Original Investigation

Is first trimester screening an opportunity for early diagnosis of structural anomalies?: A retrospective cohort study

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Abstract

Objective: To share our experience of ultrasonographic evaluation of fetal anatomy in the first trimester and pregnancy follow-up in a tertiary center.

Material and Methods: This retrospective study was conducted in the Acıbadem University Atakent Hospital and Acıbadem University Bakırköy Hospital Prenatal Diagnosis Units between April 2015 and December 2019. The study group included pregnant women referred for first-trimester aneuploidy screening and anomaly survey.

Results: The mean maternal age was 31.28±4.43 years and ranged from 20-49 years. The median gestational week at which first-trimester evaluation was made was 12.4 weeks. Of 3254 cases, 55 (1.69%) had pathologic ultrasound findings in the first-trimester anomaly scan, including increased nuchal translucency (NT) value over 95th percentile in 34 fetuses (52.3%) with structural anomaly. Median (range) crown-rump length was 58.69 (45-83) mm, and the median NT value was 3,5 (1.5-12) mm for fetuses with abnormal sonographic findings. The total detection rate for sonographic anomalies in the first-trimester scan was 60.43%. Of note, 27.3% of fetuses with detected anomalies had multiple congenital anomalies. Twenty-four new cases were diagnosed in the second trimester, and 11 new cases were detected in the last trimester from the same cohort.

Conclusion: Screening between 11-14 weeks of pregnancy may be an opportunity to evaluate maternal health and detect severe fetal anomalies. The family should be counseled about structural anomalies that may be detected later, especially in the second and third trimesters, the limitations of the technique, and the ongoing progress of fetal development. [J Turk Ger Gynecol Assoc.]

Keywords: Prenatal diagnosis, anomaly, fetus, prenatal ultrasound

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Introduction

A newly diagnosed pregnancy has a 2-3% risk of significant structural anomaly (1). The primary imaging tool to screen and diagnose structural anomalies is ultrasound and this technique has been included in all antenatal follow-up programs for 30 years. Early detection of fetal anomalies is an opportunity to diagnose comorbid genetic problems, counsel the family, and evaluate the relevance of prenatal or postnatal treatment. The earlier diagnosis of such anomalies, which are incompatible

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with life, provides parents with the option to terminate the pregnancy. The early procedure is usually safer and more acceptable for the parents. Ultrasound screening for fetal structural anomalies should be performed during pregnancy, as part of the examination during first-trimester aneuploidy screening, or in the second trimester between the 18 and 23 weeks of pregnancy. The second-trimester examination is now mandatory in the prenatal surveillance protocol in many countries. Factors affecting the prenatal diagnosis of fetal anomalies include technique, gestational age at which the examination was performed, whether the screened population is low or high-risk, the woman's body mass index (BMI), the practitioner's experience, and the region of interest (2). The detection rate of fetal anomalies increases in pregnant women with known risk factors for fetal anomalies (3). Moreover,the rate of fetal anomaly diagnosis in reference centers was reported to be 2.7 times higher than in centers that provide standard care in the RADIUS study (4). A first-trimester screening test has been performed more frequently since the end of the 1990s and simultaneously, an examination of fetal anatomy was focused on by various centers. Thus, the technical and theoretical infrastructure for anatomical examination was developed gradually. Both the International Society of Ultrasound in Obstetrics and Gynecology (ISUOG) and the American Institute of Ultrasound Medicine have set out the criteria for screening for this period (5-7).

A comprehensive first-trimester ultrasound scan, performed between 11+0 and 14+0 weeks' gestation, involves a systematic assessment to ensure accurate and thorough fetal evaluation (7). Key steps include confirming fetal viability and determining gestational age through crown–rump length (CRL) measurement. The scan should assess the number of fetuses, chorionicity in multiple pregnancies, and screen for aneuploidies by measuring nuchal translucency (NT) and evaluating the nasal bone, ductus venosus flow, and tricuspid valve regurgitation. A detailed anatomical survey should follow, covering the head, brain, face, neck, thorax, heart, abdomen, spine, limbs, and genitalia, using both transabdominal and, when necessary, transvaginal approaches for optimal visualization. Doppler studies of the uterine arteries can also be incorporated to screen for pre-eclampsia. The use of high-quality ultrasound equipment and adherence to safety standards, including the As Low As Reasonably Achievable (ALARA) principle, are essential to ensure the effectiveness and safety of the scan.

While 35-40% of fetal anomalies can be detected with fetal anatomical examinations performed at the end of the first trimester in the low-risk pregnant population, this detection rate can be as high as 60% in the high-risk group (8). Primary requirements for first-trimester anatomy exams are experienced practitioners and high-frequency transvaginal, linear, or convex abdominal probes (9-11). Detection rates of fetal anomalies were higher in the lethal or multiple congenital anomalies. The primary imaging tool to screen and diagnose structural anomalies is ultrasound. Consequently, this technique has been in all antenatal follow-up programs for 30 years. Early detection of fetal anomalies is an opportunity to diagnose comorbid genetic problems, counsel the family, and evaluate the relevance of prenatal or postnatal treatment. The earlier diagnosis of such anomalies, which are incompatible with life, allows parents to opt for termination of pregnancy. The early procedure is usually safer and more acceptable for the parents. Ultrasound screening for fetal structural anomalies could be performed during pregnancy, as part of the examination during first-trimester aneuploidy screening, or in the second trimester between the 18 and 23 weeks of pregnancy (2). History of previous surgery, high BMI, number of fetuses, and fetal position are among the factors that affect the examination's success and the detection rate of fetal anomalies.

Transvaginal evaluation between 11^{th} and 12^{th} gestational weeks provides an excellent opportunity to evaluate fetal structures. However, despite the better resolution of using a high-frequency transvaginal transducer close to the fetus, the limited flexibility and the inability to obtain different examination planes are well-known handicaps of transvaginal exams in the late first trimester. The safety of the fetus (and mother) are paramount and should be foremost when planning any ultrasonographic evaluation. The ALARA principle is also valid for first-trimester examinations. While B-mode and M-mode can be safely applied throughout the pregnancy, pulse Doppler should be used only for limited periods and in indicated cases due to its thermal effect on the developing embryo and fetus (12). Reducing the acoustic output will lower the thermal index (TI) without affecting the resolution (13). In this retrospective study, we share our experience from a tertiary center about ultrasonographic evaluation of fetal anatomy in the first trimester and pregnancy follow-up.

Material and Methods

This retrospective study was conducted in Acıbadem University Atakent Hospital and Acıbadem University Bakırköy Hospital Prenatal Diagnosis Units between April 2015 and December 2019. This study was approved by the Acıbadem University Ethics Commitee (approval number: ATADEK 2021-02/01, date: 28.01.2021). Both maternal-fetal medicine units provide early anatomy surveys to high-risk pregnancies, such as a history of previous fetal anomaly, multiple pregnancies, pregnancies with a high-risk first-trimester aneuploidy screening test, high-risk cell-free DNA test, maternal teratogen exposure, and consanguineous couples with a history of genetic disease.

The study group included pregnant women referred for first-trimester aneuploidy screening and anomaly survey. Of these, 3254 cases had follow-up data, including second-trimester examination and pregnancy outcome data. Cases that had no second-trimester examination, *in-utero* demise, higher-order multiples, and pregnancies lost from pregnancy follow-up were excluded from the study. All first and second-trimester exams were performed by the same maternal-fetal medicine specialists (TUKD and ÖP) using Voluson E8 Expert, equipped with RMC-6 or C1-5 D convex probe or an E10, equipped with a C4-8 convex probe (General Electric, Chicago, IL, USA). The RIC6-12 transvaginal probe was used in selected cases for transvaginal exam. Both operators had more than 10 years of experience in first-trimester ultrasound practice. All ultrasound examinations were performed supine and with an empty bladder. The average total examination time for the first-trimester examination was 45 minutes (including NT, nasal bone, ductus venosus and tricuspid regurgitation, fetal anatomy exam, and bilateral uterine artery Doppler measurements).

In cases of inappropriate fetal position during the 30-minute examination period, the examination was stopped and repeated following a one-hour break. The region of interest was magnified to fill 70% of the screen. The scan area was narrowed to 20-30 degrees for a better frame rate, and harmonics were adjusted in the middle. To follow the ALARA principle, ultrasound acoustic output settings were set to yield a TI value below 0.5 in the study area. Our checklist was based on a modified ISUOG guideline (Table 1 and Figures 1, 2). In case of cardiac anomaly suspicion or abnormal cardiac examination findings, fetal echocardiography was done by an experienced pediatric cardiologist with expertise in fetal cardiology. In addition, follow-up exams and postnatal echocardiography were performed to ascertain cardiac anomalies. Genetic and prognostic counseling was provided by a medical genetics specialist, pediatric cardiologist, and maternal-fetal medicine specialist.

The first-trimester examination was performed between the 11th and 14th weeks of gestation (CRL 45 mm to 84 mm).

Table 1. Checklist for the first trimester exam

Region	Examination plane	Details
Head	Transverse-sagittal	Cranial bones Midline falx Choroid plexus-filled ventricles Fourth ventricle, intracranial translucency Midbrain
Neck	Sagittal	Nuchal translucency
Face	Transverse-sagittal-coronal	Eyes with pair of lenses Nasal bone Profile view with palate Retronasal triangle
Chest and heart	Transverse	Symmetrical lung fields Four symmetrical chambers** Outflow tracts* Three-vessel trachea view* Rule out effusions and masses
Abdomen	Transverse-sagittal-coronal	Stomach (fluid filled and left upper quadrant location) Urinary bladder Kidneys
Abdominal wall	Transverse-sagittal	Normal cord insertion Rule out abdominal wall hernias
Extremities		Four limbs each with three symmetrical segment Hand and feets with normal orientation
Spine	Sagittal	Vertebra and intact overlying skin
Placenta	-----	Size, location, proximity to cervical os
Uterine Arteries	-----	Bilateral uterine artery pulsatility index
Umbilical Cord	Transverse	Three-vessel cord

*Evaluated by high-definition power Doppler flow
**Evaluated by both grayscale and high-definition power Doppler flow

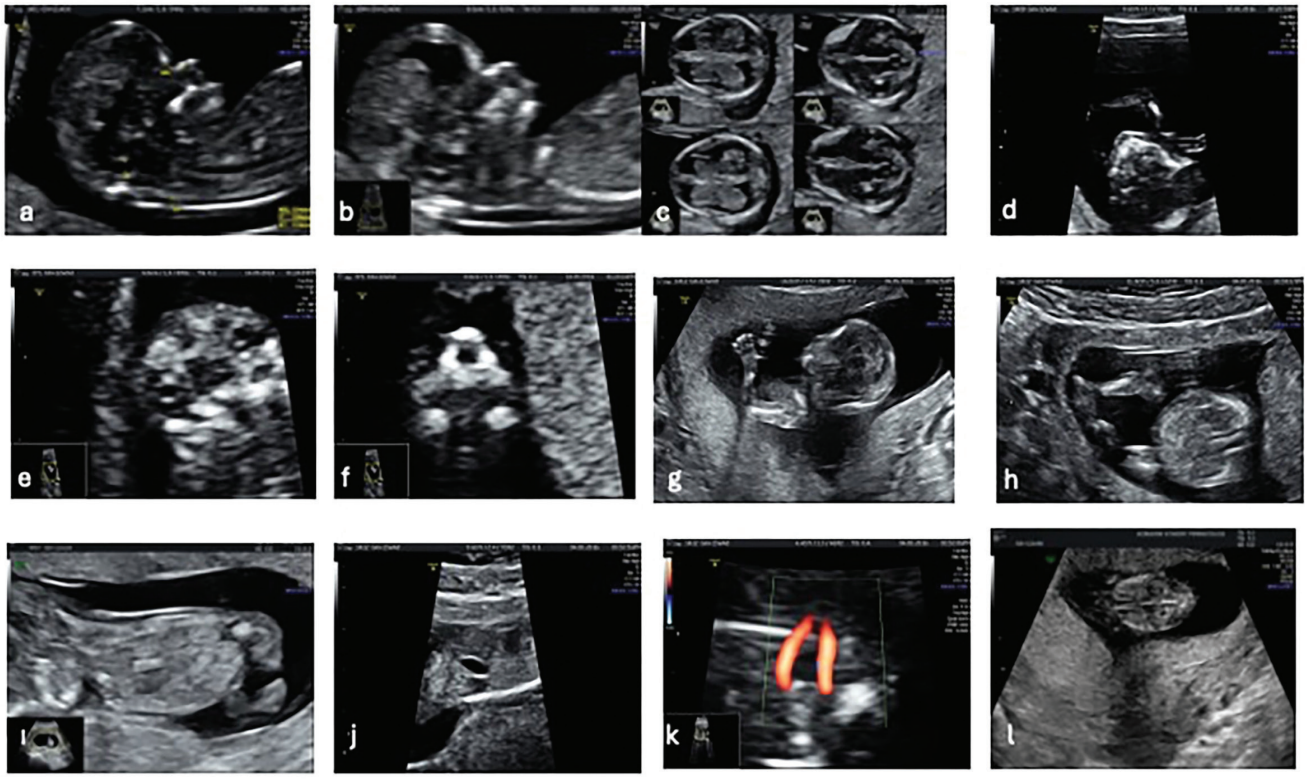

Figure 1. Standard sonographic planes for anatomical survey in the first-trimester exam. Fetal profile view to measure NT (a), fetal profile in the mid-sagittal view (b), axial planes of fetal cranium (c) , axial view of hard palate (d), bilateral orbita and lenses (e), retronasal triangle (f), upper extremity, hand, and fingers (g), lower extremity and foot (h), skin overlying fetal spine (i), fetal stomach (j), fetal bladder and bilateral umbilical arteries (k), bilateral kidneys (l)
NT: Nuchal translucency

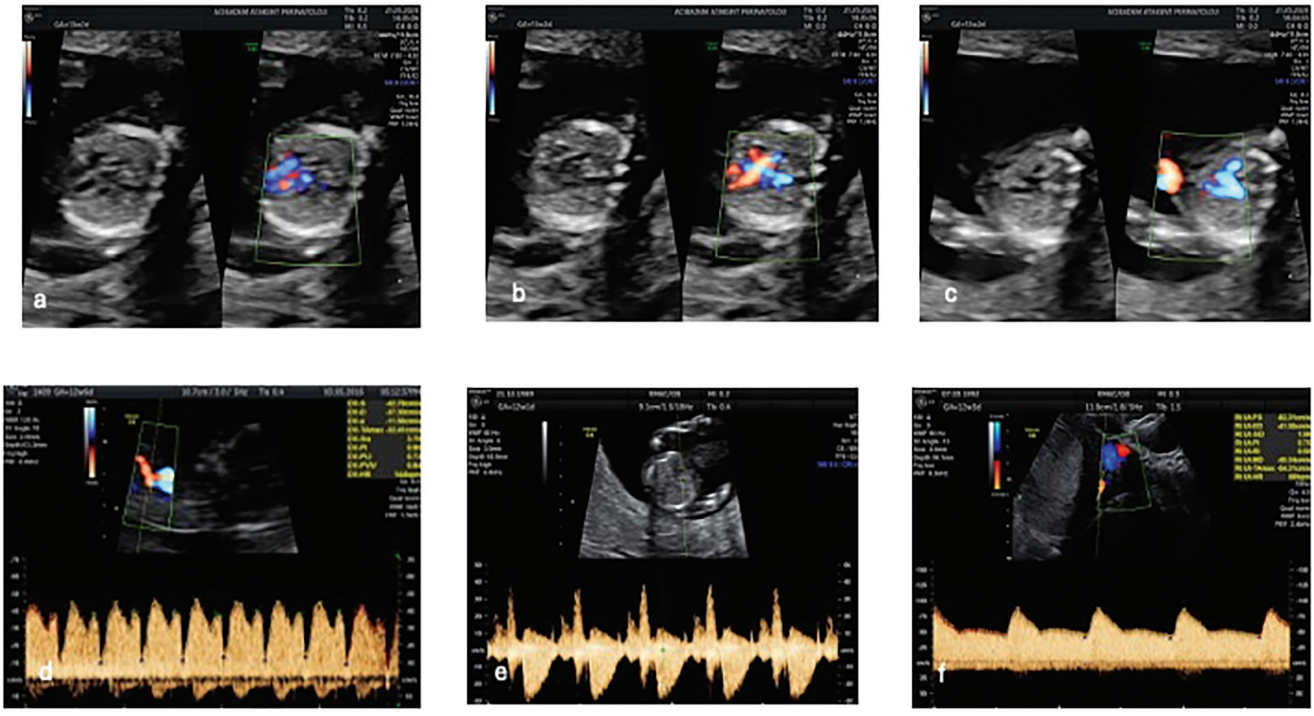

Figure 2. Standard sonographic planes for heart exam and Doppler exam in the first-trimester exam (with high definition flow Doppler). 4-chamber view (a), crossing of great vessels (b), three-vessel view (c), triphasic flow of Ductus venosus (d), assessment of tricuspid valve regurgitation (e), uterine artery Doppler (f)

Before the ultrasound examination, maternal characteristics were recorded including medical history, BMI, and mean arterial pressure. NT was measured in the midsagittal section under appropriate magnification, and the head and one third of the fetal thorax filled the screen. The largest NT value from three consecutive measurements was used for the combined aneuploidy screening test. An invasive genetic test (Chorionic Villus Sampling or amniocentesis) was suggested in case of NT measurement over 3.5 mm (99th percentile) or the existence of structural anomaly without performing a screening test. Women were informed about an estimated individual risk for trisomy 13, 18, and 21. We suggested an invasive genetic test for pregnancies with significant structural abnormalities and those who had a high-risk screening test for aneuploidy for fetal karyotyping. Maternal cell-free DNA testing for trisomies 21, 18, and 13 was suggested for cases with moderate risk (combined trisomy 21 risk was between 1/51 and 1/1000) or parental request.

Termination of pregnancy was offered in case of co-existing multiple structural anomalies, lethal anomalies, and anomalies with co-existing aneuploidies by decision of the local expert committee (including an obstetrician, maternal-fetal-medicine specialist, and pediatric cardiologist or pediatric surgeon). Fetal anatomy was re-examined between 18 and 23 weeks of gestation following an unremarkable first-trimester examination. Soft markers (pyelectasis, echogenic intracardiac focus, choroid plexus cyst) were not considered structural anomalies, and further evaluation was not performed. Genetic counseling and additional diagnostic tests were performed for fetuses with aberrant right subclavian artery, thickened nuchal fold, absence of nasal bone, ventriculomegaly, or grade 3 echogenic bowel.

Statistical analysis

Statistical analysis was performed using SPSS, version 28.0 (IBM Inc., Chicago, IL, USA). The Kolmogorov-Smirnov test was used to determine the distribution of continuous data. Comparative analysis between groups used the chi-square test for categorical data, the Mann-Whitney U test, and the Student's t-test for comparing medians and means, respectively.

Results

This retrospective study included 3,254 cases whose pregnancy follow-up data were available, including first and second-trimester examinations. Median maternal age was 31.28±4.43 years and ranged from 20-49 years. Median gestational week at which first-trimester evaluation was made was 12.4 weeks, and median (range) CRL was 64 (45.1-84) mm when the examination was performed. We performed a combined transvaginal and transabdominal approach in 32 cases (1.86%). The median maternal BMI was 24.325 (18-51.8) kg/m^2. Ninety percent of pregnancies were spontaneously conceived. The first trimester anomaly scan identified 55 of 3,254 cases (1.69%) pathologic ultrasound findings, including enlarged NT (including cystic hygromas) with an NT >95th percentile. NT value was >95th percentile in 34 fetuses (52.3%) with structural anomaly when cases with isolated enlarged NT (n=10, 15.38%) were excluded. Twenty-one (32.32%) fetuses with structural anomaly had NT <95th percentile. Moreover, 40 cases had only one, and 15 cases had multiple congenital anomalies (Table 2). Examples from the diagnosed structural anomalies are shown in Figure 3. Median CRL was 58.69 (45-83) mm and median NT value was 3.5 (1.5-12) mm for fetuses with abnormal sonographic findings.

An invasive genetic test was performed in 29 cases (CVS for 19 cases and amniocentesis for 10 cases). Karyotype results are shown in Table 3.

The distribution of fetal anomalies by systems and trimesters is summarized in Table 4. The prevalence of major fetal structural anomaly was 1.69% (55/3254) for the first-trimester exam, including high-risk pregnancies, and 0.74 % (24/3210) for the second-trimester exam. However, following the exclusion of cases with isolated increased NT (NT >95th percentile), these proportions were 1.38% for the first trimester and 0.72% for the second trimester, respectively. The total detection rate for the first trimester scan was 60.4%. Nearly half of the detected congenital anomalies were congenital heart defects (43.63%). In addition, 27.27% of fetuses with detected anomalies had multiple congenital anomalies. The coexistence of multiple anomalies contributed to earlier diagnosis of fetal defects in the first trimester.

Of the 55 case that were detected in the first trimester, nine (16.4%) were lost follow-up and 35 (63.6%) pregnancies with anomaly underwent termination of pregnancy, including intrauterine demise, selective fetocide, and radiofrequency ablation of co-twin pair in twin reverse arterial perfusion at 16 weeks of pregnancy. Only 16 (29.1%) cases resulted in term delivery, and 5 (9.1%) cases resulted in preterm live birth. A total of four selective feticide procedures were performed on multiplets with the anomaly in the first trimester by intracardiac potassium chloride, including one fetus with acrania-exencephally in triplets, and three cases with multiple and lethal anomalies including cardiac anomalies. Two cases that resulted in preterm delivery were multiplets. One of these was a monochorionic monoamniotic twin pregnancy, and the twin pair had (corrected) L-type transposition of great arteries. Planned cesarean delivery was performed in this monochorionic twin pregnancy at the 33rd weeks of gestation.

Table 2. Summary of fetal structural anomalies and distribution by trimesters

Fetal structural anomaly	First trimester	Second trimester
Acrania-exencephaly	5	0
Alobar holoprosencephaly**	1	0
Posterior fossa cyst	2	0
Lissencephaly + growth restriction	0	1
Ventricular septal defect (VSD)	5 (one case coexistent with tricuspid atresia	6
Atrioventricular septal defect (AVSD)	7	0
Tetralogy of fallot	2	0
Double outlet right ventricle	1 coexistent with VSD	0
Transposition of great arteries	2* coexistent with VSD	1
Truncus arteriosus	2 coexistent with VSD	
Coarctation of aorta	0	1
Hypoplastic left heart	2	2
Hypoplastic right ventricle	1	0
Pericardial Effusion	0	1
Absence of ductus venosus	1	0
Congenital cystic adenomatoid malformation	0	1
Pleural effusion	1	0
Non-visualization of gallbladder	0	1
Pelvic kidney	0	1
Unilateral renal agenesis	0	1
Abdominal cyst	1	0
Umbilical vein varix	0	1
Cystic hygroma	2	0
Posterior urethral valve	0	1
Bilateral moderate pyelectasis	0	1
Nasal hypoplasia	0	1
Pes equinovarus	0	2
Sacral meningocele	0	1
Unilateral phocomelia	1	0
Sirenomelia	1	0
TRAP	2	0
AVSD + pes equinovarus	1	0
AVSD + maxillary gap + cleft lip and palate**	1	0
VSD + extremity contractures	1	0
VSD + omphalocele	2	0
VSD + omphalocele + holoprosencephaly	1	0
VSD + bilateral cleft lip-palate + omphalocele + polydactyly	1	0
VSD + interrupted aorta	1	0
VSD + posterior fossa cyst + retrognati	1	0
Omphalocele + pleural effusion	1	0
VSD + nasal hypoplasia + strawberry head	0	1
Single ventricle + omphalocele	1	0
VSD + posterior fossa cyst + hypertelorism	1	0
Strawberry head + bilateral clenched hands	1	0
Posterior fossa cyst + hypoplastic left heart	1	0
Pes equinovarus + strawberry head	1	0
Atrial septal defect + unilateral pyelectasis + single umbilical artery	1	0
Total	55	24

*One of the diagnosed cases was defined as D type transposition in the first trimester, second case was evaluated as suspicious cardiac findings in the first trimester and diagnosed as corrected (L type) transposition in the early second trimester
**Retronasal triangle was not visualized
TRAP: Twin reversed arterial perfusion

Twenty-four new cases were diagnosed in the second trimester (Table 5). The median gestational age was 20 weeks for the fetal anomalies detected in the second trimester. One of the fetuses with a hypoplastic left heart (Case 19) was evaluated as suspicious for ventricular asymmetry in the first-trimester exam. Two cases underwent termination of pregnancy, two cases were delivered preterm, and two cases were lost follow-up. In addition, 11 new cases from the same cohort were detected in the last trimester. The median gestational age was 30 weeks for the fetal anomalies that were detected in the third trimester (Table 5). Case 34 had suboptimal sonographic evaluation in both the first and second-trimester exams.

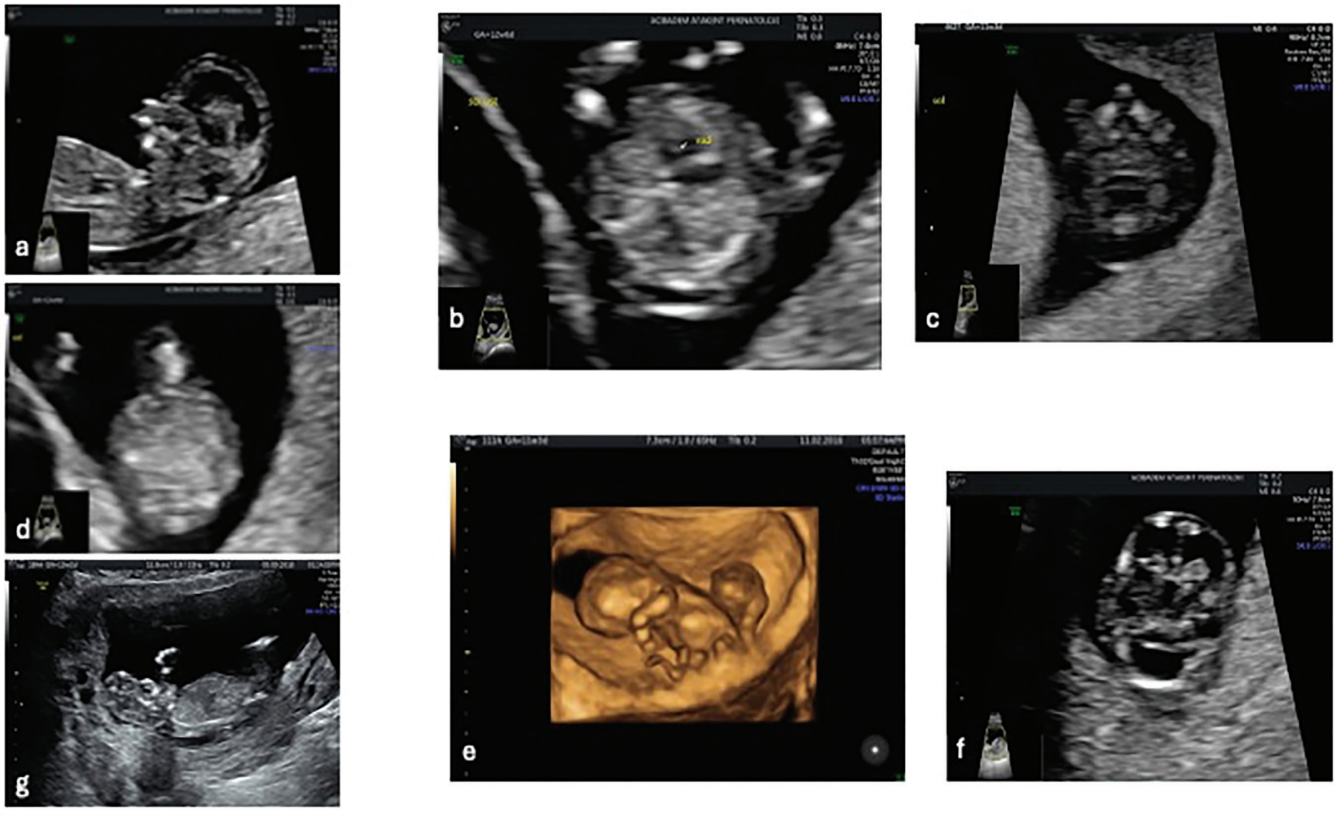

Figure 3. Examples of diagnosed fetal anomalies. Retrognatia and maxillary cleft (a), ventricular septal defect (b), bilateral cleft lip and palate (c), omphalocele (d), acardiac twin pair of monochorionic twin pregnancy (e), posterior fossa cyst (f), acrania (g)

Table 3. Karyotype results of fetuses with congenital anomalies detected in the first trimester which underwent invasive genetic diagnosis in the first/second trimester

Karyotype	n
Partial trisomy 9	1
Trisomy 13	1
Trisomy 18	4
Trisomy 21	6 (including one mosaic case)
Turner syndrome	1
Triploidy	2
Noonan syndrome	1
46; t13;14 (balanced)	1
46; t17;13 (unbalanced)	1
Normal constitutional karyotype	11

Discussion

The first-trimester combined test replaced the second-trimester serum tests to screen for common aneuploidies in the early 1990s (14). High-frequency ultrasound probes, including transvaginal techniques and increased operator experience, contributed to a better and earlier definition of fetal anatomy in the late first trimester. Meanwhile, as a suspicious sign for common trisomies, increased NT was introduced and was also shown to be a warning sign for certain genetic syndromes, congenital cardiac, and non-cardiac anomalies. However, NT has been found within standard reference ranges in 67% of fetuses diagnosed with structural anomalies in the first trimester by gestational week (15) and 95% of fetuses with increased NT had co-existent or multiple fetal anomalies (16). The median NT value of fetuses that had structural anomalies in the first-trimester exam was reported as 2.2 mm in a recent study (17). In the present study, nearly 53% of fetuses with structural anomalies in the first-trimester exam had an NT value above the 95th percentile, and the median NT value was 3.5 mm**.** In another series, the number of cases above the 95th percentile was reported as 26% (18). Of note, none of the 24 fetuses with anomalies diagnosed in the second-trimester exam had NT >95th percentile.

Following the development of the guidelines and publications about the anatomical survey of the second-trimester fetus, an area of interest is the technical aspects and extent of the

Table 4. Distribution of fetal anomalies by systems.

	1st trimester	2nd trimester	3rd trimester	Total
Central nervous system	8 (14.54 %)	1 (4.16 %)	0	9 (9.89 %)
Face-neck*	2 (3.64)	1 (4.16 %)	1 (8.33)	4 (4.4 %)
Thorax	1 (1.82 %)	1 (4.16 %)	0	2 (2.2 %)
Heart	24 (43.63 %)	11 (45.84)	3 (25 %)	38 (41.75 %)
Alimentary tract-abdomen	1 (1.82 %)	2 (8.34 %)	3 (25 %)	6 (6.59 %)
Genitourinary system	0	4 (16.68 %)	2 (16.67 %)	6 (6.59 %)
Skeleton	2 (3.64 %)	2(8.34 %)	0	4 (4.4 %)
Spine	0	1 (4.16 %)	0	1 (1.1 %)
Multiple anomalies	15 (27.27 %)	1 (4.16 %)	2 (18.18 %)	18 (20.88 %)
TRAP**	2 (3.64 %)	0	0	2 (2.2 %)
Total	55 (60.43 %)	24 (26.37 %)	11 (13.2 %)	90 (100 %)

Data shown as n (%)
*Including cervical cystic hygromas with multiple septations
**Twin reversed arterial perfusion

fetal anatomical examination in the first trimester (19). The fetuses with multiple congenital anomalies or increased NT could be detected earlier; however, it is impossible to diagnose congenital anomalies that may occur later than first trimester due to fetal developmental dynamics during the pregnancy (19,20). Furthermore, overdiagnosed structural anomalies, such as ventricular septal defects, nuchal edema, abdominal cysts, and omphalocele were reported previously (21). Our unpublished data were consistent with previous literature about high false positivity for certain suspicious findings.

Major handicaps of first-trimester anatomic examinations are the size of the fetus, the ongoing fetal development of the central nervous system, alimentary tract, lungs, and late diagnosis of non-lethal skeletal dysplasias. In addition, gestational age at fetal exam, experience of operator, number of fetuses, and patient-related conditions such as previous abdominal surgery or obesity affect the detection rates of fetal anomalies (22). The detection rate will vary depending on whether the pregnant population was in low or high-risk groups. Karim et al. (8), reported that detection rates for fetal structural anomalies in low and high-risk groups were 32% and 61.18%, respectively. Liao et al. (23) reported that 43% of 1578 diagnosed fetal anomaly cases were detected in the first-trimester exam, 95.6% of abdominal anterior wall defects, 21% of urogenital anomalies, 18.4% of thoracic anomalies, and 37% of cardiac anomalies were diagnosed by routine first-trimester ultrasonography. The diagnosis rate is lower, particularly for thoracic and central nervous system anomalies (24). In this large-scale series, the diagnosis rate of gastrointestinal tract anomalies was only 4.1%.

The detection rate may be as high as 61% for pregnancies with high NT, advanced maternal age, and a previous pregnancy history of multiple fetal anomalies (2). Our cohort consisted of both high-risk and low-risk pregnancies and 55 of 90 (60.43%) of diagnosed fetal structural anomalies were detected in the first trimester exam, a similar detection rate to the literature. Nearly half of the detected congenital anomalies were congenital heart defects. This relatively higher detection rate could be linked to the study population characteristics with many fetuses having thicker NT (over 95 percentile). Furthermore, dedicated exams by maternal and fetal medicine specialists may also result in a higher diagnosis rate for congenital heart anomalies. Notably, 27.26% of fetuses with detected anomalies had multiple congenital anomalies. The co-existence of various anomalies may contribute to the earlier diagnosis of fetal defects in the first trimester.

Syngelaki et al. (25) classified fetal structural anomalies into three different categories: consistently detectable; may be detectable; and not diagnosable in the first trimester. These authors then subdivided those who could be diagnosed into those with a diagnosis rate of more than 50% and those with a diagnosis rate of less than 50%. In the same study, encephalocele, Pentalogy of Cantrell, abdominal wall defects, congenital diaphragmatic hernia, body-stalk anomaly, congenital heart defects, open neural tube defects, fetal akinesia, and lethal skeletal anomalies were reported to have the highest association with higher NT values, with 47.9% of fetuses with congenital cardiac defects have NT values higher than the 95 percentiles. In this study, 62.5% of fetuses with heart defects had increased NT (>95th percentile). Grande et al. (20) reported that all acrania, alobar holoprosencephaly, omphalocele, hydrops, megacystis, and hypoplastic left heart cases were diagnosed in the first trimester scan.

Table 5. Late diagnosed fetal anomalies following the normal first-trimester exam

Case	Weeks of gestation	Ultrasound findings	Genetic diagnosis	Prognosis
1	24 weeks	Posterior urethral valve - bilateral vesicoureteral reflux	Normal karyotype	Live delivery at 35 weeks of gestation
2	18 weeks	Bilateral pes equinovarus	-----	Term live delivery
3	21 weeks	D type transposition of great arteries	Regretted	Term delivery, postnatal exitus
4	23 weeks	Intrauterine growth restriction and lissencephaly	Triploidy	Termination of pregnancy
5	21 weeks	VSD, unilateral hypoplasia of nasal bone	Trisomy 21	Termination of pregnancy
6	21 weeks	Pelvic kidney (left)	cf-DNA test was low-risk	Term live delivery
7	22 weeks	Membranous VSD	------	Term live delivery
8	21 weeks	Sacral meningocele (16x12 mm)	------	Term live delivery
9	19 weeks	CCAM* (Right lung)	------	Term live delivery
10	20 weeks	Muscular VSD + ARSA	cf-DNA test was low-risk	Term live delivery
11	20 weeks	Unilateral renal agenesis	------	Term live delivery
13	20 weeks	Outlet VSD	Invasive test regretted	Term live delivery
14	22 weeks	Muscular VSD	invasive test regretted	Term live delivery
15	19 weeks	Outlet VSD	cf-DNA test was high-risk, invasive test regretted	Lost-follow-up
16	22 weeks	Pericardial effusion	Parvovirus Infection ? Invasive test regretted.	Lost-follow-up
17	19 weeks	Coarctation of aorta	DiGeorge	Preterm delivery
18	20 weeks	Hypoplastic left heart	Invasive test regretted	Term live delivery
19	23 weeks	Hypoplastic left heart	Invasive test regretted	Term live delivery
20	20 weeks	Unilateral nasal hypoplasia	Invasive test regretted	Term live delivery
21	22 weeks	Muscular VSD	cf-DNA test was low-risk, invasive test regretted	Term live delivery
22	20 weeks	Muscular VSD in co-twin	Invasive test regretted	Term live delivery
23	22 weeks	Absence of gallbladder	Invasive test regretted	Term live delivery
24	20 weeks	Umbilical Vein Varix	cf-DNA test was low-risk	Term live delivery
25	32 weeks	Fetal ovarian cyst (unilateral)	cf-DNA test was low-risk	Term live delivery
26	30 weeks	Uniloculated simple cyst (3 cm) on the upper pole of left kidney	cf-DNA test was low-risk	Term live delivery
27	35 weeks	Fetal arrhythmia (trigeminy)	cf-DNA test was low-risk	Late preterm delivery (PPROM)
28	28 weeks	Coarctation of aorta in co-twin pair	------	Preterm live delivery
29	30 weeks	Unilateral renal solitary cyst (3 cm)	------	Term delivery
30	33 weeks	Fetal ovarian cyst (unilateral)	cf-DNA test was low-risk	Term delivery
31	30 weeks	Cervical lymphangioma	-----	Term live delivery
32	35 weeks	Calcification of gallbladder wall, fetal growth restriction, polymicrogyria	Invasive test regretted	Term live delivery
33	29 weeks	Non-immun hydrops fetalis	Normal karyotype	In-utero exitus
34	30 weeks	Fetal ovarian cyst (unilateral, intracystic hemorrhage)	------	Term live delivery
35	29 weeks	Muscular VSD (fetal growth restriction at 35 weeks of gestation)	Normal karyotype	Late preterm delivery

*Congenital cystic adenomatoid malformation
VSD: Ventricular septal defect

A recent meta-analysis by Karim et al. (26) reported that first-trimester ultrasound exams have a higher detection rate (>80%) for acrania, exomphalos, gastroschisis, and holoprosencephaly. Nevertheless, higher false positivity (24%) for suspected anomalies was the foremost handicap in the early anatomical examination. Data from Nationwide first-trimester anomaly scan in the Dutch national screening program revealed that first-trimester anomaly screening has 84.6% sensitivity for first-trimester major congenital anomalies and 31.6% for all anomalies. Positive predictive value was 40.9%, and 59.1% involved cases where anomalies were either not confirmed or resolved before 24 weeks gestation (27).

If the fetal evaluation is performed between 11 weeks and 11 weeks and 6 days, the total evaluation rate was 23.1%, while it was 63.8% between 12 weeks 6 days and 13 weeks 6 days. In this second period, 26.3% of the fetuses with renal, and 31.6% with cardiac evaluations were reported as “hesitant” or “inadequate” (26). Therefore, the family should be counselled about structural anomalies that can be diagnosed later, especially in the second and third trimesters, exam limitations, and ongoing progress of fetal development (28).

In the last decade, the definition of findings, such as intracranial translucency, brainstem-brainstem occipital bone distance, retronasal triangle, and maxillary gap, better visualisation of large vessel outflows, especially in the heart with colour Doppler, has increased the number of fetal anomalies that can be diagnosed in the first trimester (19). High-frequency linear and convex probes are gradually reducing the need for evaluation with transvaginal transducers. The combined transvaginal and transabdominal approach provides a better detection rate (62 %) for congenital defects than both the transvaginal (51%) and transabdominal techniques (34%) in isolation (2). A combined approach was only required in 1.86 % of cases in our study. Syngelaki et al. (25) reported that the combined approach rate was 2-3% of all examinations. We can explain the lower rate of the combined approach needed for examination than in previous studies by a later median gestational age of ultrasound exams (12.4 weeks) in our study.

Petousis et al. (17) reported the prevalence of anomaly in fetuses with normal karyotype as 1% and the diagnosis rate as 50% in their study based on the ISUOG guideline.

Among 3,254 cases in which fetal anatomy was evaluated in the first trimester, 24 cases were diagnosed in the second trimester, although no pathological finding was detected in the first-trimester examination. Maternal obesity and lower abdominal scarring could explain the delayed diagnosis of two cases with fetal congenital defects in the second trimester. However, a triploidy case has no pathological ultrasound signs until the 21st week of gestation except for early-onset growth restriction. Manegold et al. (22) conducted a cohort study between 1998 and 2008, and they reported that 116 fetuses (40%) of 8,079 fetuses examined in the first trimester had congenital anomalies. Furthermore, 6,378 fetuses had previously unremarkable first-trimester exams from the same cohort, and 102 (35 %) additional cases of congenital defects were detected. In the last step of this study, 5,044 fetuses that were evaluated as having no congenital structural defects were re-examined in the third trimester, and 44 (0.87%) abnormal ultrasound findings were found. Ficara et al. (3) reported that 67% of all congenital anomalies were detected in the first and second-trimester exams. A systematic review that covered 87 studies and 7,057,859 fetuses revealed that the first trimester scan detected 37.5% structural and 91.3% of lethal anomalies. If the second trimester exam is added to the exam protocol, combined sensitivity can reach 83.8% (29). We detected over 60% of fetal anomalies in the first-trimester exam using extended ISUOG guidelines (30). The fact that no distinction was made between low and high-risk in our cohort and that the median CRL value was 64 mm may explain the relatively high first-trimester diagnosis rates.

Study limitations

Limitations included he heterogeneous nature of the study, retrospective design, single-center nature and unavailability of neonatal exam data. The main strengths were that two maternal-fetal medicine specialists evaluated the cases and they were followed up until delivery.

Conclusion

The time between the 11-14 weeks of pregnancy is an opportunity for screening for aneuploidies and evaluating maternal health and severe fetal structural anomalies. Evaluation of fetal anatomy as late as possible in the first trimester and early second trimester will enable the detection of more structural anomalies.

Ethic

Ethics Committee Approval: *This study was approved by the Acıbadem University Ethic Commitee (approval number: ATADEK 2021-02/01, date: 28.01.2021).*

Informed Consent: *Retrospective study.*

Footnotes

Author Contributions: *Surgical and Medical Practices: T.U.K.D., Ö.P., Concept: T.U.K.D., E.K., Design: E.K., E.A., Data Collection or Processing: E.K., E.A., Analysis or Interpretation: T.U.K.D., Ö.P., Literature Search: E.K., E.A., Writing: T.U.K.D., E.K.*

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