CHAPTER 2

Second Trimester Screening of Congenital Heart Disease

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Abstract: Congenital heart diseases (CHD) are frequent fetal anomalies, with an important impact on perinatal mortality and morbidity. Prenatal diagnosis has a demonstrated effect in decreasing the overall prevalence at birth, and in improving the outcomes of specific malformations; moreover, the great majority of these malformations occurs in the absence of any risk factor. All of these features strongly evidence the need for a screening test that can be applied to the general population, to identify a selected group of fetuses for the more specific, complex, and time-consuming diagnostic test (fetal echocardiography). The systematic visualization of the four chamber view and the outflow tracts during routine anatomical scan has progressively increased the prenatal detection rate of CHD. However, a number of potentially diagnosable defects are still missed in the screening setting. Three-dimensional ultrasonography could provide a useful tool to ameliorate the current performance of CHD screening; however this possibility needs to be further explored.

Key Words: Congeniral Heart Disease, Diagnosis, Fetal Echocardiography, Screening.

INTRODUCTION

Congenital heart diseases (CHD) are the most common congenital anomalies, with a prevalence of around 9/1000 livebirth [1]; moreover they account for the majority of infant deaths due to congenital malformations [2, 3].

Prenatal diagnosis of CHD implies a number of potential advantages: 1) if it is early enough during gestation, it allows consideration of termination of pregnancy [4]; 2) it consents the planning and timing of delivery in a referral centre, leading to better conditions at surgery; 3) it permits *in utero* treatment, although, to date, few procedures have been performed (ballon valvuloplasty for aortic or pulmonary stenosis [5, 6], atrial septoplasty for hypoplastic left ventricle with resctrictive foramen ovale [7-9], cardiocentesis for pericardial effusion [10-15]) and available data are too sparse to attest a benefit [16, 17]. In contrast, pharmacological transplacental therapy for fetal arrhythmias has become a well accepted practice, based on a consistent body of evidence [18].

Although several risk factors for the development of CHD are recognized (see Table 1), the great majority of these malformations are diagnosed in low-risk pregnancies [19]. This enhances the need for a screening test, which ideally should be simple and rapid enough to be systematically applied to the general population, to identify cases eligible for fetal echocardiography [20, 21]. The usefulness of a systematic screening program is further confirmed by the fact that the majority of prenatal diagnoses of CHD actually occur in women who have been referred to echocardiography because of a suspicion at the screening exam [22].

Table 1: Risk factors for CHD (indications for fetal echocardiography). Modified from [23].

Family history	First-degree relative of proband
Maternal diseases	Pregestational diabetes mellitus
	Phenylketonuria
	Autoimmune diseases: anti-Ro (SSA) and anti-La (SSB)
Maternal infections	Parvovirus B19
	Rubeovirus
	Coxsackie virus

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Table 1: cont....

Teratogen exposure	Retinoids
	Phenytoin
	Carbamazepine
	Valproic acid
	Lithium
	Alcohol
Fetal anomalies	Suspected fetal heart anomaly at screening scan
	Extra-cardiac anomalies
	Non-immune hydrops
	Abnormal fetal karyotype
	Increased nuchal translucency
	Persistent fetal arrhythmias

The first significant effect of prenatal diagnosis of CHD has been the reduction of the prevalence of these anomalies at birth, secondary to increased termination of affected pregnancies. The proportion of termination of pregnancies, among prenatally diagnosed CHD, is 50% [24], and an increase in the number of anomalies diagnosed *in utero* as well an anticipation of the diagnoses is likely to augment the absolute number of terminated pregnancies.

Contrary to the expectations, a positive impact of prenatal diagnosis on the overall survival rate of neonates with CHD has not been demonstrated [25]. One explanation is that prenatally diagnosed CHD tend to be more severe than those diagnosed postnatally, and they are more frequently associated with chromosomal and extra-cardiac anomalies, that negatively influence their prognosis [26].

However, a positive impact of prenatal diagnosis on neonatal outcomes has been demonstrated for specific CHD, namely aortic coartation [27], transposition of great arteries [28], hypoplastic left heart syndrome [29, 30].

THE FOUR CHAMBER VIEW

A first screening test for CHD was proposed in the 80's, and it was based on the inclusion of the four chamber view in all routine ultrasound performed since 16 weeks of gestational age [31].

The main advantage of such a method is the possibility to examine several cardiac structures in one single ultrasonographic plane. Indeed, the correct visualization of the four chamber view, either from an apical or from a transverse approach, allows the evaluation of [32].

- the cardiac situs and the anatomical relationship between the heart and the abdominal organs
- the cardiac axis
- the morphology and symmetry of the ventricles and the atria
- the integrity of the ventricular septum
- the presence of the atrial septum primum
- the foramen ovale bulging toward the left atrium
- the opening of the atrioventricular valves
- the thickness of the ventricular wall
- the absence of pericardial effusion
- the cardiac rate and the regularity of the rhythm
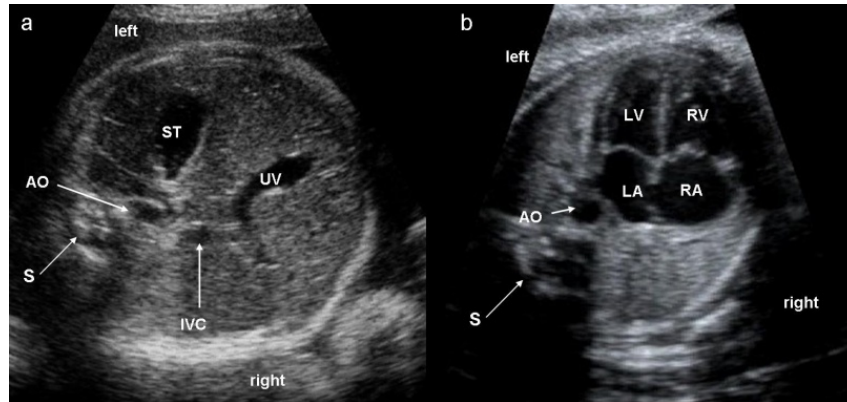
(see Figures 1 - 4).

Figure 1: a) Transverse section of the fetal abdomen: the stomach (ST) is on the left side; the transverse sections of the descending aorta (AO) and inferior vena cava (IVC) are in front of the spine (S), at the left and at the right respectively. The intrahaepatic portion of the umbilical vein (UV) is also seen in this section.
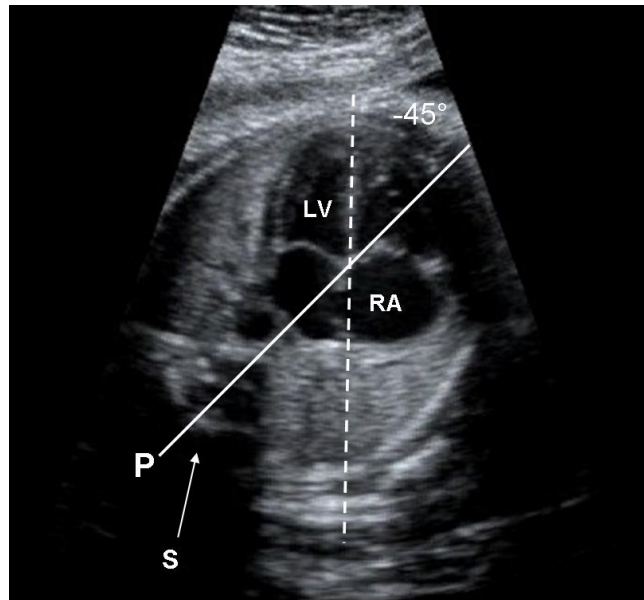

Figure 2: Transverse section of fetal thorax: the longitudinal axis of the heart (dashed line) forms an angle of about 45° with respect to the antero-posterior axis (AP) of the thorax. The apex of the heart is on the left. LV: left ventricle; RA: right atrium; S: spine.
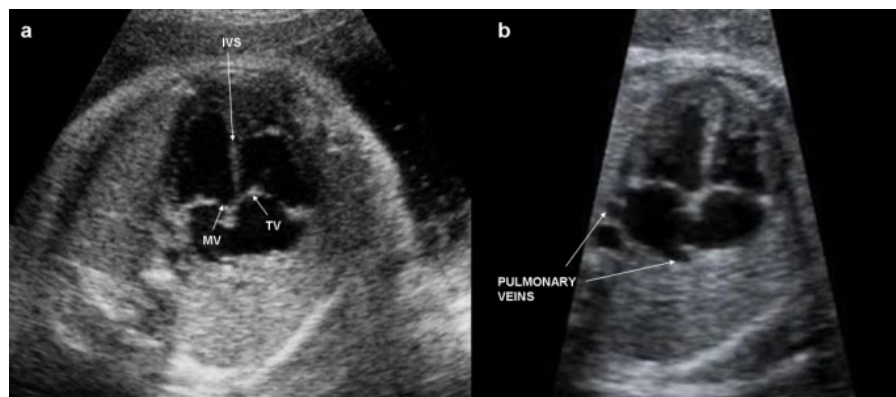

Figure 3: Apical four chamber view: a) the septal leaflet of the tricuspid valve (TV) has a more apical insertion on the interventricular septum (IVS) than the mitral valve (MV); b) pulmonary veins draining in left atrium.
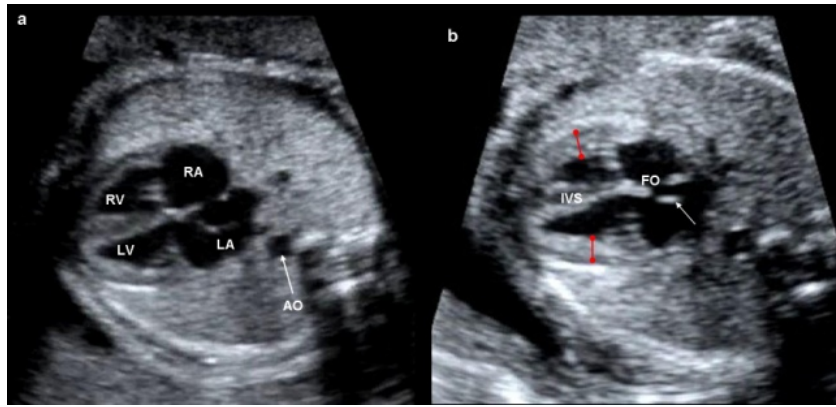
Figure 4: Transverse four chambers view: the apex of the heart is at the left of the fetal thorax. a) the interventricular septum and the walls of the ventricles are better visualized than in the apical view. b) the thickness of the ventricular walls (red lines) and septum (IVS) can be studied. The valve of the foramen ovale (arrow) moves toward the left atrium. LA: left atrium; LV: left ventricle; RV: right ventricle; RA: right atrium; FO: foramen ovale.

b) transverse section of the fetal thorax: transverse section of the descending aorta (AO) and apical four chamber view of the heart. LA: left atrium; LV: left ventricle; RV: right ventricle; RA:right atrium

Hence, the visualization of the four chamber view allows the detection of the wide range of CHD that directly or indirectly modify the above mentioned anatomical structures (see Table 2).

The first reports on the diagnostic accuracy of the four chamber view showed very encouraging results, with sensitivities ranging form 70 to 90%, thus promoting its wide diffusion [31-34]. However, several subsequent studies provided sensitivity values lower then 30% [35-37].

Many factors account for the discrepancies in the detection rate of the four chamber view, including:

- the experience of the operator

- the CHD prevalence in the study population, which can be high-risk, low-risk or unselected

- the operative definition of CHD, which can include or exclude minor defects that are more difficult to diagnose

- the gestational age at the time of the ultrasound, which influences both the possibility to obtain images of adequate quality and to detect progressive defects

- the study design, prospective or retrospective

- the duration and the accuracy of the neonatal follow-up.

Indeed, the first and more promising results came from studies that were performed in referral centres, on high-risk or unselected populations, and by highly specialized operators [31, 32], while the more disappointing results were from multicentric studies, on low-risk populations, and thus better reflect the efficacy on the field of the screening intervention [35, 36].

THE OUTFLOW TRACTS VIEWS

The main limitation of the four chamber view lies in the impossibility to detect anomalies affecting the ventricle-arterial connections, unless they indirectly alter the morphology of the cardiac chambers or the cardiac axis (see Table 2). Importantly, this group of CHD includes conditions, such as transposition of the great arteries, which require early neonatal intervention, and therefore would receive the greatest advantage from accurate prenatal diagnosis. Therefore several investigators suggested to add to the four-chamber view the visualisation of the left ventricular outflow tract (five chamber view) [38, 39], or the visualisation of both outflow tracts [40-43].

The outflow tracts can be evaluated both by the left ventricle and right ventricle "long axis" views and by the "short axis" view [44] (see Figures 5 – 7)
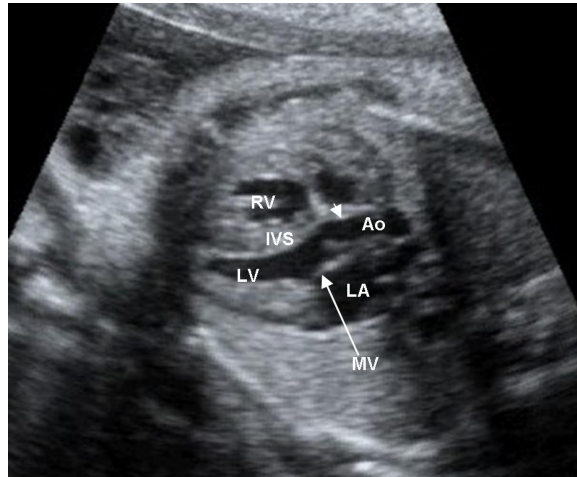

Figure 5: left ventricle long axis view: note the continuity of the aorta anterior wall (arrowhead) with the interventricular septum (IVS) and the continuity of the aorta posterior wall with the anterior leaflet of the mitral valve (MV) (arrow). LA: left atrium. LV: left ventricle; Ao: aorta. RV: right ventricle.
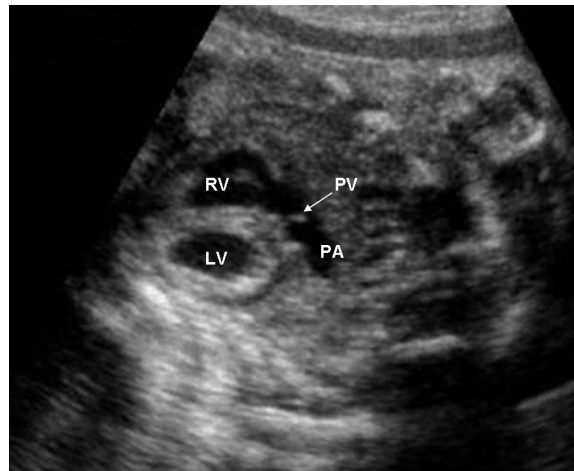

Figure 6: right ventricle long axis view: the pulmonary artery (PA) originates from the infundibular portion of the right ventricle (RV). PV: pulmonary valve; LV: left ventricle
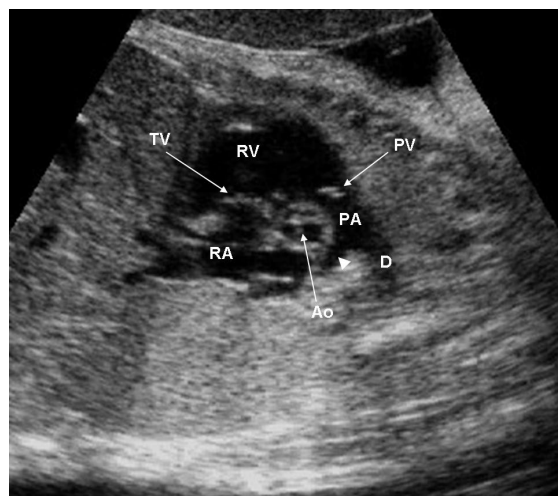

Figure 7 Longitudinal section of the fetal thorax. Short axis view of the great vessels: the aorta (Ao) is in the centre, in transverse section, while the pulmonary artery is visualized in a longitudinal plane, arising from the right ventricle (RV) and in continuity

with the ductus arteriosus (D). The right pulmonary artery is also displayed (arrowhead). RA: right atrium; TV: tricuspid valve; PA: pulmonary artery; PV: pulmonary valve.

The long axis views allow visualizing the aorta and the pulmonary artery, with approximately equal diameters, emerging from left and right ventricle respectively, and crossing at about a 70° angle just above their origin. The aorta originates from the more posterior ventricle; its anterior wall is in continuity with the ventricular septum, while its posterior wall is in continuity with the anterior leaflet of the mitral valve. The pulmonary artery originates from the more anterior ventricle, and bifurcates into the right pulmonary artery and the ductus arteriosus.

Other authors suggested to include the "three vessels and trachea" view into the screening exam of the fetal heart (see Fig. 8).
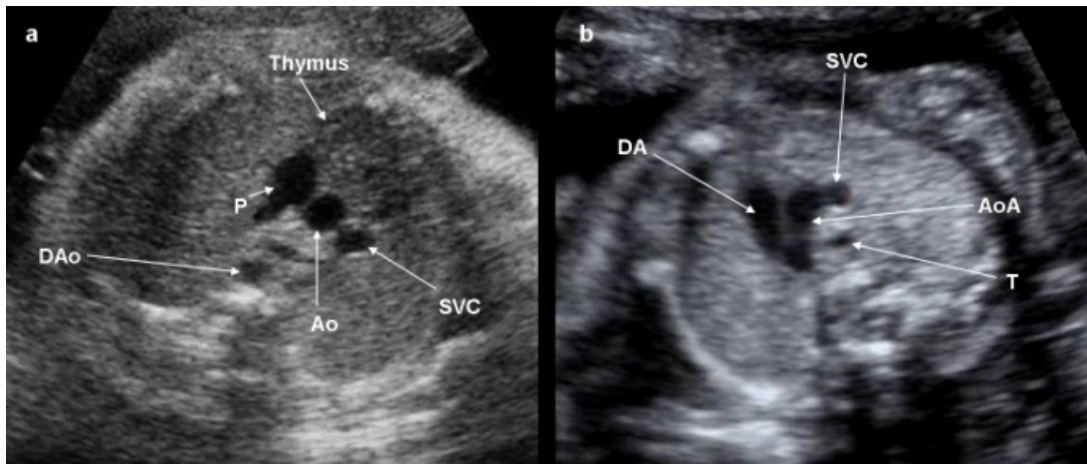

Figure 8: the three vessels can be seen with transverse sections of the fetal thorax above the heart. a) from left to right: pulmonary artery (P), aorta (Ao), superior vena cava (SVC). Note the thymus between the three vessels and the anterior wall of the thorax. b) Moving cranially from the three vessels view, making a slight caudal tilt of the ultrasound beam to the left, allows the aortic arch (AoA) and duct (DA) to be imaged simultaneously.

DAo: Descending Aorta; T: Trachea

This latter is a transverse thorax plane, which permits to verify the presence, position and size of the pulmonary artery, the ascending aorta and the superior vena cava [45], and is considered equally informative with regards to the anatomy of the great vessels compared with the outflow tracts, but more easy to obtain. Several studies have shown that the routine visualization of the outflow tracts – the "extended- basic" cardiac scan [22] – actually increases the sensitivity of the four chamber view. Although once again the highest detection rates come from studies conducted in referral centres and on the high-risk population [19, 45]. nonetheless even multicentric studies on the low-risk population could demonstrate a significant benefit compared with the four chamber view alone [46, 47].

Table 2: CHD and prenatal diagnosis

CHD usually associated with abnormal four-chamber view
1) *Heart abnormalities with a direct effect on the anatomy of the cardiac chambers*
Hypoplastic left heart syndrome
Hypoplastic right heart syndrome
Atrioventricular septal defects
Large ventricular septal defects
Atrio-ventricular valve abnormalities
Ebstein's anomaly
Double inlet ventricle
2) *Abnormalities of the great vessels with an indirect effect on the symmetry of the cardiac chambers*
Severe aortic coarctation
Severe aortic stenosis
Severe pulmonary stenosis or pulmonary atresia with intact interventricular septum

3) *Abnormalities of the situs*

4) *Myocardial hypertrophy*

5) *Cardiac tumors*

6) *Pericardial effusions*

CHD usually not associated with abnormal four-chamber view

1) *Abnormalities of the great vessels without any effect on cardiac chamber anatomy*

       Tetralogy of Fallot

       Transposition of the great arteries

       Double outlet ventricle

       Truncus arteriosus

       Mild aortic stenosis

       Mild pulmonary stenosis

       Pulmonary atresia with ventricular septal defect

Most frequent CHD with a progressive evolution possibly not detectable during the second trimester scan

       Pulmonary stenosis

       Aortic coarctation

       Ventricular hypoplasia

CHD not detectable in utero

       Isolated atrial septal defect

       Small ventricular septal defects

       Patent foramen ovale

       Patent ductus arteriosus

EARLY SCREENING

The fetal heart is completely formed 56 days after conception (10 weeks of postconceptional age, i.e. 8 weeks of gestational age). As a result of the rapid advances in the resolution power of ultrasound machines, a growing number of reports have gathered since the early 90's, showing the feasibility of examination of the fetal heart early in gestation [48-54].

The advantages of a reliable early test are intuitive: in high risk pregnancies, the confirmation of normal cardiac anatomy would reduce maternal anxiety, while the early recognition of a severe CHD would allow the termination of pregnancy in safer conditions, and would provide a longer temporal window for karyotyping, multidisciplinary counselling, the couple's decision-making, and the planning of the pregnancy's and neonatal care. However, although the feasibility of the echocardiografic study at 12-13 weeks of gestational age, by specialized operators and in high-risk pregnancies, is well demonstrated, there is no solid evidence to-date to support the advantage of the anticipation of the cardiac fetal screening in the low-risk population [55].

THE ROLE OF NUCHAL TRANSLUCENCY IN PRENATAL SCREENING OF CHD

The measurement of nuchal translucency (NT) between 11 and 14 weeks of gestational age is a widely diffuse screening test for chromosomal anomalies. In addition, an association between increased NT and CHD, in the absence of chromosomal defects, has been demonstrated, suggesting a potential role for NT as an early screening test for CHD [56-68]. Several studies designed to assess the accuracy of this screening approach have reported very heterogenic results, partly due to the differences in the prospective or retrospective study design, and the extent of the postnatal follow-up (see [69] for review). However, the most recent studies tend to evidence quite a low detection rate: the adoption of a cut-off of 2.5 multiple of the median (MoM), approximately corresponding to the 99th percentile for gestational age, allows the identification of 7% of all the CHD and 13.5% of major CHD, with 1% of the population undergoing echocardiography [70]. These data, which are definitely disappointing, compared with the midtrimester "extended basic" scan, do not justify the adoption of NT as a screening test for the general population. However, the finding of increased NT ($\geq$ 2.5 MoM) during the aneuploidies screening test, should be considered as an indication for fetal echocardiography.

IMPORTANCE OF TRAINING

There is solid evidence that the sensitivity of the prenatal screening of CHD is strongly dependent not only on the number of sonographic views, but also on the operator's experience. The systematic adoption of a training program for the visualization of the four chamber view and the outflow tracts view in Northern England, has increased the proportion of severe CHD that were diagnosed *in utero* from 17 to 30% [71]. A recent Norwegian study [72] measured the accuracy of second trimester ultrasound performed by sonographers and midwives in diagnosing CHD in an unselected population: they found that more experienced operators (who had carried more than 2000 routine scans) were more likely to obtain both four chamber view and outflow tracts view than less experienced operators (75% vs 36% of cases); as expected, this difference was associated with a significantly better detection rate of major heart defects (52% vs. 32.5%).

ROLE OF 3D ULTRASOUND IN THE PRENATAL SCREENING OF CHD

The prenatal screening for CHD is a promising field of application for 3D ultrasound, which still needs to be adequately explored. Indeed, many of the peculiar characteristics of 3D sonography make it an ideal tool for the screening setting. The possibility to reconstruct offline virtually any different plane from a single acquired volume, makes this technology more efficient, reducing the time needed per each single exam; the advantage in term of time saved (which implies the possibility to examine a greater number of subjects) appears to be significant even after considering the additional time needed for the offline manipulation and interpretation of volumes [73-77].

A precious feature of 3D ultrasound is the feasibility to reconstruct offline planes that were not acquired during the patient examination, therefore making the sonogram less operator-dependent [73,74,75] (see Fig 9).

A further advantage of the use of 3D ultrasound as a screening tool, is the opportunity to send the acquired volumes to a referral centre for evaluation in the case of a suspicion of malformation, without any need to move the patient.

The other face of the coin, however, is the new set of skills that have to be acquired by the operator, in order to obtain good informative volumes, minimize artifacts, and interpret the reconstructed planes [58].

On the basis of these considerations, several studies have been conducted to demonstrate the feasibility of the mid-trimester anatomic screening survey, demonstrating a good degree of agreement between the 3D and the 2D sonographic examination [74, 75, 77].

The application of these concepts to the screening of CHD is partly limited by the peculiarity of the motion of this organ, which clearly increases the risk of artifacts. Moreover, the evaluation of cardiac function and rhythm relies on the assessment of real-time scans. However, the possibility to study the moving heart (but not to evaluate the heart rhythm) has been overcome, to a certain extent, by the introduction of the spatio-temporal correlation image technique (STIC).

One claimed benefit of 3D technology is that the acquisition of a single volume dataset allows the visualization of other planes that might be technically more difficult to obtain. When considering the standard exam of the fetal heart, the acquisition of a cardiac volume from the chamber view, can therefore allow the visualization of the more challenging outflow tracts views[78]. Paladini *et al* [79] have recently addressed this issue by assessing the diagnostic accuracy in the evaluation of the outflow tracts using STIC volumes acquired from the four-chamber view. In this study, a group of 14 sonologists of low-to-intermediate experience in basic cardiac scanning, were given a short training in the evaluation of the outflow tracts and volume manipulation; immediately after, they were asked to examine offline 26 volumes, acquired from the four chamber view between 19 and 23 weeks of gestational age, including 16 normal cases and 10 with conotruncal anomalies. Overall sensitivity was 83%, specificity 87% positive predictive value 80% and negative predictive value 89%; the sensitivity per each single anomaly ranged from 50% for transposition of great arteries with intact ventricular septum, to 100% for double outlet right ventricle with or without pulmonary atresia, and transposition of great arteries with ventricular septal defect. However, the study was not designed to evaluate the ability of the sonologists to acquire volumes of adequate quality, and to recognize and discard those of poor quality. Maybe more importantly, the high prevalence of CHD in the study population (38%) prevents the application of these results to the general population.

In summary, three-dimensional ultrasonography possess many characteristics to become a useful tool for the screening of CHD (as well as other malformations). However, before it can be adopted in the general practice, protocols, indications, and terminology should be further standardized and accepted. Moreover, a learning curve should be anticipated, and education and training should be systematically provided to allow the operators to achieve the new skills.

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