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Original Article

Imaging the first trimester heart: ultrasound correlation with morphology

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Abstract First trimester sonography is a widely used technique to examine the foetus early in pregnancy. The desire to recognise complex anatomy already in early developmental stages stresses the need for a thorough knowledge of basic developmental processes as well as recognition of cardiac compartments based on their morphology. In this paper, we describe the possibilities and limitations of sonographic assessment of the foetal heart between 10 and 14 weeks of gestation and correlate this to morphology. Examples of the most commonly detected congenital anomalies are atrioventricular septal defects, transposition of the great arteries, and hypoplastic left heart, which are shown in this paper.

Keywords: Cardiac embryology; cardiac morphology; first trimester ultrasonography

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Heart development is a complex process during which the heart needs to evolve from a single myocardial tube towards a fully septated heart with two atria, two ventricles, and a separated outflow tract. Figure 1 shows the cardiac events that must occur to achieve a normal circulation. These developmental processes do not occur sequentially, but largely overlap in time. It is therefore not surprising that maldevelopment during one timepoint might affect multiple processes. Correct remodelling of the heart most likely requires normal haemodynamics. Studies on chick and zebrafish demonstrate that reduced blood flow during heart development leads to impaired looping, incomplete septation, and abnormal valvulogenesis;[1,2] therefore, abnormal blood flow through the cardiovascular system during early embryonic stages can result in structural heart disease.[3,4]

Congenital heart disease affects four to eight newborns per 1000 live births and is the most frequently encountered congenital malformation.[5] Congenital heart malformations are responsible for majority of infant deaths in the first year of life.[5] Second trimester ultrasound screening programmes are routine pregnancy care in most developed countries. In the last 2 decades, ultrasound systems have improved rapidly, allowing the visualisation of the first trimester heart in detail. First trimester echocardiography is defined as an attempt to visualise foetal heart anatomy at a gestational age before 14 completed weeks (13^{+6}). The use of first trimester echocardiography to detect foetal anomalies at this early gestational age is increasingly gaining popularity, driven by the urge to detect foetal anomalies at very young stages. These examinations are conducted mainly in high-risk pregnancies, for example, in cases with increased nuchal translucency or in patients with a positive family history for cardiac malformations.[6] At the same time, the desire to recognise complex anatomy already in these early developmental stages stresses the need for a thorough knowledge of basic developmental processes as well as recognition of cardiac compartments based on their morphology.

Despite several studies that stated that foetal heart examination could be incorporated in the first trimester examinations, its use is currently still limited to a few specialised centres. In the current paper, we

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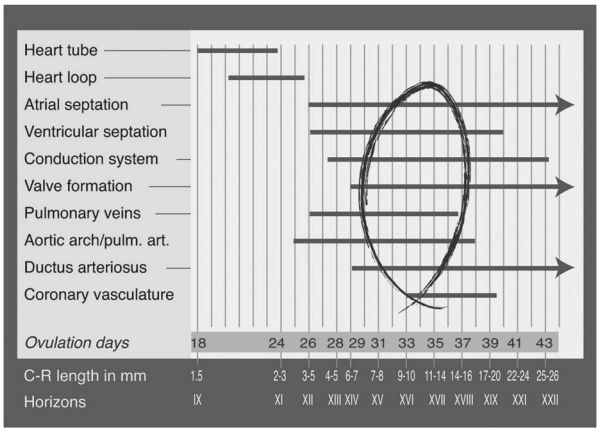

Figure 1.
Schematic overview of the time span of development of the different cardiac components. Modified after Jongbloed et al.[87]

aim to provide a comprehensive overview of the use first trimester echocardiography and the correlation with morphology. In addition, we give an overview of the current possibilities and limitations, and define the indications in which first trimester echocardiography could be offered.

Visualisation of the foetal heart before 10 weeks of gestational age: ultrasound versus morphology

Organogenesis occurs in the first 8 weeks after conception. In this relatively short period, which corresponds to 10 completed weeks of gestation, all major organ systems develop. At the end of this period, most organs have reached a size that can be visualised by ultrasound.

The cardiovascular system begins to develop within the lateral intra-embryonic mesoderm at 4 weeks gestational age.[7] At this time, the primitive heart tube is formed and starts pulsating after 5 completed weeks of gestation, that is, day 22 after conception.[8] This single tube propulses the blood initially in a peristaltic manner. The primitive myocardial heart tube undergoes a process of looping, remodelling, and septation, thereby transforming the single lumen into the four chambers of the definitive heart with a separated outflow tract. This forms the basis for the separation of the pulmonary and systemic circulations at birth.[8] The final closure of the ventricular septum and ultimate formation of the atrioventricular valves is finished at 10 completed weeks of gestation.[9,10] After development, the different cardiac compartments can be distinguished based on their morphological characteristics.[11]

Ultrasonographic studies on the foetal heart, before a gestational age of 10 completed weeks, have to take into account that heart morphology is not definitive yet. Therefore, examinations before this gestational age are studies on the developing embryo, rather than a diagnostic tool. Timor-Tritsch et al described embryonic development in 38 well-dated pregnancies.[12] He observed that foetal heartbeats could be visualised from 5^{+5} weeks gestational age. In a similar study, the ventricular septum was seen at 9^{+1} weeks and the four chambers were identified at 14 weeks.[13] With the use of 7.5 MHz transvaginal probes, more detailed structures of the foetal heart could be identified.[14] The atrial and ventricular walls were visualised at the end of week 8, and the atrioventricular valves at the end of week 10 by Blaas et al. In this study, reference curves for the diameter of the foetal heart at this early gestation were constructed.[15] Allan et al compared the results of echocardiographic studies at 5–12 weeks gestational age, using transvaginal ultrasonography, with the anatomy of microdissectioned hearts.[16] Before a gestational age of 9 weeks, cardiac morphology could not be visualised by ultrasound. The results in the study by Johnson et al, agree with these findings.[17] At 9 weeks gestational age, Allan found the foetal heart to be centrally positioned in the foetal chest, directionally opposite the foetal spine.[16] The pulmonary trunk could be visualised in the B-mode, in contrast to the ascending aorta, which could only be identified with colour Doppler. At 10 weeks gestational age, they found the heart's position changing to a more left-sided orientation, as is typical later in pregnancy. Figure 2 shows an example of first trimester echocardiography and the correlation to morphology.

Echocardiography in late first trimester foetuses

From 10 completed weeks of gestation onwards, the foetal heart has reached its definitive anatomy for foetal life. The final closure of the foramen ovale and the occlusion of the ductus arteriosus occurs after birth and results in the definitive separation of the systemic and pulmonary circulation.

In the ultrasonographic examination of the foetal heart from 10 weeks gestational age onwards, a predefined strategy can be applied, similar to the way mid-gestational cardiac examination is conducted. Owing to the increased axial (0.3–0.4 mm) and lateral resolution of the modern broadband probes, the foetal heart and its detailed structures up to 1 mm can be readily visualised. Initially, the majority of early first trimester echocardiographic studies were conducted using transvaginal probes. More recent studies showed that modern high-frequency abdominal probes could reach a sufficient level of imaging quality.[18–23] Transabdominal scanning has the advantage that the imaging plane can be acquired

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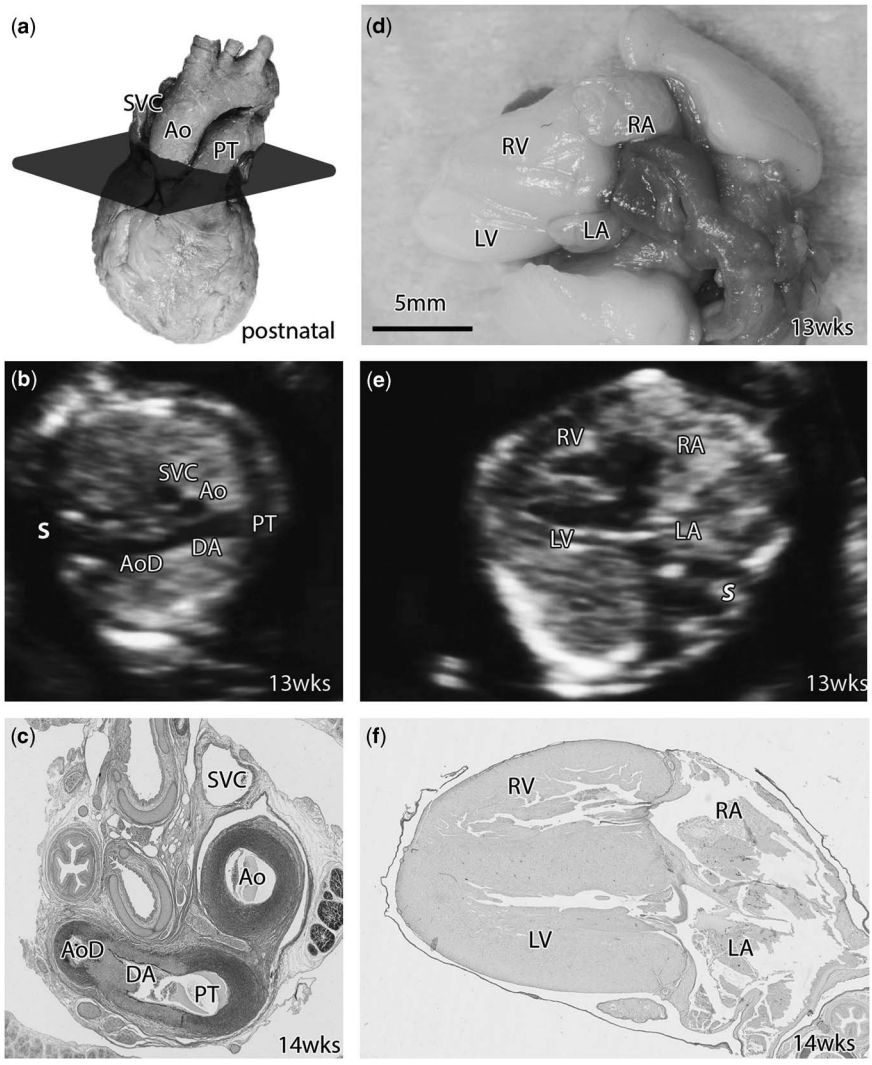

Figure 2.

*Normal echocardiography versus morphology. The transverse plane of the three-vessel view is depicted by the square (**a**). First trimester ultrasound (**b**) and a histological (**c**) section of the three-vessel view clearly show the superior vena cava (SVC), aorta (Ao), pulmonary trunk (PT), ductus arteriosus (DA), descending aorta (AoD). Plane (**d**) depicts a normal foetal heart, corresponding to ultrasound (**e**), and histological (**f**) sections of the four-chamber view showing the left ventricle (LV), right ventricle (RV), left atrium (LA), and right atrium (RA). Spine (S) marks the dorsal side of the foetus on the ultrasound plane.*

in more angles compared with transvaginal ultrasound. In a review by Rasiah et al,[24] it was stated that regarding specificity, transabdominal approach appears superior to transvaginal approach, but Gembruch et al stated that at lower gestational age transvaginal approach has better feasibility.[25] Considering these limitations it seems advisable to master both methods, to be able to individualise the approach according to the goal of the ultrasound, detecting or excluding/reassuring, and technical factors such as patient stature and size of the foetus).

The first published studies on the diagnosis of heart malformations in the first trimester foetus were case reports,[26–28] published up to 4 years before Dolkart and Reimers[29] systematically described the possibilities of examining the normal foetal heart in this early period of gestation. Following these case reports, larger series of diagnosed malformations were published by several authors. Table 2 provides an overview of the structural heart defects that have been described to be accurately diagnosed in the first trimester.

The four-chamber view

The transverse section through the foetal heart at the inflow level, called "the four-chamber view", is incorporated in routine second trimester obstetric

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Table 1. Visualisation of both four-chamber view as well as the outflow tract, obtained by different studies.

	Visualisation rates in % (no. of foetuses)			
Authors	**10 + 0–10 + 6**	**11 + 0–11 + 6**	**12 + 0–12 + 6**	**13 + 0–13 + 6**
Johnson[17]	0 (26)	0 (33)	31 (51)	43 (61)
Gembruch[73]	–	67 (15)	80 (30)	100 (51)
Gembruch[25]	44 (9)	75 (16)	93 (15)	100 (16)
Haak[37]	–	20 (85)	60 (85)	92 (85)
Vimpelli[74]	–	60 (53)	67 (201)	72 (330)
Smrcek[75]	67 (9)	100 (22)	98 (41)	100 (24)

Table 2. Overview of heart anomalies detected by first trimester sonography (up to 14 weeks of gestational age).

Structural anomalies	**Detected in first trimester – published by**
Left persisting superior caval vein	Volpe[42]
Atrioventricular defect	Gembruch,[27] Areias,[76] Carvalho,[18] Gembrug,[73] Achiron,[77] Carvalho,[18] Baschat,[78] Haak,[79] Huggon,[80] Comas,[81] Galindo,[82] McAuliffe,[38] Becker,[83] Weiner,[61] Bellotti,[23] Persico,[22] Hartge,[62] Volpe,[42] Eleftheriades[63]
Left Isomerism	Huggon,[80,21]
Ventricular septal defect	DeVore,[26] Bronshtein,[84] Haak,[79] Huggon,[80] Comas,[81] McAuliffe,[38] Weiner,[61] Persico,[22] Hartge,[62] Eleftheriades[63]
Univentricular heart	Gembruch,[73] Becker,[83] Hartge[62]
Ebstein's anomaly	Huggon,[80] Eleftheriades[63]
Tricuspid atresia/hypoplastic right heart	Comas,[81] Galindo,[82] Carvalho,[21] Weiner,[61] Bellotti,[23] Hartge,[62] Eleftheriades[63]
Hypoplastic left heart	Bronshtein,[84] Haak,[79] Huggon,[80] Comas,[81] Carvalho,[21] McAuliffe,[38] Weiner,[61] Bellotti,[23] Persico,[22] Hartge,[62] Volpe,[42] Eleftheriades[63]
Aortic stenosis (developing HLHS)	Axt-Fliedner,[85] Hartge,[62] Volpe,[42] Eleftheriades[63]
Interrupted aortic arch	Carvalho,[18] Volpe[42]
Vascular ring/right aortic arch	Volpe[42]
Truncus arteriosus	Achiron,[77] Huggon,[80] Weiner,[61] Hartge[62]
Double outlet right ventricle	Gembruch,[73] Baschat,[78] Haak,[79] Comas[81], Carvalho,[6] McAuliffe,[38] Belotti,[23] Hartge[62]
Transposition of the great arteries	Baschat,[78] Galindo,[82] Carvalho,[21] Weiner,[61] Bellotti,[23] Persico,[22] Volpe[42]
Tetralogy of Fallot (ventricular septal defect and overriding aorta)	Bronshtein,[28] Achiron,[77] Comas,[81] Galindo,[82] Weiner,[61] Persico,[22] Hartge,[62] Volpe[42]
Pulmonary stenosis	Gembruch,[73] Baschat,[78] Hartge,[62] Volpe[42]
Pulmonary atresia	Huggon,[80] Persico,[22] Hartge[62]
Uhl's disease	Achiron[77]
Ectopia cordis	Achiron,[77] Comas,[81] McAuliffe,[38] Bellotti,[23] Hartge[62]
Cardiac diverticulum	Prefumo,[86] McAuliffe[38]

HLHS = hypoplastic left heart syndrome

scanning in nearly every centre. In this ultrasonographic plane, the size and position of the heart, two equally sized ventricles and atria, the opening and closure of the mitral and tricuspid valves, and an intact ventricular septum up to the cardiac crux are evaluated (Fig 2e). Allan et al and later Copel et al described that a normal "four-chamber view" ruled out the majority of foetal heart malformations in mid-gestational foetuses.[30,31]

An attempt to visualise the four-chamber view in first trimester foetuses proved feasible in several articles, as reviewed by Haak et al.[32] In the past few decades, the visualisation of this plane has increased to 90% of the examinations from 12 weeks gestational age onwards. Furthermore, a shift towards earlier gestational ages in which the four-chamber view can be visualised is observed. These improvements in early foetal echocardiography are probably because of the development of new transvaginal and transabdominal probes. Higher frequencies are used nowadays, and the increased variety in post-processing possibilities produce a very high image quality, leading to more detailed visualisation of small structures.[33,34] The most frequently reported congenital heart defects in first trimester echocardiography are those with an abnormal four-chamber view, such as atrioventricular defects or defects with asymmetrical or disproportional ventricles. In most cases, follow-up ultrasounds are necessary to determine additional details and definitive diagnosis of the abnormalities and

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state the correct diagnosis, or sporadically conclude that there is a normal cardiac anatomy.[6,22]

Outflow tracts

During development, the outflow tract of the heart needs to develop from a single tube to a situation where the aorta and pulmonary trunk are separated and connect to the proper ventricle. During this process, a lengthening of the pulmonary part of the outflow tract will occur, whereas the aorta will stay relatively short.[35] After normal development, the great arteries are located ventrally, wedged in between both atrial appendages. In the normal heart, the aorta has a right posterior position with respect to the pulmonary trunk (Fig 3a).

Although the four-chamber view is a potent plane to screen for major heart defects, it is not sufficient to rule out heart defects concerning the outflow tracts. To detect outflow tract anomalies with a normal four-chamber view, several planes have to be added to the examination.[36] The position and size of the ascending aorta is the first plane cranial to the four-chamber view. This is a relatively difficult plane to achieve, because the probe has to be rotated and slightly tilted.

Just above the four-chamber view, above the outflow of the aorta, both the pulmonary trunk and the aorta can been seen in their spatial relationship in a transverse plane through the foetal chest. The superior caval vein is visible next to the aorta. This "three-vessel view" is not difficult to acquire and easy to teach to ultrasonographers (Fig 2a–c). It is generally accepted to be of great benefit in screening programmes, as it is abnormal in several heart malformations with abnormal position of the great vessels.

In the first trimester foetuses, the ascending aorta and pulmonary trunk measure about 1–2 mm at the valve annulus.[25,37] Haak et al[32] observed an increase in the visualisation of the outflow tracts in the past few decades up to 95% at gestational age of 13 weeks, confirmed by later studies.[38] Table 1 provides an overview of the visualisation rates of both the outflow tracts and the four-chamber view.

Reports on diagnosis of malformations solely affecting the outflow tracts, before 14 weeks gestational age, are increasingly being published, but mainly in the last decade. This suggests that these types of defects are more difficult to diagnose in the first trimester. Table 2 summarises several examples of outflow tract malformations detectable by echocardiography. Possibly, the most important of these is transposition of the great arteries, which is one of the most frequently missed severe heart defects, and could possibly benefit the most from prenatal detection[39] (Fig 3, transposition of the great arteries is further described below).

Sensitivity and specificity of echocardiography in first trimester foetuses

As discussed, echocardiography in first trimester foetuses has been proven feasible. More recent studies have assessed the reliability and accuracy for detecting or excluding congenital heart disease. In a systematic review by Rasiah et al[24] a high sensitivity (85%) and specificity (99%) were reported in a pooled group of foetuses predominantly with a high risk for congenital heart defects such as increased nuchal translucency, previous child with cardiac defect, and cardiotoxic medication. These studies had all been conducted by specialised obstetricians in tertiary care hospitals. Large population-based studies concerning *second* trimester screening of low-risk pregnancies have demonstrated the limited accuracy regarding the detection of congenital heart defects. Specialised tertiary centres markedly showed higher detection rates.[40] It is therefore probable that considering *first* trimester echocardiography in population-based screening programmes will achieve lower reliability. A large randomised control trial[41] demonstrated a low detection rate in a 12-week scan policy (11%). This did not differ significantly from an 18-week scan policy (15%), likely reflecting the level of training and experience of the ultrasonographers in this programme. Evidence regarding first trimester screening for congenital heart defects of low-risk mothers is scarce[42] and does not assess cardiac anatomy only, but focuses on first trimester detection of structural defects in general.[43–45] The results of these pioneering studies are conflicting and no systematic reviews are available yet.

Examples of cardiac malformations detectable with first trimester ultrasound; ultrasound versus morphology

The following section describes three examples of congenital malformations in the first trimester.

In *transposition of the great arteries*, there is a concordant atrio-ventricular connection in combination with ventriculo-arterial discordance. The aorta connects to the morphological right ventricle and the pulmonary trunk connects to the morphological left ventricle. There is often a parallel course of the great arteries, with a right anterior position of the aorta with respect to the pulmonary orifice[46] (Fig 3b–c). There is usually a fibrous continuity of the mitral valve and pulmonary valve, whereas the aortic valve is separated from the tricuspid valve by a muscular infundibulum. In transposition of the great arteries, both the aortic valve and the pulmonary valve are often situated at the same level, in contrast to normal hearts where the aortic valve is situated at a lower level than the pulmonary valve. In about 50% of the cases of transposition of the great arteries, a ventricular septal defect is present.[47]

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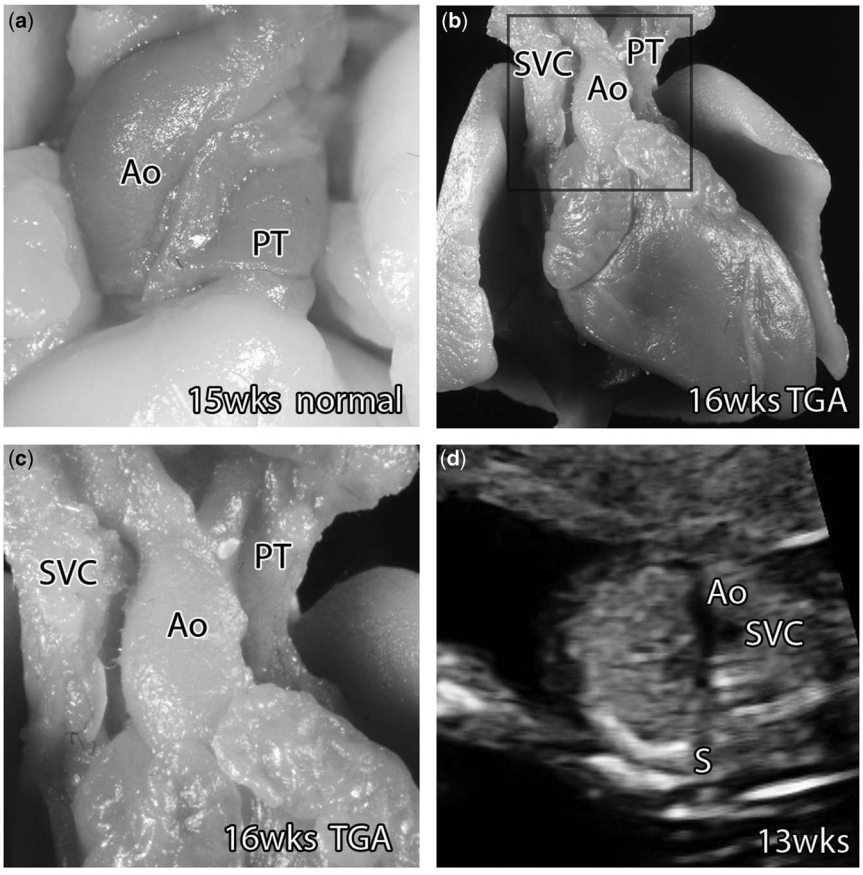

Figure 3.
*Echocardiography and morphology of a foetal heart with transposition of the great arteries. The aorta has, compared with the normal posterior position (**a**), in transposition of the great arteries, a right anterior position (panel (**b**) and enlargement (**c**)). On a transverse section through the foetal chest at the level of the "three-vessel view" (**d**), only the aorta (Ao) and superior vena cava (SVC) can be observed, owing to the caudal position of the pulmonary trunk. Spine (S) marks the dorsal side of the foetus on the ultrasound plane.*

Transposition of the great arteries is frequently missed during routine second trimester anomaly scans.[48] This is probably owing to the normal four-chamber view in this defect. In transposition of the great arteries the vessel that arises from the left ventricle branches in a transverse plane. This is called "laterally branching", which identifies the pulmonary artery. The vessel that arises from the right ventricle is the aorta, which gives rise to the neck vessels (superiorly branching). Easier to recognise is the fact that the "three-vessel view" described above cannot be achieved in transposition of the great arteries. In transposition of the great arteries, the vessel that arises from the right ventricle produces a "two-vessel view". These two vessels are the aortic arch and the superior caval vein. Figure 3d illustrates that it is possible to diagnose transposition of the great arteries, even at an early gestational age. The images are comparable to those encountered in the second trimester transposition of the great arteries.

Another example of a congenital malformation that may be detected during first trimester echocardiography is *atrioventricular septal defect*. Atrioventricular septal defects cover a spectrum of heart malformations resulting in a common atrioventricular junction and common atrioventricular valve (Fig 4). The extent of the incomplete development of the atrioventricular septum varies and is used to categorise atrioventricular septal defects. A complete atrioventricular septal defect includes an ostium primum defect of the atrial septum, as well as a defect in the inflow portion of the ventricular septum. In incomplete or partial atrioventricular septal defect, the common atrioventricular annulus and valve are combined with an atrial septal defect – only shunting at the atrial level – or, less commonly, a ventricular septal defect – shunting only at the ventricular level. Extreme disbalance of the ventricles may result in hypoplastic right heart, in cases of left ventricular predominance, or hypoplastic left heart, if the right ventricle is predominant).[49–51]

In echocardiography, atrioventricular septal defects can be recognised in the four-chamber view (Fig 4a) by the absence of the crux and a common atrioventricular valve. As the four-chamber view is the most basic plane to screen for heart defects, atrioventricular septal defects,

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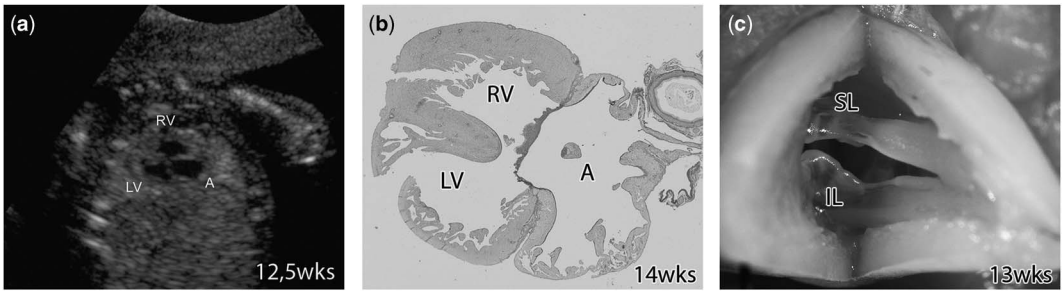

Figure 4.
*Echocardiography and morphology of a foetal heart with an atrioventricular septal defect. The common valve between the atria (**a**) and ventricles (RV and LV) can be recognised on the ultrasound four-chamber view (A; printed with permission of Ultrasound in Obstetrics and Gynaecology. Please note that this figure displays an oblique plane through the thorax. Owing to persistent foetal position, a correct four-chamber view was not obtainable) and histological section (**b**). On plane C, the common valve is seen from the left ventricle. IL = inferior bridging leaflet; SL = superior bridging leaflet.*

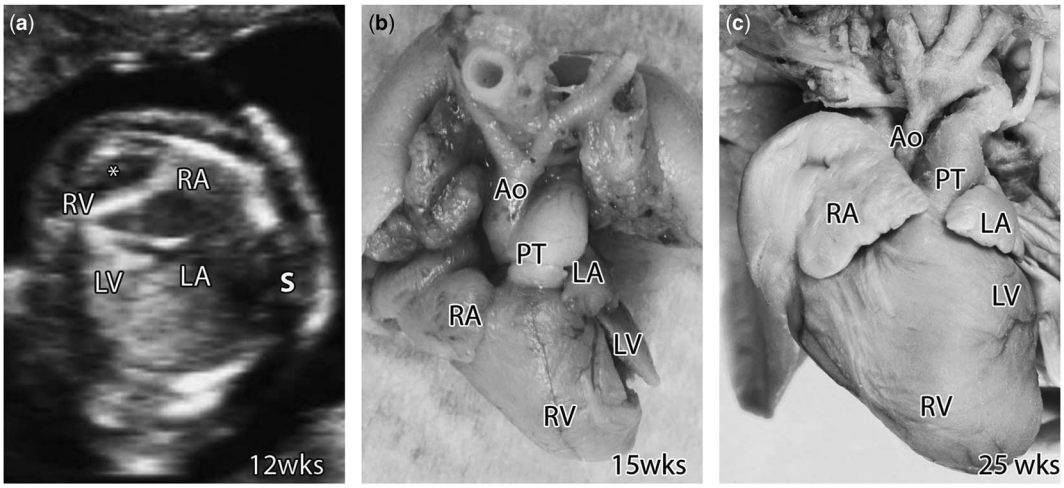

Figure 5.
*Echocardiography and morphology of a hypoplastic left heart. On ultrasound at 12 weeks gestational age (**a**), disbalance between the right ventricle (RV) and left ventricle (LV) can be observed. Foetal specimens of 13 (**b**) and 25 (**c**) weeks also show hypoplasia of the ascending aorta. Right atrium (RA), left atrium (LA), aorta (Ao), pulmonary trunk (PT). *Shows pericardial fluid.*

especially complete atrioventricular septal defects with moderate to large ventricular septal defects, are usually not missed, even in the first trimester scanning.

As balanced complete atrioventricular septal defects carry a risk of around 60–80% for Down's syndrome, karyotyping has to be offered. A careful examination of other organs is furthermore warranted, as 75% of cases with atrioventricular septal defects have anomalies in other organ systems.[49] A high prevalence of atrioventricular septal defects is also observed in patients with heterotaxy syndrome.[52,53]

The final example is the *hypoplastic left heart*, in which aortic atresia or aortic stenosis is combined with either mitral atresia or mitral stenosis. The left side of the heart is underdeveloped, with a left ventricle of about 1/3 or less of its regular size, and there is hypoplasia of the ascending aorta and left atrium.

When inflow of blood into the heart exceeds the outflow, a profound intimal thickening called fibro-elastosis can be observed. Whereas this intimal thickening can be readily observed during later development stages, this is usually not observed during first trimester echocardiography yet. A profound disbalance of the ventricles can be visible already during first trimester echocardiography (Fig 5). However, this disbalance may also occur only later in development, so that the observation of equal-sized ventricles does not always rule out the hypoplastic left heart. Follow-up studies are mandatory.

Limitations for foetal cardiac evaluation during first trimester

The most important disadvantage and therefore the major limitation of first trimester echocardiography is

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the intrauterine development of congenital heart disease at later gestation.[54,55] Several malformations, such as mild pulmonary[56,57]and aortic stenosis or coarctation[58] or even the hypoplastic left heart[59] can develop in second or third trimester foetuses. Furthermore, some heart lesions such as cardiac rhabdomyoma or cardiomyopathy may not be present in the first or second trimester and can evolve in later gestation or even after birth.[60] Therefore, it is important to clarify to parents that some lesions could be missed in early pregnancy, even after detailed examination, and that, however rarely, a serious defect can develop after the mid-trimester. This statement is also supported by reports of heart defects, being missed in the first trimester ultrasonography.[6,38,42,61–63] Thus, after the first trimester echocardiography, a follow-up examination on the second trimester of pregnancy should always be conducted. The knowledge that ventricular septal defects usually remain undetected in second trimester echocardiography,[64,65] probably because the size of these defects are beyond the resolution of the currently available ultrasound devices, makes it a neglectable aspect of first trimester examination, at which time this technical limitation is even more severe.

Another disadvantage of the first trimester echocardiography is the possible detection of defects that could resolve spontaneously in later pregnancy, such as muscular ventricular septal defects.[66] This could result in unnecessary anxiety of the parents.

If the first trimester echocardiography is performed transvaginally, the direction of probe manipulation is limited. If the foetal position is consistently unfavourable, the technique does not provide sufficient images of the foetal heart. Transvaginal scanning, however, produces images with detail comparable to the second trimester abdominal scanning. In our opinion, transvaginal scanning should therefore be the preferred approach, despite the fact that specific training is needed.

Finally, probably the most significant reason that first trimester echocardiography (abdominal or transvaginal) is still a rarely applied method is the need for highly skilled staff with several years of experience in second trimester echocardiography, and the use of high-end ultrasound equipment with high-frequency (transvaginal) probes.[67]

Conclusion

Although the advantages of first trimester transvaginal echocardiography seem of considerable value for couples at risk for having offspring with cardiac defects, this method is nowadays still limited to a few specialised centers. The numerous reports on the poor performance of mid-gestational sonography, regarding the detection of cardiac abnormalities, as well as the aforementioned limitations, could be the reason that centres are discouraged to extend echocardiography to the first trimester. Furthermore, high-end ultrasound facilities are needed, as well as operators that are experienced and have a particular interest in echocardiography. These factors, as well as the need for a follow-up examination at 20 weeks, are probably responsible for the limited utilisation of first-trimester echocardiography, and its restricted use in foetuses at a high risk of cardiac abnormalities.

In short, it seems clear that the capacity of high-frequency transvaginal probes is sufficient to perform echocardiographic examination in the late first trimester of pregnancy. However, the capability to detect and correctly diagnose heart defect is highly dependent on the operator, as is the case in the second trimester echocardiography.

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