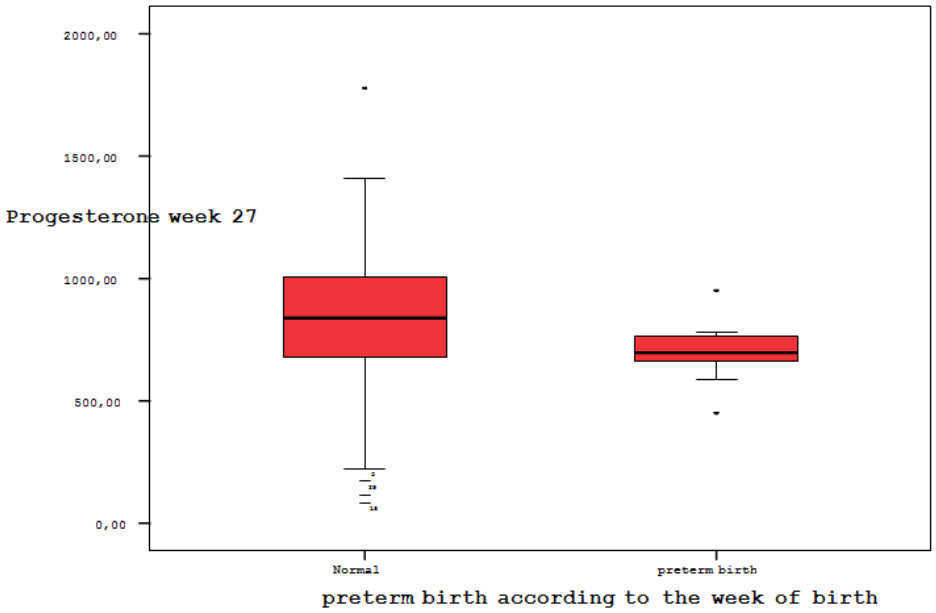
Graphic 1. Progesterone at week 24

Table 3. ROC Analysis Group Statistics

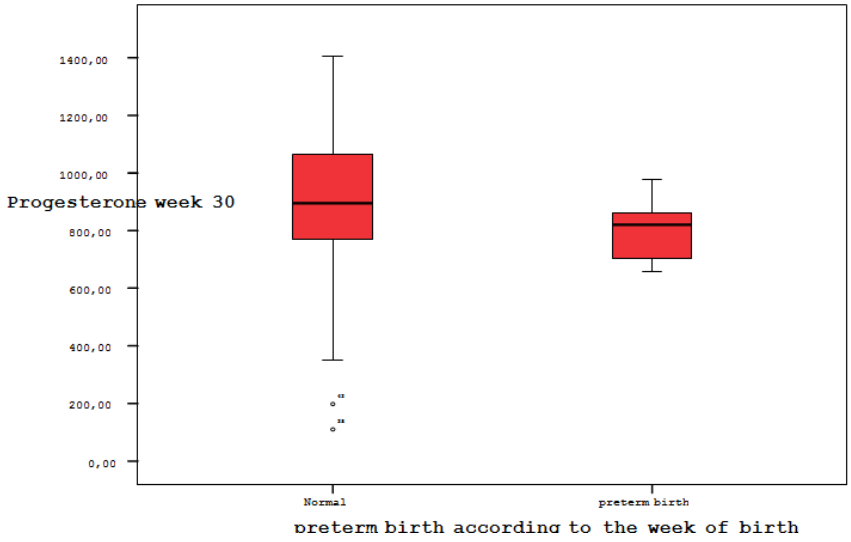
Area Under the Curve

Test Result Variable(s)	Area	Std. Error(a)	Asymptotic Sig.(b)	Asymptotic 95% Confidence Interval	
	Lower Bound	Upper Bound	Lower Bound	Upper Bound	Lower Bound
week 24.	.673	.056	.062	.564	.783
week 27.	.695	.063	.036	.572	.817
progesterone week 30	.643	.065	.123	.516	.770

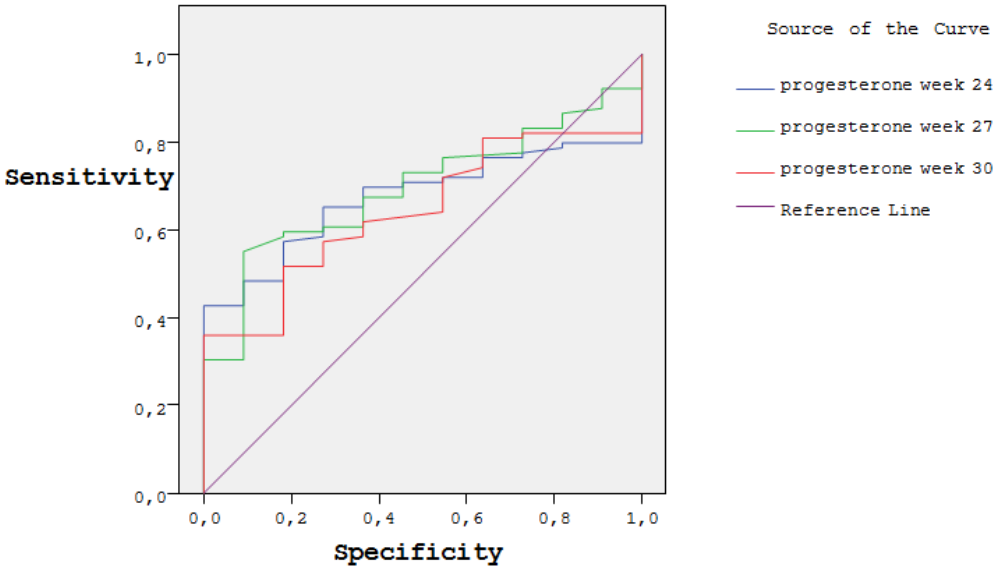
a Under the nonparametric assumption
b Null hypothesis: true Area = 0.5



Graphic 2. Progesterone at week 27



Graphic 3. Progesterone at week 30



Graphic 4. The ROC Curve

Table 4. Cross table according to preterm birth-week of birth

			Preterm birth according to the week of birth		Total
			Normal	preterm birth	Normal
History of preterm birth	negative	Count	87	8	95
		preterm birth according to the week of birth %	97.8%	72.7%	95.0%
	positive	Count	2	3	5
		Preterm birth according to the week of birth %	2.2%	27.3%	5.0%
Total		Count	89	11	100
		Preterm birth according to the week of birth %	100.0%	100.0%	100.0%

Table 5. Chi-square test according to preterm birth history - week of birth

	Value	df	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	12.908(b)	1	.000		
Continuity Correction(a)	8.177	1	.004		
Likelihood Ratio	7.675	1	.006		
Fisher's Exact Test				.009	.009
Linear-by-Linear Association	12.779	1	.000		
N of Valid Cases	100				

a Computed only for a 2x2 table

b 2 cells (50.0%) have expected Count less than 5. The minimum expected Count is .55.

Singleton pregnancies were followed until birth. Five of our patients had a positive history for preterm birth. Generally speaking, they were at low risk for preterm birth. Preterm birth occurred in 11 (9.09%) of our patients. As a risk factor, one of our patients experienced intermittent vaginal bleeding that started in the second semester and continued until the patient delivered at 28 weeks of pregnancy. The mean progesterone levels at 24, 27 and 30 weeks' gestation of the patients that delivered at term were 709 pg/ml, 841 pg/ml and 897 pg/ml respectively. The mean progesterone levels of the patients that delivered preterm were 574 pg/ml, 700 pg/ml, 802 pg/ml (p=0.031, p=0.018, p=0.061), (Table 1). When the values were reviewed it was seen that the mean progesterone levels of the patients that delivered preterm were lower (Table 1). When the p values were evaluated with a statistical point of view, the progesterone levels at 24 and 27 weeks' gestation were found to be significant for the prediction of preterm birth (Table 2). On the ROC curve, the progesterone levels at 27 weeks' gestation are more significant than the levels at 24 and 30 weeks' gestation for the prediction of preterm birth (Graphic 4, Table 3). In the patients with no history of preterm birth, the rate of preterm birth was 2.2% and this rate was 27.3% in patients with a positive history for preterm birth (p=0.004) (Table 4-5).

DISCUSSION

Despite the advances in intensive care facilities that have improved the prognosis of low birth weight babies, it has not been possible to predict preterm birth or to reduce the rates of preterm birth (20). Therefore, timely identification of preterm birth and its prevention are among the most important topics of birth medicine. There are many studies about the prediction of preterm birth. Lachelin GC. *et al.,* collected weekly saliva samples starting from 24 weeks' gestation until delivery in the study they conducted in 2009. They compared the salivary progesterone levels of 28 patients that delivered preterm and 64 patients that delivered at term. The researchers detected a statistically significant difference between the progesterone levels of 12 patients that delivered before 34 weeks' gestation and the patients that delivered after 37 weeks' gestation (p:0.007) (Mulik *et al.,* 2004). In the study they conducted in 1987, J. Darne *et al*. assessed the salivary estriol, estradiol and progesterone levels of 23 patients who spontaneously delivered preterm. In 13 patients with intact membranes that delivered preterm, they identified the estriol/progesterone rate higher than 1. In the other group with prolonged preterm rupture of membranes the estriol/progesterone ratio identified was lower than 1. They concluded that the estriol/progesterone ratio could be used to predict preterm births without premature rupture of membranes (Nageotte *et al.,* 1990). In the study they conducted in 2009, Stamatelou *et al*. assessed the plasma corticotropin-releasing hormone (CRH) and progesterone levels at the start of the third trimester to predict preterm birth. As a result, they identified that the mean progesterone levels of the group that delivered preterm was 30% lower than the levels in the group that delivered at term (p<0.001). Additionally, they identified that the CRH levels were 6 fold higher in the group that delivered preterm than the group that delivered at term (p<0.001). They concluded that maternal CRH and progesterone levels assessed in the early periods of the third trimester can be used as biochemical markers for the prediction of high-risk preterm births (Darne *et al.,* 1987). In the study conducted in 2008, Klebanoff *et al*. collected weekly saliva samples from 40 patients being delivered 17 alpha-hydroxyprogesterone caproate (17OHPC) and 40 patients being delivered placebo.As a result, high and low limit values of progesterone and estriol indicated a slightly increased risk for preterm labor. 17OHPC did not alter the salivary progesterone curve throughout pregnancy. But, it reduced the increase of estriol and the estriol/progesterone ratio substantially. 17OHPC, straightens the estriol curve and affects the feto-placental unit (Klebanoff *et al.,* 2008). In the study conducted in 1995 by McGregor *et al.,* the salivary estriol levels were assessed starting from 22 weeks' gestation in 542 patients. The mean estriol levels of singleton pregnancies that delivered preterm between 24 - 34 weeks' gestation were found to be high. The estriol levels demonstrated a fluctuation approximately 3 weeks before delivery in both the preterm and

the term births. The estriol levels of the preterm deliveries started to rise 4 weeks earlier than the term deliveries. They concluded that the early rise of the estriol levels could be useful in identifying the patients at high risk for preterm birth (Mc Gregor *et al.,* 1995). In their study carried out in 2000, Heine RP *et al*. performed serial assessments of salivary estriol to identify the risk for spontaneous preterm birth. According to this, they associated high estriol levels with preterm birth in symptomatic and asymptomatic patients (Heine, 2009).

Progesterone has a fundamental role in the maintenance of pregnancy, in facilitating uterine relaxation, in the reduction of the concentration of oxytocin receptors in the myometrium and in reducing prostaglandin concentrations. Additionally, progesterone facilitates the binding of calcium and reduces intracellular calcium. Current studies have stated that the excessive response to bacterial invasion could also contribute to premature preterm birth. One of the features of progesterone is the anti-inflammatory effect of its use in infections. The latest studies support the hypothesis that the use of progesterone in the group with a positive history of preterm birth could reduce preterm birth rates (Reddy *et al.,* 1999). Instead of performing an evaluation based on this small number of low-risk patients, it would be healthier to perform an evaluation with much larger patient groups. Not only progesterone is important, the estriol and fibronectin levels, measurement of cervical length and the use of other markers are also important for the prediction of high-risk patients. However, the sensitivity and specificity of all these markers are insufficient. Delivering progesterone to high-risk patients that will be determined according to these evaluations is important for the prevention of preterm birth.

Result

Assessing the salivary progesterone level is a non-invasive method with high sensitivity, its assessment between 20-30 weeks of pregnancy is useful for predicting preterm birth. However, it must not be forgotten that preterm birth is a multifactorial process. None of the markers investigated for the prediction of preterm birth have adequate sensitivity or specificity. Considering this, it is important to evaluate the markers and the clinical features together to predict and prevent preterm birth instead of using a single marker alone. By doing so, high-risk patients can be identified and the appropriate treatment can be delivered.

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