First and second trimester screening for fetal structural anomalies

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A B S T R A C T

Fetal structural anomalies are found in up to 3% of all pregnancies and ultrasound-based screening has been an integral part of routine prenatal care for decades. The prenatal detection of fetal anomalies allows for optimal perinatal management, providing expectant parents with opportunities for additional imaging, genetic testing, and the provision of information regarding prognosis and management options. Approximately one-half of all major structural anomalies can now be detected in the first trimester, including acrania/anencephaly, abdominal wall defects, holoprosencephaly and cystic hygromata. Due to the ongoing development of some organ systems however, some anomalies will not be evident until later in the pregnancy. To this extent, the second trimester anatomy is recommended by professional societies as the standard investigation for the detection of fetal structural anomalies. The reported detection rates of structural anomalies vary according to the organ system being examined, and are also dependent upon factors such as the equipment settings and sonographer experience. Technological advances over the past two decades continue to support the role of ultrasound as the primary imaging modality in pregnancy, and the safety of ultrasound for the developing fetus is well established. With increasing capabilities and experience, detailed examination of the central nervous system and cardiovascular system is possible, with dedicated examinations such as the fetal neurosonogram and the fetal echocardiogram now widely performed in tertiary centers. Magnetic resonance imaging (MRI) is well recognized for its role in the assessment of fetal brain anomalies; other potential indications for fetal MRI include lung volume measurement (in cases of congenital diaphragmatic hernia), and pre-surgical planning prior to fetal spina bifida repair. When a major structural abnormality is detected prenatally, genetic testing with chromosomal microarray is recommended over routine karyotype due to its higher genomic resolution.

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1. Introduction

Fetal structural anomalies complicate 2–3% of all pregnancies [1–5]. Ultrasound screening for fetal structural anomalies is an integral part of routine prenatal care in well-resourced countries. The prenatal detection of structural anomalies provides expectant parents with an early opportunity to obtain information regarding the condition, including its nature, etiology, prognosis, and the availability of prenatal or postnatal therapies. The mid-trimester anatomical survey — typically performed between 18 and 22 weeks gestation — has been the standard of care for the detection of fetal structural anomalies for several decades. The reported prenatal detection rate for fetal anomalies varies widely (15–85%), and is dependent upon multiple factors: the gestational age at which the examination is performed; the expertise of the ultrasound facility and the individual sonographer; the body mass index (BMI) of the woman; and the particular organ system being interrogated [1,2,5,6]. Superior detection rates are associated with dedicated obstetric ultrasound practices and tertiary care facilities. Detection rates are also increased in high-risk populations where the a-priori risk of finding an abnormality is higher in women with known risk factors for anomalies [7]. The RADIUS study, a large randomized trial of more than 15,000 women, reported a relative detection rate for fetal anomalies of 2.7 (95% confidence interval: 1.3–5.8) in tertiary compared to non-tertiary settings [1]. When an abnormality is suspected on routine examination, it is recommended that women be referred to a tertiary ultrasound provider or fetal

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medicine specialist for confirmation of the abnormality, and further management. For some anomalies, additional assessment with serial ultrasounds, fetal echocardiography, magnetic resonance imaging (MRI), or genetic testing of the fetus may also be recommended.

The introduction of non-invasive prenatal testing (NIPT) with cell-free fetal DNA into clinical practice over the past five years has assumed much of the original role of the 11–13-week nuchal translucency ultrasound with regards to trisomy 21 detection. Despite the further advances expected within the field of prenatal genetics, there will remain a significant role for ultrasound screening for fetal structural anomalies across all the trimesters. With continuous advances in the technical capabilities of ultrasound, along with increasing expertise of operators, anomalies are now being diagnosed with greater levels of confidence and at much earlier gestational ages than before.

2. First trimester ultrasound: advances in early detection of structural anomalies

When first trimester ultrasound was introduced into routine prenatal care, its primary functions were to confirm pregnancy viability, number of fetuses, and provide accurate dating. As combined first trimester screening for trisomy 21 with measurement of the nuchal translucency (NT) and serum markers became incorporated into prenatal care from the late 1990s, assessment of early fetal anatomy at 11–13 weeks evolved into an important component of first trimester imaging. It is now estimated that a detailed examination of fetal anatomy in the first trimester should detect approximately half of all major structural anomalies [8–10]. The International Society of Ultrasound in Obstetrics and Gynecology (ISUOG) has published practice guidelines for performance of the first trimester scan [11]. Key components of the examination are listed in Box 1. Ultrasound in the first trimester now has two major functions: from the detection and characterization of early intrauterine pregnancy (confirming viability, establishing accurate dating, assessing the number of fetuses, and in the case of multiple pregnancy, assessing chorionicity and amnionicity) to detailed fetal assessment toward the end of the trimester. Anatomy assessment can also be performed between 11 and 13^{+6} weeks (crown–rump length (CRL) between 45 and 84 mm) at the time of the NT assessment for combined first trimester screening.

2.1. Technical aspects of first trimester ultrasound

The introduction of high-frequency transvaginal ultrasound scanning in the 1990s facilitated advances in the imaging of fetal structures early in pregnancy [11]. The incorporation of a transvaginal approach at the time of the first trimester scan increases anatomical assessment and allows better visualization of particular structures, including the fetal face, kidneys and bladder [8]. However, reduced probe flexibility in obtaining different scanning planes limits its application, and transvaginal scanning alone has not proven to be superior to its use in combination with transabdominal scanning, or a transabdominal approach alone [8,9]. The safety of two-dimensional (2D) grey scale and M-mode ultrasound has been well established for any gestation, but it is recommended that pulsed Doppler (spectral, power and color flow) should not be used routinely in the first trimester, owing to potential concerns of biothermal effects on the developing fetus [12]. Pulsed Doppler ultrasound should only be used where clinically indicated, such as to refine the risk of trisomy (by use of tricuspid and/or ductus venosus Doppler assessment), or to further interrogate a suspected cardiac anomaly; when performing Doppler ultrasound, attention to the thermal index and minimizing exposure time is important [12].

2.2. The early anatomical survey (11–13^{+6} weeks nuchal translucency ultrasound)

The important structures that should be routinely identified at the time of the 11–13^{+6}-week scan are listed in Table 1 [11]. Measurement of the NT as part of the first trimester combined screening test (with maternal age, serum biochemistry and the presence/absence of the nasal bone) has been well validated and provides a detection rate of trisomy 21 of 90% for a false-positive rate of 5% [13,14]. The Fetal Medicine Foundation has published guidelines and provides a registered course on how to measure the NT appropriately, along with assessing for other markers of aneuploidy in the first trimester, such as Doppler assessment of the ductus venosus and for tricuspid regurgitation, which help to refine the risk of trisomy [15]. An increased NT is associated with a risk of aneuploidy, and other genetic syndromes (Fig. 1a) [4].

In the absence of aneuploidy, an increased NT confers a higher risk of a major structural anomaly (particularly of the cardiovascular, gastrointestinal or musculoskeletal systems), and a detailed anatomical assessment should be undertaken [16,17]. In a large cohort from California investigating the association of increased NT with non-cardiac anomalies, infants with an increased NT (defined as ≥3.5 mm or ≥95th percentile for CRL) were at risk of having one or more major structural birth defects (any defect, relative risk (RR): 1.6; 95% confidence interval (CI): 1.3–1.9; multiple defects, RR: 2.1; 95% CI: 1.3–3.4) [17]. The most frequent anomalies included pulmonary, gastrointestinal, genitourinary, and musculoskeletal anomalies. Associated anomalies are not always detectable at the time of the NT scan, however, and a tertiary level midtrimester anatomy scan is recommended in this setting.

2.3. Detection rates in the first trimester

Overall detection rates for structural abnormalities in first trimester ultrasound range from 46.1% to 76.1%, but vary substantially according to organ system [8,10,18,19]. A systematic review of 19 publications with more than 78,000 fetuses sought to determine the detection rate of fetal anomalies by early ultrasound (11–14 weeks). A total of 996 anomalies were present in the study cohort (a prevalence of 12 per 1000), of which 501 (50.3%) were detected prenatally [8]. Highest detection rates were noted for neck anomalies (92%) and abdominal wall defects, such as omphalocele (Fig. 1b) (88%), with lower detection rates for brain and spine (51%), heart (48%), limbs (34%), genitourinary system and the face (both 34%) (Table 2).

The use of a systematic, detailed protocol is associated with an

Table 1
Anatomical assessment checklist at $11-13^{+6}$-week ultrasound scan.

Organ/ anatomical area	Present and/or normal
Head	Present
	Cranial bones
	Midline falx
	Choroid-plexus-filled ventricles
Neck	Normal appearance
	Nuchal translucency thickness (if accepted after informed consent and trained/certified operator available)[a]
Face	Eyes with lens[a]
	Nasal bone[a]
	Normal profile/mandible[a]
	Intact lips[a]
Spine	Vertebrae (longitudinal and axial)[a]
	Intact overlying skin[a]
Chest	Symmetrical lung fields
	No effusions or masses
Heart	Regular cardiac activity
	Four symmetrical chambers[a]
Abdomen	Stomach present in left upper quadrant
	Bladder[a]
	Kidneys[a]
Abdominal wall	Normal cord insertion
	No umbilical defects
Extremities	Four limbs each with three segments
	Hands and feet with normal orientation[a]
Placenta	Size and texture
Cord	Three-vessel cord[a]

Reproduced with permission from Salomon et al. [11].
^a Optional structures.

Fig. 1. First trimester anomalies: (a) increased nuchal translucency, skin oedema, micrognathia (image courtesy of Dr Simon Meagher); (b) omphalocele.

increased detection rate of fetal anomalies [9,18,20]. The detection rate appears to increase with advancing gestational age (Fig. 2), when multiple rather than isolated anomalies are present (60% vs 44%), in women who are deemed to be at high risk rather than an unselected population (65% vs 50%), and with the use of a combined transabdominal and transvaginal approach (62%), rather than either technique in isolation (51% and 34% respectively) [8]. Decreased first trimester detection rates are seen with advancing maternal BMI and in the presence of uterine fibroids [9,21]. Other modifiable factors thought to impact on the detection of anomalies in the first trimester include the gestational age at the time of the scan, the time allocated for screening, sonographer experience and training, and knowledge of embryology including normal developmental milestones [9,18].

2.4. Limitations of first trimester ultrasound

The majority of studies published do not detail false-positive rates; however, this is thought to be lower in the first trimester than for second trimester sonography [9,10]. False-positive rates of 0.09% for first trimester, and 0.6% for second trimester scans have been reported [10]. False positives can be difficult to capture, as the natural evolution of some anomalies may involve resolution, for example in megacystis, hydronephrosis, or with the physiological herniation of bowel, or spontaneous closure of small ventricular septal defects [8,9,18]. Whereas the detection of a major anomaly no doubt provides parents with earlier access to prenatal diagnosis and management options, the anxiety raised by the suggestion or uncertainty of an anomaly in the first trimester which may require confirmation in the second trimester should not be underestimated, and is perhaps the biggest downside to performing more detailed first trimester anatomy screening. Caution should be exercised with respect to definitive pregnancy management options, such as termination, in such cases when the diagnosis is not certain. Other limitations include cost and the accessibility in some
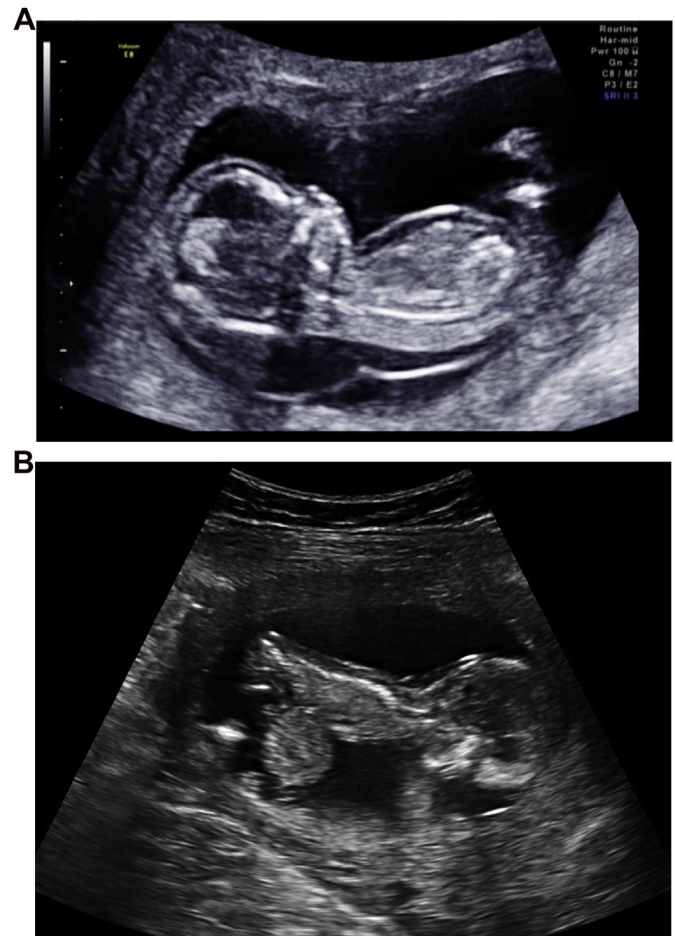
settings, along with the lack of standardization between ultrasound providers and the need for further sonographer training.

The identification of a major anomaly in the first trimester allows for earlier genetic testing, and potentially more management options than at a later gestation. However, because of the late development of some organ systems and the delayed onset of a number of major anomalies, it is unlikely that the first trimester scan will replace the routine mid-trimester anatomy scan. Furthermore, many abnormalities suspected in first trimester will require a second trimester review before a definitive diagnosis or prognosis can be made.

3. Second trimester ultrasound: overview of current standard of care

Whereas an increasing number of fetal anomalies can be detected in the first trimester, further fetal growth in the second trimester allows improved visualization, making the mid-trimester scan the standard of care for fetal anatomical assessment in both low- and high-risk pregnancies [11,22,23]. The major professional societies throughout the world recommend that all pregnant women be offered a mid-trimester ultrasound scan for the detection of structural fetal anomalies [24–27]. This is generally performed between 18 and 22 weeks, though 'at risk' women may receive additional scans. The second trimester allows for optimal examination of fetal anatomy, along with screening for soft markers for aneuploidy, evaluation of fetal size and the presence of

Table 2
Detection rates of fetal malformations in the first trimester.

Detection rate	Fetal malformation
100%	Acrania, anencephaly, ectopia cordis, encephalocele
50—99%	Cystic hygroma, double-outlet right ventricular flow, Fallot, gastroschisis, omphalocele, holoprosencephaly, hypoplastic left heart syndrome, limb reduction, megacystis, polydactyly, septal defects, transposition of great vessels, valvular disease
1—49%	Spina bifida, hydrocephalus, skeletal dysplasia, facial cleft, Dandy—Walker, aortic coarctation, arthrogryposis
0%	Corpus callosum agenesis, bladder exstrophy, congenital cyst adenomatoid malformation, cerebellar hypoplasia, duodenal atresia, hydronephrosis, renal agenesis, duplex kidneys, bowel obstruction, extralobar sequestration

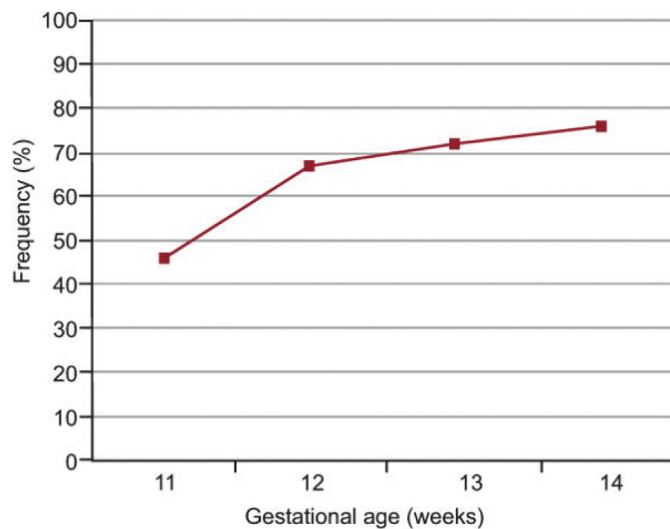Reproduced with permission from Rossi and Prefumo [8].

Fig. 2. Detection rates of fetal structural anomalies from 11 to 14 weeks of gestation. Reproduced with permission from Rossi and Prefumo [8].

abnormal placentation. Extensive guidelines for the performance of the second trimester anatomical survey have been published by international organizations such as ISUOG and the UK National Health Service (NHS) [24,28]. In addition to screening for fetal anomalies, the mid-trimester scan should confirm the number of fetuses, the gestational age (appropriate size), the location of the placenta, and assess the cervical length (Table 3). The majority of identifiable anomalies will be detected with 2D ultrasound, but in certain cases (such as facial clefts or talipes equinovarus) three-dimensional (3D) ultrasound may provide additional detail.

3.1. Soft markers

Along with the detection of major structural anomalies, the mid-trimester ultrasound can also detect markers for aneuploidy (most usually trisomy 21). Minor or 'soft' markers were first reported in the 1980s, and include several ultrasound features, which in isolation may represent normal variants, but which are also seen with increased frequency in trisomy 21 [25]. The presence of a soft marker, such as an increased nuchal fold, hypoplastic or absent nasal bone, aberrant right subclavian artery, echogenic bowel, or short long bones, should prompt the operator to undertake a more detailed examination of the fetal anatomy as the risk of an underlying chromosome abnormality is increased in the presence of multiple findings. Nasal bone hypoplasia, thickened nuchal fold,

and aberrant right subclavian artery are the best-performing second trimester markers for trisomy 21 [30,31]. Table 4 lists pooled estimates of positive likelihood ratios for the most widely used soft markers [31]. There has been recent debate in the literature about the contemporary relevance of isolated markers, especially in the setting of prior cell-free DNA screening [32]. Given the very high negative predictive value of NIPT, the detection of an isolated soft marker is no longer considered an independent risk factor for diagnostic testing if a woman has previously had a low-risk NIPT result [33]. Although this may alter genetic counseling regarding soft markers in countries with high uptake of NIPT, soft markers may also have important associations independent of aneuploidy. In the setting of echogenic bowel, further growth scans and consideration of testing for congenital infections (such as cytomegalovirus) and cystic fibrosis are also recommended. Short long-bones may represent the evolution of skeletal dysplasia and further fetal growth assessments may be required for clarification. Conversely, little clinical significance is now attributed to choroid plexus cysts and intracardiac echogenic foci when present in isolation in a fetus with a low risk of aneuploidy, as they are not associated with other conditions, and have no functional consequence in postnatal life [25,31].

3.2. Detection rates for structural anomalies in the mid-trimester

As with first trimester sonography, the more detailed the examination protocol, the more likely that fetal anomalies will be detected. The American Institute of Ultrasound in Medicine (AIUM) and the Society for Maternal—Fetal Medicine (SMFM) have produced guidelines for an advanced anatomy scan, to be performed when an indication exists for a more detailed fetal structural examination [29]. Such indications may include a known or suspected fetal anomaly in the current pregnancy; a past history of a previous fetus or child with a congenital, genetic, or chromosomal condition; maternal and pregnancy risk factors such as BMI >35 kg/m^2, teratogen exposure, pre-gestational diabetes; and NT > 3.0 mm or positive first trimester screening test. In addition to the components of a basic fetal ultrasound examination, a detailed anatomical survey is undertaken (Table 3).

Detection rates for major anomalies at the mid-trimester scan vary, and have been reported at around 60%, based on the anatomical system involved and on the expertise of the sonographer [2,3,22,23,26]. As with first trimester assessment, higher detection rates are reported for major and lethal anomalies (84%) [1,2]. Compared with selective screening for 'at risk' pregnancies, a Cochrane Review concluded that the performance of a routine scan for all pregnant women prior to 24 weeks improves the prenatal detection rate of major fetal abnormality (RR: 3.46; 95% CI: 1.67—7.14) [5]. The first randomized control trial to assess the effectiveness of routine ultrasound in low-risk women was published in 1994. The RADIUS study demonstrated a three-fold increase in the prenatal detection of fetal anomalies in the screening group, compared to the control group (35% vs 11%) [1]. The rationale for offering routine morphology screening is supported by the fact that 75% of anomalies occur in low-risk women [6]. Even in the most expert hands however, not all fetal anomalies can be detected, and, prior to commencing an examination, appropriate counseling about the benefits and potential limitations of the study should be undertaken [28].

In a large contemporary population of 10,344 unselected pregnancies at a county hospital in Sweden, 73 of 187 structural anomalies (39%) were detected prenatally, after excluding aneuploid fetuses [3]. The detection rate of major malformations (45/82; 54.9%) was twice as high as for minor malformations (28/105; 26.7%). Atrial and ventricular septal defects and hypospadias

Table 3
Components of the basic and advanced mid-trimester ultrasound examinations.

Anatomical area	Basic	Advanced
Head and neck	Intact cranium	Integrity and shape of cranial vault
	Cavum septi pellucidi	Brain parenchyma
	Midline falx	Corpus callosum
	Thalami	3rd ventricle[a]
	Lateral cerebral ventricles	4th ventricle[a]
	Cerebellum	Lateral ventricles
	Cisterna magna	Cerebellar lobes, vermis and cisterna magna
	Absence of masses (i.e. cystic hygroma)	Neck, nuchal fold
Face	Intact upper lip	Profile
		Coronal face (nose, lips, lens)
		Palate, maxilla, mandible and tongue
		Ear position and size
		Orbits
Chest/heart	Cardiac activity	Aortic arch
	Four-chamber view	Superior and inferior venae cavae
	Left ventricular outflow tract	Three-vessel view
	Right ventricular outflow tract	Three-vessel and trachea view
		Lungs
		Integrity of diaphragm
		Ribs[a]
Abdomen	Stomach (presence, size and situs)	Small and large bowel
	Kidneys	Adrenal glands
	Urinary bladder	Gallbladder
	Cord insertion into fetal abdomen	Liver
	Umbilical cord vessel number	Renal arteries
		Spleen[a]
		Integrity of abdominal wall
Spine	Cervical/thoracic/lumbar/sacral	Integrity of spine and overlying soft tissue
		Shape and curvature
Extremities	Legs	Number; architecture and position
	Arms	Hands
		Feet
		Digits: number and position
Genitalia[a]	In multiple gestation	Sex
Placenta	Location	Masses
	Relationship to internal os	Placental cord insertion
	Appearance Placental cord insertion	Accessory/succenturiate lobe and vascular supply
Standard evaluation	Fetal number	
	Presentation	
	Qualitative estimate of amniotic fluid	
Maternal anatomy	Cervix (transvaginal[a])	
	Uterus	
	Adnexa	
Biometry	Biparietal diameter	Cerebellum
	Head circumference	Inner and outer orbital diameters[a]
	Femur length	Nuchal thickness
	Abdominal circumference	Nasal bone measurement
	Fetal weight estimate	Humerus
		Ulna/radius[a]
		Tibia/fibula[a]

Adapted with permission from Salomon et al. [28] and Wax et al. [29].
   [a] When medically indicated.

Table 4
Pooled estimates of positive likelihood ratios for isolated sonographic markers for trisomy 21.

Marker	Likelihood ratio
Increased nuchal fold	3.79
Echogenic bowel	1.65
Aberrant right subclavian artery	3.94
Absent or hypoplastic nasal bone	6.58

Adapted with permission from Agathokleous et al. [31].

accounted for two-thirds of the minor anomalies that were not detected prenatally. With the exclusion of these minor malformations, the overall detection rate increased to 56%, in line with other cohorts [2,22,23]. The sensitivity for prenatal detection varied depending on the organ system involved, with higher detection rates for pulmonary (83%) (Fig. 3a), and central nervous system (CNS) (82%) anomalies, and lower detection rates for cardiac anomalies (13%). The false-positive rate (malformations that could not be confirmed after delivery) was 5.3%, including hydronephrosis and pleural effusions that resolved during pregnancy [3]. These results are similar to those of other published reports that have detection rates at 47–83% [2,23,34–36].

Each institution performing fetal anatomy assessment should have protocols in place in the event that an abnormality is detected, as timely notification to the referring doctor and immediate care of the woman/couple are equally important in the management of such cases [26]. When a fetal abnormality is detected in the mid-trimester, referral to a tertiary level ultrasound provider and/or a fetal medicine subspecialist is recommended. Confirmation of the anomaly and further counseling regarding management and
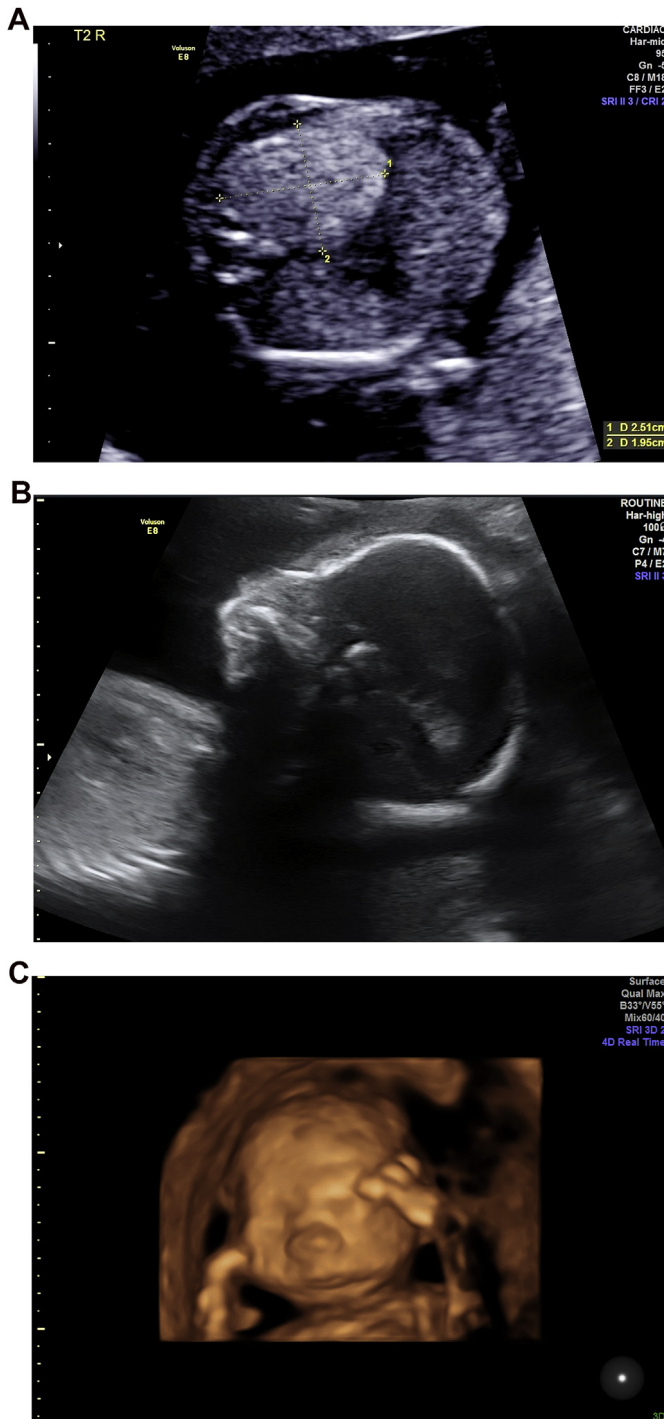
Fig. 3. Second trimester scan: (a) echogenic lung lesion; (b) micrognathia (2D ultrasound); (c) micrognathia (three-dimensional ultrasound, same fetus as (b)).

prognosis can then be undertaken. Given that fetuses with structural anomalies are at an increased risk for karyotypic and other genetic abnormalities, amniocentesis for chromosomal assessment with microarray should also be considered [37,38].

3.3. Technical considerations in the detection of structural malformations

Just as there are technical limitations in the first trimester, the same factors can also adversely affect the detection rates of fetal anomalies in the second trimester. These include technical factors, such as the experience of the operator and the sophistication of the machine; and patient factors, including gestational age, maternal obesity and fetal crowding in multiple pregnancy. It is estimated that maternal obesity alone is associated with at least a 20% reduction in the detection of structural anomalies, and an increase in the need for repeat imaging [4,39]. This is of concern, as obesity is a known independent risk factor for adverse maternal and fetal complications, including the risk of fetal structural anomalies [39–41]. In one study, only 49% of women with BMI >40 mg/kg^2 (class III obesity) were able to have their basic anatomy scan completed in a tertiary setting [39]. This has a major impact on resources, as more than one-third of women of reproductive age in developed countries are obese, and the prevalence of obesity is increasing worldwide [40,41]. Delaying the anatomy scan until 22–23 weeks may improve the ability to complete the assessment in obese women, but this may delay the diagnosis of major fetal conditions and impact on management options for the pregnancy. Wherever possible, patients with more complex pregnancies, including those with morbid obesity, should be referred to practices with specific expertise in obstetric ultrasound [39].

3.4. The role of 3D ultrasound

Some major anomalies will be detectable with routine 2D ultrasound; however, there are some conditions in which 3D ultrasound may provide additional information when an anomaly is suspected. Such anomalies include oro-facial clefts, talipes equinovarus, and micrognathia. In these conditions, 3D ultrasound can assist in further characterization of the defect, and in the counseling of the parents when explaining the nature of the anomaly. A systematic review comparing 2D and 3D ultrasound reported 3D detection rates of 100% for cleft lip, and 86–90% for cleft lip and palate in high-risk women, compared to 9–100% with 2D ultrasound (for cleft lip with or without cleft plate). 3D ultrasound was less sensitive for cleft palate in isolation [42].

Micrognathia may be detected as early as the first trimester, and the use of 3D ultrasound and 3D rendering technology has improved the accuracy of measurements of the mandible and the detection of micrognathia (Fig. 3b and c) [43]. Owing to its numerous chromosomal and syndromal associations, micrognathia is an important structural anomaly to detect prenatally in order to facilitate early diagnostic testing and counseling.

4. Second trimester neurosonography: beyond the routine morphology scan

Detection of CNS anomalies is a high priority in prenatal screening as they are relatively frequent, and have a strong association with chromosomal abnormalities, genetic syndromes, and neurodevelopmental delay [1]. Even in unselected populations, detection rates for CNS malformations of up to 80% have been reported [1]. Improvements in ultrasound capabilities with high-speed digital electronics, and the adaptation of a high-frequency transvaginal approach has led to a further improvement in detection rates of fetal CNS malformations [44]. To this extent, fetal neurosonography is defined as a targeted ultrasound examination of the fetal brain, performed by an experienced sonologist using a multiplanar, and possibly transvaginal, approach [45]. Guidelines for both the basic and detailed examination (or neurosonogram) of the fetal brain have been published by ISUOG [46].

In addition to the structures examined in the basic ultrasound assessment, a neurosonogram involves a systematic examination with additional coronal and sagittal planes. Coronal examination

through the anterior fontanelle demonstrates the interhemispheric fissure and the anterior horns of the lateral ventricles. The occipital horns of the lateral ventricles, the interhemispheric fissure, and the hemispheres and vermis of the cerebellum can be demonstrated through the posterior fontanelle. The mid-sagittal plane is used to examine the corpus callosum, the cavum septi pellucidi, brain stem, pons, vermis and posterior fossa, and the parasagittal plane demonstrates the lateral ventricle, choroid plexus, periventricular tissue and the cortex [46].

A dedicated neurosonogram has superior detection ability than a standard routine examination; however, it requires expertise that may not be available in all centers. The diagnosis of specific CNS anomalies may be made by direct visualization of the presence/absence of a structure, or by indirect findings, suggestive of an underlying abnormality, for example colpocephaly as a marker for agenesis of the corpus callosum (ACC) [47].

4.1. MRI of the fetal brain

Although ultrasound will no doubt remain the primary imaging modality for the assessment of the fetal brain, MRI plays an important contributory role. There have been conflicting reports about the perceived benefit of fetal MRI over expert neurosonography for the detection of CNS anomalies [44,45,48]. Both Malinger and Paladini and their colleagues report similar sensitivities and diagnostic accuracy for each modality (85–95%), with MRI providing additional information in only 7–8% of cases [44,45]. Conversely, a systematic review by Rossi and Prefumo found that MRI provided additional detail in 22.1% of cases, and that in 30% the information changed clinical management [48]. Local practice therefore should be tailored to where the expertise is available, either with expert neurosonography, fetal MRI, or both.

5. Role of MRI in assessment of fetal structural anomalies

The primacy of ultrasound for the detection of fetal anomalies remains undisputed, but MRI is now recognized as an important complementary modality in specific circumstances. MRI is usually employed as a second-line investigation for fetal anomalies that are either incompletely assessed by ultrasound, or in the setting of an apparently isolated abnormality to exclude associated conditions. MRI is rarely used as a primary screening tool, but it may have a role in selected cases at risk of specific anomalies, such as screening for brain tubers or subependymal nodules associated with tuberous sclerosis [49]. MRI utilizes electromagnetic fields rather than radiation, and is therefore safe in pregnancy, with no harmful fetal effects reported [50]. Since its introduction into fetal medicine in the 1990s, improvements have led to the expansion of the use of MRI, and the development of ultrafast techniques has decreased artifacts due to fetal movement, negating the need for maternal (or fetal) sedation.

5.1. Technical aspects of fetal MRI

Specific techniques and indications for fetal MRI have been reported from the fetal imaging workshop hosted by the National Institute of Child Health and Human Development, in the recently published ISUOG published practice guideline, and by other organizations, such as the American College of Radiology [25,49,50]. The use of gadolinium contrast is not recommended in pregnancy as it is known to cross the placenta [51]. MRI is best performed late in the second and third trimesters, especially in the setting of a fetal brain anomaly that is likely to evolve with advancing gestation. Little additional benefit is thought to occur at earlier gestations, such as prior to 18–22 weeks, when small fetal size and marked

fetal activity can have a significant effect on MRI image quality [49]. Single-shot and other rapid acquisition techniques are employed to counteract fetal movement. T2-weighted fast (turbo) spin-echo sequences are best for imaging the fetal brain, and provide the most detail on fetal anatomy. T1-weighted images provide less detail but can be useful for defining certain tissue or fluid characteristics, such as fat, hemorrhage, calcification, and meconium. Single-shot high-resolution echoplanar sequences are used for bony structures, calcification and hemorrhage, and other additional sequences, such as diffusion-weighted imaging (DWI) or fluid attenuated inversion recovery (FLAIR), may be useful in certain settings (such as ischemia) [49].

5.2. Indications for fetal MRI

Indications for prenatal MRI include suspected or confirmed CNS anomalies (such as ventriculomegaly (Fig. 4), ACC, absent or abnormal cavum septi pellucidi, posterior fossa abnormalities, cortical malformation or migrational anomalies, and solid or cystic masses); suspected vascular abnormalities of the brain (including infarction, hemorrhage, hydranencephaly, and complications of monochorionic twin pregnancies); congenital anomalies of the spine (such as neural tube defects, sacrococcygeal teratomas, sacral agenesis and vertebral anomalies); masses of the face and neck that may lead to airway obstruction (goiter, teratoma, vascular or lymphatic anomalies and facial clefts); thoracic pathologies (congenital lung malformations, congenital diaphragmatic hernia, effusions and mediastinal masses); and the assessment of some renal anomalies (including renal agenesis, bladder exstrophy and lower urinary tract obstruction) especially when severe oligohydramnios precludes adequate ultrasound assessment [49,50]. MRI may also be used in the assessment of residual fetal lung volume in cases where pulmonary hypoplasia is a significant risk (such as diaphragmatic hernia, skeletal dysplasia, or in the presence of a large chest mass) [52]. MRI is increasingly used after single fetal demise in monochorionic twin pregnancies in order to detect brain injury in the surviving twin [53]. An important emerging role of MRI is in the preoperative workup for specific fetal surgical conditions, such as myelomeningocoele assessment prior to fetal surgery. Fetuses with large neck masses can have the extent of the mass and the risk of airway obstruction assessed prior to delivery, so that an ex-utero intrapartum treatment procedure can be planned if required [54]. Finally, MRI may provide additional information in cases of suspected morbid placentation, such as placenta accreta [55].

5.3. MRI versus ultrasound

MRI overcomes some of the limitations of ultrasound, such as beam attenuation by adipose tissue in obese women, and shadowing due to bony structures, and it is not as dependent upon fetal position as ultrasound [25]. MRI may be superior to ultrasound when oligohydramnios is present, and it provides a greater imaging window and improved contrast between different tissues. Despite these advantages, fetal MRI is unlikely to replace ultrasound as a primary screening modality as it is more expensive and expertise in fetal imaging is less widely available. Furthermore, a recent prospective blinded case–control study comparing 2D ultrasound (2D US), 3D ultrasound (3D US) and MRI for the diagnosis of fetal anomalies demonstrated no difference in the sensitivities between each of the modalities for the diagnosis of non-CNS anomalies (2D US 77.8% vs 3D US 75.6% vs MRI 80%) [56].
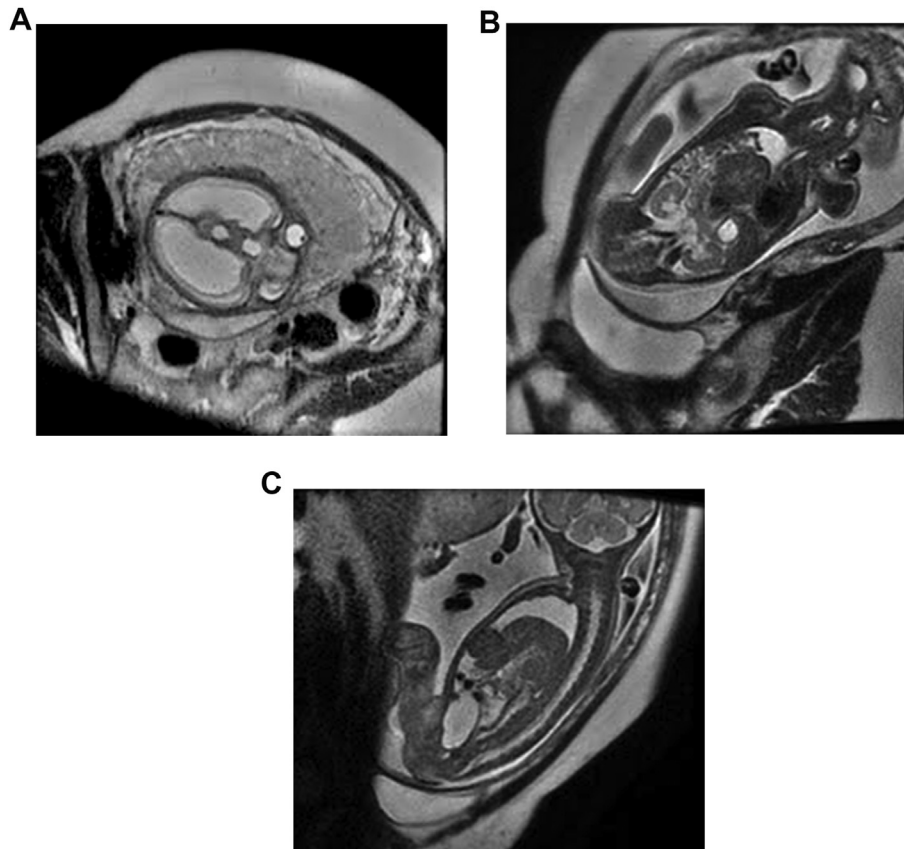
Fig. 4. Fetal magnetic resonance imaging: (a) severe bilateral cerebral ventriculomegaly; (b) and (c) congenital diagphragmatic hernia (images courtesy of Department of Medical Imaging, Royal Hobart Hospital).

6. Role of chromosome testing after a structural abnormality

The discovery of a major structural abnormality during pregnancy should prompt a thorough examination of the remainder of the fetal anatomy and consideration of diagnostic testing for chromosome abnormalities [37,38]. Strong associations with aneuploidy are seen with some specific anomalies such as omphalocoele, congenital diaphragmatic hernia, cystic hygroma, and many cardiac anomalies, such as Tetralogy of Fallot, and atrioventricular septal defect. Though many of these are associated with conditions that would be detected on a standard G-banded karyotype (e.g. autosomal trisomies), chromosomal microarray is the preferred test in the presence of structural abnormalities due to the additional yield of pathogenic subchromosomal copy number variations. The clinical utility of chromosomal microarray was demonstrated by a large, prospective study of more than 4400 pregnancies undergoing invasive testing; in one-quarter of cases the indication for invasive testing was a structural anomaly on ultrasound. In this group, chromosomal microarray provided additional information of clinical significance in 6.0% of cases [57].

Recent advances in aneuploidy screening has led to a widespread decline in diagnostic procedures performed for high-risk serum screening tests, whereas testing following the detection of an ultrasound abnormality remains stable. In a large population-based study, ultrasound abnormality was shown to have surpassed first trimester combined screening as the most frequent indication for invasive testing in the year 2015 (35% of all indications for diagnostic tests) [58]. In this Australian population, 20.9% of pregnancies that had diagnostic testing for a fetal abnormality had a major chromosome abnormality confirmed. Though NIPT has an undisputed role either as a first or second tier screening test, it is not recommended following the detection of a fetal structural abnormality, as high-resolution chromosome assessment with microarray is now the standard of care for fetuses with structural abnormalities [59].

7. Role of ultrasound at the time of NIPT

Prior to proceeding with cell-free DNA screening in the first trimester, ultrasound is recommended to confirm viability, to establish accurate dating and to identify the number of fetuses present. In the absence of a recent ultrasound, results may be inaccurate or unobtainable, for example, if the sample is drawn too early (prior to 10 weeks), if multiple fetuses are present, or if there has been demise of one or more fetuses in a multiple pregnancy. The Society of Maternal Fetal Medicine has recently addressed the role of first trimester ultrasound in women who intend to undergo cell-free DNA screening, and though it states that an 11–13 week scan is not required for the sole indication of nuchal translucency measurement, it may still be useful to identify some major fetal anomalies, as well as the other reasons listed above.

8. Conclusion

Ultrasound-based screening for fetal structural anomalies is an integral part of routine maternity care, providing prenatal opportunities for additional genetic testing, specialist imaging, prognostic information and discussion of management options. MRI is now well established for the assessment of CNS anomalies and is being investigated for a range of other indications, such as lung

volume measurement, and preoperative planning for fetal surgery. The role of the 11—13-week ultrasound continues to evolve in the context of rapid advances in cell-free DNA-based screening. Whereas more than 50% of major structural abnormalities can be detected in the first trimester, screening for fetal anatomy in the second trimester will remain the cornerstone for the detection of structural abnormalities for the foreseeable future.

8.1. Practice points

- Fetal structural anomalies complicate approximately 3% of all pregnancies.
- The second trimester anatomy scan (between 18 and 22 weeks) remains the standard of care for the detection of fetal structural anomalies.
- Fifty percent of all major structural anomalies may be detected in the first trimester.
- Detection rates vary according to various factors, including the gestational age, the organ system, maternal size, ultrasound equipment, and sonographer expertise.
- MRI plays a complementary role to ultrasound, and its major role is in the assessment of fetal CNS abnormalities and in the pre-surgical planning of selected anomalies.
- When a major structural abnormality is detected prenatally, genetic testing with chromosomal microarray should be offered.

8.2. Research directions

- The evolving role of the routine 11—13-week scan in populations with high uptake of cell-free DNA screening.
- The first trimester detection rate of fetal anomalies following the implementation of a detailed screening protocol in non-tertiary settings.
- Potential clinical utility of fetal exome sequencing following the detection of a fetal structural anomaly.
- Expanded role of MRI for predicting outcome in specific fetal anomalies.

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