The Effect of Fetal Gender on the Markers of First Trimester Down Syndrome Screening

Devrim Ertunç, Ekrem Tok, Gürkan Yazıcı, Mustafa Kaplanoğlu, Meral Aban, Saffet Dilek

Department of Gynecology and Obstetrics, Faculty of Medicine, Mersin University, Mersin

Abstract

Objective: The aim of this study was to investigate the effect of fetal gender on first trimester Down syndrome screening markers.

Methods: 256 pregnancies in that fetal nuchal translucency and maternal serum free β-hCG and PAPP-A were evaluated and delivered in our clinics were included in the study. We investigated if these markers differed on the basis of fetal gender.

Results: Fetal nuchal translucency was measured 0.11 mm more in male fetuses than in female fetuses (P = 0.026). Although free β-hCG and PAPP-A levels were higher in female fetuses the difference was not statistically significant.

Conclusion: The data of previous literature and the results of the present study suggest that first trimester markers differ on the basis of fetal gender, however it has no clinical meaning.

Keywords: First trimester Down syndrome screening, fetal gender.

Fetal cinsiyetin ilk trimester Down sendromu tarama belirteçlerine etkisi

Amaç: Bu çalışmanın amacı, fetal cinsiyetin ilk trimester Down sendromu tarama belirteçlerine etkisini araştırmaktı.

Yöntem: 10-14 haftalar arasında fetal nukal translusensi, maternal serum serbest β-hCG ve PAPP-A bakılmış ve kliniğimizde doğum yapmış olan 256 gebelik çalışmaya dahil edildi. Bu belirteçlerin cinsiyete göre farklılık gösterip göstermediği araştırıldı.

Bulgular: Fetal nukal translusensinin, erkek fetuslarda, kız fetuslardan ortalama 0.11 mm daha fazla olduğu gözlendi (P = 0.026). Serbest β-hCG ve PAPP-A değerleri kız fetuslarda daha yüksek olsa da istatistiksel olarak anlamlı değildi.

Sonuç: Literatürdeki diğer veriler ve çalışmamızdan elde ettiğimiz sonuçlar bize, ilk trimester belirteçlerinin cinsiyete göre farklılık gösterdiğini ancak bunun klinik bir anlamı olmadığını düşündürmektedir.

Anahtar kelimeler: İlk trimester Down sendromu taraması, fetal cinsiyet

Introduction

At present, the most effective trisomy 21 screening method is the estimate of risk combining maternal age, fetal nucal translucence and serum free β-human-corionic-gonadotropin (β-HCG) and pregnancy-associated plasma protein-A (PAPP-A), which were performed at weeks 11 and 14. In prospective studies, it has been observed that false positivity was 5% while determination rate for trisomy 21 was 90%, which, in fact, was superior to the maternal age only (35%), or combination of the

Correspondence: Dr. Devrim Ertunç
Mersin Üniversitesi Tıp Fakültesi Hastanesi Kadın Hastalıkları ve Doğum Anabilim Dalı, Mersin
e-mail: devrimertunc@hotmail.com

maternal age and the second trimester serum biochemical markers (65%).[1,2]

As already known, adjustments are required particularly in the interpretation of biochemical tests depending on the maternal age, gestational age, maternal weight, multiple pregnancy and presence of diabetes mellitus. In the meantime, a recent study suggested that ethnical origin should be taken into consideration while interpreting the nucal translucence.[3] It has been proposed that gender also should be taken into consideration during the measurement of nucal thickness, and in case where the fetal gender can be determined, correction would be necessary accordingly.[4]

Later studies have shown that NT is not the only marker which is affected by the gender, but β-HCG and probably PAPP-A are also related to the fetal gender. If there is really such a divergence in the markers of the first trimester Down syndrome, then it is obvious that the sensitivity and specificity values of these screening tests would also be changing. The objective of our study was to investigate the impact of fetal gender on the first trimester Down syndrome screening markers in our population.

Methods

256 patients, who had complete records of first trimester serum screening and fetal NT between 11th and 14th week of pregnancy and in whom gender was confirmed after delivery, were included in this retrospective study. All pregnancies were single and no problem was observed during pregnancy and delivery. Patients identified with chromosomal abnormalities in screening tests and patients in whom gender was identified by only sonography and patients who were lost to follow up were excluded.

According to clinical protocol, invasive diagnostic interventions were applied if any abnormality was identified in screeening tests of pregnant woman at the age of 39 or less. Fetal NT measurements were performed by specialists in our clinic and in measurements, the method recommended by Nicolaides[5] was used. In brief, fetal CRL was measured first, by using 5 MHz transabdominal probe with videoloop function (GE Logic 500, Milwaukee, USA). After differentiating the posterior wall of the neck from amnion, markers were located in the inner part. In sagittal cross sections of the fetuses (with a CRL of 45-84 mm) NT measurements were done under magnification in which distance varied 0.1 mm by every movement of the marker. In serum screening, free β-hCG and PAPP-A measurements were performed with Immulite (BioDPC, İstanbul) device by using solid phase, chemiluminescence immunometric sandwich method. MoM values and adjusted risk was calculated by Prisca 4.0 package screening programme (Typolog Software GmBH, Germany).

Data analysis were performed by SPSS 9.0 (SPSS Inc. Chicago, IL). Student t test was used for comparison of MoM values of biochemical markers and for NT measurements in mm. P value of 0.05 and less was considered to be significant.

Results

Of the 256 babies whose gender were identified and first trimester records were complete, 159 were female and 117 were male. Baseline characteristics of these fetuses at the time of testing are summarized in Table 1. Male and female fetuses showed no difference in terms of maternal age, weight at the time of testing and mean gestational week ($p>0.05$). None of the mothers had type 1 or type 2 diabetes. Mothers of 8 female and 9 male fetuses were smokers at the time of testing ($p=0.54$). Although the number of male fetuses whose combination risk was found to be 1/270 or less and who demonstrated normal chromosomal structure in the amniosynthesis, was slightly higher, there were no statistically significant difference (Table 1)

In Table 2 fetal NT maternal serum free β-hCG and PAPP-A values are compared according to the gender of the fetuses. Fetal NT measurements of male fetuses were found to be 0.11 mm in average which was higher than female fetuses and the difference was statistically significant ($p=0.026$). However there was no difference between free ß-hCG and PAPP-A levels in terms of fetal gender ($p>0.05$).

Discussion

PAPP-A is a dimeric structured glycoprotein consisting of two equal subunits. It is found in circulation depending on the eosinophile major binding protein (eMBP). While PAPP-A is secreted from

Table 1. The comparison of the features of female and male fetuses (Mean ± SS or n, %)*

	Female fetus (n = 139)	Male fetus (n = 117)	p
Materna age	29.83 ± 7.61	30.01 ± 8.24	0.86
Maternal weiht	64.11 ± 10.34	62.75 ± 9.22	0.27
Mean pregnancy week at the time of testing	12.08 ± 1.04	12.15 ± 1.04	0.59
Diabetes†	0 (%0)	0 (%0)	
Smoking	8 (%5.76)	9 (%7.69)	0.54
Combined risk‡	6 (%4.32)	8 (%6.84)	0.39

*Mean ± standart deviation
†Type I or type II diabetes
‡Maternal age, NT, free β-hCG, PAPP-A

synsitiotrophablastic and septal X cells, eMBP is only secreted from septal X cells. PAPP-A is presented into obstetric practice in Down syndrome screening by Brambati et al.[6] hCG is secreted mainly from placental cytotrophoblasts and especially during the advanced period of pregnancy it is secreted from synsitiotrophablasts. After it reaches to maximum maternal serum level in 9-10 weeks it decreases gradually until 20th week and draws a plateau till delivery. It is proposed that in Down syndrome, the differentiation ability of the cytotrophablasts are disordered and can not form the syncitium therefore hCG levels are high.[7]

It is first and extensively suggested by Spencer et al8 that the fetal NT levels which is measured at the 11th and 14th weeks can differ according to gender. In this trial which is established in England a total of 2923 normal and 223 fetus with trisomy 21 are investigated. In normal pregnancies mean fetal NT MoM level in male fetuses were high in 3% ($p<0.01$), while mean free β-hCG and PAPP-A MoM levels were 15% and 10% respectively ($p<0.0001$). However in this trial in which combined risk of 1/300 and lower considered to be risky, there was no significant difference in the male and female fetuses who have a risk potential (6.5% vs. 6.9%, $p>0.05$). In this trial it is observed that female and male fetuses with trisomy 21 have similar differences. In female fetuses mean fetal NT MoM level is found to be 4% lower ($p=0.018$), mean free ß-hCG and PAPP-A MoM levels are found to be higher in male fetuses (11% and 13% respectively, $p>0.001$). In our study although the fetal NT level in mm is found to be 8.1% (0.11) higher, there was no difference between ß-hCG and PAPP-A MoM levels (Table 2).

In a study in which 12189 fetusus are included and which is performed in China, fetal NT values of 10-14 week male and female fetuses compared and while in 10 week fetuses there were no differences, it is observed that female fetuses who are in 11-14 week NT thicknesses are 5% lower than males.[9] However authors concluded that it is 0.06-0.1 mm and its' clinical significance is sceptical. In contrast to these, Yaron et al[10] from Israel reported that NT and PAPP-A levels showed no differences, free ß-hCG is higher in female fetuses but this difference decreases after the 12 weeks. Larsen et al[11] observed that NT is significantly thinner in female fetuses than male fetuses which is consistent with the literature, but free β-hCG and PAPP-A levels are higher. In our study, although the mean free β-hCG and PAPP-A MoM levels are found to be higher in

Tablo 2. The comparison of the first trimester screening results of female and male fetuses (mean ± SS)*

	Female fetus (n = 139)	Male fetus (n = 117)	p
Fetal NT	1.35 ± 0.37	1.46 ± 0.41	0.026
PAPP-A	1.32 ± 0.71	1.20 ± 0.63	0.153
Free β-hCG	1.22 ± 0.70	1.14 ± 0.66	0.349

*Mean ± standart deviation

female fetuses, there were no significant difference probably due to lesser patient number.

As a conclusion, it seems that gender has an effect on Down syndrome markers in the first trimester, however its' clinical significance is not clear. As in our study and in other studies fetal NT values are approximately 0.1 mm higher. In our opinion this difference rarely provides any contribution to the treatment of the fetus. In addition to Spencer et al, we also showed that the sonographic and biochemical parameters did not increase the rate of invasive interventions significantly. Another obstacle in the adjustment of Down syndrome markers according to gender in the first trimester is the limitation of the possibility of gender identification in only 70-90% of fetuses in these weeks.[12,13]

Conclusion

The results of our study and other data suggest that first trimester markers vary according to gender but this has no clinical significance.

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