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The role of ultrasound in the diagnosis of fetal genetic syndromes

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Abstract

The use of ultrasound in the prenatal diagnosis of fetal genetic syndromes is rapidly evolving. Advancing technology and new research findings are aiding in the increased accuracy of ultrasound-based diagnosis in combination with other methods of non-invasive and invasive fetal testing. Ultrasound as a screening tool for aneuploidy and other anomalies is increasingly being used throughout pregnancy, beginning in the first trimester. Given the number of recorded syndromes, it is important to identify patterns and establish a strategy for identifying abnormalities on ultrasound. These syndromes encompass a wide range of causes from viral, substance-linked, chromosomal, and other genetic syndromes. Despite the ability of those experienced in ultrasound, it is important to note that not all fetal genetic syndromes can be identified prenatally, and even common syndromes often have no associated ultrasound findings. Here, we review the role of ultrasound in the diagnosis of fetal genetic syndromes.

Keywords

ultrasound; genetic; syndrome; anomalies

Advancing technology

Two-dimensional ultrasonography has long been the modality of choice for diagnosis of fetal anomalies. However, the limitations of two-dimensional ultrasonography include the

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inability to store volume images for future manipulation, non-intuitive interpretation of the images for patients, and inability to simultaneously view images in a multiplanar view. Increasingly, because of the limitations of two-dimensional ultrasound, three dimensional and four-dimensional ultrasonography are being used to aid in diagnosing and visualising suspected fetal anomalies. Previous studies that have compared two-, three- and four-dimensional imaging to determine which has the best diagnostic ability or results in the best clinical outcomes in fetuses with anomalies have found some conflicting results. One study aimed to determine whether two-dimensional ultrasonography adds diagnostic information over three-dimensional and four-dimensional images. This study, which included 54 normal fetuses and 45 fetuses with anomalies, reported 90.4% agreement between two-, three-, and four-dimensional images. Six anomalies were missed by three- and four-dimensional imaging but observed by two-dimensional ultrasonography; however, the investigators concluded that the sensitivity and specificity of the imaging modalities were not significantly different.¹ Another study by Dyson et al.² comparing the results of two-dimensional with three-dimensional imaging found that three-dimensional ultrasonography offered additional information in 51% of cases, was equivalent in 45%, and was disadvantageous in 4%. Additional information obtained in three-dimensional imaging influenced clinical management in 5% of patients.² Merz and Welter³ studied two-dimensional and three-dimensional ultrasound in 3472 high-risk pregnancies and discovered 1012 anomalies, excluding cardiac defects. They found that 4.2% of the malformations were correctly identified on three-dimensional ultrasound only. Although all these studies showed a benefit or at least equivalence of the imaging modalities, Scharf et al.⁴ concluded that three-dimensional visualisation was not superior to standard two-dimensional imaging, and should be restricted to specific malformations. Currently, three- and four-dimensional ultrasonography can be considered an adjunct to two-dimensional sonography, and can aid in the diagnosis of many fetal anomalies, especially those related to facial abnormalities (Figs. 1 and 2), neural tube defects, and skeletal anomalies.^{5,6}

The use of three-dimensional ultrasound in the diagnosis of fetal oro-facial clefts when suspected on two-dimensional ultrasound greatly improves the sensitivity and specificity. In a recent systematic review, Maarse et al.⁷ found that use of three-dimensional ultrasound in women at high risk of fetal oro-facial clefts improves diagnostic accuracy. The detection rate of three-dimensional ultrasound was 100% in fetuses with cleft lip and 86–90% in fetuses with cleft lip and palate.⁷ Baumler et al.⁸ found that three-dimensional ultrasound of the fetal palate has a high accuracy in the diagnosis of cleft palate when cleft lip is identified on two-dimensional screening ultrasound.⁸

The use of three-dimensional ultrasound in the diagnosis of neural tube defects has been advocated by the American Institute of Ultrasound in Medicine to define the upper level of the lesion.⁹ With three-dimensional ultrasound, through the use of multiple views, accuracy within one vertebral body can be achieved in 80% of cases.¹⁰

For the diagnosis of skeletal dysplasias, in which a precise diagnosis can significantly affect postnatal prognosis, three-dimensional ultrasound has been found to have an improved diagnostic accuracy. In a study by Ruano et al.¹¹ three-dimensional ultrasound correctly identified 77.1% of cases compared with 51.4% with two-dimensional ultrasound.

Additionally, three-dimensional ultrasound can improve patient understanding of the skeletal dysplasia and aid clinicians in counselling.¹²

Timing of ultrasound in diagnosis of fetal genetic syndromes

Ultrasound can be used throughout pregnancy to detect fetal abnormalities. First-trimester ultrasound is increasingly being used for nuchal translucency tests and also for an early limited anatomic survey. Ultrasound in the first trimester has been shown to be effective in screening for aneuploid conditions, such as trisomy 21.¹³ The nuchal translucency measurement in the first trimester, with a cut-off of 3 mm or greater, has been shown to have a high sensitivity and specificity for identifying pregnancies at risk for chromosomal anomalies.¹⁴ In addition, early anatomic surveys have been shown to have good detection rates of most structures when carried out by an experienced sonographer.¹⁵ Picklesimer et al.,¹⁶ in a retrospective cohort study of aneuploid fetuses, investigated the effect of gestational age at time of ultrasound on the detection of sonographic markers of aneuploidy. The fetal ultrasounds in this study were carried out between 14 and 32 weeks' gestation, and the investigators showed that sonographic markers of aneuploidy were present at all gestational ages. In the earlier gestational ages, a shift was observed from detection of soft markers, non-structural abnormalities, to detection of major anomalies at later gestational ages.¹⁶

It is advised that all pregnant women undergo a fetal anatomic survey in the second trimester. Fetal anatomy is assessed systematically through ultrasound after about 18 weeks. Specifics of standard fetal anatomic evaluations are detailed in the American Institute of Ultrasound in Medicine practice guidelines.¹⁷ It is important to use a methodical routine in the execution and evaluation of the anatomic survey to assure complete assessment of fetal anatomy. The first trimester ultrasound largely focuses on nuchal translucency measurement in the assessment of chromosomal syndrome risk; however, the second trimester ultrasound can identify much more specific defects that follow a different pattern for each genetic syndrome. Importantly, some fetal anatomy is more easily visualised later in the second trimester. A prospective randomised study by Schwärzler et al.¹⁸ evaluated three different groups of fetuses distinguished by gestational age at time of anatomic survey for the outcome of need for additional ultrasound to complete the evaluation. The investigators concluded that fetuses that underwent an anatomic survey at 20–22 6/7 weeks are less likely to need repeat examination than women who have an ultrasound 18–18 6/7 weeks' gestation.

Third-trimester ultrasound can also be used as an adjunct to second-trimester anatomic survey to follow the evolution of identified fetal abnormalities. Third-trimester ultrasound as a screening tool for fetal genetic syndromes, however, has limited utility. In 2008, it was concluded in a Cochrane review¹⁹ that routine use of third-trimester ultrasound screening in an unselected population of women does not confer benefit.

Infectious syndromes: ultrasound findings

Antepartum ultrasound can aid in the diagnosis of several intrauterine congenital infections. These infectious syndromes all have the potential to cause devastating in-utero and postnatal

consequences, and even demise. Fortunately, the infectious syndromes rarely occur in developed nations. If identified prenatally, many of the infections can be treated. Therefore, it is important to understand the applications and limitations of ultrasound in the diagnosis of infectious syndromes. Additionally, it is important to note that infants with symptomatic congenital infections at birth do not always have abnormalities on prenatal ultrasound. The incidence and ultrasound findings most often associated with individual infectious syndromes are listed in Table 1.⁷ Although ultrasound can be a clue in the diagnosis of infectious syndromes, the findings are not diagnostic, and definitive diagnosis should be determined by other means.

Chromosomal syndromes

Invasive testing is the gold standard for prenatal diagnosis of chromosomal syndromes. Although the risks of invasive genetic testing are relatively low, chorionic villus sampling and amniocentesis both increase the risks of pregnancy loss, preterm labour, and premature rupture of membranes, among other risks.^{37,38} Therefore, genetic screening tests have been developed and implemented in the general obstetric population to stratify women by risk category. The available genetic screening tests include first-trimester serum and nuchal translucency, second-trimester serum screening, and maternal plasma cell-free fetal DNA testing. The sensitivities and specificities of these screening tests vary. Often, patients use the addition of ultrasound markers of aneuploidy to determine whether they desire invasive diagnostic testing. Although a normal second-trimester anatomic survey does not eliminate possibility of aneuploidy, the absence of any marker can convey a significant risk reduction.^{39,40} Ultrasound can be used to identify structural anomalies, and also to detect soft markers of aneuploidy. The use of soft markers alone in the decision to pursue diagnostic testing in otherwise low-risk women can lead to unnecessary invasive procedures. On the other hand, a normal anatomic survey can give false reassurance to patients at high risk of aneuploidy.⁴¹ Therefore, although we must acknowledge that aneuploidy can be present with a normal sonographic exam, ultrasound performs an important role in the diagnosis of fetal chromosomal syndromes.⁴² Among the most common chromosomal syndromes that are identified through screening in pregnancy are trisomy 21, trisomy 18, and trisomy 13. The associated ultrasound findings that have been found are included in Table 2.⁷ Many of the chromosomal syndromes have similar sonographic findings, and definitive diagnosis cannot be determined on the basis of ultrasound alone.

Triploidy

Ultrasound can also aid in the identification of other chromosomal syndromes such as triploidy, Turner syndrome, and 22q11.2 deletion syndrome. Triploidy refers to the presence of a complete extra set of chromosomes. In triploid pregnancies, multiple associated abnormalities can be detected by ultrasound in almost every organ system. Data surrounding ultrasound findings of triploid fetuses are not robust, and largely consist of case reports and case series. One of the largest case series involved 30 triploid fetuses that all had first-trimester nuchal translucency and serum screening. Most (83%) of the triploid fetuses were ultimately diagnosed after invasive testing, which was ordered because of abnormalities on first-trimester screening.⁶¹ In addition to anomalies of every organ system, triploidy is

commonly associated with severe intrauterine growth restriction and an abnormal placental appearance.^{62,63}

Turner syndrome

Turner syndrome, also called monosomy X, frequently ends in spontaneous abortion. The frequency among female live births is about 1 in 2500.⁶⁴ Infants with Turner syndrome have a highly variable but characteristic phenotype, including short stature, webbed neck, widely spaced nipples, lymphoedema, cardiac, and renal malformations, infertility, and other comorbidities. Although many of the phenotypic expressions of Turner syndrome are identified post-natally, ultrasound can be used to identify some characteristics in the fetus. Baena et al.⁶⁵ showed that, in an unselected population, cystic hygroma (Fig. 6) was present in 59.5%, and hydrops was present in 19%, of prenatally diagnosed Turner syndrome cases. Furthermore, in another study,⁶⁶ 68% of fetuses with Turner syndrome diagnosed on karyotype had sonographic abnormalities. In addition to cystic hygroma and hydrops fetalis, ultrasound findings in fetuses with Turner syndrome can include congenital heart defects, specifically coarctation of the aorta, ventricular septal defect, tetralogy of Fallot, and a dilated right ventricle. Additionally, ultrasound may identify renal abnormalities, short femur, choroid plexus cysts, ventriculomegaly, echogenic intracardiac focus, or echogenic bowel.^{65,66}

22q11.2 deletion syndrome

Another chromosomal syndrome that can be suspected on the basis of ultrasound findings is 22q11.2 deletion syndrome, also known as DiGeorge and velocardiofacial syndrome. This syndrome is usually sporadic, but can be inherited in an autosomal dominant fashion from an affected parent. Affected fetuses usually have a cardiac anomaly such as tetralogy of Fallot, ventricular septal defect, truncus arteriosus, pulmonary atresia, or interrupted aortic arch.^{67,68} Additionally, ultrasound can identify polyhydramnios, thymic hypoplasia, renal anomalies, microcephaly, and cleft palate in fetuses with 22q11.2 deletion.^{69–73}

5p Deletion syndrome

Also known as Cri du Chat Syndrome, 5p deletion syndrome is a rare genetic syndrome. With this syndrome, a number of associated ultrasound features can lead to suspicion, and possible prenatal diagnosis. The most common ultrasound findings with 5p deletion syndrome include growth restriction, microcephaly, micrognathia, and hypertelorism.⁷⁴ Other findings may include nasal bone hypoplasia, neurological abnormalities such as ventriculomegaly, and cardiac defects.^{75–77}

Other genetic syndromes

Most genetic syndromes have been identified, and many others remain to be discovered. Some genetic syndromes have associated sonographic findings, whereas others do not. For example, genetic disorders of metabolism such as glycogen storage diseases, disorders of fatty acid oxidation, and lysosomal storage disorders, have no identifiable features on ultrasound. Because of the large number of genetic disorders with associated ultrasound

findings, it is not possible to discuss them all within the scope of this review. As examples, however, Beckwith–Wiedemann and Noonan syndromes will be discussed.

Beckwith–Wiedemann syndrome

Beckwith–Wiedemann syndrome is characterised by congenital anomalies, tumour predilection, and overgrowth. This syndrome is an imprinting disorder caused by abnormalities on chromosome 11p15.5.⁷⁸ The diagnosis of Beckwith–Wiedemann syndrome is usually made after birth, but prenatal ultrasonography can contribute clues to this condition. Ultrasound findings can include an abdominal wall defect such as omphalocele, macroglossia, macrosomia, nephromegaly, and polyhydramnios.^{79,80}

Noonan syndrome

The prevalence of Noonan syndrome is estimated at 1 in 1000 to 1 in 2500 people in the general population.⁸¹ Noonan syndrome is autosomal dominant in nature, and results from mutations in signal transduction pathway genes, including *PTPN11*, *SOS1*, *KRAS*, *NRAS*, *BRAF*, *RAF1*, and *MAP2K1*.^{81–83} The clinical findings in patients with Noonan syndrome include typical facial dysmorphisms, cardiovascular defects, short status, pectus excavatum or carinatum, mental retardation, and other varying anatomic abnormalities. In a retrospective cohort study by Baldassarre et al.,⁸⁴ mean age at diagnosis of Noonan syndrome was 7 years. Twenty-one per cent of molecularly confirmed cases, however, had fetal anomalies present at prenatal ultrasonography, 41% had nuchal translucency over 2.5 mm, and 38% had polyhydramnios.⁸⁴ This study concluded that, although abnormal prenatal findings are frequent in fetuses with Noonan syndrome, they are not specific and therefore are not useful for predicting the postnatal phenotype. Other studies have suggested that, in the absence of karyotype abnormalities, Noonan syndrome should be considered in the presence of cystic hygroma or increased nuchal translucency, cardiac defects, and polyhydramnios.^{85,86}

Conclusion

The role of ultrasound in the diagnosis of fetal genetic syndromes is as a screening tool to identify fetal, placenta, and amniotic abnormalities. With the knowledge of patterns seen with individual syndromes, identification of these abnormalities can lead to recommendations on definitive diagnostic testing, preparation for the post-natal period, or both. Current evidence supports the application of first-trimester ultrasound as a screening tool for select genetic syndromes. Second-trimester ultrasound provides the most information on fetal abnormalities and should be carried out in a structured and systematic manner. Use of three-dimensional and four-dimensional ultrasound as an adjunct to two-dimensional ultrasound in the diagnosis of fetal structural abnormalities is a developing modality, and will likely be used in the future. Genotypic and phenotypic links are known for numerous genetic syndromes. In this chapter, we have only touched on a few of the genetic syndromes in existence to highlight the role of ultrasound as a screening tool in diagnosis. More invasive methods that are safer and more accurate when carried out under ultrasound guidance are needed for more definitive diagnosis.

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Practice points

- Ultrasound is a valuable tool in screening for fetal genetic syndromes.
- First-, second-, and third-trimester ultrasounds provide information on possible fetal abnormalities; however, routine second-trimester anatomy ultrasound is the most accurate at identifying structural abnormalities.
- Three-dimensional and four-dimensional ultrasound are useful adjuncts in the diagnosis of select fetal anomalies.
- A normal ultrasound does not eliminate the possibility of a fetal genetic syndrome.
- Ultrasound does not replace invasive testing for definitive diagnosis of genetic syndromes.

Research agenda

- Effect of timing of ultrasound on accuracy in diagnosis of fetal genetic syndromes and effects on maternal and fetal outcomes.
- Routine use of three- and four-dimensional ultrasound when a structural malformation is identified.
- Accuracy of ultrasound in screening for individual genetic syndromes.

Fig. 1.
Two-dimensional image of bilateral cleft lip.

Fig. 2.
Three-dimensional image of a unilateral cleft lip.

Fig. 3.
Ultrasound image of placentomegaly.

Fig. 4.
Ultrasound image of an echogenic intra-cardiac focus.

Fig. 5.
Ultrasound image of pyelectasis.

Fig. 6.
Ultrasound image of large septated cystic hygroma.

Table 1

Incidence and ultrasound findings most often associated with individual infectious syndromes.

Infection	Incidence of acute maternal infection	Most common ultrasound findings
Cytomegalovirus	0.2–2.2% ^{20,21}	Neurological intracranial calcifications periventricular echogenicities Gastrointestinal echogenic bowel hepatosplenomegaly Cardiac cardiomegaly Other intrauterine growth restriction placentomegaly (Fig. 3) hydrops, ^{22–25}
Parvovirus	1–4% ^{26,27}	Hydrops, elevated middle cerebral artery dopplers ^{28,29}
Toxoplasmosis	0.2–1% ³⁰	Neurological ventriculomegaly intracranial calcifications periventricular calcifications microcephaly Gastrointestinal hepatomegaly Cardiac myocardial calcifications Other hydrops placentomegaly ^{25,31}
Varicella	0.01–0.4% ³²	Neurological microcephaly ventriculomegaly or atrophy microcalcifications microphthalmia Gastrointestinal echogenic bowel hepatic calcifications Musculoskeletal Clubfeet abnormal position of hands limb hypoplasia

Infection	Incidence of acute maternal infection	Most common ultrasound findings
		flexed limbs Other intrauterine growth restriction hydrops ^{33,34}
Syphilis	0.4–1.3% ³⁵	Gastrointestinal Hepatosplenomegaly Other Placentomegaly Hydrops ^{25,36}

Table 2

Ultrasound findings associated with common chromosomal syndromes.

Organ system	Trisomy 21 (Down's syndrome)	Trisomy 18 (Edward's syndrome)	Trisomy 13 (Patau syndrome)
Cardiac	Echogenic intra-cardiac focus (Fig. 4); atrial-ventricular canal defect; atrial septal defect; ventricular septal defect; and other cardiac defects ^{43,44}	Ventricular septal defect; atrial-ventricular canal defect; hypoplastic left heart syndrome; other cardiac defects. ⁴⁵⁻⁴⁷	Ventricular septal defect; hypoplastic left heart syndrome; double outlet right ventricle; and other cardiac defects. ⁴⁸⁻⁵¹
Neurological	Choroid plexus cyst; and ventriculomegaly ^{42,52}	Ventriculomegaly, choroid plexus cyst; Dandy-Walker malformation; and neural tube defects ⁴⁵⁻⁴⁷	Microcephaly, Holoprosencephaly. ⁴⁸⁻⁵¹
Gastrointestinal	Hyperechoic bowel; duodenal atresia; oesophageal atresia ⁵³	Omphalocele, diaphragmatic hernia; tracheoesophageal fistula; duodenal atresia; and hyperechoic bowel. ⁴⁵	Omphalocele. ⁴⁸⁻⁵¹
GU	Pyelectasis (Fig. 5). ⁵⁴	Pyelectasis. ⁴⁵	Hyperechoic kidneys, polycystic kidneys. ⁴⁸⁻⁵¹
Facial	Absent or hypoplastic nasal bone ⁵⁵⁻⁵⁷	Micrognathia, cleft lip/palate ⁴⁵	Cleft lip/palate ⁴⁸⁻⁵¹
Musculoskeletal	Short humerus, short femur, clinodactyly ⁵⁸	Clenched hands, overlapping digits, radial dysplasia, foot abnormalities ^{45,46}	Post-axial polydactyly ⁴⁸⁻⁵¹
Other	Thickened nuchal fold; and intrauterine growth restriction. ^{59,60}	Thickened nuchal fold; single umbilical artery; and intrauterine growth restriction. ^{46,47}	Thickened nuchal fold; and intrauterine growth restriction. ⁴⁸⁻⁵¹