Obstetrics; *Maternal-Fetal Medicine and Perinatology*

Antenatal Ultrasound Findings in Fetus with Down Syndrome

Mehmet Serdar KÜTÜK[1], Mahmut Tuncay ÖZGÜN[1], Mehmet DOLANBAY[1], Gülsüm UYSAL[1], Aslı UZAK[2], Elif KULENGİR[1], Semih ULUDAĞ[1], Mustafa BAŞBUĞ[1]

Kayseri, Turkey

OBJECTIVE: The aim of the present study is to assess the importance and role of the ultrasound imaging in the diagnosis of Down syndrome based on our own experience.

STUDY DESIGN: The study was conducted in Erciyes University, Department of Obstetrics and Gynecology, Prenatal Diagnosis Unit between 2010-2012. The data of 67 fetus prenatally diagnosed as Down syndrome were analyzed retrospectively with special emphasizes on ultrasound findings.

RESULTS: A total of 67 women were included in the study. The main maternal age 33.5 (min-max: 18-46). The most common indication for invasive testing was advanced maternal age (23.8%). The invasive testing consisted of chorionic villus sampling (10.4%), amniocentesis (83.5%), and cordocentesis (5.9%). In 54 patients, the ultrasonographic evaluation revealed major malformation and/or Down syndrome marker (80.5%), and 38 cases had more than one marker/malformation (56.7%). The most common Down syndrome marker was mild pyelectasia (25.3%), and the most common major congenital anomaly was atrioventricular canal defect that was seen in six fetuses (8.9%).

CONCLUSION: Despite improvement in ultrasound technology and experiences, no anomaly and/or aneuploidy marker can be detected with ultrasound in a considerable proportion of fetus with Down syndrome. Therefore, invasive prenatal testing should be standard of care in the presence of abnormal serum screening for Down syndrome and/or in pregnant women of advanced maternal age.

Key Words: Down syndrome, Ultrasonography, Prenatal diagnosis

Gynecol Obstet Reprod Med 2014;20:1-4

Introduction

Down syndrome (DS) is the most common chromosomal abnormality among the newborn infants that occurring in 1 of every 800 live born. Since DS is compatible with long term life, and associated with mental and somatic problems that put affected families under social and economic stress, prenatal diagnosis of the DS has been the major focus for maternal fetal specialist.[1-4]

Nearly two decades ago, the use of maternal serum marker has been suggested as screening test for fetal anomalies (NTD etc), and chromosomal abnormalities.[1,2] Despite great effort to optimize its sensitivity, the value of serum screening test for detecting DS in high risk pregnancies is far from satisfying. Therefore, direct analysis of fetal chromosomes extracted from fetal cells obtained by chorionic villous sampling, amniocentesis, and fetal blood sampling is still the gold standard. However, the invasive prenatal tests are associated with fetal loss due the premature rupture of membranes, and fetal cardiac arrest, and premature uterine contractions. The current risk of pregnancy loss due to invasive prenatal testing are small, but it has important effects on decision making process of the families, especially in the highly-desired pregnancies.[5]

The fetuses with DS have some special phenotypic characteristics. These features include a flat facial profile, short stature, epichantal folds, muscle hypotonia, simian crease of the palm, and excess skin at the back of the neck, hypoplastic middle phalanx of the fifth digit, duodenal atresia, heart defects, and abnormal iliac bone angels. Over the past decade perinatologist have been able to identify some of these features, such as slightly short femur, and/or humerus, thickened

[1] *Erciyes University Faculty of Medicine Department of Obstetrics and Gynecology, Kayseri*

[2] *Erciyes University, Faculty of Medicine Department of Genetics, Kayseri*

Address of Correspondence: *Mehmet Serdar Kütük*
Erciyes University, Faculty of Medicine
Department of Obstetrics and
Gynecology Gevher Nesibe Hospital
Kayseri, Turkey
mskutuk@erciyes.edu.tr

Submitted for Publication: *10. 10. 2013*
Accepted for Publication: *05. 12. 2013*

nuchal fold, hypoplasia of the middle phalanx of the fifth digit. Recently, the combined sensitivity of screening tests and ultrasound (US) markers for DS is still very active area of investigation.[6-10]

In the present study, we aimed to present our US findings in 67 fetus prenatally diagnosed as having DS, and thus evaluate the place of US in the antenatal diagnoses of these fetus.

Material and Method

The study was conducted in Erciyes University, Department of Obstetrics and Gynecology, Prenatal Diagnosis Unite between 2010 - 2012. The data of 67 fetus prenatally diagnosed as DS were retrospectively analyzed with special emphasizes on US findings. In our department, all fetuses are undergone US evaluation for major malformation and aneuploidy marker before invasive diagnostic procedures. The scans were performed transabdominally with Voluson 730 Pro equipped with a 5- to 8-MHz transabdominal transducer (GE, Healthcare). The maternal age, indication for invasive testing, gestational age, and US findings were noted. The sonographic markers were defined as the following: (1) ventriculomegaly was considered to be present if the diameter of the lateral cerebral ventricle was 10 mm or more, (2) increased nuchal fold thickness was present if the thickness was 6 mm or more and (3) the diagnosis echogenic bowel required that this was equal echogenicity to that of bone, (4) the diagnosis of mild hydronephrosis was based on minimum anteroposterior diameter of the pelvis was 3 mm or more before 20 weeks, 5 mm or more after 20 weeks, (5) the definitions of short femur, short humerus and hypoplastic nasal bone were based on the ratio of the bone length to biparietal diameter.[6] The statistical analysis was primarily descriptive. Overall data are reported as means, standard deviations, minimum and maximum values.

Results

A total of 67 women were included in the study. The main maternal age 33.5 (min-max: 18-46). The most common indication for invasive testing was advanced maternal age (23.8%) (Table 1). The invasive testing consisted of chorionic villus sampling (10.4%), amniocentesis (83.5%), and cordocentesis (5.9%). In 54 patients, the US evaluation revealed major malformation and/or DS marker (80.5%). Eighteen of all fetuses (26.8%) had only one marker, 13 fetuses (19.4%) had two markers and other 26 fetuses (38.8%) had more than two markers for Down syndrome. The most common DS marker was mild pyelectasia (25.3%), and the most common major congenital anomaly was atrioventricular canal defect that was seen in six fetuses (8.9%). The frequencies of marker/ malformation were presented in table 2.

Table 1: The distrubution of ultrasonographic findings

FETAL ANOMALY	n = 67	
Hyperechogenic focus	9	
Pyelectasis	11	bilateral, 6 unilateral
Cystic Hygroma	8	
Increased nuchal fold	14	
Atrioventricular septal defect	6	
Nasal bone hypoplasia/atresia	6	
Choroid plexus cyst	1	
Short femur	10	
Ventricular septal defect	5	
Brachycephaly	8	
Hyperechogenic bowel	5	
Hyperechogenic lung	1	
Agenesis of corpus callosum	1	
Club foot	1	
Clinodactyly	2	
Chorio-amniotic fusion defect	3	
Sandal gap	1	
Extremity defect	1	
Normal ultrasonography	10	

Table 2: The frequencies of marker/ malformation

INDICATION	n = 67
Advanced maternal age	16
First trimester screening test risk	7
Second trimester screening test risk	23
Advanced maternal age + First trimester screening test risk	2
Advanced maternal age + Second trimester screening test risk	7
Anomaly in ultrasonography	12

Discussion

The presence of major malformation such as ventriculomegaly, holoprosencephaly, heart defects, facial defects, genitourinary malformation, gastrointestinal anomalies, and skeletal abnormalities is an indication for karyotype evaluation.[11] Although majority of fetus with trisomy 13 or 18 or triploidy displays these major multisystem malformations, sonographically apparent major malformations are present in only 25% to 33% fetus with trisomy 21.[12] This makes the sonographic structural markers particularly crucial in the detection of DS.

Cardiovascular malformations are detected in greater than 40 to 50% of fetuses with DS.[13] Therefore; the presence of cardiac malformation significantly increases the risk of underlying chromosomal abnormalities. The risk of aneuploidy is

much higher for atrioventricular septal defect (endocardial cushion defect, AVCD), double outlet right ventricle, tetralogy of Fallot, or hypoplastic heart compared to isolated ventricular septal defect or valvular stenosis. According to our results, AVCD was the most common cardiac defect in fetus with DS that support previous literature.[14] During the study period 14 cases of fetus with AVCD were detected in our department, and four of these had normal karyotype, and the remaining four cases declined karyotype analysis, and thus unknown chromosomal status. Hence, the six of ten cases who had known karyotype were associated with DS (6/10, 60%). The absence of other major cardiac defects probably reflects the fact that these fetuses were usually abnormal nuchal thickness, and/or cystic hygroma in the first trimester and diagnosed and terminated before being evaluated by echocardiography.

The most common US markers for fetus with DS in the present study were mild pyelectasis, increased nuchal fold, and short femur. The mild pyelectasis and short proximal bones are relatively frequent findings in both euploid and aneuploid foetuses.[15,16] However, increased nuchal fold is very strong predictor of abnormal karyotype with a likelihood ratio of 17.[6] Although the sensitivity and specifity rates vary with gestational age and the exact criteria for a positive scan, sensitivities in the range of 20 to 40% are most common.[17,18] In four of our cases, increased nuchal fold was the only marker for DS. In two cases, increased nuchal fold were associated with AVSD, and in the remaining 6 cases one or more of the soft markers mentioned above accompanied INT. During the study period 61 fetuses with increased nuchal thickness were detected and 14 of these were found to have DS which is concordant with the previous literature.[17,18]

Very recently, a study by Agathokleous remarkably changed our understanding of the value and application of second trimester US markers for detection of DS.[6] Their comprehensive meta- analysis showed that the likelihood ratio for DS in the absence of all markers, excluding humerus length, is 0.13. In other words, the absence of second trimester ultrasonographic markers of Down Syndrome (UMDS) reduces the chance of having a child with Down Syndrome 7.7 fold. In addition, involvement of more sophisticated markers to the US screening such as short ear, sandal gap, clinodactyly, seems to have no additional effect on detection ratio.[19] In the presence of isolated single soft marker, such as HICF (Hyperechogenic intracardiac focus), the basal risk was slightly increased. However, the effect of gestational age on the screening power of these markers is yet to be determined.

Almost any congenital anomaly increases the risk of an underlying chromosomal abnormality. Some of these anomalies such as talipes, choroid plexus cyst, extremity defects, agenesis of corpus callosum are associated with chromosomal abnormalities other than trisomy 21. In the present study, five abnormal findings that associated with trisomy 13 and 18 were detected in fetus with DS (One choroid plexus cyst, one agenesis of corpus callosum, one case of extremity anomaly, one case of talipes, and one case of hyperechogenic lung). Of importance, the total absence of hand (right) in fetus with DS has not been reported before (Figure 1). It is possible that the detection of 'unconventional' findings for Down syndrome can be explained by coincidence, as some of the abnormal findings such as choroid plexus cyst, and talipes are relatively common in fetus with normal karyotype.

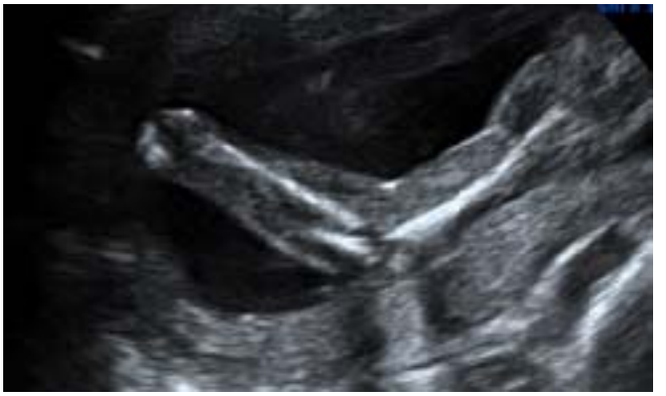

Figure 1: Ultrasonographic picture of 22 weeks-old fetus showing absence of the left hand

Major or structural abnormalities are seen in fewer than 20% of fetuses with trisomy 21 during the second trimester. Combined with sonographic marker markers of fetal aneuploidy, sonographic markers are identified in 50 to 70% of fetus with Down syndrome. In our group, no sonographic abnormality was detected in 10 cases (10/67, 14.9%). Of the cases that had no abnormal US findings, nine were evaluated at second trimester. Based on these data, it can be surmised that performance of US evaluation in our clinics is comparable to literature. In addition, the high detection rate for US in our clinic probably reflects selection bias resulting from high risk patients referred to our center which constitutes a patient population who has a high base-line risk of Down syndrome.

Despite improvement in US technology and experiences, no anomaly and/or aneuploidy marker can be detected with US in a considerable proportion of fetus with DS. Therefore, invasive prenatal testing should be standard of care in the presences of abnormal serum screening for DS and/or in pregnant women of advanced maternal age.

Down Sendromlu Fetuslarda Antenatal Ultrason Bulguları

AMAÇ: Bu çalışmanın amacı, kendi deneyimimizden faydalanarak, ultrasonografik görüntülemenin Down Sendromu tanısındaki yeri ve önemini değerlendirmektir.

GEREÇ VE YÖNTEM: Çalışma, 2010 - 2012 yılları arasında, Erciyes Üniversitesi Kadın Hastalıkları ve Doğum Bölümü, Prenatal Tanı Ünitesi'nde yürütüldü. Antenatal dönemde Down Sendromu tanısı alan 67 fetusa ait bilgiler, prenatal ultrasonografi bulguları temel olmak üzere, retrospektif olarak incelendi.

BULGULAR: Çalışmaya toplam 67 kadın dahil edildi. Ortalama maternal yaş 33,5 idi (18-46). En sık görülen invazif test endikasyonu ileri anne yaşı idi. İnvazif test olarak hastaların %10,4'üne koryon villus örneklemesi, %83,5'ine amniyosentez ve %5,9'una da kordosentez yapıldı. Ellidört hastada (%80,5) ultrasonografik değerlendirme ile Down Sendromu bulgu ve / veya malformasyonu gösterilmekle birlikte, 38 hastada (%56,7) birden fazla bulgu / malformasyon izlendi. En sık karşılaşılan bulgu ılımlı piyelektazi ve en sık izlenen majör konjenital anomali, 6 fetusta gözlenen atriyoventriküler kanal defekti idi.

SONUÇ: Ultrasonografik teknoloji ve deneyimlerdeki gelişmelere rağmen, Down Sendromlu fetusların önemli bir bölümünde ultrason ile saptanabilir marker ya da anomali izlenmemiştir. Bu nedenle Down Sendromu lehinde anormal serum seviyeleri ve / veya ileri maternal yaş varlığında, invazif prenatal testler standart olarak uygulanmalıdır.

Anahtar Kelimeler: Down sendromu, Ultrasonografi, Prenatal tanı

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