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The Investigation of Prenatal Screening Test Parameters in Predicting HELLP Syndrome

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ABSTRACT

We aimed to investigate whether first and second-trimester prenatal screening test parameters may be useful in predicting HELLP Syndrome.

HELLP syndrome was defined according to Sibai criteria. The collected data were as follows; age, gravida, parity, body mass index, gestational week at labor, route of delivery, birth weight, aspartate aminotransferase (AST), Lactate dehydrogenase (LDH), bilirubin, first trimester multiple of medians (MOM) of pregnancy-associated plasma protein-A (PAPP-A) and Beta human chorionic gonadotropin (B hCG), second trimester B hCG, unconjugated estriol (uE_3) and AFP levels were measured.

A total of 80 patients in the study group and 135 patients in control groups were included in the study. All the markers of HELLP syndrome were significantly higher in the study group due to the markers was the criteria for HELLP syndrome. While first-trimester PAPP-A was significantly lower in the study group, B hCG levels were similar between groups. The second trimester B hCG level was significantly higher in the study group. AFP level and uE3 level were not different in the control and study groups.

Low PAPP-A levels and high second trimester B hCG levels may be associated with HELLP syndrome in subsequent gestational weeks.

Key Words: Hellp syndrome, screening tests, PAPP-A, beta hCG

Introduction

Hypertensive disorders of pregnancy complicate up to 10% of pregnancies, and ıt is one of the important causes of maternal and perinatal mortality and morbidity. (1). HELLP (Hemolysis, Elevated Liver enzymes, Low Platelet count) syndrome is a potentially life-threatening condition manifesting in the context of preeclampsia, which poses challenging diagnostic and management issues to the clinician (2). It affects 0.2-0.8% of pregnancies, and it is associated with preeclampsia (PE) in 70-80% of cases (3).

The pathogenesis of HELLP syndrome is not fully explained. Some articles state the HELLP syndrome as an advanced form of preeclampsia. Some of the papers suggest that there are different diseases with similar clinical pictures (4). Early diagnosis of the clinical picture and early follow-up will reduce the problems that the mother and fetus may encounter. Some algorithms that use maternal biochemical/clinical changes in early pregnancy are used to predict the development of preeclampsia. However, there is no precise algorithm to predict HELLP syndrome (5).

Nowadays, first-trimester maternal serum PAPP-A and B hCG levels (called the double test) and second-trimester maternal serum AFP, B hCG and uE3 levels (called the triple test) are used for fetal aneuploidy screening frequently (6). Many studies have demonstrated the relationship between first and second-trimester screening test values and low birth weight, preterm labor and preeclampsia (7).

In this study, we aimed to evaluate whether the first and second-trimester screening test parameters may be useful in predicting "HELLP Syndrome".

Materials and Methods

After approval of the institutional review board, this retrospective study was conducted at a tertiary referral perinatal medicine center between January 2013 to January 2015. HELLP syndrome was defined according to Sibai criteria. Hemolysis (peripheric blood findings, Elevated LDH>600, bilirubin>1.2) Elevated enzymes of the liver (AST>70), low platelet<100.000 strict criteria were used for diagnosis of HELLP syndrome. Patients with hematologic diseases, liver diseases, and lack of hospital records

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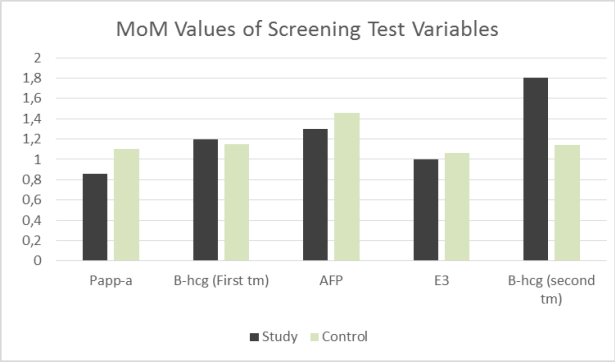

Fig. 1. Comparison of Study and Control groups in terms of screening tests' MoM Values

were excluded. Patients with abnormal screening tests suggesting suspected fetal anomalies were also excluded. Patients without any pregnancy-associated complications were assigned as the control group during the same study period. The uncomplicated pregnancy during the study period was numbered and randomly selected using computed randomization. The collected data were as follows; age, gravida, parity, body mass index, gestational week at labor, route of delivery, birth weight, aspartate aminotransferase (AST), Lactate dehydrogenase (LDH), bilirubin, first trimester multiple of medians (MOM) of pregnancy-associated plasma protein-A (PAPP-A), and Beta human chorionic gonadotropin (B hCG), second trimester B hCG, uE_3 and AFP levels were measured. Multiple of medians were calculated using the software. Blood samples were obtained at 11 to 13 weeks of gestation for first-trimester screening and 16 to 18 weeks for the second-trimester screening test. The results of blood samples were reported as International Unit (IU). Statistical analyses were performed using SPSS 17 (IBM, New York). The normality of the continuous variables in data were tested using the Kolmogorov Smirnov test. Non-parametric variables were compared using the Mann Whitney U test, and parametric variables were compared using independent sample t-test. Categoric variables were compared with the chi-square test. P-value <0.05 was regarded as statistically significant.

Results

A total of 80 patients in the study group and 135 patients in control groups were included in the study. The mean age in the study group and control groups was 28 and 27 in the study and control groups, respectively. There was no significant difference between study and control groups in terms of age. BMI of the control group compared to the study group was significantly higher (35 vs. 26). Median gravida and parity in study and control groups were 2 and 1 respectively, and no significant difference was found. Cesarean delivery was significantly higher in the study group (86.1% vs. 48.9%, $p<0.001$). Preterm delivery was higher in the study group compared to the control group (33 weeks and 38 weeks, $p<0.001$). All the markers of HELLP syndrome were significantly higher in the study group due to the markers was the criteria for HELLP syndrome (Table 1). First-trimester PAPP-A in the study was significantly lower in the study group compared to the control group (0.8 vs. 1.1, $p=0.014$). First trimester B hCG levels were similar in study and control groups. The second trimester AFP level was similar in the control group compared to the study group (1.46 vs. 1.30, $p=0.07$). uE_3 was not different in control and study groups ($p>0.05$). Second trimester B hCG was significantly higher in the study group (1.80 vs. 1.14, $p<0.001$) (Table 2) (Figure 1).

Discussion

In our study, We found that MoM values of PAPP-A and B hCG levels used in the first-trimester screening tests were statistically significantly different between the patients with HELLP syndrome and the control group. In cases with HELLP syndrome, first-trimester PAPP-A levels were lower, and second trimester B hCG levels were higher than the control group. Additionally, In cases with HELLP syndrome, lower gestational age, birth weight, platelet counts, and higher bilirubin, LDH, AST values were detected as expected.

Abnormal placentation and consequently impaired uteroplacental perfusion are thought to be the underlying mechanism of preeclampsia, growth retardation, and stillbirths (8). In these pathologies that emerged in the late weeks of pregnancy, it was shown that the trigger was pulled in the first trimester (9). PAPP-A, one of the first-trimester aneuploidy screening markers induced from the placenta, is a protease that acts on "insulin-like growth factor binding proteins". It is effective in the level of these hormones and in fetal growth and thus in adverse perinatal events (10, 11). Of the first trimester markers, both PAPP-A and B hCG are of syncytiotrophoblast origin (12). Differences in levels of these markers are expected in placental-induced pathologies. According to the results of a meta-analysis investigating the predictability of stillbirth with markers, they have low predictivity for antepartum stillbirth, SGA related, hemorrhage related and placental abruption related stillbirth; have moderate predictivity for preeclampsia and hypertension-related stillbirth (13). In particular, evidence has been found that low PAPP-A levels

Table 1. Clinical and demographic data of study and control groups

	Study	Control	p
Age (years)	28.4±5.1	27.4±5.9	0.140a
BMI (kg/m2)	26.1±4.84	35.9±3.79	0.025a
Gravida	2 (1-6)	2 (1-7)	0.09b
Parity	1 (0-4)	1 (0-4)	0.50b
Route of Delivery			<0.001c
Vaginal	11 (13.9)	69 (51.1)	
C/S	68 (86.1)	66 (48.9)	
Week of Gestation	33 ±2.3	38.8±1.69	<0.001a
Birthweight (gr)	2344±334	3269±440	<0.001a
Bilirubin (mg/dL)	2.76±2.23	0.69±0.29	<0.001b
LDH (U/L)	1050±495	169±40	<0.001a
Platelets (K/uL)	78.1±14	188±39	<0.001a
AST (U/L)	138±73	22±7	<0.001a

[a]P value calculated by Independent Sample T-Test, [b]P value calculates by Mann Whitney U Test, [c] Chi-square Test

Table 2. Comparison of Study and Control groups in terms of screening tests' MoM values

	Study	Control	p
PAPP-A (mIU/ml)	0.86±0.63	1.10±0.70	0.014
B hCG (mIU/ml) (First trimester)	1.20±0.64	1.15±0.15	0.384
AFP (IU/ml)	1.30±0.60	1.46±0.19	0.070
uE3 (ng/ml)	1.00 (0.67)	1.06±0.24	0.331
B hCG (mIU/ml) (second trimester)	1.80±0.92	1.14±0.61	<0.001

P value calculates by Mann Whitney U Test

(<0.4 Mom) are associated with stillbirths associated with placental dysfunction such as preeclampsia. Furthermore, patients with HELLP syndrome in the subsequent gestational week showed lower PAPP-A levels than the patients who developed subsequent preeclampsia. However, PAPP-A levels in the first trimester were similar to controls. In the current study, PAPP-A levels were lower in patients with HELLP syndrome (14). Second-trimester aneuploidy screening tests include alpha-fetoprotein (AFP), which provides information on placental permeability, and B hCG (intact and/or b-subunit), uE3, and inhibin A, which provide information on placental endocrine activity. The predictive value of these markers in placental related pathologies has been evaluated in different studies (15-17). The relationship between the parameters of both first and second-trimester aneuploidy screening tests and poor pregnancy outcomes has been demonstrated in previous studies. (13, 18, 19) In their study, Nunthapiwat et al. showed that AFP has the highest predictive value, but all second trimester screening markers are associated with preterm delivery. (19) In the current study, B hCG levels were higher in patients with HELLP syndrome. Elevated second trimester B hCG levels was found to be associated with adverse maternal events including severe preeclampsia and HELLP syndrome (20). Similarly elevated B hCG levels was found in women with HELLP syndrome that may be associated with impaired blood.

Early prediction of Hellp syndrome will always be popular, and the existence of a meaningful relationship between the tests performed in the early weeks of pregnancy and HELLP syndrome will continue to be of interest to the researchers.

As a result, our findings suggested that low PAPP-A levels and high second trimester B hCG levels may be associated with HELLP syndrome in subsequent gestational weeks.

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