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Original Article

The implications for fetal outcome of an abnormal arrangement of the abdominal vessels

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Abstract In a prospective audit of consecutive referrals for fetal echocardiography between 1997 and 2003, we documented all instances of an abnormal arrangement of the abdominal vessels. We then established the structure of the heart in these fetuses, noting any extra-cardiac associations, and the eventual outcomes.

We found a cardiac abnormality in 572 of the 2,136 fetuses examined during this period (27 percent), with 16 (0.8 percent) having an abnormal arrangement of the abdominal great vessels. Mirror-imaged arrangement was found in 3, while the arrangement suggested right isomerism in 6, and left isomerism in 7. Of these 16 fetuses, 14 had cardiac malformations. Isomerism of the right atrial appendages was found in 7 fetuses, all with either a right-sided stomach or cardiac apex, and 6 with a common atrioventricular junction guarded by a common valve. Only 1 of these fetuses survived. Of the 3 fetuses with mirror-imaged abdominal great vessels, 2 also had mirror-imaged atrial arrangement, while the 3rd had isomeric right appendages. Only one of 7 fetuses with an abdominal great vein posterior to the aorta had bilateral left atrial appendages. The remaining 6 had usual atrial arrangement, with normal pulmonary venous connections in all but one, who had infra-diaphragmatic totally anomalous pulmonary venous connection. Of these fetuses, 2 had coarctation of the aorta, and 2 others had complex cardiac malformations resulting in neonatal death. One died in childhood from biliary atresia, and three are alive.

Abnormal arrangements of the abdominal great vessels, therefore, were found in 0.8 percent of our total fetuses, and in 2.4 percent of those with cardiac malformations. Those with an abnormal arrangement of the abdominal vessels combined with an abnormal arrangement of the atrial appendages, however, made up only 0.5 percent and 1.6 percent, respectively. While screening for an abnormal arrangement of the abdominal vessels overestimated the incidence of left, but not right, isomerism of the atrial appendages, it did predict the presence of important extra-cardiac malformations that required urgent recognition and management after birth.

Keywords: Fetal heart; abdominal situs; isomerism; echocardiography; biliary atresia

NOWADAYS, MOST FETAL ECHOCARDIOGRAPHERS analyse the heart using the concept of sequential segmental analysis.[1] The first step in such analysis is to establish the atrial arrangement. In the strictest sense, this is based on the disposition of the atrial appendages rather than variable features such as the venous connections. If assessed according to the arrangement of the appendages, there are only four possibilities, these being the usual arrangement, the mirror-imaged variant, and right or left isomerism of the atrial appendages. In the clinical setting, however, it is usual to use the arrangement of the aorta and inferior caval vein as seen in the abdomen relative to the spine to infer the arrangement of the appendages.[2] In part, this reflects the limited ability to image the atrial appendages non-invasively using ultrasound.

Using such inferential methods, it is possible to identify the arrangement known as visceral heterotaxy. Although, taken literally, heterotaxy can be used to

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describe any departure from the normal, the situation typically described in this fashion broadly encompasses those defects in right-left determination that affect not only the relationship of the abdominal aorta and inferior caval vein to the spine, but also the morphology of the atrial appendages, the presence of multiple spleens, absence of the spleen, abnormal location of the gallbladder, abnormal bronchial branching and lung lobation, and malrotation of the bowel.[2] The prevalence of such abnormal arrangements is consistently estimated at about 1 per 10,000 total births.[3–5] These estimates, however, have not been based on true studies of populations, and hence might under-represent isolated abnormal arrangements of the abdominal great vessels, or those associated with only a minor cardiac abnormality. It is also now generally accepted that, when analysing the nature of the so-called "heterotaxy syndromes", isomerism of the atrial appendages is a much more constant feature than the state of the spleen, since there can be mismatch between the arrangement of the appendages and the abdominal organs, and also between the cardiac and pulmonary arrangements.[6–8]

In England and Wales, it is now routine practise to screen pregnant mothers for cardiac malformations at around 20 weeks gestation. This screening now includes not only examination of the four-chamber view but also, in many obstetric departments, the arrangement of the outflow tracts. Assessment of the arrangement of abdominal organs and great vessels, in contrast, is often omitted, resulting in under-ascertainment of potential fetuses with abnormal arrangements that are not accompanied by a cardiac malformation or heart block. The transverse abdominal view, nonetheless, used routinely for biometry during the 20 week scans, is the ideal plane with which to assess the arrangement of the abdominal great vessels. The fetal screening examination, therefore, if performed to a uniformly high standard, presents us with an ideal opportunity to obtain true prevalences for various cardiac abnormalities based on studies of the population, potentially permitting us to obtain a clearer understanding of the diversity of cardiac and extra-cardiac associations with an abnormal arrangement of the great vessels as seen in the abdomen. In this study, we report our findings on these associations, along with the outcomes in neonatal life, for all fetuses referred over a seven-year period for echocardiography who were found to have an abnormal arrangement of the great vessels in the abdomen.

Methods

We recorded prospectively the arrangement of the abdominal great vessels in all fetuses referred for echocardiography from 1 January 1997 to 31 December 2003 to a tertiary unit dealing with fetal medicine.

We examined each fetus in a systematic way, beginning with 5 transverse views[9] designed to reveal the arrangement of the abdominal organs, the course of the intra-hepatic venous conduit and the relative positions of the abdominal great vessels, the four-chamber view, the structure of the aortic and pulmonary outflow tracts, and the arrangement of the transverse aortic and ductal arches together with the superior caval vein, the latter providing the so-called "three vessel view". We recorded colour flow mapping and pulsed wave Doppler traces across the cardiac valves, in at least two pulmonary veins, and in the arterial and venous ducts. Additional short axis and longitudinal views were used to clarify any suspected abnormalities, and M-mode tracings were taken if we suspected any arrhythmias. All studies were performed on an Acuson Sequoia 512 machine with curvilinear 8C4 or 6C2 probe (Siemens Medical Solutions, Acuson Division, Mountain View, CA, USA).

We suspected isomerism of the right atrial appendages when both the aorta and the abdominal inferior caval vein were seen on the same side of the spine, and considered the finding suspicious for isomerism of left atrial appendages when a posterior venous channel, representing an azygous or hemiazygous vein, was seen on the transverse abdominal scan (Fig. 1a), with its course being traced longitudinally alongside the aorta (Fig. 1b). We diagnosed a mirror-imaged arrangement when the aorta was seen to the right, and the inferior caval vein to the left of the spine. During subsequent sequential segmental analysis of the heart, we determined the arrangement of the atrial chambers by examining their shape (Fig. 2), along with the presence or absence of the coronary sinus (Fig. 3), rather than by identifying directly the extent of the pectinate muscles relative to the atrioventricular junctions.[10] Our sequential segmental analysis, including the appearances of the atrial appendages, the morphology of the bronchuses and lungs, and the arrangement of the abdominal organs in all cases in which we had found an abnormal arrangement of the abdominal great vessels, were confirmed at postnatal echocardiography, abdominal ultrasound, penetrated chest X-ray, surgery or autopsy (Table 1).

Results

During the seven-year period of the study, we were referred 2,136 fetuses for detailed echocardiography, with 61 percent belonging to groups considered to be at high risk, 17 percent suspected to have a cardiac malformation on initial ultrasonic screening, and 22 percent referred for other indications. We diagnosed

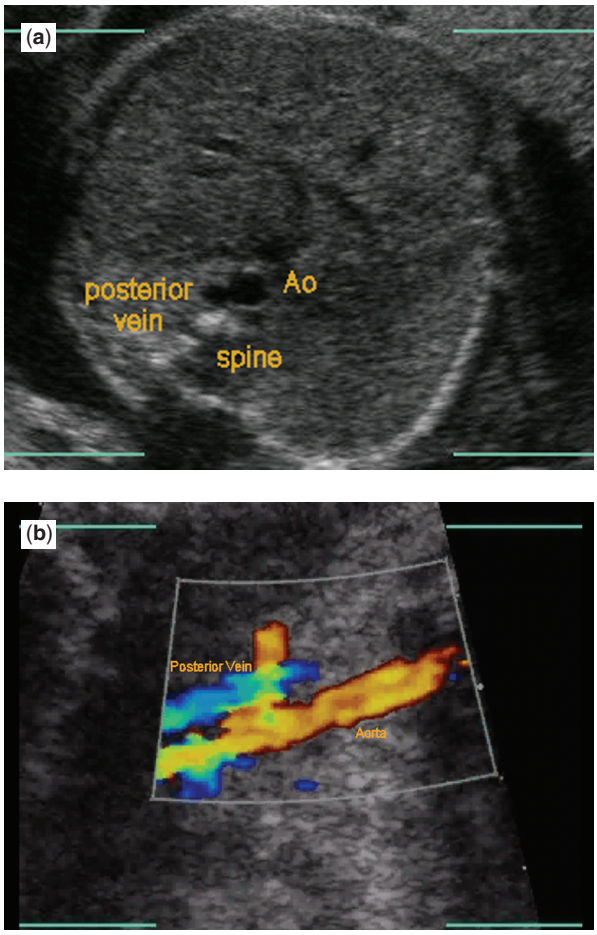

Figure 1.
*This transverse scan of the fetal abdomen (**a**) shows the aorta (Ao) to the left of the spine, with a posterior venous channel. The suprarenal course of the inferior caval vein was interrupted, with the venous channel continued via the azygous or hemiazygous vein, with the channel juxtaposed to the aorta (**b**), but on the same side of the spine and in posterior position.*

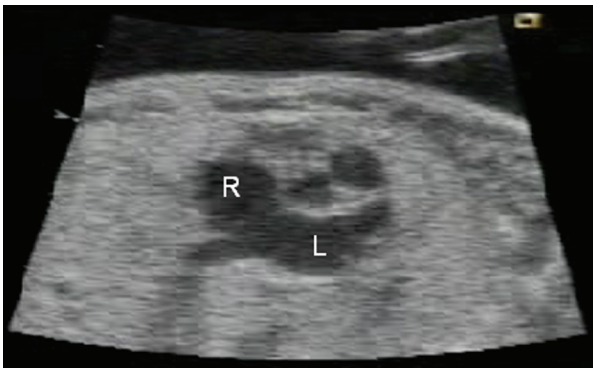

Figure 2.
This short axis view of the fetal atriums demonstrates the morphologically right atrium (R) with a broad triangular appendage, and the morphologically left atrium with its tubular and hooked appendage (L).

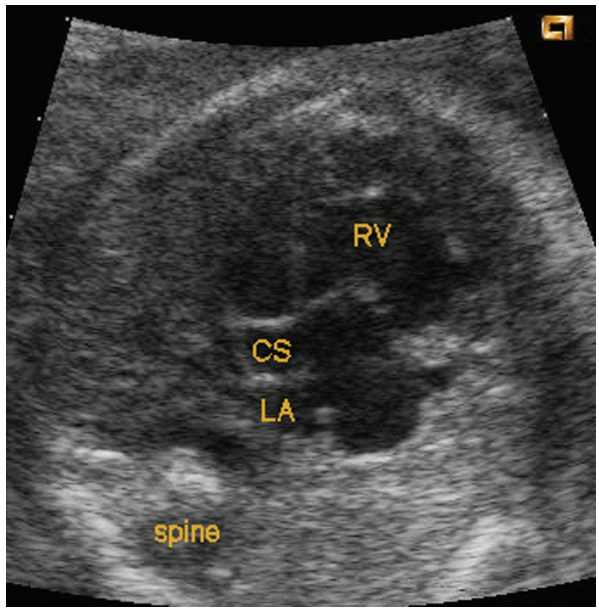

Figure 3.
The four-chamber view of the fetal heart shows an enlarged coronary sinus behind the morphologically left atrium.

a cardiac abnormality in 572 fetuses (27 percent), of whom 14 had an abnormal arrangement of the abdominal great vessels (2.4 percent). We also identified two further fetuses, one with a venous channel posterior to the aorta, and another with mirror-imaged arrangement, but both with normal intra-cardiac anatomy, albeit that the heart and organs were also mirror-imaged in the second case. Table 1 summarises the reasons for referral, the cardiac and extracardiac malformations identified, the manner of confirmation of the arrangement of the atrial appendages, and the outcome in neonatal life for the 16 fetuses found to have an abnormal arrangement of the abdominal great vessels.

Cardiac status and outcome

Abdominal vessels to the same side of the spine. In these six cases, fetal echocardiography suggested an isomeric arrangement of the right atrial appendages. This was confirmed postnatally at surgery or postmortem in all (Table 1). All fetuses were found to have a common atrioventricular junction, along with pulmonary valvar stenosis or atresia. Outcome was poor in all cases, with no survivors after the neonatal period.

Mirror-imaged arrangement of the abdominal great vessels. Of the three fetuses with this arrangement, one had isomeric right atrial appendages confirmed at surgery, with absence of the left atrioventricular connection, and two had mirror-imaged arrangement of the atrial appendages. The patient with right isomerism is now well following surgery. One of the

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Table 1. Referral reasons, cardiac and extracardiac malformations and outcome in fetuses with abnormal arrangement of the abdominal vessels.

	Gestation	Referral reason	Abdominal great vessels	Atrial appendage	Confirmation of diagnosis	Cardiac apex	Stomach position	Cardiac connections & anomalies	Associated anomalies	Outcome
1	22 + 0	CHD? SI	Ao left, PV (hemiazygous)	Usual	Surgery	Right	Left	Concordant, CoA, LSCV	None	Well post surgery
2	21 + 2	CHD Right stomach	Ao left, PV (hemiazygous)	Usual	Surgery	Left	Right	Concordant, CoA, VSD, LSCV	7p-deletion, intestinal obstruction, biliary atresia	Died at 2 years
3	21 + 5	Right heart? CHD	Ao left, PV (azygous)	Usual	Postmortem	Right	Left	Concordant, unbalanced AVSD, aortic atresia, LSCV	None	NND, no surgery
4	31 + 6	CDH	Ao left, PV (hemiazygous)	Usual	Postnatal echo	Left	Left	Concordant, sub-diaphragmatic TAPVC, LSCV	Diaphragmatic hernia	NND, pulmonary sequestration
5	26 + 0	CHD	Ao left, PV (hemiazygous)	Usual	Surgery	Left	Left	Concordant AV & discordant VA connections, criss-cross ventricular relationship, PS, VSD, LSCV	None	Well post surgery
6	38 + 1	CHD second opinion	Ao left, PV (hemiazygous)	Usual	Postnatal echo	Left	Left	Concordant, cardiac disproportion	None	Well, no surgery
7	21 + 2	Right stomach	Ao left, PV (hemiazygous)	Left isomerism	Postmortem	Left	Right	Concordant VA connections, pulm veins to both atriums, heart block	Increased NT, absent gallbladder	TOP
8	30 + 4	Absent stomach	Ao right, ICV right	Right isomerism	Surgery	Left	Right	AVSD, DORV, supracardiac TAPVC to brachiocephalic vein	None	Post-operative death
9	21 + 5	Exom-phalos	Ao right, ICV right	Right isomerism	Postmortem	Right	Left	AVSD, pulmonary stenosis, infradiaphragmatic TAPVC	T18, CPCs, Dandy-Walker, exomphalos, short femurs	TOP

10	20 + 0	CHD	Ao right, ICV right	Right isomerism	Postmortem	Right	Left	AVSD, TAPVC, left pulm veins to left-sided atrium, small pericardial effusion	Poland sequence Accessory thumb pre-auricular tag, absent right lung & pulm veins	TOP
11	32 + 0	Maternal DM	Ao right, ICV right	Right isomerism	Postmortem	Right	Left	AVSD, pulmonary atresia, pulm veins to both atriums	None	NND, no surgery
12	18 + 0	Right stomach CHD	Ao right, ICV right	Right isomerism	Postnatal echo	Left	Right	Unbalanced AVSD, PS	Increased NT	NND, no surgery
13	22 + 1	Right stomach CHD	SI/mirror	Right isomerism	Surgery	Midline	Right	Absent left connection, dominant RV with discordant VA connections, pulmonary atresia, right arch, bilateral superior caval veins, pulm veins via confluence to left-sided atrium	None	Well, cavo-pulmonary shunt
14	39 + 4	FHx CHD Polyhydr-amnios pleural effusion	Ao right, ICV right	Right isomerism	Postnatal echo	Left	Right	AVSD, discordant VA connections, obstructed TAPVC (infradiaphragmatic)	Polyhydramnios, bilateral pleural effusions	NND
15	21 + 0	Right stomach	SI/mirror	Mirror-imaged	Postnatal echo	Right	Right	Concordant	None	Well
16	21 + 4	Right stomach CHD	SI/mirror	Mirror-imaged	Surgery	Right	Right	Concordant AV connections, DORV, normally related GA, straddling MV, LSCV	None	Died, post-surgical arrhythmia

Abbreviations: Ao: abdominal aorta; AV: atrioventricular; AVSD: atrioventricular septal defect; CoA: aortic coarctation; CHD: congenital heart disease; Concordant: concordant AV & VA connections; CPCs: choroid plexus cysts; DM: diabetes mellitus; DORV: double outlet right ventricle; FHx: family history of heart disease; GA: great arteries; ICV: inferior caval vein; LSCV: persistence of the left superior caval vein; MV: mitral valve; NND: neonatal death; NT: nuchal translucency; PS: pulmonary stenosis; pulm veins: pulmonary veins; PV: posterior abdominal vein; RV: right ventricle; SI/mirror: "situs inversus" or mirror imaged abdominal vessels; T18: trisomy 18; TAPVC: total anomalous pulmonary venous connections; TOP: termination of pregnancy; VA: ventriculoarterial; VSD: ventricular septal defect

two with mirror-imaged arrangement had a structurally normal heart, confirmed postnatally, and required no further surveillance. The second had surgical repair of double outlet right ventricle with straddling cords of the mitral valve. He developed post-operative junctional tachycardia and died.

Venous channel posterior to the abdominal aorta. We identified seven such cases. Only one of the seven, however, was also shown to have morphologically left atrial appendages bilaterally. In this fetus, there was right-hand ventricular topology and concordant ventriculo-arterial connections, but we also found associated heart block, and the parents opted for termination of the pregnancy. In the remaining six fetuses, we found usual atrial arrangement, with the pulmonary veins draining to the left-sided morphologically left atrium in all but one case, in which there was infra-diaphragmatic anomalous pulmonary venous connection to the inferior caval vein and a fetal diagnosis of left-sided diaphragmatic hernia. This neonate had severe respiratory distress at delivery and postmortem resonance imaging demonstrated extensive bilateral pulmonary sequestration in addition to the hernia (Fig. 4). In 3 fetuses, we observed disproportion at atrial and ventricular levels, associated with coarctation of the aorta in two cases, but without abnormality in the third. In 7 fetuses, a persistent superior left caval vein (Table 1) was imaged in the so-called four-vessel view (Fig. 5) all being associated with dilation of the coronary sinus (Fig. 3). Complex cardiac malformations were found in two fetuses, with an unbalanced atrioventricular septal defect with aortic atresia found in one, and discordant ventriculo-arterial connections with pulmonary stenosis and criss-cross atrioventricular relationships in the other. Of the infants coming to term, two died in the neonatal period, one died in childhood from biliary atresia, while the other three are alive (Table 1).

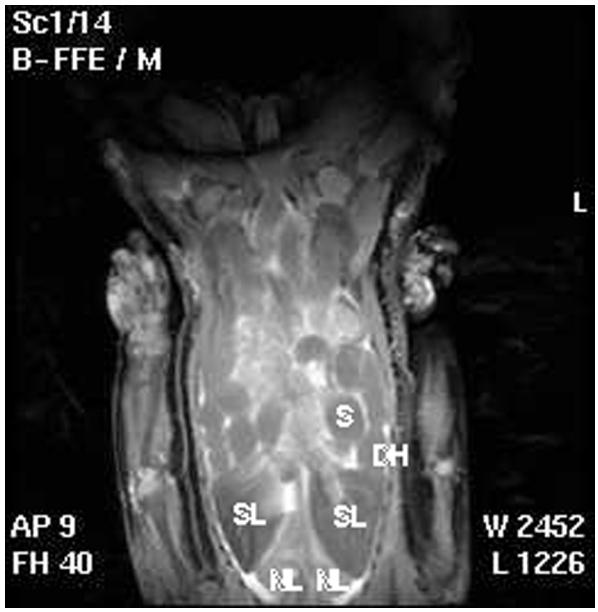

Figure 4.
Postmortem magnetic resonance imaging of the thorax in our 4th case, showing bilateral extensive pulmonary sequestration (SL), with a small area of normally inflated lung (IL) bilaterally, with a diaphragmatic hernia (DH) and stomach (S) on the left.

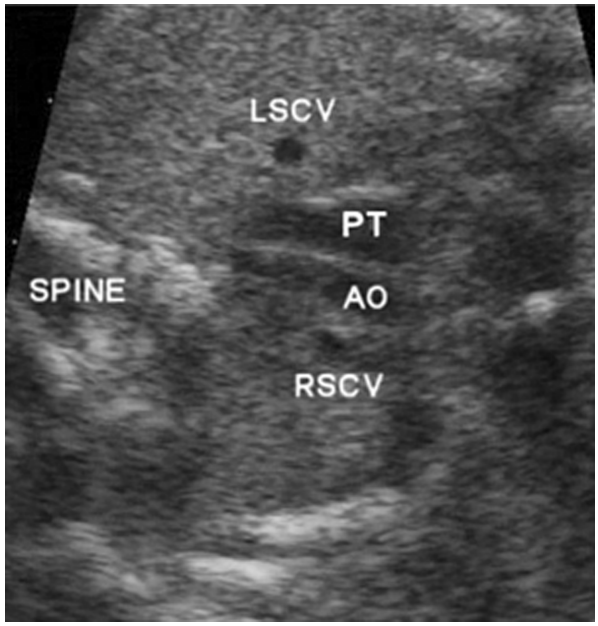

Figure 5.
The azygous vein may drain into a persistent left superior caval vein (LSCV) imaged on the "four vessel" view of the fetus comprising the transverse aortic arch (AO), the pulmonary trunk (PT) leading to the ductal arch and the right superior caval vein (RSCV).

Extra-cardiac malformations

The two fetuses with mirror-imaged atrial arrangement had both the stomach and cardiac apex located to the right. Of the 14 fetuses with findings suspicious for isomerism, 11 had abnormally located abdominal organs. In 6, the stomach was right-sided with a left sided or midline cardiac apex, while in 5, the stomach was left-sided with a right sided cardiac apex. All 7 fetuses with proven isomerism of the right atrial appendages showed discordance between the sides of the cardiac apex and stomach. This was also seen in 4 of the 7 fetuses with suspected left isomerism. Extracardiac sonographic abnormalities were identified in 6 cases, and proved to be important postnatally in cases #4, 9, 10, and 14. Our ninth fetus had trisomy 18 in addition to isomerism of right atrial appendages, but no extra-cardiac abnormality was recognised in the fetus with 7p-deletion, who developed intestinal obstruction and biliary atresia

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after birth. The mother of our 14th case showed mosaicism for Trisomy 21, and had undergone surgical repair of a ventricular septal defect in childhood.

Discussion

Although the morphologic analysis of congenital cardiac malformations is based on the arrangement of the atrial appendages as the first step in sequential analysis of the chambers of the heart, it is the arrangement of the abdominal great vessels that is used routinely to infer the true arrangement.[1] In our study, we found that 16 of the fetuses referred consecutively for echocardiography had abnormalities in the arrangement of the abdominal great vessels, giving prevalence in those with cardiac malformations of 2.4 percent. If we include only those in whom we subsequently confirmed an abnormality in the arrangement of the atrial appendages, the prevalence in the referred population is 0.5 percent, and is 1.6 percent for those with cardiac malformations. Our data suggests that, if fetal screening for an abnormal arrangement of the abdominal great vessels was instituted as a routine procedure, it would over-estimate the incidence of left, but not right, isomerism of the atrial appendages. Furthermore, our audit suggests that the prevalence of isomerism in the fetus at increased risk of having a congenital cardiac malformation lies between the figure of 1 per 10,000 live births, and the proportion of 4 to 10 percent associated with postnatal congenital cardiac disease.[11–13] All 7 fetuses we identified with isomerism of the right atrial appendages showed the expected association with complex cardiac malformations, and all did poorly, with all but one dying in infancy. The fetuses we initially suspected of exhibiting left isomerism proved more interesting, since we subsequently found that only one of the 7 had morphologically left atrial appendages bilaterally, this fetus also having associated heart block. In the remaining 6, the appendages were arranged in usual fashion, with normal pulmonary venous connections in all but one with associated pulmonary sequestration. The abnormal location of the stomach relative to the heart in 3, and the association with biliary atresia and intestinal obstruction in one baby, suggest that there was a disturbance of laterality despite the usual arrangement of the atrial appendages.

In 11 of the 16 fetuses we found to have abnormal abdominal vessels, we also found mismatch between the location of the heart or stomach, or between atrial and abdominal arrangement or cardiac and pulmonary anatomy. Such mismatch has been reported occasionally in postmortem series,[12,13] and it should not be surprising that a posterior abdominal venous channel is not always associated with bilateral morphologically left atrial appendages. Thus, although it remains a useful marker of isomerism, our study highlights the fact that a posterior abdominal venous channel can be associated with relatively mild cardiac lesions, or even a normal heart. Indeed, such vessels may be more common in the population than we have hitherto suspected. The opportunity to assess the position of the abdominal vessels relative to the spine, and the location of the cardiac apex and stomach, exists in every routine fetal scan conducted at 20 weeks. Our findings suggest that such procedures should now be considered as a routine.

It is the case that absence of the spleen, or so-called "asplenia", typically accompanies isomerism of the right atrial appendages, while multiple spleens, or polysplenia, are to be expected in patients with left isomerism. Such associations, nonetheless, are far from constant. Absence of the spleen, furthermore, is difficult to diagnose by fetal sonography before the third trimester. The most accurate diagnosis of cardiac isomerism, of course, depends on establishing the morphological appearances of the atrial appendages. It should be remembered, nonetheless, that the course of the coronary sinus postero-inferior to an atrial chamber, readily seen on the four-chamber view of the fetal heart, is indicative of that atrium being of left morphology. The coronary sinus is always absent in the setting of right isomerism.

Recognition of the atrial appendages ultrasonically may become more feasible with improvements in the equipment used for imaging. The morphologically right appendage can usually be identified by its broad triangular shape, while the morphologically left atrium is characterized by its tubular and hooked appendage seen on the coronal view of the fetal chest, equivalent to postnatal subcostal views. The most useful indirect sign of left isomerism, nonetheless, remains interruption of the suprarenal course of the inferior caval vein, with its continuation via the azygous or hemiazygous vein seen juxtaposed and posterior to the aorta. The abnormal abdominal venous channel may drain into a persistent left superior caval vein seen on high transverse views, and thence to the coronary sinus.

In 8 of our 16 fetuses, the stomach was right-sided, while 7 had a right-sided cardiac apex, features that should be readily detected at fetal screening, provided the fetal lie is correctly assessed. These findings proved more valuable as a marker of right isomerism in our study, since the heart and stomach were both located normally on the left side of the fetus in four of the seven with a posterior abdominal vein and azygous continuation. As is well documented in the literature, aneuploidy is rarely associated with abnormalities of bodily arrangement. In our study, we found that one fetus with right isomerism had

Trisomy 18, while another with a posterior venous channel, but usual arrangement of the atrial appendages, had 7p-deletion, postnatal intestinal obstruction, and biliary atresia. This patient died at the age of 2 despite optimal treatment in a major liver unit. Our 4th patient, with an antenatal diagnosis of left diaphragmatic hernia and infradiaphragmatic totally anomalous pulmonary venous connections, could not be ventilated after delivery. Postnatal ultrasound showed large lungs, but with the consistency of liver. The baby was shown by resonance imaging to have extensive bilateral pulmonary sequestration incompatible with survival.

Interruption of the inferior caval vein, with continuation via a posterior venous channel in association with multiple spleens and left bronchopulmonary isomerism, but with a structurally normal heart, has a well-recognised association with biliary atresia.[14] Optimal treatment requires early diagnosis and management in an experienced centre,[15,16] with an increase in overall five year survival to 90 percent from the previously reported 60 percent mortality when these conditions are satisfied. Hence, when a posterior abdominal venous channel has been diagnosed at fetal screening, visualisation of the gallbladder is needed to exclude associated biliary atresia, or to forewarn the neonatologist to observe the baby for persistent jaundice.

Our study suggests that, given ideal imaging capabilities, the arrangement of the thoracic and abdominal organs and large vessels should be analysed and described separately, noting any disharmony between the arrangement of the various organs. We have shown that, in the fetus, isomerism of the left atrial appendages cannot be inferred reliably from the arrangement of the abdominal great vessels. The detection of a posterior venous channel, nonetheless, with or without associated cardiac lesions, may predict important extra-cardiac pathology requiring urgent recognition and management after birth. It could be considered good practice, therefore, to incorporate an assessment of the relationship of the aorta and the inferior caval vein to the spine within the abdomen at the time of the routine scan for detection of fetal anomalies, and at any subsequent fetal echocardiographic examination.

Acknowledgments

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