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**Sonographic markers for early diagnosis of fetal malformations**

**Renna MD *et al.*** Ultrasound in prenatal diagnosis

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**Abstract**

Fetal malformations are very frequent in industrialized countries. Although advanced maternal age may affect pregnancy outcome adversely, 80%-90% of fetal malformations occur in absence of specific risk factor for parents. The only effective approach for prenatal screening is currently represented by ultrasound scan. However, ultrasound methods present two important limitations: the substantial absence of quantitative parameters and the dependence from the sonographer experience. In recent years, together with the improvement in transducer technology, quantitative and objective sonographic markers highly predictive of fetal malformations have been developed. These markers can be detected early in the gestation (at 11-14 wk) and, generally, are not pathologic theirself, but have an increased incidence in abnormal fetuses. Thus, prenatal ultrasonography during the second trimester of gestation provides a “genetic sonogram”, including for instance nuchal translucency, short humeral length, echogenic bowel, echogenic intracardiac focus, choroid plexus cyst, that is used to identify morphologic features of fetal Down syndrome with a potential sensitivity of more of 90%. Other specific and sensitive markers can be seen in the case of cardiac defects and skeletal anomalies. In the future, sonographic markers could ever more limit the use of invasive and dangerous techniques of prenatal diagnosis (amniocentesis, *etc.*).

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**Key words:** prenatal diagnosis; prenatal sonography; chromosome abnormalities; nuchal translucency; fetal echocardiography; skeletal dysplasia

**Core tip:** The aim of this paper is to review sonographic markers associated with the most frequent fetal abnormalities (chromosomal anomalies, cardiac defects, skeletal dysplasia) and their sensitivity in prenatal diagnosis. Fetal malformations are very frequent in industrialized countries and the only effective approach for prenatal screening is currently represented by ultrasound scan. Early detection of abnormalities can optimize pregnancy management and childbirth timing, give the possibility of performing simpler procedures for termination of pregnancy in those patients in whom findings are abnormal and plan therapeutic treatment of objectively selected diseased fetuses.

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**Introduction**

Congenital malformations of different type and severity occur in 2%-3% of fetuses in industrialized countries, leading to perinatal death in 25%-30% of cases, and these percentages are increasing mainly because of the marked increment of pregnancies in women older than 40 years. However, although advanced maternal age may affect pregnancy outcome adversely, with increased miscarriages, ectopic pregnancies, twinning, fetal and chromosomal abnormalities, low birth weight and prematurity, 80%-90% of fetal malformations occur in presence of parents that did not show any specific risk factor. A further cause of legal litigations starting in the delivery room is represented by the unexpected birth of a disabled child: in such cases parents often denounce the gynaecologist that did not provide a prenatal malformation diagnosis, but it is clear that ultrasound (US) potential in the field of obstetrics and gynecology is still far from being fully exploited. The only effective approach for prenatal screening is currently represented by prenatal US examinations[1], being the only possible way to reduce both child disability and perinatal mortality through early malformation diagnosis. US techniques definitely have the potential to provide accurate early diagnosis of fetal malformations, but their employment is significantly hindered by two main limitations: the substantial absence of fully objective approaches and the very low number of available quantitative parameters. It is also clear that pregnancy management needs new approaches and new guidelines to rely on, exploiting objective indications through suitable methods and technologies for standardized quantitative monitoring and appropriate medical decision taking[2]. Quantitative monitoring of pregnancy is improving by the use of sonographic markers that are objective and predictive of specific fetal malformations becoming a powerful tool of prenatal diagnosis.

Early detection of abnormalities can optimize pregnancy management and childbirth timing, in case timely addressing the pregnant woman to specialized facilities for specific disease treatment.

***The state of art***

US monitoring of pregnancy consists of at least three scans, one for each trimester of gestation. The most important US examination for the study of fetal anatomy is the second trimester scan[3], whose sensitivity in different malformation detection is anyway highly variable: 70%-90% for central nervous system malformations, 40%-50% for heart disease (*e.g.,* aorta coarctation), 25%-70% for urinary tract, 46%–100% for abdomen and gastrointestinal abnormalities (*e.g.,* obstructive anomalies, omphalocele or gastroschisis), 20%-50% for bone dysplasias (*e.g.,* spina bifida, limb reduction defects), 7%–55% for cleft lip and palate[4]. US examination in the second trimester may show markers of suspected chromosomopathies, with a detection rate of 16%–45%[5], but until now its actual clinical usefulness is limited to an indication for more accurate but also more invasive cytogenetic tests[6] (Figure 1). However, invasive testing with a detection rate of 95%, such as amniocentesis, chorionic villus sampling or cordocentesis, is associated with a risk of miscarriage of about 1%-2%. Moreover, the false positive rate of about 0.2% is calculated only on a 20% of women selected to receive DNA testing. If all pregnant women had DNA testing, the false-positive rate would be 30 times greater. Therefore, cytogenetic tests are carried out only in pregnancies considered to be at high-risk for chromosomal defects[7,8].

Then, on the one hand, the effectiveness of available US methods for prenatal malformation diagnosis is limited by a number of factors, as period of gestation, variability of the fetal morphogenesis, natural history of the disease, thickness of maternal abdominal wall, possible unfavorable fetus position, but, above all, by the absence of objective parameters for most malformation types and by the strong dependence on operator experience[9]. On the other hand, US examinations are non-invasive and safe, and there is a growing international interest in the development of new methods for US detection of malformations, driven also by recent improvements in transducer technology that through increased lateral resolutions and optimized transvaginal probes[2] has enabled examinations of first trimester fetus with unprecedented level of detail. As a consequence, since the introduction of these technologies together with quantitative sonographic markers, there have been advances in first trimester prenatal diagnosis of major fetal anomalies, in particular concerning chromosomal abnormalities (80% detection rate), cardiac defects (57% detection rate) and skeletal anomalies (69% detection rate)[10,11].

**Chromosomal abnormalities**

The main part of fetal malformations are related to chromosomal abnormalities that occur in 0.1% to 0.5% of live births[12,13]. The risk for many of the chromosomal defects increases with maternal age. Additionally, because fetuses with chromosomal defects are more likely to die *in utero* than normal fetuses, the risk decreases with gestation[7]. There is a great deal of interest in the US detection of aneuploidy and second trimester US scan is able to detect, prior to karyotyping, two types of sonographic markers suggestive of aneuploidy[12]. The first group includes those that have a high rate of association with fetal chromosome abnormalities whether in isolation or present with multiple other sonographic anomalies; and the second includes those that are much more likely to have associated chromosome abnormalities when seen in combination with other markers than in isolation[14].

Examples of data for the latter group are ventriculomegaly, 2% (isolated) *vs* 17% (combined with other anomalies); holoprosencephaly, 4% *vs* 39%; choroid plexus cyst, 1% *vs* 48%; posterior fossa cyst, 0% *vs* 52%; facial clefting, 0% *vs* 51%; micrognathia, unknown percentage *vs* 62%; diaphragmatic hernia, 2% *vs* 49%; echogenic bowel, 7% *vs* 42%; renal abnormalities, 3% *vs* 24%; and exomphalos, 8% *vs* 46%. Examples of the former group are cystic hygroma, 52% *vs* 71%; nuchal edema, 19% *vs* 45%; duodenal atresia, 38% *vs* 64%; and in a less pronounced way for cardiac defects, 16 %*vs* 66%[15].

Multiple anomaly associations, in particular cardiovascular anomalies together with other markers are a more powerful indicator of aneuploidy[14]. Sonographically detectable aneuploidies include Down syndrome (trisomy 21), trisomy 13 and 18, Turner syndrome (monosomy X), and triploidy.

***Sonographic markers of Down syndrome***

The most common clinically significant aneuploidy among live-born infants is Down syndrome with an estimated prevalence of 1.21 in 1000 live births[16]. Trisomy 21 is associated with a tendency for brachycephaly, mild ventriculomegaly, nasal hypoplasia, cardiac defects (mainly atrioventricular septal defects), duodenal atresia and echogenic bowel, mild hydronephrosis, shortening of the femur and more so of the humerus, sandal gap and clinodactyly or mid-phalanx hypoplasia of the fifth finger[7]. There are different screening methods to identify this ‘‘high risk group’’: advanced maternal age, maternal serum biochemical screening in the first and second trimester, and US screening in the first and second trimester[17]. US screening has recently been shown to decrease the prevalence of fetal Down syndrome in the second trimester to less than 85% by early identification of affected fetuses[18]. Sonographic findings in fetuses with Down syndrome or another detectable aneuploidy include both structural abnormalities and nonstructural abnormalities or “markers.” These markers are not pathologic themselves, but have an increased incidence in infants with chromosomal abnormalities, and can be readily detected during the second-trimester US scan, although they are nonspecific and often transient.

The first reported marker associated with Down syndrome was the thickening of the neck area (nuchal fold)[19]: 40%–50% of affected fetuses have, in second-trimester, a thickened nuchal fold measuring ≥ 6 mm, with a false-positive rate of 0.1%[20,21]. Nicolaides, subsequently, developed the measurement of the fetal nuchal soft tissues for use in the first-trimester, calling it the nuchal translucency (NT) and measuring it in the longitudinal midline plane of the fetus, using a very standardized technique (Figure 2B). NT is defined as the transient subcutaneous collection of fluid behind the fetal neck seen ultrasonographically at 11-14 wk and became a highly specific marker of Down syndrome. After the introduction of screening by NT, 83% of trisomy 21 pregnancies were identified in the first trimester[22]. Later, it was demonstrated that screening by a combination of maternal age, fetal NT and bi-test [pregnancy-associated plasma protein (PAPP-A) with second-trimester free chorionic gonadotropin (β-hCG)] or tri-test [alpha-fetoproteina (AFP), estriol and free β-hCG], has a potential sensitivity of 94% for a 5% false-positive rate[23].

In addition to nuchal thickening, sonographic findings that are generally accepted as potential markers of trisomy 21 during the second trimester include shortened femur or humerus, renal pyelectasis, hyperechoic bowel, echogenic intracardiac focus, and, recently, nasal bone ossification[24]. The effectiveness of these markers will be detailed below (Table 1).

Ultrasound studies have shown that fetuses with Down syndrome have a shorter femur and even shorter humerus when compared with normal fetuses[18]. The sensitivity for detecting trisomy 21 using the femoral length is 40%–50%, with a false-positive rate of up to 7%[25,26]. The humeral length is considered a slightly more efficient marker, with a sensitivity of 50%–54% and a false-positive rate of 5%–6%[27-29]. Combination of humeral length and nuchal fold increases the sensitivity to 75%, without substantially changing the false-positive rate based on humeral length alone[18,30].

Pyelectasis, defined as a diameter of the renal pelvis measuring ≥ 4 mm, is another second-trimester marker, in fact renal dilatation has a higher incidence among fetuses with Down syndrome. However, pyelectasis remains a minor marker because the sensitivity is 17%–25%, with a false-positive rate of 2%–3%[31,32].

The sensitivity of hyperechoic bowel in Down syndrome ranges from 3.3% to 27% in dependence of the sonographer and of the frequency of the US transducer[33,34,35,36]. Its false-positive rate is less than 1%[33,37]. Hyperechoic bowel also conveys an increased risk of cystic fibrosis, cytomegalovirus, and severe early growth issues[18].

The echogenic intracardiac focus is the least efficient marker among those that we use for detecting Down syndrome. It occurs in 16% of fetuses with Down syndrome, 29% of those with trisomy 13, and 2% of normal fetuses[38]. A recent study also confirms that the finding of an isolated echogenic intracardiac focus on prenatal sonography does not significantly increase the risk for fetal trisomy 21[39]. The false-positive rate is 17%[40].

In literature, there are important examples of soft markers that have been successfully incorporated into fetal abnormality screening. It’s the case of the nasal bone that is the newest and most powerful marker (Figure 2A). The absence of nasal bone in fetus at the 11-14 wk scan is related to Down syndrome (Figure 2B); this marker, initially, was found in 73% of trisomy 21 fetuses and in only 0.5% of chromosomally normal fetuses[41] and, subsequently, it was estimated that the combination of maternal age, nuchal translucency, maternal serum biochemical screening (by bi-test or tri-test) and examination of nasal bone could increase the detection rate to 97%[42]. After the completion of further confirmation studies, it is generally accepted that fetal nasal bone is a very good sonographic marker, even if there are racial differences in the length of this bone[43,44].

Furthermore, there are minor markers of Down syndrome less used to screen the general population. These include iliac angle, specific cardiac features, choroid plexus cysts and others. The mean iliac wing angle is a useful marker in prenatal screening in the fetuses with trisomy 21. A recent study demonstrates that in affected fetuses it is 90.32°, significantly higher than those seen in fetuses with normal karyotype in which the mean iliac wing angle was 63.72°[45]. The specific cardiac features associated with an increased risk of Down syndrome are primarily ventricular disproportion and the presence of septal defects[18]. In addition, the phenomenon of tricuspid regurgitation is highly associated and its prevalence increases with the NT[46]. Other findings suggest that the mitral valve–tricuspid valve distance could prove useful as an additional marker at the time of the second trimester sonogram. It increases with gestational age and is lower in fetuses with trisomy 21[47].Fetal aberrant right subclavian artery is another potential marker, because, in a small group, its prevalence in fetuses with Down syndrome is 37.5% *vs* 1.4% in low-risk population[48]. Choroid plexus cysts were suggested as a possible minor marker, but it has been demonstrated that the risk of Down syndrome is not raised in their presence[49,50]. Anyway, choroid plexus cysts are a well-known marker for trisomy 18. Finally, ear length at 11-14 wk of gestation has been evaluated in screening for chromosomal defects, but the degree of deviation from normal is too small for this measurement to be useful as a marker for trisomy 21[51].

***Other aneuploidies***

Trisomy 18 is the second most common autosomal trisomy syndrome after trisomy 21. The estimated prevalence is of 1 in 6000-8000 live births, but the overall prevalence is higher (1 in 2500-2600) due to the high frequency of fetal loss and pregnancy termination after prenatal diagnosis. Currently most cases of trisomy 18 are prenatally diagnosed, based on screening by maternal age, maternal serum marker screening, or detection of sonographic abnormalities. The prenatal sonographic pattern of trisomy 18 is characterized by growth retardation, polyhydramnios, “strawberry-shaped” cranium, choroid plexus cyst, absent corpus callosum, enlarged cisterna magna, facial cleft, micrognathia, nuchal edema, heart defects, diaphragmatic hernia, esophageal atresia, overlapping of hands fingers, congenital heart defects, omphalocele, renal defects, echogenic bowel and single umbilical artery[52-55]. The prevalence of growth retardation and polyhydramnios increases with gestational age: 28% and 29% in the second trimester and 87% and 62% in the third trimester, respectively[56]. In particular, choroid plexus cyst is detected in about 50% of trisomy 18 fetuses, while hands abnormalities, exomphalos and single umbilical artery have been found in more than 30% of affected fetuses[55,56]. The most common soft sonographic markers detected in the early second trimester are, as in Down syndrome, the increased nuchal translucency thickness and the absence or hypoplasia of the nasal bone[57,58]; the screening by assessment of nuchal fold and nasal bone identifies 66.7% of cases with trisomy 18 (and 13)[58]. Combinig nuchal translucency with bi-test or tri-test sensitivity is at least 78%[59,60]. Anyway, one or more sonographic anomalies are detected in over 90% of fetuses; two or more abnormalities are present in 55% of cases[61].

In trisomy 13, common defects include holoprosencephaly and associated facial abnormalities, microcephaly, cardiac and renal abnormalities with often enlarged and echogenic kidneys, exomphalos and postaxial polydactyly[7]. In particular, among craniofacial malformations detected by prenatal sonography, cleft deformities are found in 65.2% and ocular and orbital abnormalities were found in 28%[62]. Fetal tachycardia is observed in about two-thirds of cases and early-onset intrauterine growth restriction in about 30% of cases[63]. In trisomy 13, as well as in trisomy 18, maternal serum free β-hCG and PAPP-A are decreased[7,63,64].

Turner syndrome, usually due to loss of the paternal X chromosome, is the most common monosomy (45, X) in the fetus with a prevalence of 25-55 cases per 100000 females and, unlike that of trisomies, is unrelated to maternal age[66]. Characteristic sonographic markers are highly predictive in early pregnancy: huge septated cystic hygroma, hydrops, subcutaneous edema, narrowed aortic arch, renal anomalies and short femur are detected in about 90% of affected fetuses. Some studies have reported that fetuses with Turner syndrome have cystic much larger than in trisomy 18 or trisomy 21[67]. The classic webbed neck in Turner syndrome is probably the end result of the huge fetal cystic hygroma. Coarctation of the aorta is observed in approximately 20% of the affected fetuses at 14 to 16 weeks of gestation[68], and tachycardia observed in about 50% of cases.

Polyploidy is extremely rare and lethal and affects about 2% of recognized conceptions. In particular, triploidy is associated with molar placenta if the extra set of chromosomes is paternally derived. While, in case of double maternal chromosome contribution, the fetus demonstrates severe asymmetrical growth restriction. Ventriculomegaly, micrognathia, cardiac abnormalities, myelomeningocele, syndactyly are also common[7].

**CONGENITAL HEART DISEASES**

Congenital heart disease (CHD) is one of the most common congenital anomalies and incidence in different studies varies from about 0.4% to 5% live births[69], while the prevalence rate in the general population is 0.8%–1%[70]. Approximately half of infant deaths are due to CHD and 3.0-4.4 per 1000 live births require intervention during the first year of life[71]. Most fetal CHDs occur in patients without any risk factors. Because of this, prenatal US screening of CHD is justified in the general low-risk population. Fetal echocardiography (echoCG) is considered an accurate diagnostic tool well reflecting postnatal outcomes. Fetal echoCG is now widely used in pediatric cardiology and perinatology and even for fetal cardiac intervention improving the preoperative condition, morbidity, and mortality of patients with CHD[72].

The fetal heart is the organ that presents the most problems in diagnosis[73]. This is undoubtedly reflected in the low detection rate of cardiac abnormalities as compared to those of most other organ systems in the fetus[74]. It is still a challenge, even for the most experienced ultrasonographer, to visualise the different cardiac structures at early stage in gestation. All the changes producing the venous connections, the atrial and ventricular chambers, the arterial roots, and the intrapericardial arterial trunks, have been completed by 8 wk of gestation when the total length of the heart is no more than 8 mm, and the distance between different structures is of the order of millimeters. At 12 wk of gestation, the fetal heart is positioned within the chest normally and, fortunately, between the 12th and 17th wk, the heart doubles in size, and triples in size by the 21st wk[75]. At this time cardiac structures can be visualised and identified (Figure 3).

The application of an extended basic US cardiac examination improves the detection of CHD, in particular the conotruncal anomalies. The stepwise method suggested for fetal heart US screening during the mid–second trimester sonogram is based on 4 routine axial views of heart and great vessels: (1) a transverse view of the superior abdomen (Figure 4A); (2) a 4-chamber view (Figure 4B); (3) a 3-vessel view (Figure 4C); and (4) a transverse view of the aortic arch (Figure 4D)[70].

***Abnormalities of the right heart***

Anatomically, the right atrium possesses all its morphologic characteristics from at least 10 wk’ gestation and is usually a triangular structure, whereas the left atrium is more tubular and meandering.

In the structurally normal heart (Figure 3), the right atrium accepts the superior and inferior caval veins at its cranial and caudal ends. The third systemic venous to enter the right atrium is the coronary sinus[74]. Generally, abnormalities of the coronary sinus are rare, but there can be fenestrations within its walls creating a second interatrial communication, or else dilation when it drains anomalously the pulmonary venous return[76]. The most frequent anomaly, however, is the dilation of the coronary sinus (Figure 5B) in the setting of persistence of the left superior caval vein. Actually, this anomaly is present in up to one-thirtieth of the normal population, but is many times more common when the heart is malformed [77].

The right ventricle is usually easily identified on US by the coarse trabeculations found within its apex. One trabeculation is usually particularly prominent, but it is the multiple prominent muscle bundles present within the apex of the right ventricle that give it a ‘filled-in’ appearance on US. In almost all structurally abnormal hearts, the trabeculated portion of the right ventricle is also present[78]. In some forms of cardiac disease, such as pulmonary atresia (Figure 5C) or stenosis with intact ventricular septum, the apical muscle bundles become even more prominent during fetal life, eventually obliterating completely the apical portion of the right ventricle. In others, such as tricuspid atresia or double inlet left ventricle, they are hypoplastic as well as the all right ventricle[74]. The tricuspid valve is very important in recognizing the right ventricle. In this side of the heart, the tricuspid valve closes in trifoliate fashion, although a discrete septal leaflet is not seen prior to 12 wk’ gestation. When formed, the septal leaflet has multiple cordal and muscular attachments to the right side of the ventricular septum. On US, the septal leaflet appears to be hinged from the right side of the ventricular septum, more towards the ventricular apex than the mitral valve. The displacement of the tricuspid valve, seen in a four-chamber section, is largely caused by draping of the right atrium over the right side of the ventricular septum, as a result of the atrioventricular canal closure, and the creation of discrete right and left inlets to the heart[79]. Consequently, in fetuses with atrioventricular septal (or canal) defects (Figure 5D), this draping cannot occur since there is no offsetting of the atrioventricular valves at the centre of the four-chamber view. Similarly, in fetuses with a large ventricular septal defect, asymmetry of the atrioventricular valves is also lost, principally because there is no septum over which the tricuspid valve can be draped. The Ebstein’s defect is characterized by an apically displaced septal insertion of the tricuspid valve leaflet with an atrialized portion of the right ventricle. Closely related to this, is the tricuspid valvar dysplasia. In this situation, the delamination of the leaflets of the tricuspid valve is normal, but there is a marked dysplasia of their leaflets and cords. Moreover, in some fetuses, the connection between the right atrium and ventricle is entirely lacking, creating classical tricuspid atresia. In others, a right-sided atrioventricular valve may be formed, but malalignment of the ventricular and atrial septums leads to double inlet left ventricle or straddling tricuspid valve[74].

***Abnormalities of the left heart***

The left ventricle is characterized by fine trabeculations, and the leaflets of the mitral and aortic valves are in fibrous continuity in the roof of the left ventricle. The three or four pulmonary veins enter at the left atrium in the form of a cross, and the lower ones can be seen in a standard four-chamber section of the heart (Figure 5A). A narrow junction of the pulmonary veins, or a wide separation between the pulmonary venous confluence and the left atrium, can indicate anomalous pulmonary venous connection. Usually, such anomalous veins drain either *via* an ascending channel to the superior caval vein, or through a descending channel to the hepatic portal venous system. They can also drain directly to the heart *via* a dilated coronary sinus. In ultrasonic four-chamber sections, the two unequal leaflets forming the mitral valve are also seen. In the structurally normal heart, arterial leaflet is long and with apron-shaped structure and the second leaflet is shallower than the first one, but appreciably longer. Both the leaflets are supported by the same paired papillary muscle groups leaving the left side of the ventricular septum smooth, in contrast to its right-sided counterpart. Abnormalities of the mitral valve are very similar to those in the right heart. In mitral atresia there is the complete atresia of the connection between the left atrium and ventricle, or a malalignment of its orifice leading to double inlet right ventricle[74]. In some malformations a complex and abnormal connection of the cardiac segments can be seen. Isolated dysplasia of the mitral valvar leaflets is rare, and is usually encountered in the setting of aortic valvar stenosis or atresia[80].

Major abnormalities of the left ventricle usually involve the spectrum of left heart hypoplasia. On the one hand, the left ventricle is slitlike, with both the mitral and aortic valves being atretic. On the other hand there are patency of the mitral valve, aortic valvar stenosis or atresia and a thick-walled and calcific left ventricle. However, the first marker of abnormalities involving arterial malformations such as discordant ventriculo-arterial connections (’transposition’) or double outlet right ventricle is often the lack of crossover of the arterial valves[74]. Finally, in assessment of left ventricle it is important to distinguish between real and false outflow in the region of the membranous septum. In fact, the ventricular septum is abnormal in many malformations of the outflow tract, including tetralogy of Fallot, most forms of double outlet, common arterial trunk, and the type of perimembranous ventricular defect seen in many chromosomal abnormalities[81]. Unfortunately, this region is filled by thin, fibrous tissue, and is therefore prone to loss of signal when imaged in some orientations by US[74].

***Abnormalities of the great arteries***

The arrangement and branching of the distal great arteries is altered in many cardiac abnormalities. Normally, by an US oblique view of the fetal thorax, it is easy to see the aortic arch running to the left of the trachea and to the right of the arterial duct. Other inferior views show the branching pattern of the pulmonary trunk, as well as the linear relationship between the pulmonary trunk, aorta, and superior caval vein. In case of discordant ventriculo-arterial connections (Figure 5F) and in some forms of double outlet right ventricle, the pattern of branching that allows recognition of the pulmonary trunk from the aorta is the reverse of that seen in the normal fetal heart. Alterations in the size and shape of the distal arteries are seen when there is an abnormal balance of aortic to pulmonary blood flow. The sizes of the aortic or ductal arches reflects also the flow of blood through them. For instance, in fetuses with aortic coarctation (Figure 5E), or hypoplasia of the left heart, the aortic arch is small and enters into the side of a dominant ductal arch. In contrast, in fetuses with obstruction to the pulmonary outflow tract, the ductal arch is usually hypoplastic and enters into the underside of a dominant aortic arch.

***Fetal echocardiography: markers and diagnostic outcomes***

Fetal echoCG becomes more consistently successful at a later gestational age, and therefore early scanning does require justification. Cardiac examination was carried out in high-risk

fetuses by a fetal cardiologist and/or gynecologist with particular experience in fetal echocardiography. Risk factors for a cardiac defect are increased nuchal translucency (NT ≥4 mm), a first-degree relative with a significant congenital heart defect (CHD) and suspicion of a cardiac or extracardiac abnormality on the 10–14-wk scan. Occasionally a full cardiac examination is performed at the parents’ request[82]. The NT measurement is only a modestly effective screening tool for all CHD when used alone, however the combination of an increased NT, tricuspid regurgitation (TR) and an abnormal ductus venosus (DV) Doppler flow profile, is a strong marker for CHD. Generally, an increased NT is considered a marker of fetal chromosomal aneuploidies, although the nuchal edema can be caused by the fluid accumulation due to a cardiac failure[83]. The phenomenon of TR is also associated with aneuploidy and its prevalence increases with the NT thickness and is substantially higher in fetuses with, than those without CHD. In chromosomally normal fetuses the finding of TR at 11 to 13 + 6 wk’ gestation is associated with an eight-fold increase in the risk of CHD[84]. Moreover, an abnormal DV Doppler flow profile, where during late diastole, coincident with atrial contraction, reduced or reversed flow is seen, has been interpreted as indicative of cardiac failure as it was assumed to reflect increased central venous pressure[85]. The performance of a complete fetal echocardiogram at the end of the first trimester requires expertise. With modern equipment, it is usually possible, using the abdominal approach, to define the situs and cardiac connections, identify the cardiac chambers and their symmetry, the crossing of the great vessels and to evaluate the flow in the chambers and the great vessels using Doppler and colour flow mapping[46].

Fetal echoCG results have been ranked in 5 classes: normal, minor abnormalities, simple cardiac anomalies, moderate cardiac anomalies, and complex cardiac anomalies (Table 2). The criteria of this classification are as follows: simple cardiac anomalies are defined as a defect able to be corrected by medical treatment or percutaneous cardiovascular interventions and only sometimes by surgery, such as ventricular septal defect (VSD), atrial septal defect (ASD), possible coarctation of the aorta (possible CoA). Moderate cardiac anomalies are defects able to be corrected surgically with a low risk for reoperation, such as tetralogy of Fallot, CoA, atrioventricular septal defect (AVSD), complete transposition of the great arteries (TGA). Complex cardiac anomalies are defined as defects able to be corrected anatomically by surgery but with a high risk for sequelae or a Fontan operation candidate, such as double outlet right ventricle, TGA with pulmonary stenosis (PS), critical PS, and Fontan candidates [pulmonary atresia with intact ventricular septum (PA with IVS), functional single ventricle (f-SV), hypoplastic left heart syndrome (HLHS)][72].

The relative frequency of different major forms of CHD differs greatly from study to study because of many reasons. Some studies are restricted to infancy and so miss patients who present later in life; some others not detect patients with a small ventricular or ASD, an abnormal patent ductus arteriosus (PDA) or many with CoA; moreover, the increasing use of fetal echocardiography also leads to therapeutic abortion for complex heart diseases, and can substantially reduce the incidence of specific lesions. However, isolated VSDs are the most common form of CHD and the incidence of these varies from 2% to 5%[86,87]. About 85% to 90% of these defects close spontaneously by one year of age[88,89]. PDAis another common lesion, the incidence of which varies with the age at the time of study and the gestational age of the subject. Preterm infants have an increased incidence of PDA based on abnormal physiology rather than on a structural abnormality. In term infants the normal ductus may stay open for some time after birth. Isolated partial anomalous pulmonary venous connection is a rare lesion clinically, and it resembles an ASD in producing a right ventricular volume overload. Some studies, however, have shown an incidence of 0.6% to 0.7%. AVSDs(endocardial cushion defects, common atrioventricular canal) have an incidence that varies with the age of the involved mothers. Trisomy 21 is much more common in mothers more than 34 years old, and AVSDs are much more frequent in fetuses with trisomy 21 than with normal chromosomes. Bicuspid aortic valves(BAV) are important because of their frequency and their late complications. Most subjects with BAVs develop stenosis or incompetence after 40 years of age. There is some variation in incidence from about 0.4% to 2.25%. Mitral incompetenceas an isolated congenital lesion is rare in children, however mitral valve prolapse is common occurring in perhaps 4% to 5% of the population[69,90,91].

With the recent advances in fetal echoCG on both technical and educational sides, the prenatal diagnosis of rare CHD, as well as the left isomerism, is also increasing. Left isomerism is associated with paired left-sided viscera, whereas right-sided viscera may be absent. Typical findings in left isomerism are bilateral morphologic left atrial appendages, viscerocardiac heterotaxy, multiple cardiac anomalies, congenital heart block, bilateral morphologic left lungs with hyparterial bronchi, polysplenia, intestinal malrotation, and interruption of the inferior vena cava with azygos continuation. By these markers prenatal diagnosis of left isomerism is feasible and with high accuracy[92].

Generally, the diagnostic accuracy of fetal echoCG is in the range 94.3%-99.0%[93-95]. Also considering discrepancies between prenatal and postnatal echoCG results the diagnostic accuracy is 98.6%[72]. Moreover, the diagnostic accuracy of fetal echoCG performed by a pediatric cardiologist is much higher than the reported diagnostic accuracy of sonographic screening performed by an obstetrician (59%)[95]. Anyway, paramount in the approach to the fetus with CHD is a multidisciplinary team composed by obstetrician, geneticist, perinatologist, pediatrician, pediatric cardiologist and cardiac surgeon that review each case of fetal malformation, refining the diagnosis, establishing management plans and facilitating issues relating to the delivery of the patient[96]. The three main types of cardiovascular malformations in which prenatal diagnosis has been shown to be beneficial are Coarctation of the Aorta, Hypoplastic Left Ventricle, and Transposition of the Great Arteries.

Recently, upgrades to commercially available equipment have improved image quality in order to use high-resolution real-time three-dimensional echocardiography in evaluation of fetal cardiac anatomy and function. With conventional imaging, the accuracy and reproducibility of quantifying ventricular size and function are limited by image plane positioning errors and geometric assumptions. Three-dimensional ultrasonography (3D-US) has been shown to provide more accurate measurements of volume and area than two-dimensional methods, possibly even for volumes encountered in the fetal heart. Moreover, by minimizing some of the time and imaging expertise demands compared to conventional fetal echocardiography, real-time 3D-imaging also may represent a more effective way for sonographers to screen for congenital heart disease in low risk pregnancies[97].

Early diagnosis of CHD gives the parents more time to make an informed decision regarding continuation of the pregnancy. Should they decide to interrupt the pregnancy, then this can be performed earlier, more safely and with less long-term psychological sequelae. If the pregnancy is continued, the timing, location (hospital with neonatal intensive care, pediatric cardiology and pediatric cardiac surgery facilities), mode of delivery and direct postnatal care can be planned. In this way the postnatal outcome of these babies can be improved. Where the early fetal echocardiogram shows no evidence for a cardiac defect it allows earlier reassurance of couples considered at high risk for CHD[46].

**SKELETAL DYSPLASIAS**

Skeletal dysplasias are a heterogeneous group of conditions associated with various anomalies in shape and size of the skeleton[98]. These conditions are caused by widespread disturbance of bone growth, beginning during the early stages of fetal development and evolving throughout life[99]. The prevalence of skeletal dysplasias is low, being approximately 3.2 in 10000 live births[100] and the overall frequency of skeletal dysplasias among perinatal deaths is about 9 per 1000[98]. Based on postnatal radiological classification, more than 150 different conditions have been described[101]. Despite recent advances in imaging, fetal skeletal dysplasias are difficult to diagnose before birth (especially in the absence of a familial history) due to a number of factors, including their large number, their phenotypic variability with overlapping features, lack of precise molecular diagnosis for many disorders, lack of a systematic approach, variability in the time at which findings manifest the inability of US to provide an integrated view. It must be emphasized that the analysis of bone anomalies requires expertise and great knowledge of postnatal features and, at present, accurate prenatal diagnosis of skeletal dysplasia remains a challenge, with only approximately 65% of cases being accurately diagnosed by conventional two-dimensional ultrasound (2D-US) [102].US of suspected skeletal dysplasia involves systematic imaging of the long bones, thorax, hands and feet, skull, spine, and pelvis[99].

***Long bones***

The bones should be assessed for presence, curvature, fractures and degree of mineralization[99]. All the long bones of each limb and segment should be examined and measured. The shortened segments must be identified (rhizo-, meso- or acromelic shortening). A femur length–abdominal circumference ratio < 0.16 suggests lung hypoplasia and a femur length–foot length ratio < 1 is in favour of dysplasia[98]. In achondroplasia femur length becomes abnormally short only in the third trimester. The presence of abnormal angulation (Figure 6A) suggests a fracture and joint deformities or disruption or incongruence are compatible with luxations. Anterior angulation of the tibia and the short fibula are pathognomonic features of campomelic dysplasia[103]. Abnormal epiphyseal calcification should also be looked for, but bone mineralization is still very difficult to appreciate on US scans[98].

***Thorax***

The thorax must also be measured: a chest circumference less than the 5th percentile has been proposed as an indicator of pulmonary hypoplasia which is the main cause of neonatal death in many lethal skeletal dysplasias[104]. Hypoplastic thorax occurs in many skeletal dysplasias such as thanatophoric dysplasia (Figure 6C), achondrogenesis, hypophosphotasia, camptomelic dysplasia, chondroectodermal dysplasia, osteogenesis imperfecta, and short-rib polydactyly and may lead to pulmonary hypoplasia[99].The shape and size of the ribs, clavicles and scapula should be analysed, since absence or hypoplasia of the clavicles is seen in cleidocranial dysplasia[105] and absence of the scapula is a useful defining feature of camptomelic dysplasia[106].

***Hands and feet***

The hands and feet should be carefully analyzed to exclude the presence ofpre- or postaxial polydactyly (the presence of more than five digits;)syndactyly (soft-tissue or bone fusion of adjacent digits),clinodactyly (deviation of a finger). Foot deformities such as hitchhicker thumb, rocker-bottom or clubbed feet should also be evaluated[98]. Clubbing of the hand is suggestive of the spectrum of “radial ray” anomalies, which include an abnormal thumb (Holt-Oram syndrome), hypoplasia and absence of the thumb, and sometimes, absence of the radius or of both the radius and the hand[99]. In diastrophic dysplasia, the fingers are short, with ulnar deviation and ‘hitchhiker’ thumbs. There are clubfeet and micrognathia. In achondroplasia, the phalanges are short; typical gaps between the fingers and digital deviation lead to the appearance of a “trident” hand[103].

***Skull***

Head circumference and biparietal diameter should be measured to exclude micro- or macrocephaly. The shape, mineralization, and degree of ossification of the skull should be evaluated: osteogenesis imperfecta can be suspected in cases of cranial vault distortion upon probe pressure (Figure 6B). Interorbital distance should be measured to exclude hyper- or hypotelorism[99].Other features such as clover-leaf deformity, brachycephaly or scaphocephaly should suggest craniosynostosis (premature fusion of the sutures). In thanatophoric dysplasia the head circumference is large in half of cases, with the nasal bridge depressed and an abnormal sonographic translucency can be detected[103]. Facial dysmorphisms may be better depicted by 3D-US[107-109].

***Spine***

The spine should be carefully imaged to assess the relative total length and the presence of

curvature or incomplete closure of the neural tube. Mineralization of vertebral bodies and neural arches should be evaluated. Only marked platyspondyly (vertebral body height < disk height) which is typically seen in thanatophoric dysplasia, can be diagnosed.

***Pelvis***

In pelvis the presence of the three ossification points (iliac, pubic and ischial bones) and the shape of the iliac bone (round, flat, lack of iliac flaring) can be important in certain dysplasias and dysostoses, such as limb-pelvic hypoplasia, femoral hypoplasia–unusual face syndrome, achondroplasia. Pelvic shape may be difficult to evaluate at routine US, and 3D-US may be necessary[99].

***Technical improvement in early diagnosis of skeletal displasias***

In the absence of a previous history of skeletal dysplasia, fetal morphological examination by conventional 2D-US remains the screening test of choice[100]. As observed in different studies, most skeletal dysplasias are detected late in the second or third trimester of pregnancy[102].Assessment of the fetus with 3D-US has been shown to improve diagnostic accuracy, since additional phenotypic features not detectable at 2D-US may be identified[107,108] (Table 3).

3D-US provides a global rather planar view of the anatomy by means of depth perception cues, rotation, surface-rendering techniques and multiplanar displays. In particular, multiplanar viewing capability allows to identify scapular anomalies, appreciate limb abnormalities, evaluate fetal facial profile and improve visualization of spine[107]. 3D-US is superior in elucidating some of the features typical of each skeletal dysplasia. For example, brachydactyly, almost pathognomic for achondroplasia, is under-appreciated by 2D-US, while 3D-US allows precise measurements of the phalanges, palms and feet and captures the trident configureuration of the hands (Figure 7B); 3D-imaging has also the significant advantage of showing the relative disproportion of limb segment. Moreover, surface rendering of fetal facies allows the evaluation of the metopic prominence contour, bony structure, nasal contour and overall relationship of facial features. Facial dysmorphisms such as frontal bossing and mid-face hypoplasya are found by 3D-US in achondroplasia and thanatophoric dysplasia (Figure 7A). The Binder facies (depressed nasal bridge, mid-face hypoplasia, small nose with upturned alae) that is part of the spectrum of chondrodysplasia punctata is also visualized. The very rare case of laryngeal stippling found in some case of chondrodysplasia punctata is preferentially seen by 3D-imaging because of the ability to rotate the image 180°: multiple punctuate calcifications are visualized throughout the larynx[108]. The great advantage of 3D-US is the lower cost and the absence of fetal irradiation. However, this examination is more dependent on the amniotic fluid volume and fetal position[102].

Sometimes US and genetic data are inconclusive to diagnose or exclude a suspected skeletal dysplasia[98], then radiological findings are required in cases with possible termination of pregnancy. For example, long bone deformities (curvature, fractures), cranial deformities (clover leaf skull) and spinal angulations (segmentation anomalies) are good indications for prenatal three-dimensional helical computer tomography (3D-HCT)[110]. Indeed, 3D-HCT can image the entire fetal skeleton, while 3D-US can image only limited and specific fetal parts[102] (Figure 8).

Nevertheless, this technique has important limitations since requires ionizing radiation and additionally, the image quality is dependent on bone mineralization (better after 30 wk’ gestation) and fetal immobility. CT is still often insufficient in the precise and complete visualisation of the fetal extremities (hands and feet) [98].

**CONCLUSION**

Despite the advances in US technology, the diagnosis of multiple fetal structural defects and genetic syndromes currently still depends on the experience of physicians and sonographers. New diagnostic protocols are required to improve the accuracy of US detection of fetal abnormalities. In particular, an objective method based on quantitative parameters is of paramount importance to increase the use of US in prenatal diagnosis. In the last years, quantitative and objective sonographic markers highly predictive of specific fetal malformations have been studied and adopted in order to increase the sensitivity of sonography. US scan represents the most safe and non-invasive method for prenatal diagnosis. Then, innovative research approaches will need to allow the quantitative exploration of several new parameters and the identification of new sonographic markers for aneuploidy or other pathologies. In the future, highly innovative systems with respect to the state of the art of US-based prenatal diagnosis should be able to generate appropriate combinations of multiple sonographic markers with expected significant improvements in both sensitivity and specificity of the corresponding diagnoses. Moreover, these innovative methods should perform automatic comparisons among the values of the same parameter measured at different gestation ages, so automatically providing the temporal evolution of selected parameters, in order to easily check if fetal growth resembles an expected path and also if there are some “disproportions” between different anatomical regions. Therefore, research in prenatal diagnosis should introduce into clinical practice a number of new prenatal diagnostic parameters that must be all quantitative, accurate and independent from operator experience. Early diagnosis of fetal malformations based on these new systems will be also useful for parental counseling and fetal treatment planning. In particular, main specific benefits will be related to optimized pregnancy management and childbirth timing, possibility of performing simpler procedures for termination of pregnancy in those patients in whom findings are abnormal (reducing physical and psychological morbidity associated with late abortions), extension of malformations identifiable already in the first trimester of pregnancy, timely therapeutic treatment of objectively selected diseased fetuses.

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**Table 1** **Sensitivity of sonographic markers of aneuploidies**

|  |  |  |
| --- | --- | --- |
| **Markers of aneuploidy** | **DR (%)** | **FPR (%)** |
| NT | 83 |  |
| NT+ PAPP-A + βhCG + AFP + estriol | 94 | 5 |
| Femoral length | 40-50 | 7 |
| Humeral length | 50-54 | 5-6 |
| Humeral length + NT | 75 |  |
| Pyelectasis | 17-25 | 2-3 |
| Hyperchoic bowel | 3.3-27 | 1 |
| Absence of nasal bone | 73 | 0.5 |
| Nasal bone + NT + PAPP-A + βhCG + AFP + estriol+ maternal age | 97 |  |
| Aberrant right subclavian artery | 37.5 | 1.4 |

DR: Detection rate; FPR: false-positive rate; NT: Nuchal translucency; PAPP-A: pregnancy-associated plasma protein; βhCG: chorionic gonadotropin; AFP: alpha-fetoproteina.

**Table 2 Classes of fetal cardiac anomalies**

|  |  |  |
| --- | --- | --- |
| Complex CHD | Moderate CHD | Simple CHD |
| Transposition of the great arteries | Mild or moderate AS or aortic incompetence | Small VSD |
| Tetralogy of Fallot,Hypoplastic right heart | Moderate PS or incompetence | Small PDA |
| SV, DORV,Truncus arteriosus | Noncritical Coarc | Mild PS |
| Total anomalous pulmonary venous connection | Large ASD | BAV without AS or aortic incompetence |
| AVSD, Large VSD,Large PDA | Complex forms of VSD | Small or spontaneously closed ASD |
| Critical or sever PS, Critical or severe AS, Critical Coarc |  |  |

CHD: congenital heart disease; AS: aortic stenosis; VSD: ventricular septal defect; PS: pulmonary stenosis; PDA: patent ductus arteriosus; SV**:** single ventricle; DORV: double outlet right ventricle; ASD: atrial septal defect; BAV: bicuspid aortic valves; AVSD: atrioventricular septal defect.

**Table 3 Comparison between two-dimensional ultrasound and three-dimensional ultrasound detection power of skeletal dysplasia markers**

|  |  |
| --- | --- |
|  | Power of detection |
| Markers of skeletal dysplasia | **2D-US** | **3D-US** |
| Shortening of long bones | +++ | +++ |
| Increased thickness of femoral metaphysis | - | +++ |
| Bone fracture | ++ | +++ |
| Bowing of long bones | ++ | +++ |
| Decreased mineralization | - | ++ |
| Phalangeal hypoplasia | + | +++ |
| Point-calcified epiphysis | + | ++ |
| Macrocephaly | ++ | + |
| Frontal bossing | ++ | +++ |
| Facial dysmorphism | + | +++ |
| Narrow thorax | +++ | +++ |
| Increased intervertebral space | ++ | ++ |
| Deformation of the fetal pelvis | + | ++ |

+++: hight; ++: medium; +: low; -: very low.

**Figure 1 Prenatal** **cytogenetic tests.** A: Amniocentesis:a small amount of amniotic fluid surrounding the baby during pregnancy is removed by a long needle for testing; B: Karyotype: the presence of an extra chromosome 21 is shown (diagnosis of Down syndrome). Adapted from Medicinamaternofetale.it[111] and Vividown.org[112]*.*

**Figure 2** **Markers of chromosomal defects.** A: Normal fetus: measurements of nuchal translucency (NT, red circle), facial angle (red dashed line) and nasal bone length (NBL, red square) at 13 wk of pregnancy; B: Fetus with Down syndrome: increased nuchal translucency (NT, red circle), and absent nasal bone (red square where nasal bone was expected) at 11 wk of pregnancy. The image has been certified by the Fetal medicine Foundation. Photos taken by Wolfgang Moroder. Creative Commons.Adapted from It.wikipedia.org[113].

**Figure 3 Fetal normal heart.** Schematic representationof the blood circulation in fetus: the blood that comes into the right side of the fetal heart (blue part) is pumped into the pulmonary trunk (PA) and flows through the ductus arteriosus (circled in yellow) directly out into the aorta (AO). The ductus arteriosus is an extra blood vessel of the fetal heart that creates a bypass for the blood oxygenated not by the lungs, but through the placenta. Adapted from NeonatologyForParents.org[114].

**Figure 4 Four routine axial views of heart and great vessels.** A: Transverse view of the superior abdomen: the stomach on the fetal left side; the descending aorta (D. AO) to the left side and inferior vena cava (IVC) to right side of the spine, respectively; B: Four-chamber view: in a normal fetal heart, approximately equal size of the right and left chambers, intact ventricular septum and normal offset of the two atrioventricular valve; C: Three-vessel view: pulmonary artery (PA), aorta (AO) and superior vena cava (SVC) in the correct position and alignment; PA, to the left, is the largest of the three and the most anterior, whereas the SVC is the smallest and most posterior. (D.AO: descending aorta); D: Transverse view of the aortic arch: in the normal heart, both the AO arch and the ductal arch (DA) are located to the left of the trachea, in a ‘V’-shaped configureuration. (Adapted from Carvalho *et al*[115]*.*) RV: right ventricle; LV: left ventricle; LA: left atrium; RA: right atrium; AS: aortic stenosis.

**Figureure 5 Markers of congenital heart disease.** A: Four-chamber echo view in a normal mid-trimester fetus; B: Enlarged coronary sinus seen as a circular structure (arrow) within the left atrium adjacent to the mitral valve; C: Pulmonary atresia with intact ventricular septum: apical muscle bundles are prominent in the apical portion of the right ventricle with trabeculations coarser than usual.; D: Atrioventricular septal defect with a common junction leading to loss of off-setting of the atrioventricular valves (arrows); E: Severe aortic stenosis with patent mitral valve: the left ventricle becomes bulb-shaped (arrow); F: Transposition of the great arteries (discordant ventriculo-arterial connections): the arteries are parallel to one another with the aorta arising from the right ventricle and positioned to the right of the pulmonary trunk. LA: left atrium; RA: right atrium; RV: right ventricle; LV: left ventricle; AO and AOA: Aorta; PA: Pulmonary trunk. Adapted from Cook *et al*[74].

**Figureure 6 Marker of skeletal dysplasya by two-dimensional ultrasound.** A: Abnormal angulated femur; B: Osteogenesis imperfecta: cranial vault distortion upon probe pressure. (Adapted from Cassart[98]); C: Features of thanatophoric dysplasia: depressed nasal bridge (arrowhead), prominent forehead (double arrows), and undersized thorax (single arrow) compared with the abdomen. Adapted from Dighe *et al*[99]*.*

**Figureure 7 Skeletal anomalies detected by three-dimensional ultrasonography.** A: Facial dysmorphisms: frontal bossing (double arrows) and flattened mid-face (single arrow), disproportionate limb segments and brachydactyly (dotted arrow) typical of achondroplasia; B: Trident conFigureuration of the digits and brachydactyly suggestive of achondroplasia. Adapted from Krakow *et al*[108]*.*

**Figureure 8 Prenatal diagnosis by three-dimensional helical computer tomography.** A: Achondroplasia (sagittal view): macrocephaly (double arrows), short ribs (dotted arrow) and increased thickness of the femoral metaphysis (single arrow); B: Osteogenesis imperfecta (posterior view): fractures of ribs and femur (arrows); C: Chondrodysplasia punctata (frontal view): epiphyseal calcifications of long bones (arrows). Adapted from Ruano *et al*[102]*.*