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Original Article

Prenatal findings of patients diagnosed with Down syndrome: The value of ultrasound and biochemical screening

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Abstract. The aim of this study was to determine the association among ultrasound findings, biochemical markers, and Down syndrome

A retrospective analysis was conducted of the files and electronic records of 70 Down syndrome patients who were diagnosed in the prenatal or postnatal periods between July 2006 and May 2013.

Forty-nine of the 70 Down syndrome patients had prenatal ultrasound findings (70%). Thirty-five patients had 1st trimester nuchal translucency (NT) measurements, 17 of whom had elevated values, above the 95th percentile of the gestational week. Twenty-nine patients had first-trimester biochemical markers; the median PAPP-A was 0.53 MoM (±0.27) and the median fB-HCG was 1.87 MoM (±1.55). Twenty-six patients had second-trimester biochemical markers; the median AFP was 0.67 MoM (±0.27), the median uE3 was 0.79 MoM (±0.33), and the median HCG was 2.09 MoM (±1.33). Two or more minor anomalies were found in 45% of the patients, and 20% had at least one major anomaly.

In this retrospective analysis, prenatal ultrasonographic examination detected minor or major anomalies in 70% of the patients. Eighteen patients had normal NT values, ten patients showed increased biochemical risk in the combined test, and 12 patients had ultrasonographic anomalies in the second trimester. In expert hands, mid-trimester ultrasound markers are highly sensitive for Down syndrome detection.

Key words: Screening, soft markers, Down syndrome, genetic sonogram

1. Introduction

The typical flat facial profile and poor skin elasticity in fetuses with Down syndrome (DS) was first described by Dr. J.L. Down in 1866 (1). Nowadays, on the basis of those features, the prenatal detection of DS by using ultrasound for findings such as nuchal fold thickness, an absent or hypoplastic nasal bone (NB), prenasal thickness, and a flat face has been a subject of interest. Biochemical screening with maternal serum alpha-fetoprotein (MS-AFP) was begun in the 1980s, and many markers have been used since that time. In particular, important steps have been taken in first-trimester diagnosis. The second-trimester screening test, which is a quad test, has a detection rate of 75%, with a 5% false-positive rate. In the first trimester, the combination of nuchal translucency (NT) with serum markers PAPP-A and fB-HCG has a detection rate of 87%, with a 5% false-positive rate (2). NT alone has a sensitivity of 75–87% in the first trimester (3). The most widely investigated ultrasonographic markers are lateral cerebral ventriculomegaly, absent or hypoplastic nasal bone, increased nuchal fold thickness, intracardiac hyperechogenic focus, aberrant right subclavian artery (ARSA), hyperechogenic bowel, mild hydronephrosis, and shortening of the femur or humerus (4).

There is an increased risk of DS with advanced maternal age and advanced maternal age pregnancies have been increasing in the last 3

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decades. Genetic sonograms are conducted in many centers, and the number of invasive procedures is increasing. The most widely performed procedures are chorionic villus sampling (CVS) and amniocentesis. In rare cases, cordocentesis is performed. In addition, cell-free DNA testing has recently become quite popular as a non-invasive procedure. However, these procedures cause patients anxiety and confusion regarding the procedure-related fetal demise in normal fetuses and results indicating serious genetic diseases. In the literature, fetal loss rates related to AS and CVS have been reported as 0.6% and 0.7%, respectively (5); these rates are lower at experienced centers (6).

Thus, the aim of this study was to determine the genetic sonogram and biochemical markers of fetuses diagnosed with Down syndrome.

2. Materials and methods

After receiving approval from the Baskent University Hospital Ethics Board (KA13/201), a retrospective analysis was conducted using files and electronic records of 70 patients who had invasive procedures and results as Down syndrome performed between July 2006 and May 2013. Data of the patients were obtained from the reports of Baskent Universty, Ankara and Adana Hospitals. All patients were examined by Aloka ProSound Alpha 10 or GE Voluson 730 Ultrasound or GE Voluson E8. Two clinicians who were expert at genetic sonogram examined all patients. The study data were analyzed using Statistical Package for the Social Sciences software, version 17.0 (SPSS Inc, Chicago, IL).

3. Results

In the study period, there were 70 patients among 2006 to 2013. The mean age of the patients was 33.2 ± 6.4 years. Forty-nine patients underwent amniocentesis, 15 patients underwent CVS, and two patients underwent cordocentesis. Three patients were diagnosed in the postpartum period and one patient was diagnosed by the karyotyping the abortion material.

Forty-nine patients had ultrasound findings (70%), 19 patients showed increased risk in the first-trimester screening, 19 patients showed increased risk in the second-trimester screening, and three patients were of increased maternal age (Table 1).

Twenty-nine patients had first-trimester biochemical markers; the median PAPP-A was 0.53 MoM (±0.27) and the median fB-HCG was 1.87 MoM (±1.55). Twenty-six patients had second-trimester biochemical markers; the median AFP was 0.67 MoM (±0.27), the median uE3 was 0.79 MoM (±0.33), and the median HCG was 2.09 MoM (±1.33) (Table 2).

Table 1. Indications of invasive procedure

Indications of invasive procedure	No. of patients
Advanced maternal age	1
Advanced maternal age + USG findings*	2
Increased aneuploidy risk at first-trimester screening	6
Increased aneuploidy risk at first-trimester screening + USG findings*	13
Increased aneuploidy risk at second-trimester screening	11
Increased aneuploidy risk at second-trimester screening + USG findings*	7
USG findings* only	29

*Increased NT and major anomaly or two or more minor anomalies

Table 2. Median values of first- and second-trimester markers

Marker	Values MoM (Std. Dev.)
NT	1.57 (±1.25)
PAPP-A	0.53 (±0.27)
HCG (first trimester)	1.87 (±1.55)
AFP	0.67 (±0.27)
uE3	0.79 (±0.33)
HCG (second trimester)	2.09 (±1.33)

Thirty-five patients had NT measurements; the median NT value was 2.45mm ± 2.01 (min 1.2mm, max 8.80mm) and the median NT MoM value was 1.57 MoM ± 1.25 (min 0.72, max 5.23). Seventeen patients had increased NT values (≥95th percentile); eight patients had nasal bone hypoplasia, four patients had tricuspid regurgitation, four patients had abnormal wave at the ductus venosus, and four patients had echogenic fetal bowel.

Eighteen patients had normal NT values; ten of those patients had increased biochemical risk in the combined test. One patient who had no abnormalities in the screening tests was diagnosed as DS postpartum. Twelve patients had ultrasonographic anomalies in the second trimester, such as nasal hypoplasia, nuchal fold thickness, and cardiac anomaly. Three patients only had increased biochemical risk in the first-trimester screening test and no ultrasound findings. One patient had increased biochemical risk in the first-trimester screening test and one minor USG finding (bilateral hydronephrosis).

Second-trimester ultrasonography indicated 25 cases with nasal hypoplasia, 10 cases with echogenic intracardiac foci (EIF), 9 cases with short femur/humerus, 8 cases with echogenic fetal bowel, 7 cases with clinodactyly, 6 cases with mild hydronephrosis, 14 cases of major anomalies, and 32 cases with two or more minor anomalies (Table 3).

Table 3. Incidence of abnormalities

Marker	No. of patients (%)
Hypoplasia or agenesis of the nasal bone	25 (35)
Nuchal thickness	14 (20)
Echogenic intracardiac foci	10 (14)
Short femur/humerus	9 (12)
Echogenic fetal bowel	8 (11)
Clinodactyly	7 (10)
Mild hydronephrosis	6 (8,5)
Major anomalies	14 (20)
Two or more minor anomalies	32 (45)

Table 4. Incidence of major abnormalities

Anomaly	Number
Cardiac	10
Exomphalos	1
Ventriculomegaly	3
Duodenal Atresia	2
Pleural Effusion	1

Three patients were diagnosed in the postpartum period, even though they were referred to our clinic before delivery. Two of these patients had a cardiac anomaly, one of them at the same time had intrauterine growth restriction, and also the other one had clinodactyly. The third patient diagnosed in the postpartum period had a normal first-trimester screening and genetic sonogram.

Fourteen patients had one major anomaly (20%) (Table 4) and 32 patients had two or more minor anomalies (45%) (Table 3).

4. Discussion

In the last decade, multiple studies have confirmed that, in expert hands, mid-trimester ultrasound markers are highly sensitive for DS detection (7). Similarly, first-trimester NT measurement has also been shown to be a highly sensitive DS marker. In our study, 35 patients had NT measurements; the median NT value was 2.45mm ± 2.01 (min 1.2mm, max 8.80mm) and the median NT MoM value was 1.57 MoM ± 1.25 (min 0.72, max 5.23). Seventeen patients had increased NT values (≥95th percentile) and 18 patients had normal NT values; 12 of those patients had an ultrasonographic anomaly in the second trimester. Hypoplasia or agenesis of the nasal bone is one of the most recently described ultrasound markers for DS (8). In our study, hypoplasia or agenesis of the nasal bone was observed in 35% of the patients. According to a published study, this rate is between 30% and 100%; there is a wide heterogeneity (8,9). Agathokleous et al. (4) in a recently published meta-analysis, reported this rate as 59.8%. NT (≥6mm), another sensitive marker for DS, has been reported to have a 39.4% sensitivity and 0.6% false-positive rate compared with 16.7% and 0.6% for gross ultrasound abnormalities (7,10). In our study, 20% of the patients had increased NT. Bahado-Singh et al. (7) reported that rate as 25.9% and Agathokleous et al. (4) reported it as 26%. In sonography, EIFs are seen in 15–30% of DS fetuses, compared with 4–7% of euploid cases (11,12). Although associated with an increased risk of DS in multiple studies, the positive LR is small (1.4–1.8) and non-significant in many series. In our study, EIF was seen in ten (14%) patients. In the meta-analysis of Agathokleous et al. (4), this rate was found to be 24.4% and a study of 218 patients by Shanks et al. (13) reported this rate as 15.6%. Echogenic fetal bowel can be diffuse or focal and is present in 0.4-1.8% of second-trimester fetal sonographic examinations (14,15,16). The association with DS is somewhat greater than most other soft markers, with a reported LR of 5.5–6.7 (10,17,18). In our study, echogenic fetal bowel was seen in 11% of the patients. A recent meta-analysis reported this rate as 16.7% (4), and another study reported it as 21.3% (7). Shortened humerus (HL) and femur (FL) length are also sonographic features of DS fetuses. The positive LR for DS is reported as 2.5–5.8 for HL and 1.2–2.2 for FL (17,18). In our study, short femur and humerus were interpreted

together, and the detection rate was 12%. A recent meta-analysis reported these rates as 27.7% for shortened femur and 30.3% for shortened humerus (4). Bahado-Singh et al. (7) reported a rate of 27.8% for shortened femur and a rate of 27.8% for shortened humerus. Clinodactyly was seen in 10% of the patients in our study. The sensitivity was reported as 59.1% with a 6.2% false positive rate if it was detected before 16 weeks of gestational age. If it was detected after 16 weeks of gestational age, the sensitivity was reported as 28.2% with a false positive rate of 2.9%. The likelihood ratio was 9.5 before 16 weeks and 9.7 after 16 weeks (7). Mild renal pelviectasis (4–10mm) has been reported in 0.6–4.5% of fetuses in the second trimester (19,20,21). While most commonly a transient physiologic state, it can also be a sign of renal pathology and a marker of fetal DS. While common in normal fetuses, mild pelviectasis is somewhat more common in DS, and therefore, confers a small increase in risk, with LR reported as 1.5–1.6. (10,17,18). In our study, the detection rate was 8.5% (six patients), compared with 13.9% in a recent meta-analysis (4).

According to this retrospective analysis, genetic sonogram detected minor (two or more) or major anomalies in 70% of patients; 30% had no sonographic findings. In their meta-analysis, Agathokleous et al. (4) detected no anomaly in 30.9% of their patients (95% CI, 23.1–39.9%), similar to our study (4). In our study, 20% of the patients had at least one major anomaly. One patient had exomphalos, ten patients had a cardiac anomaly, three patients had ventriculomegaly, two patients had duodenal atresia, and one patient had pleural effusion (Table 4). Two or more minor anomalies were seen in 45% of the patients. Many other ultrasound findings have been reported to be associated with DS, including sandal gap toe, widened iliac angle, shortened frontal lobe, prefrontal nasal thickness, ear length, transverse cerebellar diameter, flat faces, ARSA, liver calcification, and a persistent right umbilical vein (16). Recently, some authors have studied the validity of the prenasal thickness/NB or frontonasal fold thickness/NB ratios as a screening method for DS. Despite the good results obtained to date, with a detection rate ranging from 75% to 100% and a false positive rate of 1–5%, the number of published studies is small, and there is a need for adequately designed prospective studies to ensure the accuracy of these results.

The limitations of this study include retrospective design, respectively less number of cases (70 patients), collecting data by different ultrasound machines, by two different clinician from two centers. Also including the patients only with anomalies may also limit interpreting study results.

In conclusion, there were 29 first-trimester screening test results and 26 second-trimester screening test results. With the exception of HCG, the mean values of the other markers were not significant. Although ultrasound findings are quite reliable, DS is still not detectable by ultrasound in some fetuses with DS. First-trimester and second-trimester screening tests are quite sensitive, but the false positive rates of these tests are still too high. Therefore, the numbers of invasive procedure are too high. The cell-free fetal DNA test, a recently developed test, can be useful in reducing this rate.

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