Obstetrics; *Maternal-Fetal Medicine and Perinatology*

The Ability of a Single Serum Progesterone Measurement to Predict the Prognosis of First Trimester Pregnancy

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ABSTRACT

OBJECTIVE: There are cases where ultrasonographic evaluation is inadequate in determining first-trimester healthy pregnancy. In these cases, both the patient and the clinician are involved in a worrying expectation. The single serum progesterone measurement was tried to predict pregnancy prognosis in short time period. This study evaluated the predictive value of a single serum progesterone measurement in first-trimester pregnancy loss.

STUDY DESIGN: A prospective case-control study was conducted between July 2013 and July 2014 in Tertiary Hospital. The study compared 106 patients with threatened abortion (vaginal bleeding or spotting) before 13 weeks of gestation with 110 healthy control pregnancies. Samples of serum progesterone were obtained on the day each patient was admitted to the hospital. A Beckman-Coulter macro-Enzyme-linked immunoassay (ELISA) system was used to measure serum levels of progesterone (Beckman-Coulter, Ireland).

RESULTS: Progesterone levels were measured when the patients first visited the hospital and they were followed until the end of the first trimester. Progesterone levels differed significantly (*p*=0.013) between the two groups. The spontaneous abortion rate was significantly (*p*=0.044) higher in the case group. Progesterone levels differed significantly (*p*=0.001) between ongoing pregnancy and spontaneous abortion groups. Using a cut-off level of 10.7 ng/mL, the sensitivity, specificity, and positive and negative predictive values were 92.1%, 44%, 92.6%, and 42.3%, respectively, for viable pregnancies.

CONCLUSION: A single measurement of progesterone levels in serum can predict the prognosis of a viable first-trimester pregnancy, while it is less effective for identifying non-viable pregnancies.

Keywords: First trimester, Prognosis, Serum progesterone

Introduction

Early pregnancy loss is defined as a loss before 13 weeks of gestation. Wilcox et al. determined that the pregnancy loss rate after implantation was 31% over 707 menstrual cycles in 221 healthy women and found that two-thirds of early pregnancies were lost before pregnancy was diagnosed (1). Spontaneous pregnancy loss seems in up to 20% of recognized pregnancies and it is high rate (2). Above 80% of spontaneous abortion occur before 12 weeks of gestation (1,3). Of all abortions, 50% are anembryonic abortions with no embryonic findings (4). The etiology of the other 50% is related to embryonic or placental defects. Aneuploidy is seen in 50% of the latter (25% of all abortions).

Clinically, abortions are classified as complete, incomplete, inevitable, and missed. Ultrasonography (USG), clinical findings, and laboratory markers are used to confirm preg-

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nancy. In the early stages of pregnancy, USG and clinical findings may provide confounding evidence (5). The USG findings are sonographer dependent, and the determination of early pregnancy is not repeatable. In these situations, both the patient and the clinician are involved in a worrying expectation. Consequently, a reliable marker of viable early pregnancy is required. Progesterone is a 21-carbon steroid hormone that is produced by granulosa cells. It is essential for pregnancy, implantation, and decidualization (6). It also inhibits uterine contractions and plays a role in the immunological rejection of pregnancy.

Some studies have demonstrated that progesterone is a very specific biomarker of non-viable and viable pregnancies (7,8), although its different cut-off values decrease its diagnostic power (9-11).

In this study, we examined the ability of a single measurement of progesterone levels from serum samples for discriminating between viable and non-viable pregnancies in patients with threatened abortion and asymptomatic pregnancies. The main aim of our study was to predict the first-trimester prognosis with a single serum progesterone value. The difference between our study and other studies is the inclusion of both symptomatic and asymptomatic pregnant.

Material and Method

This prospective case-control study was carried out between June 2013 and June 2014 in the Department of Obstetrics and Gynecology of Suleymaniye Education and Research Hospital, Istanbul, Turkey. The study included 106 patients with threatened abortion (with vaginal bleeding or spotting) before 13 weeks of gestation and 110 healthy control pregnancies. Double blinding performed between technicians performing enzyme-linked immunoassay (ELISA) and clinicians looking after the patients. Exclusion criteria were cervical polyps, cervical cancer, trauma, assisted reproductive technology (ART), multiple pregnancy, and ectopic pregnancy. Women treated with progesterone or any other medications were also excluded.

The study was approved by the ethical review committee of Haseki Education and Research Hospital, Istanbul, Turkey (Approval number: 29). Written informed consent was obtained from all participants. The study was conducted according to the International Conference of Harmonization/Good Clinical Practice (ICH/GCP) guidelines and the latest version of the Helsinki Declaration by World Medical. Age, body mass index (BMI), parity, history of abortion, and age of a pregnancy (according to the last menstrual cycle) were noted. All pregnancies were followed until the end of the first trimester. A Beckman-Coulter macro-Enzyme-linked immunoassay (ELISA) system was used to measure serum levels of progesterone (Beckman-Coulter, Ireland). Samples were obtained on the day each patient was admitted to the hospital.

Statistical analysis

Statistical analyses were conducted using IBM SPSS statistics 22.0 (IBM SPSS, Turkey). The conformity of the parameters to the normal distribution was evaluated by the Shapiro-Wilks test. Descriptive statistics and the Student's t-test, Mann-Whitney U test, and chi-square test were used to compare groups. The cut-off point was determined according to an area under the receiver operating characteristics curve (AUC) and the 95% confidence interval was calculated; $p < 0.05$ was considered significant. For power calculation, we used the G*Power program. According to serum progesterone cut-off value, when effect size for viable pregnancy rates continuing at the end of the first trimester was taken d=0.699; the minimum number of samples was determined as n=68 for power=0.80 and α=0.05.

Results

We compared 106 patients with threatened abortion and 110 healthy pregnancies. The mean ages were 27.02±5.02 and 27.43±4.63 years in the patient and control groups, respectively (Table I, p=0.535). Gravidity, parity, BMI, and history of abortion did not differ between the two groups (Table I, all p >0.05). Serum progesterone levels are higher in the controls group (Table I, p=0.013). Viable pregnancy rate is higher in the controls group when compared threatened abortion group (Table I, p=0.044). When progesterone levels were compared according to pregnancy prognosis (viable or non-viable), they were significantly higher in all subjects (patients and controls) with viable pregnancies (Table II, p=0.001). In all participants, when viable and non-viable pregnancies were compared according to progesterone levels using the ROC curve (Figure 1), the sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) were 92.1%, 44%,
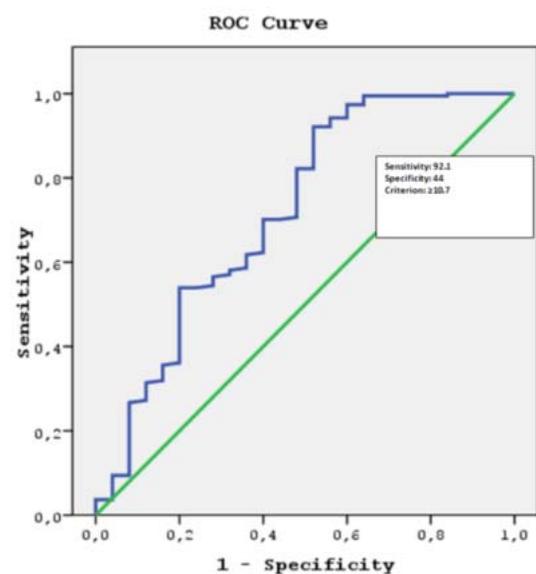

Figure 1: Association between single serum progesterone levels and prognosis of first-trimester pregnancy. This figure showed the ROC curve of progesterone cut-off.

Table I: Demographical and clinical characteristics of the study population

	Threatened Abortion (n=106)	Controls (n=110)	p
Age (year)mean±SD	27.02±5.02	27.43±4.63	[1]0.535
Body Mass Index (kg/m^2) mean±SD	24.74±4.69	24.49±4.12	[1]0.678
Gravidity mean±SD (median)	2.47±1.72 (2)	2.35±1.32 (2)	[2]0.820
Parity mean±SD (median)	1.10±1.39 (1)	1.06±1.10 (1)	[2]0.625
Φ**History of Abortionn** (%)			
Absent of history n (%)	82 (77.4%)	89 (80.9%)	[3]0.521
Present of history n (%)	24 (22.6%)	21 (19.1%)	
Gestational age of progesterone measurement (week)mean±SS (median)	8.03±2.12 (8)	8.21±1.80 (8)	[2]0.391
Serum progesterone level (ng/mL)	17.07±8.37 (14.55)	18.79±6.46 (17.2)	[2]0.013*
Prognosis of first-trimester pregnancy			
Non-viable pregnancies	17 (16%)	8 (7.3%)	[3]0.044*
Viable pregnancies	89 (84%)	102 (92.7%)	
Distribution of participants according to serum progesterone cut-off (ng/mL)			
≥10.7	84 (79.2%)	106 (96.4%)	[3]0.000*
<10.7	22 (20.8%)	4 (3.6%)	**

[1]Studen t Test, [2]Mann-Whitney U Test, [3]Chi-square test, ΦMaximum 1 abortion, *p<0.05, **p<0.01, ***p<0.001

Table II: Association between single serum progesterone level and prognosis of first-trimester pregnancy

	Prognosis of first-trimester pregnancy	Serum progesterone level (ng/mL) mean±SD (median)	p
Threatened Abortion	Non-viable	12.62±9.35 (7.77)	0.003**
	Viable	17.92±7.95 (15.5)	
Controls	Non-viable	14.53±4.06 (15.35)	0.037*
	Viable	19.12±6.51 (17.55)	
All participants	Non-viable	13.23±7.99 (12.2)	0.001**
	Viable	18.56±7.22 (16.8)	

*Mann-Whitney U Test, *p<0.05, **p<0.01*

92.6%, and 42.3%, respectively, for viable pregnancies using a progesterone cut-off value of 10.7 ng/mL. 79.2% of the threatened abortion group and 96.4% of the controls group had a serum progesterone level ≥10.7 ng/mL; 20.8% of the threatened abortion group and 3.6% of the controls group had a serum progesterone level of <10.7 ng / mL. The weakness of the test was that the specificity was low. The AUC was 0.719 (95% CI 0.596-0.842) for the serum progesterone level.

Discussion

Numerous different biochemical parameters are being explored to predict early pregnancy prognosis. Early pregnancy is maintained by hormones and endocrine-immune interactions (12). Progesterone plays an important role during implantation; provides decidualization, controls uterine contraction, and increases the immune tolerance of the mother against the fetus (13). High serum progesterone levels have a protec-

tive effect against spontaneous pregnancy losses, whereas low serum progesterone levels increase spontaneous pregnancy loss risk especially in first trimester patients with threatened abortion (14).

This study investigated the predictive value of a single measurement of progesterone levels from serum in patients with threatened abortion and asymptomatic pregnancies. Levels were significantly higher in viable pregnancies than in non-viable pregnancies in both groups. Clinical features of threatened abortion (vaginal bleeding or spotting) were also significant predictors for the prognosis of pregnancy. While progesterone levels were effective for identifying viable pregnancies in both groups, they were not effective for identifying non-viable pregnancies. The main aim of our study was to predict the first-trimester prognosis with a single serum progesterone value. The difference between our study and other studies is the inclusion of both symptomatic and asymptomatic

pregnant. The studies performed in this area are usually done with symptomatic pregnant (14-17), and very few studies with asymptomatic pregnant (18,19).

Many studies have reported that progesterone levels are an effective marker (7,20,21). We found that the cut-off level for diagnosing viable pregnancies was 10.7 ng/mL, which had a sensitivity, specificity, PPV, and NPV of 92.1%, 44%, 92.6%, and 42.3%, respectively. One weakness of this test was its low specificity for identifying non-viable pregnancies. In their study, Kelekci et al. determined cut off value as 15 ng/mL for serum progesterone. They indicated that when the cut-off value increased, sensitivity increased and specificity decreased; when cut-off value decreased, sensitivity decreased and specificity increased (19). The Royal College of Obstetricians and Gynaecologists' guideline stated that the value of single serum progesterone in early pregnancy is useful for predicting the outcome of pregnancy, and when serum progesterone threshold is 20 nmol/L (about 6.2 ng/mL), it can be predicted non-viable pregnancies with 93% sensitivity, 94% specificity in symptomatic pregnant (22). In the study of Abdelazim et al. when the serum progesterone cut-off level was 10 ng/ml, it was 79.3% sensitive for non-viable pregnancy diagnosis, 93.3% specific for viable pregnancy diagnosis; when serum progesterone cut-off level was 20 ng/ml, it was 95.1% sensitive for non-viable pregnancy diagnosis and 98.9% specific for viable pregnancy diagnosis (23). Elson et al. reported that the 25 ng/mL serum progesterone cut-off value obtained by ROC curve statistical analysis predicts viable pregnancies with 100% sensitivity and 43% specificity (5). In our study, cut-off value specificity was similar to that of Elson et al. Different cut-off results and different specificity among studies may be due to differences in measurement, standardization, and performance of progesterone assay (16), and differences in progesterone value in a different population of women of geographical origin (24).

The cut-off level that distinguished between viable and non-viable pregnancies was similar to that of many previous studies (7,15,11,25). al-Sebai et al. (7) reported a significantly lower progesterone level in non-viable and ectopic pregnancies; using a cutoff of 45 nmol/L (14.1 ng/mL), the sensitivity and specificity were 87.6% and 87.5%, respectively. Using a cut-off 11.5 ng/mL, Al Mohamady et al. reported a specificity of 97.5% and sensitivity of 100% (15). Hanita and Hanisah reported that a progesterone cut-off of 32.7 ng/mL, which was much higher than in other studies, had a sensitivity of 92% and specificity of 90% (16); they argued that the large difference in cut-off value was a result of geographic and measurement differences. Cowan et al. found that the most discriminative progesterone level was 10 ng/mL, based on ROC curves, and the productivity of the test was maximal between 9 and 14 ng/mL (80%) (26). In that study, when the progesterone levels were below 10 ng/mL, the predictive value was above 90% for abnormal pregnancy loss. A meta-analysis showed that a single progesterone measurement in early pregnancy with bleeding or pain and an inconclusive USG assessment can rule out a viable pregnancy (17). We found that a single progesterone measurement was sufficient to identify viable pregnancies in both patient and control groups.

Generally, serum levels of progesterone are above 25 ng/mL in viable pregnancies (27), while 5 ng/mL indicates an abnormal pregnancy prognosis (28). More studies are needed to eliminate extreme cut-off levels such as <5 ng/mL for non-viable and >25 ng/mL for viable.

In conclusion, a single measurement of progesterone levels from serum in the first trimester is useful for identifying viable pregnancies, but cannot predict non-viable pregnancies.

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