REVİEW

Contemporary Screening in Pregnancy

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Abstract

Screening tests and genetic ultrasonography have great importance in pregnancy management and follow-up. First-trimester screening, second trimester screening and genetic ultrasonography have widespread use globally. Although, some obstetricians still insist on using the second trimester screening as a first line choice, first-trimester screening with ultrasound including nuchal thickness, nasal bone, tricuspid regurgitation, ductus venosus blood flow and biochemical tests are getting more pronounced rather than the second trimester screening test in the upcoming literature. In this paper, we have aimed to review the new approaches and current screening methods in pregnancy.

Keywords: nuchal translucency, nasal bone, free-β-human chorionic gonadotrophin, pregnancy-associated plasma protein-A

Özet

Gebelikte Güncel Tarama

Gebelik yönetimi ve takibinde tarama testleri ve genetik tanı amaçlı ultrasonografinin çok büyük önemi vardır. Birinci trimester taraması, ikinci trimester taraması ve genetik tanı amaçlı ultrasonografi tüm dünya üzerinde yaygın olarak kullanılmaktadır. Ultrasonografi ile ense kalınlığı, nazal kemik, triküspid regürjitasyon, *ductus venosus* akımını içeren tetkikler ve biyokimyasal testlerden oluşan birinci trimester taraması yeni literatürde ikinci trimester taramasından daha fazla vurgulanmaktadır, bununla birlikte, bazı doğum uzmanları halen ikinci trimester taramasını ilk tercih olarak kullanmakta ısrar etmektedirler. Biz bu yazıda, yeni yaklaşımları ve güncel tarama yöntemlerini gözden geçirmeyi amaçladık.

Anahtar sözcükler: ense kalınlığı, nazal kemik, serbest-β-insan korionik gonadotropini, gebelik ile ilişkili plazma proteini-A

Introduction

Screening methods either by biochemical markers, by ultrasound or by both have constituted a major part in pregnancy management and follow-up. The effort of detecting chromosomal abnormalities as well as structural abnormalities has been directed to the first-trimester rather than second trimester in the recent years. Here, we report the current strategies in pregnancy screening.

The first screening method used to detect fetal Down syndrome was maternal biological age and presence of a previous infant with Down syndrome. Especially in the United States with the widespread use of genetic amniocentesis since 1970's, 100% of Down syndrome cases were detected in pregnant women who were 35 years or older. However, by using 35 years of age as a cut-off level, only 30% of Down syndrome cases in the normal population could be detected and 70% of them would be missed (1). Second trimester serum biochemical screening also known as the triple test, including alpha fetal protein (AFP), unconjugated estriol (E_3) and human chorionic gonadotrophin (hCG) had been offered in the 1980's and been used worldwide thereafter. The triple test has detected 66-77% of Down syndrome cases at a 5% false positive rate (2,3).

In 1985, Benacerraf et al. had reported about the increased soft tissue at the back of the fetal neck in Down syndrome cases in the second trimester of pregnancy (4). Introduction of the term nuchal translucency (NT) by Nicolaides to the medical literature in 1992 had led the way to first-trimester screening (5). It has been shown that first-trimester screening using NT and biochemical markers such as maternal serum free-β-human chorionic gonadotropin (hCG) and pregnancy-associated plasma protein-A (PAPP-A) have a 90% detection rate of Down syndrome with a 5% false positive rate (6). This high detection rate of Down syndrome in the first trimester has turned the

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faces to the first-trimester ultrasonography to detect other chromosomal abnormalities as well as Down syndrome.

Ultrasonographic parameters used to detect chromosomal abnormalities in the first trimester are described below.

Nuchal Translucency (NT):
Fetal NT defines the subcutaneous fluid collection in the fetal neck with or without any septation and whether it is limited to the fetal neck or surrounds the whole body in the first trimester of pregnancy (5). The measurement of NT thickness should be performed between 11 weeks and 13 weeks and 6 days gestational age according to the last menstrual period (8). If the last menstrual period is suspicious fetal crown-rump length (CRL) should be between 45 and 84 mm while performing the fetal NT measurement (8). Either transabdominal or transvaginal methods could be used for fetal NT measurement (9). For the measurement, a sagittal section image of the fetus in the largest magnification including fetal head and upper thorax in the neutral position should be obtained (Figure 1). The calipers (+) should be located on the inner borders of the NT, between the soft tissue over the cervical spine and the skin. While locating the caliper on the fetal skin, the sonographer should take into account that the amniotic membrane is separated from the fetal skin. The calipers should measure the maximum NT thickness perpendicular to the long axis of the body. The calipers should be sensitive to a 0.1 mm change in every movement. Multiple measurements should be performed and the maximum one should be taken for the analysis (10). Also, the length of NT has a correlation with its thickness but the length has no use in the detection of chromosomal anomalies (11).

There are a few reasons to perform the NT measurement between 11 weeks and 13 weeks and 6 days. Firstly, it is easy to achieve a neutral position of the fetus, abnormal nuchal thickness related to fluid accumulation is less, chorion villus sampling can be performed if necessary and termination is safer early in pregnancy. Additionally, it is hard to detect other major anomalies such as acrania, anencephaly before 11 weeks and it is also possible and safer to detect 4-chamber view of the heart, main arteries and exomphalos as well as visualization of bladder in this period of pregnancy (10).

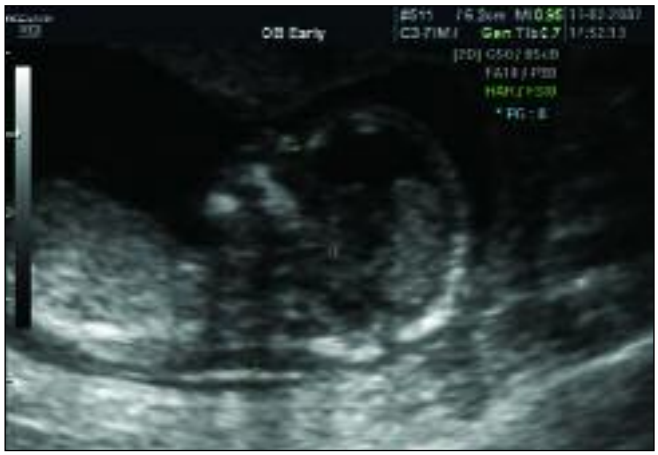

Figure 1. Nuchal translucency (bold arrow) and nasal bone (arrow) are demonstrated in a chromosomally normal fetus.

The median and percentile values of fetal NT thickness for a CRL are determined because the fetal NT thickness increases with CRL (8). The median and 95th percentile values of fetal NT for 45 mm CRL are 1.2 and 2.1 mm and for 84 mm CRL are 1.9 and 2.7 mm respectively. The 99th percentile value of fetal NT is not influenced by CRL and it is 3.5 mm.
Ethnicity, parity, gravidity, smoking, diabetic control, assisted reproduction technologies, bleeding in early pregnancy or fetal gender do not affect fetal NT thickness (12,13,14,15, 16,17,18,19). The umbilical cord around the fetal neck can cause approximately 0.8 mm false increase of fetal NT (20).

The proposed mechanisms for NT thickness are summarized below.
1- Cardiac dysfunction (21)
2- Venous congestion in the head and fetal neck (amnion rupture sequence, diaphragmatic hernia, skeletal dysplasias, body stalk anomaly) (22,23,24)
3- Altered composition of the extracellular matrix (25)
4- Failure of lymphatic system (26)
5- Fetal anemia (α–thalassemia, Blackfan–Diamond anemia, dyserythropoietic anemia, Fanconi anemia, congenital erythropoietic porphyria) (27,28,29,30)
5- Fetal hypoproteinemia (congenital nephritic syndrome) (30)
6- Fetal infection (parvovirus B19) (31)

Increased NT thickness was found to be associated with trisomy 21, trisomy 18, trisomy 13, Turner syndrome, triploidy, other chromosomal abnormalities, fetal malformations and genetic syndromes in previous reports (10,23). The NT thickness was found to be less then 4.5 mm in fetuses with trisomy 21 and triploidy, between 4.5-8.5 mm in fetuses with trisomy 13 or 18 and higher than 8.5 mm in fetuses with Turner syndrome (32). Increased NT thickness alone can detect 75% of fetuses with trisomy 21 and other chromosomal abnormalities with a false positive rate of 5% (33). This represents a greater achievement rather than maternal age alone and triple test, which have a detection rate of 30% and 65% respectively. Also it was reported that advanced maternal age and increased NT thickness was associated with chromosomal abnormalities, but low NT thickness lowered the risks associated with advanced maternal age (34). For an increased NT the likelihood ratio (LR) that a fetus should have trisomy 21 was 13.2 and for a normal NT the negative LR was 0.25 (1).

Combination of maternal age, fetal NT thickness and serum biochemistry including maternal serum free-β-hCG and PAPP-A between 11 weeks to 13 weeks and 6 days known as first-trimester screening test has a detection rate of 90% of trisomy 21 with a false positive rate of 5% (6,7). Also first-trimester screening test can detect 90% of other chromosomal abnormalities (trisomies 18, 13, Turner syndrome and triploidy). Maternal serum free-β-hCG and PAPP-A levels for chromosomal anomalies are given in Table 1 (34).

Measurement of NT thickness in dichorionic twin pregnancies is effective for screening of chromosomal abnormalities and

by using a combination of fetal NT and maternal serum free-β-hCG and PAPP-A levels can detect 85-90% of trisomy 21 pregnancies with a false positive rate of 10% (35). Although in monochorionic twins, due to early onset twin-twin transfusion syndrome, increased NT thickness has a higher false positive detection rate (8% for each fetus and 14% for pregnancy) of chromosomal abnormalities, the average risk calculated should be taken as the risk of pregnancy (36).

The consequence of increased NT thickness after 13 weeks and 6 days is lessening, but in few cases it merges into nuchal edema or cystic higroma (23). The terms cystic higroma and nuchal edema defines the abnormal fluid collection behind the fetal neck in the second or third trimester of pregnancy (37). Cystic higromas usually presents as cystic, septated dilatations surrounding the fetal neck in the ultrasonography (38), and they were believed to be the dilatation of jugular lymphatic sacs due to the failure of drainage (37). About 75% of cystic higromas are related to chromosomal abnormalities and 95% of them are associated with Turner syndrome (10). If the chromosomes are normal, the obstetrician must be careful about cardiac defects and genetic syndromes. However, cystic higromas have a poor prognosis and survival is less than 5% (37). The term nuchal edema describes the nuchal translucency thickening of 6 mm or more. Nuchal edema may be limited to the fetal neck or it may be generalized in fetuses with hydrops fetalis (37). One third of fetuses with nuchal edema are associated with chromosomal abnormalities, especially with trisomies 21, 18 and 13. Furthermore, nuchal edema can be seen in cardiac, pulmonary, skeletal, metabolic, hematological disorders and congenital infections. The prognosis of nuchal edema is also poor, even in fetuses with normal chromosomes (39).

Increased NT thickness in chromosomally normal fetuses is also associated with major fetal abnormalities. The prevalence of those abnormalities is 1.6% for NT below 95th centile, 2.5% for 95-99th centiles and 45% for NT above 6.5 mm (40). Also fetal death and miscarriage incidence increases with NT in chromosomally normal fetuses from 1.3% for NT below 99th centile, to about 20% for NT above 6.5 mm (41). In addition, the prevalence of major cardiac defects irrespective of specific typing increases with fetal NT and if it is above 3.5 mm the risk is more than the previous family history of cardiac defects (21).

Commonly used ultrasonographic markers for the detection of Trisomy 21 are described below.

Table 1. Changes in maternal serum free-β-hCG and PAPP-A levels in different chromosomal abnormalties

Chromosomal Abnormality	Free-β-hCG	PAPP-A
Trisomy 21	Increased	Decreased
Trisomy 18	Decreased	Decreased
Trisomy 13	Decreased	Decreased
Turner	Normal	Decreased
Diandric Triploidy	Increased	Decreased
Digynic Triploidy	Decreased	Decreased

1- Nasal Bone:

It was demonstrated in previous studies that 65% of fetuses with trisomy 21, 55% of fetuses with trisomy 18, 35% of fetuses with trisomy 13, 10% of fetuses with Turner syndrome, 5% of fetuses with sex chromosomal abnormalities and 1% of fetuses with normal karyotype had absent or hypoplasic nasal bone (41,42). The fetal nasal bone should be visualized and measured at 11 to 13 weeks and 6 days of gestation, because the nasal bone ossification does not start before 11 weeks of gestation (43). A midsagittal section of the fetus only including the head and upper thorax and the longitudinal axis of the nasal bone perpendicular to the ultrasound transducer (90° insonation angle) should be obtained. When the proper position is obtained, the ultrasound transducer should be tilted from one side to the other to get the exact image of the nasal bone (44). Three echogenic lines should be visualized: The skin over nasal bridge, nasal bone and the skin over nasal tip (Figure 1). The skin over nasal bridge lies above horizontal and parallel to the nasal bone and these two parallel echogenic lines are termed as "equal sign" (43,44). The equal sign should be detected in front of the forehead. The nasal bone is thicker and more echogenic than the overlying skin. A little far and above the nasal bridge, the third echogenic line as a part of the skin is located as the skin over the nasal tip (43,44). If the angle between the transducer and the longitudinal axis of the nasal bone is 0° or 180° it will be detected artificially absent (43). If the nasal bone under the skin over nasal bridge is less echogenic or presented as a small echogenic spot or if there is no echogenity it is considered as absent. If the nasal bone is absent between 11 and 12 weeks it is recommended to make a re-evaluation in 1 week. The obstetrician should also avoid fetal hands by the fetal face not to make false positive or false negative measurements (43). It was also reported that the prevalence of absent nasal bone decreased with increasing fetal CRL, increased with NT thickness and is more common in Afro-Caribbean societies (42). Nasal bone examination can be incorporated to the first-trimester screening in two ways. First, it can be included in the first-trimester screening. Thus, it has been calculated that, if the absence or presence of nasal bone were added to the routine first-trimester screening the detection rate of trisomy 21 would reach to more than 95% with a false positive rate of 5% or to a detection rate of 90% with a false positive rate of 2.5% (44, 45). Secondly, examination of the nasal bone is a time consuming event and the obstetrician needs must be well experienced such that it should be performed only in patients in the intermediate-risk group according to the first-trimester screening result (44).

The risk groups for first-trimester screening are discussed below.

2- Tricuspid Regurgitation:

Tricuspid regurgitation was found in 70% of fetuses with trisomy 21, 50% of fetuses with trisomy 18 or 13 and 5% of normal fetuses between 11 to 13+6 weeks of gestation (34,46). Tricuspid regurgitation is determined by using pulsed wave Doppler. To detect the absence or presence of a tricuspid regurgitation, first of all an apical four-chamber view is obtained

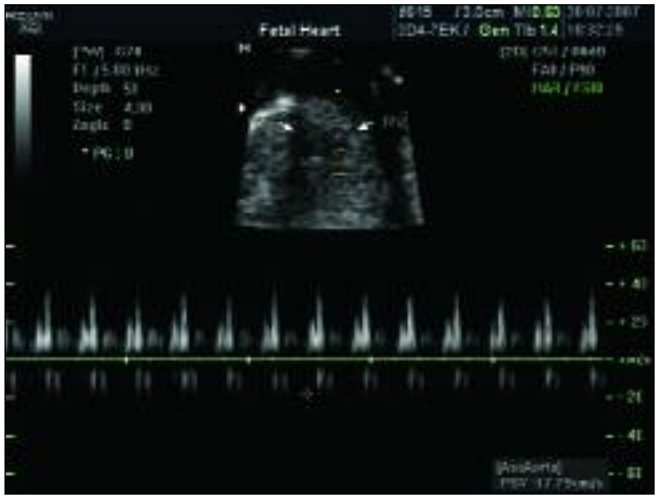

Figure 2. Normal tricuspid flow with no regurgitation in a healthy fetus. Note that the Doppler sample volume is positioned across the tricuspid valve including right atrium and ventricle (RV: right ventricle, LV: left ventricle).

and than the Doppler sample volume is located across the tricuspid valve including the right atrium and ventricle with an angle of less than a 30° to the flow direction (46,47) (Figure 2). The presence of regurgitation is determined as a minimum velocity of over 60 cm/s during the half of the systole (47). The sonographer must be very careful about a false regurgitation up to 50 cm/s that can be caused by aorta or pulmonary artery, or by a reverse spike caused by the closure of the tricuspid valve (48). If tricuspid regurgitation is detected, the sonographer should always keep in mind that the risk for cardiac defects are increased. Combining fetal NT, maternal serum free-β-hCG and PAPP-A with tricuspid regurgitation could improve the trisomy 21 detection rate to 95% with a false positive rate of 5% or a detection rate of 90% with a false positive rate of 2% (47). Assessment of tricuspid regurgitation can be performed as part of routine first-trimester scan or it can be reserved as further research for the intermediate-risk group according to the first-trimester screening test results (48).

3- Ductus Venosus Flow Velocity Waveform:

Another new first-trimester screening marker in 11 to 13+6 weeks of gestation is ductus venosus flow-velocity waveform (DV-FVW). Ductus venosus (DV) is a functional blood vessel during intrauterine life that provides a means for oxygenated blood from umbilical vein to inferior vena cava (IVC) to bypass the liver (1). DV enters into IVC before the entrance of IVC into the right atrium. The DV-FVW pattern is found to be abnormal in 80% of fetuses with trisomy 21 and 5% of euploid fetuses (49). A right ventral mid-sagittal section of fetal trunk is obtained and using color Doppler DV is identified. The pulsed Doppler gate is located in the inlet of DV and classic triphasic DV-FVW is obtained (Figure 3). The normal DV-FVW is pulsatile concurrently with a forward flow (50). Abnormal DV is determined when the flow seems absent or is reversed during atrial contraction in late diastole (A-wave) (51). This abnormal DV-FVW pattern is also associated with major cardiac defects as well as tricuspid regurgitation (51,46).

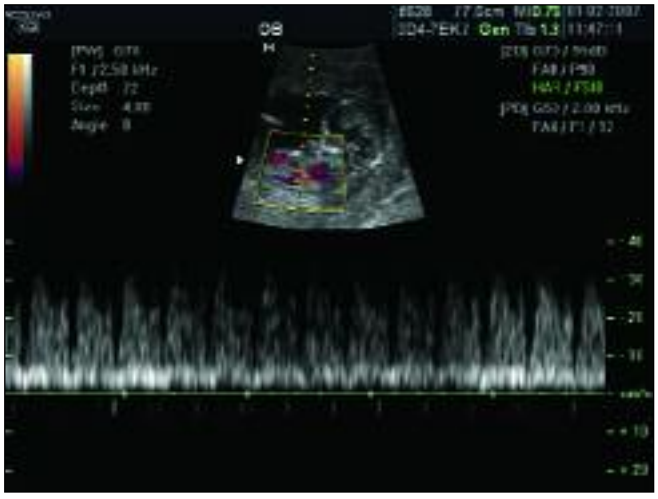

Figure 3. Normal ductus venosus flow pattern in a chromosomally normal fetus.

4- Frontomaxillary Facial Angle:

The frontomaxillary facial (FMF) angle is a new promising sonographic marker between 11 to 13+6 weeks gestation for trisomy 21. The FMF angle is found to be above 85° in 69% of trisomy 21 fetuses and in 5% of normal fetuses (52). A midsagittal plane showing maxilla is obtained. The FMF angle is defined as the angle between two imaginary lines that transverse the upper surface of the maxilla and the external surface of the frontal bone (Figure 4) (52). There is no significant association between the FMF angle, CRL, NT and the presence or absence of nasal bone. Therefore, FMF angle should be used to reduce false-positive ratios (53). Three-dimensional ultrasonography is used in the innovator studies but prospective studies using two-dimensional ultrasonography is ongoing. Nomogram for fetal maxillary bone for first-trimester of pregnancy in Turkish population has been determined and ready for clinical studies (54).

These sonographic markers are used to reduce the false positive ratio in detecting trisomy 21 fetuses.

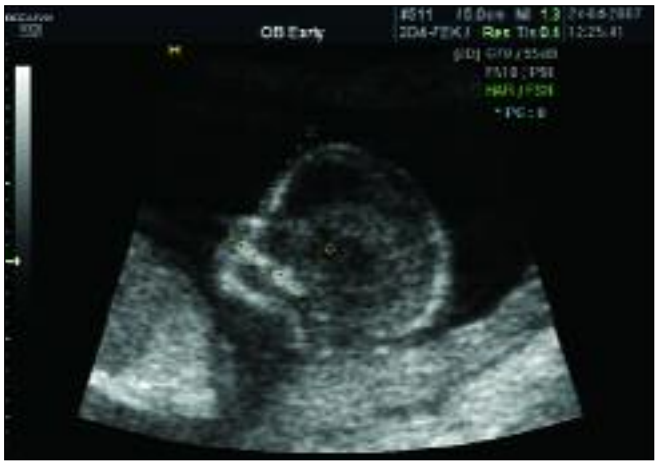

Figure 4. The FMF angle between maxilla and frontal bones which is smaller than 90° in a healthy fetus.

Determination of risk categories due to first-trimester screening test results:
Nicolaides et al. described a new individual risk-orientated two-stage approach for first-trimester screening according to the results of a multicenter study (49). In the first stage, the risk is calculated using a combination of the maternal age, NT and maternal serum free-β-hCG and PAPP-A. Estimated maternal age-related risk is recalculated by multiplying with each LR for NT and maternal weight-adjusted serum free- β-hCG and PAPP-A. The maximum and minimum LR is between 0.12 and 55 for NT, 0.018 and 7.138 for each maternal serum marker and 0.1 and 80 for the combined sonographic and biochemical markers. If the estimated risk is 1 in 100 or more, associated with the high risk group, chorionic villus sampling or amniocentesis should be offered to all parents. If the estimated risk is less than 1 in 1000 associated with the low risk group, no need for invasive testing and routine follow up should be performed. If the estimated risk is between 1 in 101 and 1 in 1000 associated with the intermeadiate risk group, than the risk is reevaluated as a second stage approach using the LR for absence of nasal bone, abnormal DV-FVW and tricuspid regurgitation. The LR for absence of nasal bone is 49.3, for abnormal DV-FVW is 16.5 and for tricuspid regurgitation is 12.9. The LR for each of these markers is greater than 10 and the readjusted risk would be at least 1 in 100. Therefore, if one of these markers is positive than CVS or amniocentesis should be offered to the parents. If all of these markers are negative than the patient should be re-evaluated in the low risk group.

The effort to detect chromosomal abnormalities in the first trimester of pregnancy has led the investigators to check many sonographic markers like CRL, maxillary length, ear length, femur length, humerus length, single umbilical artery, bladder length, exomphalos, choroid plexus cysts, pyelectasis, hiperechogenic cardiac foci, placental volume, fetal heart rate, and Doppler assessments have been studied (10,55,56,57,58). Detection of an abnormality in each of these markers has a relation with chromosomal abnormalities but none of them alone can detect a chromosomal abnormality and any of them could be detected in normality. The relation between some of these sonographic markers and chromosomal abnormalities are summarized in Table 2.

In women whose gestation exceeds 13 weeks and 6 days or the CRL measurement greater than 84 mm should be offered a triple test. If the calculated risk is greater than 1/270 as a result of triple test, the parents should be offered amniocentesis. Whether first-trimester screen or triple test is normal or missed, women should be called for 18-23 weeks mid-trimester genetic sonogram (59). Common sonographic markers of Trisomy 21, Trisomy 18, Trisomy 13, Turner syndrome and triploidy are summarized in Table 3 (60,61).

Recently, The American College of Obstetrics and Gynecology (ACOG) reported a new practice bulletin for Down syndrome screening for pregnant women of all ages (62). ACOG has changed the previous offer that all women who of 35 years and older should have genetic amniocentesis or CVS. Also, ACOG has advised that all women should optionally choose diagnostic tests like amniocentesis or CVS. ACOG has offered that all pregnant women regardless of their age should attend to the first-trimester screening test. If a pregnancy were found to be at increased risk for chromosomal abnormalities than the women should be offered diagnostic testing. ACOG also offered neural tube defect screening in the mid-trimester to women who choose first-trimester screening.

Also, in Turkey the Maternal Fetal Medicine & Perinatology Society and the Turkish Perinatology Society (accessible fromhttp://www.tmfmp.org/society/ and http://www.perinatology.org.tr/) have recommended the first-trimester screening test for all pregnancies.

In conclusion, first-trimester screening using fetal NT and serum biochemical markers have a high detection rate of fetuses with trisomy 21, 18, 13, Turner syndrome and triploidy. Adding other sonographic markers like nasal bone, tricuspid regurgitation, ductus venosus blood flow wave form and frontomaxillary facial angle can improve this detection rate. Also, the advantage of getting early results makes the first-trimester test preferable over second trimester test. Whether the screening test results are positive or negative all women should be offered the mid-trimester genetic sonogram.

Table 2. Some sonographic markers and their relation with chromosomal abnormalities

Sonographic Marker	Trisomy 21	Trisomy 18	Trisomy 13	Turner	Triploidy
CRL	Normal	Moderate restriction	Mild restriction	Mild restriction	Moderate restriction
Maxilla length	Smaller				
Ear length	Smaller				
Femur and humerus length	Smaller				
Single umblical artery		Risk is 7 times higher			
Megacystis		Increase the LR by a factor of 6.7	Increase the LR by a factor of 6.7		
Exomphalos		+			
Placental volume		Decreased			
Fetal heart rate		Bradycardia	Tachycardia	Tachycardia	Bradycardia
Pulsatile umblical venous flow		+	+		

Table 3. Sonographic markers of chromosomal abnormalities

	Trisomy 21	Trisomy 18	Trisomy 13	Turner	Triploidy
Strawberry-shaped head	–	+	–	–	–
Ventriculomegaly	+	+	+	–	+
Holoprosencephaly	–	–	+	–	–
Dandy-Walker complex	–	+	+	–	–
Mega cisterna magna	–	+	–	–	–
Corpus callosum agenesia	–	+	–	–	–
Brachycephaly	+	+	–	+	–
Microcephaly	–	–	+	–	–
Spina bifida	–	+	–	–	–
Nasal bone hypoplasia	+	–	–	–	–
Nuchal edema	+	+	+	–	–
Cystic hygroma	–	–	–	+	–
Facial cleft	–	+	+	–	–
Micrognathia	–	+	–	–	+
Duodenal atresia	+	–	–	–	–
Esophageal atresia	+	+	–	–	–
Diaphragmatic hernia	–	+	+	–	–
Cardiac abnormalities	+	+	+	+	+
Pleural effusion	–	–	–	+	–
Generalized edema	–	–	–	+	–
Exomphalos	–	+	+	–	–
Renal abnormalities	+	+	+	+	+
Hyperechogenic bowels	+	–	–	–	–
Short limbs	+	+	–	+	+
Radius aplasia	–	+	–	–	–
Clinodactyly	+	–	–	–	–
Clenched hands	–	+	–	–	–
Polydactyly	–	–	+	–	–
Syndactyly	–	–	–	–	+
Talipes equinovarus	–	+	+	–	+
Rocker-bottom foot	–	+	–	–	+
Sandal gap	+	–	–	–	–
Fetal growth restriction	–	+	–	+	+
Single umbilical artery	–	+	–	–	–
Placental abnormalities	–	–	–	–	+

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