Characterization of the phenotypic spectrum of fetal heterotaxy syndrome by combining ultrasound and magnetic resonance imaging

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Contribution:

What are the novel findings of this work?
Fetal MRI can be helpful in subtype identification in fetuses with heterotaxy as non-cardiac anomalies were systematically found by MRI. These findings may further facilitate prenatal counselling and postnatal management.

What are the clinical implications of this work?
Fetal MRI can be helpful in the diagnosis of abdominal situs anomalies and malrotation, the diagnosis of the spleen, and other non-cardiac structural anomalies. We found subtype specific bronchial patterns in RAI and LAI fetuses. Fetal MRI depicted a specific configuration of the fetal liver ("hooked-shaped" portion of liver parenchyma) only in LAI fetuses. This data that can help in prenatal counselling.
ABSTRACT

OBJECTIVES

Heterotaxy or isomerism of the atrial appendages, is defined as an abnormal arrangement of inner organs across the left-right axis of the heart. Left-atrial isomerism (LAI) is frequently associated with fetal arrhythmia and two-ventricle congenital heart disease (CHD), whereas right-atrial isomerism (RAI) is typically associated with more complex CHD. Both LAI and RAI can exhibit various non-cardiac anomalies with serious impact on fetal outcome. The aim of this exploratory study was to describe the morphologic spectrum encountered in heterotaxy by combining prenatal ultrasound (US), fetal echocardiography (FE) with fetal magnetic resonance imaging (MRI).

METHODS

This retrospective study included 27 fetuses who underwent a fetal MRI following the prenatal suspicion of heterotaxy on US from 1998 to 2019 in a tertiary referral center. Type of heterotaxy was defined by FE. In addition to routine prenatal US a fetal MRI was offered routinely to enhance the diagnosis of non-cardiac anomalies which might have been missed on US. Prenatal findings (US, FE MRI) were systematically reviewed and compared to postnatal imaging and autopsy reports.
RESULTS

Twenty-seven fetuses with heterotaxy and cardiovascular pathology, of which 19 (70%) had LAI and 8 (30%) RAI, were included. Seven fetuses (7/27, 26%) with LAI had a normal intracardiac anatomy, whereas all fetuses with RAI featured a cardiac malformation. All 27 fetuses featured non-cardiac anomalies on fetal MRI including situs and spleen anomalies. In 12/19 (63%) fetuses with LAI fetal MRI depicted a specific configuration of the fetal liver. Three fetuses revealed signs of total anomalous pulmonary venous obstruction on fetal MRI. An abnormal bronchial tree pattern was suspected in 6/19 (32%) fetuses with LAI and in 3/8 (38%) fetuses with RAI.

CONCLUSION

Visualization of non-cardiac anomalies in fetuses with a suspected heterotaxy is feasible and can aid in the complex diagnosis of this specific entity, albight its limitations. It potentially enables differentiation of less severe cases from more complex ones, which may have a poorer prognosis. Fetal MRI can assist in prenatal counselling and can help in planning postnatal management.
INTRODUCTION

Heterotaxy or isomerism of the atrial appendages is a rare congenital disorder with an incidence of 1 in 5000-7000 livebirths\(^1\), characterized by an unspecific dearrangement of the left-right axis of the fetal body\(^2,3\). Left atrial isomerism (LAI) is distinguished from right atrial isomerism (RAI) by pathognomonic patterns: In LAI there are usually two left atrial appendages (defined by the specific muscle pattern)\(^4\) and a situs anomaly of the abdominal organs, typically with balanced congenital heart defects (CHD), an interrupted inferior vena cava, and non-cardiac conditions such as malrotation of the intestines and polysplenia. In RAI, two right atrial appendages can be found, together with severely unbalanced CHD involving abnormal drainage of the pulmonary veins and abnormal intraabdominal location of the aorta and the inferior vena cava; in the majority, there is asplenia\(^2,3\). Discordance between bronchopulmonary branching, atrial appendage arrangement, and splenic status in more than one fifth of patients with heterotaxy has been reported\(^5\). Both nomenclature and classification are a matter of discussion, therefore the International Society for Nomenclature of Paediatric and Congenital Heart Disease proposed a definition in 2007\(^6\) to facilitate the precise use of the term, which will be used in this study.

The variability of heterotaxy challenges fetal imaging interpretation. Reported investigations on fetal heterotaxy rely mainly on ultrasound (US) including fetal echocardiography (FE) and autopsy findings\(^7-13\). In our center, fetal magnetic resonance imaging (MRI) is routinely offered to all patients with US suspicion of severe non-cardiac anomalies. Fetal MRI complements ultrasound by providing unique tissue contrast and characterization\(^14\).
As technical and maternal limitations (e.g. maternal obesity, fetal position, lack of amniotic fluid, ultrasound machines) influence the detection of cardiac and non-cardiac anomalies on prenatal US, fetal MRI can be used as an adjunct to US and FE, eventually facilitating prenatal clarification of diagnoses and counselling on postnatal interventional strategies. Reports on heterotaxy and fetal MRI, however, are limited and numbers of cases are small\textsuperscript{2,15,16}.

The aim of this study was to assess the additional value of fetal MRI for the diagnosis of heterotaxy in utero and not compare different imaging modalities.
METHODS

This retrospective series included fetal MRI studies of 27 fetuses with the diagnosis of fetal heterotaxy carried out between 01/1998 and 12/2019 (Table 1). Patients were identified from fetal cardiac databases of the Department for Obstetrics and Gynecology, Division of Pediatric Cardiology, and Department of Pediatric and Adolescent Medicine of the Medical University of Vienna. The ethics committee of the Medical University of Vienna approved the study protocol (1306/2020). During the study period fetal medicine imaging was carried out in the standardized fashion according to ISUOG guidelines. After the suspicion of heterotaxy syndrome on US a detailed FE was performed (Table 2). Type of heterotaxy was diagnosed on FE on the abdominal situs view: presence of an interrupted inferior vena cava with azygos continuity was found to be most likely the subtype of left isomerism, juxtaposition of the aorta and inferior vena cava in combination with a cardiac malformation and abnormal cardiac or abdominal organ situs most likely to be the subtype of right isomerism. After prenatal diagnosis of heterotaxy, all patients were offered genetic assessment and fetal MRI for further evaluation. A retrospective chart review of available pre and posnatal US reports and medical records (autopsy reports) was performed. Available fetal MRI images were systematically reevaluated with the focus on heterotaxy specific findings.

Fully informed, written consent was obtained from all parents prior to fetal US, MRI, genetic investigation, postnatal imaging and autopsy. Prenatal US examination and FE were performed on a variety of ultrasound machines during the study period: GE Voluson E8/E10 (GE Healthcare, Austria), GE Vivid 7, Vivid E9, GE Loqic (GE Healthcare, Austria), Philips EPIQ 7 (Philipps Heathcare, Austria).
FETAL MRI

Fetal MRI was performed without maternal sedation on a 1.5 Tesla MR system, using an 8 channel body coil and a protocol which followed the guidelines of the International Society of Ultrasound in Obstetrics and Gynecology using ultrafast T2-weighted sequences, performed in 3 orthogonal planes, T1-weighted gradient-echo, diffusion-weighted and steady-state free precession sequences. An expert in fetal MRI (G.K.) with 15 years of experience performed a standardized analysis of all MRIs in a systematic fashion. The following features were addressed with specific focus to their relation to the midline of the fetal body: the position of the cardiac apex, the position and size of the large cardiac vessels, the umbilical vein, the position and size of the stomach, the rotational appearance of the small and large intestines, the shape and configuration of the fetal liver and the presence or absence of spleen tissue. In addition, the feasibility to characterize the branching pattern of the bronchial tree and the appearance of the pulmonary lobes was evaluated. As the goldstandard postnatal definition of bilateral hyparterial or eparterial bronchus was difficult in the setting of fetal MRI the following definition was taken: Bronchial tree pattern with short bronchial arms and an early bilateral rise of the upper lobe bronchi with a distance to the middle lobe bronchi was suspected as RAI and a bronchial tree pattern with long bronchi arms and a late bilateral rise of the upper lobe bronchi was suspected as LAI.

The nutmeg lung pattern was defined on T2-weighted images as a heterogeneous signal with tubular structures radiating peripherally from the hila indicating pulmonary lymphangiectasia.
STATISTICS

Only descriptive statistics were applied. Demographic, anatomic and outcome data were included in the analysis. Results are presented as frequencies (percentage) and means with standard deviations or medians with range, where appropriate. Postnatal findings (when available) were compared to fetal findings.
RESULTS

Twenty-seven fetuses met the inclusion criteria (prenatally diagnosed heterotaxy with further evaluation with fetal MRI) (Figure 1). Nineteen fetuses (19/27, 70%) were categorized as LAI, 8 (8/27, 30%) as RAI. Clinical characteristics of the study population are shown in Table 1. Termination of pregnancy occurred in 2/19 (11%) fetuses with LAI and 2/8 (25%) fetuses with RAI. Overall 15/19 (79%) fetuses with LAI and 6/8 (75%) fetuses with RAI were liveborn (2 fetuses were lost to follow up during pregnancy) (Figure 1). Mean gestational age at diagnosis was 23 weeks (range 14-37 weeks). Fetal MRI was performed at a mean gestational age of 25 weeks (range 17-38 weeks) (Table 1). Distribution of cardiovascular malformations according to LAI and RAI are detailed in Table 2. Seven fetuses (7/19, 37%) with LAI had a normal intracardiac anatomy, whereas all fetuses with RAI featured a cardiac malformation. Delayed or interrupted conduction between atria and the ventricles was defined as atrioventricular block. Higher degree heart block was found in 2/19 (11%) fetuses with LAI and not in fetuses with RAI. None of these fetuses developed hydrops. Complex intracardiac malformations with obstruction of the right ventricular outflow tract was more common in fetuses with RAI (75%). Complex atrioventricular septal defects were more common in RAI 5/8 (63%). Coarctation of the aorta was only present in LAI fetuses (n=4; 21%). D-Transposition of the great artieres was seen in 38% (3/8) fetuses with RAI. Hypoplastic left ventricle or single right ventricle was found in 3/19 (16%) fetuses with LAI and in 2/8 (25%) fetuses with RAI. Single ventricle morphology was more common in right isomerism (3/8 38% vs 2/19 11% LAI). Fetal genetic testing was performed in 67% (18/27). All fetuses had a basic chromosomal investigation with karyotype, one fetus had a microarray and one fetus was tested with noninvasive prenatal testing (NIPT). One fetus was diagnosed with Microdeletion 22q11 and one with Bardet-Biedel Syndrome. One child was tested positive for ATD3 Jeune Syndrome postnatally.
Magnetic resonance imaging findings.

Two fetuses with LAI had two MRIs, resulting in a total of 29 MRI scans, at a mean gestational age (GA) of 25 (range 17-38) weeks. Fetal MRI findings with postnatal confirmation are summarized in Table 3. Overall 63% of fetuses revealed one or more non-cardiac anomalies on fetal MRI. Examples of specific fetal MRI findings are given in Figure 2 and 3.

**Central nervous system (CNS)**

Five fetuses (1/19, 5% LAI and 3/8, 38% RAI) had abnormal CNS findings. One fetus with LAI showed Dandy Walker Malformation. In RAI fetuses 1/8 (13%) showed cerebellar hypoplasia, hydrocephalus and stenosis of the aqueduct, 1/8 (13%) had ventricular asymmetry, 1/8 (13%) showed ventriculomegaly. In one child hydrocephalus was diagnosed in childhood.

**Craniofacial abnormalities**

Cleft lip and cleft palate and hypertelorism was seen in one fetus with LAI (1/19; 5%). In addition this fetus had a short curved femur visible on fetal MRI. Retrognathia was diagnosed in one fetus with RAI (1/8;13%) and facial dysmorphism was described on one fetus with LAI (1/19; 5%).

**Bronchial tree pattern and lungs**

The fetal bronchial tree was indicative (double left or double right sided bronchial pattern for the presence of LAI or RAI in 9/27 (33%) fetuses (32% LAI and 38% with RAI). The diagnosis was based on the shape and pattern of the main bronchial arms as the early or late bilateral rise of the upper lobe bronchi could not be seen with confidence (Figure 4).

Five fetuses (19%; LAI 1/19 5%, RAI 4/8 50%) with total anomalous pulmonary venous connection (TAPVC) underwent fetal MRI at 22 to 37 weeks. In three fetuses with TAPVC and RAI (3/8; 38%), there was pulmonary lymphangiectasia which can be associated with
TAPVC obstruction (Figure 5). FE suspected obstruction in 2 of these fetuses. No pulmonary findings were seen on ultrasound. Obstructed TAPVC was confirmed on transthoracic echocardiogram postnatally and pulmonary lymphangiectasia was documented by postnatal chest X-ray in two newborns, one pregnancy was terminated. No specific description of the lung was noted in the autopsy report.

In the other two fetuses with TAPVC (one with LAI and one with RAI) no signs of obstruction were suspected on FE. In these cases fetal MRI of the lungs appeared normal. Postnatally, neither echocardiography nor chest X-ray revealed TAPVC obstruction nor pulmonary lymphangiectasia in these 2 cases.

The lobulation pattern of the lungs could not be fully differentiated by fetal MRI in any case.

Gastrointestinal findings

Anomalies of the gastrointestinal organs were seen in all 27 fetuses that underwent MRI. 85% of fetal MRI’s (23/27) revealed situs anomalies with a midline liver and atypical location of abdominal organs. Four fetuses (4/27, 15%) showed situs inversus abdominalis on MRI. A right sided stomach was seen in 18/19 (95%) fetuses with LAI and in 5/8 (63%) fetuses with RAI. The heart/stomach position was contralateral (stomach either on the same side of the heart or contralateral side) in 13/19 (68%) fetuses with LAI and in all eight fetuses with RAI. Dextrocardia was documented in 5/19 (26%) fetuses with LAI and in 2/8 (25%) fetuses with RAI. A specific configuration of the fetal liver visible as a “hooked-shaped” portion of liver parenchyma was only seen in LAI fetuses (12/19 63%) (Figure 6).

Malrotation of the intestines was noted on MRI in 9/27 (33%) fetuses and additionally diagnosed on postnatal imaging in 2/27 (7%). (32% of LAI and 38% of RAI cases).

Gallbladder aplasia was diagnosed in one fetus (MRI at 33+2 weeks) with postnatally confirmed biliary atresia and LAI. Esophageal atresia was suspected on MRI in one fetus with RAI, with postnatal diagnosis of duodenal atresia. This fetus did not have the typical
double bubble sign on ultrasound and the stomach was not filled at the time of fetal MRI. (Suppl. Table 1). Correct diagnosis of asplenia or polysplenia was achieved in 19/27 (70%) fetuses. Of all 19 LAI fetuses the diagnosis of the spleen was correct in 11 fetuses (58%), (4 fetuses with asplenia, 2 with polysplenia and 4 fetuses with a right sided spleen). In all 8 RAI fetuses the diagnosis of the spleen was correct, (6 fetuses with asplenia, and two fetuses with a right sided spleen). All findings were confirmed by postnatal ultrasound or autopsy studies.

**Kidney findings**

Abnormalities of the kidneys were noted in two fetuses with LAI: polycystic kidneys in one fetus (1/19; 5%) and duplex kidney in one fetus (1/19; 5%) with LAI. In RAI fetuses there was kidney agenesis in one fetus (1/8; 13%) and bilateral duplex kidney in one fetus (1/8; 13%).

Apart from situs and the spleen anomalies, 14/27 (52%) fetuses revealed one or more non-cardiac structural malformations on fetal MRI. Postnatal extracardiac findings such as uterine agenesis or biliary atresia are usually not depicted by fetal MRI. However biliary atresia was indirectly suspected due to gallbladder aplasia. All findings - diagnosed on postnatal imaging or autopsy studies and missed on fetal MRI are listed in Suppl. Table 1.
DISCUSSION

This report on fetal MRI results of 27 fetuses with heterotaxy is the largest fetal MRI study in this specific group so far. In the present analysis, fetal MRI documented information on abnormal arrangement of the internal organs as well as extracardiac anomalies (ECA) and helped to provide a phenotypic characterization of fetal heterotaxy. Smaller fetal MRI series provided promising preliminary data on its ability to affirm the diagnosis of heterotaxy\textsuperscript{15,16}.

The definition of heterotaxy implies an abnormal arrangement of the abdominal organs not always in a distinct pattern. Especially liver position in heterotaxy syndromes is quite variable. In both conditions - RAI and LAI - the liver can be positioned in the midline or predominantly in the right upper abdominal quadrant. Further, a liver position predominantly in the left upper abdominal quadrant has been reported in both conditions\textsuperscript{22}. In LAI the left liver lobe has occasionally been described to be very prominent\textsuperscript{23}. Here, we describe a specific configuration of the fetal liver, characteristically encountered in LAI: a “hook-shaped” portion of liver parenchyma, extending towards the small curvature of the stomach (Figure 6) and apparently being derived from the left liver lobe – either from liver segments 2/3 or segment 4a/b. Embryologically, the human liver bud is asymmetric from its first appearance\textsuperscript{24}. In animal models it was recently shown, that lateralized expression of Pitx2 results in cellular asymmetries of the epithelium of the hepatic diverticulum and thus leads to the generally asymmetric liver morphogenesis\textsuperscript{25}. Here, we were able to demonstrate an atypical liver morphology in association with a specific lateralization defect – LAI – potentially linked to an abnormal local expression of left lateralizing morphogens.

Interestingly, the characteristic hook shaped liver configuration was not encountered in RAI cases. Previously the definition of heterotaxy was defined as asplenia or polysplenia\textsuperscript{2,3,26}. Gaur et al. investigated thirteen fetuses with polysplenia using fetal MRI, and was able to visualize the spleen in 6/13 fetuses (46\%)\textsuperscript{16}. In our study fetal MRI diagnosis of the spleen...
was correct in 100% of RAI cases and in 58% of LAI cases. The limitations in the diagnosis of the spleen lie in the smallness of the structure especially on early fetal MR investigations, due to low spatial resolution and fetal motion.

Bronchial tree pattern diagnosis\textsuperscript{27} is used postnatally. Fetal MRI identified a- for the subtype typically- shaped bronchial tree in 6/19 (32%) fetuses with LAI and in 3/8 (38%) fetuses with RAI, which added clues to the diagnosis of heterotaxy.

A recent study by Yim et al points out that the typical signs of isomerism were breached in over 20% of cases with heterotaxy. 7.5% of investigated cases revealed a discrepancy between the arrangement of the bronchial tree pattern and the atrial appendages arrangement\textsuperscript{3}.

In our study we found concordance with postnatal imaging modalities in four of six investigated cases.

ECA can be present in fetuses with heterotaxy\textsuperscript{26, 28-30}, regardless of the subtype. In our study, ECA were present in 17/27 (63%). Escobar-Diaz et al. report non-cardiac anomalies in 62.2% of 154 fetuses\textsuperscript{29}. Gottschalk et al report a lower incidence (15.8%)\textsuperscript{30}. Ticho et al. emphasis the idea that the midline plays an important role in the formation of the normal left-right asymmetry\textsuperscript{28,30-31,33}. Malrotation was seen in 32% of LAI and 38% of RAI cases with an overall detection rate of 83%. MRI helps to visualize meconium, which is difficult in US. Ticho et al. report the presence of malrotation in 33% of their cohort\textsuperscript{28}.

Obstruction of TAPVC is a major risk factor for postnatal mortality. Ganesan et al recently published a group of fetuses with fetal TAPVC, promoting Doppler flow waveforms for the specific subtypes\textsuperscript{34}. Due to the retrospective fashion of our study it was not possible to evaluate doppler wave forms in our TAPVC fetuses.

In our study fetal MRI aided in identifying pulmonary findings reflective of severely obstructed TAPVC. In three fetuses with suspected obstruction due to TAPVC on FE fetal
MRI revealed a pulmonary “nutmeg pattern” sign. The “nutmeg pattern” has been described in fetuses with hypoplastic left heart syndrome and restricted atrial septal flow\textsuperscript{35}, interpreted as a sign for lymphangiectasia and venous arterialization.

In our institution fetal MRI is offered to all women with a cardiac and/or non-cardiac anomaly on a voluntary basis. We make it clear prior to the fetal MRI that the diagnostic information might not exceed ultrasound information.

This retrospective study has several limitations. This study due to its retrospective fashion was not a comparative study of US and fetal MRI. We only included fetuses with a fetal diagnosis of heterotaxy who underwent a fetal MRI. Thus this is a highly selected patient cohort and no general conclusion on sensitivity or specificity of the detection by MRI can be drawn from our cohort. It is beyond the scope of this study to state that if there are possible advantages of MRI over US as these have not been systematically evaluated. This study only provides information on the possibilities of this specific modality, but does not imply a general recommendation for the use of fetal MRI in the setting of heterotaxy. However it might be of help as a complimentary tool if fetal MRI is available. We are fully aware that the diagnosis of disharmony challenges fetal and postnatal subtype specification and thus prenatal diagnosis of the subtype of left and right isomerism can never be fully complete. Postnatal evaluation is warranted to address this important question and learn more about disharmonious patterns of heterotaxy.

In conclusion, the merit of the paper lies in its systematic phenotypic characterization of fetuses with heterotaxy using the maximally available prenatal imaging methods (MRI and US). By this, we were able to identify a series of extracardiac abnormalities which can help to further specify the subtype of heterotaxy. Future prospective studies will need to demonstrate if US is equivalent to MRI in the detection and/or exclusion of these findings in individual cases.
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Figure Legends

Figure 1: Flowchart of patients with heterotaxy and fetal MRI included in the analysis.

Figure 2: Fetus with LAI at GW 28+6. Polysplenia as indicated by the short arrows in images A, B, and C. Intestinal malrotation demonstrated as the absence of the colonic flexure in the left epigastric region, indicated by the long arrows in images D and E.

Figure 3: Fetus with LAI at GW 23+0 (fetal MRI) and 23+4 (postmortem MRI-images C and E). Dandy-Walker-malformation with vermian hypoplasia and malrotation as indicated by the arrowhead in image A. Abnormal liver configuration with an additional liver lobule indicated by the short arrows in images B and C. Aberrant azygos vein with coinciding agenesis of the inferior vena cava as indicated by the long arrows in images D and E.

Figure 4: Fetus with RAI at GW 25+5. Suspected abnormal branching pattern with short bronchial arms pattern as indicated by the arrow in image A. Fetus with LAI at GW 24+2. Suspected abnormal branching pattern with long bronchi arms as indicated by the arrow in image B.

Figure 5: Fetus with RAI at GW 32+2. Coronal (A) and sagittal (B) T2-weighted fetal MRI sequences. The fetal lungs show hyperintense linear signal intensity changes with the characteristic nutmeg pattern of the lung in a fetus with pulmonary lymphangiectasia in the setting of obstructed total anomalous pulmonary venous drainage and heterotaxy.
Figure 6: Fetus with LAI at GW 21+1 (A) Coronal T2 weighted (B) coronal T1-weighted (c) axial T2 weighted fetal MRI images. The arrow points at the T2-weighted hypointense and T1-weighted hyperintense “hooked shaped” portion of liver parenchyma being derived from the left liver lobe. The abnormal liver segment extends towards the small curvature of the stomach.
Supplementary Legend

Supplement Table 1:. Summary of non-cardiac findings on fetal magnetic resonance imaging (fetal MRI) and additional postnatal or autopsy findings in patients with a prenatal diagnosis of heterotaxy sorted by left atrial isomerism (LAI; n = 18) or right atrial isomerism (RAI; n = 9), according to gestational week of fetal MRI investigation.
27 Fetuses

LAI: left atrial isomerism, RAI: right atrial isomerism, TOP: termination of pregnancy, LTFU: lost to follow up, LB: livebirth, * 2 fetuses had cardiac surgery and extracardiac surgery

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| Clinical characteristic                                      | Number and Percent |
|------------------------------------------------------------|--------------------|
| Maternal age at diagnosis (mean)                           | 31 (range 20-42) years |
| Gestational age at diagnosis (mean)                        | 23 (range 14-37) weeks |
| Gestational age at fetal MRI (mean)                        | 25 (range 17-38) weeks |
| Gender known                                               | 25/27 (93)         |
| Male sex                                                   | 12/25 (48)         |
| LAI                                                       | 19/27 (70)         |
| RAI                                                       | 8/27 (30)          |
| SUA                                                       | LAI: 4/19 (21)     |
|                                                           | RAI: 2/8 (25)      |
| Nuchal translucency (>2.5mm)                               | LAI: 0             |
|                                                           | RAI: 1/8 (13)      |
| Growth restriction                                         | LAI: 1/19 (5)      |
|                                                           | RAI: 0             |
| Termination of pregnancy                                   | LAI: 2/19 (11)     |
|                                                           | RAI: 2/8 (25)      |
| Genetic assessment                                         | 19/27 (70)         |

Data are given as number (percent). LAI: Left atrial isomerism, RAI: right atrial isomerism, SUA: single umbilical artery.
Table 2: Distribution of cardiovascular malformations among 27 fetuses with left atrial isomerism (LAI n=19) and right atrial isomerism (RAI n=8)

|                                   | LAI (n = 19) | RAI (n = 8) |
|-----------------------------------|-------------|-------------|
| **Systemic venous anomalies**     |             |             |
| Bilateral superior vena cava      | 6 (31)      | 3 (37)      |
| **Pulmonary venous anomalies**    |             |             |
| Total anomalous pulmonary venous connection | 1 (5)  | 4 (50)    |
| Partial anomalous pulmonary venous connection | 4 (21) | 2 (25)     |
| **Septation defects**             |             |             |
| Isolated ventricular septal defect | 1 (5)      | 0           |
| Common atrium                     | 1 (5)       | 2 (25)      |
| Complete atrio-ventricular septal defect | 3 (16) | 4 (50)     |
| **Anomalies of the ventricles**   |             |             |
| Hypoplastic left ventricle/single right ventricle | 3 (16)      | 2 (25)      |
| Hypoplastic right ventricle/single left ventricle | 2 (10)     | 1 (12)     |
| Single ventricle morphology       | 2 (10)      | 3 (37)      |
| Double chambered right ventricle  | 1 (5)       | 0           |
| **Ventriculo-arterial anomalies** |             |             |
| d-Transposition/malposition of the great arteries | 3 (16)      | 3 (37)      |
| Double-outlet right ventricle      | 3 (16)      | 2 (25)      |
| Double-outlet left ventricle       | 1 (5)       | 0           |
| Truncus arteriosus communis       | 0           | 1 (12)      |
| **Outflow tract obstructions**    |             |             |
| Pulmonary stenosis/atroesia        | 5 (26)      | 6 (75)      |
| Aortic stenosis/atresia           | 2 (10)      | 1 (12)      |
| Coarctation of the aorta          | 4 (21)      | 0           |
| **Heart rhythm**                  |             |             |
| Fetal sinus rhythm                | 14 (74)     | 8 (100)     |
| Fetal higher degree heart block   | 2 (10)      | 0           |
| Fetal sinus rhythm, postnatal sinus bradycardia | 2 (10)  | 1 (12)    |
| Fetal sinus rhythm, postnatal heart block | 1 (5) | 0         |

Data are given as number (percent). Some fetuses had more than one cardiac anomaly.
Table 3: Fetal MRI findings with postnatal confirmation in 27 fetuses with heterotaxy

|                  | LAI (n = 19) | RAI (n = 8) |
|------------------|--------------|-------------|
| **Situs**        |              |             |
| Anomaly          | 17/19 (89)   | 6 (75)      |
| Inversus         | 2/19 (11)    | 2 (25)      |
| **Stomach position** |        |             |
| - midline        | 0            | 1 (13)      |
| - right          | 18/19 (95)   | 5 (63)      |
| - left           | 1/19 (5)     | 2 (25)      |
| **Heart/Stomach position** |      |             |
| Ipsilateral      | 6/19 (32)    | 0           |
| Contralateral    | 13/19 (68)   | 8 (100)     |
| **Brain**        |              |             |
| Ventricular asymmetry | 1/19 (5)   | 1 (13)      |
| Dandy Walker Malformation | 1/19 (5) | 0           |
| Cerebellar hypoplasia | 0          | 1 (13)      |
| Hydrocephalus    | 0            | 1 (13)      |
| Stenosis of the aqueduct | 0          | 1 (13)      |
| Ventriculomegaly | 0            | 1 (13)      |
| **Craniofacial** |              |             |
| Hypeptelorism    | 1/19 (5)     | 0           |
| Cleft (lip) Palate | 1/19 (5)  | 0           |
| Retrognathia     | 0            | 1 (13)      |
| **Skeletal**     |              |             |
| Short curved femur | 1/19 (5)  | 0           |
| **Lungs**        |              |             |
| Suspected abnormal branching pattern | 6/19 (32) | 3 (38)      |
| Nutmeg pattern   | 1/19 (5)     | 2 (25)      |
| **Gastrointestinal tract** |     |             |
| Liver            |              |             |
| - Midline        | 17/19 (89)   | 6 (75)      |
| - left           | 2/19 (11)    | 2 (25)      |
| Abnormal liver configuration | 12/19 (63) | 0           |
| Gallbladder      |              |             |
| - midline/       | 4/19 (21)    | 3 (38)      |
| Condition                        | Number (Percent) |
|---------------------------------|------------------|
| Gallbladder aplasia             | 1/19 (5)         |
| Malrotation                     | 6/19 (32)        |
| Duodenal atresia                | 1/19 (5)         |
| **Spleen**                      |                  |
| Asplenia                        | 4/19 (21)        |
| Polysplenia                     | 2/19 (11)        |
| Spleen right sided              | 4/19 (21)        |
| **Urinary tract**               |                  |
| Duplex kidney (unilateral/bilateral) | 1/19 (5)    |
| Kidney agenesis unilateral      | 0                |
| Polycystic kidneys              | 1/19 (5)         |
| **Umbilical vein**              |                  |
| Abnormal course                 | 6/19 (32)        |
| Persistent right umbilical vein | 1/19 (5)         |

Data are given as number (percent). Some fetuses had more than one non-cardiac anomaly.