10.5005/jp-journals-10009-1411

ORIGINAL ARTICLE

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

[1]Dominic Iliescu, [2]Monica Cara, [3]Stefania Tudorache, [4]Panos Antsaklis, [5]Iuliana Ceausu
[6]Daniela Paulescu, [7]Liliana Novac, [8]Nicolae Cernea, [9]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.

How to cite this article: Iliescu D, Cara M, Tudorache S, Antsaklis P, Ceausu I, Paulescu D, Novac L, Cernea N, Antsaklis A. Challenges in Sonographic Detection of Fetal Major Structural Abnormalities at the First Trimester Anomaly Scan. Donald School J Ultrasound Obstet Gynecol 2015;9(3):239-259.

Source of support: Nil

Conflict of interest: None

[1,2,3,5,7,8]Department of Obstetrics and Gynecology, University of Medicine and Pharmacy of Craiova, Craiova, Romania

[4,6,9]"Alexandra" Maternity Hospital, University of Athens, Athens Greece

Corresponding Author: Dominic Iliescu, Department of Obstetrics and Gynecology, University of Medicine and Pharmacy of Craiova Craiova, Romania, e-mail: dominic.iliescu@yahoo.com

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.[1]

Indeed, algorithms based on combinations of maternal characteristics, early ultrasound findings and biochemical testing of maternal blood, are efficient in predicting most major aneuploidies,[2] miscarriage and fetal death[3,4] preterm delivery,[5,6] pre-eclampsia,[7] gestational diabetes,[8-10] fetal growth restriction[11] and macrosomia.[12] 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.[13-16] 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.[13,17]

Early detection of fetal malformations showed in the last decade significant improvement[18,19] 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.[20] 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.[21]

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^{+0} to 23^{+6} GW, with 20 minutes allocated for systematic detailed examination of the fetus.[22] 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.[23-28]

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).[29]

Table 1 summarizes the results of 19 large screening studies[24,30-47] providing data on the prevalence of overall MA in the study populations and the proportion of those detected during the FT scan. A wide range of MA detection rates were reported during the FT evaluation: 12.5 to 83.7%, with an average of 43.2%. One of the main reasons for such a wide detection interval is the US protocol used in the FT fetal evaluation: low detection of MA was noted in studies when the abnormalities were either a coincidental finding during the basic screening for aneuploidies or they were detected after detailed examination because of increased NT.[48] Contrarily, the studies that used a systematic detailed morphological protocol reflected the true performance of the FT scan in general population, which can detect around 80% of the fetal MA.[24,40-47]

Searching the literature we observe that this is comparable with the efficiency of ST anomaly scan.[22,27,49] A systematic review on the ST anomaly scan effectiveness reported that about 45% of the MA were detected routinely,[50] 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.[51] 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.[24] However, we should not forget the particular role of FT scan in the detection of genetic syndromes.[2]

Table 2 summarizes the minimum requirements recommended by the ISUOG practice guidelines[22] 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,[52] 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.[18,19, 52,53]

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 retronasal triangle (RNT) view, fetal abdominal cysts have been demonstrated to identify high-risk

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

				Fetal abnormalities	
Authors	*Total*	*Scan route*	*GA (weeks)*	*Total*	*FT detection*
Hernadi and Torocsik, 1997[30]	3991	TA, TV	11–14	49 (1.2%)	20 (40.8%)
D'Ottavio et al, 1998[31]	4078	TV	13–15	88 (2.2%)	54 (61.4%)
Bilardo et al, 1998[32]	1690	TA, TV	10–14	23 (1.4%)	10 (43.5%)
Hafner et al, 1998[33]	4233	TA	10–13	56 (1.3%)	7 (12.5%)
Whitlow et al, 1999[34] includes data from: Economides and Braithcoaite,[35] 1998	6443	TA, TV	11–14	63 (1.0%)	37 (58.7%)
Guariglia and Rosati, 2000[36]	3478	TV	10–16 25% above 14 w	57 (1.6%)	33 (57.9%)
Taipale et al, 2004[37]	4789	TV	10–16, 10% above 14 w	33 (0.7%)	6 (18.2%)
Chen et al, 2004[38]	1609	TA, TV	12–14	26 (1.6%)	14 (53.8%)
Souka et al, 2006[39]	1148	TA, TV	11–14	14 (1.22%)	7 (50%)
Becker and Wegner, 2006[40]	3094	TA, TV	11–13	86 (2.8%)	72 (83.7%)
Cedergren and Selbing, 2006[41]	2708	TA	11–14 15% above 14 w	32 (1.2%)	13 (40.6%)
Saltvedt et al, 2006[24]	18053 after aneupl excl	TA	11–14	371 (2.1%)	74 (19.9%)
Dane et al, 2007[42]	1290	TA	11–14	24 (1.9%)	17 (70.8%)
Chen et al, 2008[43]	7642	TA	10–14	127 (1.7%)	51 (40.2%)
Oztekin et al, 2009[44]	1805	TA	11–14	21 (1.2%)	14 (66.7%)
Ebrashy et al, 2010[45]	2876	TA, TV	13–14	31 (1.1%)	21 (67.7%)
Syngelaki et al, 2011[46]	(45191) 44859 after aneupl excl	TA, TV	11–14	488 (1.1%)	213 (43.6%)
Iliescu et al, 2013[47]	5472	TA, TV	12–14	76 (1.4%)	58 (76.3%)
Total	118110	TA, TV	10–16	1651 (1.4%)	714 (43.2%)

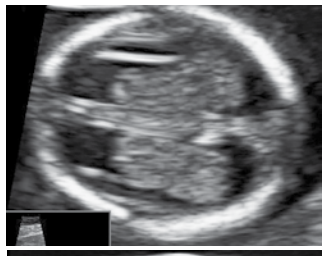
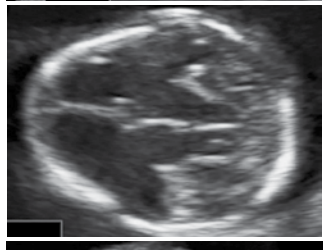
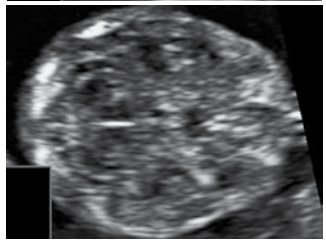
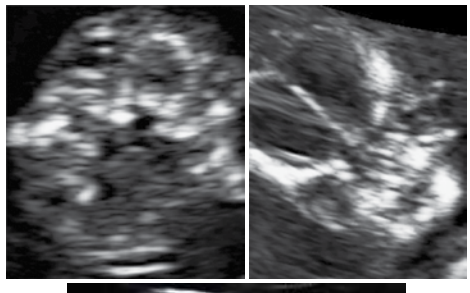
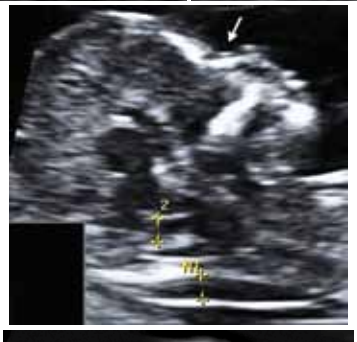
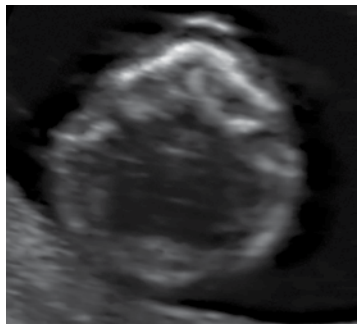
pregnancies for variable adverse outcome[54] cardiac,[55-57] neurological,[58-60] palate defects,[61,62] micrognathia,[63] skeletal abnormalities,[46,64-66] diaphragmatic hernia[67] and gastrointestinal malformations.[68-70] A recent large study found that abnormal aneuploidy markers were associated 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.[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.[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,[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).

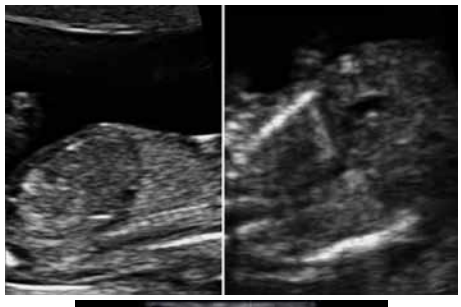
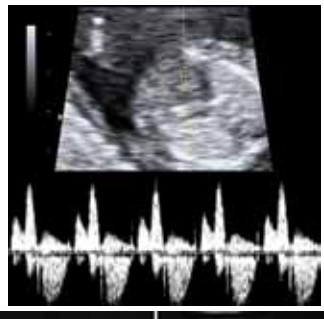
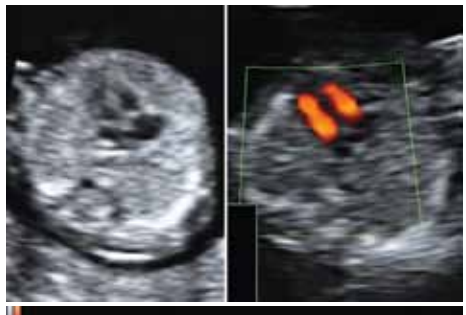
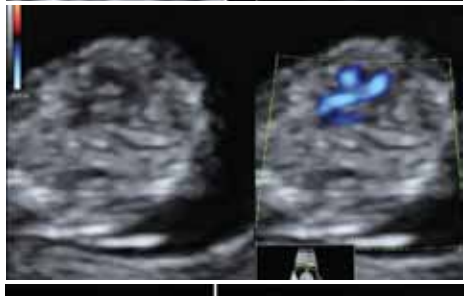
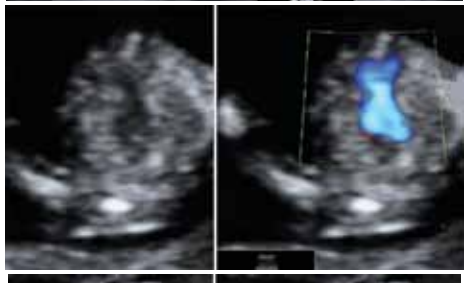
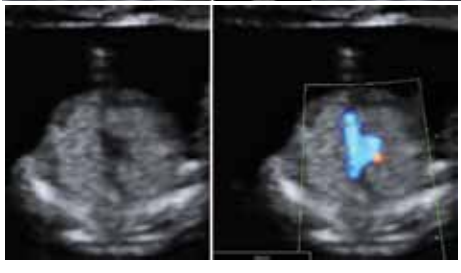
An important point in our view is that indifferently of the considered protocol, the checklist should be completed with adequate views of the targeted features. Otherwise, the diagnostic providers may encounter

Table 2: Minimum requirements recommended by ISUOG guidelines for basic mid-trimester fetal anomaly scan

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

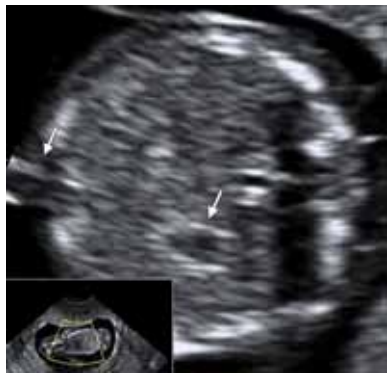
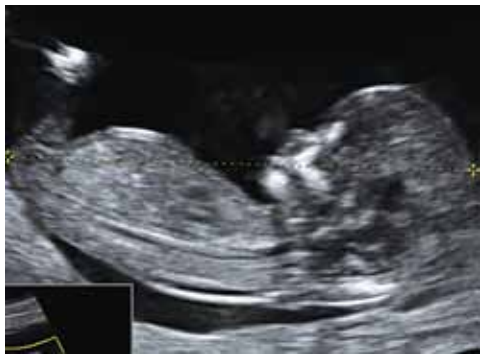
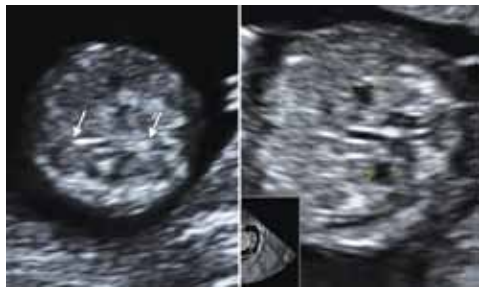
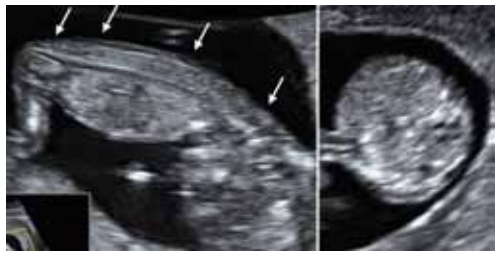
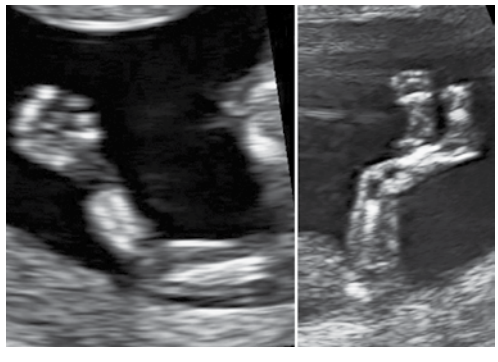
Contd...

Contd...

Minimum requirements recommended by ISUOG guidelines for basic mid-trimester fetal anomaly scan		*First trimester acquisitions demonstrating the respective features*
Chest/Heart	Normal appearing shape/size of chest and lungs No evidence of diaphragmatic hernia	
	Heart activity present	
	Four-chamber view of heart in normal position	
	Aortic outflow tracts *	
	Pulmonary outflow tract* Crossing*	
	Confluence of the arterial arches*	

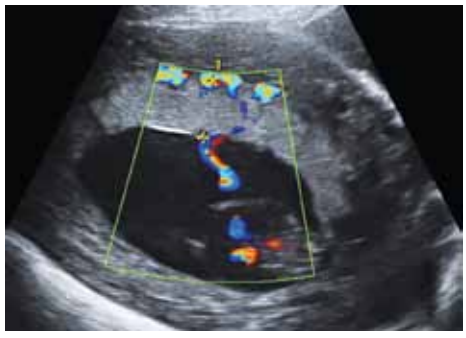
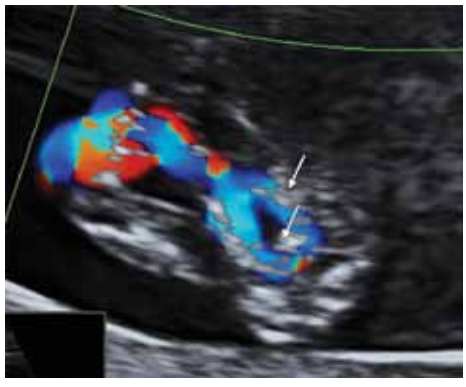
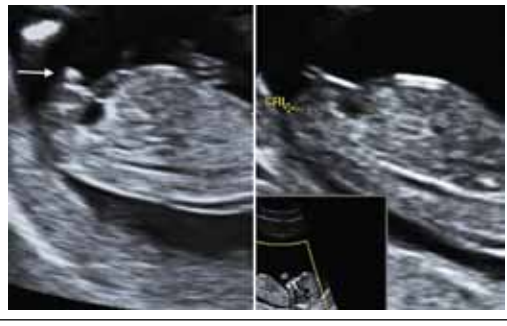
Contd...

Contd...

Minimum requirements recommended by ISUOG Guidelines for basic mid-trimester fetal anomaly scan		*First trimester acquisitions demonstrating the respective features*
Abdomen	Stomach in normal position Cord insertion site	
	Bowel not dilated	
	Both kidneys present	
Skeletal	No spinal defects or masses (transverse and sagittal views)	
	Arms and hands present, normal relationships Legs and feet present, normal relationships	

Contd...

Contd...

Minimum requirements recommended by ISUOG guidelines for basic mid-trimester fetal anomaly scan		*First trimester acquisitions demonstrating the respective features*
Placenta	Position No masses present Accessory lobe	
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[74,75] fetal heart evaluation,[71,76] and genetic markers[76-81] and similar detection achievements from diagnostic units using a similar protocol.[40,47]

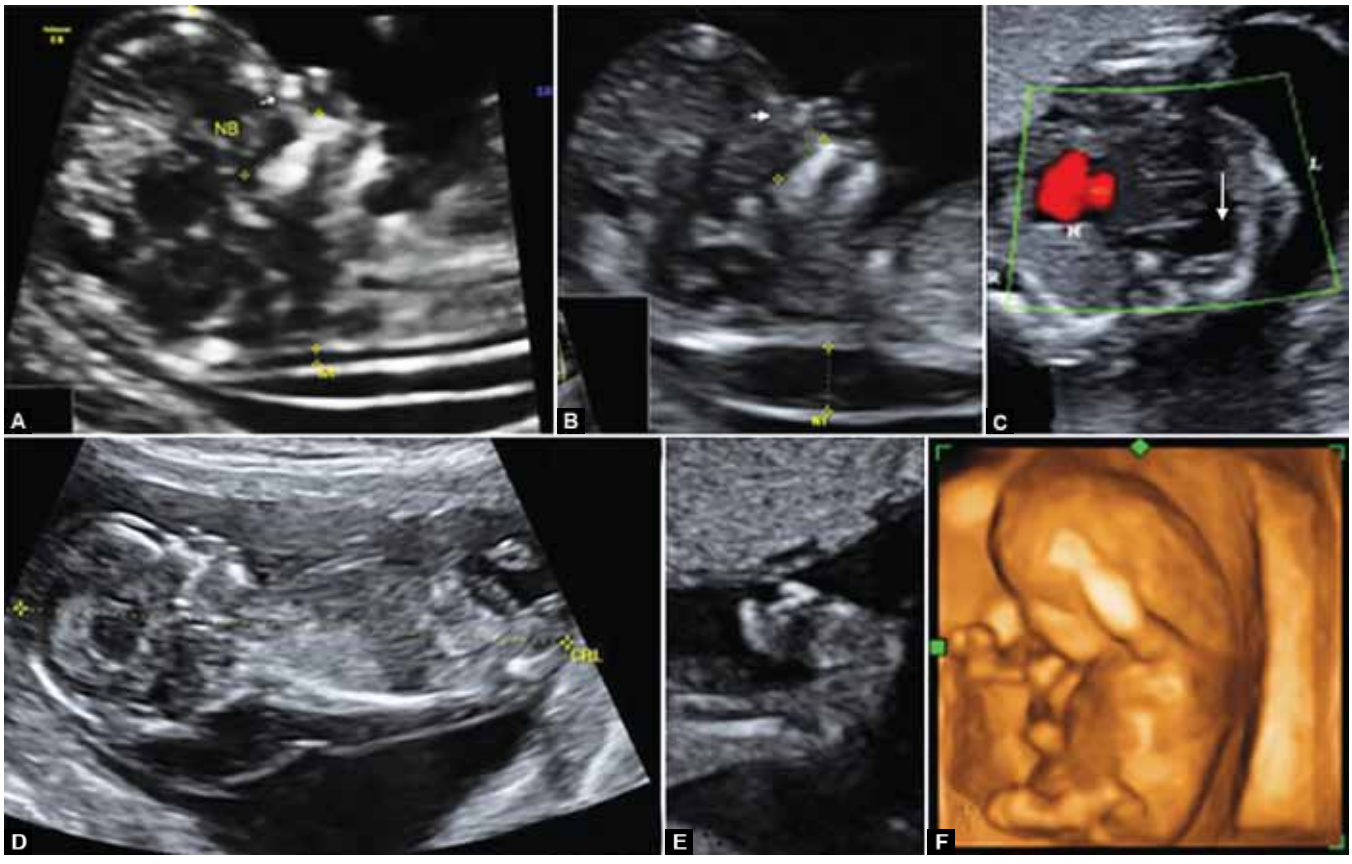
We chose to discuss separately the aspects regarding the early detection of cardiac and CNS malformations because of their high importance in the prenatal diagnosis and the remarkable progress from the last decades.

HEART ASSESSMENT DURING THE FIRST TRIMESTER SCAN

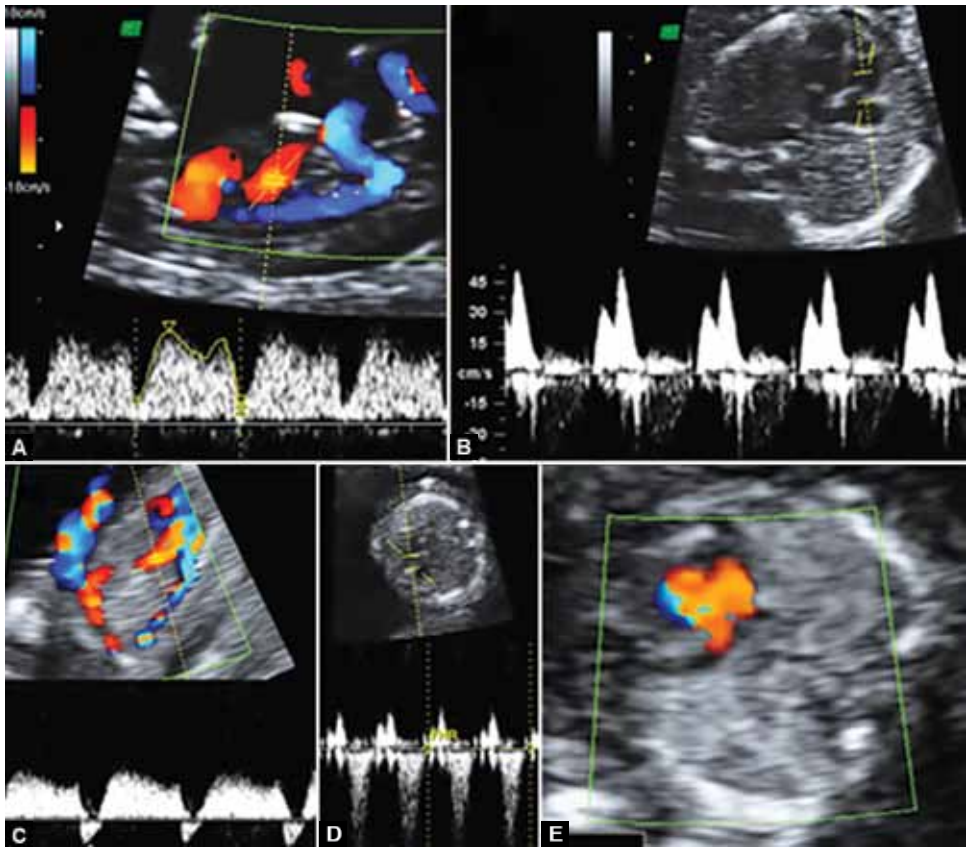
Whom should be early Screened for Heart Defects

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]

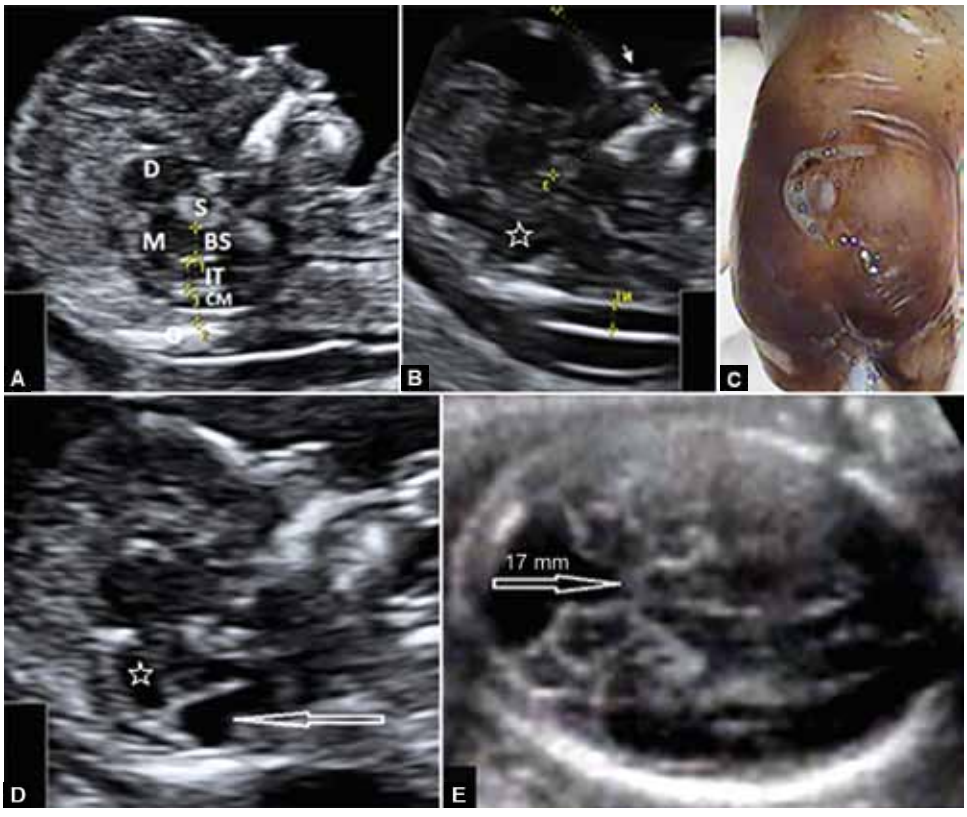
However, some consider early screening for heart anomalies in unselected population not advisable yet due to high number of false negatives and costs in term of time and machines.[93] Completion of the heart visualization protocol differ between unselected population and



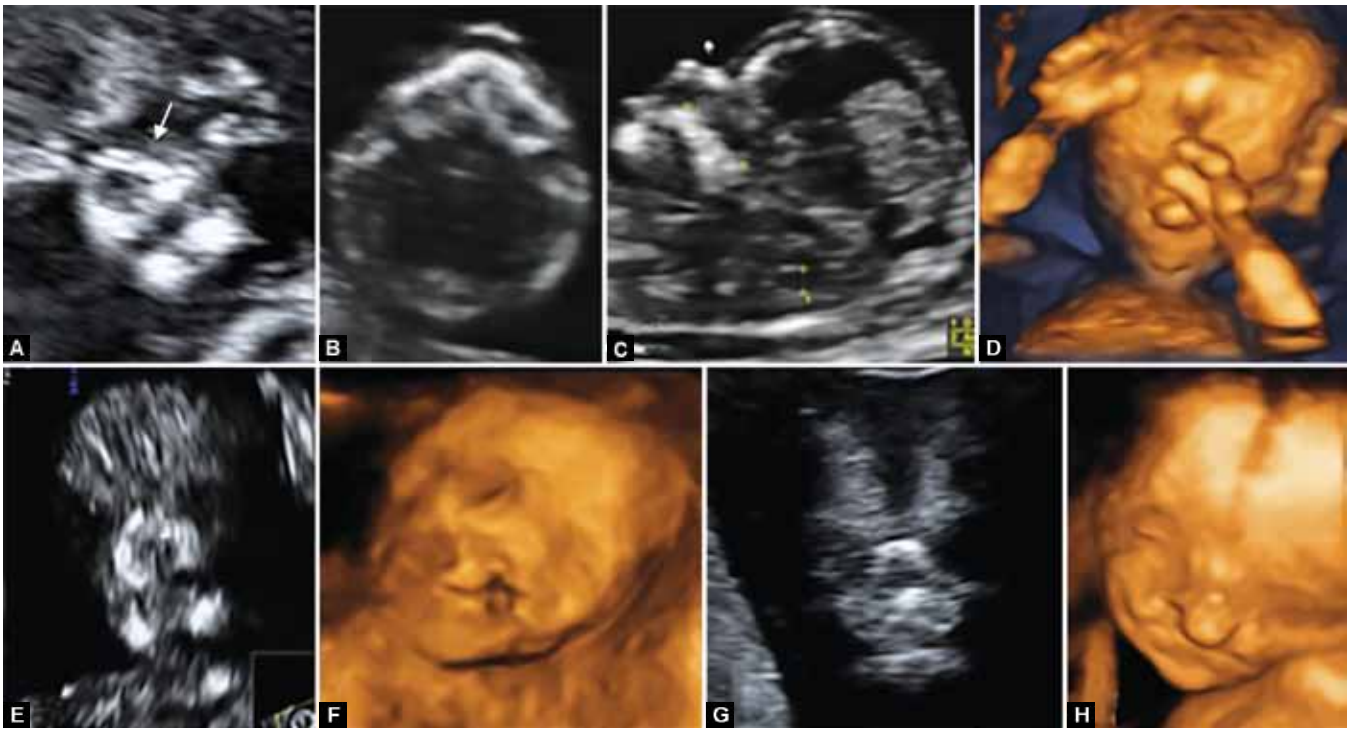
Figs 1A to F: Increased NT in fetuses with congenital diaphragmatic hernia and skeletal dysplasia: (A) normal NT, (B) increased NT in fetus with congenital diaphragmatic hernia, (C) dextrocardia with abnormal echogenicity of the pulmonary area, due to the presence of abdominal content in the thorax, (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 diencefalon (D), sphenoid bone (S), midbrain (M), brainstem (BS), fourth ventricle—intracranial translucency (IT), future cistern cerebello-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 3: Comparative first-trimester ultrasound protocols for fetal morphogenetic evaluation

	Extended protocol	*Basic protocol*
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.

Contd...

Contd...

	Extended protocol	*Basic protocol*
Abdomen	• Presence of stomach in left upper abdomen; • Abdominal wall and umbilical cord insertion; • Bowel echogenicity.	Transverse and sagittal sections of the trunk to demonstrate: • Stomach; • Bladder; • Kidneys; • Abdominal insertion of the umbilical cord.
Kidney and urinary tract	• Presence of both kidneys; renal artery investigation if kidneys not visualized; • Presence of pyelectasis; • Evaluation of bladder; • Paravesical presence of umbilical arteries.	Transverse and sagittal sections of the trunk to demonstrate: • Stomach; • Bladder; • Kidneys; • Abdominal insertion of the umbilical cord.
Extremities	• Symmetry of limbs and segments; • Movements; • Presence, subjective aspect and echogenicity of long bones; • Fingers on both hands, halux posture.	Transverse section of extremities to demonstrate: • All the long bones; • Hands and feet.

IT: intracranial translucency; NT: nuchal translucency

referral population (47.5% *vs* 76.9%)[87] 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.[48,82,88,89,97]

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.[57,79,83,85,103-107]

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 coarctation 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.[109-112] 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[113] 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.[37,40,47,88,90]

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[114] reported a pooled sensitivity and specificity were 85% (95% CI, 78–90%) and 99% (95% CI, 98–100%), respectively. This demonstrated that FT US scan 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.[52,84,89,115] Other heart defects such cardiomyopathy or cardiac tumors can evolve even after birth.[52,58,94] 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.[116] congenital heart disease (CHD) are the most common disorders that can be observed in fetuses with enlarged NT and normal karyotype.[48,91,116-118] 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%.[40,48] However, all studies agree that the prevalence of CHD is about six times higher in fetuses with a NT $\geq$ 99th percentile than in an unselected population.[118-120]

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.[97] These detection rates are higher that detection rate below 5% when only maternal risk factors are considered.

The data combined from several studies[121] 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.[116,117]

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[88,91] and when fetuses with septated cystic hygromas are excluded.[122]

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.[104] 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.[118] A recent meta-analysis of Papatheodorou[106] 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,[65,83] as cromosomally normal fetuses with TR have an 8-fold increased risk for CHD.[103]

The risk of a CHD increases when an increased NT is associated with TR and/or an abnormal DV.[65]

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.[123] 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,[46,124] 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 holoproencephaly 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,[131] reduced BPD diameter,[60] and abnormal aspects in the posterior brain of the fourth ventricle—intracranial translucency,[58] or brainstem/brainstem-occipital bone distance ratio (BS/BSOB).[59] 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.[132-134]

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.[46] 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.[40,47,72] 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,[38,51,136] from 6% at 10 GW to 75%

at 11 GW, 96% at 12 GW and 98% at 13 to 14 GW.[53] Many countries offer the FT genetic scan at 11^{+0} to 13^{+6} GW. It is generally accepted that an acceptable compromise between genetic and transabdominal structural assessments is achievable at 12 to 13 GW.[45,47,53,137]

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.[137-139] 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.[137]

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.[38,46,48,52] 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[46] to 29%,[40] 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.[48]

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.[53,73,82,84,89]

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%.[53] 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%).[45] 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.[84] 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%).[114]

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.[52] 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.[45]

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.[46] This should be an important component of couple counseling regarding the benefits and limitations of FT anomaly scan,[13] similar to recommendations for the routine mid-trimester fetal structural investigation.[22]

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.[72,73,76]

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.[52,73] However,

due to the similarities between the first and second trimester scanning protocols, the examiners already involved in ST anomaly detection can easily be trained for the FT anomaly scan.[47] They should be made aware of the sonographic appearance of the FT fetal anatomy and early structural or functional particular features of MA.

As suggested in the ISOUG Practice Guidelines regarding the performance of FT fetal ultrasound scan,[13] 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.[40,52,73,87] 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.[72,73] 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.[72]

Documentation

An important good practice point outlined by the practice guidelines[13] 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.[140] 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.[141]

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.[142,143] 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.[101,144] 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 TIb of 0.5 or 0.1.[145] In order to limit the duration of the fetal exposure, a cineloop 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 cineloop and stored.[81]

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 [40,47,72,73] and the recent FT guidelines emitted by ISUOG that 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,[146] during STIC investigation of the fetal heart and evaluation of a wide range of abnormalities, especially those that imply surface anatomy.[147,148] 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.[149] Furthermore, couples prefer earlier screening, when possible.[150] However, supplementary resources are 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.[34,151]

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,[76,152,153] but the majority of severe abnormalities derive from low-risk pregnancies.[48,116] 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

1. Nicolaides KH. A model for a new pyramid of prenatal care based on the 11 to 13 weeks' assessment. Prenat Diagn 2011; 31(1):3-6.
2. Nicolaides KH. Screening for fetal aneuploidies at 11 to 13 weeks. Prenat Diagn 2011;31(1):7-15.
3. Akolekar R, Bower S, Flack N, Bilardo CM, Nicolaides KH. Prediction of miscarriage and stillbirth at 11–13 weeks and the contribution of chorionic villus sampling. Prenat Diagn 2011;31(1):38-45.
4. van Ravenswaaij R, Tesselaar-van der Goot M, de Wolf S, van Leeuwen-Spruijt M, Visser GHA, Schielen PCJI. First-trimester serum PAPP-A and fß-hCG concentrations and other maternal characteristics to establish logistic regression-based predictive rules for adverse pregnancy outcome. Prenat Diagn 2011;31(1):50-57.
5. Beta J, Akolekar R, Ventura W, Syngelaki A, Nicolaides KH. Prediction of spontaneous preterm delivery from maternal factors, obstetric history and placental perfusion and function at 11–13 weeks. Prenat Diagn 2011;31(1):75-83.
6. Greco E, Lange A, Ushakov F, Rodriguez Calvo J, Nicolaides KH. Prediction of spontaneous preterm delivery from endocervical length at 11 to 13 weeks. Prenat Diagn 2011; 31(1):84-89.
7. Akolekar R, Syngelaki A, Sarquis R, Zvanca M, Nicolaides KH. Prediction of early, intermediate and late pre-eclampsia from maternal factors, biophysical and biochemical markers at 11–13 weeks. Prenat Diagn 2011;31(1):66-74.
8. Waugh N, Scotland G, McNamee P, Gillett M, Brennan A, Goyder E, Williams R, John A. Screening for type 2 diabetes: literature review and economic modelling. Health Technol Assess 2007;11:1-125.
9. Nanda S, Savvidou M, Syngelaki A, Akolekar R, Nicolaides KH. Prediction of gestational diabetes mellitus by maternal factors and biomarkers at 11 to 13 weeks. Prenat Diagn 2011;31(2):135-141.
10. Plasencia W, Garcia R, Pereira S, Akolekar R, Nicolaides KH. Criteria for screening and diagnosis of gestational diabetes mellitus in the first trimester of pregnancy. Fetal Diagn Ther 2011;30(2):108-115.
11. Karagiannis G, Akolekar R, Sarquis R, Wright D, Nicolaides KH. Prediction of small-for-gestation neonates from biophysical and biochemical markers at 11-13 weeks. Fetal Diagn Ther 2011;29(2):148-154.
12. Poon LC, Karagiannis G, Stratieva V, Syngelaki A, Nicolaides KH. First-trimester prediction of macrosomia. Fetal Diagn Ther 2011;29(2):139-147.
13. Salomon LJ, Alfirevic Z, Bilardo CM, Chalouhi GE, Ghi T, Kagan KO, Lau TK, Papageorghiou AT, Raine-Fenning NJ, Stirnemann J, et al. ISUOG practice guidelines: performance of first-trimester fetal ultrasound scan. Ultrasound Obstet Gynecol 2013;41(1):102-113.
14. National Collaborating Centre for Women's and Children's Health. Antenatal care Routine care for the healthy pregnant woman NICE clinical guideline 62 [Internet]. 2008. Available at: http://www.nice.org.uk/nicemedia/pdf/CG062NICEguideline.pdf.
15. American College of Obstetricians and Gynecologists. Issues Position on First-Trimester Screening Methods. ACOG NEWS RELEASE [Internet]. 2004 June. Available at: http://www.

acog.org/from_home/publications/press_releases/nr06-30-04.cfm.

16. American College of Obstetricians and Gynecologists. New recommendations for down syndrome: screening should be offered to all pregnant women; 2006 Dec. Available at: http://www.acog.org/from_home/publications/press_releases/nr01-02-07-1.cfm.
17. American Institute of Ultrasound in Medicine. AIUM practice guideline for the performance of obstetric ultrasound examinations [Internet]. 2007 Oct. Available at: http://www.aium.org/resources/guidelines/obstetric.pdf.
18. Timor-Tritsch IE, Gupta SK. Evolving applications of first-trimester ultrasound. OBG Management 2012;24(12):36-45.
19. Katorza E, Achiron R. Early pregnancy scanning for fetal anomalies—the new standard? Clin Obstet Gynecol 2012; 55(1):199-216.
20. Filly RA, Crane JP. Routine Obstetric Sonography. J Ultrasound Med 2002;21(7):713-718.
21. World Health Organization. Training in Diagnostic Ultrasound: essentials, principles, and standards. World Health Organ Tech Rep Ser 1998;875:i-46.
22. Salomon LJ, Alfirevic Z, Berghella V, Bilardo C, Hernandez-Andrade E, Johnsen SL, Kalache K, Leung KY, Malinger G, Munoz H, et al. Practice guidelines for performance of the routine mid-trimester fetal ultrasound scan. Ultrasound Obstet Gynecol 2011;37(1):116-126.
23. Schwarzler P, Senat MV, Holden D, Bernard JP, Masroor T, Ville Y. Feasibility of the second-trimester fetal ultrasound examination in an unselected population at 18, 20 or 22 weeks of pregnancy: a randomized trial. Ultrasound Obstet Gynecol 1999;14(2):92-97.
24. Saltvedt S, Almstrom H, Kublickas M, Valentin L, Grunewald C. Detection of malformations in chromosomally normal fetuses by routine ultrasound at 12 or 18 weeks of gestation —a randomised controlled trial in 39,572 pregnancies. BJOG 2006;113(6):664-674.
25. Tegnander E, Williams W, Johansen OJ, Blaas HG, Eik-Nes SH. Prenatal detection of heart defects in a non-selected population of 30149 fetuses—detection rates and outcome. Ultrasound Obstet Gynecol 2006;27(3):252-265.
26. Goldberg JD. Routine screening for fetal anomalies: expectations. Obstet Gynecol Clin North Am 2004;31(1):35-50.
27. Grandjean H, Larroque D, Levi S. The performance of routine ultrasonographic screening of pregnancies in the Eurofetus Study. Am J Obstet Gynecol 1999;181(2):446-454.
28. Eurenius K, Axelsson O, Gallstedt-Fransson I, Sjoden PO. Perception of information, expectations and experiences among women and their partners attending a second-trimester routine ultrasound scan. Ultrasound Obstet Gynecol 1997;9(2):86-90.
29. Royal College of Obstetricians and Gynaecologists. Ultrasound screening for fetal abnormalities. Report of the RCOG Working Party [Internet]. London: The Royal College of Obstetricians and Gynaecologist; 1997. Available at: http://www.febrasgo.org.br/site/wp-content/uploads/2013/10/Ultrasound_Screening-GUIDELINE-ROYAL_COLLEGE.pdf
30. Hernadi L, Torocsik M. Screening for fetal anomalies in the 12th week of pregnancy by transvaginal sonography in an unselected population. Prenat Diagn 1997;17(8):753-759.
31. D'Ottavio G, Mandruzzato G, Meir YJ, Rustico MA, Fischer-Tamaro L, Conoscenti G. Comparison of first trimester and second trimester screening for fetal anomalies. Ann NY Acad Sci 1998;847(1):200-209.
32. Bilardo CM, Pajkrt E, de Graaf I, Mol BW, Bleker OP. Outcome of fetuses with enlarged nuchal translucency and normal karyotype. Ultrasound Obstet Gynecol 1998;11(6):401-406.
33. Hafner E, Schuchter K, Liebhart E, Philipp K. Results of routine fetal nuchal translucency measurement at weeks 10–13 in 4233 unselected pregnant women. Prenat Diagn 1998;18(1):29-34.
34. Whitlow BJ, Chatzipapas IK, Lazanakis ML, Kadir RA, Economides DL. The value of sonography in early pregnancy for the detection of fetal abnormalities in an unselected population. Br J Obstet Gynaecol 1999 Sep;106(9):929-936.
35. Economides DL, Braithwaite JM. First trimester ultrasonographic diagnosis of fetal structural abnormalities in a low risk population. Br J Obstet Gynaecol 1998;105(1):53-57.
36. Guariglia L, Rosati P. Transvaginal sonographic detection of embryonicfetal abnormalities in early pregnancy. Obstet Gynecol 2000;96(3):328-332.
37. Taipale P, Ammala M, Salonen R, Hilesmaa V. Two-stage ultrasonography in screening for fetal anomalies at 13–14 and 18–22 weeks of gestation. Acta Obstet Gynecol Scand 2004;83:1141-1146.
38. Chen M, Lam YH, Lee CP, Tang MH. Ultrasound screening of fetal structural abnormalities at 12 to 14 weeks in Hong Kong. Prenat Diagn 2004;24(2):92-97.
39. Souka AP, Pilalis A, Kavalakis I, Antsaklis P, Papantoniou N, Mesogitis S, Antsaklis A. Screening for major structural abnormalities at the 11- to 14-week ultrasound scan. Am J Obstet Gynecol 2006;194(2):393-396.
40. Becker R, Wegner RD. Detailed screening for fetal anomalies and cardiac defects at the 11–13-week scan. Ultrasound Obstet Gynecol 2006;27(6):613-618.
41. Cedergren M, Selbing A. Detection of fetal structural abnormalities by an 11–14-week ultrasound dating scan in an unselected Swedish population. Acta Obstet Gynecol Scand 2006;85(8):912-915.
42. Dane B, Dane C, Sivri D, Kiray M, Cetin A, Yayla M. Ultrasound screening for fetal major abnormalities at 11–14 weeks. Acta Obstet Gynecol Scand 2007;86(6):666-670.
43. Chen M, Lee CP, Lam YHH, Tang RY, Chan BC, Wong SF, Tse LH, Tang MH. Comparison of nuchal and detailed morphology ultrasound examinations in early pregnancy for fetal structural abnormality screening: a randomized controlled trial. Ultrasound Obstet Gynecol 2008;31(2):136-146.
44. Oztekin O, Oztekin D, Tinar S, Adibelli Z. Ultrasonographic diagnosis of fetal structural abnormalities in prenatal screening at 11–14 weeks. Diagn Interv Radiol 2009;15(3): 221-225.
45. Ebrashy A, El Kateb A, Momtaz M, El Sheikhan A, Aboulghar MM, Ibrahim M, Saad M. 13–14-Week fetal anatomy scan: a 5-year prospective study. Ultrasound Obstet Gynecol 2010;35(3):292-296.
46. Syngelaki A, Chelemen T, Dagklis T, Allan L, Nicolaides KH. Challenges in the diagnosis of fetal non-chromosomal abnormalities at 11–13 weeks. Prenat Diagn 2011;31(1):90-102.
47. Iliescu D, Tudorache S, Comanescu A, Antsaklis P, Cotarcea S, Novac L, Cernea N, Antsaklis A. Improved detection rate of structural abnormalities in the first trimester using an extended examination protocol. Ultrasound Obstet Gynecol 2013;42(9):300-309.

48. Souka AP, von Kaisenberg CS, Hyett JA, Sonek JD, Nicolaides KH. Increased nuchal translucency with normal karyotype. Am J Obstet Gynecol 2005;192(4):1005-1021.
49. Romosan G, Henriksson E, Rylander A, Valentin L. Diagnostic performance of routine ultrasound screening for fetal abnormalities in an unselected Swedish population in 2000-2005. Ultrasound Obstet Gynecol 2009;34(5):526-533.
50. Bricker L, Garcia J, Henderson J, Mugford M, Neilson J, Roberts T, Martin MA. Ultrasound screening in pregnancy: a systematic review of the clinical effectiveness, costeffectiveness and women's views. Health Technol Assess 2000; 4(16):1-193.
51. Timor-Tritsch IE, Bashiri A, Monteagudo A, Arsian AA. Qualified and trained sonographers in the US can perform early fetal anatomy scans between 11 and 14 weeks. Am J Obstet Gynecol 2004;191(4):1247-1252.
52. Khalil A, Nicolaides KH. Fetal heart defects: Potential and pitfalls of first-trimester detection. Seminars in Fetal & Neonatal Med 2013;18(5):251-260.
53. Souka AP, Pilalis A, Kavalakis Y, Kosmas Y, Antsaklis P, Antsaklis A. Assessment of fetal anatomy at the 11–14-week ultrasound examination. Ultrasound Obstet Gynecol 2004;24(7):730-734.
54. Bilardo CM, Timmerman E, De Medina PG, Clur SA. Low-resistance hepatic artery flow in first-trimester fetuses: an ominous sign. Ultrasound Obstet Gynecol 2011;37(4):438-443.
55. Hyett J, Sonek J, Nicolaides K. Nuchal translucency and the risk of congenital heart disease. Obstet Gynecol 2007; 109(6):1455-1456.
56. Pereira S, Ganapathy R, Syngelaki A, Maiz N, Nicolaides KH. Contribution of fetal tricuspid regurgitation in first-trimester screening for major cardiac defects. Obstet Gynecol 2011;117(6):1384-1391.
57. Chelemen T, Syngelaki A, Maiz N, Allan L, Nicolaides KH. Contribution of ductus venosus Doppler in first-trimester screening for major cardiac defects. Fetal Diagn Ther 2011;29(2):127-134.
58. Chaoui R, Nicolaides KH. From nuchal translucency to intracranial translucency: towards the early detection of spina bifida. Ultrasound Obstet Gynecol 2010;35(2):133-138.
59. Lachmann R, Chaoui R, Moratalla J, Picciarelli G, Nicolaides KH. Posterior brain in fetuses with open spina bifida at 11 to 13 weeks. Prenat Diagn 2011;31(1):103-106.
60. Bernard J-P, Cuckle HS, Stirnemann JJ, Salomon LJ, Ville Y. Screening for fetal spina bifida by ultrasound examination in the first trimester of pregnancy using fetal biparietal diameter. Am J Obstet Gynecol 2012;207(4):306.e1-5.
61. Sepulveda W, Wong AE, Martinez-Ten P, Perez-Pedregosa J. Retronasal triangle: a sonographic landmark for the screening of cleft palate in the first trimester. Ultrasound Obstet Gynecol 2010;35(1):7-13.
62. Martinez-Ten P, Adiego B, Perez-Pedregosa J, Illescas T, Wong AE, Sepulveda W. First-trimester assessment of the nasal bones using the retronasal triangle view: a 3-dimensional sonographic study. J Ultrasound Med 2010; 29(11):1555-1561.
63. Sepulveda W, Wong AE, Viñals F, Andreeva E, Adzehova N, Martinez-Ten P. Absent mandibular gap in the retronasal triangle view: a clue to the diagnosis of micrognathia in the first trimester. Ultrasound Obstet Gynecol 2012;39(2):152-156.
64. Khalil A, Pajkrt E, Chitty LS. Early prenatal diagnosis of skeletal anomalies. Prenat Diagn 2011;31(1):115-124.
65. Grande M, Arigita M, Borobio V, Jimenez JM, Fernandez S, Borrell A. First-trimester detection of structural abnormalities and the role of aneuploidy markers. Ultrasound Obstet Gynecol 2012;39(2):157-163.
66. Ngo C, Viot G, Aubry MC, Tsatsaris V, Grange G, Cabrol D, Pannier E. First-trimester ultrasound diagnosis of skeletal dysplasia associated with increased nuchal translucency thickness. Ultrasound Obstet Gynecol 2007;30(2):221-226.
67. Sebire NJ, Snijders RJ, Davenport M, Greenough A, Nicolaides KH. Fetal nuchal translucency thickness at 10–14 weeks' gestation and congenital diaphragmatic hernia. Obstet Gynecol 1997;90(6):943-946.
68. Khalil A, Cooke PC, Mantovani E, Bhide A, Papageorghiou AT, Thilaganathan B. Outcome of First Trimester Fetal Abdominal Cysts: A Cohort Study and Review of the Literature. Ultrasound Obstet Gynecol 2014;43(4):413-419.
69. Holschbach V, Lattrich CR, Ortmann O, Müller AM, Germer U. Upper abdominal cysts in first trimester fetuses. Ultraschall Med 2012;33(7):E372-373.
70. Sepulveda W, Dickens K, Casasbuenas A, Gutierrez J, Dezerega V. Fetal abdominal cysts in the first trimester: prenatal detection and clinical significance. Ultrasound Obstet Gynecol 2008;32(7):860-864.
71. Tudorache S, Cara M, Iliescu DG, Novac L, Cernea N. First trimester two- and four-dimensional cardiac scan—intra- and interobserver agreement, comparison between methods and benefits of color Doppler technique. Ultrasound Obstet Gynecol 2013;42(6):659-668.
72. Lombardi CM, Bellotti M, Fesslova V, Cappellini A. Fetal echocardiography at the time of the nuchal translucency scan. Ultrasound Obstet Gynecol 2007;29(3):249-257.
73. Persico N, Moratalla J, Lombardi CM, Zidere V, Allan L, Nicolaides KH. Fetal echocardiography at 11–13 weeks by transabdominal high-frequency ultrasound. Ultrasound Obstet Gynecol 2011;37(3):296-301.
74. von Kaisenberg CS, Kuhling-von Kaisenberg H, Fritzer E, Schemm S, Meinhold-Heerlein I, Jonat W. Fetal transabdominal anatomy scanning using standard views at 11 to 14 weeks' gestation. Am J Obstet Gynecol 2005;192(2):535-542.
75. Karl K, Kagan KO, Chaoui R. Intra- and interoperator reliability of manual and semi-automated measurements of intracranial translucency. Ultrasound Obstet Gynecol 2012;39(2):164-168.
76. Bellotti M, Fesslova V, De Gasperi C, Rognoni G, Bee V, Zucca I, Cappellini A, Bulfamante G, Lombardi CM. Reliability of the first-trimester cardiac scan by ultrasound-trained obstetricians with high-frequency transabdominal probes in fetuses with increased nuchal translucency. Ultrasound Obstet Gynecol 2010;36(3):272-278.
77. Pruksanusak N, Pranpanus S, Suwanrath C, Kor-anantakul O, Suntharasaj T, Hanprasertpong T, Liabsuetrakul T. Reliability of manual and semi-automated measurements of nuchal translucency by experienced operators. Int J Gynaecol Obstet 2013;121(3):240-242.
78. Abele H, Hoopmann M, Wright D, Hoffmann-Poell B, Huettelmaier M, Pintoffl K, Wallwiener D, Kagan KO. Intra- and interoperator reliability of manual and semi-automated measurement of fetal nuchal translucency by sonographers

with different levels of experience. Ultrasound Obstet Gynecol 2010;36(4):417-422.
79. Borrell A, Perez M, Figueras F, Meler E, Gonce A, Gratacos E. Reliability analysis on ductus venosus assessment at 11-14 weeks' gestation in a high-risk population. Prenat Diagn 2007;27(5):442-446.
80. Ninno MA, Liao AW, Lamberty CO, Miguelez J, Zugaib M. Fetal tricuspid valve Doppler at 11-13 weeks and 6 days: reference values and reproducibility. Prenat Diagn 2010;30(8): 790-794.
81. Suwanrath C, Pruksanusak N, Kor-Anantakul O, Suntharasaj T, Hanprasertpong T, Pranpanus S. Reliability of fetal nasal bone length measurement at 11-14 weeks of gestation. BMC Pregnancy Childbirth 2013;13:7.
82. Huggon IC, Ghi T, Cook AC, Zosmer N, Allan LD, Nicolaides KH. Fetal cardiac abnormalities identified prior to 14 weeks' gestation. Ultrasound Obstet Gynecol 2002;20(1):22-29.
83. Huggon IC, DeFigueiredo DB, Allan LD. Tricuspid regurgitation in the diagnosis of chromosomal anomalies in the fetus at 11-14 weeks of gestation. Heart 2003;89(9): 1071-1073.
84. Smrcek JM, Berg C, Geipel A, Fimmers R, Axt-Fliedner R, Diedrich K, Gembruch U. Detection rate of early fetal echocardiography and in utero development of congenital heart defects. J Ultrasound Med 2005;25(2):187-196.
85. Martinez JM, Comas M, Borrell A, Bennasar M, Gomez O, Puerto B, Gratacos E. Abnormal first-trimester ductus venosus blood flow: a marker of cardiac defects in fetuses with normal karyotype and nuchal translucency. Ultrasound Obstet Gynecol 2010;35(3):267-272.
86. Volpe P, De Robertis V, Campobasso G, Tempesta A, Volpe G, Rembouskos G. Diagnosis of congenital heart disease by early and second-trimester fetal echocardiography. J Ultrasound Med 2012;31(4):563-568.
87. Rustico MA, Benettoni A, D'Ottavio G, Fischer-Tamaro L, Conoscenti GC, Meir Y, Natale R, Bussani R, Mandruzzato GP. Early screening for fetal cardiac anomalies by transvaginal echocardiography in an unselected population: the role of the operator experience. Ultrasound Obstet Gynecol 2000;16(7):614-619.
88. Mavrides E, Cobian-Sanchez F, Tekay A, Moscoso G, Campbell S, Thilaganathan B, Carvalho JS. Limitations of using first-trimester nuchal translucency measurement in routine screening for major congenital heart defects. Ultrasound Obstet Gynecol 2001;17(2):106-110.
89. Carvalho JS, Moscoso G, Tekay A, Campbell S, Thilaganathan B, Shinebourne EA. Clinical impact of first and early second trimester fetal echocardiography on high risk pregnancies. Heart 2004;90(8):921-926.
90. Becker R, Albig M, Gasiorek-Wiens A, Entezami M, Knoll U, Wegner RD. The potential of first trimester anomaly scan and first trimester fetal echocardiography as screening procedures in a medium risk population. J Obstet Gynecol Ind 2005;55(3):228-230.
91. Westin M, Saltvedt S, Bergman G, Kublickas M, Almström H, Grunewald C, Valentin L. Routine ultrasound examination at 12 or 18 gestational weeks for prenatal detection of major congenital heart malformations? A randomised controlled trial comprising 36 299 fetuses. BJOG 2006;113(6):675-682.
92. Ebrashy A, Attia A, Momtaz M, Kader M A, Mahmoud A, Abdel-Fataah G. The diagnostic accuracy of the 13-14 weeks scan and nuchal translucency measurement in the early detection of fetal congenital anomalies. KAJOG 2012;1(1):10-14.
93. Salomon LJ, Alfirevic Z, Bilardo CM, Chalouhi GE, Ghi T, Kagan KO, Lau TK, Papageorghiou AT, Raine-Fenning NJ, Stirnemann J, et al. ISUOG Practice Guidelines: performance of first-trimester fetal ultrasound scan. Ultrasound Obstet Gynecol 2013;41(1):102-113.
94. Haak MC, van Vugt JM. Echocardiography in early pregnancy: Review of literature. J Ultrasound Med 2003;22(3):271-280.
95. Smrcek JM, Berg C, Geipel A, Fimmers R, Diedrich K, Gembruch U. Early fetal echocardiography: heart biometry and visualization of cardiac structures between 10 and 15 weeks' gestation. J Ultrasound Med 2006;25(2):173-182.
96. Haak MC, Twisk JWR, Van Vugt JMG. How successful is fetal echocardiographic examination in the first trimester of pregnancy? Ultrasound Obstet Gynecol 2002;20(1):9-13.
97. Makrydimas G, Sotiriadis A, Ioannidis JPA. Screening performance of first-trimester nuchal translucency for major cardiac defects: A meta-analysis. Am J Obstet Gynecol 2003;189(5):1330-1335.
98. International Society of Ultrasound in Obstetrics & Gynecology. Cardiac screening examination of the fetus: guidelines for performing the 'basic' and 'extended basic' cardiac scan. Ultrasound Obstet Gynecol 2006;27(1):107-113.
99. Fetal Echocardiography Task Force, American Institute of Ultrasound in Medicine Clinical Standards Committee, American College of Obstetricians and Gynecologists, Society for Maternal-Fetal Medicine. AIUM practice guideline for the performance of fetal echocardiography. J Ultrasound Med 2011;30(1):127-136.
100. Eggebø TM, Heien C, Berget M, Ellingsen CL. Routine Use of Color Doppler in Fetal Heart Scanning in a Low-Risk Population. ISRN Obstet Gynecol 2012;2012:496935.
101. Salvesen K, Lees C, Abramowicz J, Brezinka C, Ter Haar G, Marsal K, Board of International Society of Ultrasound in Obstetrics and Gynecology (ISUOG). ISUOG statement on the safe use of Doppler in the 11 to 13+6-week fetal ultrasound examination. Ultrasound Obstet Gynecol 2011;37(6):628.
102. Yagel S, Cohen SM, Shapiro I, Valsky DV. 3D and 4D ultrasound in fetal cardiac scanning: a new look at the fetal heart. Ultrasound Obstet Gynecol 2007;29(1):81-95.
103. Faiola S, Tsoi S, Huggon IC, Allan LD, Nicolaides KH. Likelihood ratio for trisomy 21 in fetuses with tricuspid regurgitation at the 11 to 13+6-week scan. Ultrasound Obstet Gynecol 2005;26(1):22-27.
104. Maiz N, Nicolaides KH. Ductus Venosus in the First Trimester: Contribution to Screening of Chromosomal, Cardiac Defecxts and Monochorionic Twin Complications. Fetal Diagn Ther 2010;28(2):65-71.
105. Oh C, Harman C, Baschat AA. Abnormal first-trimester ductus venosus blood flow: a risk factor for adverse outcome in fetuses with normal nuchal translucency. Ultrasound Obstet Gynecol 2007;30(2):192-196.
106. Papatheodorou S, Evangelou E, Makrydimas G, Ioannidis J. First-trimester ductus venosus screening for cardiac defects: a meta-analysis. BJOG 2011;118(12):1438-1445.
107. Ahmed B, Stanojevic M, Kopjar T. Accuracy of the Fetal Echocardiography in the High Risk Pregnancies. Donald School J Ultrasound Obstet Gynecol 2007;1(1):86-95.
108. Bronshtein M, Zimmer EZ. The sonographic approach to the detection of fetal cardiac anomalies in early pregnancy. Ultrasound Obstet Gynecol 2002;19(4):360-365.

109. Vinals F, Mandujano L, Vargas G, Giuliano A. Prenatal diagnosis of congenital heart disease using four-dimensional spatio-temporal image correlation (STIC) telemedicine via an Internet link: a pilot study. Ultrasound Obstet Gynecol 2005;25(1):25-31.
110. Vinals F, Poblete P, Giuliano A. Spatio-temporal image correlation (STIC): a new tool for the prenatal screening of congenital heart defects. Ultrasound Obstet Gynecol 2003; 22(4):388-394.
111. Bennasar M, Martinez JM, Gomez O, Bartrons J, Olivella A, Puerto B, Gratacos E. Accuracy of four-dimensional spatiotemporal image correlation echocardiography in the prenatal diagnosis of congenital heart defects. Ultrasound Obstet Gynecol 2010;36(4):458-464.
112. Bennasar M, Martinez JM, Olivella A, del Rio M, Gomez O, Figueras F, Puerto B, Gratacos E. Feasibility and accuracy of fetal echocardiography using four-dimensional spatiotemporal image correlation technology before 16 weeks' gestation. Ultrasound Obstet Gynecol 2009;33(6): 645-651.
113. Li Y, Hua Y, Fang J, Wang C, Qiao L, Wan C, Mu D, Zhou K. Performance of Different Scan Protocols of Fetal Echocardiography in the Diagnosis of Fetal Congenital Heart Disease: A Systematic Review and Meta-Analysis. PLoS ONE 2013;8(6):e65484.
114. Rasiah SV, Publicover M, Ewer AK, Khan KS, Kilby MD, Zamora J. A systematic review of the accuracy of first-trimester ultrasound examination for detecting major congenital heart disease. Ultrasound Obstet Gynecol 2006;28(1):110-116.
115. Simpson JM, Jones A, Callaghan N, Sharland GK. Accuracy and limitation of transabdominal fetal echocardiography at 12 to 15 weeks of gestation in a population at high risk of congenital heart disease. BJOG 2000;107(12):1492-1497.
116. Makrydimas G, Sotiriadis A, Huggon IC, Simpson J, Sharland, Carvalho JS, Daubeney PE, Ioannidis JPA. Nuchal translucency and fetal cardiac defects: a pooled analysis of major fetal echocardiography centers. Am J Obstet Gynecol 2005;192(1):89-95.
117. Ghi T, Huggon IC, Zosmer N, Nicolaides KH. Incidence of major structural cardiac defects associated with increased nuchal translucency but normal karyotype. Ultrasound Obstet Gynecol 2001;18(6):610-614.
118. Clur SA, Ottenkamp J, Bilardo CM. The nuchal translucency and the fetal heart: a literature review. Prenatal Diagnosis 2009;29(8):739-748.
119. Atzei A, Gajewska K, Huggon IC, Allan LD, Nicolaides KH. Relationship between nuchal translucency thickness and prevalence of major cardiac defects in fetuses with normal karyotype. Ultrasound Obstet Gynecol 2005;26(2):154-157.
120. Bilardo CM, Timmerman E, Pajkrt E, van Maarle M. Increased nuchal translucency in euploid fetuses—what should we be telling the parents? Prenat Diagn 2010;30(2):93-102.
121. Perez-Pedregosa J, Burgos MBA, Martínez-Ten P. First trimester fetal echocardiography. state of the problem. TMJ 2009;59(2):173-183.
122. Simpson LL, Malone FD, Bianchi DW, Ball RH, Nyberg DA, Comstock CH, Saade G, Eddleman K, Gross SJ, Dugoff L, et al. Nuchal translucency and the risk of congenital heart disease. Obstetrics Gynecol 2007;109(2 Pt 1):376-383.
123. Vinay, Kumar.; Abbas, AL.; Fauston, N.. Robbins and Cotran's Pathologic Basis of Disease. 7th ed. New York: Saunders; 2004. 470 p.
124. Malinger G, Lerman-Sagie T, Watemberg N, Rotmensch S, Lev D, Glezerman M. A normal second-trimester ultrasound does not exclude intracranial structural pathology. Ultrasound Obstet Gynecol 2002;20(1):51-56.
125. Simonazzi G, Segata M, Ghi T, Sandri F, Ancora G, Bernardi B, Tani G, Rizzo N, Santini D, Bonasoni P, Pilu G. Accurate neurosonographic prediction of brain injury in the surviving fetus after the death of a monochorionic cotwin. Ultrasound Obstet Gynecol 2006;27(5):517-521.
126. Ghi T, Simonazzi G, Perolo A, Savelli L, Sandri F, Bernardi B, Santini D, Bovicelli L, Pilu G. Outcome of antenatally diagnosed intracranial hemorrhage: case series and review of the literature. Ultrasound Obstet Gynecol 2003;22(2):121-130.
127. Ghi T, Brondelli L, Simonazzi G, Valeri B, Santini D, Sandri F, Ancora G, Pilu G. Sonographic demonstration of brain injury in fetuses with severe red blood cell alloimmunization undergoing intrauterine transfusions. Ultrasound Obstet Gynecol 2004;23(5):428-431.
128. Sepulveda W, Wong AE, Fauchon DE. Fetal spinal anomalies in a first-trimester sonographic screening program for aneuploidy. Prenat Diagn 2011;31(1):107-114.
129. Carvalho MH, Brizot ML, Lopes LM, Chiba CH, Miyadahira S, Zugaib M. Detection of fetal structural abnormalities at the 11-14 week ultrasound scan. Prenat Diagn 2002;22(1):1-4.
130. Sebire NJ, Noble PL, Thorpe-Beeston JG, Snijders RJM, Nicolaides KH. Presence of the 'lemon' sign in fetuses with spina bifida at the 10–14-week scan. Ultrasound Obstet Gynecol 1997;10(6):403-405.
131. Buisson O, De Keersmaecker B, Senat MV, Bernard JP, Moscoso G, Ville Y. Sonographic diagnosis of spina bifida at 12 weeks: heading towards indirect signs. Ultrasound Obstet Gynecol 2002;19(3):290-292.
132. Iliescu D, Comanescu A, Antsaklis P, Tudorache S, Ghilusi M, Comanescu V, Paulescu D, Ceausu I, Antsaklis A, Novac L, et al. Neuroimaging parameters in early open spina bifida detection. Further benefit in first trimester screening? Rom J Morphol Embryol 2011;52(3):809-817.
133. Garcia-Posada R, Eixarch E, Sanz M, Puerto B, Figueras F, Borrell A. Cisterna magna width at 11-13 weeks in the detection of posterior fossa anomalies. Ultrasound Obstet Gynecol 2013;41(5):515-520.
134. Egle D, Strobl I, Weiskopf-Schwendinger V, Grubinger E, Kraxner F, Mutz-Dehbalaie IS, Strasak A, Scheier M. Appearance of the fetal posterior fossa at 11 + 3 to 13 + 6 gestational weeks on transabdominal ultrasound examination. Ultrasound Obstet Gynecol 2011;38(6):620-624.
135. International Society of Ultrasound in Obstetrics & Gynecology Education Committee. Sonographic examination of the fetal central nervous system: guidelines for performing the 'basic examination' and the 'fetal neurosonogram'. Ultrasound Obstet Gynecol 2007;29(1):109-116.
136. Whitlow BJ, Economides DL. The optimal gestational age to examine fetal anatomy and measure nuchal translucency in the first trimester. Ultrasound Obstet Gynecol 1998;11(4): 258-261.
137. Kagan KO, Wright D, Baker A, Sahota D, Nicolaides KH. Screening for trisomy 21 by maternal age, fetal nuchal

translucency thickness, free betahuman chorionic gonadotropin and pregnancy-associated plasma protein-A. Ultrasound Obstet Gynecol 2008;31(6):618-624.

138. Kirkegaard I, Petersen OB, Uldbjerg N, Tørring N. Improved performance of first-trimester combined screening for trisomy 21 with the double test taken before a gestational age of 10 weeks. Prenat Diagn 2008;28(9):839-844.
139. Wright D, Spencer K, Kagan KK, Tørring N, Petersen OB, Christou A, Kallikas J, Nicolaides KH. First-trimester combined screening for trisomy 21 at 7–14 weeks gestation. Ultrasound Obstet Gynecol 2010;36(4):404-411.
140. Abramowicz JS, Fowlkes JB, Skelly AC, Stratmeyer ME, Ziskin MC. Conclusions regarding epidemiology for obstetric ultrasound. J Ultrasound Med 2008;27(4):637-644.
141. American Institute of Ultrasound in Medicine. Medical ultrasound safety. Laurel, Maryland: AIUM; 1999.
142. Abramowicz JS, Kossoff G, Marsal K, Ter Haar G, International Society of Ultrasound in Obstetrics and Gynecology. Safety Statement, 2000 (reconfirmed 2003). Ultrasound Obstet Gynecol 2003;21(1):100.
143. Torloni MR, Vedmedovska N, Merialdi M, Betran AP, Allen T, Gonzalez R, Platt LD, ISUOG-WHO Fetal Growth Study Group. Safety of ultrasonography in pregnancy: WHO systematic review of the literature and meta-analysis. Ultrasound Obstet Gynecol 2009;33(5):599-608.
144. Hershkovitz R, Sheiner E, Mazor M. Ultrasound in obstetrics: a review of safety. Eur J Obstet Gynecol Reprod Biol 2002;101(1):15-18.
145. Sande RK, Matre K, Eide GE, Kiserud T. Ultrasound safety in early pregnancy: reduced energy setting does not compromise obstetric Doppler measurements. Ultrasound Obstet Gynecol 2012;39(4):438-443.
146. Martinez-Ten P, Adiego B, Illescas T, Bermejo C, Wong AE, Sepulveda W. First-trimester diagnosis of cleft lip and palate using three-dimensional ultrasound. Ultrasound Obstet Gynecol 2012;40(1):40-46.
147. Pooh RK, Kurjak A. 3D/4D sonography moved prenatal diagnosis of fetal anomalies from the second to the first trimester of pregnancy. J Matern Fetal Neonatal Med 2012; 25(5):433-455.
148. Bhaduri M, Fong K, Toi A, Tomlinson G, Okun N. Fetal anatomic survey using three-dimensional ultrasound in conjunction with first-trimester nuchal translucency screening. Prenat Diagn 2010;30(3):267-273.
149. Davies V, Gledhill J, McFadyen A, Whitlow B, Economides D. Psychological outcome in women undergoing termination of pregnancy for ultrasound-detected fetal anomaly in the first and second trimesters: a pilot study. Ultrasound Obstet Gynecol 2005;25(4):389-392.
150. Kornman LH, Wortelboer MJM, Beekhuis JR, Morssink LP, Mantingh A. Women's opinions and the implications of first versus second-trimester screening for fetal Down's syndrome. Prenat Diagn 1997;17(11):1011-1018.
151. Dolkart LA, Reimers FT. Transvaginal fetal echocardiography in early pregnancy: normative data. Am J Obstet Gynecol 1991;165(3):688-691.
152. den Hollander NS, Wessels MW, Niermeijer MF, Los FJ, Wladimiroff JW. Early fetal anomaly scanning in a population at increased risk of abnormalities. Ultrasound Obstet Gynecol 2002;19(6):570-574.
153. Weiner Z, Goldstein I, Bombard A, Applewhite L, Itzkovits-Eldor J. Screening for structural fetal anomalies during the nuchal translucency ultrasound examination. Am J Obstet Gynecol 2007;197(2):181.e1-5.