Changes in first trimester screening test parameters in pregnancies complicated by placenta previa and association with hyperemesis gravidarum

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Abstract

Objective: To assess the possible changes in first trimester screening test parameters in pregnancies complicated with placenta previa and to determine whether there is an association between hyperemesis gravidarum and placenta previa.

Material and Methods: A total of 131 singleton spontaneously conceived pregnancies that were complicated by placenta previa and delivered between May 2006 and May 2013 were evaluated from birth charts. Ninety patients without placenta previa were selected amongst patients who delivered within the same period of time as the control group. Cases of low lying placenta (n=52) within the study group were assessed as a separate group. The rest of the cases was considered to be in a different group.

Results: Beta human chorionic gonadotropin (BhCG) multiples of medians (MoMs) and nuchal translucency (NT) MoMs were significantly higher in the placenta previa group in comparison with the low lying placenta and control groups. Apgar scores at both the 1st and 5th minutes were significantly lower in the placenta previa group. Hyperemesis gravidarum was found to be significantly more frequent in the placenta previa group.

Conclusion: The prevalence of hyperemesis gravidarum in the first trimester is higher in pregnancies complicated by placenta previa. Paying more attention to the development of placenta previa in the routine pregnancy follow-up of patients with hyperemesis gravidarum could be considered. (J Turk Ger Gynecol Assoc 2014; 15: 212-6)

Key words: Placenta previa, hyperemesis gravidarum, first trimester screening, BhCG, PAPP-A

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Introduction

Placenta previa is a condition in which the placenta partially or completely obstructs the internal cervical os and is seen approximately 0.3%-0.5% of pregnancies (1). This condition leads obstetric complications, like antepartum second or third trimester bleeding, preterm delivery, and transient tachypnea of the newborn, and also increases the risk of peripartum hysterectomies (2). The pathogenesis of placenta previa remains an obscure issue. Advanced maternal age, multiparity, prior cesarean delivery, multiple pregnancies, prior spontaneous or induced abortions, maternal smoking, and drug abuse are factors that are known to increase the occurrence of placenta previa (3). Impaired placental blood supply in early pregnancy was proposed as an underlying cause by some authors (3). Although there are conflicting results in the literature, the vast majority of the studies does not demonstrate an association between placenta previa and markers of placental insufficiency in term pregnancies. However, placental insufficiency in early pregnancy could be compensated for as placenta previa develops. We aimed to investigate the changes in the first trimester in pregnancies later complicated by placenta previa. In this study, we compared cases of placenta previa and pregnancies with a normal placentation in terms of first trimester screening test parameters, fetal birth weight, and time of delivery and also history of hospitalization due to hyperemesis gravidarum in the first trimester.

Material and Methods

This retrospective cohort study was conducted in the Department of Obstetrics and Gynecology of Ankara University in Ankara. The aforementioned hospital is a tertiary care setting in Turkey. Approval from the institutional board was obtained. Birth records between May 2006 and May 2013 were evaluated. Pregnancies conceived by assisted reproduction and cases with diabetes mellitus, chronic hypertension, and other co-morbidities were excluded from the study. From 8256 singleton births, 131 cases were found to have placenta previa in the third trimester. Ninety patients that gave birth in the selected period of time were established as the control group. Pregnancies with chromosomal abnormalities or

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neural tube defects were intended to be excluded from the study; however, neither of the situations was found amongst the randomly selected women. First trimester screening test parameters of these women were obtained. Placenta previa was classified as 4 types. The term "type 1 placenta previa (low lying placenta)" was used for women with a placental edge between 2-5 cm from internal cervical os. "Type 2 placenta previa (marginal placenta previa)" was described as a placental edge between 0-2 cm far from the internal cervical os. "Type 3 placenta previa (partial placenta previa)" was defined as a placenta partially covering the internal cervical os. "Type 4 placenta previa (complete placenta previa)" was described as a placenta fully covering the internal cervical os. Cases of placenta previa were diagnosed with trans-abdominal ultrasound, and the diagnosis was confirmed by trans-vaginal ultrasound. For the first trimester screening tests, plasma samples were collected following nuchal translucency (NT) measurements. Collected plasma samples were analyzed within 3 hours for beta human chorionic gonadotropin (BhCG) (Siemens 06601846 Immulite® Free Beta hCG Kit; Siemens Medical Solutions Diagnostics, London, United Kingdom) and pregnancy-associated plasma protein A (PAPP-A) (Siemens 06609553 Immulite® 2500 PAPP-A Kit; Siemens Medical Solutions Diagnostics, London, United Kingdom).

All cases with a low lying placenta had attempted spontaneous or induced vaginal deliveries. All cases that had type 2, type 3, or type 4 placenta previa had elective or emergent cesarean sections and were included in the placenta previa group. Cases with a low lying placenta were included in another study group, and 90 women without placenta previa were established as the control group. Categorical variables were expressed as number and percentages. Non-parametric data were compared by Kruskal-Wallis test. P values less than 0.05 were considered statistically significant. Significant differences obtained by Kruskal-Wallis test were further evaluated with post hoc analysis (IBM SPSS Statistics 20.0; IBM Corporation Software Group, New York, United States of America).

Results

A total of 12,069 birth charts were retrospectively evaluated, and 8256 were found to be singleton spontaneously conceived pregnancies. Following exclusion of patients with co-morbidities, 131 cases were found to have placenta previa in the third trimester; 52 of them were found to be low lying placenta, 40 of them were type 2 placenta previa (marginal placenta previa), 2 of them were type 3 placenta previa (partial placenta previa), and 37 of them were diagnosed with type 4 placenta previa (complete placenta previa).

The mean maternal ages were significantly higher in the low lying placenta and placenta previa groups in comparison with controls (p=0.012 and p=0.003, respectively) (Table 1, 2). Mean gravidity, parity, and abortion numbers were significantly higher in the low lying placenta and placenta previa groups in comparison with the controls (Table 1, 2).

Mean PAPP-A levels were 1239.6 ng/mL, 1137.5 ng/mL, and 1619.3 ng/mL in the control group, low lying placenta group, and placenta previa groups, respectively (Table 3). There were no significant differences observed between groups (p=0.934). Mean BhCG levels were 86,892 IU/mL, 85,193 IU/mL, and 112,674 IU/mL in the control, low lying placenta, and placenta previa groups, respectively. Similarly, there were no significant differences observed between groups (p=0.151). PAPP-A MoM values were also similar between groups (p=0.604). BhCG MoM value was significantly higher in the placenta previa group in comparison with the low lying placenta group and control group (p=0.029 and p=0.011, respectively). There were no significant differences found between the low lying placenta group and control group in terms of BhCG MoMs (p=1). Although there were no significant differences found in NT measurements, NT MoM values were significantly higher in the placenta previa group in comparison with controls (p=0.020). Gestational ages at delivery were significantly lower in the placenta previa group in comparison with the control and low lying placenta groups (p<0.001 and p=0.017, respectively). No

Table 1. Characteristics of the study population and neonatal outcomes

	Control group	Low lying placenta group	Placenta previa group	p values
Number of patients	90	52	79	
Maternal age (years)	27.45±5.023	29.77±4.035	29.68±5.988	0.001
Gravidity	2.1±1.1	3.4±0.9	3.5±0.8	<0.001
Parity	0.8±0.4	1.9±0.3	2.2±0.6	<0.001
Abortion history (number)	0.6±0.4	1.3±0.8	1.8±0.5	<0.001
Maternal body weight[a] (kg)	63.45±11.76	60.41±8.241	62.08±8.627	0.528
Fetal birth weight (gr)	3253.6±456.9	3127.6±684.7	3122.4±594.1	0.384
Gestational age at delivery (weeks)	39.3±1.06	38.3±2.83	37.9±1.85	<0.001
Apgar score at 1 minute	8.5±1.06	7.87±1.92	7.92±1.04	<0.001
Apgar score at 5 minute	9.6±0.66	8.98±1.96	9.16±0.77	<0.001

Values are compared by Kruskal-Wallis test and are given as mean±standard deviations. P<0.05 is significant.

[a]Maternal weight in first trimester.

Table 2. Post hoc analysis of Table 1 and Table 3

p values	Control group vs low lying placenta group	Low lying placenta group vs placenta previa group	Placenta previa group vs control group
Maternal age	0.012	1	0.003
Bhcg MoM	1	0.029	0.011
NT MoM	1	0.152	0.020
Gravidity (number)	0.009	0.214	<0.001
Parity (number)	0.012	0.068	<0.001
Abortion (number)	0.002	0.096	<0.001
Gestational age at delivery	0.213	0.017	<0.001
Apgar score at 1 minute	0.021	0.414	<0.001
Apgar score at 5 minute	0.029	0.880	<0.001

p<0.05 is significant

NT: nuchal translucency; Bhcg: beta human chorionic gonadotropin; MoMs: multiples of medians

Table 3. Comparison of first trimester screening test parameters of control group and study groups

First trimester screening test parameters	Control group (n=90)	Low lying placenta group (n=52)	Placenta previa group (n=79)	p values
PAPP-A (ng/mL)	1239.6±791.6	1137.5±549.2	1619.3±4311.8	0.934
PAPP-A MoM	1.14±0.64	1.04±0.51	1.16±0.71	0.604
Bhcg (IU/mL)	86.892±47. 653	85.193±42.063	112.674±13.6793	0.151
Bhcg MoM	1.04±0.54	1.01±0.50	1.27±0.56	0.005
NT (mm)	1.35±0.35	1.4±0.39	1.48±0.48	0.150
NT MoM	1.1±0.28	1.13±0.29	1.26±0.42	0.019

Values are compared by Kruskal-Wallis test and are given as mean±standard deviations.

p<0.05 is significant

PAPP-A: pregnancy-associated protein A; Bhcg: beta human chorionic gonadotropin; NT: nuchal translucency; MoM: multiples of median

differences were observed between these two study groups and the control group in fetal birth weight (p=0.384) (Table 1). Both 1-minute and 5-minute Apgar scores were significantly lower in the low lying placenta and placenta previa groups in comparison with the control group (Table 1, 2). No significant differences were observed between the low lying placenta and placenta previa groups in terms of 1-minute and 5-minute Apgar scores (p=0.880).

Hospitalization due to hyperemesis gravidarum was observed in 3 cases within the control group (3.3%), 2 cases within the low lying placenta group (3.8%), and 8 cases within the placenta previa group (10.1%). The prevalence of hyperemesis gravidarum in the placenta previa group was significantly higher in comparison with the control and low lying placenta groups (p=0.029) (data not shown).

Discussion

According to the results of this study, the prevalence of hyperemesis was significantly higher in the placenta previa group, which was also demonstrated to have significantly higher values of BhCG MoM.

Some previous studies demonstrated elevated mean BhCG levels in cases with hyperemesis gravidarum (4). Despite the presence of studies with controversial results, stimulation of the thyroid gland with BhCG seems to play a role in the development of this condition (4), and the higher levels of BhCG observed in cases with placenta previa might be the cause of the higher prevalence of hyperemesis in the placenta previa group.

BhCG is a glycoprotein, and its maternal serum levels are used to assess the risk of aneuploidies in the first and second trimesters. This glycoprotein is secreted from syncytiotrophoblasts that form the outer layer of chorionic villi in the human placenta (5). Previously, increased mean numbers of trophoblastic giant cells were demonstrated in deciduas and myometrial blood vessels of cases with placenta previa in comparison with normal placentas (6). This could explain the higher BhCG MoM values observed in the placenta previa group. Increased BhCG MoMs might be a consequence of an increased number of syncytiotrophoblasts in placenta previa cases, or better oxygenation might have resulted from increased fusion of cytotrophoblasts.

In considering the higher prevalence of hyperemesis in women with placenta previa, it could be suggested that a history of hyperemesis in a pregnancy might be predictive for the devel-

opment of placenta previa in the second and third trimester. Nevertheless, this issue should be clarified by specifically designed studies with larger populations prior to considering hyperemesis as a risk factor for later development of placenta previa. However, paying more attention to the development of placenta previa in the routine pregnancy follow-up of patients with hyperemesis gravidarum could be kept in mind.

The pathogenesis of placenta previa has not been fully understood yet. According to the trophotropic theory, the placenta migrates to better vascularized tissues. In normal pregnancies, the placenta grows towards the fundus, which can provide more blood. Distal portions of the placenta, close to the lower segment that has a relatively lower blood supply, regress or undergo atrophy. This process is known as "trophotropism." In accordance with the growing fetus, the uterus enlarges as the gestation progresses, and differential growth is observed at the lower uterine segment. These changes also increase the distance between the lower placental edge and cervix in normal pregnancies. Prior uterine damage or uterine scarring is known to be associated with the development of placenta previa. Defective vascularization of the endometrium due to scarring or atrophy caused by previous trauma, surgery, or infection may result in reduced differential growth of the lower uterine segment and less of an upward shift in placental location (7). The isthmic segment of the uterine artery's ascending branch has a wider diameter and a freer course than distal parts of blood vessels in placenta previa. It was previously suggested that a better blood supply and oxygenation might be provided in cases of placenta previa as a consequence of this condition (8). Factors, such as advanced maternal age, multiparity, prior cesarean delivery, multiple pregnancies, prior spontaneous or induced abortions, maternal smoking, and drug abuse, increase the occurrence of placenta previa (3). Utero-placental underperfusion due to atherosclerotic changes in uterine blood vessels was previously demonstrated in older women (9). The surface area of the placenta might be enlarging in these women to maintain sufficient blood supply, which may lead to encroachment of the placenta to the lower uterine segment. Similarly, uterine blood vessels localized at the prior placental attachment site might be deteriorated (10), and decreased utero-placental blood flow in early pregnancy owing to these changes in blood vessels in the prior placental attachment site might lead to the development of placenta previa in multiparous women. Moreover, scarring of the endo-myometrium in women with a history of cesarean delivery is thought to predispose them to the development of placenta previa, possibly due to decreased blood supply provided by the scarred portion of the endometrium (3). Therefore, it could be supposed that the development of placenta previa could be a measure against impaired placental blood supply in early pregnancies. The higher NT MoM values found in the placenta previa group could be a consequence of increased fetal cardiac workload due to subclinical placental dysfunction in early pregnancy. Although they were below the limit of statistical significance, NT MoM values were also higher in the low lying placenta group in comparison with controls. Lower levels of the increase in NT MoMs in the low lying placenta group in comparison with the placenta previa group could be associated with the mildness of the condition.

Although it should be primarily demonstrated by studies directly focusing on the status of supply maintenance of the early placenta, a period of impaired placental nutrition or blood supply in early pregnancy might induce the development of placenta previa as a compensatory mechanism, as mentioned above. However, placenta previa did not seem to be associated with findings of placental insufficiency in later periods of pregnancy (11). Therefore, if placenta previa is a compensatory mechanism against placental insufficiency in early pregnancy, it could be suggested that it usually succeeds.

There were no significant differences observed in fetal birth weights between the control and study groups in our study, and there are some studies with conflicting results about this aspect. Some of the studies indicate an increased incidence of fetal growth restriction in cases of placenta previa (12, 13), while others found no association after adjusting for confounding factors, like prematurity, preeclampsia, and smoking status (14, 15), and suggested that placenta previa was not associated with placental insufficiency, which also seems to be consistent with our results.

Atherosclerotic changes in uterine blood vessels of older women have shown to cause impairments in blood supply to the uterus and endometrium (9), and advanced maternal age was defined as a risk factor for placenta previa in previous studies (16). In our study, consistent with previous studies, maternal ages were significantly higher in the low lying placenta and placenta previa groups in comparison with controls.

Not surprisingly, mean gravidity, parity, and abortion rates were higher in the low lying placenta and placenta previa groups in comparison with controls. The association between multiparity, prior cesarean sections, prior abortion history, and placenta previa has already been demonstrated in previous studies (3).

Gestational ages at delivery were significantly lower in the placenta previa group in comparison with the low lying placenta and control groups. As we mentioned above, all cases in the placenta previa group were delivered by emergent or elective cesarean sections as soon as they reached sufficient fetal maturity. Contrarily, all cases with low lying placenta were attempted to be delivered by spontaneous or induced vaginal birth. This explains the difference in gestational ages at delivery between groups.

Both the 1- and 5-minute Apgar scores were lower in the low lying placenta and placenta previa groups in comparison with controls. This finding has been demonstrated in previous studies and is probably associated with possible adverse neonatal outcomes due to lower gestational age at delivery or maternal bleeding (13).

In conclusion, the prevalence of hyperemesis gravidarum in the first trimester seems to be increased in pregnancies that are complicated with placenta previa in the third trimester, and higher values of BhCG MoMs could be observed in these pregnancies in the first trimester aneuploidy screening tests.

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