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Importance of isolated minor findings on fetal ultrasound examinations in the diagnosis of Down syndrome

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Abstract

Objective: To investigate the importance of prenatal ultrasound in the detection of Down syndrome by evaluating ultrasonographic and minor ultrasonographic findings in fetuses with this aneuploidy.

Methods: Patients who were reported to have trisomy 21 as a result of karyotype analysis performed by cordocentesis, amniocentesis, or chorionic villus biopsy materials and who underwent ultrasound scan before diagnosis between 18 and 26 weeks of gestation by the Maternal Fetal Medicine Department between 2013 and 2020 were included in the study group.

Results: The results of 132 of 4525 (2.9%) invasive procedures were reported to have trisomy 21 and ultrasound scans of each fetus were performed in our department. The mean gestational age at the ultrasound scans was 19.2±3.8 (SD) weeks. At least one major structural anomaly or minor ultrasonographic finding was detected in 99.2% of all fetuses. Major structural anomalies were present in 80 (60.6%) fetuses. In fetuses with major structural anomalies, cardiac defects (53.7%) were the most detected anomalies. No ultrasound findings could be detected in one (0.8%) of the remaining 52 patients, and only isolated minor findings were detected in 51 (38.6%) fetuses. More than half (60.7%) of these fetuses had a single minor finding. The most common isolated single minor finding was nuchal fold thickness in 13 (41.9%) fetuses followed by aberrant right subclavian artery in six (19.3%) fetuses.

Conclusion: Down syndrome displays a large variety of different sonographic findings on fetal ultrasound. Although major structural anomalies and multiple minor findings are generally considered more important, the presence of any isolated minor marker may be the only detectable finding of Down syndrome.

Keywords: Down syndrome, fetal ultrasound, prenatal ultrasound, trisomy 21.

Introduction

Trisomy 21 (Down syndrome) is the most common chromosomal abnormality detected in pregnancies resulting in a live birth, with a prevalence of approximately 1 in 700 live births.[1,2] Due to the higher risk of intrauterine death in fetuses with chromosomal anomalies, its prevalence is 30% higher between 16–20 weeks and 48–50% higher between 9–14 weeks compared with term deliveries.[3,4]

There are different methods to screen and identify high-risk groups for Down syndrome such as advanced maternal age, first- and second-trimester screening tests,

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cell-free DNA, and ultrasound screening in the first- and second trimesters. Maternal age increases the risk of chromosomal anomalies and is used as a component of first- and second-trimester screening tests.

Trisomy 21 is associated with many major structural anomalies and minor (soft) ultrasonographic markers in the fetus that can be recognized in prenatal ultrasound.[5] Major structural anomalies are associated with chromosomal abnormalities and the presence of major structural anomalies increases the likelihood of a genetic disease. The most common major malformation in Down syndrome is cardiac defects, especially atrioventricular septal defects. The second most common malformations are gastrointestinal system anomalies. It is known that the most associated anomaly with Down syndrome in this group is duodenal atresia. These two anomalies highly increase the suspicion of Down syndrome.[6] On the other hand, minor ultrasonographic markers are nonspecific findings that are also seen in normally developed fetuses but are more common in fetuses with trisomy 21. When a minor marker is detected on fetal ultrasound, it is difficult to use these findings to understand whether the pregnancy is affected by aneuploidy or not.[5,7] In 2013, Agathokleous et al. conducted a meta-analysis and demonstrated that each detected marker affected screening tests' pre-test odds. In this meta-analysis of 48 studies, the authors found that the estimated positive likelihood ratio for increased nuchal fold thickness and aberrant right subclavian arteries was about 20 and absent or hypoplastic nasal bone was 25, somewhat higher than others such as pyelectasis, short femur and humerus, hyperechogenic bowel, and hyperechogenic cardiac focus. They also showed that post-test odds could be calculated by multiplying the positive likelihood ratio for each marker detected and the negative likelihood ratio for each marker proven to be absent. In addition, they found that the exclusion of all major defects and minor markers resulted in a 7.7-fold risk reduction for trisomy 21.[8] However, in light of this information, detecting abnormal ultrasound findings and identifying the high-risk group is important because it alerts physicians to the necessity of fetal karyotyping as a diagnostic procedure.

In the current study, our objective was to investigate the importance and effectiveness of first- and second-trimester ultrasound scans in detecting Down syndrome by evaluating the ultrasonographic findings, especially the minor ultrasonographic findings, in fetuses with Down syndrome in a tertiary center.

Methods

This retrospective cross-sectional study was conducted on the electronic records of patients who underwent cytogenetic analysis in the Maternal-Fetal Medicine department of our hospital between 2013 and 2020. Patients whose fetal karyotype results were reported to be trisomy 21 and patients who underwent an ultrasound scan performed by the Maternal-Fetal Medicine department between 12 and 26 weeks of gestation were included in the study. The study was approved by the institutional Ethics Committee in 2020 (approval number: 113).

The diagnosis of Down syndrome was confirmed in the institution using the following processes: fetal material was obtained by chorionic villus biopsy, amniocentesis, or cordocentesis for fetal cytogenetic analysis, and long-term cell culture (2–4 weeks) was performed for chorionic villus biopsy and amniotic fluid. For cord blood, cell culture was performed for 48–96 hours. For each patient, two cultures were planted. Metaphases obtained by harvesting processes after cell culture were stained using Giemsa staining. The karyotype was reported by performing at least 20 metaphase analyses for each patient.

All ultrasound examinations were performed in the Maternal-Fetal Medicine department of our hospital using Voluson Pro and Voluson E6 scanners (GE Healthcare, Milwaukee, WI, USA), and the detected anomalies of the fetal systems were recorded. Ultrasound findings of the patients were grouped as major structural anomalies or minor sonographic findings (soft markers). Major structural anomalies were defined as cardiac malformations, central nervous system anomalies, gastrointestinal system anomalies, genitourinary anomalies, cystic hygroma, and hydrops fetalis, and abnormalities of the extremities detected in any week of gestation. Cystic hygroma was defined as the presence of fluid-filled enlarged spaces with or without septa in the fetal neck or the whole subcutaneous area during first-trimester scans, and hydrops fetalis was defined as the presence of at least two of the following: ascites, pleural effusion, or pericardial effusion in any gestational age.[7] Lateral ventricular atrial measurements of more than 10 mm were used to diagnose ventriculomegaly. Minor sonographic findings were defined as nuchal fold thickness during the second trimester (>6 mm), pyelectasis (>4 mm), short femur and humerus

(<10 percentile), hyperechogenic bowel, hyperechogenic cardiac focus, hypoplastic or absent nasal bone, and aberrant right subclavian artery (ARSA) in patients with a fetal ultrasound. Pyelectasis was defined with the anteroposterior diameter of the renal pelvis greater than 4 mm in the second trimester based on the Society for Fetal Urology consensus statement.[9] All ultrasound examinations were performed before the cytogenetic results of the fetuses were revealed. If a patient underwent more than one ultrasound examination, the ultrasound results from the most advanced gestational age before the cytogenetic results were included.

Descriptive data of the pregnant women such as age, the reason for referral for cytogenetic analysis, gestational age at the time of ultrasonography, and perinatal outcomes were also recorded from our hospital's electronic database. Indications for referral were grouped as advanced maternal age (>40 years), positive cell-free DNA screening test results, positive first- or second-trimester screening test results, and suspected fetal anomalies. Descriptive statistics and percentages were used for statistical analysis.

Results

Down syndrome was detected in 191 (4.2%) of the 4525 invasive procedures performed in our hospital during the study period. A flow chart of the fetuses included in the study group and ultrasound findings of fetuses diagnosed as having trisomy 21 are shown in **Fig. 1**. The ultrasound scans of the 132 patients were performed in the Maternal-Fetal Medicine department.

Our hospital is a referral center and patients with suspected trisomy 21 are referred for further cytogenetic analysis. We perform an obstetric ultrasound before invasive procedures to confirm gestational age, placental location, and fetal viability, and make an appointment for a more detailed ultrasound. Patients from other cities

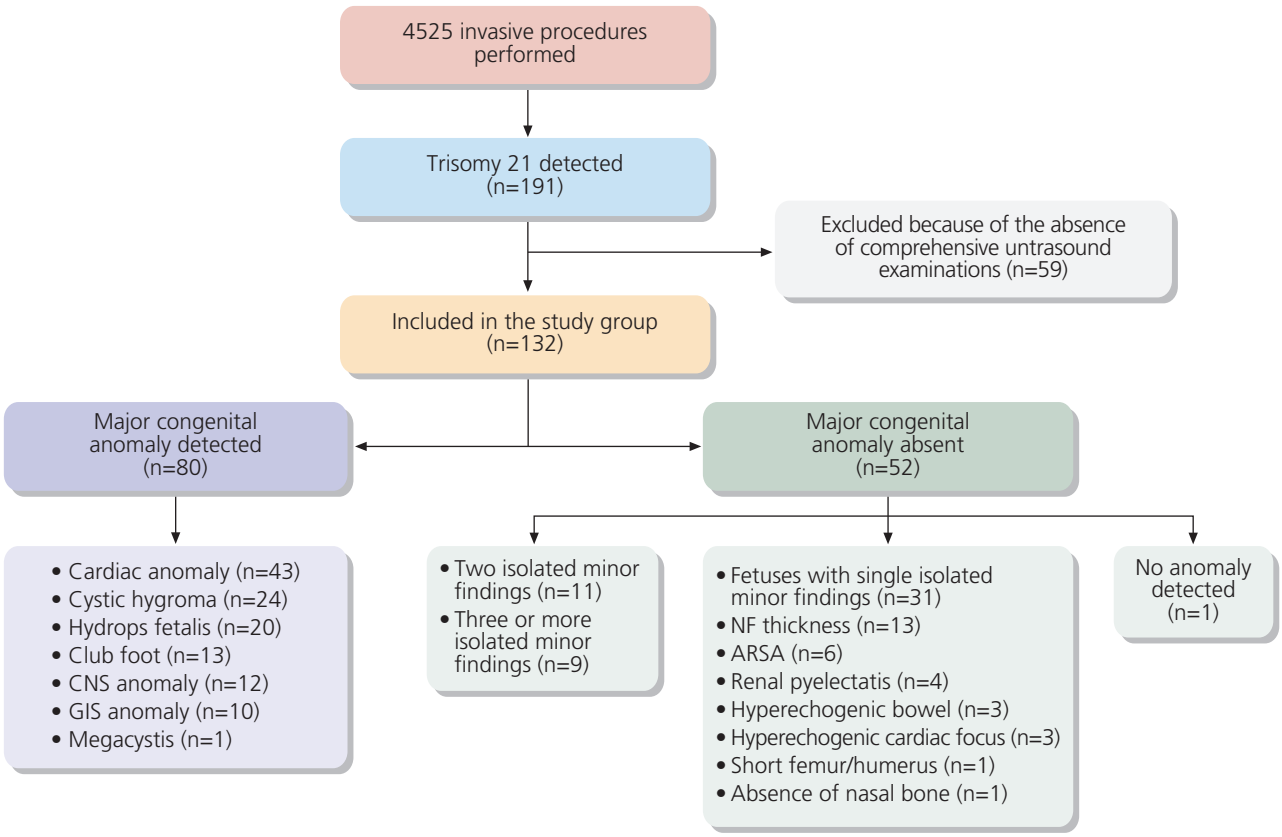

Fig. 1. Flow chart of the fetuses included in the study group and ultrasound findings of fetuses diagnosed to have trisomy 21.

often do not attend their next appointments and return to their hometowns after the invasive procedure. Therefore, 59 patients did not have comprehensive ultrasound examinations performed in our department.

Among the 132 patients with comprehensive ultrasound examinations, one or more major structural anomalies were detected in 80 (60.6%) fetuses. No ultrasound findings could be detected in one fetus (0.8%), and only minor findings were detected in 51 (38.6%) fetuses. The fetus with no ultrasound findings was referred due to a positive non-invasive prenatal test and advanced maternal age (45 years). After performing a chorionic villus biopsy and an ultrasound scan at 13 weeks of gestation, the patient discontinued follow-up and the pregnancy outcomes could not be reached.

The demographic features of the study group are shown in **Table 1**. The mean age of the patients was 37.9±6.5 (SD) years, and the mean gestational age at ultrasound was 19.2±3.8 (SD) weeks. When the karyotyping indications of the fetal cytogenetic analysis of the patients were evaluated, 67 (50.8%) pregnant women were suspected of having fetal anomalies, 53 (40.1%) had positive first- or second-trimester screening test results, seven (5.3%) had positive cell-free DNA tests, and five (3.8%) were due to advanced maternal age.

The incidence of major structural anomalies in the 132 fetuses with trisomy 21 is shown in **Table 2**. Considering the detected major structural anomalies, cardiac defects were the most common, present in 43 (53.7%) fetuses with major structural anomalies. Also, in 23 (53.4%) of 43 fetuses, cardiac defects were isolated and no additional major structural anomalies were observed. Regarding the incidence of cardiac anomalies in fetuses with trisomy 21, the most common were atrioventricular septal defect (AVSD) (n=22, 16.7%) and ventricular septal defect (VSD) (n=15, 11.4%), accounting for 86.0% of the total cardiac defects.

Cystic hygroma was detected in 24 (18.2%) fetuses and fetal hydrops in 20 (15.2%). These were followed by clubfoot (also known as talipes equinovarus) in 13 (9.8%) fetuses, central nervous system (CNS) anomalies in 12 (9.1%), and gastrointestinal system anomalies (GIS) in nine (6.8%) fetuses. The most common CNS anomaly was ventriculomegaly in seven (5.3%) fetuses, and duodenal atresia was detected in five (3.8%) fetuses with GIS anomalies.

Table 1. Demographic features of the study group.

Variables	Total group (n=132)
Mean maternal age (years)	37.9±6.5
Maternal age range (years)	20–49
Mean gestational age at ultrasound (weeks)	19.2±3.8
Indication for referral	
Suspected fetal anomaly	67 (50.8%)
Positive first- or second-trimester screening test	53 (40.1%)
Positive cell-free DNA test	7 (5.3%)
Advanced maternal age	5 (3.8%)

Values are stated as mean ±standard deviation, number, and percentage (%).

Minor anomalies detected in fetuses with trisomy 21 are shown in **Table 3**. When all the patients were evaluated (n=132), including fetuses with minor findings and/or major structural anomalies in detailed ultrasound examination, the most common minor findings were nuchal fold thickness in 64 (48.5%) fetuses, hypoplastic nasal bone in 35 (26.5%), and the presence of hypere-

Table 2. Major structural anomalies incidence in 132 fetuses with trisomy 21.

Anomalies	n (%)
Cardiac defects	43 (32.6)
AVSD	22 (16.7)
VSD	15 (11.4)
Inlet	9 (6.8)
Malalignment	4 (3.0)
Perimembranous	1 (0.8)
Muscular	1 (0.8)
DORV	3 (2.3)
Tetralogy of Fallot	3 (2.3)
Cystic hygroma	24 (18.2)
Fetal hydrops	20 (15.2)
Pes equinovarus	13 (9.8)
Central nervous system anomalies	12 (9.1)
Ventriculomegaly	7 (5.3)
Spina bifida	2 (1.5)
Vermian hypoplasia	2 (1.5)
Agenesis of corpus callosum	1 (0.8)
Gastrointestinal anomalies	9 (6.8)
Duodenal atresia	5 (3.8)
Omphalocele	2 (1.5)
Absent stomach	2 (1.5)
Megacystis	1 (0.8)

Values are stated as number and percentage (%). **AVSD:** atrioventricular septal defect; **DORV:** double outlet right ventricle; **VSD:** ventricular septal defect.

Table 3. Minor anomalies detected in fetuses with trisomy 21.

Anomalies	Total group (n=132) n (%)
Nuchal fold thickness	64 (48.5)
Hypoplastic nasal bone	35 (26.5)
Echogenic intracardiac focus	28 (21.2)
Pyelectasis	28 (21.2)
Short long bones	22 (16.7)
Echogenic bowel	16 (12.1)
ARSA	11 (8.3)
Absent nasal bone	7 (5.3)

Values are stated as mean number and percentage (%). **ARSA:** aberrant right subclavian artery.

chogenic cardiac focus in 28 (21.2%) fetuses. Of the 51 (38.6%) fetuses without major anomalies, 31 (60.7%) had one minor finding, 11 (21.5%) had two minor findings, and nine (17.6%) fetuses had three or more minor findings. In fetuses with a single minor finding, the most common finding was isolated increased nuchal fold thickness in 13 (41.9%) fetuses, followed by isolated aberrant right subclavian artery (ARSA) in six (19.3%) fetuses, and isolated renal pyelectasis in four (12.9%) (**Fig. 1**).

When karyotyping indications of fetuses with isolated single findings were evaluated, of the 13 fetuses with isolated nuchal fold thickness, nine were referred with indications of nuchal translucency (NT) increase (>3.5 mm) in the first trimester, three were referred due to positive maternal cell-free DNA tests performed for advanced maternal age and the other fetus was referred due to increased risk in screening tests. Of the six fetuses with isolated ARSA, two were referred due to increased NT, two fetuses were referred due to increased risk in screening tests, one was referred due to a positive cell-free DNA test result, and one fetus was referred due to advanced maternal age. Finally, of the four fetuses with isolated renal pyelectasis, two were referred due to advanced maternal age and two were referred due to high risk in screening tests. Regarding the pregnancy outcomes, 94 (71.2%) of the 132 pregnancies were terminated, 15 (11.3%) resulted in live births, and 14 (10.6%) pregnancies resulted in stillbirths or missed abortions. Nine women (6.8%) discontinued their follow-up and the pregnancy outcomes could not be obtained.

Discussion

Detailed ultrasonographic examinations should be recommended for all pregnant women, especially in the second trimester, to detect fetal anomalies, regardless of the results of screening tests.[10] Although major structural anomalies are detected with high rates in fetuses with trisomy 18 and trisomy 13, in fetuses with Down syndrome, major structural anomaly rates were found 27% by Broomley et al. and 17.7% by Nyberg et al.[11,12] In our study, this rate was 60.6%, which was remarkably higher than other studies. The difference may be caused by the mean gestational age at the ultrasound, which was 16.9 weeks in the study by Nyberg et al. and 16.4 weeks in the study by Broomley et al., whereas it was 19.2 weeks in our study, which possibly increased the detection rate of structural anomalies. It should also be taken into account that the rate of detection of fetal anomalies with ultrasound has increased with the development of technology.

The most common group of major structural anomalies is fetal cardiac defects, which are seen in more than half of these fetuses (53.7%). Also, in more than half (53.4%) of all fetuses with cardiac defects, no additional major structural anomalies are detected and they are isolated findings. We believe that fetal echocardiography is important to detect Down syndrome because of the high frequency of cardiac anomalies, especially given that the only findings of Down syndrome may be cardiac defects.

Cystic hygroma and hydrops fetalis were the second most common major structural anomalies, and when they were evaluated together, they were observed with a rate of 33.4% in fetuses with trisomy 21. Considering that the most common minor finding is nuchal fold thickness, it is obvious that abnormal fluid accumulation and edema in the fetal neck are important findings for performing fetal karyotyping.[13,14]

Cystic hygroma (18.2%) and fetal hydrops (15.2%) were followed by clubfoot in 13 (9.8%) fetuses. Clubfoot is a congenital foot deformity diagnosed in about every one in 1000 pregnancies and could be even more common in some populations.[15,16] In fetuses detected as having clubfoot with additional anomalies, chromosomal abnormalities could be identified in up to 30%.[17] However, aneuploidy risk in isolated cases is controversial and there is no consensus on whether to propose fetal karyotyping when isolated clubfoot is diagnosed in prenatal ultrasound. In a population-based study on

6210 fetuses with Down syndrome, the authors found that clubfoot was detected in 39 children (0.8%), which is a considerably lower rate than ours.[18] This difference may be because the study group in the previous study included fetuses with prenatal diagnoses, also children who were diagnosed after birth. There is a higher risk of intrauterine death of fetuses with chromosomal anomalies, and patients with Down syndrome who were not diagnosed prenatally may have been missed.

The second most common minor finding was hypoplasia or the absence of a nasal bone with a total rate of 31.8%. Hypoplasia of the nasal bone is seen in approximately 50-60% of fetuses with Down syndrome, and the absence of a nasal bone is seen in 30–40%.[5] However, this situation may change in populations of different ethnicities.

When we evaluated fetuses with isolated single minor findings, increased nuchal fold thickness was the most commonly detected finding in 13 fetuses. The accepted definition of increased nuchal fold thickness is 6 mm or above.[5] Studies are reporting that the sensitivity of increased nuchal fold thickness for fetuses with Down syndrome is 40–50% and the specificity is up to 99%.[10,11] In our study, considering all fetuses, nuchal fold thickness was also the most common minor finding; we detected it in almost half of the fetuses.

The second most common isolated single finding, ARSA, was the most commonly detected finding in six fetuses with Down syndrome. ARSA is observed in 1–1.5% of the normal population and is considered by some authors as an anatomic variation.[19,20] In previous studies, ARSA was reported to be seen in 3% of fetuses with congenital heart disease and 23.6% in autopsy series in fetuses with Down syndrome, and because it is seen more commonly in major congenital and chromosomal anomalies, it is accepted as a soft marker.[19–22] In our study, one patient with ARSA had no screening tests or other ultrasound findings; therefore, advanced maternal age and the presence of isolated ARSA were warning signs for us to suspect Down syndrome. When an isolated ARSA is detected in pregnant women who do not have screening tests, especially those of advanced maternal age, we inform them about invasive procedures.

The third most common single finding was renal pyelectasis, which was detected in four fetuses. Renal pyelectasis is defined as the anteroposterior diameter of the pelvis being 4 mm or above, detected in 0.6–4.5% of second-trimester ultrasounds.[23,24] Although studies are suggesting a relationship between renal pyelectasis and Down syndrome,[25] it is mostly considered a normal variant, especially in male fetuses.[26] Therefore, it is recommended that in cases with isolated renal pyelectasis, aneuploidy testing should be offered if not previously performed and the renal pelvis diameter should be re-evaluated in the third trimester to assess the need for postnatal imaging.[5] Considering our findings, like the fetuses with ARSA, two fetuses with isolated renal pyelectasis and without screening tests were also referred due to advance maternal age.

When we examined the fetuses that were diagnosed as having Down syndrome, we detected at least one major or minor sonographic finding in 99.2% of all fetuses and the rate of anomaly detection on ultrasound was higher than in previous studies. Papp et al. found abnormal ultrasound findings in 63.7% of 207 fetuses with Down syndrome, Sohl et al. reported a rate of 67.3%, and Deren et al. documented a rate of 63.2%.[23–26] We think that the high anomaly rate detected in ultrasound could be due to pregnant women in our country often not wanting to have screening tests and avoiding invasive procedures unless abnormal findings are detected on ultrasound examinations. The most common reason why patients were referred for invasive procedures was the suspicion of an anomaly in ultrasound at a rate of 50.7%, which supported our hypothesis. Considering the pregnant women who have positive screening tests and who do not accept invasive procedures because there are no abnormal findings on ultrasound, the rate of fetuses with Down syndrome without findings on ultrasound may be higher.

We found no ultrasound findings in one patient. The absence of ultrasound findings may be because the patient underwent fetal ultrasound at the 13 weeks of gestation. In the following weeks, different ultrasound findings could be detected in this patient. Unfortunately, we could not access the patient's follow-up information. However, it should be kept in mind that fetuses with Down syndrome may not have any ultrasound findings and these patients may be easily missed if screening tests are not performed or if they are found to be low risk.

The role and utility of minor findings detected on ultrasound are now questioned because the use of cell-free DNA has become more popular. Cell-free DNA has increased the detection rate of Down syndrome and

allowed early diagnosis. However, it is not cost-effective in some countries and is not routinely performed. In our study, we detected at least one minor ultrasonographic finding or major congenital anomalies in all fetuses except one and we believe that ultrasound maintains its importance in Down syndrome screening, especially in countries where pregnant women refuse invasive procedures, first- or second-trimester screening, or cannot access cell-free DNA tests. In addition, anomaly scanning with ultrasound is the only tool available to physicians for this population, in a world where medicolegal issues are increasing gradually.

In our department, we manage patients with minor findings as in **Fig. 2**. We inform all patients about the purpose, benefits, and limitations of screening and diagnostic tests. For patients with two or more minor findings, we recommend diagnostic tests regardless of the risk status of first- or second-trimester screening tests. For patients with a single isolated finding, we have two different approaches depending on the detected marker. We recommend cell-free DNA tests for patients with ARSA even if the first- or second-trimester screening tests indicate low risk because of their stronger association with Down syndrome, nuchal fold thickness, and hypoplastic or absent nasal bone. In this group, for patients without screening tests and with advanced maternal age, due to the higher risk of aneuploidy, we believe that offering invasive procedures is also an acceptable approach. For patients with pyelectasis, short femur and humerus, hyperechogenic bowel, and hyperechogenic cardiac focus as a single isolated finding, we recommend screening tests if not performed previously and continuing routine prenatal care for patients with low risk. We should also take into consideration that some minor findings are not only associated with aneuploidies. It is known that ARSA could also be a sign of DiGeorge syndrome in which further genetic evaluation is warranted to detect submicroscopic defects. Hyperechogenic bowel may be a prenatal sign of cytomegalovirus infection or cystic fibrosis. It is important to counsel patients about aneuploidies and the possible relation of each marker with other diseases.

There are some limitations of our study. One limitation is the heterogeneity of gestational age during the ultrasound examinations. It is known that anomalies that can be detected on ultrasound increase as the gestation-

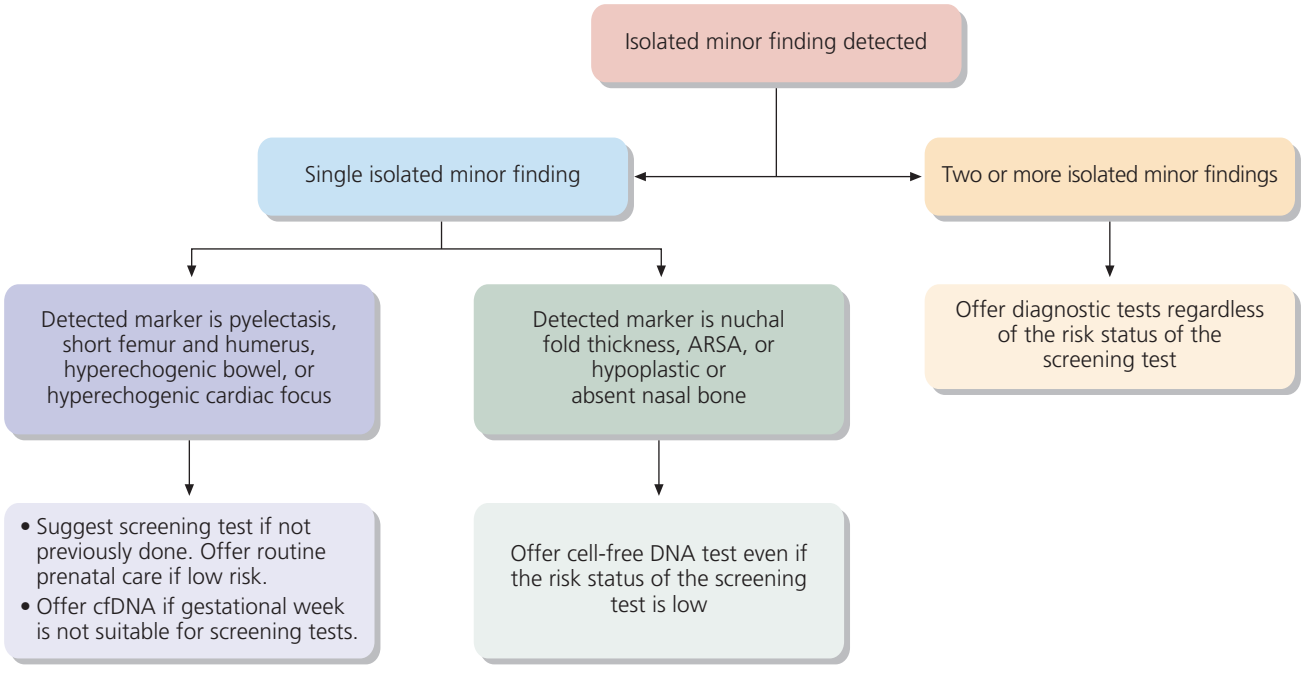

Fig. 2. Evaluation of fetuses with isolated minor findings.

al age progresses, and some ultrasound findings such as nuchal fold thickness may disappear in advancing weeks of gestation. However, due to the termination requests of patients, it is difficult to perform ultrasound examinations in the same weeks. Another limitation is that we cannot exactly detect the screening efficiency of abnormal sonographic findings for Down syndrome because our starting point was ultrasound examinations of patients with a diagnosis of trisomy 21 as a result of fetal karyotyping, so we did not have data on euploid fetuses with soft markers in ultrasound examinations.

The strengths of this study are that we present 8 years of experience in a tertiary center and that all ultrasound examinations were performed by maternal-fetal medicine subspecialists with advanced expertise in prenatal ultrasound.

Conclusion

Down syndrome displays a large variety of major and minor anomalies on ultrasound. There are no characteristic diagnostic findings of this aneuploidy, but in our study, at least one major or minor sonographic finding was detected in almost all fetuses, and more than half of the fetuses without major anomalies had only one minor finding. The most detected major structural anomaly was cardiac defects, and AVSD was the most frequent, as in the literature. The most common minor finding is nuchal fold thickness and considering that the second most common major structural anomalies are cystic hygroma and hydrops, edema in the fetal neck is an important finding for performing fetal karyotyping. We also believe that although multiple minor findings are generally considered more important, the presence of any isolated minor finding in pregnant women who have not undergone screening tests or do not accept invasive procedures, especially in women of advanced age, should serve as a warning to physicians to suspect Down syndrome.

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Compliance with Ethical Standards: The authors stated that the standards regarding research and publication ethics, the Personal Data Protection Law and the copyright regulations applicable to intellectual and artistic works are complied with and there is no conflict of interest.

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