12 The Fetal Heart in Early Pregnancy

Edgar Hernandez-Andrade and Erin S. Huntley

Introduction

Congenital heart defects (CHD) are the most frequent fetal anomalies during pregnancy [1, 2]. The prevalence of CHDs can be estimated at 8–12 per 1000 live births with some minor variations in relation to the types of cardiac defects [3]. CHDs are more frequently seen in fetuses with chromosomal and other congenital anomalies [4]. Major CHDs increase the risk of perinatal death and can be identified before birth, whereas minor CHDs may not increase the risk of mortality but are difficult to diagnose prenatally. Minor cardiac defects are usually undiagnosed unless clinical manifestations are present after birth [5]. Some cardiac anomalies evolve during pregnancy and became more apparent in later stages of pregnancy [6, 7], while others, as muscular interventricular septal defects, may resolve before delivery [8]. All these factors have an impact in the different detection rates reported in the literature.

First trimester ultrasound was originally proposed as a screening test to identify fetuses at risk of chromosomal anomalies by identification of indirect ultrasound markers [9]. This approach has changed in recent years as noninvasive prenatal testing (NIPT), or quantification of cell-free fetal DNA in maternal blood, has become the gold standard to identify fetuses at risk of aneuploidies [10]. These advances have challenged the utility of sonographic markers such as the nuchal translucency (NT) [11]; however, an increased NT is still the most important marker for congenital heart defects in the first trimester of pregnancy [12].[1] In addition, better ultrasound systems and more experienced operators have improved the evaluation of the fetus, making first trimester ultrasound a reliable method for early identification of fetal cardiac anomalies and providing more time for confirmation tests and for parental counseling. First trimester ultrasound does not replace the anatomy scan at 20–22 weeks but offers a good opportunity to identify major cardiac anomalies.

First trimester ultrasound can be an advantage for pregnant women with a high body mass index (BMI). It has been reported that among women with BMI ≥30, adequate visualization of the fetal cardiac structures in the second trimester of pregnancy can be achieved in only 50% of cases as compared to 87–90% in women with normal BMI (18–25) [13]. Early fetal evaluation combining TAU and TVU may be a valid alternative in these patients. Even in women with BMI >25,

[1] See also Chap. 9.

E. Hernandez-Andrade (✉) · E. S. Huntley
Department of Obstetrics and Gynecology and Reproductive Sciences, McGovern Medical School, University of Texas, Health Science Center at Houston (UTHealth), Houston, TX, USA
e-mail: Edgar.A.HernandezAndrade@uth.tmc.edu; Erin.S.Huntley@uth.tmc.edu

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the combination of TAU and TVU seems to provide a more complete evaluation of the fetal heart at 13 weeks than TAU alone at 16 weeks of gestation [14]. In general, it has been estimated that approximately 7–10% of all pregnant women, and about 40–50% with high BMI, require TVU to complete the fetal cardiac examination during the first trimester ultrasound scan [15].

Basic Description of Cardiac Development[2]

Formation of the fetal heart begins at around the 23–25th day of gestation when the embryo is 2 mm long and it is completed when the embryonic length is 15 mm, at approximately day 46 of gestation. Some structures, such as the atrioventricular septum, complete their development later in pregnancy. The fetal heart starts contracting at approximately 23 days of gestation. Four main processes occur during cardiac development (Fig. 12.1): (1) formation of the cardiac tube, (2) looping of the heart, (3) formation of the conotruncus, and (4) septation. In each of these processes, specific cardiac defects can originate [16–19].

At the 23–25th days of gestation (2 mm embryo), clusters of angiogenic cells called blood islands create a vascular plexus in the anterior segment of the embryo. These clusters generate two primitive cardiac tubes which will later fuse,

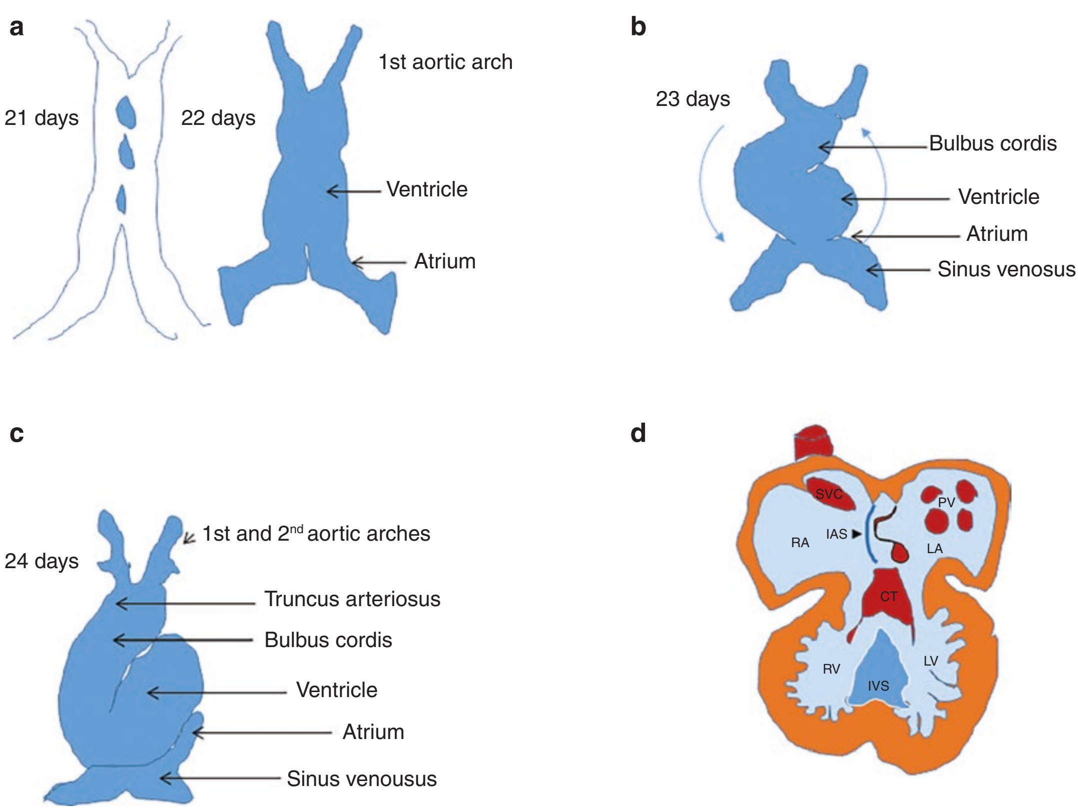

Fig. 12.1 Four main processes during cardiac development: (**a**) formation of the cardiac tube, (**b**) looping of the heart, (**c**) formation of the conotruncus, and (**d**) septation. *CT* Conotruncus, *IVS* interventriclar septum, *IAS* interauricular septum, *LA* left atrium, *LV* left ventricle, *PV* pulmonary veins, *RA* right atrium, *RV* right ventricle, *SVC* superior vena cava

[2] See also Chap. 5.

forming the bulboventricular tube (Fig. 12.1a). The primitive ventricles and the outflow tracts originate from this structure. At this stage, the aortic sac and aortic arches begin to develop and cardiac looping is initiated through a process of bending of the cardiac tube toward the anterior and right parts of the embryo (Fig. 12.1b). One of the main cardiac defects originating at this stage is transposition of the great arteries.

On gestational day 28 (3 mm embryo), the early embryonic ventricle originates from the diverticula located near the left ventro-lateral border of the cardiac tube. These diverticula penetrate the myocardium, increasing its thickness and creating multiple trabeculae forming the primitive left ventricle. The bulbus cordis splits into three sections: the proximal third forms the primitive right ventricle; the middle third forms the conus cordis and the outflow portions of the ventricles; and the terminal third forms the aortic and pulmonary roots or primitive truncus arteriosus (Fig. 12.1c). The formation of the primitive atria, the septum primum, septum secundum, as well as the process of septation begins at this stage. Cardiac defects that can develop during this period are single ventricle, double inlet and double outlet right ventricle, atrial septal and truncus arteriosus.

On gestational days 29–30 (4–5 mm embryo), the sinus venosus and the sinus cordis are formed, and the external shape of the heart resembles a four-chamber structure. Cardiac defects that can occur during this period are persistent left superior vena cava, Tetralogy of Fallot, and ventricular septal defects.

On gestational days 30–32 (5–6 mm embryo), the atrioventricular canal, the pulmonary veins and septation of the truncus arteriosus are formed (Fig. 12.1d). Cardiac defects developing during this period are anomalous pulmonary venous return, persistent atrioventricular canal, ventricular septal and aortico-pulmonary defects, and persistent truncus arteriosus.

Formation of the arterial valves begins on gestational day 36 (9 mm embryo), and of the atrioventricular valves on days 39–40 (10–12 mm embryo). Cardiac defects occurring during this period are bicuspid arterial valves, absent arterial valves, tricuspid valve atresia, and Ebstein's anomaly. The development of the aortic arch is completed by approximately the 46th day of gestation (17 mm embryo). Cardiac defects that may develop during this period are double aortic arch, interrupted aortic arch, right aortic arch, and coarctation of the aorta. At the time of the first trimester ultrasound when the embryonic length is >45 mm, all cardiac structures are already formed.

Why Do We Have to Scan the Fetal Heart Early in Pregnancy?

Early evaluation of the fetal heart can be performed in selected pregnant women with high risk for CHD characterized by family or obstetric history of congenital heart defects [20, 21], uncontrolled diabetes [22], under medication, i.e., anticonvulsants [23], monochorionic twin pregnancies [24], in pregnancies from assisted reproductive techniques [25]; and in fetuses with indirect markers of congenital heart defects, e.g., increased nuchal translucency [26–28], abnormal ductus venous waveform [29–32], tricuspid regurgitation [33], or cystic hygroma [34, 35]; and fetuses with any other structural defect [36, 37] (Table 12.1). Fetal cardiac evaluation can also be part of the routine anatomy scan performed to all pregnant women undergoing an ultrasound scan at 11 to 13+6 weeks of gestation. Protocols and methods may differ when evaluating either group; however, to achieve a successful evaluation in a basic or in an extended cardiac scan, operators experience, the use of a standard protocol, and good quality imaging are essential.

Table 12.1 Risk factors associated with the presence of congenital heart defects (CHD)

Indication	Association with cardiac defects
Non-cardiac major structural anomalies [114]	21%
Previous history of congenital heart defects [20]	8.7%
Maternal exposure to anticonvulsants [23]	7.8%
Abnormal ductus venosus waveform [115]	7.5%
Increased nuchal translucency [116]	7%
Monochorionic twins [24]	5.5% (9.3% in cases with TTS)
Tricuspid regurgitation [33]	5.1%
Aberrant right subclavian artery [82]	5.1%
Consanguinity [117]	4.4%
Assisted Reproductive Technologies [118]	4.3%

Operator Experience and Route of Ultrasound Examination

Experienced operators can identify most cardiac anomalies in the first trimester scan, but confirmation is always required by a pediatric cardiologist with extensive experience in fetal heart imaging [38]. A minimum number of 180 first trimester fetal cardiac evaluations are needed to reach enough expertise to obtain good quality cardiac images in at least 80% of all scans [39]. Chen and colleagues [40] showed that most of major cardiac anomalies and nearly half of all fetal cardiac defects can be detected in low-risk pregnant women by highly trained maternal-fetal experts. They evaluated 10,294 pregnant women with singleton pregnancies, 129 had cardiac anomalies, 50% of them were diagnosed in the first trimester of pregnancy. The highest detection rates were for hypoplastic left heart (100%), truncus arteriosus (100%), atrioventricular septal defect (100%), and complex cardiac defects (93%); moderate detection rates for transposition of the great arteries (75%), coarctation (67%), and Tetralogy of Fallot (62.5%); and a low detection rate for ventricular septal defects (20%). Similar results were described by Hutchinson et al. [41] showing that experienced operators can visualize the four-chamber view in 98% of cases, the aortic and ductal arches in 91% of cases, and outflow tracts in 72% of pregnant women at 12 weeks of gestation using gray scale and color Doppler imaging. Rasiah and colleagues [42] reported that despite TVU providing better quality images than TAU, training and experience of the operators, and the use of high-quality ultrasound (US) systems can lead to similar detection rates using only TAU. They performed a systematic review and identified ten good quality studies showing a pooled sensitivity of 85% (95% CI, 78–90%), specificity of 99% (95% CI, 98–100%), positive LR of 59.6 (95% CI, 26.5–133.6), and negative LR 0.25 (95% CI, 0.1–0.6) for congenital heart defects.

When Is the Optimal Time to Perform Early Fetal Cardiac Evaluation?

Visualization of cardiac images improves with gestational age (Table 12.2, Fig. 12.2). Despite having good quality images at 11 weeks (Figs. 12.3 and 12.4) and 12 weeks (Fig. 12.5), examining the heart at 13 weeks is probably the best (Fig. 12.6). Haak et al. [43] reported that at 11 weeks, successful evaluation of the heart can be achieved in about 20% of fetuses, whereas at 13 weeks, the success rate increases to 92%. Smrcek et al. [44] studied fetuses from 10 to 15 weeks of gestation and evaluated the following cardiac planes: four-chamber view, three-vessel view, origin and crossing of the great arteries, aortic and ductal arches, superior and inferior vena cava, and at least two pulmonary veins. They were able to identify all structures in 80% of fetuses between 12 and 14 weeks, and in 100% of fetuses at 15 weeks of gestation. The authors reported an increment in the detection rate of cardiac defects from 67% at 10 weeks to 100% at 15 weeks of gestation. They mentioned that between 10 and 13 weeks, TVU was better than TAU; between 12 and 14 weeks both TAU and TVU had a similar detection rate; and from 15 weeks of gestation onwards TAU was better.

Table 12.2 Visualization of fetal cardiac structures during the early ultrasound fetal cardiac examination between 11 and 13+6 weeks of gestation

	10 weeks	11 weeks	12 weeks	13 weeks	13+6 weeks
Four-chamber view	Yes	Yes	Yes	Yes	Yes
Outflow tracts	–	–	Yes	Yes	Yes
Aortic and ductal arches	–	–	Yes	Yes	Yes
Both cava veins	–	–	Yes	Yes	Yes
Pulmonary veins	–	–	–	Yes	Yes

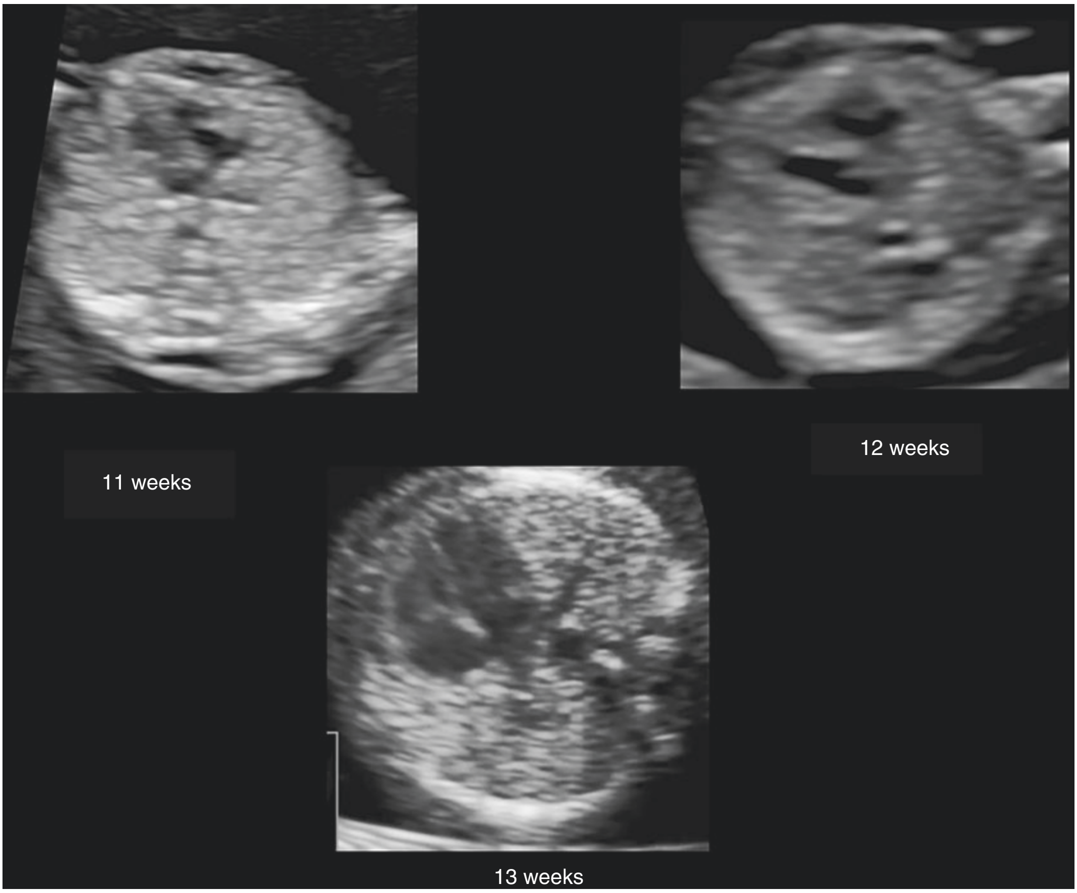

Fig. 12.2 The four-chamber view at 11, 12, and 13 weeks of gestation

The authors mentioned that complementary use of color directional Doppler or power Doppler and not limiting the scanning time can improve the optimal visualization of the fetal heart.

Vimpelli et al. [45] evaluated the feasibility of performing fetal cardiac examination at different weeks during the first trimester of pregnancy. The authors aimed to obtain the following planes: four-chamber, longitudinal views of the aorta and pulmonary trunks, crossing of the great arteries, and both aortic and ductal arches. They reported that visualization of all structures varied from 43% at 11 weeks to 62% at 13+6 weeks. The four-chamber view was obtained in 74% of cases at 13 weeks. McAuliffe et al. [46] evaluated a high-risk group of 160 women defined by previous history of congenital heart disease, increased nuchal translucency, or presence of a non-cardiac malformation during the NT scan. The author's protocol included the following cardiac parameters: four-

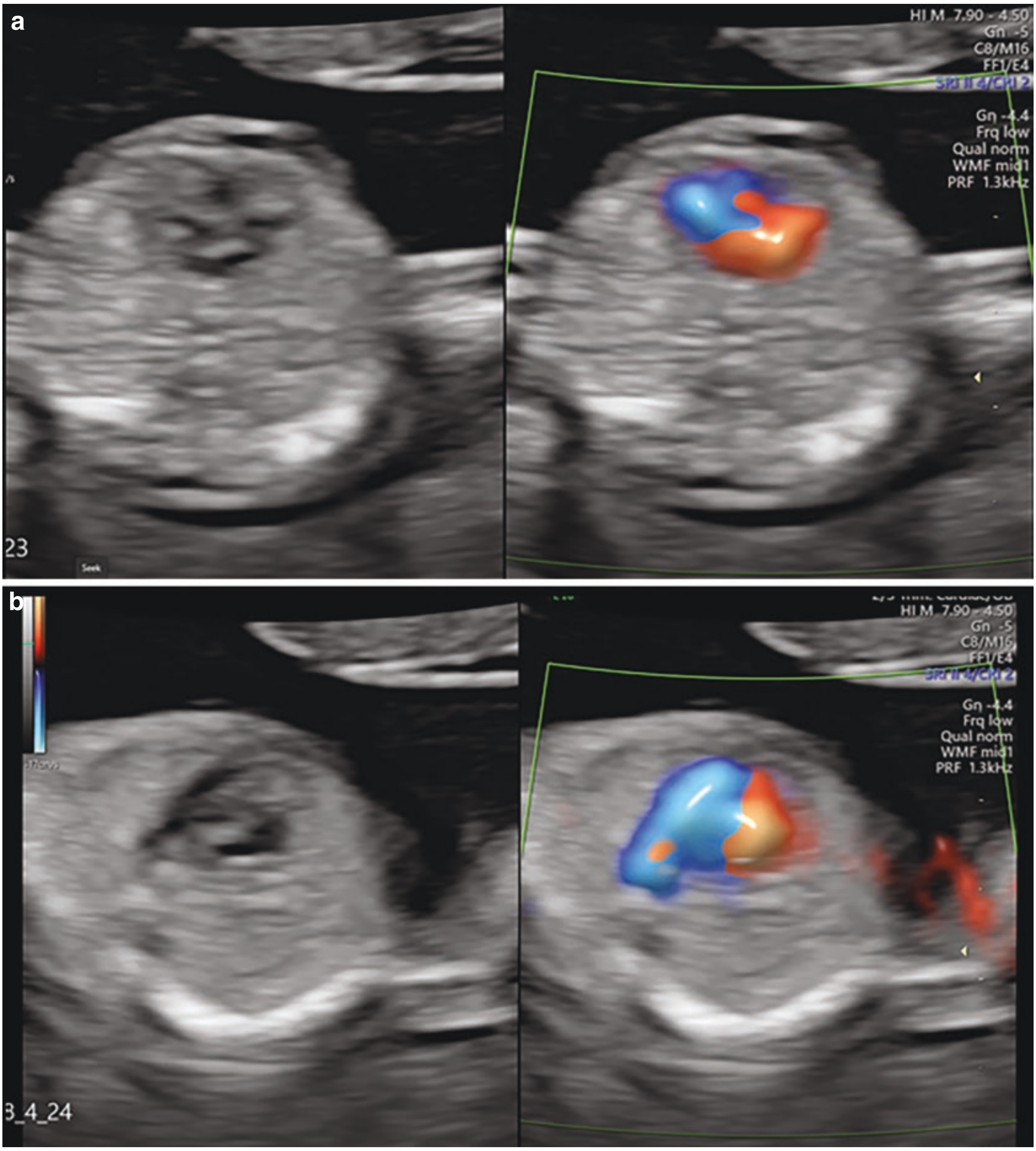

Fig. 12.3 Gray scale and directional power Doppler of the left (**a**) and right (**b**) ventricular outflows at 11 weeks of gestation

chamber view, symmetry of the cardiac chambers, atrioventricular valves, outflow tracts, crossing of the great arteries, and when possible, the ductal and aortic arches. The mean gestational age at examination was 13 weeks when the four-chamber view was seen in 100% of fetuses, the tricuspid and mitral valves in 96%, the outflow tracts in 95%, the aortic and ductal arches in 45%, and the pulmonary veins in 16% of all fetuses. Marques Carvalho et al. [47] explored the feasibility of obtaining the four-chamber view and outflow tracts with TVU in early pregnancy. They obtained the three planes in 37% of fetuses at 11 weeks of gestation, and in 85% of fetuses at 12 weeks of gestation; at 14 weeks, the three planes were obtained in all fetuses.

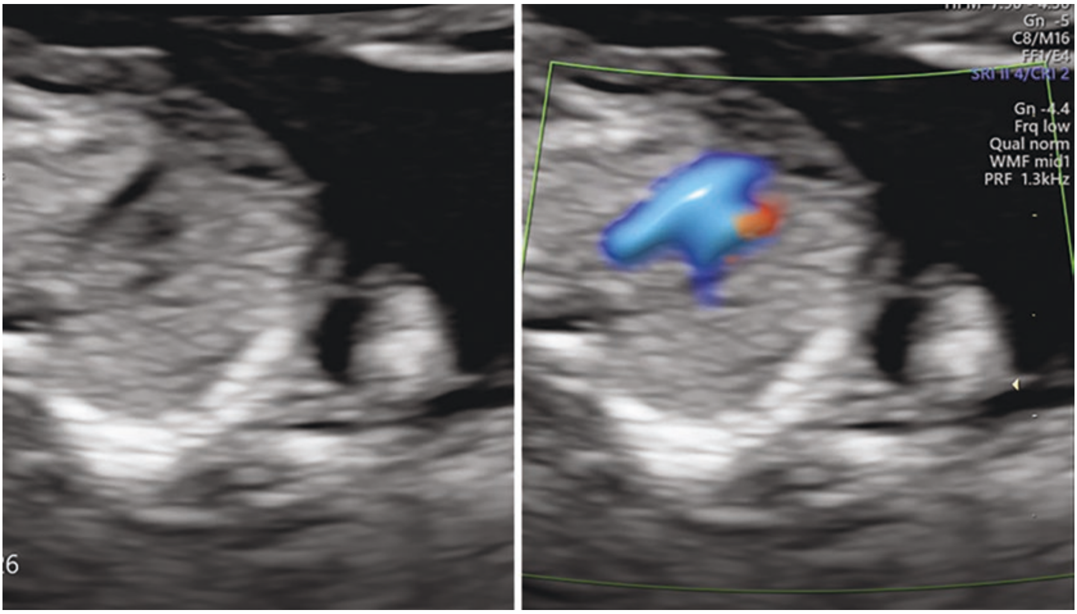

Fig. 12.4 Three-vessel view at 11 weeks of gestation

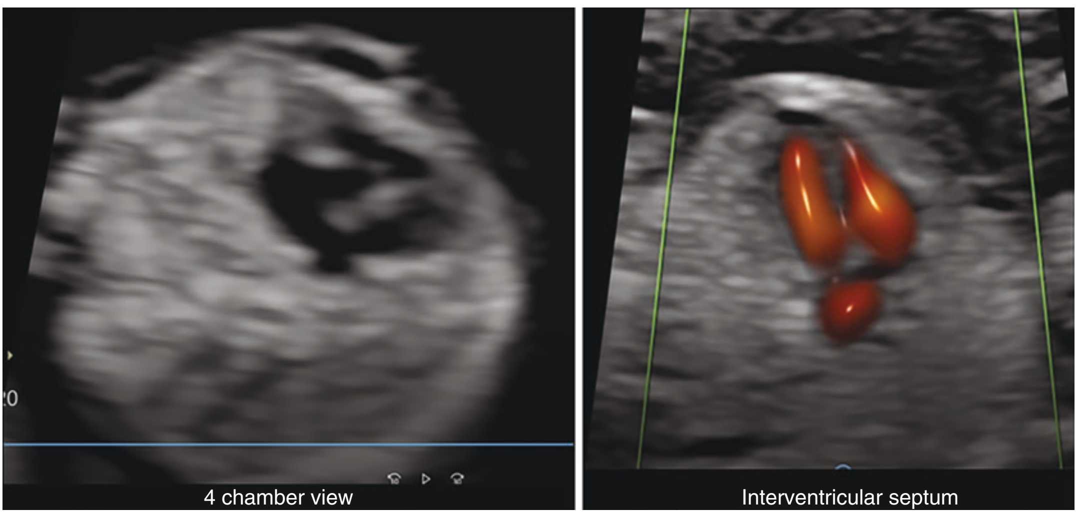

Fig. 12.5 Four-chamber view and interventricular septum using gray scale and color directional Doppler at 12 weeks

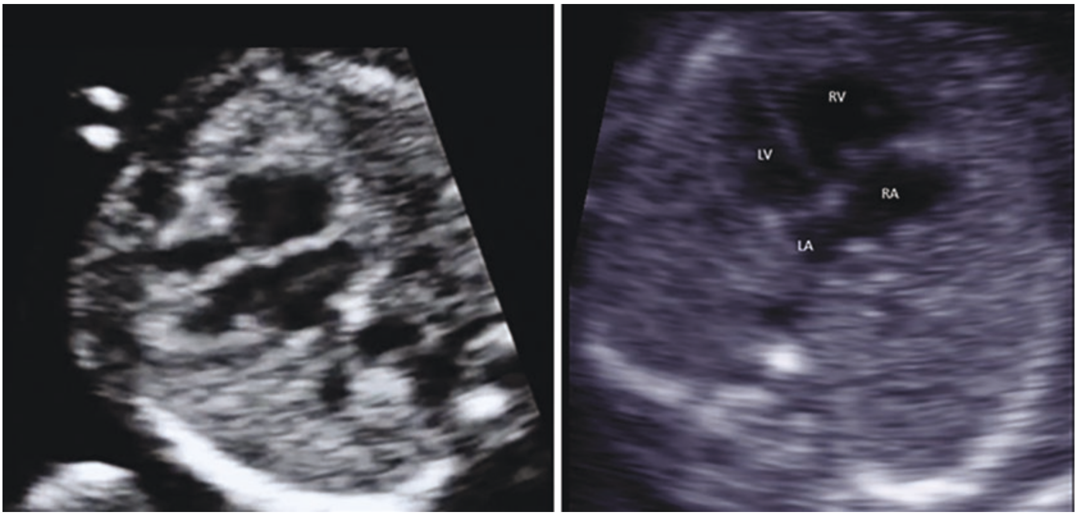

Fig. 12.6 Four-chamber views obtained at 13+0 to 13+6 weeks of gestation. *LA* left atrium, *LV* left ventricle, *RA* right atrium, *RV* right ventricle

Practical Recommendations

The ultrasound settings should be adjusted prior fetal cardiac examination, and the ALARA (As Low As Reasonable Achievable) principle must be followed for limiting fetal exposure to gray scale and Doppler ultrasound [48, 49]. Thermal and mechanic indices should always be maintained <1.0 [50]. Allowance of enough time for scanning as determined by operators experience to obtain good quality images is ideal. High frequency transducers are the best option for fetal cardiac evaluation [51]. Linear transabdominal probes emitting at 5–9 MHz might be preferred at 12–13 weeks of gestation, whereas transvaginal probes emitting at 9–12 MHz might be preferable at 11–12 weeks of gestation. Adjustment of ultrasound settings should include high frame rate (≥80 frames/s), increased contrast, high resolution, a single acoustic focal zone, and a narrow image field. Depth adjustment and magnification should also be employed when possible. Harmonic imaging can be used to improve image quality, particularly for patients with increased BMI.

What Constitutes a Cardiac Scan in the First Trimester?

Identification of the cardiac views—A cross-sectional plane of the fetal thorax with the heart in an apical projection and the fetal spine in the lower part of the ultrasound screen is the optimal image for cardiac examination. The four-chamber view (Fig. 12.6), crossing of the big arteries, and three-vessel view can be obtained from this view by performing a slow sweep toward the fetal head and maintaining cross-sectional images of the studied planes (Fig. 12.7a). The two outflow tracts can be visualized by rotating the ultrasound probe clockwise or anticlockwise from the four-chamber view (Fig. 12.7b, c). By rotating the probe 90° from the four-chamber view, a sagittal plane of the thorax is obtained, and by gently moving the ultrasound probe from side to side, the aortic and ductal arches, and inferior and superior vena cava can be observed (Fig. 12.8). Color directional Doppler might be helpful in assessing the integrity of the interventricular septum, to visualize the crossing of the great arteries, and to document the direction of flow in the aortic arch (Fig. 12.9).

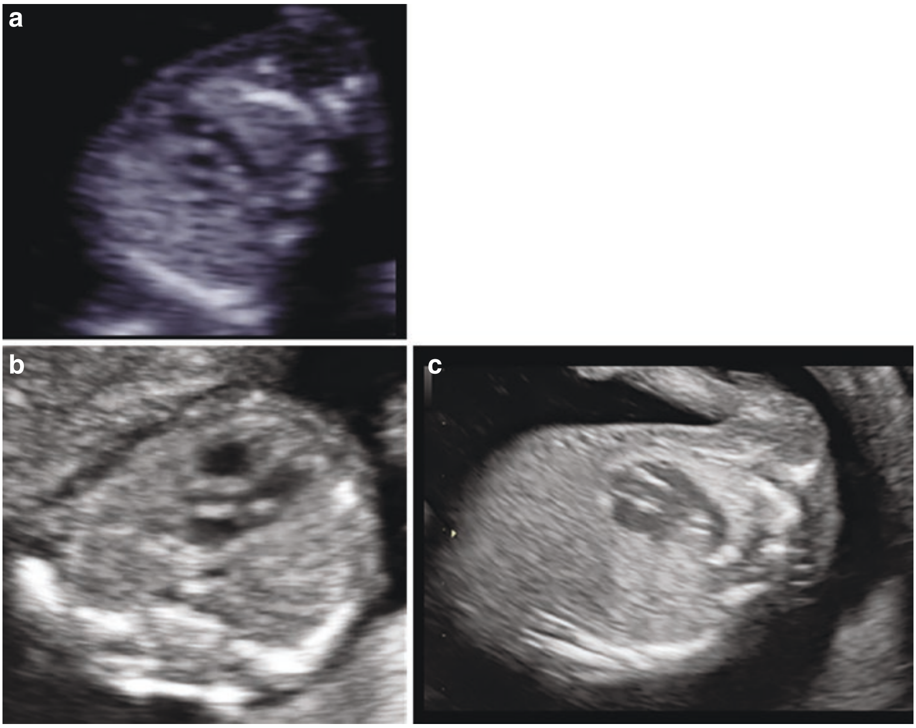

Fig. 12.7 (**a**) Three-vessel view (3-VV); (**b**) left and right (**c**) outflow tracts at 13 weeks of gestation

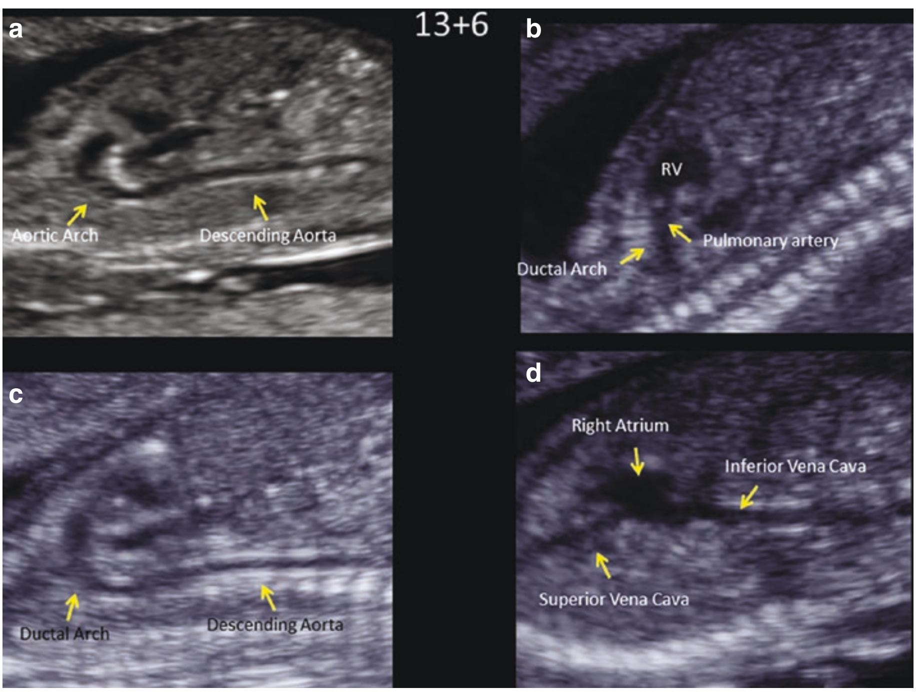

Fig. 12.8 Sagittal images of the aortic (**a**) and ductal (**b**, **c**) arches, and the superior and inferior vena cava (**d**) at 13 weeks and 6 days of gestation

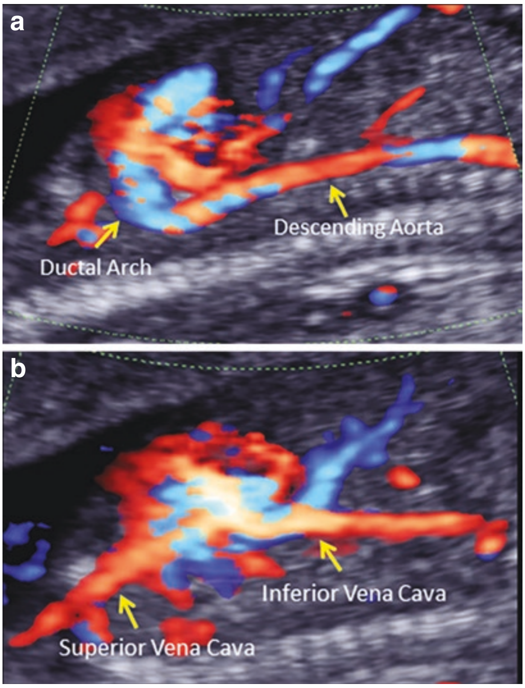

Fig. 12.9 Sagittal images of the ductal arch (**a**) and the superior and inferior vena cava (**b**) at 13 wees and 6 days of gestation using gray scale and directional color Doppler

Color Doppler

The use of color Doppler either directional or power improves the evaluation of the fetal heart and characterization of normal or abnormal cardiac anatomy [13, 52]. It provides great information in the evaluation of the four-chamber view, three-vessel view (3-VV), and the three-vessel trachea view (3-VTV) images [53–55]. Wiechec et al. [56] reported different filling patterns in the cardiac ventricles identified using color Doppler in 1084 fetuses with postnatal or autopsy data. They classified color images obtained in the four-chamber view in four different patterns (1) biventricular function with clear septum (normal heart but also seen in transposition of the great arteries, double outflow right ventricle, atrioventricular septal defect (AVSD), ventricular septal defect (VSD), and right aortic arch); (2) differences in color image in one of the ventricles (coarctation and Ebstein's anomaly); (3) separation only in the distal part of the septum (AVSD); (4) color in only one ventricle (hypoplastic left ventricle syndrome [HLHS], univentricular heart). In 3-VTV, six different color patterns were also described. They reported sensitivity of 43% only when the four-chamber view was evaluated, 71.4% when only the 3-VTV was evaluated, and 88.6% when both images were included.

Prefumo et al. [57] reported two cases of cardiac diverticula with large pericardial effusions in which Color flow and Doppler demonstrated bidirectional flow into a saccular dilatation at the ventricular apex filling the pericardial space in both cases. Gottschalk et al. [58] reported a detection rate of 25% of cases with absent pulmonary valve syndrome in the first trimester of pregnancy. The diagnosis was done using color Doppler techniques by presence of rudimentary or dysplastic pulmonary valve leaflets with bidirectional blood flow in the pulmonary trunk.

Alternatives for an Early Cardiac Scan

In many centers, the basic examination of the fetal heart in the first trimester of pregnancy includes the four-chamber view, NT measurement, and ductus venosus Doppler waveform as markers for cardiac defects [30, 59]. Different alternatives for a more complete fetal cardiac scan have been proposed. Carvalho et al. [60] suggested that the routine examination of the fetal heart at 11 to 13+6 weeks should include visceral situs, cardiac position (axis), normal and symmetric four-chamber view, two separate atrioventricular valves, normal outflow tracts, two great arteries of similar size, and evidence of aortic and ductal arches. The authors mentioned that septal defects cannot be completely excluded and that evolving cardiac lesions might not be visible in early pregnancy. Krapp et al. [61] reported that during the 11 to 13+6 week scan, the four-chamber view could be visualized in 96% of fetuses, the left ventricular outflow tract in 97%, the 3-VV view in 98%, and the aortic arch in 72% of fetuses, whereas the pulmonary veins were observed in only 23% of cases. Yagel et al. [62] proposed the following planes for fetal heart examination: upper abdomen, four-chamber view, five-chamber view, bifurcation of the pulmonary artery, 3-VTV, and the short axis of the right ventricle. TVU was suggested to be better than TAU for detailed examination of the fetal heart. The authors reported that all proposed cardiac planes were obtained in 98% of fetuses at 11–12 weeks, and in 100% of fetuses at 13–15 weeks of gestation. They reached 64% detection rate for CHD when the cardiac examination was performed before 15 weeks of gestation and an extra 17% detection when the heart was re-evaluated at 20–24 weeks, with an overall detection rate of 85% for CHD. Khalil et al. [63] proposed the following steps for cardiac evaluation in the first trimester: assessment of the fetal position, orientation of the fetal heart, visualization of the four-chamber view, assessment of the tricuspid valve and tricuspid regurgitation, visualization of the outflow tracts, and identification of the aortic and pulmonary arches. Abu-Rustum et al. [64] reported the following success rate for visualization of the cardiac structures during an early fetal cardiac scan: four-chamber view (100%), presence/absence of tricuspid regurgitation (100%), crossing of the great vessels (90%), bifurcation of the pulmonary artery (81%), 3-VV (55%), aortic arch (76%), superior and inferior vena cava (65%), and ductus venosus (99%). They also suggested that operators should perform a minimum of 70 fetal heart examinations at 11 to 13+6 weeks to gain reliable experience for obtaining the proposed anatomical planes with an allocated time of up to 10 min for fetal cardiac evaluation.

Including the 3-VV, 3-VTV, and Outflow Tracts in the Fetal Cardiac Evaluation in the First Trimester of Pregnancy

Quarello et al. [65] reported their results in screening using a simplified fetal echocardiography including nuchal translucency, four-chamber view, and 3-VTV. The combined use of color and gray scale allowed the following planes to be visualized: two atrioventricular and separate filling flow patterns, two separate atrioventricular filling flow patterns from atria to the apex of the ventricles, and convergence of the two filling flow patterns (V-shaped) in the upper part of the thorax. Another proposal for extended cardiac scan included seven views using gray scale and color Doppler modalities: abdominal situs, four-chamber view, left and right outflow tracts, 3-VTV, and ductal and aortic arches view [66]. High experienced operators applying this protocol in high-risk population achieved a detection rate of 94.9% and specificity of 96.9% for CHD. For most major cardiac defects, the detection rate was above 75% but for ventricular septal defects they only achieved a 20% detection.

By adding the 3-VTV view, De Robertis et al. [67] reported 57 major cardiac defects (0.1%) confirmed after birth when evaluating 5343 low-risk pregnant women in the first trimester of pregnancy. The 3-VTV was obtained in 94% of all fetuses; a cardiac anomaly was suspected in 22 fetuses based on the 3-VTV and conformed in 21 cases. The detection rate improved to 75.6% when the 3-VTV was added to the standard cardiac examination. The most frequent anomalies were Tetralogy of Fallot, coarctation, transposition of the great arteries, right aortic arch, AVSD, and aortic and pulmonary stenosis.

Lafouge et al. [68] reported a right aortic arch and ductus arteriosus in the first trimester identified by the presence of a mirror image-like appearance of the main vessels in a 3-VTV.

Bravo-Valenzuela et al. [69] reported two important markers for suspicion of early diagnosis of transposition of the great arteries: presence of only two vessels in the 3-VV and reversed curvature of the aorta emerging from the right ventricle. The authors reported that all cases with confirmed transposition of the great arteries ($n = 6$) had those two findings.

Dmitrovic et al. [70] proposed an extended examination of the heart including: four-chamber, left ventricle outflow tract (LVOT), descending aorta, heart size, cardiac axis, atrial size, identification of right and left atrioventricular valves crossing of the great arteries 3-VV, 3-VTV, two great arteries of equal diameter, V configuration of the aortic and ductal arch, ductus venosus, diastolic filling of the left ventricle, tricuspid regurgitation, and forward flow in both arches. They evaluated 2643 (2010 low risk and 633 high risk) fetuses and reported a prevalence of 4.2% (n = 111) of cardiac anomalies, 1.8% (36/2010) in the low-risk group and 11.8% (75/633) in the high-risk group. They used TAU and TVU and showing 79% detection rate with 10% false positive rate (FPR) for CHD. Similarly, Duta et al. [71] performed an extended cardiac evaluation in the first trimester in 7597 pregnant women including cardiac position, abdominal situs, four-chamber view, outflow tracts, 3-VTV, heart position, orientation and size of the heart chambers, the crux, the offsetting of the atrioventricular valves, and assessed ventricular filling by color Doppler mapping. The aorta, pulmonary artery, 3-VTV, and subclavian artery were visualized only with the contribution of color Doppler. They reported 39 cardiac defects with a detection rate of 76.9% and a FPR of 10%. The most frequently diagnosed defects were Tetralogy of Fallot, coarctation, hypoplastic left heart, and AVSD. Using an extended cardiac scan, a 62.5% detection rate with 1.5% false positive rate and a positive predictive value of 56% was achieved [72]. The success rate for obtaining the 3-VV improved from 47% at 11 weeks to 97.3% at 13 weeks, the aortic root from 47% at 11 weeks to 92% at 13 weeks, and the longitudinal axis of the aorta from 28% at 11 weeks to 92% at 13 weeks. Adding the 3-VV and 3-VTV as part of the routine examination of the fetal heart in the first trimester of pregnancy has been supported by other authors [73].

Indirect Markers for Early Fetal Cardiac Evaluation

Nuchal Translucency and Ductus Venosus

Borrell et al. [29] reported that among fetuses with congenital heart disease identified at 11–14 weeks, 40% had increased nuchal translucency (Fig. 12.10a), and 39% reversed atrial flow in the ductus venosus (Fig. 12.10b). Clur et al. [74] showed that among fetuses with normal chromosomes but increased nuchal translucency and abnormal ductus venous, 63% had cardiac defects. The authors also suggested that analysis of the pulsatility index of the ductus venosus instead of presence/absence of atrial flow might improve to 70% the detection rate of fetal cardiac anomalies. Other researchers have confirmed the association between abnormal ductus venosus and cardiac defects [75]. In a study from Finland [76], the authors evaluated 31,144 births including 170 congenital heart defects. They reported a significant increase in NT in the group with cardiac anomalies. They showed that using a NT cut-off value of 1.8 mm, 36.7% of major cardiac anomalies can be detected; using a NT cut-off value corresponding to the 99th percentile (2.4 mm approx.), 24.1% of major cardiac anomalies could be identified, and using a defined NT cut-off value of 3.0 mm, a detection rate of 17.7% could be achieved. The authors concluded that using a NT threshold of 1.8 mm, a large proportion of normal fetuses will be considered at risk (18.5% FPR); however, with a high NT (3.5 mm) a low detection rate (1/5 major cardiac anomalies) would be achieved; therefore, a NT value of 2.0 mm may provide the best predictor with a detection rate of 25.3% at a FPR of 3.3%.

Tricuspid Regurgitation

Pereira et al. [33] studied 85 euploid fetuses with major congenital heart defects and found an increased NT (>95th percentile) in 35.3%, tricuspid regurgitation in 32.9% (Fig. 12.10c), and reversed A wave in the ductus venosus in 28.2% of them during first trimester ultrasound. In fact, any one of these ultrasound markers was observed in 57.6% of fetuses with cardiac defects and in 8% of structurally normal fetuses. They concluded that these three markers improved the performance of screening for congenital heart defects in the first trimester. Presence of tricuspid regurgitation (TR) has a detection rate of 31.2% of cardiac anomalies in low-risk population and 53.4% detection rate in high-risk population.

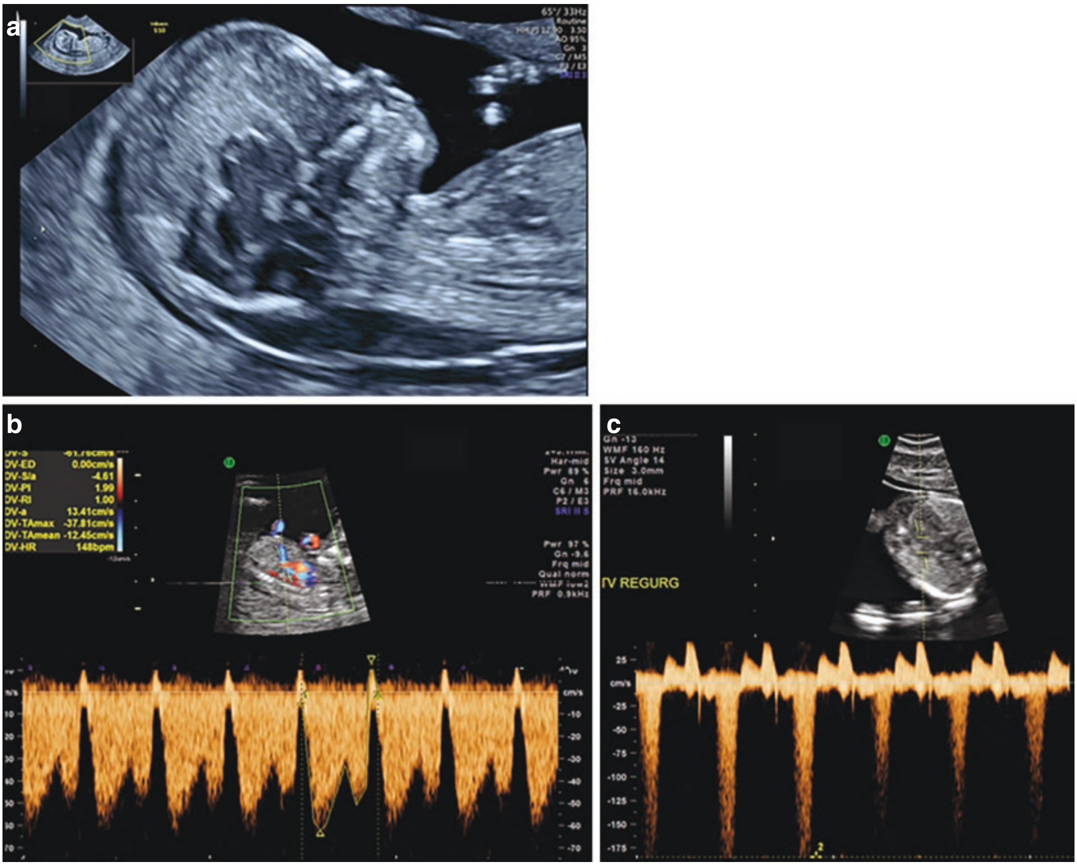

Fig. 12.10 Indirect sonographic markers of congenital heart defects. (**a**) Increased nuchal translucency; (**b**) reversed atrial flow in the ductus venosus; (**c**) tricuspid regurgitation. (Image courtesy of Dr. Rogelio Cruz Martinez)

Fetuses with tricuspid regurgitation and increased NT had an association 9.6 times higher for cardiac anomalies than fetuses without TR [77].

Cardiac Axis

The complex process of cardiac looping during embryonic development is demonstrated by the cardiac axis being fairly midline at 8 weeks and then gradually levo-rotating by 12 weeks after which it stabilizes at the end of the first trimester (Fig. 12.11a). Fetuses with cardiac defects might show an abnormal deviation of the cardiac axis in relation to gestational age. Mc Brien et al. [78] studied the normal variation in the fetal cardiac axis between 8 and 15 weeks of gestation and reported that the cardiac axis is orientated more to the midline of the thorax in early gestation, and then rotates to the left with advancing gestation. The authors noted that the cardiac axis changed from 39° at 11 weeks to 50° at 14 weeks. Sinskovskaya et al. [79] reported a normal variation in the cardiac axis from 34.5° at 11 weeks to 56.8° at 13+6 weeks of gestation, and that an abnormal cardiac axis in early gestation can be associated with coarctation of the aorta, Ebstein's anomaly, transposition of the great arteries, and heterotaxy. The same group compared 197 cases with cardiac defects and 394 structurally normal fetuses at 11–14 weeks [80]. The authors reported that 74.1% (n = 129) of fetuses with cardiac defects had an abnormal axis, 110 with left deviation (increased angle) and 19 with right deviation (smaller angle). After excluding cases with chromosomal anomalies, the cardiac axis was abnor-

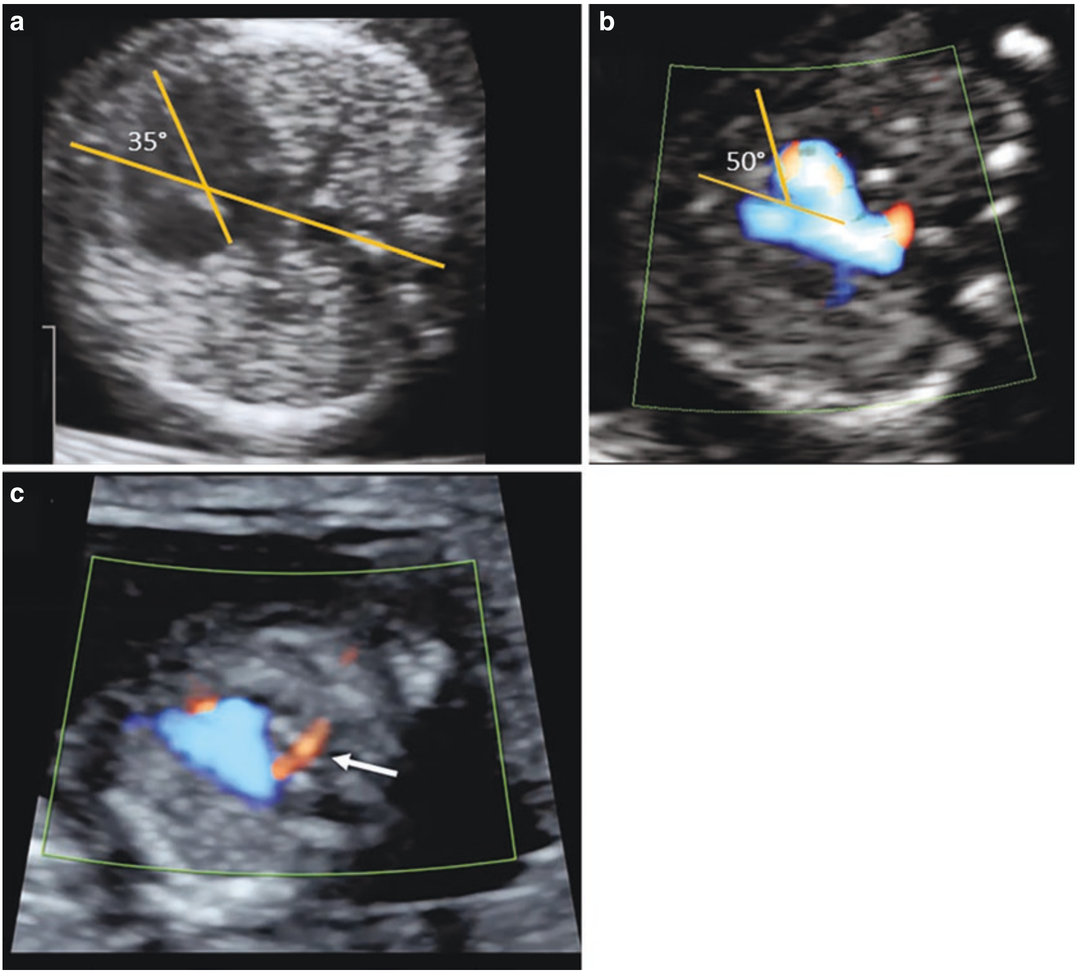

Fig. 12.11 (**a**) Cardiac axis; (**b**) "V" axis; (**c**) aberrant right subclavian artery. (Images **b** and **c**, courtesy of Dr. Rogelio Cruz Martinez)

mal in 75.6% of fetuses with cardiac anomalies. The authors also reported that in normal fetuses, the cardiac axis does not change between 11 and 14 weeks maintaining a mean value of 45°, and a 95th percentile value corresponding to 60°. The authors conclude that an abnormal cardiac axis during first trimester ultrasound should be considered an indication for fetal echocardiogram.

In addition to the cardiac axis, measuring the "V axis" (angle between the aorta and pulmonary artery) may improve identification of fetuses at risk of cardiac defects (Fig. 12.11b). Zheng et al. [81] reported a normal V angle of 20°–40°, corresponding to the 2.5th and 97.5th percentiles, respectively. The authors showed that 66.7% of fetuses with major cardiac anomalies had an abnormal V axis (<30° in hypoplastic left heart, >40° in atrioventricular septal defect). They reported that an abnormal cardiac axis or an abnormal "V axis" was observed in 28/30 (93.3%) of fetuses with cardiac defects.

Aberrant Right Subclavian Artery (ARSA)

Rembuskos et al. [82] suggested an association between an Aberrant Right Subclavian Artery (ARSA) and fetal cardiac defects (Fig. 12.11c). The authors studied 4,566 fetuses and identified

89 fetuses with ARSA, and of them, 12 fetuses had a chromosomal anomaly. The prevalence of fetal cardiac defects in chromosomally normal fetuses with ARSA was 4/77 (5.1%), including Tetralogy of Fallot (*n* = 1), aberrant umbilical vein (*n* = 1), and tricuspid atresia (*n* = 2). The authors suggested that early fetal echocardiography is indicated in the presence of ARSA.

Heart-to-Chest Ratio

Although the size of the fetal heart increases with gestational age, the mean heart-to-chest area ratio of 0.20 (SD 0.04) is maintained between 11 and 14 weeks [83]. The cardiothoracic ratio in early gestation may contribute in the diagnosis of anemic fetuses due to Hemoglobin Bart's Disease [84].

Detection of Cardiac Anomalies in All Fetuses Undergoing First Trimester Ultrasound

The reported prenatal detection for all cardiac anomalies ranges from 25% to 50% and for major cardiac anomalies from 60% to 100% [15, 85–88] (Table 12.3). Variations in detection rate are related to four important factors: (1) targeted population either high or low-risk, or both, (2) the protocol for cardiac evaluation either basic or extended, (3) training and expertise of the operators, and (4) confirmation by a pediatric cardiologist in the prenatal or postnatal periods.

Syngelaki et al. [89] in a large study including 100,997 women evaluated between 11 and 13+6 weeks in singleton gestations by TAU (with 2–3% of cases requiring TVU) reported a prevalence of cardiac defects (major and minor) of 0.38% (*n* = 389), and an overall detection rate of 30% (117/389). When classified by anomaly, >90% of tricuspid or pulmonary atresia, hypoplastic left heart syndrome and atrioventricular septal defects were detected, 60% for complex cardiac defects and left atrial isomerism, 30–40% for Tetralogy of Fallot and arches anomalies, and 15% for transposition of the great arteries, and right aortic arch. The authors also reported that aortic and pulmonary stenosis, common trunk, ventricular septal defects, arrhythmias, rhabdomyoma, and ventricular aneurisms were diagnosed either in the second trimester or at birth. They concluded that many anomalies can be detected in the first trimester, but it varies according to the type of defect; therefore, additional scans in the second and third trimesters of pregnancy are still needed. The same group [90] evaluated twin pregnancies in the first trimester (*n* = 6,366; 4,979 dichorionic and 1,387 monochorionic) and reported a similar prevalence of cardiac defects in dichorionic twins as compared to singletons (1/262 vs 1/260), and a higher prevalence in monochorionic twins (1/139). Detection rate in dichorionic twins was 28.9% (11/38) and 15% (3/20) in monochorionic twins. A similar

Table 12.3 Studies published between 2015 and 2022 on the detection rate of congenital heart defects when the fetus is evaluated at 11–14 weeks of gestation (from the highest to the lowest sample size)

Study	Total (*n*)	Scan route	GA (weeks)	Prevalence of CHD [*n* (%)]	First trimester detection rate [*n* (%)]
Karim [94]	328,214	TA/TV	11–14	1925 (0.6)	1105 (57%)
Singelaki [89]	100,997	TA/TV	11 to 13+6	389 (0.38)	119 (30%)
Minella [59]	93,209	TA/TV	11–13	211 (0.23)	113 (56%)
Jorgensen [96]	86,121	TA/TV	11–14	408 (0.47)	87 (21.3%)
Yu [93]	26,201	TA/TV	11–13	448 (1.7)	336 (75%)
Bardi [11]	13,417	TA/TV	11 to 13+6	21 (0.16)	4 (19%)
Chen [40]	10,294	TA/?	11 to 13+6	129 (1.2)	66 (51%)
Duta [71]	6912	TA/TV	11–14	39 (0.56)	30 (76%)

CHD congenital heart defects, *GA* gestational age, *TA* transabdominal, *TV* transvaginal detection rate of cardiac defects in twin pregnancies (20%) was reported by D'Antonio et al. [91].

In a study from the United Kingdom [59], the authors included 93,209 women evaluated in the first trimester with no signs of chromosomal anomalies. Major cardiac defects were observed in 211 cases (0.23%), and 53.6% (113) were diagnosed at 11+0 to 13+6 weeks/days. Their protocol included transverse section of the thorax, use of color Doppler to assess the four-chamber view, blood flow across the tricuspid valve, outflow tracts, and ductus venosus. The authors reported than in 36.5% of all major cardiac anomalies, an increased NT, tricuspid regurgitation, or an abnormal ductus venosus Doppler waveform were observed. They reported a detection rate >60% for tricuspid or pulmonary atresia, polyvalvular dysplasia, hypoplastic left heart, atrioventricular septal defects, and left atrial isomerism. Additionally, they found a moderate detection rate of 30–40% for Tetralogy of Fallot and arch anomalies, and a low detection rate (<25%) for tricuspid valve anomalies and transposition of the great arteries. No cases with aortic or pulmonary stenosis, or common arterial trunk were identified.

There are differences in the type of defects diagnosed in the first and second trimesters of pregnancy. Jicinska et al. [92] described defects mainly seen in the first trimester: hypoplastic left heart, atrioventricular septal defects, disproportion of the great vessels (coarctation), and pulmonary atresia. Among these defects, 65% had another major anatomical anomaly and/or a chromosomal defect, and only 33.1% were isolated defects. In the second trimester (n = 344), the most frequent defects were atrioventricular septal defects, transposition of the great arteries, coarctation, and hypoplastic left heart syndrome. Isolated defects were observed in 67.4% of fetuses, whereas in 32.6% of cases, other anomalies were detected. The authors showed that severe CHDs with associated anomalies were more frequently diagnosed in the first trimester.

In a recent meta-analysis, Yu et al. [93] included 18 studies published between 1993 and 2017 with a total of 26,201 low- and high-risk fetuses evaluated in the first trimester of pregnancy. The authors reported a pooled sensitivity for major and minor cardiac defects of 75% (95% CI 70–79), (336/448), and specificity of 99%. From the 112 missed cases, 60 had minor cardiac anomalies and 52 major cardiac anomalies.

Another recent meta-analysis included 63 studies from 1998 to 2020 with a total of 328,214 screened fetuses [94]. Low-risk fetuses (306,872) had a prevalence of major cardiac defects (0.41%) from where 767 were correctly identified with a pooled sensitivity of 55.8% and specificity of 99.8%. In the high-risk population including 21,342 fetuses, 480 were found with major cardiac defects (prevalence 1.3%), 67% of them (n = 338) were identified in the first trimester. The authors reported an increase in detection rate when a more detailed examination was performed, in particular with the addition of the outflow tracts and color Doppler. A similar report [95] in low-risk pregnant women detected >67% of major cardiac anomalies, 50% of them diagnosed during the first trimester scan.

In Denmark, among women undergoing first and second trimester screening, researchers reported their experience in detection of cardiac anomalies in 86,121 low-risk pregnancies from 2008 to 2010 [96]. The prevalence of heart defects changed in relation to the exclusion criteria, finally including 408 fetuses with cardiac anomalies (135 major) evaluated in the first trimester of pregnancy. They reported 21.3% detection rate for all anomalies, and 47.4% for major cardiac defects. Smrcek et al. [97] studied 2,165 low and high-risk fetuses using the combination of fundamental 2-D ultrasound imaging and color directional Doppler. They reported a detection rate for congenital heart defects of 63.0% (29/46), whereas nine more fetuses (19.5%) were diagnosed during the second trimester ultrasound scan with a total detection rate of 82.6%. The authors mentioned that cardiac defects that tend to progress—such as myocardial hypertrophy, ventricular hypoplasia, fibroelastosis, and coarctation of the aorta—might not be identified at 11–14 weeks. Among fetuses with an abnormal cardiac examination, 32.2% had an increased nuchal translucency and 51.2% an abnormal ductus venosus.

It can be concluded that when all pregnant women are evaluated in the first trimester of pregnancy, a detection rate between 20% and 50% for all fetal cardiac anomalies can be achieved, 70% detection for major cardiac anomalies, and <20% for minor cardiac anomalies (Figs. 12.12, 12.13, 12.14, 12.15, 12.16, and 12.17).

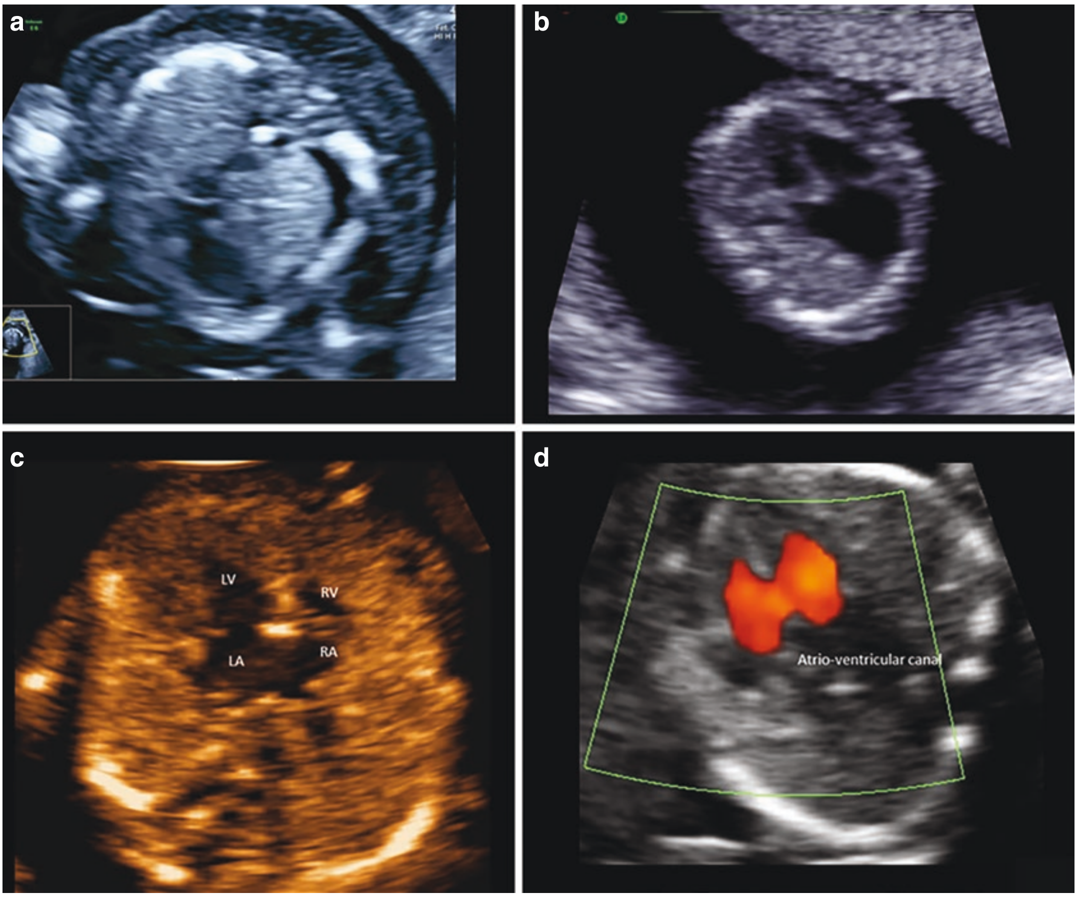

Fig. 12.12 Abnormal four-chamber views: (**a**) single ventricle with one atrioventricular valve; (**b**) dilatation of the right atrium due to pulmonary stenosis; (**c**) severely small right ventricle and increased thickness of the left ventricular walls; (**d**) atrioventricular septal defect. (Image **a** courtesy of Dr. Rogelio Cruz Martinez)

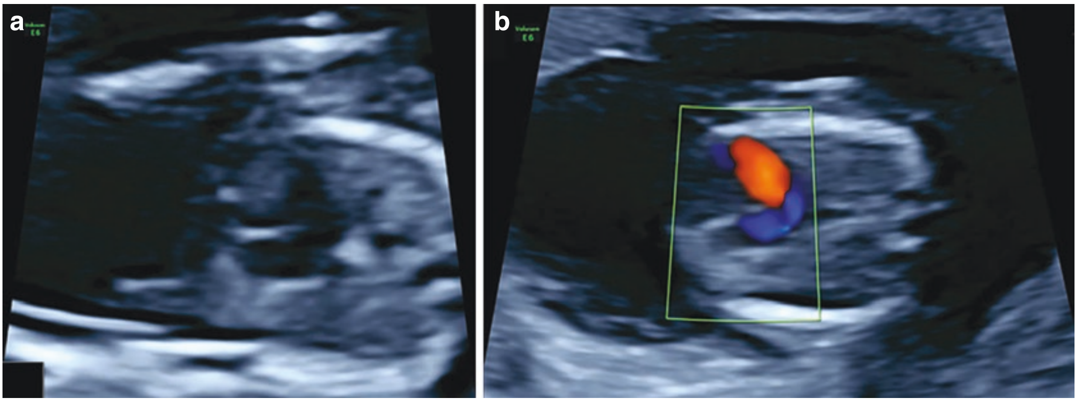

Fig. 12.13 Four-chamber view in a 13 weeks fetus showing (**a**) hyperechogenic right atrioventricular valve. (**b**) Color Doppler demonstrates lack of blood flow from the right atrium to the right ventricle. (Image courtesy of Dr. Rogelio Cruz Martinez)

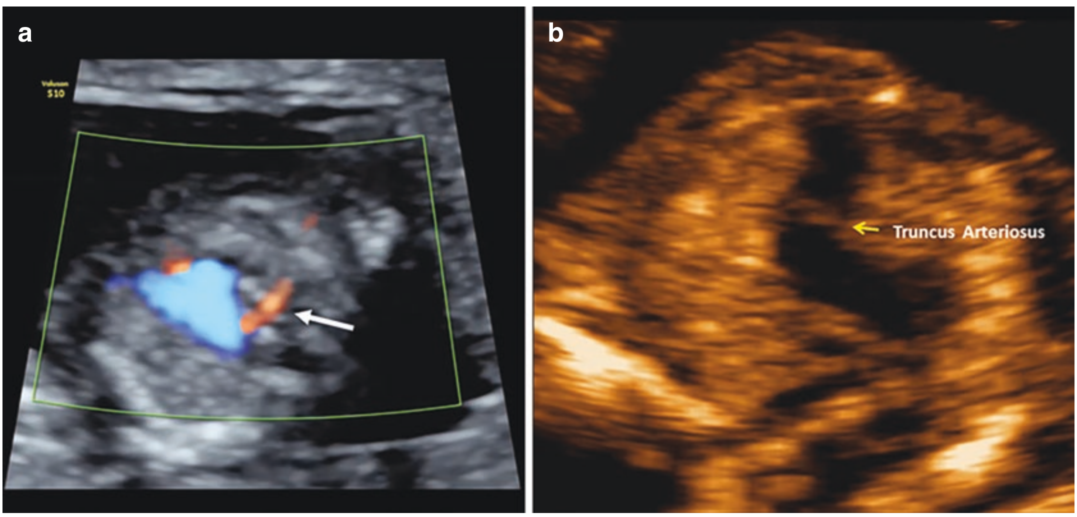

Fig. 12.14 Aberrant right subclavian artery (**a**), and truncus arteriosus (**b**). (Image **a** courtesy of Dr. Rogelio Cruz Martinez)

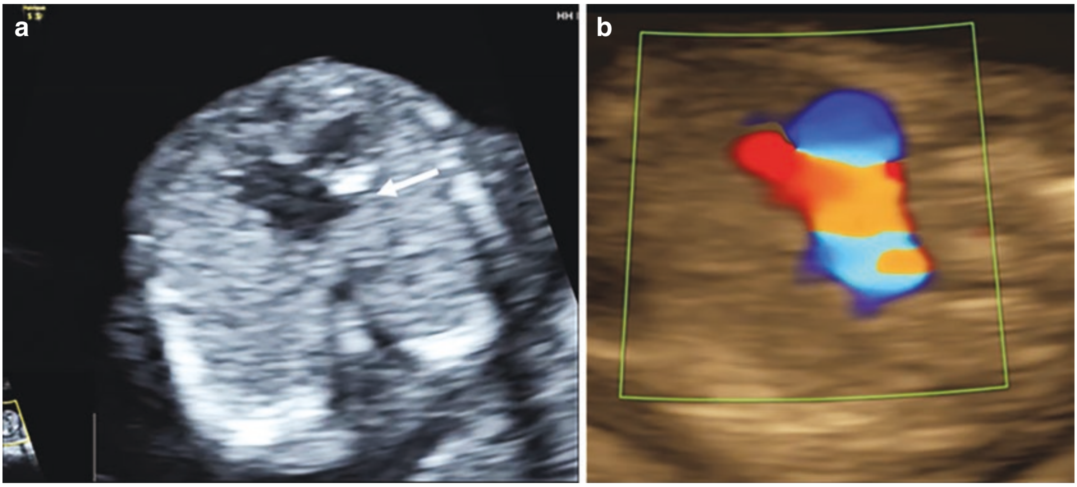

Fig. 12.15 Single ventricle at 11 weeks of gestation (**a**) gray scale image; (**b**) color Doppler ultrasound. (Image courtesy of Dr. Rogelio Cruz Martinez)

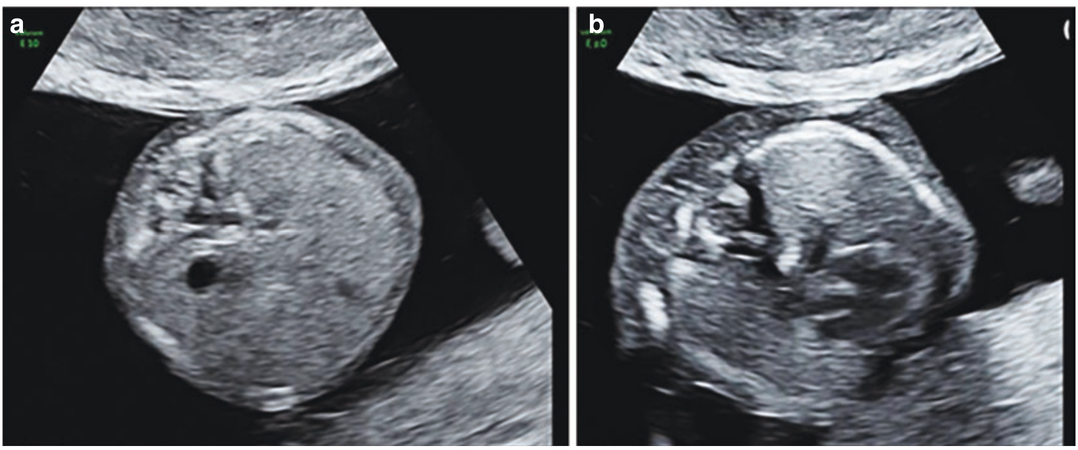

Fig. 12.16 Fetal echocardiography in a 12 weeks fetus with heterotaxy: (**a**) the stomach is on the right side; (**b**) levocardia and large interventricular septal defect; (**c**) three-vessel and trachea view showing a single vessel arising from the hearth on the right side of the fetal trachea (right aortic arch), and a persistent left superior vena cava on the left of the aortic arch. (Image courtesy of Dr. Rogelio Cruz Martinez)

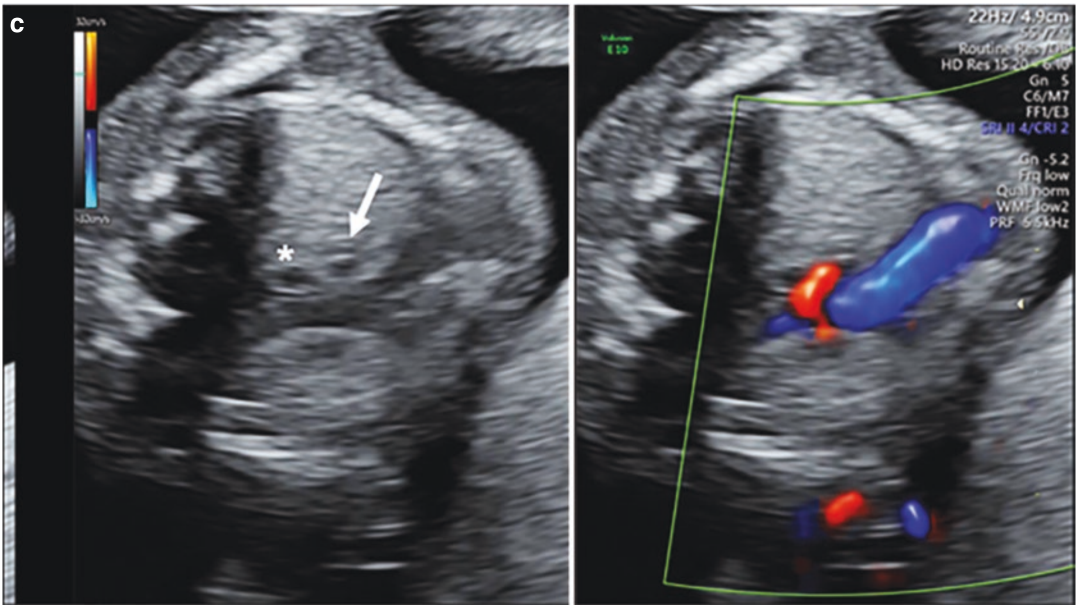

Fig. 12.16 (continued)

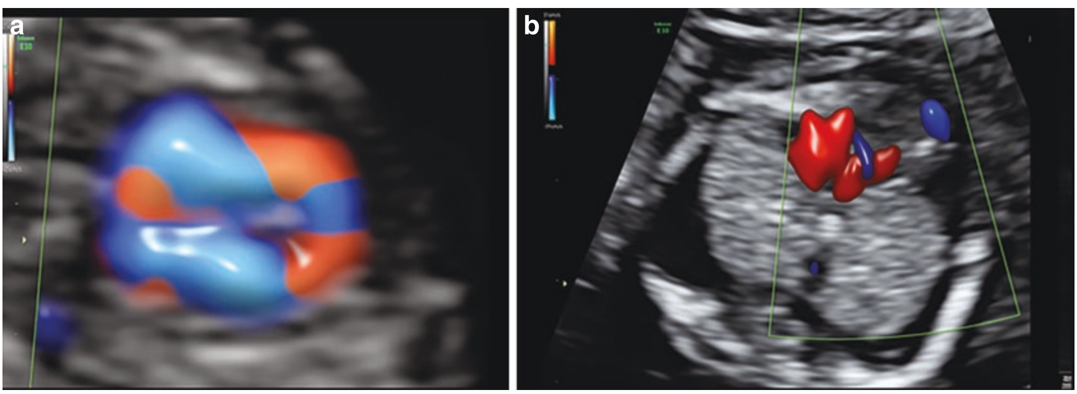

Fig. 12.17 Interventricular septal defects: (**a**) muscular apical; (**b**) perimembranous (fetus with pleural effusions). (Image courtesy of Dr. Rogelio Cruz Martinez)

High-Risk Population

In high-risk pregnant women with at least one risk factor associated with fetal congenital heart defects, Turan et al. [98] proposed the use of a standardized early fetal heart assessment performed by experienced operators using gray scale and power Doppler ultrasound in the four-chamber, outflow tract relationship (OTR), and transverse arches views reaching 93.2% sensitivity and 99.9% specificity for detection of major cardiac anomalies (70/1,024) (6.8%). Volpe et al. [99] reported their experience in cardiac evaluation in 870 high-risk women for CHD in the first and second trimesters of pregnancy referred due to increased NT, history of cardiac defects, or extracardiac anomalies. An abnormal cardiac evaluation was observed in 68 fetuses (7.8%) and confirmed in 36 (52%) at the second trimester scan. Among the 32 remaining fetuses, in 26 diagnosis changed in the second trimester. Persico et al. [100] evaluated the fetal heart in 855 pregnant women undergoing chorionic villus sampling due to presence of ultrasound markers, or altered maternal biomarkers of fetal chromosomal anomalies. They reported 100 cases in which a cardiac defect was suspected (54% major and 46% minor). The authors showed 93.1% detection rate of cardiac anomalies using TAU and a high association between congenital heart defects and increased nuchal translucency and tricuspid regurgitation.

Carvallo et al. [101] reported the diagnostic performance of targeted cardiac examination in 230 high-risk pregnant women for fetal cardiac defects (increased NT, family history of congenital heart disease, abnormal findings during the routine US scan) at the end of the first and early second trimesters of pregnancy. The following structures were visualized: visceral situs solitus, normal cardiac position, normal four-chamber view, two separate atrioventricular valves, normal aortic and pulmonary outflow tracts, two great arteries of similar size, and visualization of the aortic and ductal arches. An abnormal cardiac evaluation was observed in 21 of 199 fetuses, and in 10 fetuses the cardiac scan was not completed. The authors reported a 96% diagnostic accuracy of early fetal echocardiography, and a high association between increased nuchal translucency, chromosomal anomalies and cardiac defects.

Becker et al. [102] evaluated 3,094 fetuses referred due to an abnormal US examination or increased nuchal translucency, and reported a 2.8% prevalence of CHD ($n = 86$) with 84.2% of them detected during the first trimester scan. The cardiac evaluation included visualization of the four-chamber view, outflow tracts, and pulmonary and aortic valves. They reported that fetuses with nuchal translucency >2.5 mm had a 9.8% prevalence of heart defects, whereas fetuses with a nuchal translucency <2.5 mm had a prevalence of 0.3%.

Complementary Ultrasound Techniques

Fundamental 2-D imaging and color Doppler are the cornerstones for fetal cardiac evaluation; however, M-mode ultrasound might contribute in the diagnosis of septal defects and cardiac arrhythmias [8, 103]. Baschat et al. [104] evaluated four fetuses referred due to an increased nuchal translucency and bradycardia. Fetal heart block was diagnosed using M-mode ultrasound, and a congenital heart defect was present in all four fetuses; three had heterotaxy confirmed on autopsy.

4D-Spatio-Temporal Imaging Correlation (STIC)

4D-STIC (Figs. 12.12, 12.13, 12.14, 12.15, 12.16, 12.17 and 12.18) can be applied for offline evaluation of the fetal heart either by the same or by different operators to confirm/exclude congenital heart defects. Tudorache et al. [105] reported an adequate visualization of cardiac planes in about 78% of cases and a good to excellent agreement in defining cardiac planes using STIC volumes. Similar results were shown by Turan et al. [106] who reported a good agreement in images obtained with gray scale 2D ultrasound with those obtained using STIC to define specific planes for cardiac evaluation.

Espinoza et al. [107] obtained STIC volumes from 17 normal fetuses and 16 fetuses with congenital heart defects. The STIC volumes were evaluated by operators blinded to the clinical diagnosis. The results showed 79% sensitivity and 90% specificity for identification of fetal cardiac defects. The authors concluded that acquisition of cardiac STIC volumes and evaluation by an expert in fetal heart can be used to confirm/exclude the presence of a cardiac defect. Lima et al. [108] explored the combined value of color Doppler ultrasound and STIC volume analysis in the identification of the basic planes for first tri-

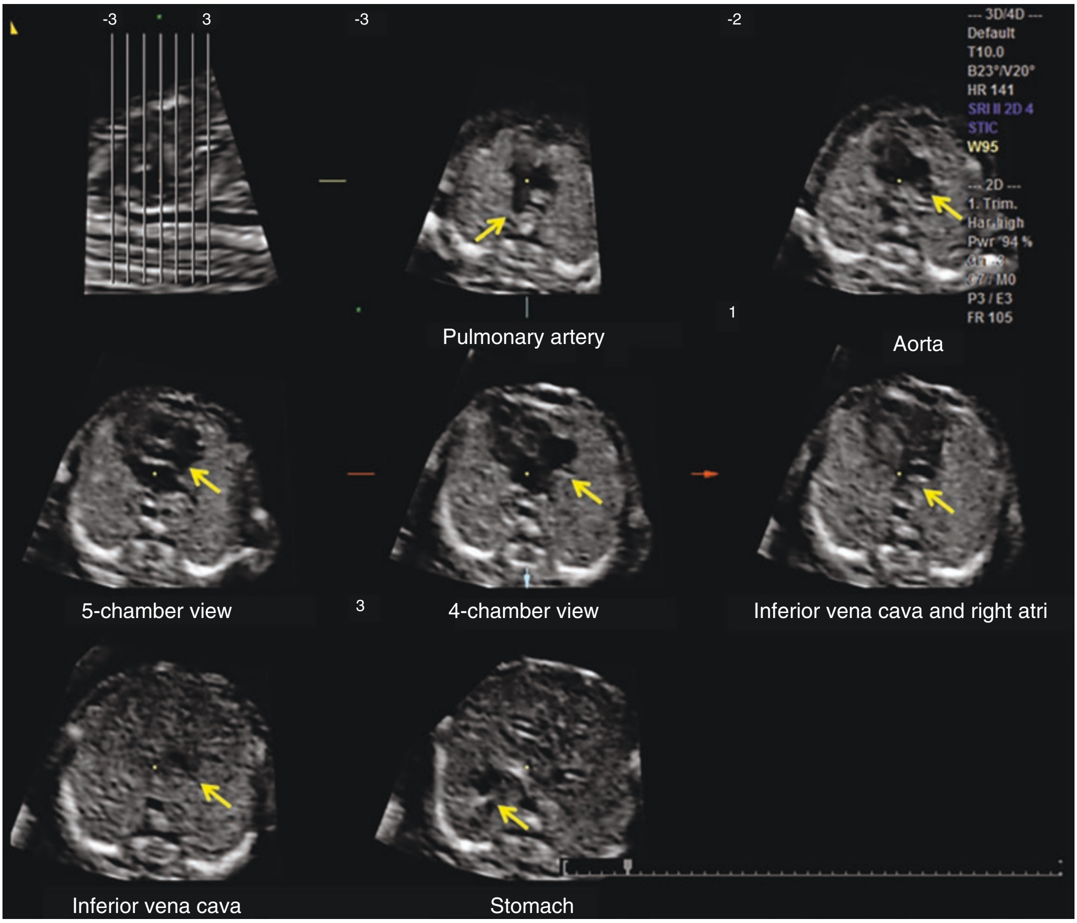

Fig. 12.18 Spatiotemporal imaging correlation (STIC) at 14 weeks of gestation. From a sagittal plane where the ductal arch and descending aorta can be visualized, seven cross-sectional planes are generated using tomographic ultrasound imaging (TUI)

mester fetal cardiac examination. The authors reported that this combination allowed identification of most of fetal cardiac planes in 90.6% of women from STIC volumes obtained either using TAU or TVU.

Evaluation of the Cardiac Function in Early Pregnancy

The evaluation of the fetal cardiac function in early pregnancies might be a complementary method for improving the identification of congenital heart defects.

In normal fetuses in the first trimester, Clur et al. [74] reported discrepancies in E/A ratios, outflow velocities, stroke volume, and cardiac output between the two cardiac ventricles, with a predominant function of the right ventricle. Ninno et al. [109] evaluated the tricuspid valve at 11 to 13+6 weeks and showed an increment in the E velocity and in the E/A ratios, and mild changes in the A velocity as gestation progresses. Rozmus-Warcholinska et al. [83] described normal values for fetal cardiac function parameters obtained between 11 and 13+6 weeks of gestation. The authors reported stable myocardial performance index (MPI) values during this gestational period with mild differences between the left and right ventricles. There was an increment in the E/A ratio and in the E velocity but no changes in the A velocity. Turan et al. [110] reported a high association between abnormal fetal cardiac function parameters in early pregnancy and maternal hyperglycemia in women with pregestational diabetes. The authors showed reduced left E/A ratio, prolongation of the isovolumetric relaxation time in both ventricles, reduction in the isovolumetric contraction time in the left ventricle and prolonged MPI in the two ventricles in diabetic women with poor glycemic control.

Cardiac strain can be evaluated in the first trimester of pregnancy. Chelliah et al. [111] reported that strain values can be obtained in 68% of fetuses at 12–14 weeks of gestation from an apical image of the four-chamber view; however, only in half, an adequate endocardial tracking was achieved with moderate to poor agreement between operators. The results showed similar peak systolic longitudinal strain in the left and right ventricles.

Precautions When Evaluating Fetuses at 11 to 13+6 Weeks?

Despite the high detection rate reported by several groups, mainly for major cardiac anomalies, not all cardiac defects can be identified at the 11 to 13+6 weeks scan (Table 12.4). Gardiner et al. [112] suggested caution when defining cardiac anomalies in the first trimester of pregnancy due to the risk of false positive cases in which parents might decide to terminate the pregnancy in a structurally normal fetus. The authors mentioned that based on morphologic information provided by High-Resolution Episcopic Microscopy (HREM), growth of the atrioventricular septum occurs later in the first trimester of pregnancy and offset of the mitral and tricuspid valves might not be visualized before 14 weeks of gestation in a structurally normal fetus. The authors concluded that there is a risk of incorrect diagnoses of atrioventricular septal defects in early pregnancy. Volpe et al. [99] evaluated the contribution of the first and second trimester echocardiography in the diagnosis of CHD and reported that a considerable proportion of cases considered as normal in the first trimester examination might develop cardiac defects at later stages of pregnancy. They also mentioned that a high percentage of fetuses with an abnormal cardiac examination might actually have a structurally normal heart.

Table 12.4 Congenital heart defects that can be identified during the early ultrasound fetal cardiac examination at 11 to 13+6 weeks of gestation

Cardiac defects with the highest detection rate in the first trimester	Atrioventricular septal defect Hypoplastic left heart Tricuspid and pulmonary atresia
Cardiac defects with a moderate detection rate	Coarctation Tetralogy of Fallot Truncus arteriosus Transposition
Cardiac defects unlikely to be diagnosed	Ventricular septal defects Ebstein's anomaly Mild aortic and pulmonary stenosis Cardiac tumors Myocardial hypertrophy Fibroelastosis Abnormal pulmonary venous return
	Aortic pulmonary stenosis

Safety

Guidelines of the International Society of Ultrasound in Obstetrics and Gynecology recommend maintaining the thermal index (TI) <1.0 during Doppler examination at 11 to 13+6 weeks [49, 113]. They suggest that the main reason for advocating the ALARA principle in the first trimester of pregnancy is the unknown effect of Doppler ultrasound during embryogenesis [113]. Nemescu et al. [50] assessed the safety of first trimester fetal echocardiography by measuring the thermal index (TI) and mechanical index (MI) generated during 399 examinations. Although there was an increase in TI values from gray scale to color flow and power Doppler studies, these values were always lower than 0.5. Satisfactory Doppler images were obtained using these settings.

Teaching Points

- When all pregnant women are evaluated between 11 and 14 weeks of gestation, a detection rate of 20–50% for all fetal cardiac anomalies (70% major, and <20% minor cardiac anomalies) can be achieved.
- Evaluation of the fetal heart at 11–14 weeks of gestation is indicated in pregnant women with history of cardiac defects, diabetes, under medication, with monochorionic twins and from assisted reproductive techniques; and in fetuses with increased nuchal translucency, tricuspid regurgitation, reversed atrial flow in the ductus venosus, aberrant right subclavian artery, abnormal cardiac axis, hydrops, or any other fetal structural defect.
- Experience and training of ultrasound operators are the most important factors for early identification of fetal cardiac defects; highly trained operators achieve a better detection rate. Good quality ultrasound imaging greatly contributes.
- Gray scale imaging and color Doppler are the cornerstones for fetal cardiac evaluation and additional techniques, i.e., M-mode, and 3D and 4D ultrasound, may also contribute in improving the detection rate of congenital heart defects in early pregnancy.
- Prior to 12 weeks of gestation, transvaginal ultrasound provides adequate images for cardiac examination; from 13 weeks onwards, fetal cardiac evaluation can be reliably performed with transabdominal ultrasound.
- The four-chamber is the most important ultrasound view to identify a normal or abnormal heart. When adding the outflow tracts, the 3-vessel, and 3-vessel and trachea views, the detection of cardiac anomalies can be improved.

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