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Original Article

Effects of fetal gender and low first trimester aneuploidy screening markers on preterm birth

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ABSTRACT

Objective: To show the relation between fetal gender and preterm birth (PTB) in low values of first trimester aneuploidy test markers.
Material and method: A total of 29,528 patients included the study of them 7382 was PTB and all patients grouped according to fetal gender. Demographic data and perinatal complications were determined. According low PAPP-A MoM (<0.4) and low free BhCG MoM (<0.5) values PTB subgroup relative risks were calculated for each fetal gender.
Results: The PTB rate and birth weight was significantly higher in male gender. At low PAPP-A MoM values Late PTB in male infant (aRR 95% CI 2.028) and late miscarriage (LM) category with low free BhCG MoM values in female infant (aRR 95% CI 0.907) was determined statistically significant.
Conclusions: Male gender has an effect on PTB rate. İn low values of first trimester aneuploidy test markers late PTB risk is increasing in male gender and also LM risk is decreasing in female gender. Further studies are required in order to determine the relation between PTB and fetal gender and first trimester aneuploidy screening test.

Introduction

Preterm birth (PTB) is a pregnancy complication and may cause numerous obstetric problems, such as fetal morbidity and mortality. PTB may occur due to potential interactions among multiple factors. In early gestational weeks, PTB occurs due to cervical insufficiency, inflammation, infection, and immune reaction, whereas in the later weeks of gestation, it occurs due to placental hemorrhage, multiple pregnancies, and polyhydramnios, which may cause hemorrhage and uterine distention [1]. Studies have been conducted to predict the occurrence of PTB owing to its high rate of occurrence and the associated difficulties in treatment. Some studies have reported higher rates of PTB for male fetuses [2].

Fetal gender is determined via complex interactions among gonadal, hormonal, and genetic factors acting during the intrauterine period. By increasing intrauterine pressure, studies have attempted to clarify the higher rate of PTB in mothers carrying a male fetus than in those carrying a female fetus because male fetuses are larger and heavier than female ones [3–5]. However, the review published by Challis et al. [1] in 2013 suggested that the higher rate of PTB in mothers carrying a male fetus than in those carrying a female one may be attributed to the activation of placental enzyme and the fetal pituitary–adrenal axis being affected by the fetal genotype.

In addition, a possible relationship between pregnancy complications and low first trimester aneuploidy screening markers, including nuchal translucency (NT), free beta-human chorionic gonadotropin (free β-hCG), and pregnancy-associated plasma protein-A (PAPP-A), has been reported. Studies indicating a relationship between low PAPP-A multiples of median (MoM) and primarily PTB but also preeclampsia, eclampsia, spontaneous abortion, and intrauterine fetal growth retardation have also been reported [6–8]. Along with low PAPP-A MoM, albeit less frequently, studies relating low free β-hCG to NT MoMs less frequently with PTB have also been published [9]. In addition, it was determined whether PAPP-A and free β-hCG levels are affected by fetal gender [10]. Considering the higher rate of PTB among women carrying

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male fetuses and the effect of fetal gender on PAPP-A and free β-hCG levels, the present study aimed to demonstrate the effects of low first trimester aneuploidy screening markers on PTB in male and female fetuses.

Materials and methods

This is a retrospective, nested, case-control study included pregnant women who underwent first trimester aneuploidy screening at our clinic from 11 + 0 to 13 + 6 gestational weeks between January 2014 and June 2017 and delivered their baby at our hospital. The women included were those with singleton pregnancies who delivered phenotypically normal infants after 16 weeks of gestation. Pregnant women who had a miscarriage before 16 weeks of gestation, had multiple pregnancies, or delivered an infant with aneuploidy or fetal anomaly were excluded. The women finally included in the study were grouped according to the fetal gender and MoM values of low first trimester aneuploidy screening markers. PAPP-A <0.4 MoM and free β-hCG <0.5 MoM were considered low values.

In the current study, PTB was defined as birth at or before 37 weeks of gestation, late miscarriage (LM) was defined as birth between 16 and 24 weeks of gestation, extreme PTB was defined as birth between 24 and 28 weeks of gestation, very PTB was defined as birth between 28 and 34 weeks of gestation, and late PTB was defined as birth between 34 and 37 weeks of gestation.

The gestational weeks of the pregnant women included in the current study were determined based on their last menstrual period or crown-rump length, which was determined at the time of pregnancy detection. Demographic data, such as maternal age, parity, body mass index (BMI), gestational age, diseases before pregnancy, maternal risks that may cause PTB, and pregnancy outcomes were retrieved from the hospital information system. Neonatal outcomes, such as fetal gender, birth weight, gestational week at birth, need for admission to the neonatal intensive care unit, and stillbirth were recorded from the newborn examination cards.

For low first trimester aneuploidy screening, a certified physician or perinatologist first measured NT on ultrasound after obtaining consent of the pregnant women. Following ultrasonographic examinations, venous blood samples from the pregnant women within 24 h were collected into a tube containing approximately 5 mm^3 EDTA. The sample was centrifuged at 5000 rpm for 10 min and the levels of serum PAPP-A and free β-hCG were determined using İmmulite 2000 XPi (Siemens) device in the biochemistry laboratory of our clinic. The expected MoM values of PAPP-A, free β-hCG, and NT measurements among the pregnant women are calculated using PRISCA 5.0 Prenatal Risk Calculation software (Siemens). The calculated MoM values were then adjusted for maternal age, weight, adjusted gestational age, presence of insulin-dependent diabetes, smoking status, need for assisted reproductive techniques, and history of neural tube defects.

Statistical analysis

Data are presented as frequency and percentage. Normality tests were performed in accordance with the number of pregnancies, and a normal distribution pattern was accepted if $p > 0.05$. The results are presented as mean ± standard deviation for normally distributed data, and independent sample *t*-test was used for parametric variables in univariate analyses. Chi-square test was used for assessing intergroup differences of categorical variables. Adjusted relative risk (aRR) and 95% confidence intervals (CI) were calculated to compare the outcomes between the male and female gender groups. A p value of <0.05 was considered statistically significant. All statistical analyses were performed using SPSS 22.0 for Windows (SPSS Inc., Chicago, IL).

Results

Using data from the hospital information system, we screened for and retrospectively evaluated pregnant women who underwent first trimester aneuploidy screening at our hospital between January 2014 and June 2017 and who delivered their baby before 37 weeks of gestation. Of the total 8134 pregnant women with PTB, 752 were excluded as they did not satisfy the set inclusion criteria; hence, a total of 7382 pregnant women were included in the study. The control group comprised 22,146 women who delivered between 39 and 41 weeks of gestation; these women were randomly selected among 35,000 pregnant women using a computer software (case:control ratio, 1:3) (SPSS 22.0 for windows). Of the pregnant women included in the study, 51.1% delivered a male infant; furthermore, 25.7% and 24.3% of those who delivered a male and a female infant had PTB, respectively.

The demographic data of the pregnant women included in the study and the factors that may pose a risk of PTB before and during pregnancy are presented in Table 1. The prevalence of maternal type 2 diabetes mellitus before pregnancy was significantly higher in pregnant women who delivered a male infant ($p < 0.001$). The rate of PTB was significantly higher in pregnant women who delivered a male infant ($p = 0.004$). Furthermore, the birth weight of male infants was found to be higher than that of female infants ($p < 0.001$).

Table 2 presents the effects of low PAPP-A MoM values and fetal gender on all PTB categories. No significant correlation was observed between low PAPP-A MoM values and all PTB categories in the pregnant women who delivered a female infant (LMs <24 weeks as well as <28, <34, and <37 weeks). A significant correlation was observed between low PAPP-A MoM values and late PTB (<37 weeks) in the pregnant women who delivered a male infant (aRR 1.153; 95% CI, 1.164–2.028; $p = 0.006$). Although no statistically significant correlation was observed between low PAPP-A MoM values and LM (aRR, 2.088; 95% CI, 0.751–5.802, $p = 0.159$) and extreme PTB (aRR, 2.014; 95% CI, 0.819–4.954; $p = 0.131$), their relative risks were found to be higher.

Table 3 presents the effects of low free β-hCG MoM values and fetal gender on all PTB categories. No statistically significant correlation was observed between low free β-hCG MoM values and all PTB categories in the pregnant women who delivered a male infant. A statistically significant difference was observed in the LM category with low free β-hCG MoM values in pregnant women who delivered a female infant (aRR, 0.568; 95% CI, 0.356–0.907;

Table 1
Demographic data of pregnant women included in study and risk factors for preterm birth.

	Male sex n = 15,091 (%)	Female sex n = 14,437 (%)	p value
Maternal age	27.21 ± 6.19	27.22 ± 6.21	0.916
Parity	5443 (36.1%)	5184 (35.9%)	0.774
Nulliparity	9648 (63.9%)	9253 (64.1%)	
Multiparity			
Current Smoker	633 (4.2%)	592(4.1%)	0.362
BMI	24.6 ± 6.12	24.5 ± 5.42	0.763
Number of previous pregnancies lost	650 (4.3%)	576 (4%)	0.172
Previous cesarean section	3105 (20.5%)	3052 (21.1%)	0.143
Preexisting hypertension	226 (1.5%)	202 (1.4%)	0.534
Type 2 diabetes mellitus	166 (1.1%)	719 (0.8%)	**<0.001**
Heavy worker	660 (4.4%)	661 (4%)	0.721
Preterm birth	3881 (25.7%)	3501 (24.3%)	**0.004**
Birthweight (gr)	3078 ± 768	2973 ± 719	**<0.001**
Stillbirth	305 (2%)	286 (2%)	0.806

p value is signified as bold if it's statistically significant.

Table 2
Effect of fetal gender and low PAPP-A MoM values on preterm birth.

	PAPP-A MoM <0.4 (n, %)	PAPP-A MoM >0.4 (n, %)	Adjusted relative risk[a,b]	P value
Male sex				
Late Miscarriage	30 (18.4%)	133 (81.6%)	2.08 (0.75–5.80)	0.159
Extreme PTB	56 (17.9%)	256 (82.1%)	2.01 (0.81–4.95)	0.131
Very PTB	214 (15%)	1210 (85%)	1.47 (0.99–2.20)	0.071
Late PTB	672 (17.3%)	3212 (82.7%)	1.15 (1.16–2.02)	**0.006**
Female sex				
Late Miscarriage	6 (4.2%)	135 (95.8%)	0.57 (0.81–4.10)	0.571
Extreme PTB	41 (14.8%)	235 (85.2%)	1.88 (0.70–5.07)	0.231
Very PTB	116 (9.4%)	1117 (90.6%)	1.15 (0.64–2.07)	0.640
Late PTB	449 (12.9%)	3101 (87.1%)	1.40 (0.98–1.99)	0.083

PAPP-A MoM, pregnancy-associated plasma protein-A multiples of median; PTB, preterm birth.
p value is signified as bold if it's statistically significant.
[a] Reference group: Pregnant women in the control group [male (n = 9308) and female infants (n = 9237)].
[b] Adjustment was performed for birthweight and past medical history (pregestational diabetes).

Table 3
Effect of fetal gender and low free β-hCG MoM values on preterm birth.

	Free β-hCG MoM <0.5 (n, %)	Free β-hCG MoM >0.5 (n, %)	Adjusted Relative risk[a,b]	P value
Male gender				
Late Miscarriage	141 (88.3%)	22 (11.7%)	0.656 (0.431–1.013)	0.075
Extreme PTB	287 (92%)	25 (8%)	0.973 (0.658–1.438)	0.890
Very PTB	1318 (92.5%)	106 (7.5%)	1.044 (0.882–1.235)	0.617
Late PTB	3596 (92.5%)	288 (7.5%)	1.039 (0.907–1.189)	0.579
Female gender				
Late Miscarriage	122 (86.5%)	19 (13.5%)	0.568 (0.356–0.907)	**0.018**
Extreme PTB	253 (91.7%)	23 (8.3%)	0.948 (0.630–1428)	0.799
Very PTB	1151 (93.3%)	82 (6.7%)	1.160 (0.953–1.413)	0.130
Late PTB	3623 (93.2%)	261 (6.8%)	1.124 (0.968–1.306)	0.116

Free β-hCG MoM, free free beta-human chorionic gonadotropin multiples of median; PTB, preterm birth.
p value is signified as bold if it's statistically significant.
[a] Reference group: Pregnant women in the control group [male (n = 9308) and female infants (n = 9237)].
[b] Adjustment was performed for birthweight and past medical history (pregestational diabetes).

p = 0.018); however, no significant correlation was observed for the other PTB categories.

Discussion

We demonstrated that pregnant women with low PAPP-A MoM values who delivered a male infant are at increased risk for PTB and that women carrying a female fetus and having low free β-hCG MoM values are at increased risk for LM before 24 weeks of gestation.

Few studies have suggested that pregnancy outcomes, particularly fetal gender-related PTB, may be affected by fetal genotype owing to the placental enzyme activity and the fetal pituitary–adrenal axis [1,11]. According to DiPietro et al the levels of salivary cortisol between 24 and 30 weeks of gestation in mothers carrying a male fetus are reportedly equal to the levels after 30 weeks of gestation in mothers carrying a female fetus [14]. They stated that salivary maternal cortisol could be used for detecting maturational delay and according to them sex specific adaptations across a broad array of physiological and molecular processes in the developmental rate of behaviors indicative of neural maturation is support their hypothesis [14]. Hence the early maturation could be cause of high PTB rate in male delivered mother.

Furthermore, chronic inflammation at the implantation site is reportedly more common in the placenta of male fetuses; therefore, PTB could also occur due to a more aggressive maternal inflammatory response to the trophoblasts of male fetuses [15]. Goldenberg and Ghidini stated that in preterm male infants rates of chronic decidual inflammation of the lymphohistiocytic and lymphoplasmacytic variety was higher than female infants [15,16]. Also, mothers who giving birth male fetus have higher circulating pro-inflammatory cytokines, with lower anti-inflammatory IL 10 and GCSF and IL 6. Additionally, Goldenberg et al determined that male infants were significantly more likely to have placental membrane bacterial infection [16]. According to Ghidini differences in the biology of X chromosome could be the clue [15].

In addition, few studies have suggested that the high birthweight of male fetuses could serve as a risk factor for PTB; this finding corroborates with the findings of the current study. [3–5]. Moreover, the relative risk for PTB in mothers who delivered a male infant is reportedly 1.11%–1.5%. [12,13]. However, contrary to our results, a study on pregnant women who are at high risk for PTB identified no difference between women who delivered male and female infants [17].

A low PAPP-A MoM value detected in the first trimester aneuploidy screening is one of the strong indicators of chromosomal anomalies [9]. Impaired placental function and implantation are the reasons for the correlation between poor pregnancy outcomes and low PAPP-A MoM values [18]. Trophoblastic activity and inflammation in the implantation site are affected by fetal genotype and as a result all placental functions such as enzyme activities involved in delivery mechanism may also be affected by fetal genotype [1,11]. Also, PAPP-A play a significant role in the autocrine and paracrine control of trophoblast invasion of the decidua [10]. PAPP-A is a protease for insulin-like growth factor (IGF) binding protein-4 and it regulates all the fetal growth by levels of free IGF. Hence low PAPP-A value and male gender may have a role of impaired placental function and implantation [18]. Consequently, the PTB ratio may be increased in male fetus carrying pregnant women with low PAPP-A values.

Here, we determined that the risk for PTB is high in both genders provided the PAPP-A MoM values are low, and this finding corroborates with those reported in the literature [6,9,18]. However, a few studies have suggested there is no correlation between PTB and low PAPP-A MoM values [19].

We observed no increase in the risk for LM in women who delivered a female infant and had low PAPP-A MoM values (aRR, 0.57; 95% CI, 0.81–4.10) who delivered a female infant; however, an increase in the risk for LM was observed in women who delivered a male infant (aRR, 2.08; 95% CI, 0.75–5.80). The results for LM obtained in our study were not completely compared owing to the lack of a similar study in the literature; however, the study conducted by Teoh et al. in 2018 reported a 1.33× higher risk for spontaneous LM in women carrying a male fetus than in women carrying a female fetus, a finding similar to that observed in our study [17]. An increase in the rate of LM can be expected in the presence of low PAPP-A MoM values owing to a decrease in the PAPP-A MoM values below normal levels, which is caused by the release of free radicals and inflammatory processes and the resulting effects on the decidua and placenta, all of which are more commonly observed in male fetuses from the early weeks of gestation.

Low free β-hCG MoM values and the risk for chromosomal anomalies are inversely related. We determined that the rate of LM significantly increased only in women with low free β-hCG MoM values who delivered a female infant. Although no increase in the risk for LM was observed in women who delivered a male infant in the present study, a study conducted employing faster trial subanalyses identified a significant correlation between low free β-hCG MoM values and pregnancy loss before 24 weeks of gestation [18]. Moreover, in the PTB categories reported in the above-mentioned study [18], no significant correlation was observed between low free β-hCG MoM values and PTB in women who delivered male or female infants, a finding consistent with that of other studies in the literature [6,9,18].

Therewithal we determined that higher prevalence of maternal type 2 diabetes mellitus in pregnant women with a male fetus. In the literature there is no consensus about gestational diabetes mellitus risk and fetal gender [11,20,21]. Especially, male gender has been held responsible from higher gestational diabetes mellitus and also increased risk of Type 2 diabetes mellitus after gestational diabetes mellitus [20]. However, there is no evidence to support our data about higher prevalence of maternal type 2 diabetes mellitus in pregnant women with a male fetus.

The present study is different from other studies reported in the literature in that the increases in the risk for PTB and LM have been separately assessed for both genders, considering the effect of fetal gender in the presence of low PAPP-A and free β-hCG MoM values. A major strength of the present study is that it evaluated a higher number of patients compared with most single-center studies reported in the literature.

In conclusion, it is important to consider that the risk for PTB may be increased in both fetal sexes in the presence and absence of low PAPP-A MoM values and genetic anomalies, respectively. However, further multicenter, prospective, large-scale studies are warranted to draw more accurate conclusions.

Conflicts of interest

The authors have no conflicts of interest to disclose.

Contributors' statements

Ahkam Göksel Kanmaz contributed to the conception, design, statistical analysis, data collection, and writing and editing of the manuscript.

Adnan Budak, Abdurrahman Hamdi İnan, Emrah Beyan reviewed and approved the final manuscript.

Volkan Karataşlı, İlker Çakır contributed to the data collection.

Volkan Emirdar writing and editing of the manuscript.

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