Challenges in Sonographic Detection of Fetal Major Structural Abnormalities at the First Trimester Anomaly Scan

Dominic Iliescu, Monica Cara, Stefania Tudorache, Panos Antsaklis, Iuliana Ceausu, Daniela Paulescu, Liliana Novac, Nicolae Cernea, Aris Antsaklis

ABSTRACT
First-trimester (FT) ultrasound examination appears to have a very good sensitivity in the detection of fetal abnormalities, especially when an extended protocol that is achievable with reasonable resources of time, personnel and ultrasound equipment, is used. It has been shown that the efficiency of the routine anomaly scan varies widely between the studies performed both in early or mid-pregnancy. The analysis of technique and study designs reveals that in each gestational age, the extension of the investigational protocol is the most important factor in modulating the detection rate. Moreover, the use of similar basic checklists at the FT and second trimester (ST) examinations revealed comparable anomaly detection rates in large population groups. First trimester combined test have been demonstrated as a useful screening tool for genetic syndromes and consecutively the FT ultrasound scan became a routine examination in most prenatal diagnostic centers. Its performance in structural abnormalities detection has been communicated in high-, medium-risk populations or unselected low-risk variable number of patients and compared to the ST anomaly scan effectiveness. A detailed first-trimester anomaly scan using an extended protocol is an efficient screening method to detect major fetal structural abnormalities in low-risk pregnancies. It is a method that it is feasible at 12 to 13 + 6 weeks with ultrasound equipment and personnel already used for routine first-trimester screening. Rate of detection of severe malformations is greater in early- than in mid-pregnancy and on postnatal evaluation. Early heart investigation could be improved by an extended protocol involving use of color Doppler.

Keywords: Anomaly scan, Early or mid pregnancy, First trimester.

INTRODUCTION
During the last decades, sonography had a dramatic impact on the practice of obstetrics and perinatal medicine, providing important data in understanding the structural and physiological development of the fetus from early stages of pregnancy. If we add the long-term safety record of pregnancy ultrasound imaging, it is easy to understand its extensive use in modern obstetric care. The value and safety of the technique have resulted in a long list of indications in pregnant women and the scientific advances in the last 20 years have raised the hope that many pregnancy complications are potentially detectable from the late first trimester (FT) assessment, encouraging a model for a new pyramid of prenatal care. Indeed, algorithms based on combinations of maternal characteristics, early ultrasound findings and biochemical testing of maternal blood, are efficient in predicting most major aneuploidies, miscarriage and fetal death, pre-term delivery, preeclampsia, gestational diabetes, fetal growth restriction and macrosomia. In the past years, the specialized medical societies, as International Society of Ultrasound in Obstetrics and Gynecology (ISUOG), National Institute for Clinical Excellence (NICE) and American College of Obstetricians and Gynecologists (ACOG) have issued guidelines on routine prenatal care recommending that pregnant women should be offered the first trimester ultrasound scan. The primary aims of the first scan at 11 to 13 gestational weeks (GW) are to establish gestational age from the measurement of fetal crown-rump length (CRL), detect multiple pregnancies, determination of chorionicity, measurement of fetal nuchal translucency (NT) thickness as part of combined screening for trisomy 21 and the detection of certain fetal major structural abnormalities.

Early detection of fetal malformations showed in the last decade significant improvement and FT scan tends to become the first structural evaluation of the fetus. It also offers the possibility of an earlier and safer termination of pregnancy in cases detected with severe structural abnormalities, with less economic and emotional costs. This is an important shift in the timing of mortality, because major fetal abnormalities (MA) account for 25% of neonatal deaths and can lead to debilitating long-term disabilities at considerable socio-
economic costs. However, an extensive assessment of the fetal anatomy at the FT scan necessitates appropriate training and equipment. This can be related to the availability of qualified practitioners and equipment, local medical practice and legal considerations and insurance-related cost reimbursements. Indeed, instead of asking the question regarding whether routine detailed early ultrasound investigation should be performed, it may be more appropriate to ask whether it is justified from a cost-benefit perspective. In order to expect a certain benefit, the medical system has to assure the needs of equipment and trained sonographers and also should provide audit to be sure that the scans are being performed by professionals.

Regarding the fetal morphologic assessment, the current policy of most healthcare systems is to offer routinely a transabdominal ultrasound examination performed by competent personnel or by trainees under the supervision of certified sonographers, at 18 to 23 GW, with 20 minutes allocated for systematic detailed examination of the fetus. Structural anomalies may develop at later stages of pregnancy or may develop from pathophysiological process undetectable in the FT. Thus, the value of the standard ST ultrasound scan is undisputed, as it represents an important baseline against which earlier or later scans should be compared for the fetal health evaluation.

**IS FIRST TRIMESTER ANOMALY SCAN EFFICIENT?**

Gradually, the 11 to 13 GW scan evolved over the last 20 years from essentially a dating and genetic scan to one which also includes a basic checklist for examination of the fetal anatomy with the intention of diagnosing MA, which are either lethal or are associated with possible survival and severe immediate or long-term morbidity (Royal College of Obstetrics and Gynecology, 1997). The analysis showed that about 45% of the MA were detected routinely, with large differences between studies in detection rates which ranged from 15 to 85%, and also large differences in overall detection rates according to the type of fetal anomaly. The analysis showed that the variations were due to the differences in the type of studied malformations, the follow-up method and the extension of the scan protocols.

We should not be surprised by the comparable performance of the first and second trimester anomaly scans, as the increased resolution of the recent US equipment allowed the upgrade of the FT structural investigation to a comparable level as the ST protocol. One decade ago, Timor-Tritsch et al concluded that FT US examination, with appropriate equipment and in expert hands, can visualize as many structures as it could at 16 weeks 5 to 10 years previously and at 20 to 22 weeks 15 to 20 years previously. In a randomized controlled trial of 39,572 women Salvedt et al concluded that neither of the two strategies (first/second trimester anomaly scan) is significantly superior to detect fetal MA. However, we should not forget the particular role of FT scan in the detection of genetic syndromes.

Table 2 summarizes the minimum requirements recommended by the ISUOG practice guidelines for a basic fetal anatomical survey during the mid-trimester of pregnancy, emitted based on the main morphological investigation studies. In the same table, we present FT transabdominal acquisitions that demonstrate the respective features.

Few comments are important for the general practice. Some of the structures displayed (cerebellum, septum pellucidum, ventricular outflow tracts) can usually be assessed after 12 to 13 GW, depending on the examination conditions.

However, an important body of literature showed that the higher resolution of transvaginal evaluation adds a better and earlier discrimination of the anatomical structures.

On the other hand, contingent policies that offer early markers for underlying abnormalities (Figs 1 to 4) were found effective. Thus, increased nuchal translucency (NT), tricuspid regurgitation (TR), absent/ reversed ductus venosus (DV) flow, low-resistance of hepatic artery (HA) flow, abnormal cardiac axis, abnormal posterior brain complex, reduced fetal biparietal diameter (BPD), abnormal palate or absent mandibular gap in coronal retronal triangle (RNT) view, fetal abdominal cysts have been demonstrated to identify high-risk conditions.
pregnancies for variable adverse outcome,\textsuperscript{54} cardiac,\textsuperscript{55-57} neurological,\textsuperscript{58-60} palate defects,\textsuperscript{61,62} micrognathia,\textsuperscript{63} skeletal abnormalities,\textsuperscript{46,64-66} diaphragmatic hernia,\textsuperscript{67} and gastrointestinal malformations.\textsuperscript{68-70} A recent large study found that abnormal aneuploidy markers were associated with MA in chromosomal normal fetuses in 23\% for NT > 99th percentile, 17\% for absent or reversed DV blood flow and 5\% for NB absence.\textsuperscript{65}

What is more, regarding the fetal heart assessment, the color Doppler investigation is of great importance, given the low discrimination of the heart structures in gray-scale assessment at this gestational age.\textsuperscript{52,71-73}

The protocol used in our routine is described in Table 3. It is similar to previous extended protocols used for the early diagnostic of major abnormalities,\textsuperscript{40} and led to similar detection rates for MA, of about 80\%. What makes a FT morphologic protocol ‘extended’ or ‘detailed’? The differences between the protocols used in the FT are outlined from Table 3, where we present comparatively the basic and extended protocols generally used in screening studies. The main differences refers mainly to heart evaluation: whereas the basic protocol evaluate only the appearance of four chamber view in B-mode, the detailed protocol investigate all the classic five key-planes of the cardiac sweep and propose color Doppler technique to increase the confidence of the operator regarding the cardiac features. Other differences are related to the spine evaluation (posterior brain assessment, axial evaluation of the spine, underlying skin layer) and facial features (palate, upper lip and orbits assessment).

Table 1: Screening studies reporting on the effectiveness of the first-trimester scan in the diagnosis of fetal major abnormalities

<table>
<thead>
<tr>
<th>Authors</th>
<th>Total</th>
<th>Scan route</th>
<th>GA (weeks)</th>
<th>Fetal abnormalities</th>
<th>FT detection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hernadi and Torocsik, 1997\textsuperscript{30}</td>
<td>3991</td>
<td>TA, TV</td>
<td>11–14</td>
<td>49 (1.2%)</td>
<td>20 (40.8%)</td>
</tr>
<tr>
<td>D’Ottavio et al, 1998\textsuperscript{31}</td>
<td>4078</td>
<td>TV</td>
<td>13–15</td>
<td>88 (2.2%)</td>
<td>54 (61.4%)</td>
</tr>
<tr>
<td>Bilardo et al, 1998\textsuperscript{32}</td>
<td>1690</td>
<td>TA, TV</td>
<td>10–14</td>
<td>23 (1.4%)</td>
<td>10 (43.5%)</td>
</tr>
<tr>
<td>Hafner et al, 1998\textsuperscript{33}</td>
<td>4233</td>
<td>TA</td>
<td>10–13</td>
<td>56 (1.3%)</td>
<td>7 (12.5%)</td>
</tr>
<tr>
<td>Whitlow et al, 1999\textsuperscript{34}</td>
<td>6443</td>
<td>TA, TV</td>
<td>11–14</td>
<td>63 (1.0%)</td>
<td>37 (58.7%)</td>
</tr>
<tr>
<td>Guariglia and Rosati, 2000\textsuperscript{36}</td>
<td>3478</td>
<td>TV</td>
<td>10–16</td>
<td>57 (1.6%)</td>
<td>33 (57.9%)</td>
</tr>
<tr>
<td>Taipale et al, 2004\textsuperscript{37}</td>
<td>4789</td>
<td>TV</td>
<td>10–16, 25% above 14 w</td>
<td>33 (0.7%)</td>
<td>6 (18.2%)</td>
</tr>
<tr>
<td>Chen et al, 2004\textsuperscript{38}</td>
<td>1609</td>
<td>TA, TV</td>
<td>12–14</td>
<td>26 (1.6%)</td>
<td>14 (53.8%)</td>
</tr>
<tr>
<td>Souka et al, 2006\textsuperscript{39}</td>
<td>1148</td>
<td>TA, TV</td>
<td>11–14</td>
<td>14 (1.2%)</td>
<td>7 (50%)</td>
</tr>
<tr>
<td>Becker and Wegner, 2006\textsuperscript{40}</td>
<td>3094</td>
<td>TA, TV</td>
<td>11–13</td>
<td>86 (2.8%)</td>
<td>72 (83.7%)</td>
</tr>
<tr>
<td>Cedergren and Selbing, 2006\textsuperscript{41}</td>
<td>2708</td>
<td>TA</td>
<td>11–14 15% above 14 w</td>
<td>32 (1.2%)</td>
<td>13 (40.6%)</td>
</tr>
<tr>
<td>Saltvedt et al, 2006\textsuperscript{42}</td>
<td>18053 after aneupl excl</td>
<td>TA</td>
<td>11–14</td>
<td>371 (2.1%)</td>
<td>74 (19.9%)</td>
</tr>
<tr>
<td>Dane et al, 2007\textsuperscript{43}</td>
<td>1290</td>
<td>TA</td>
<td>11–14</td>
<td>24 (1.9%)</td>
<td>17 (70.8%)</td>
</tr>
<tr>
<td>Chen et al, 2008\textsuperscript{44}</td>
<td>7642</td>
<td>TA</td>
<td>10–14</td>
<td>127 (1.7%)</td>
<td>51 (40.2%)</td>
</tr>
<tr>
<td>Oztekin et al, 2009\textsuperscript{45}</td>
<td>1805</td>
<td>TA</td>
<td>11–14</td>
<td>21 (1.2%)</td>
<td>14 (66.7%)</td>
</tr>
<tr>
<td>Ebrashy et al, 2010\textsuperscript{46}</td>
<td>2876</td>
<td>TA, TV</td>
<td>13–14</td>
<td>31 (1.1%)</td>
<td>21 (67.7%)</td>
</tr>
<tr>
<td>Syngelaki et al, 2011\textsuperscript{47}</td>
<td>(45191) 44859 after aneupl excl</td>
<td>TA, TV</td>
<td>11–14</td>
<td>488 (1.1%)</td>
<td>213 (43.6%)</td>
</tr>
<tr>
<td>Iliescu et al, 2013\textsuperscript{48}</td>
<td>5472</td>
<td>TA, TV</td>
<td>12–14</td>
<td>76 (1.4%)</td>
<td>58 (76.3%)</td>
</tr>
<tr>
<td>Total</td>
<td>118110</td>
<td>TA, TV</td>
<td>10–16</td>
<td>1651 (1.4%)</td>
<td>714 (43.2%)</td>
</tr>
</tbody>
</table>
Table 2: Minimum requirements recommended by ISUOG guidelines for basic mid-trimester fetal anomaly scan

<table>
<thead>
<tr>
<th>Minimum requirements recommended by ISUOG guidelines for basic mid-trimester fetal anomaly scan</th>
<th>First trimester acquisitions demonstrating the respective features</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Head</strong></td>
<td></td>
</tr>
<tr>
<td>Intact cranium</td>
<td></td>
</tr>
<tr>
<td>Midline falx</td>
<td></td>
</tr>
<tr>
<td>Cerebral ventricles</td>
<td></td>
</tr>
<tr>
<td>Cavum septi pellucidi</td>
<td></td>
</tr>
<tr>
<td>Thalami</td>
<td></td>
</tr>
<tr>
<td>Cerebellum</td>
<td></td>
</tr>
<tr>
<td>Cisterna magna</td>
<td></td>
</tr>
<tr>
<td><strong>Face and neck</strong></td>
<td></td>
</tr>
<tr>
<td>Both orbits present</td>
<td></td>
</tr>
<tr>
<td>Median facial profile*</td>
<td></td>
</tr>
<tr>
<td>Absence of masses (e.g. cystic hygroma)</td>
<td></td>
</tr>
<tr>
<td>Mouth present</td>
<td></td>
</tr>
<tr>
<td>Upper lip intact</td>
<td></td>
</tr>
</tbody>
</table>

Contd...
<table>
<thead>
<tr>
<th>Minimum requirements recommended by ISUOG guidelines for basic mid-trimester fetal anomaly scan</th>
<th>First trimester acquisitions demonstrating the respective features</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Chest/Heart</strong></td>
<td></td>
</tr>
<tr>
<td>Normal appearing shape/size of chest and lungs</td>
<td><img src="image1.png" alt="Image" /></td>
</tr>
<tr>
<td>No evidence of diaphragmatic hernia</td>
<td><img src="image2.png" alt="Image" /></td>
</tr>
<tr>
<td>Heart activity present</td>
<td><img src="image3.png" alt="Image" /></td>
</tr>
<tr>
<td>Four-chamber view of heart in normal position</td>
<td><img src="image4.png" alt="Image" /></td>
</tr>
<tr>
<td>Aortic outflow tracts *</td>
<td><img src="image5.png" alt="Image" /></td>
</tr>
<tr>
<td>Pulmonary outflow tract*</td>
<td><img src="image6.png" alt="Image" /></td>
</tr>
<tr>
<td>Crossing*</td>
<td><img src="image7.png" alt="Image" /></td>
</tr>
<tr>
<td>Confluence of the arterial arches*</td>
<td><img src="image8.png" alt="Image" /></td>
</tr>
</tbody>
</table>

Contd...
Minimum requirements recommended by ISUOG Guidelines for basic mid-trimester fetal anomaly scan

<table>
<thead>
<tr>
<th>Abdomen</th>
<th>First trimester acquisitions demonstrating the respective features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stomach in normal position</td>
<td><img src="image1.png" alt="Image" /></td>
</tr>
<tr>
<td>Cord insertion site</td>
<td><img src="image2.png" alt="Image" /></td>
</tr>
<tr>
<td>Bowel not dilated</td>
<td><img src="image3.png" alt="Image" /></td>
</tr>
<tr>
<td>Both kidneys present</td>
<td><img src="image4.png" alt="Image" /></td>
</tr>
</tbody>
</table>

Skeletal

<table>
<thead>
<tr>
<th>No spinal defects or masses (transverse and sagittal views)</th>
<th><img src="image5.png" alt="Image" /></th>
</tr>
</thead>
<tbody>
<tr>
<td>Arms and hands present, normal relationships</td>
<td><img src="image6.png" alt="Image" /></td>
</tr>
<tr>
<td>Legs and feet present, normal relationships</td>
<td><img src="image7.png" alt="Image" /></td>
</tr>
</tbody>
</table>

Contd...
Minimum requirements recommended by ISUOG guidelines for basic mid-trimester fetal anomaly scan

<table>
<thead>
<tr>
<th>Placenta</th>
<th>Position</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No masses present</td>
</tr>
<tr>
<td></td>
<td>Accessory lobe</td>
</tr>
</tbody>
</table>

| Umbilical cord   | Three-vessel cord*      |

| Genitalia        | Male or female*         |

*Optional component of checklist: can be evaluated if technically feasible

situations found in the cited literature, like missing acrania, renal agenesis, or absent hand or foot, although the respective features were part of the diagnostic protocol. Although sometimes is difficult to finish in one session the entire morphological checklist evaluation because of the local conditions (mother tissues or fetal position), re-examination and transvaginal approach should overcome these problems. Not all the fetuses can be satisfactory examined in one session and this is acknowledged also for the mid-trimester scan.

Regarding the reliability of the FT morphological evaluation, we have encouraging results regarding the early fetal morphologic assessment°°,75 fetal heart evaluation,71,76 and genetic markers76-81 and similar detection achievements from diagnostic units using a similar protocol.40,47

We chose to discuss separately the aspects regarding the early detection of cardiac and CNS malformations because of their high importance in the prenatal diagnosis and the remarkable progress from the last decades.

**HEART ASSESSMENT DURING THE FIRST TRIMESTER SCAN**

**Whom should be early Screened for Heart Defects**

Most research into FT US heart anomaly screening was directed at high-risk groups or selected populations.73,76,82-86 Many authors agreed that CHD screening should be offered and performed in all pregnancies, because a high percent of CHD occurred in low-risk population.37,45,47,57,87-92

However, some consider early screening for heart anomalies in unselected population not advisable yet due to high number of false negatives and costs in term of time and machines.93 Completion of the heart visualization protocol differ between unselected population and
Figs 1A to F: Increased NT in fetuses with congenital diaphragmatic hernia and skeletal dysplasia: (A) normal NT, (B) increased NT in fetus with congenital diaphragmatic hernia, (C) dextrocardia with abnormal echogenicity of the pulmonary area, due to the presence of abdominal content in the thorax, (D) increased NT and skin edema in fetus with skeletal dysplasia, (E) limb deformities and (F) 3D surface rendering showing the skin edema and shortening of the limbs.

Figs 2A to E: Abnormal tricuspid and ductus venosus flows in congenital heart disease. Normal ductus venosus (A) and tricuspid (B) flows; Reversed a-wave (C) and tricuspid regurgitation (D) in fetus with major congenital heart disease—large atrioventricular defect (E).
Figs 3A to E: Posterior brain complex and intracranial translucency. A: Sagittal plane of the fetal face with visualization of diencephalon (D), sphenoid bone (S), midbrain (M), brainstem (BS), fourth ventricle—intracranial translucency (IT), future cistern cerebellum-medullaris (CM), occipital bone (O); B: abnormal architecture of the posterior brain with non-identifiable/measurable IT in fetus with open spina bifida. C: evident spinal lesion after the termination of pregnancy (C). D: abnormal IT appearance in fetus unaffected by OSB (arrow) with cystic aspect of a structure next to the midbrain (star) and E: Cerebellar cleft (Dandy-Walker syndrome) confirmed in second trimester of gestation with CM measuring 17 mm.

Figs 4A to H: Normal and abnormal aspects of the retronasal triangle. (A) normal retronasal triangle in coronal insonation of the fetal face; supplementary views of the fetal face used to confirm in the first trimester the integrity of the fetal palate and lip: transverse view of the fetal face for the visualization of the anterior palate and upper lip (B), sagittal view of the fetal face for the visualization of the normal rectangular shape of the palate (C) and fetal face 3D surface rendering for the visualization of the lips (D). (E) abnormal retronasal triangle showing median large discontinuity of the palate and later confirmation using 3D reconstruction of the fetal face (F). (G) coronal insonation with abnormal RNT and (H) Bilateral palate defect with maxillary protrusion in the same fetus at early mid-trimester 3D evaluation.
<table>
<thead>
<tr>
<th></th>
<th><strong>Extended protocol</strong></th>
<th><strong>Basic protocol</strong></th>
</tr>
</thead>
</table>
| **Skull and brain** | - Transverse planes of cranium:  
  • Contour and shape;  
  • Midline echo;  
  • Choroid plexus and cerebral peduncles.  
  Sagittal plane:  
  • Posterior brain morphometry: IT, brainstem diameter to brainstem–occipital bone distance ratio in case of abnormal IT suspected (added latter). | - Transverse planes of cranium to demonstrate:  
  • Skull;  
  • Midline echo;  
  • Choroid plexuses                                                                                                                                                                                                 |
| **Face and neck**  | - Transverse planes:  
  • Orbits;  
  • Anterior palate, upper lip.  
  Frontal planes:  
  • Examination of orbits (if not properly visualized in transverse plane);  
  • Retronasal triangle (if palate not properly visualized in transverse plane).  
  Sagittal plane (facial profile):  
  • Measurement of NT and frontomaxillary angle;  
  • Nasal bone assessment;  
  • Normal rectangular palate, normal aspect of mandible | - Sagittal view of the face:  
  • Measurement of NT and frontomaxillary angle;  
  • Nasal bone assessment;  
  • Normal rectangular palate.                                                                                                                                                                                                 |
| **Spine**         | - Longitudinal and transverse planes (preferable in posterior incidence of fetus):  
  • Regularity of spine;  
  • Continuity of underlying skin layer (take special care to note presence of adjacent cystic masses). | - Sagittal section of the spine                                                                                                                                                                                                                                                   |
| **Thorax**        | - Transverse planes (transverse cardiac sweep):  
  • Situs evaluation;  
  • Area one quarter to one third of chest and angle 45 ± 15° from anteroposterior midline (subjective appreciation, measured only if seems abnormal),  
  • Atrioventricular valve offsetting in four-chamber view and tricuspid valve flow assessment using pulsed Doppler;  
  • (Not mandatory) aorta arising from left ventricle and pulmonary trunk arising from anteriorly placed right ventricle and crossing to fetal left side over ascending aorta;  
  • Color-flow investigation of four-chamber view, emergence of outflows and their crossing—being equal in size, and three vessel view—"V" sign (connection of aortic arch and ductus arteriosus);  
  • Ductus venosus flow assessment using pulsed Doppler | - Transverse section of the thorax to demonstrate:  
  • Four-chamber view of the heart;  
  • Record blood flow across the tricuspid valve.                                                                                                                                                                                                                               |
referral population (47.5% vs 76.9%)\(^{72}\) because the early heart evaluation is not easy and operator is constrained to finish the protocol of heart investigation when dealing with high-risk pregnancy for cardiac defects.

**When**

With improved technology it has become feasible to obtain images of the fetal heart in the FT, with visualization of the four heart chambers and outflow tracts of the great vessels from as early as 10 weeks.\(^{94,95}\) Thus, fetal cardiac abnormalities can be scanned and diagnosed as early as 11 weeks’ gestation by experienced groups.\(^{95}\)

However, the rate of a complete cardiac evaluation improves as gestational age increases: between 20% at 11 GW and 92% at 13 GW with a TV probe.\(^{96}\) Other authors\(^ {53} \) and\(^ {84} \) reported similar success rates with 100% of visualization at 14 to 15 GW. The end-point is that comprehensive visualization of fetal cardiac anatomy is already possible at the end of the FT.\(^ {48,82,89,97}\)

**Imaging Technique**

Gray scale is the basis of a reliable fetal cardiac scan in the ST. However, advanced sonographic techniques offer supplementary important information. For example, Doppler US can imagine and measure blood flow velocity or identify abnormal flow patterns across valves and within heart chambers. M-mode echocardiography offers an important method for analyzing cardiac dysrhythmias, suspected ventricular dysfunction, and abnormal wall thickness. The routine use of color Doppler in low-risk populations remains controversial and is not implemented even in ST scanning ISUOG guidelines.\(^ {93,98}\)

In AIUM guidelines color Doppler is regarded as an optional method, but recommended for suspected cardiac flow abnormalities.\(^ {99,100}\) For safety reasons routine use of pulsed color Doppler is advised against in the FT (Opinion Safe use of Doppler ultrasound during the 11 to 13+6-week scan: is it possible?\(^ {101}\) Nevertheless, the use of color Doppler in FT is necessary because of the low discrimination of the heart structures in B-mode. Studies have demonstrated that colors improve the visualization of normal cardiac structures\(^ {71}\) and early detection of conotruncal anomalies.\(^ {102}\) Also, tricuspid and ductus venosus flow patterns proved useful in early detection of CHD.\(^ {97,99,80,85,103-107}\)

### The Examination Protocol of the Fetal Heart

During the last decades, five scan protocols for fetal CHD diagnosis have been commonly used: four chamber view (4 CV), 4 CV + outflow tracts view (OTV)/three vessels and trachea view (3 VTV), 4 CV + OTV + 3 TV, extended cardiac echography examination (ECEE) and 4D spatio-temporal image correlation (STIC). In ST scan 4 CV alone detects up to 77% of prenatally developed CHD, while OTV increases prenatal detection rate between 83 and 92%.\(^ {107}\) Using only the 4 CV for fetal heart examination is insufficient as many anomalies may not be detected, thus imaging of the outflow tracts is mandatory.\(^ {108}\) Most of MA are detected by imaging the great vessels such in a coartation of the aorta, hypoplastic left heart, tetralogy of Fallot, double outlet right ventricle, truncus arteriosus, corrected or non-corrected transposition of great vessels.
Recent studies have reported that the use of STIC in the FT is feasible and is likely to improve the detection of CHD in expert hands. Spatiotemporal image correlation technology also offers other advantages, such as access to virtual planes not available for direct visualization in 2D US. Vinals et al and Bennasar et al demonstrated that volume datasets from a first-trimester fetal heart can be acquired in a high proportion of cases by properly trained non-expert operators and sent to an expert in ECEE for offline evaluation via telemedicine. One recent study reported the overall performance of pooled sensitivities of STIC, ECEE and 4 CV + OTV + 3 VTV were around 0.90, which was significantly higher than that of 4 CV + OTV or 3 VTV and 4 CV alone. However, the pooled specificity of STIC was 0.92, significantly lower than that of other 4 protocols which reached at 1.00. Thus, STIC technique cannot be used to make a definite diagnosis alone with its low specificity, but should be used to provide more information for local details of defects.

Detection Rate, Accuracy

The detection rate of major CHD at the 11 to 13+6-week scan varies widely (5.6–90%) depending on the protocol used, studied population (high or low-risk), scan route (TV, TA or both), definition and prevalence of major CHD. Recently, there are reports of high early detection rates for CHD even in unselected or low risk population 80 to 90% especially when using an extended standardized heart screening protocol.

Due to the lack of appropriate verification test, only few studies report real accuracy of FT US examination in detecting major CHD. A recent systematic review of the literature reported a pooled sensitivity and specificity were 85% (95% CI, 78–90%) and 99% (95% CI, 98–100%), respectively. This demonstrated that FT US can diagnose major CHD with high accuracy (specificity approaching 100%). When negative, FT US diagnosed fetuses with a normal heart with reasonable accuracy (sensitivity around 85%).

Although visualization of fetal cardiac anatomy is already possible at the end of the FT, normal results from echocardiographic examinations at any time of pregnancy do not exclude CHD, because some cardiac lesions may evolve in utero as gestational age advances or even occur later during pregnancy: hypoplastic left heart syndrome, coarctation of the aorta, endocardial fibroelastosis due to aortic stenosis, pulmonary stenosis, tetralogy of Fallot. Other heart defects such as cardiac tumors can evolve even after birth. Ventricular septal defects were the most missed lesions during prenatal echocardiographic evaluation because of limited resolution, the small size of the lesion and low flow velocities in the FT.

Screening for CHD using NT Measurement, DV and TR

Increased NT is not only a marker for chromosomal anomalies, but also a nonspecific sign of an abnormal development of the fetus, being associated with cardiac dysfunction, even in chromosomally normal fetuses. Congenital heart disease (CHD) are the most common disorders that can be observed in fetuses with enlarged NT and normal karyotype. It is hard to analyze together the screening studies on this marker due to differences in cut-offs used to define an increased NT (95th or 99th percentile, 1.7, 2, 2.5 or 3 MoM), gestational ages at the time of NT measurement (10 + 4 to 13 + 6 vs 11 to 14 weeks’ gestation), study populations (high vs low-risk), study design (prospective vs retrospective) and even the definition of a major CHD.

When using the 95th percentile cut-off, the reported prevalence of CHD varied between 2 and 20%. However, all studies agree that the prevalence of CHD is about six times higher in fetuses with a NT ≥ 99th percentile than in an unselected population.

In fetuses with increased NT and normal karyotype, a recent meta-analysis reported a 31% detection rate for CHD and a specificity of 98.7% using the 99th centile for NT cut-off and 37% sensitivity and 96.6% using the 95th centile. These detection rates are higher that detection rate below 5% when only maternal risk factors are considered.

The data combined from several studies shows a high prevalence of major CHD, that increases exponentially with increasing NT thickness from 0.6 to 6.2% in those with NT of 2.5 to 3.4 mm to 2.3 to 12.2% in those with a NT of 3.5 mm or more. From these pooled data resulted an overall detection rate of 28.4% and a false positive rate of 3% for major CHD in chromosomally normal fetuses with increased NT. Enlarged NT is not obviously related to any particular type of cardiac anomaly.

Several studies stated that NT measurement is not a reliable screening test for CHD during FT. Low detection rates for CHD (around 15%) are reported in studies where NT is measured in unselected or low-risk populations and when fetuses with septated cystic hygromas are excluded.

The performance of early screening for cardiac defects achieved by measurement of fetal NT is improved by assessment of flow in the ductus venosus (DV) and tricuspid regurgitation (TR). Study of DV flow patterns in fetuses with enlarged NT (above 95 centile) may improve the selection of those requiring...
specialized echocardiography as absent or reversed a-wave is associated with a 3-fold risk for major CHD. In continuing pregnancies with chromosomally normal fetuses the finding of reversed a-wave increased by almost 10 times the risk of cardiac defects, with a predominance of right-heart anomalies regardless of the measurement of NT. A recent meta-analysis of Papatheodorou on chromosomally normal fetuses demonstrates that the DV waveform examination has a moderate sensitivity for detecting CHD. Regardless of NT status DV has a sensitivity of 50% and a specificity of 93%, when associated with increased NT, the summary sensitivity and specificity were 83 and 80%, and for those with normal NT, they were 19 and 96%, respectively.

Tricuspid regurgitation at 11 to 13 + 6 weeks’ gestation may also play a role in identifying fetuses with CHD as chromosomally normal fetuses with TR have an 8-fold increased risk for CHD.

The risk of a CHD increases when an increased NT is associated with TR and/or an abnormal DV.

**CENTRAL NERVOUS SYSTEM EARLY MORPHOLOGICAL EVALUATION**

Central nervous system (CNS) malformations are some of the most common congenital abnormalities. Some authors consider that congenital anomalies involving the brain are the largest group at 10 per 1000 live births, compared to heart at 8 per 1000, kidneys at 4 per 1000, and limbs at 1 per 1000. The FT scan was reported recently with a higher degree of detection for major CNS anomalies—53 to 69%, 47,65

There are important limitations in the prenatal diagnostic of CNS abnormalities ultrasound, as most of the congenital anomalies of the nervous system are undetectable during the FT evaluation. They may be associated only with subtle findings in early gestation as the brain continues to develop during pregnancy and into the neonatal period. Agenesis of corpus callosum, microcephaly and hydrocephaly usually cannot be detected in the FT, and sometimes these findings are apparent only in late stages of pregnancy. Also, some cerebral lesions are not due to faulty embryological development but represent the consequence of acquired prenatal or perinatal insults. 125-127

Fortunately, the most important congenital anomalies of the nervous system concerning prevalence and severity are usually detectable during the FT scan, including holoprosencephaly and neural tube defects (NTDs). Has been suggested that the diagnosis of these small and/or isolated defects is difficult, and they are often detected during ST. 34,46,128-130

The visualization of the falx cerebri, calvaria and head shape are easily achieved in the FT transverse incidence, thus, holoprosencephaly and encephalocele are detectable. The direct visualization of the spine NTDs at the FT scan may be difficult even with the help of high-resolution ultrasound machines. Consequently, early morphological markers for open spina bifida were proposed to diagnose this condition during FT: retraction of frontal bones and parallel aspect of cerebral peduncles, reduced BPD diameter, and abnormal aspects in the posterior brain of the fourth ventricle—intracranial translucency, or brainstem/brainstem-occipital bone distance ratio (BS/BSOB). These parameters are easily assessed in the standard facial mid-sagittal sectional plane used for the genetic markers, with no investment in additional scanning time. Moreover, these parameters could prove useful for the detection of other brain abnormalities. 122-124

However, a satisfying comprehensive evaluation of the fetal CNS can be obtained in the second and third trimesters of pregnancy. 135

**IS FIRST TRIMESTER ANOMALY SCAN TIME CONSUMING?**

The main argument against routine detailed FT anomaly scan is related to the increased examination time. Usually the time allocated for the FT examination of the fetus was 20 minutes in studies that aimed to determine gestational age, to assess the ultrasound genetic markers and to diagnose major fetal abnormalities using a basic protocol. The examination time depends in a great manner on the protocol used, fetomaternal local conditions (fetal position, maternal BMI, fibromyomas, abdominal scar, placental location). Detailed fetal evaluation including heart key-features requires an additional examination time of about 10 minutes. This represents a significant increase in examination time, as being half of the former allocated time.

As mentioned before, the transvaginal route can reduce the examination time when technical difficulties do not allow adequate views of the aimed fetal anatomic features. Another certain amount of our additional examination time can be reduced if contingent markers are used instead standard evaluation of the respective features and if the color Doppler cardiac sweep replaces tricuspid and ductal flow assessment, thus also diminishing the energy administered to the fetus by pulsed Doppler.

**SETTINGS FOR FIRST TRIMESTER ANOMALY DETECTION**

**Timing**

The fetal structural evaluation was found to improve with increasing gestational age, from 6% at 10 GW to 75%
at 11 GW, 96% at 12 GW and 98% at 13 to 14 GW. Many countries offer the FT genetic scan at 11 to 13 weeks. It is generally accepted that an acceptable compromise between genetic and transabdominal structural assessments is achievable at 12 to 13 GW. The ideal gestation for one-stop clinics for assessment of genetic risk (OSCAR) is 12 GW because the aim of the FT scan is not just to screen for trisomy 21 but also to diagnose MA. The trisomy 21 detection rate with OSCAR technique at 12 GW is 90% with 5% false-positive rate. Alternative multistep strategies were imagined that optimize the biochemical performance, with biochemical testing at 9 to 10 GW and US scan at 12 to 13 GW, or biochemical PAPP-A evaluation at 9 GW and free β-hCG at the time of the scan at 12 to 13 GW. This would increase the trisomy 21 detection rate to 95% but the potential disadvantage of the protocol may be the patient non-compliance with the additional steps.

Serial Scans
Serial scans may be helpful for specific situations of not satisfactory visualization of anatomical structures (unfavorable fetal position, unfriendly maternal conditions) or for better visualization of fetal abnormalities. However, in general practice, repeated or detailed examinations are not routinely performed.

Route of Examination: Transabdominal vs Transvaginal Approach
Previous studies presented technical difficulties in obtaining adequate views of FT fetal anatomy using solely transabdominal (TA) route. Transvaginal (TV) approach offers a better discrimination of the structural features and reduces the examination time when the fetal TA visualization is poor. However, it has some drawbacks: its limitation to a single axis leads to the difficulty to obtain some other important anatomical insonations and planes, it is highly dependent on the position of the fetus and the visualization is affected by fetal movements. Transabdominal approach, more easily accepted by the patient, has the advantage of a higher number of different planes that can be obtained but at a lower resolution.

Depending on the extension of the US protocol, TV route was used to complete the investigation in various rates, ranging from 1% when basic anatomic evaluation were performed to 29% when detailed fetal evaluation was aimed at 11 to 13 GW. We use this route in 7% of the cases aiming to complete the detailed protocol mentioned in Table 3, at a gestational age of 12 to 13 GW. Regarding the detection of CHD in first trimester, the majority of the initial studies were carried out using TV while more recent studies used TA, especially after 13 weeks.

Souka et al found that at 11 to 14 weeks, the addition of the TV scanning slightly increased successful examination rates of the heart by about 5%. A more recent study showed that TV US improves the rate of adequate visualization of most of the fetal organs at 11 to 13 weeks, but in the case of fetal heart there was no difference between the two approaches in the rate of successful examination (61.4% vs 62.7%). The gestational age is important when choosing the route of examination, as Smrcek et al found that between 10 and 13 GW TV was superior to TA in visualization of fetal heart structures, at 14 GW both methods were similar to each other and at 15 GW TA sonography allowed adequate visualization of all fetal heart structures in all cases. It was suggested that although both TV and TA approaches provide adequate visualization of FT heart anatomy, TA approach may have a higher sensitivity than the TV approach in detecting major CHD (96% vs 62%).

Therefore, there is no optimal approach for FT study of the fetal heart and most authors recommended the usage of TVUS anytime when TAS views are suboptimal or the usage of both methods simultaneously as a routine in order to provide complementary information. However, the use of TV approach also depends on the general use of the technique in the respective center and the acceptability of the patients. Refusals were associated with cultural features and misconceptions that TV examination may cause miscarriage.

Counseling
Although the majority of MA can be detected in the FT, some may be missed even by experienced examiners using high resolution US equipment in the best of hands, because some malformations may develop or become apparent later. This should be an important component of couple counseling regarding the benefits and limitations of FT anomaly scan, similar to recommendations for the routine mid-trimester fetal structural investigation.

The early scan should always be followed by a ST assessment of cardiac anatomy at 18 to 22 weeks to reconfirm normality, to monitor and reassess those cases with abnormal findings at 11 to 13 weeks, and to identify the MA missed in the first trimester.

Resources: Operator Skills and Equipment
The implementation of the detailed scan protocol depends on the availability of specialized personnel and appropriate equipment. This is particularly important for the early detection of fetal heart defects.
Regarding the performance of FT fetal ultrasound scan, early structural or functional particular features of MA. The sonographic appearance of the FT fetal anatomy and for an early cardiac scan.

The individuals who perform this type of extended early examination should have completed training in the use of diagnostic ultrasonography and related safety issues, participate in continuing medical education activities, have established appropriate care pathways for suspicious or abnormal findings and participate in established quality assurance programs. First trimester fetal heart scan should be performed by obstetricians, fetal cardiologists with extensive experience in both the 11 to 13-week scan and early fetal echocardiography. All cases classified as abnormal should be referred for specialist fetal echocardiography for better evaluation of the abnormality, to confirm the correct diagnosis.

Ultrasound examinations should be performed with high-frequency linear transducers (6–15 MHz) usually used for imaging small parts with an optimal resolution of 5 to 7.5 cm depth, which corresponds to the depth at which the fetus is lying in the majority of pregnancies at 12 to 14 weeks. The original preset of transducers should be modified in order to obtain images of diagnostic quality and to ensure adequate safety limits for an early cardiac scan.

Documentation

An important good practice point outlined by the practice guidelines is that an electronic or paper document should be stored locally and emitted to the patient and referring healthcare provider. This should contain the features aimed to be visualized in the morphologic protocol and the documentation with pictures of the respective findings.

SAFETY OF THE FIRST TRIMESTER FETAL MORPHO-FUNCTIONAL ASSESSMENT

Prenatal ultrasonography appears to be safe for clinical practice, as to date there has been no study to suggest otherwise. However, ultrasound energy delivered to the fetus may have certain biological effects that could be identified in the future. Thus, early fetal diagnostic providers should respect the principle of lowest possible ultrasound exposure setting to gain the necessary diagnostic information, under the as-low-as-reasonably achievable (ALARA) concept.

There is an agreement of international professional bodies that the use of B- and M-mode, appears to be safe for all stages of pregnancy, due to its limited acoustic output. An increased risk of harm is related to the use of Doppler technique that comports a greater energy output especially when applied to a small region of interest. However, in the FT color Doppler improves the visualization of normal and abnormal cardiac features and spectral Doppler is largely used to investigate the tricuspid flow pattern—thus, to refine the risk for trisomies and to investigate the uterine artery flow resistance for the early pre-eclampsia risk assessment. The uterine artery assessment has no effect on the fetus, but the investigation of the heart necessitates some comments.

The general recommendations regarding Doppler techniques, especially spectral mode state that they should be employed only when there is a clear benefit/risk advantage and both thermal index (TI) and examination duration are kept low. The displayed TI should be less than or equal to 1.0 and exposure time should be kept as short as possible (usually no longer than 5 to 10 minutes). Doppler ultrasound, especially pulsed Doppler, should be limited in the FT to specific indications guided by an abnormal gray-scale or color Doppler evaluation. The potential risk should be balanced to the benefit of diagnosis when a complex cardiac malformation is suspected. These recommendations allow the color Doppler investigation of the fetal heart, and for general FT necessities, current sonographic techniques are within the energy output limits mentioned above. Furthermore, recent studies show that reliable first-trimester Doppler ultrasonography can be carried out at lower output energies than the currently advocated limits, reduced to a Tlb of 0.5 or 0.1. In order to limit the duration of the fetal exposure, a cine-loop sweep may be acquired in color Doppler and after the image is frozen, single images representing the key-features of the heart can be retrieved from the cine-loop and stored.

A potential conflict may appear because of the increasing number of studies that show the importance of fetal heart screening in the FT using color Doppler and the recent FT guidelines emitted by ISUG recommend that Doppler examinations should only be used in the first trimester if clinically indicated. However, all the studies cited above mentioned that heart investigation was feasible by respecting ALARA principles and respected the effectual ethical issues. In our view, fetal heart screening should be performed during the FT because the large majority of major CHD is detectable at this gestational age, but the informed consent should contain information regarding the Doppler use during the examination.
ROLE OF 3D/4D ULTRASOUND TECHNIQUES

In expert hands, 3D and 4D ultrasound proved to be useful in the FT scan to identify primary and secondary palates in both healthy and abnormal fetuses affected by a cleft lip and palate, during STIC investigation of the fetal heart and evaluation of a wide range of abnormalities, especially those that imply surface anatomy. However, the resolution of these techniques is not yet comparable to the second trimester assessment. Although they provide confidence in the suspected diagnostic, especially in complex structural defects and assists in offering cogent advice to patients, they are not currently used for routine FT structural evaluation.

CONCLUSION

The main advantages of a FT anomaly scan using an extended protocol is the early reassurance to all/at-risk pregnancies, and that the option of earlier and safer termination of pregnancy is offered for the majority of MA, with less parental psychological morbidity. Furthermore, couples prefer earlier screening, when possible. However, supplementary resources are involved regarding the additional examination time and specialized personnel. This issue should be dealt by each involved regarding the additional examination time and specialized personnel. This issue should be dealt by each healthcare system considering the local resources and the procedure cost-effectiveness. Previous studies, using inferior equipment and a less extended examination protocol, found that the FT anomaly scan is cost-efficient in terms of medical and economic expenses.

An important limitation for the detailed FT screening evaluation is that the protocol is achievable by skilled sonographers in specialized centers, which is still low even in developed countries. Therefore, to implement the protocol two approaches may be considered. One option is to lower the number of examinations, by recommending the detailed assessment to high-risk pregnancies, but the majority of severe abnormalities derive from low-risk pregnancies. Another alternative would be to confine FT evaluation to specialized centers, making the FT detailed anomaly scan feasible and cost-efficient in large population groups.

Another weakness of the routine early fetal structural evaluation is that certain malformations are undetectable because of the late development of some anatomical structures. Also, the pathological evaluation cannot be performed systematically, which makes impossible the certification of the fetal abnormalities and the audit of the examiners. In order to reduce that source of bias, the suspected cases should be evaluated by another expert(s), but this again implies supplementary time and personnel resources.

REFERENCES


with different levels of experience. Ultrasound Obstet Gynecol 2010;36(4):417-422.


Challenges in Sonographic Detection of Fetal Major Structural Abnormalities at the First Trimester Anomaly Scan


