CHAPTER 15

First Trimester Study of Fetal Heart with 4D Echocardiography

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Abstract: The following chapter discusses the added value of various novel 3- and 4-Dimensional Ultrasound (3D/4D US) applications for assessing fetal cardiac anomalies at the first trimester of pregnancy. Information on the importance of the early diagnosis, the feasibility, the anomalies that can be detected at early stages of pregnancy and the limitation of such early examination are discussed in details.

Key words: First Trimester, Fetal Echocardiography, 4D Fetal Echocardiography.

INTRODUCTION

Congenital heart disease (CHD) is the most common major congenital malformation with a birth incidence of 4-8 per 1000 neonates, and high rates of neonatal mortality (20-30%) [1, 2]. High risk population for CHD includes fetuses with increased NT, family history of CHD, and pre-gestational diabetes (Table **1**).

Table 1: Common indications for early fetal echocardiography [19, 38, 39]:

	Maternal indications	
1.	Family history	First-degree relative
2.	Pre-existing metabolic disease	Diabetes
3.	Maternal infections	Parvovirus B19, Rubella, Coxsackie
4.	Cardiac teratogen exposure	Retinoids, Phenytoin, Carbamazepine, Lithium, carbonate, Valproic acid
	Fetal indications	
5.	Suspected fetal heart anomaly	
6.	Abnormal fetal karyotype	
7.	Major extracardiac anomaly	
8.	Abnormal nuchal translucency	≥3.5 mm before 14 weeks' gestation
9.	Fetal cardiac rate or rhythm disturbances	Persistent bradycardia, Persistent tachycardia, Persistent irregular heart rhythm
10.	Reversed end diastolic flow in the umbilical artery	

Prenatal diagnosis of CHD has several purposes: First, patients can be advised about the prognosis and the possible options of treatment and can be referred to tertiary centers for delivery. Second, because there is a strong association between cardiac defects and chromosomal abnormalities [3-5], karyotyping can be offered when CHD are diagnosed. Third, patients can choose termination of pregnancy when severe CHD is diagnosed.

Imaging of the fetal heart in the first trimester of pregnancy is technically more demanding than in mid-gestation because of the relatively smaller size of the fetus and the cardiac structures (the diameter of the heart is about 3 mm at 12 weeks' gestation) (Table **2**).

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Giuseppe Rizzo and Domenico Arduini (Eds)

Table 2: Cardiac anomalies that can be detected at the first trimester of pregnancy.

	No.	Patients	GA	4CV	Complete echo	Anomalies detected	Anomalies missed
Achiron [40]	660	Low risk	13-15	100%	98%	n=3:aortic atresia, TOF, persistent truncus arteriosus	n=3: 2XVSD, rhabdomyoma
Russel [41]	32	Low risk	12-14	100%			
Carvalho [31]	46	Low risk	11-14.6		37-100%		
McAuliffe [3]	160	High risk	11-15.6		95%	n=14: hypoplastic left heart, AV canal, VSD, hypoplastic right heart	n=6:TGA, VSD
Weiner [4]	392	High risk	11-14	100%	88-99%	n=7: hypoplastic left heart, TGA, truncus arteriosus, AV canal, VSD, hypoplastic right heart	n=6: TOF, VSD, ASD
Weiner [5]	200	High risk	11.2-13.5	100%	41-94%	n=12: hypoplastic left heart, AV-canal, truncus arteriosum, hypoplastic right heart, VSD, TGA, TOF	n=6: TOF, pulmonic stenosis, VSDX4, ASD, coarctation of arorta
Gabriel [42]	330	High risk	12-17	100%	94.6%	n=38:VSD, hypoplastic right heartAV canal, TGA, pulmonary atresia, TOF, tricuspid atresia, hypoplastic left heart	n=10:hypoplastic left heart, VSD, ASD, TOF
Carvalho [43]	222	High risk		100%	96%	n=14: AV canal, hypoplastic left heart, VSD, TGA, pulmonary atresia, tricuspid atresia	n=2: VSD, pulmonary stenosis

GA - gestational age 4CV - four chamber view TOF - tetralogy of Fallot.Technological improvements extended the boundaries of the diagnosis of fetal anomalies. The introduction of 3D/4D US opened new era and advanced our capabilities in the demonstration of in-vivo cardiac performance and diagnosis of various fetal malformations. The ultimate goal of 3D and 4D ultrasound is to improve the detection rates of CHD with the ability to navigate the volume and to rotate it, and thus demonstrate additional angles other than the original angle of acquisition. As a result, it has the potential to decrease the dependency on fetal position and sonographer skill because it provides a volume dataset that can be used to display the desired images [6-10].

The objective of this chapter is to review the value of 4DUS examination of the fetal heart during the first trimester.

3D/4D VERSUS 2D US EXAMINATION OF THE FETAL HEART

3D/4D US overcomes major limitation of the 2D US: It provides the examiner with an unlimited number of images for review; it allows for correlation between image planes that are perpendicular to the main image acquisition plane; it enables navigation through the volume dataset and examination of the fetal heart in the absence of the patient; it enables the operator to follow abnormal vessels and to find their origin; it has the potential to shorten the evaluation time, especially when complex heart defects are suspected; it enables the reconstruction of a 3D rendered image that contains depth and volume which may provide additional information that is not available from the thin 2D image slices; it provides examination of the fetal heart using a tomographic approach similar to that used to read computerized tomography; the data volume can be stored and reviewed offline by the examiner or it can be viewed by experts at a remote site; it provides the examiner with the ability to review all images in a cine-loop format; and it enables to slow down the heart rate and detect fast details in slow [10-14].

BASIC PRINCIPLES OF 3D AND 4D ECHOCARDIOGRAPHY:

Gating: Gating is the accurate temporal assignment of 3D images within the cardiac cycle, and is essential for the 3D reconstruction of dynamic cardiac structures. Cardiac motion cannot be depicted using non-gated, static reconstructions, which have been shown to be of reduced resolution and suboptimal accuracy. The dynamic changes in the anatomical structures during the cardiac cycle can be displayed using continuously gated, dynamic 3D (i.e. 4D) echocardiography [15-16].

Spatio-temporal image correlation - STIC: STIC is a technique that allows examination of the fetal heart within a real time 3D (i.e. 4D) volume, displayed in a cineloop that was developed at University of San Diego California [17,18].

Acquisition of the STIC Volume [12, 13, 16, 19-21].

In order to have a good STIC volume the 2D image should be optimized: narrow angle, higher frame rate, avoidance of acoustic shadow and other artifacts. After acquiring the best 2D image the operator has to focus on two points: the window of acquisition and the angle of acquisition. In the window of acquisition it is important to include part of the chest and not to be focused only on the heart. It is important to define the anterior, posterior, right and left sides, and to be able to diagnose enlargement and deviations of the heart. The angle of acquisition should be the minimal angle that includes the information, and by this the acquisition time would be shorter and the movement artifact reduced.

The resultant consecutive volumes are a reconstructed complete heart cycle that displays in an endless loop. This loop may be played in slow motion or stopped at any time for detailed analysis of specific phases of the cardiac cycle. Because there is a volume dataset, each of the scan planes can be moved and rotated while maintaining the synchronized cardiac loop. Thus, the four-chamber view, long axis, short axis, great vessels and all other views can be displayed both in cine loop and as still images (Fig. **1**, **2**, video1).

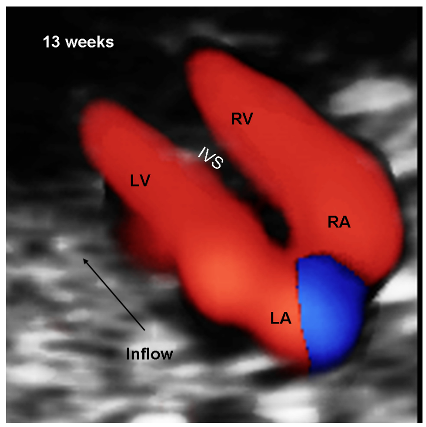

Figure 1: Render mode of four chamber view from normal fetus at 13 weeks gestation. The volume acquired with STIC and High Definition Doppler (HDD). Render mode with glass body at the initial acquisition plane was made. RV=right ventricle; LV=left ventricle, IVS=inter ventricular septum; RA=right atrium; LA=left atrium; arrow demonstrate the direction of blood flow from the atria to the ventricles during the diastole.

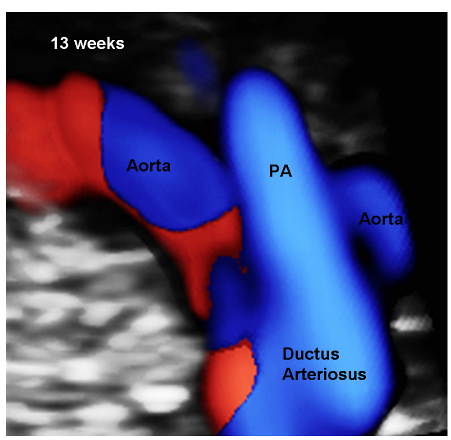

Figure 2: The same volume as in figure 1. The volume now is in the upper chest where the PA (pulmonary artery) crosses the aorta.

Post Processing

We can use the volume as 2D images or 3D images. The multiplanar mode demonstrates 2D images that are perpendicular to each other (the axial, sagittal and coronal planes) at the same time. The tomographic ultrasound imaging (TUI) demonstrate 2D images that are parallel to each other and the whole 5 axial views of the heart can be detected at the same time (Fig. **3**).

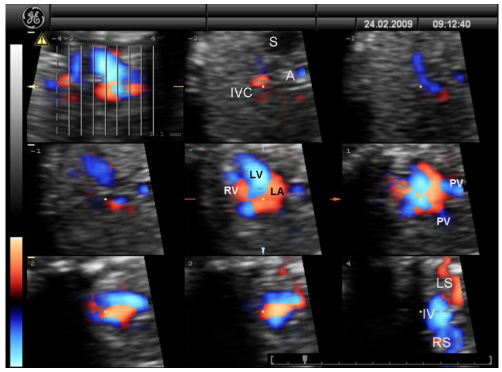

Figure 3: Tomographic ultrasound imaging (TUI) of normal fetus at 11 weeks. The volume acquired with STIC and High Definition Doppler (HDD). S=stomach, IVC=inferior vena cava, A=aorta, LA=left atrium, RV=right ventricle, LV=left ventricle, PV=pulmonary vein.

The volume can be demonstrated as a 3D image using rendering tools. The 3D can be manipulated by editing the colors, the image settings, the different modes. Those variable options can extract different information from the same dataset (Fig. **4** video 2, video 3).

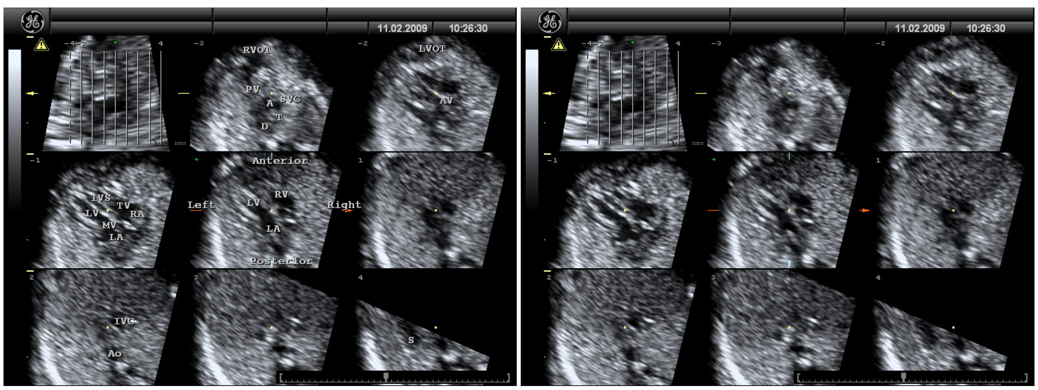

Figure 4: Tomographic ultrasound imaging (TUI) of 12w5d normal fetus. The original volume was acquired with STIC on axial plane. Figure Ais labeled and figure b is the same but unlabeled. Parallel axial planes of the chest allows whole the axial 2D images that are needed for routine cardiac examination. A=aorta; PV=pulmonic valve; SVC=superior vena cava; D=ductus arteriosus; T=trachea; IVS=interventricular septum; TV=tricuspid valve; LV=left ventricle; MV=mitral valve; RA-right atrium; LA=left atrium; RV=right ventricle; IVC=inferior vena cava; Ao=descending aorta; S=stomach.

Multiplanar Reconstruction and Volume Rendering

In multiplanar reconstruction the screen is divided into four frames, referred to as A (the plane seen at the 2D ultrasound), B (the coronal plane) and C (the sagital plane); the fourth frame shows the rendered image (Fig. **5, 6,7** video 4).

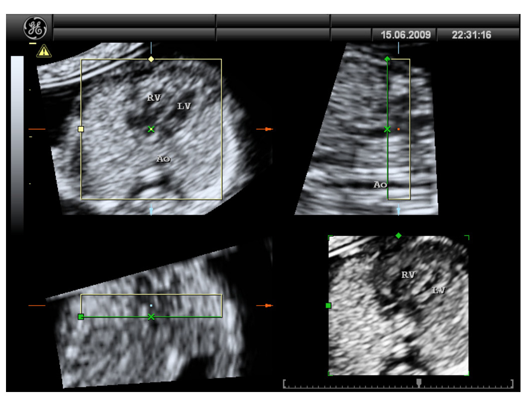

Figure 5: 12w3d Normal fetus. The volume was acquired at the level of 4CV in grey scale. Plane A is 2D image of the axial plane of the chest, demonstrate the right ventricle (RV), left ventricle (LV), descending aorta (Ao). Plane B is the calculating plane of the transverse chest view. The ROI (region of interest) dot is on the ascending aorta in all three planes. The descending aorta is clearly visualized in plane B. Plane C demonstrate the aortic, mitral and tricuspid valves. D is the render mode of Plane A.

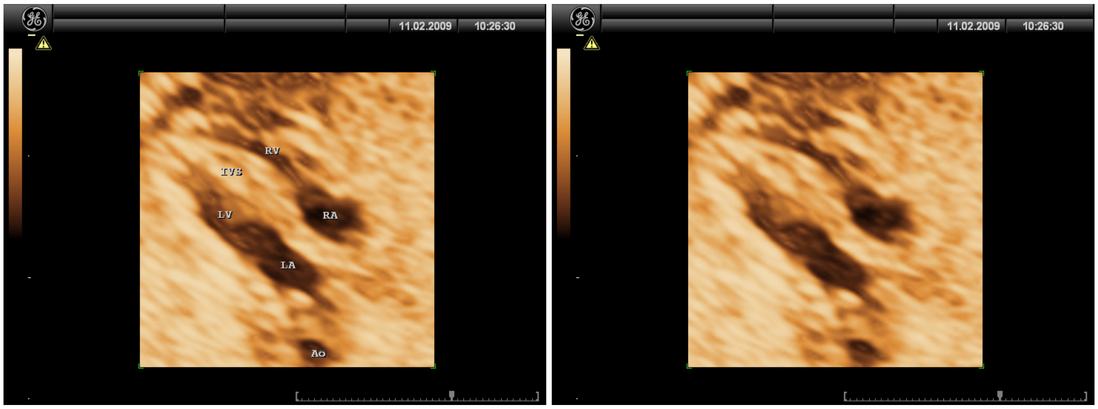

Figure 6: The same volume as in figure 5. Render mode with 30% surface and 70% gradient light mode demonstrating the 4CV. Figure 5a is labeled and 5b is not. IVS=interventricular septum; LV=left ventricle; RV=right ventricle; RA-right atrium; LA=left atrium;

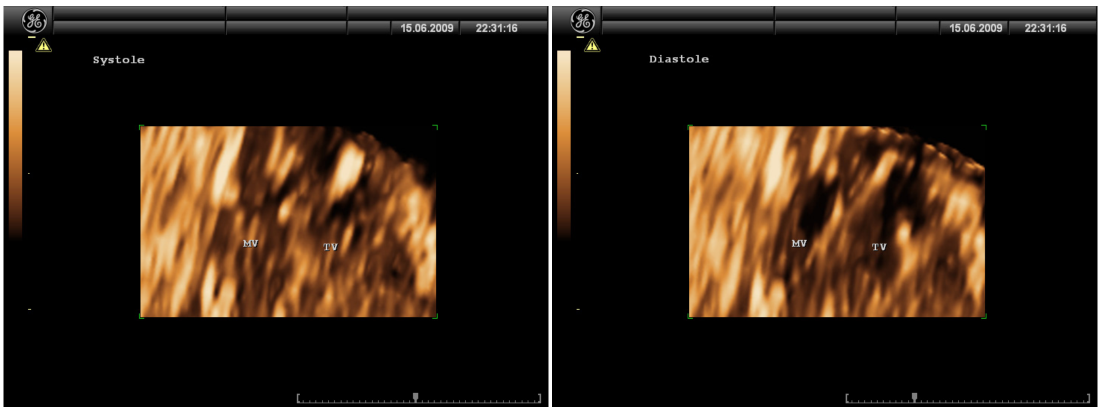

Figure 7: Same volume as figure 5. 3D Render of the atrioventricular valves. Figure a the valves are opened. In Figure b the valves are closed

From a good STIC acquisition the operator can scroll through the acquired volume to obtain sequentially each of the classic five axial planes of fetal echocardiography, and any plane may be viewed at any time-point throughout the reconstructed cardiac cycle loop. The cycle can be run or stopped frame-by-frame to allow examination of all phases of the cardiac cycle (video 5).

Visualization of the intraventricular septum, for example, is possible with the A-frame showing a good four-chamber view, and the bounding box tightly placed around the interventricular septum. The rendered image will show the view of the septum. The operator can determine whether the plane will be displayed from the left or right. Gindes et al demonstrated that the use of render mode with minimal transparency resulted in clearer demonstration of abnormal organs and vessels positions in *situs* abnormalities [21] (Fig. **8**).

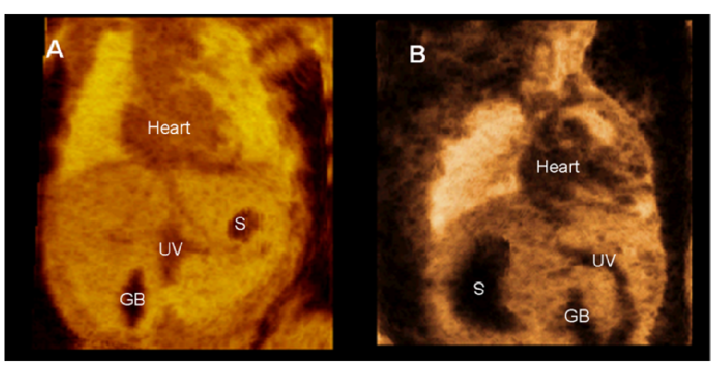

Figure 8: The minimal mode rendering allows imaging of hipoechoic structures. In figure a normal situs is demonstrated in fetus of 14 weeks gestation. In figure b another 14 weeks fetus with situs inversus is demonstrated. The heart is on the left side but the stomach is on the right. The gallbladder in on the left and there is persistent right umbilical vein. S=stomach; GB=gallbladder; UV=umbilical vein.

Tomographic Ultrasound Imaging (TUI) or Multislice Imaging

Multislice analysis (such as TUI) in which parallel slices are displayed simultaneously from the plane of interest (the 'zero' plane), giving sequential views. The number of slices and their thickness, i.e. the distance between one plane and the next, can be adjusted by the operator. The upper left frame of the display shows the position of each plane within the region of interest, relative to the reference plane. This application has the advantage of displaying sequential parallel planes simultaneously, giving a more complete picture of the fetal heart. The arches and outflow tract anomalies are best visualized with Render mode and TUI [21] (Figs. **3, 4**).

Color Doppler may be added to detect the flow through the cardiac cycle (video 6, video 7 , video 8, video 9, video 10).

Inversion Mode

Inversion mode analyzes the echogenicity of tissue (white) and fluid-filled areas (black) in a volume and inverts their presentation, i.e. fluid-filled spaces such as the cardiac chambers appear white, while the myocardium disappears. In fetal echocardiography it can be applied to create 'digital casts' of the cardiac chambers and vessels, and to reconstruct extracardiac vascular tree. Inversion mode shows the stomach and gall bladder as white structures, which can aid the operator in navigating within a complex anomaly scan.

B-Flow

B-flow modality is a direct volume non-gated scanning method able to show blood flow in the heart and great vessels in real-time, without color Doppler flow information [16] (video 11). The resulting image is a live gray-scale depiction of the blood flow and part of the surrounding lumen. The combination of B-flow with STIC along with the creation of a render image allows very sensitive demonstration of blood vessels and heart chambers (Figs. **9-12** video 12).

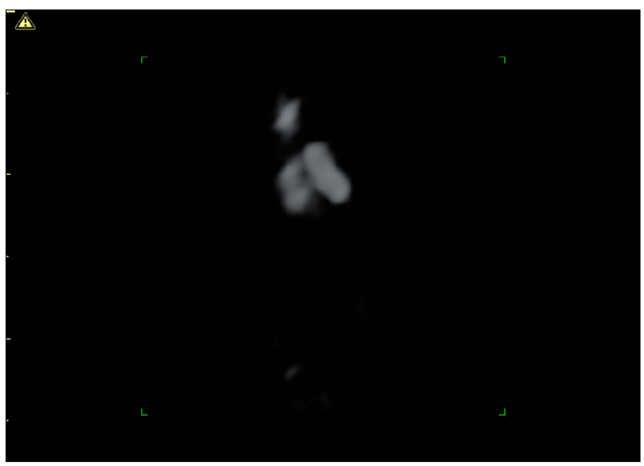

Figure 9: B-flow demonstration of the heart at 10.2 weeks.

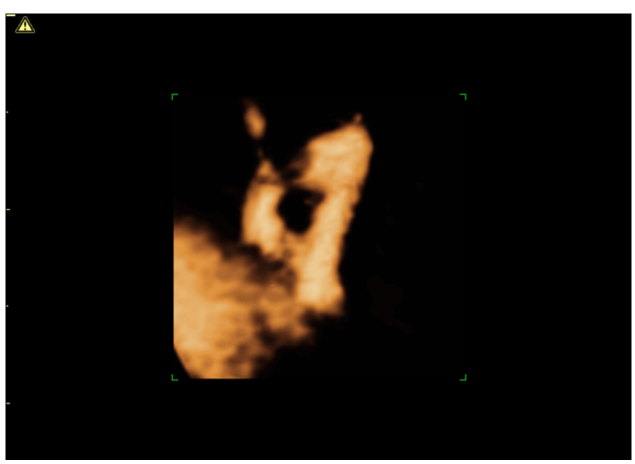

Figure 10: B-flow demonstration of the outflow tracts at 13 weeks.

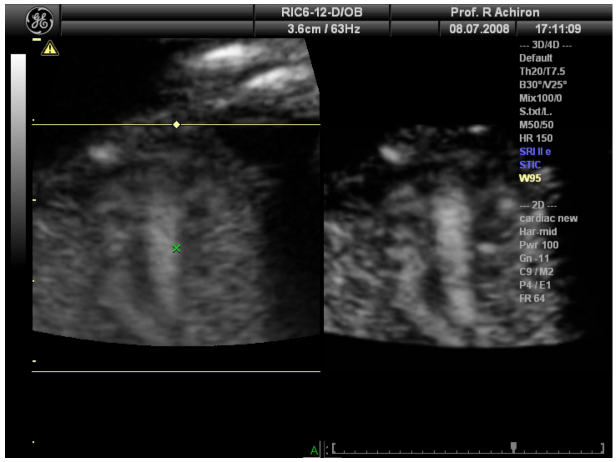

Figure 11: Demonstration of the outflow tract at 14 weeks. This volume was acquired with B-mode grey scale, but the transducer received the beam of the blood flow. A is the 2D image and B is the volume of the same image. The blood vessels are much more bolt in the volume. Ao=aorta; PA=pulmonary artery.

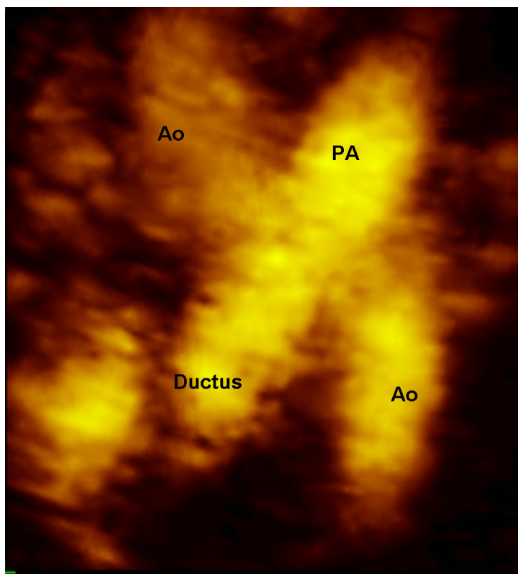

Figure 12: B-flow of the outflow tracts at 14 weeks. 23a presents the render mode. Ao=aorta, PA=pulmonary artery.

Gindes et al demonstrated that inversion mode and B-flow were most informative for detecting arches anomalies. Systemic veins were best shown with B-flow [21].

The 3D-4D ultrasound volume presentation tools and their contribution to the diagnosis of fetal cardiac anomalies are presented in Table **3**.

Table 3: 3D-4D ultrasound volume presentation tools and their contribution to the diagnosis of fetal cardiac anomalies.

	Situs	4 C view	Outflow tract	Arches	Vein
multiplanar	+	+	+	+	+
render	+	++	++	++	+
TUI	+	++	++	++	+

The comparison of the different 3D-4D rendering modes in demonstration cardiac malformations is demonstrated in Table **4**.

Table 4: Comparison of the different 3D-4D rendering modes in demonstration cardiac malformations.

	Situs	4 C view	Outflow tract	Arches	Vein
Minimal mode	++	-	+	+	+
Surface mode and Gradient light	-	+	+	+	+
Inversiom mode	-	+	++	++	+
Glass body	-	++	++	+	+
Color	-	+	++	+	+
B-Flow	-	+	++	++	++

APPROACH TO EARLY 3D/4D FETAL ECHOCARDIOGRAPHY [12-14, 19, 22]:

The most basic approach for the examination of a volume dataset of the fetal heart acquired with STIC is to scroll through the volume from top to bottom along the original plane of acquisition. This approach allows the examiner to determine quickly the relationship between the apex of the heart and stomach, and to evaluate the four-chamber view, and, in most cases, the five-chamber and three-vessel views [23, 24].

If the examiner wants to review the aortic and ductal arches, or the venous return to the heart, datasets are best acquired using sagittal sweeps through the fetal thorax. These images can be generated by acquiring volume datasets with color Doppler, power Doppler or B-flow imaging, as well as by rendering gray-scale volume datasets with inversion mode.

One of the advantages of the STIC acquisition in the first trimester is the possibility to gain the volume of the entire fetus, resulting in better tracing of the blood vessels. Performed properly, this methodology will provide the examiner with all the necessary planes to conform to the guidelines [7]. A pitfall of this technique is that the heart is small (about 3mm at 12 weeks' gestation), making the observation of small details meticulous.

TIPS FOR BETTER VOLUME ACQUISITION [22, 25]:

- The ideal fetal position is one in which the fetus is lying on its back.
- Selection of a region of interest (ROI) as narrow as possible maximizes the frame rate during acquisition and improves the temporal resolution of the volume dataset.
- Because of the small size of the fetal heart at the first trimester a relatively narrow acquisition angle can be used. For first and second-trimester fetuses, acquisition angles of between 20◦ and 25◦ are usually sufficient to include the stomach, the heart, and the great vessels in the volume dataset.
- The longer the acquisition time, the higher the spatial resolution of the volume dataset. However, for highly active fetuses, faster acquisition time is needed, at the expense of optimal spatial resolution.
- 3D acquisition is preferred in order to obtain higher resolution of the blood vessels.

CARDIAC ANOMALIES THAT CAN BE DETECTED AT THE FIRST TRIMESTER OF PREGNANCY [5, 13, 24, 26-28].

The cardiovascular system begins to mature in the 3rd embryonic week, as the heart is a tubular structure. Formation of the septae, and arterial and venous connections are completed only after 8 weeks gestation. A complete four chambers view may be seen at 10 weeks' gestation [29]. The literature demonstrates that it is possible to perform first trimester echocardiography in both low and high risk population and detect many cardiac anomalies, with higher detection rate from 12 weeks' gestation [4, 5,30, 31].

At the level of 4CV (four chamber view) early detection of ventricular septal defects (VSD), atrial septal defects (ASD), atrioventricular septal defects (AVSD) and tricuspid regurgitation, hypoplastic left heart and truncus arteriosus is possible [5, 13]. At the level of the outflow tract detection of transposition of the great arteries, right and double aortic arch is feasible [5, 26]. Achiron et al also demonstrated anomalies in the fetal central veins and umbilico-portal system including absence of ductus venosus and total anomalous pulmonary venous connection and interrupted inferior vena cava with azygus continuation [27]. In a recent study this group reported on evaluation of thoracic anomalies with 3D and 4D ultrasound, including abnormal situs, diaphragmatic hernia, and lung dysplasia as early as 14 weeks [28].

Table **2** summarizes the cardiac anomalies that can be diagnosed on early echocardiography. According to the literature and in our experience we recommend that full examination of the fetal heart starts at 14 weeks' gestation as a routine. In some cases echocardiography may begin as early as 12 gestational weeks.

EXAMPLES:

Atrioventricular Septal Defect (AVSD):

STIC acquisition with color Doppler demonstrates AVSD. Partial defects may be difficult to diagnose (video 13).

Hypoplastic Left Heart:

Color Doppler used in the four-chamber view demonstrates blood flow through the right side of the heart in comparison to the hypoplastic left heart (Fig. **13**).

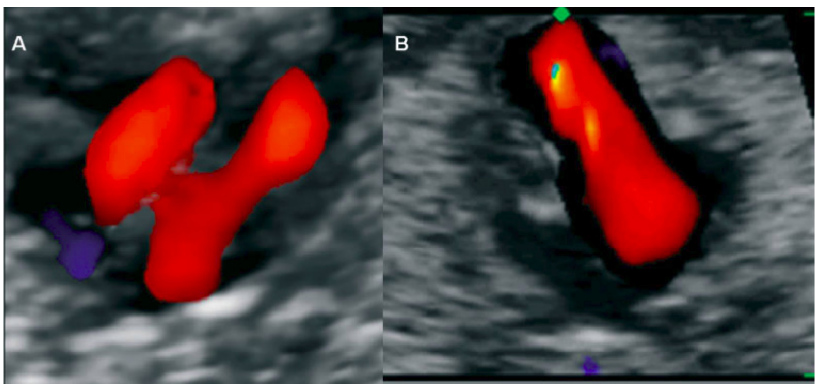

Figure 13: Render mode with Color Doppler demonstration of normal four chamber view (A) and hypoplastic left heart at 14 weeks (B).

Anomalies in the Venous System

3D color Doppler reconstruction may demonstrate anomalies of the venous system such as absence of the ductus venosus (Figs. **14-15**).

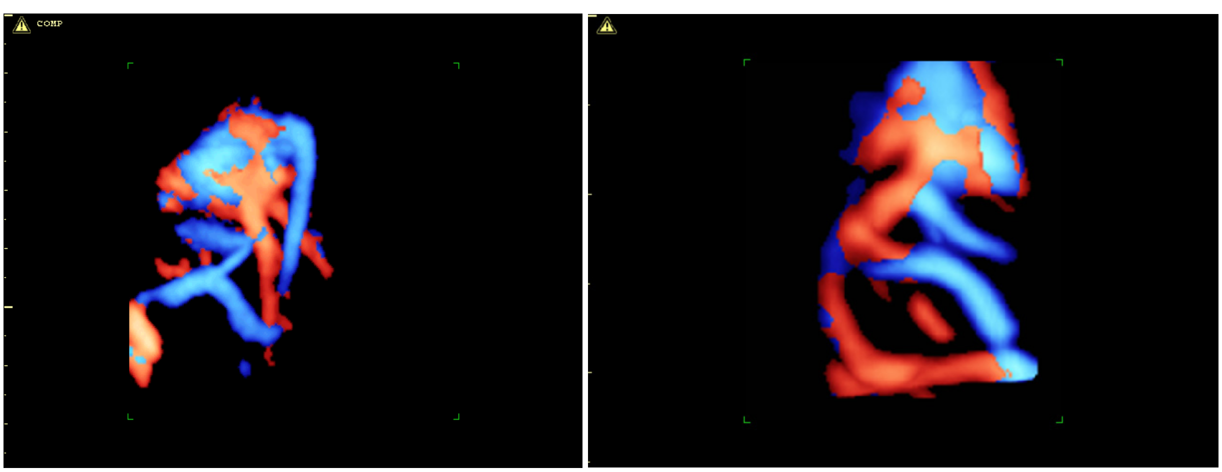

Figure 14: Render mode with Color Doppler demonstration of normal blood vessels (A) and absence of ductus venosus at 11+6 weeks (B).

The 3D reconstruction of the fetal venous system was described in detailed by Gindes et al [44].

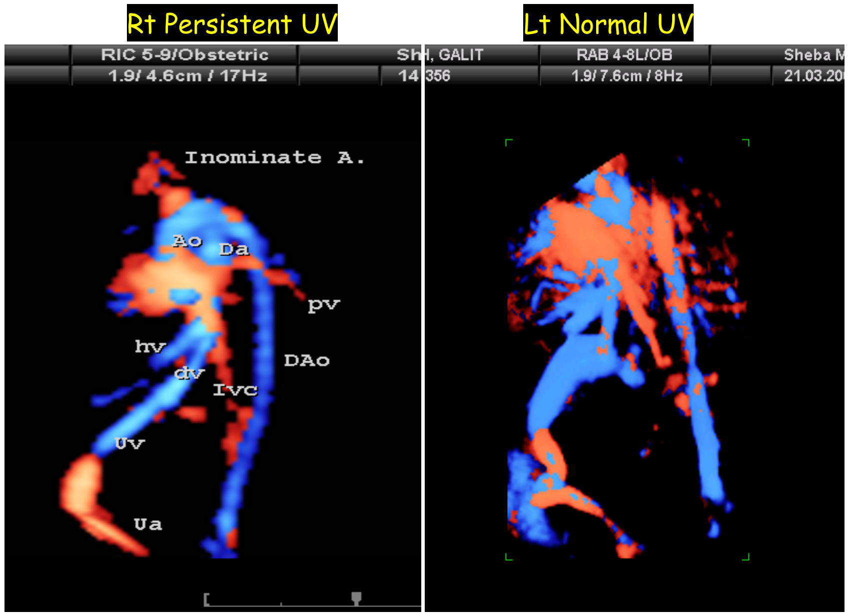

Figure 15: Render mode with Color Doppler demonstration of normal blood vessels (A) and right persistent umbilical vein (B). Ao=aorta, Da=ductus arteriosus, hv=hepatic veins, IVC=inferior vena cava, Uv=umbilical vein, Ua=umbilical artery, Pv=pulmonary vein, Dao=descending aorta, Dv=ductus venosum.

LIMITATIONS OF EARLY FIRST TRIMESTER 3D/4D ECHOCARDIOGRAPHY [26,27]:

Imaging of the fetal heart in the first trimester of pregnancy is technically more demanding than in mid-gestation because of the relatively smaller size of the fetus and cardiac structures (the semilunar valves are about 1.2mm at 13 weeks).

Advances in ultrasound technology have led to improved visualization of the fetus in the first trimester (high frequency transducers 6-12 MHz, better resolution), yet, special orientation compared with transabdominal sonography is more limited. The exploration is more time-consuming and requires a high level of training of the examiner. Furthermore, in some CHD there are later manifestations of structural and functional changes.

3D/4D fetal echocardiography scanning is prone to artifacts similar to those encountered in 2D ultrasonography (resolution, propagation and attenuation artifacts), and some that are specific to 3D/4D acquisition and post-processing [16, 25]:

1. Movement artifacts: The quality of a STIC acquisition may be adversely affected by fetal body or breathing movements as well as by maternal movements. Quality is improved by scanning with the fetus in a quiet state, and using the shortest scan time possible. When reviewing a STIC acquisition, the B-frame will reveal artifacts introduced by fetal breathing movements.
2. Acoustic shadows: Adjacent structures can produce shadows, but since the orientation has changed it may not be immediately obvious. The consequences for the rendered image may include producing defects in surfaces in which there are no defects. It is essential to review suspected defects with repeated 2D and 3D scanning to confirm their presence in additional scanning planes. One may think that at the first trimester the fetal bones are less calcified and thus allow demonstration of the heart from the back of the fetus, but this is not the case. Bones of young fetuses do create acoustic shadows making the optimal position to view the heart with fetus lying with the back down.
3. Small render box artifacts: Limiting the region-of-interest may result in missing important structures from the rendered image. The render box should include some of the chest structures for orientation.
4. Flow direction interpretation: Rotation of the volume with Doppler directional flow information can be misleading: if the directions are reversed, flow data can be misinterpreted. The operator must confirm any suspected pathological flow patterns by confirming the original direction of scanning, whether flow was toward or away from the transducer during the acquisition scan.

SAFETY OF FIRST TRIMESTER 3D/4D ECHOCARDIOGRAPHY (6,7,32)?

The use of ultrasound as a diagnostic tool in obstetrics may have biological effects on living tissues. Therefore, safety considerations should to be taken into account in order to ensure that first trimester 3D/4D echocardiography remains harmless. Grayscale ultrasound is unlikely hazardous to the fetus because of low thermal index. However, the use of Doppler ultrasound may increase that temperature above 1.5^{0}C. The European Federation for Societies in Medicine and Biology in 1998 concluded that Doppler should be carried out with careful control.

The mechanical index is probably nonexistent because it indicates the potential of the ultrasound to induce tissue cavitation, which involves the occurrence of gaseous bubble formation in an air-water interface (such as lungs and bowel). Fetal lungs and bowel do not contain gas, making the mechanical risk absent [6, 7, 32].

Sheiner *et al* performed 40 examinations consisting of 2D, 3D and 4D ultrasounds. They found that the mean thermal index during the 3D and 4D examinations were comparable with the thermal index during B-mode scanning. The mean mechanical index during the 3D volume acquisition was significantly lower than that in the B-mode [33].

The American Institute of Ultrasound in Medicine, the International Society for Ultrasound in Obstetrics and Gynecology and the World Federation for Ultrasound in Medicine and Biology summarized that 3D sonography did not present more risk than native B-mode imaging [34-36]. Since 3D/4D echocardiography has the ability to shorten the total time of echocardiography in high-risk patients, the ALARA principle is kept: as low as reasonably achievable, i.e. perform the scan for the shortest time possible and with the lowest output possible to permit adequate diagnostic acuity [37]. For flow investigation it is possible to combine the B-flow technique with the STIC. The B-flow has the same TI and MI as the B-mode and it is a non Doppler technique.

In summary, the prenatal detection of fetal heart defects remains challenging. The goal of prenatal echocardiography is to visualized structural and functional anomalies of the fetal heart and great vessels, to optimize diagnostic accuracy and to provide images that will aid both management teams and parents in the understanding of the nature of anomalies. With the technological improvement we can detect part of the cardiac anomalies as early as the first trimester. The application of first trimester 3D/4D ultrasound improves the visualization of both normal and anomalous anatomy and function and offers clearer and better images. Early 3D/4D echocardiography is possible, and should be recommended to high-risk patients as part of the routine sonographic follow-up of their pregnancies.

REFERENCES

[1] Hoffman JI, Kaplan S. The incidence of congenital heart disease. J Am Coll Cardiol 2002;39:1890-900.

[2] Hoffman JI. Incidence of congenital heart disease:I. Postnatal incidence. Pediatr Cardiol 1995;16:103-113.

[3] Mc Auliffe FM, Trines J, Nield LE, Chitayat D, Jaeggi E, Hornberger LK. Early fetal echocardiography--a reliable prenatal diagnosis tool. Am J Obstet Gynecol 2005;193:1253-9.

[4] Weiner Z, Lorber A, Shalev E. Diagnosis of congenital cardiac defects between 11 and 14 weeks' gestation in high-risk population. J Ultrasound med 2002;21:23-9.

[5] Weiner Z, Weizman B, Beloosesky R, Goldstein I, Bombard A. Fetal cardiac scanning performed immediately following an abnormal nuchal translucency examination. Prenat Diagn 2008;28:934-8.

[6] DeVore GR, Falkensammer P, Sklansky MS, Platt LD. Spatiotemporal image correlation (STIC): new technology for evaluation of the fetal heart. Ultrasound Obstet Gynecol 2003; 22:380-7.

[7] Garne E, Stoll C, Clementi M. Evaluation of prenatal diagnosis of congenital heart diseases by ultrasound: experience from 20 European registries. Ultrasound Obstet Gynecol 2001;17:386-91.

[8] Tegnander E, Williams W, Johansen OJ, Blaas HG, Eik-Nes SH. Prenatal detection of heart defects in a non-selected population pf 30149 fetuses - detection rates and outcome. Ultrasound Obstet Gynecol 2006;27:252-65.

[9] DeVore GR, Polanko B, Sklansky MS, Platt LD. The „spin technique“: a new method for examination of the fetal outflow tracts using three-dimentional ultrasound. Ultrasound Obstet Gynecol 2004;24:72-82.

[10] Sklansky M, Miller D, Devore G, Kung G, Pretorius D, Wong P, Chang RK. Prenatal screening for congenital heart disease using real-time three-dimentional echocardiography and a novel „sweep volume“ acquision technique. Ultrasound Obstet Gynecol 2005;25:435-43.

[11] Tegnander E, Eik-Nes SH. The examiner’s ultrasound experience has a significant impact on the detection rate of congenital heart defects at the second trimester fetal examination. Ultrasound Obstet Gynecol 2006;28:8-14.

[12] Yagel S, Benachi A, Bonnet D, Dumez Y, Hochner-Celnikier D, Cohen SM, Valsky DV, Fermont L. Rendering in fetal cardiac scanning: the intracardiac septa and the coronal atrioventricular valve planes. Ultrasound Obstet Gynecol 2006;28:266-74.

[13] Vinals F, Ascenzo R, Naveas R, Huggons I, Giulliano A. Fetal echocardiography at 11+0 to 13+6 weeks using four-dimentional spatiotemporal image correlation telemedicine via an Internet limk: a pilot study. Ultrasound Obstet Gymecol 2008;31:633-8.

[14] Uittenbogaard LB, Haak MC, Spreeuwenberg MD, Van Vugt JMG. A systematic analysisof the feasibility of four-dimentional ultrasound imaging using spatiotemporal image correlation in routine fetal echocardiography. Ultrasound Obstet Gynecol 2008;31:625-32.

[15] Hergerg U, Goldberg H, Breuer J. Three- and four-dimentional freehand fetal echocardiography: a feasibility study using a hand-held Doppler probw for cardiac gating. Ultrasound Obstet Gynecol 2005;25:362-71.

[16] 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;29:81-95.

[17] Sklansky MS, Nelson T, Strachan M, Pretorius D. Real-time three-dimentional fetal echocardiography: initial feasibility study. J Ultrasound Med. 1999;18:745-52.

[18] Sklansky MS, Nelson TR, Pretorius DH. Three-dimensional fetal echocardiography: gated versus nongated techniques. J Ultrasound Med. 1998;17:451-7.

[19] Carvalho JS. Fetal heart scanning in the first trimester. Prenat Diagn 2004;24:1060-7.

[20] 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;22:388-94.

[21] Gindes L, Hegesh J, Weisz B, Gilboa Y, Achiron R. Three and four dimensional ultrasound: a novel method for evaluating fetal cardiac anomalies. Prenat Diagn 2009.

[22] Goncalves LF, Lee W, Espinoza J, Romero R. Examination of the fetal heart by four-dimentional (4D) ultrasound with spatio-temporal image correlation (STIC).Ultrasound Obstet Gynecol 2006;27:336-48.

[23] Yoo SJ, Lee YH, Kim SH. Three vessel view of the fetal upper mediastinum: an easy means of detecting abnormalities of the ventricular outflow tracts and great arteries during obstetric screening. Ultrasound Obstet Gynecol 1997;9:173-82.

[24] Yagel S, Cohen SM, Achiron R. Examination of the fetal heart by five short-axis views: a proposed screening method for comprehensive cardiac evaluation. Ultrasound Obstet Gynecol 2001;17:367-9.

[25] Nelson TR, Pretorius DH, Hull A, Sklansky MS, James G. Sources and impacts of artifacts on clinical three-dimensional ultrasound imaging. Ultrasound Obstet Gynecol 2000;16:374-83.

[26] Achiron R, Rotstein Z, Heggesh J, Bronshtein M, Zimand S, Lipitz S, Yagel S. Anomalies of the fetal aortic arch: a novel sonographic approach to in-utero diagnosis. Ultrasound Obstet Gynecol. 2002;20:553-7.

[27] Achiron R, Hegesh J, Yagel S, Lipitz S, Cohen SB, Rotstein Z. Abnormalities of the fetal central veins and umbilico-portal system: prenatal ultrasounographic diagnosis and proposed classification. Ultrasound Obstet Gynecol .2000;16:539-48.

[28] Achiron R, Gindes L, Zalel Y, Lipitz S, Weisz B. Three- and four-dimentional ultrasound: new mwthods for evaluating fetal thoracic anomalies. Ultrasound Obstet Gynecol 2008;32:36-43.

[29] Dolkart LA, Reimers FT. Transvaginal fetal echocardiography in early pregnancy: normative data. Am J Obstet Gynecol 1991;165(3):688-91.

[30] Haak MC, Twisk JW, Van Vugt JM. How successful is fetal echocardiographic examination in the first trimester of pregnancy? Ultrasound Obstet Gynecol 2002;20:9-13.

[31] Carvalho SRM, Mendes MC, Neto OBP, Berezowski AT. First trimester fetal echocardiograophy. Gynecol Obstet Invest 2008;65:162-8.

[32] Abramowicz JS. Prenatal exposure to ultrasound waves: is there a risk? Ultrasound Obstet Gynecol 2007;29:363-7.

[33] Sheiner E, Hackmon R, Shoham-Vardi I, Pombar X, Hussey MJ, Strasser HT, Abramowicz JS. A comparison between acoustic output indices in 2D and 3D/4D ultrasound in obstetrics. Ultrasound Obstet Gynecol 2007;29:326-8.

[34] Abramowicz JS, Kossof G, Marsal K, ter Haar G. International Society of Ultrasound in Obstetrics and Gynecology (ISUOG) Safety and Bioeffects Committee: safety statement. Ultrasound Obstet Gynecol 2000;16:594-6.

[35] Barnett SB. WFUMB Symposium on Safety of Ultrasound in Medicine: conclusions and recommendations on thermal and mechanical mechanisms for biological effects of ultrasound. Ultrasound Med Biol 1998;24:S1-58.

[36] American Institute of Ultrasound in Medicine. Mechanical bioeffects from diagnostic ultrasound: AIUM consensus statements. J Ultrasound Med 2000;19:69-168.

[37] Abramowicz JS. Ultrasound in obstetrics and gynecology: Is this hot technology too hot? J Ultrasound Med 2002;21:1327-33.

[38] The international society of ultrasound in obstetrics and gynecology. Cardiac screening examination of the fetus: guidelines for performing the basic and extended cardiac scan. Ultrasound Obstet Gynecol 2006;27:107-13.

[39] Berg C, Thomsen Y, Geipel A, Gembruch U. Reversed end-diastolic flow in the umbilical artery at 10-14 weeks of gestation is associated with absent pulmonary valve syndrome. Ultrasound Obstet Gynecol 2007;30:254-8.

[40] Achiron R, Weissman A, Rotstein Z, Lipitz S, Mashiach S, Hegesh J. Transvaginal echocardiographic examination of the fetal heart between 13 and 15 weeks' gestation in a low-risk population. J Ultrasound Med 1994;13:783-9.

[41] Russell NE, McAuliffe FM. First-trimester fetal cardiac function. J Ultrasound Med. 2008;27:379-83.

[42] Gabriel CC, Galindo A, Martinez JM, Carrera JM, Gutierrez-Larraya F, de la Fuente P, Puerto B, Borrell A. Early prenatal diagnosis of major cardiac anomalies in a high-risk population. Prenat Diag 2002;22:586-93.

[43] 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;90:921-6.

[44] Gindes L , Pretorius DH ,Romine LE, Kfir M, D'Agostini D, Hull A, Achiron R. 3-Dimentional Ultrasound Demonstration of Fetal Abdominal Blood Vessels. JUM 2009; 977-88.