Is there any effect of fetal gender on the markers of first trimester Down's Syndrome screening?

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Summary

Introduction: At present, the most effective trisomy 21-screening method is the estimate of risk combining maternal age, fetal nuchal translucency, beta-hCG and pregnancy-associated PAPP-A. *Objective:* The aim of this study was to investigate the possible effect of fetal gender in first trimester Down's syndrome screening markers. *Design:* Retrospective study. *Setting:* Prenatal Diagnosis Centre in a tertiary hospital in Lagos. *Methods:* Of a total of 350 pregnancies in which fetal nuchal translucency and maternal serum free beta-hCG and PAPP-A were performed were included in this study. These markers were investigated to see if they differed on the basis of fetal gender. *Results:* PAPP-A levels were higher in female fetuses although the difference was not statistically significant. Nuchal translucency was 0.099 mm more in male fetuses. *Conclusion:* The results suggest that first trimester markers differ on gender but are of no clinical significance, confirming the result of other authors.

Key words: Gender; Down's syndrome; Screening; Biochemical; Nuchal translucency.

Introduction

Today, the most effective trisomy 21 screening method is the calculation of risk combining maternal age, fetal nuchal translucency, free beta human chorionic-gonadtropin (beta-hCG) and pregnancy-associated plasma protein-A (PAPP-A) performed at 10-14 weeks of gestation [1, 2]. In some prospective studies it has been observed that false positivity was 5%, while determination rate for trisomy 21 was 90% – which is superior to maternal age only (35%), or a combination of the maternal age and second trimester serum biochemical markers. It is known that adjustments are required, particularly in the interpretation of biochemical tests, depending on the maternal age, gestational age, maternal weight, multiple pregnancies and diabetes mellitus. Recently it was suggested that origination should be taken into consideration when interpreting nuchal translucency [3]. It has been proposed that gender also should be taken into consideration during the measurement of nuchal thickness, and in cases where fetal gender can be determined correction would be necessary according to Drughan *et al.* [4]. Other studies have shown that nuchal translucency (NT) is not the only marker which is affected by gender; beta-hCG and probably PAPP-A are also related to fetal gender. Based on this, if there is really such a divergence in the markers of the first trimester of Down's syndrome, then it is obvious that the sensitivity and specifity values of these screening tests should also be changing. In this study, the effect of fetal gender on first trimester Down's syndrome screening markers were investigated in a Nigerian population.

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Material and Methods

A total of 350 women, who had complete records of first trimester serum screening and fetal NT between the 10th and 14th weeks of gestation and in whom fetal gender was confirmed after delivery, were included in this retrospective study. All pregnancies were single and the course of pregnancy and delivery were without any complications. Excluded were patients with identified chromosomal abnormalities during screening test and patients in whom gender was identified by only sonography and those patients lost to follow-up. Invasive diagnostic procedures were applied only if any abnormality was seen in the screening tests of pregnant women aged 39 years or less.

Fetal NT measurements were performed according to the recommendation by Nicolaides *et al.* [5]. After measurement of the fetal crown-rump-length (CRL), using a 5MHZ transabdominal transducer with video and differentiating the posterior wall of the fetal neck from the amnion, markers were located in the inner part in a sagittal cross section of the fetuses (with a CRL of 45-84 mm). NT measurements were carried out under magnification at a distance of 0.1 mm by every movement of the marker. In serum screening, free beta-hCG and PAPP-A measurements were performed with the solid phase chemiluminescence immunometric sandwich method. Median multiple of the median (MoM) values and adjusted risk were calculated by the Prisca 4.0 package screening programme (Typology Software Gmbh, Germany). For statistical analysis the Student's t-test was performed and used to compare MoM values of biochemical markers and for NT measurements in mm; p values of 0.05 and less were considered to be significant.

Results

Out of the 350 fetuses whose gender were identified and first trimester data were complete, 191 were females and 159 were males. Baseline characteristics of these fetuses at the time of testing are shown in Table 1. Male and female fetuses differed in terms of maternal age, weight at the time of testing, and mean gestational week

Table 1. — *Baseline characteristics of female and male fetuses.*

Characteristic	Females n = 191	Males n = 159
Maternal age	31.11 ± 24 ± 8.26	30.8 ± 8.79
Maternal weight	69.47 ± 9.82	68.86 ± 9.79
Mean gestational week at the time of testing	12.20 ± 1.06	12.16 ± 1.05
Diabetes	0 (0%)	0 (0%)
Smoking	6 (3.14%)	7 (4.40%)
Combined risk	9 (4.71%)	7 (4.40%)

Mean ± SD; Type 1 or type II diabetes; Maternal age NT, free hCG, PAPP-A.

Table 2. — *Comparison of screening results of female and male fetuses in the first trimester (mean ± SD).*

Parameter	Female fetus	Male fetus	*p* value
Fetal NT	1.340 ± 0.36	1.439 ± 0.39	0.025
PAPP-A	1.33 ± 0.69	1.24 ± 0.61	0.151
Free beta-hCG	1.24 ± 0.68	1.16 ± 0.69	0.342

but not statistically. None of the pregnant women had type I or type 2 diabetes. Mothers of six female and seven male fetuses were smokers at the time of testing. 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 amniocentesis, there were no statistically significant differences between the two sex (Table 1).

Table 2 shows fetal NT, maternal serum free beta-hCG, and PAPP-A values compared according to the gender of the delivered fetuses. Fetal NT measurements of male fetuses were found to be 0.099 on average, which was higher than female fetuses and differences were statistically significant ($p = 0.027$). However, there was no difference between free beta-hCG and PAPP-A levels in terms of fetal gender.

Discussion

PAPP-A is a dimeric structured glycoprotein consisting of two equal subunits. It is found in the circulation depending on the eosinophil major protein (eMBP). While PAPP-A is secreted from syncytiotrophoblastic and septal X cells, eMBP is only secreted from septal X cells – presented into obstetrics practice in Down's syndrome screening by Brambati *et al.* [6]. Beta-hCG is secreted mainly from placental cytotrophoblasts and especially during the advanced period of pregnancy it is secreted from syncytiotrophoblasts. After it reaches the maximum maternal serum level in nine to ten weeks, it decreases gradually until the 20th week and draws a plateau till delivery. It is proposed that in Down's syndrome, the different abilities of cytotrophoblasts are disordered and can not form the syncitium, therefore hCG levels are high [7]. It is first and extensively suggested by Spencer *et al.* [8] that the fetal NT levels which are measured at the 11th and 14th weeks can differ according to gender. In that trial in England, a total of 2,923 normal and 223 fetuses with trisomy 21 were investigated. In pregnancies the mean fetal NT MoM levels in male fetuses were high in 3% ($p < 0.01$) while mean free beta-hCG and PAPP-A MoM levels were 15% and 10%, respectively ($p < 0.0001$). However in this study in which combined risk of 1/300 and lower is considered to be risky, there was no difference in the male and female fetuses who had a risk potential (6.5% vs 6.9%). In this study it was observed that female and male fetuses with trisomy 21 had similar differences. In female fetuses mean fetal NT MoM was found to be 4% lower ($p = 0.018$) and PAPP-A MoM levels were found to be higher in male fetuses (10.9% and 13.3%, respectively $p > 0.001$). In our study, although the fetal NT level in mm was found to be (0.099) higher, there was no difference between beta-hCG and PAPP-A MoM levels (Table 2). In a study from China, in which 12,189 fetuses were included, fetal NT values in 10-14 week male and female fetuses were compared and while in ten-week fetuses there weas no difference, it was observed that female fetuses who were at 11-14 weeks NT thickness was 5% lower than males [9]. However the authors concluded that it was 0.06-0.1 mm and its clinical significance was sceptical. Recently Devrin *et al.* [10] in Turkey reported an 11 mm (8.1%) difference. In contrast to these findings Yaron *et al.* [11] from Israel reported that NT and PAPP-A levels showed no differences. Free beta-hCG was higher in female fetuses but this difference decreased after 12 weeks. Larsen *et al.* [12] observed that NT was significantly thinner in female fetuses than male fetuses which is consistent with reports in the literature, but free beta-hCG and PAPP-A levels were higher. In our results, although the mean. Free beta-hCG and PAPP-A MoM levels were higher in female fetuses, there were no significant differences, probably due to the low number of patients studied.

In conclusion, it seems that gender has an effect on Down syndrome markers in the first trimester, however its clinical significance is not yet clear. According to our results and those of other studies, fetal NT values are approximately 0.1 mm higher and this difference rarely provides any contribution to the treatment of the fetus. According to Spencer *et al.* [8], Devrim *et al.* [10], and our study, the sonographic and biochemical parameters did not increase the rate of invasive intervention significantly. According to Efrat *et al.* [13] and Whitlow *et al.* [14] another problem in the adjustment of Down Syndrome markers according to gender in the first trimester is the limitation of the possibility of gender in only 70-90% of fetuses during this period.

In conclusion, these results and data from others suggest that first trimester markers vary according to gender and have no clinical significance.

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References

[1] Bindra R., Heath V., Liao A.W., Spencer K., Nicolaides K.H.: "One-stop clinic for assessment of risk for trisomy 21 at 11-14 weeks: a prospective study of 15030 pregnancies". *Ultrasound Obstet. Gynecol.,* 2002, *20,* 219.

[2] Wapner R., Thom E., Simpson J.L., Pergament E., Silver R., Filkins K. *et al.*: "First trimester screening for trisomies 21 and 18". First Trimester Maternal Serum Biochemistry and Fetal Nuchal Translucency Screening (BUN) Study Group. *N. Engl. J. Med.,* 2003, *349,* 1405.

[3] Chen M., Lam Y.H., Tang M.H.Y., Lee C.P., Sin S.Y., Tang R. *et al.*: "The effect of ethnic origin on nuchal translucency at 10-14 weeks of gestation". *Prenat. Diagn.*, 2002, *22*, 576.

[4] Drugan A., Weissman A., Avrahami R., Zamir R., Evans M.I.: "Sonographic nuchal markers for Down syndrome are more common but less ominous in gestations with a male fetus". *Fetal Diagn. Ther.*, 2002, *17,* 295.

[5] Nicolaides K.H., Heath V., Cicero S.: "Increased fetal translucency at 11-14 weeks". *Prenat. Diagn.*, 2002, *22,* 308.

[6] Brambati B., Macintosh M.C.M., Teisner B., Maguiness S., Shrimanker K., Lanzani A. *et al.*: "Low maternal serum levels of pregnancy associated plasma protein A (PAPP-A) in the first trimester in association with abnormal fetal karyotype". *Brit. J. Obstet. Gynaecol.*, 1993, *100,* 324.

[7] Eldar-Geva T., Hochberg A., deGroot N., Weinstein D.: "High maternal serum choronic gonadotrophin levels in Down Syndrome pregnancies is caused by elevation of both submits messenger ribonucleic acid level in trophoblasts". *J. Clin. Endocrinol. Med.,* 1995, *80,* 3528.

[8] Spencer K., Ong C.Y., Liao A.W., Papademetriou D., Nicolaides K.H.: "The influence of fetal sex in screening for trisomy 21 by fetal nuchal translucency, beta-hCG and PAPP-A at 10-14 weeks of gestation". *Prenat. Diagn.,* 2000, *20,* 673.

[9] Lam Y.H., Tang M.H.Y., Lee C.P., Sin S.Y., Tang R., Wong S.F.: "The effect of fetal gender on nuchal translucency at 10-14 weeks of gestation". *Prenat. Diagn.*, 2001, *21,* 627.

[10] Devrim E., Ekrem T., Gurkan Y., Mustafa K., Meral A., Saffet D.: "The effect of fetal gender on the markers of first trimester Down syndrome screening". *Perinatoloji Dergisi*, 2005, *13*, 35.

[11] Yaron Y., Wolman I., Kupferminc M.J., Ochshorn Y., Many A., Orr-Ur treger A.: "Effect of fetal gender on first trimester markers and on Down syndrome screening". *Prenat. Diagn.,* 2001, *21*, 1027.

[12] Larsen S.O., Wojdemann K.R., Shalmi A.C., Sund berg K., Christian M., Tabor A.: "Gender impact on first trimester markers in Down syndrome". *Prenat. Diagn.*, 2002, *22*, 1207.

[13] Efrat Z., Akinfenwa O.C., Nicolaides K.H.: "First trimester determination of fetal gender by ultrasound". *Ultrasound Obstet. Gynecol.*, 1999, *13,* 305.

[14] Whitlow B.J., Lazanakis M.S., Economides D.L.: "The sonographic identification of fetal gender from 11 to 14 weeks gestation". *Ultrasound Obstet. Gynecol.*, 1999, *13,* 301.

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