Isomerism and related heart malpositions belong to the most difficult chapters in pediatric cardiology. According to the Baltimore–Washington Infant Study, which analyzed 4390 congenital heart defects (CHDs) detected in the first year of life over a period of 10 years (1981–1989), isomerism was found in 99 cases, accounting for 2.2% of CHDs. The mortality in this small group was 51% within the first year of life. In the fetus the true prevalence is, however, not known, since some forms, especially when associated with heart block and fetal hydrops, would end as fetal death, and some other more mild forms of cardiac malposition or isolated situs inversus may be overlooked even in a child. The early prenatal detection of an abnormality of this group has a large impact on counseling the pregnant woman, especially because small details can radically change the prognosis. There are difficulties in achieving a final fetal diagnosis, as the examiner can rely only on ultrasound, where there are limited possibilities for the precise differentiation of structures. Furthermore, some basic knowledge is needed in order to understand some definitions as well as the classification of defects. In this chapter, not all aspects of these abnormalities can be covered in detail. It is tried rather to supply the reader with basic information for a practical approach to suspected abnormal conditions.

**Developmental aspects and normal body configuration**

In contrast to other embryological organs, the thoracic and abdominal structures develop asymmetrically. There are well-defined right-sided and left-sided organs and structures. After completion of lateralization, the ‘normal’ and most common condition found is then called situs solitus for the visceral arrangement, and levocardia (heart on the left side) for the thoracic arrangement (Figure 16.1).

In Chapter 12, on fetal cardiac anatomy, the focus was on the segmental analysis of the upper abdomen and the heart, showing that under normal conditions in situs solitus the stomach and descending aorta are on the left and the liver and the inferior vena cava on the right. The umbilical vein bends to the right, continuing with the portal sinus. In levocardia the heart apex points to the left anterior thoracic cavity with normal atrial and ventricular arrangement (Figure 16.1) and, under normal conditions, the inferior vena cava is connected to the right atrium and the pulmonary veins to the left atrium.

**Situs inversus, malrotations, and malpositions of the heart**

Compared to the most common condition of situs solitus and levocardia, there is very rarely a situation where all organs are rotated exactly to the opposite side, leading to a mirror-image arrangement. This situation is called situs inversus. When this mirror-image rotation of abdominal and intrathoracic organs is complete, the liver and inferior vena cava are on the left, whereas the stomach and the descending aorta are on the right (Figures 16.2 and 16.3).

Since the inferior vena cava and the right atrium are concordant, the right atrium and right ventricle are on the left anteriorly and the left atrium and left ventricle are on the right posteriorly and the heart axis points to the right anterior thorax, a situation called dextrocardia (Figure 16.4) (mirror-image dextrocardia or situs inversus with dextrocardia, or situs inversus completus). In these conditions associated heart defects are rare. The true incidence of this situation is low, but also not exactly known, since persons with this abnormality are asymptomatic and are not identified until an X-ray, ultrasound, or medical intervention is performed. Because this condition is extremely rare, it can be recommended that, before making this diagnosis, the examiner checks the fetal position and the transducer orientation. According to our experience, we have found
Figure 16.1
The two important planes in assessing isomerism and other cardiac malpositions. The normal sonoanatomy of the upper abdomen with situs solitus (left) and the heart in levocardia (right). R, right; L, left; ST, stomach; VCI, inferior vena cava; AO, aorta; RV, right ventricle; LV, left ventricle.

Figure 16.2
Situs inversus. The fetus is in vertex position and in the upper abdomen a mirror-image rotation is found with the stomach (St.) and the aorta (Ao) on the right side and the inferior vena cava (VCI) and liver on the left side.

Figure 16.3
The heart in a fetus with complete situs inversus and mirror-image dextrocardia. The fetus is in vertex position. The heart points to the right anterior thorax (arrow). The right ventricle (RV) (with trabeculation) is on the left side and in the anterior thorax. The descending aorta (Ao) is on the right side. LA, left atrium; RA, right atrium.
Cardiac malpositions and isomerism

Similarly, levoposition (displacement to the left) is seen when the heart is shifted into the left thoracic cavity with the axis still pointing to the left, as typically found in right-sided diaphragmatic hernia or some other right-sided thoracic lesions.

Right and left atrial isomerisms in the fetus

Conversely to the above-cited very rare abnormalities with a mirror-image arrangement of the visceral and intrathoracic organs, there are more common conditions with an incomplete lateralization (heterotaxy) of these organs during embryological rotation, showing an indeterminate visceral situs. In these conditions, the arrangement is called situs ambiguus (indeterminate or uncertain situs) and is the most complex form of visceral and atrial arrangement. This group of defects has many synonyms, such as heterotaxy syndromes, cardiopulmonary syndromes, or asplenia–polysplenia syndromes or isomerisms, and the conditions are regularly associated with complex cardiac defects.

In these abnormal lateralizations of the visceral and intrathoracic structures, there is a tendency to symmetric development of the normally asymmetric organs, associated with either a bilateral right-sidedness.
Figure 16.5
Fetus with left isomerism showing, in the upper abdomen, situs ambiguous with the stomach (ST) on the right side (R) and an interruption of the inferior vena cava with azygos (AZ) vein persistence. The double-vessel sign is typical of left isomerism. In the four-chamber view the heart shows an atrioventricular septal defect (green arrows) and behind the heart again the double-vessel aorta (Ao) and azygos (compare with Figure 16.13). These cases of atrioventricular septal defects are not associated with Down syndrome.

Figure 16.6
This fetus was referred with bradycardia. M-mode shows the presence of a complete heart block: the atria (A) have a normal sinus rhythm (yellow arrows) whereas the ventricles show bradycardia (50 beats per minute) (red arrows). Examination of the four-chamber view reveals the diagnosis: a dilated heart with pericardial effusion, and behind the heart side-by-side with the descending aorta there is a second vessel, which is the dilated azygos vein; this is a typical finding in left isomerism.
Cardiac malpositions and isomerism

Figure 16.7
Two examples of left isomerism with the ‘double vessel sign’ (dilated azygos and aorta side-by-side) with the stomach on the left (left case) and on the right (right case). This example shows that the diagnosis is achieved by evaluation of the vessels’ position rather than the position of the stomach (compare also Figure 16.3).

Figure 16.8
Left isomerism with atrioventricular (AV) septal defect with azygos continuation side-by-side with the aorta. (right isomerism) or bilateral left-sidedness (left isomerism). Ivemark noted the association of spleen anomalies with some cardiac defects. Because the spleen develops as a left-sided organ it was in the past a sign for classification, asplenia being the previous name of right isomerism and polysplenia of left isomerism. This group of developmental defects were therefore called cardiosplenic syndromes. However, it was found that spleen presence, position, and number do not have definitive diagnostic value, and this terminology was abandoned (although it is often still used in clinical pediatric cardiology).

Knowing that the heart develops according to well-defined cardiac segments, Van Praagh proposed a classification according to the anatomy and connections of these segments, known as the segmental approach. The constant starting point for classifying these conditions is the anatomy of the atria. Therefore, diseases with isomerism are now divided into right atrial and left atrial isomerism.

The identification of these anomalies and their differentiation may be easier for the pathologist during necropsy. In the fetus the diagnostic possibilities are reduced, and the reliable diagnosis or differentiation between right or left isomerism can be very difficult to achieve prenatally. Even for the experienced examiner this group of anomalies is considered a challenge. The diagnostic approach using ultrasound is based on the approach proposed by Huhta et al for neonatal echocardiography, focusing on the upper abdomen and the relationship between the venous system and the atria. The central point of diagnosis is the anatomy of the atria defined by their shape and their appendages. The left atrial appendage is finger-like and has a narrow base, whereas the right atrial appendage is pyramidal in shape and its base is rather broad. The
appendages can be visualized in a plane slightly cranial to the four-chamber view, but are not identified reliably under many conditions. In a recent retrospective study on 30 fetuses with isomerism it was, however, shown that prenatally the morphology of the atrial appendages could have been suspicious in 19 cases, with the typical bilateral sickle-shape appearance in left and the blunt-shape appearance in right isomerism.

Since the connecting veins are part of the atrial anatomy, the venoatrial connection is the leading diagnostic sign for
Cardiac malpositions and isomerism

The types of cardiac malformation associated with left and right isomerism are complex, showing a considerable overlap. Except the azygos continuation of the inferior vena cava, considered as a typical sign of left isomerism,

**Left atrial isomerism**

In this condition of double left-sidedness, right-sided structures such as the inferior vena cava and the right atrium with sinus node are absent or may have developed abnormally. Therefore, two leading signs in left isomerism can be expected: first, the ‘interruption’ of the inferior vena cava in its intrahepatic part and its persistence as the azygos (or hemiazygos) vein (Figures 16.6–16.10); second, arrhythmia with heart block (malformed sinus node) (Figures 16.10 and 16.11). The azygos continuation of the interrupted inferior vena cava has been shown to be present in most cases with left isomerism (>80%). It can be recognized by the observation of the aorta and the (dilated) azygos vein on its right or left side (hemiazygos) either in the upper abdomen (Figure 16.7) or at the level of the four-chamber view (Figure 16.8). Sheley et al. described it as the ‘double-vessel sign’, and found it in all eight fetuses with left isomerism that they examined, but also in one false-positive case with right isomerism. In another more recent study in 22 fetuses with left isomerism, showed this azygos continuation sign. If the examiner is aware of this sign, he can easily detect it prenatally on real-time imaging and confirm it using color Doppler (Figures 16.9 and 16.10). The azygos vein is then visualized leading into the superior vena cava or into a persisting left superior vena cava (Figures 16.10 and 16.12).

**Figure 16.11**
Transverse view across the upper thorax showing the so-called three-vessel view (VCS, superior vena cava; AO, aorta; TP, pulmonary trunk). In this fetus with left isomerism the (dilated) azygos vein is seen to connect to the superior vena cava. Furthermore, to the left of the pulmonary trunk, there is a fourth vessel, which is the left persistent superior vena cava (LVCS).

**Figure 16.12**
This fetus was referred at 14 weeks because of nuchal edema (and beginning hydrops) associated with bradycardia. We found a heart block, a stomach (St) on the right side (left) and levocardia (H) with a heart defect. The heart showed a univentricular atrioventricular connection with a small (v) and a dilated ventricle (V) connected by a ventricular septal defect (*). The liver lay centrally. After termination of pregnancy because of suspected left isomerism, the diagnosis was confirmed at autopsy (see Figure 16.14).
ventricular septal defect or an atrioventricular septal defect is present. The association of an atrioventricular septal defect with complete heart block is considered to be pathognomonic for left atrial isomerism and should prompt careful examination of the venous connections.

Heart block detected in the early second trimester is also there are no cardiac defects permitting a strict classification into one or other group of isomerism. The conditions of a heart with left atrial isomerism seem to be less severe than those with right isomerism, demonstrating a normal ventriculoarterial junction in almost 70% of cases. These hearts tend to be biventricular, and on many occasions a ventricular septal defect or an atrioventricular septal defect is present. The association of an atrioventricular septal defect with complete heart block is considered to be pathognomonic for left atrial isomerism and should prompt careful examination of the venous connections. Heart block detected in the early second trimester is also
Cardiac malpositions and isomerism

Figure 16.15
In this fetus with right isomerism the stomach was also found to be central. In late pregnancy we observed a herniation of the stomach into the thoracic cavity (arrows) through the intact diaphragm.

Figure 16.16
Right isomerism with the typical sign of the juxtaposition of inferior vena cava (VCI) and aorta as in Figure 16.15 either on the left (left case) or on the right side of the spine (right case). The position of the stomach can be on the right or on the left side (the stomach is generally more central and the liver is more enlarged).

Very likely to be due to left isomerism and not to maternal autoantibodies\textsuperscript{14} (Figures 16.13 and 16.14). In the study reported above in 22 fetuses with left isomerism, a persisting bradycardia was found in 12/22 cases.\textsuperscript{11} The position of the heart can be on the left, on the right, or in the midline. The most severe complex extracardiac malformation observed in left isomerism is extrahepatic biliary atresia with absence of the gallbladder.

**Right atrial isomerism**

In this condition of double right-sidedness, left-sided structures such as the left atrium, the pulmonary veins, and the upper gastrointestinal tract are likely to be found malformed. In this group of complex malformations there are no characteristic features, such as interruption of the inferior vena cava or the heart block described for left isomerism.

The inferior vena cava is present and is generally on the same side as the descending aorta (Figures 16.15–16.17). The visceral heterotaxy is more common and severe in right isomerism, and anomalies of the upper abdomen are more likely to be found in right than in left isomerism; these include not only the common absence of the spleen, but also the symmetrical liver, and non-fixation of the gastrointestinal tract leading to various degrees of malrotation (Figures 16.15 and 16.16). Atresia of the esophagus or
much higher incidence of abnormal ventriculoarterial connections (double outlet ventricle, malposition of the great arteries). These hearts show a much higher frequency of pulmonary stenosis or atresia (Figure 16.20). An absence of the coronary sinus is found in 85\% of cases. A left persisting superior vena cava is found very frequently (Figure 16.12). In a recent study of 21 fetuses with right isomerism, 15 had complex cardiac anomalies, predominantly atrioventricular septal defects and right ventricular obstruction in 62\% and 48\%, respectively. Only 12 fetuses in this study showed a juxtaposition of aorta and inferior vena cava, and out of six cases with anomalous pulmonary venous return four were not diagnosed prenatally. Therefore, when right isomerism is suspected in a fetus, the connections of the pulmonary veins should be examined carefully to rule out the critical infradiaphragmatic pulmonary venous return.

**Figure 16.18**
Fetus with right isomerism. Owing to the inferior vena cava connection the atrium on the left is recognized as a right atrium and the atrium on the right receives the (abnormal) connections of the pulmonary veins. There is a univentricular atrioventricular connection to one ventricle (V). The outflow tract evaluation revealed pulmonary atresia: color Doppler demonstrates a normal antegrade flow through the aorta (Ao) and retrograde flow across the ductus arteriosus (DA) into the pulmonary trunk (TP). Univentricular hearts and right-sided obstructions are more represented in right isomerism (see text).
Cardiac malpositions and isomerism

Figure 16.19
Abnormal pulmonary venous drainage in a fetus with right isomerism.

Figure 16.20
Summary of the four typical findings in the upper abdomen in situs solitus (top left), situs inversus (top right), right isomerism (bottom left), and left isomerism (bottom right). The inferior vena cava (blue) and its position relative to the aorta (red) are main landmarks.

uteru. Under some conditions, children with left isomerism show a better survival rate than those with right isomerism.

The diagnosis of right atrial isomerism is very difficult in utero and should be considered in every fetus with a complex cardiac malformation, especially when cardiac or situs malposition are suspected. The severity of the disease usually appears postnatally, and is due to the abnormal pulmonary venous connection, to the ductus-dependent pulmonary perfusion in right outflow tract obstruction, or to the complex chamber anatomy. Within the first year of life, 79–94% of all children with right isomerism were reported to die, with or without operation. A long-term risk in patients with right isomerism is also infection due to asplenia, which is often associated.

The association with chromosomal aberrations such as trisomy 21, 13, 18, or others is extremely rare, since the diagnosis of isomerism rather rules out such chromosomal aberrations. Yates et al reported, however, a fetus with
isomerism associated with a 22q11 deletion. Recent results in families with recurrences of visceral heterotaxy cases showed that the gene for these malformations is probably localized on the long arm of the X chromosome (region between Xq24 and X27.1 but probably on Xq26). In the near future, the prenatal diagnosis of these abnormalities may be revolutionized by this new knowledge.

**Conclusion**

Every fetal heart defect should be analyzed in a segmental approach in order to detect (or rule out) an isomerism. This approach can be difficult to achieve in some cases and even omitted in others. Therefore, the examiner should always rule out isomerism when the following ultrasound signs are found: cardiac or stomach malpositions, a complex cardiac defect, fetal heart block, abnormal venous connections, and dilatation of the azygos vein.

**References**