

## Case report

# Fetal diagnosis of left isomerism not associated with other cardiac malformations



Pedro Pires<sup>1</sup> , Sandra Silva Mattos<sup>2</sup> , Sônia Cristina Araújo Hinrichsen<sup>3</sup> ,  
Nathalie Jeanne Bravo-Valenzuela<sup>4</sup> , Gabriele Tonni<sup>5</sup> , Edward Araujo Júnior<sup>6</sup> 

<sup>1</sup>Department of Obstetrics and Gynaecology, University of Pernambuco (UPE), Recife-PE, Brazil

<sup>2</sup>Maternal Fetal Cardiac Unit, Real Português Hospital, Recife-PE, Brazil

<sup>3</sup>Sector of Obstetrics and Gynaecology, Pernambuco Maternal and Child Institute (IMIP), Recife-PE, Brazil

<sup>4</sup>Department of Paediatrics, Federal University of Rio de Janeiro (UFRJ), Rio de Janeiro-RJ, Brazil

<sup>5</sup>Department of Obstetrics and Neonatology, Istituto di Ricerca a Carattere Clinico Scientifico (IRCCS), AUSL di Reggio Emilia, Reggio Emilia, Italy

<sup>6</sup>Department of Obstetrics, Paulista School of Medicine-Federal University of São Paulo (EPM-UNIFESP), São Paulo-SP, Brazil

## Abstract

Left atrial isomerism is a rare and complex congenital condition characterized by bilateral left-sidedness of atria. It is frequently associated with the loss of normal asymmetry of thoracoabdominal organs (heterotaxy syndrome) and congenital heart defects. The authors studied a rare case of left atrial isomerism with bradycardia and no associated cardiac defects. The authors reviewed important features to improve this diagnosis by applying ultrasound. A healthy pregnant woman was referred for fetal echocardiography at 20 weeks of gestation due to persistent fetal bradycardia. The fetal echocardiogram confirmed arrhythmia (fetal heart rate ranging from 95 to 100 beats per minute) with a 1:1 atrioventricular (AV) relationship and a normal AV interval time. In addition, the fetal echocardiogram showed left-sided atrial morphology with no associated cardiac defects. Absence of the hepatic segment of the inferior vena cava with azygous continuation drew attention for the diagnosis of left isomerism. The fetal heart rate remained stable until term, and a male baby was born healthy. The diagnosis of left isomerism can be very difficult to achieve prenatally, especially in the absence of associated heart defects. An interrupted inferior vena cava with azygous and hemi-azygous continuation should draw attention to this diagnosis.

**Key words:** left isomerism, heterotaxy, bradycardia, ultrasound imaging, fetal echocardiography.

### Corresponding author:

Prof. Edward Araujo Júnior, PhD  
Rua Belchior de Azevedo, 156 apto. 111 Torre Vitoria  
São Paulo-SP, Brazil  
CEP 05089-030  
phone/fax: +55-11-37965944  
e-mail: [araujojred@terra.com.br](mailto:araujojred@terra.com.br)

## Introduction

Left atrial isomerism is a rare condition in which morphologically left atria are found on both sides of the body. It is frequently associated with visceral heterotaxy syndrome (situs ambiguous), which is characterized by an abnormal arrangement of thoracoabdominal organs, especially the lungs and

spleen. The classic example of left atrial and visceral isomerism is the polysplenia syndrome, which implies that the patients have 2 atria with left atrium morphology, bilobated lungs, centralized liver, and polysplenia [1, 2].

Absence of an intrahepatic segment of the inferior vena cava and atrioventricular septal defect associated with heart

block detected in the first or early second trimester are important features of left atrial isomerism [3-5]. Prenatal diagnosis of left isomerism is challenging, especially in cases where there are no associated heart defects. Antenatal diagnosis of left isomerism may alert to the risk of arrhythmias, including heart block (absence of sinus node located at the morphological right atrium), polysplenia (small hypofunctional multiple spleens), and gastrointestinal defects (gastrointestinal malrotations) [4, 6]. Therefore, since in left atrial isomerism the sinus node is could be absent or hypoplastic, this diagnosis should be considered in fetuses with persistent bradycardia.

In this report, we describe a rare case of left atrial isomerism with no associated cardiac defects, presenting with persistent bradycardia diagnosed at 20 weeks of gestation.

## Case report

A 38-year-old woman, gravida 3 para 1, was referred for fetal echocardiography due to persistent fetal bradycardia and bilateral choroid plexus cyst (CPCs) at routine second trimester ultrasound. The mother had no comorbidities, and there was no history of infectious diseases or consumption of any drugs during pregnancy. Her previous child was born healthy.

First trimester ultrasound screening for chromosomal abnormalities was performed at 13 weeks. The nasal bone was present, and nuchal translucency and Doppler of the ductus venosus were normal with no tricuspid regurgitation. However, fetal heart rate (FHR) was slow (120 bpm). Non-invasive prenatal testing (NIPT) was performed after signed informed consent and indicated low risk for fetal aneuploidies and 22q11.2 deletion syndrome. NIPT reported fetal sex as male (identification of Y chromosome in the cell-free DNA sequences in the maternal blood sample).

Fetal echocardiogram performed at 20 weeks of gestation confirmed bradycardia with FHR ranging from 95 to 100 bpm with no signs of heart failure. The atrial and ventricular heart rate were similar with a 1:1 atrioventricular (AV) relationship and a normal AV interval time. In addition, the fetal echocardiogram showed left-sided atrial morphology (bilateral sickle-shaped atrium) and absence of the hepatic segment of the

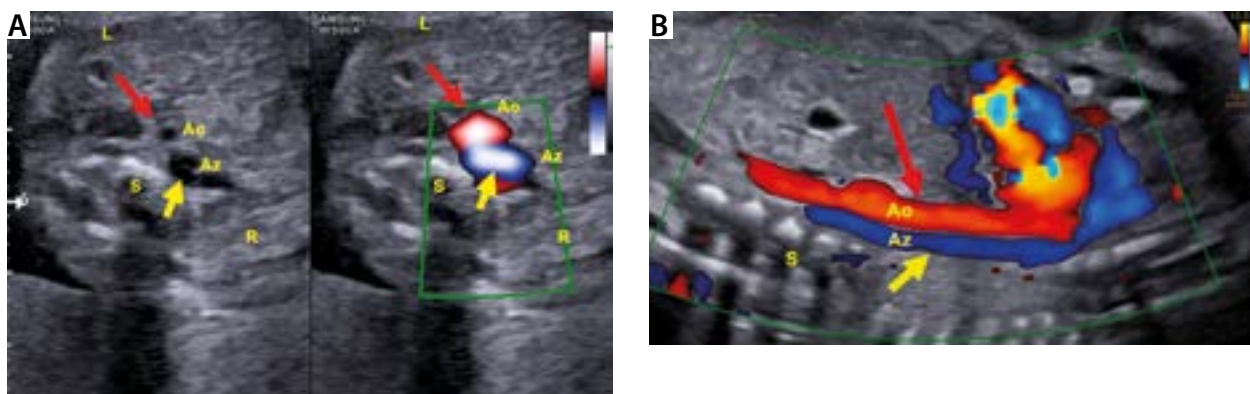
inferior vena cava (IVC) with azygous continuation (Figures 1 and 2A). No other associated cardiac defects were observed. Bilateral CPCs with no ventriculomegaly were the only associated extra-cardiac soft marker. The parents were warned about the possible risk of chromosomal abnormalities. After counselling, the patient refused an invasive karyotyping procedure. Autoimmune workup and screening for diabetes and thyroid function tests yielded normal results.

Serial ultrasound and fetal echocardiograms were performed on a monthly basis to monitor the finding of persistent bradycardia (FHR ranging from 100 to 90 bpm) and bilateral CPCs (Figure 2B). Between 24 and 38 weeks of gestation, FHR ranged from 100 to 90 bpm with no signs of hydrops. Fetal echocardiography at 33 weeks detected the presence of supraventricular extrasystoles. During follow-up scans, no fetal growth disorders were observed and the CPCs remained stable. The FHR remained stable until term with preserved fetal well-being, and a male baby weighing 3598 g with Apgar scores of 9 and 10 at 1 and 5 min, respectively, was born at 38 weeks by an elective caesarean section.

Postnatal echocardiography confirmed left atrial isomerism with no other associated cardiac anomalies (Figure 3A). The neonatal electrocardiogram (ECG) demonstrated normal rhythm with normal measurements of PR and QTc intervals, and low HR for age (65-95 bpm) (Figure 3B). Holter monitoring confirmed persistent bradycardia. Abdominal ultrasound was performed, and a normal spleen was detected with normal liver position. Intestinal malrotations were excluded from the study. The cardiac arrhythmia NGS (next-generation sequencing) multi-gene panel test indicated the absence of genetic arrhythmias. The newborn was stable and was discharged home after 5 days of detailed evaluation. Currently, the 1-year-old child is well. The child alternates between sinus and junctional rhythm with a heart rate in the lower range of normality, and no cardiac pacemaker has been required.

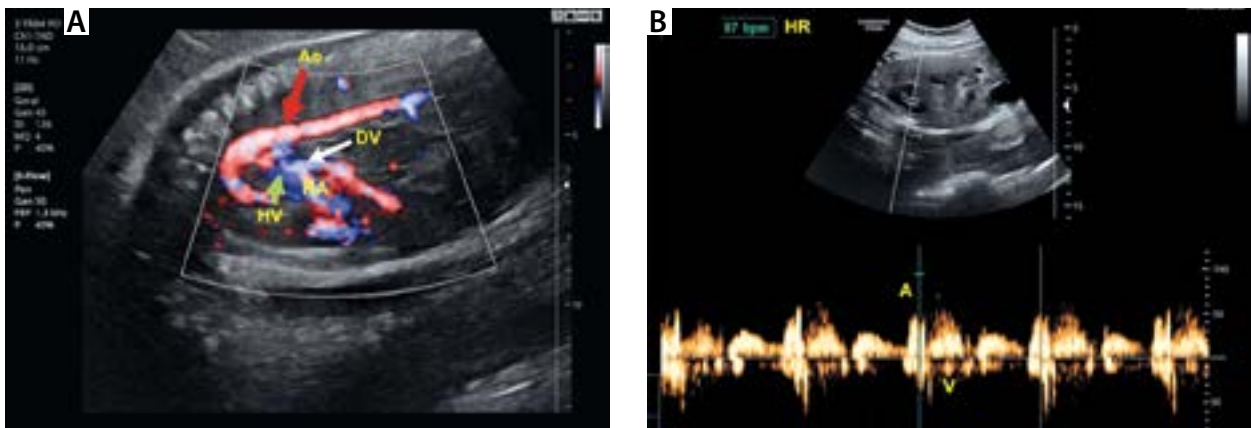
## Discussion

Left atrial isomerism is characterized by bilateral left morphological atria and is commonly associated with loss



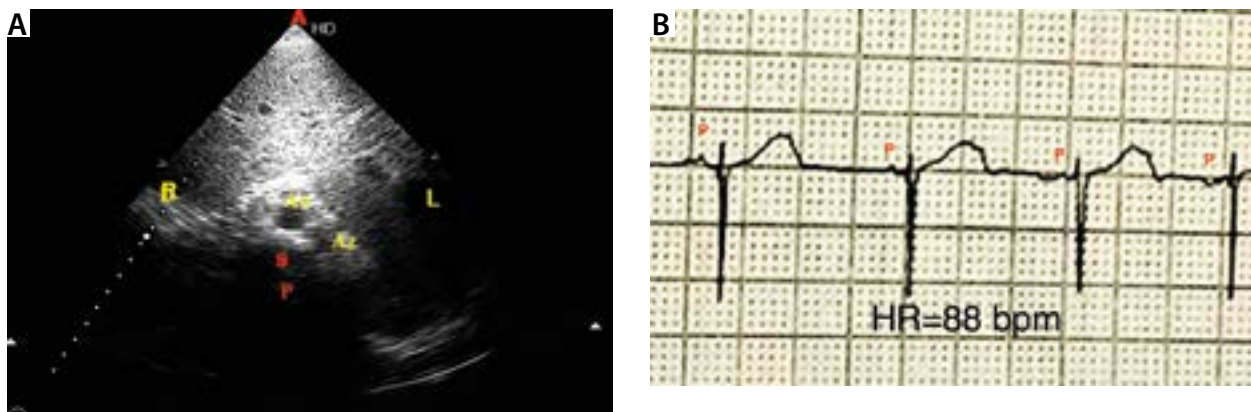
**Figure 1.** Fetal echocardiogram performed at 20 weeks of gestation showing absence of the intrahepatic portion of the inferior vena cava (IVC) with azygous continuation. (A) Upper-abdomen view with the “double vessel sign”: aorta (red colour Doppler and arrow) and dilated azygos (blue colour Doppler, yellow arrow) side-by-side in left isomerism. (B) Longitudinal view of the descending aorta with the dilated azygos and aorta (red arrow) side-by-side. The azygos vein (yellow arrow) crosses the diaphragm and drains into the superior vena cava

AO – descending aorta, Az – azygos vein, L – left, R – right, S – spine; red arrow – aorta, yellow arrow – dilated azygos vein.



**Figure 2.** (A) Longitudinal view of the descending aorta with the absence of intrahepatic IVC using colour Doppler. Note the aorta (red arrow) and absence of IVC mapping. The ductus venosus (white arrow) joins with the hepatic veins (green arrow) and drains into the right atrium. (B) Fetal echocardiography with spectral Doppler showing the persistent sinus bradycardia (fetal HR: 97 bpm)

IVC – inferior vena cava, Ao – descending aorta, DV – ductus venosus, HV – hepatic veins, RA – right atrium, HR – heart rate.



**Figure 3.** (A) Postnatal echocardiogram showing left isomerism. Note the subxiphoid short-axis view with the aorta in midline position and the dilated azygos, which is located posterior and on the left of the spine (arterial and venous vessels are side-by-side: 'double vessel sign'). (B) Postnatal electrocardiogram showing the sinus bradycardia

Ao – aorta, Az – azygos vein, L – left, R – right, s – spine, A – anterior, P – posterior, HR – heart rate.

of normal asymmetry of thoraco-abdominal organs, known as heterotaxic syndrome [2]. This abnormal symmetrical development of organs during embryological rotation is a rare condition that accounts for 1-10,000 to 40,000 live births [7]. Familial history of visceral malrotations and maternal diabetes has been strongly linked to isomerism [8]. In the current case, family history was negative, and the fetal karyotype and neonatal genetic screening for arrhythmias were normal.

Classically, atrial and visceral left isomerism encompasses bilateral morphological atria and lungs, spleen anomalies (most common: polysplenia), and other gastrointestinal malformations (stomach in an indeterminate position, midline liver, intestinal malrotation, and biliary tract anomalies) [1, 3, 6]. Conversely, in the present case, no other cardiac anomalies were observed. Concerning the cardiac spectrum, the most common anomalies described in left isomerism are the absence of hepatic follow-up of the IVC with drainage through the azygos (Az) or hemiazygos veins (approximately 80%), and complete heart block associated with structural cardiac defects, such as atrioventricular septal defect (AVSD) [5, 6]. This can be explained by the duplicated left-sided atria in this condition.

Therefore, structures related to the morphological right atrium (intrahepatic part of the inferior vena cava and sinus node) are absent or undeveloped in almost all cases of left isomerism. In this case report, we observed the absence of the hepatic part of the IVC with the azygos vein and persistent bradycardia with no heart block. Furthermore, left isomerism is commonly associated with structural cardiac defects such as atrioventricular septal defect and left or right ventricular outflow tract obstruction [4, 6]. However, in 3% to 18% of cases, there are no associated cardiac defects, such as in the case reported [7]. The main characteristics of left isomerism are described in Table 1.

The central point of diagnosis of left atrial isomerism is the anatomy of atria, defined by their appendages and shapes. The morphological left atrium contains the membrane of the foramen ovale, and its appendage is finger-like (narrow base). However, visualization of the left atrium appendage in the fetus is not easy to achieve. Accordingly, Berg et al. [5] reviewed 30 cases of prenatally diagnosed isomerism, focusing on the shape of atrial morphology instead of analysing the characteristics of atrial appendages. The authors concluded that this as-

**Table 1.** Main prenatal ultrasound diagnostic clusters of fetal left isomerism

Left isomerism
Bilateral morphological LAA (LAA with finger shaped, bilateral sickle-shaped atria, absence of/or underdeveloped SN)
Absence of the intrahepatic IVC, presence of Azy or Hazy*
Heart diseases: complete HB, AVSD, LV, or RV outflow tract obstruction*
Bilobed lungs*
Multiple spleens (polysplenia)*
Midline liver. Stomach in indeterminate position*
Intestinal malrotation*
Biliary tract anomalies*

\*not pathognomonic of left isomerism. AVSD – atrioventricular septal defect, Azy – azygos vein, HB – heart block, Hazy – hemiazygos vein, IVC – inferior vena cava, LA – left atrium, LAA – left atrial appendage, LV – left ventricle, RV – right ventricle.

assessment was sufficient to achieve a diagnosis in the majority of cases. In this study, bilateral sickle-shaped atrial morphology in the 4-chamber view was associated with left isomerism. In addition, interruption of the intrahepatic part of the IVC persisting as the azygos (or hemiazygos) vein is present in almost all cases of left isomerism. This is fundamental to the examination of the upper abdomen view of the fetus. In left isomerism, the aorta and the venous vessel are on the right (Az) or on the left (hemiazygos) of the fetal spine in the upper abdomen or in the 4-chamber views. Sheley et al. [9] described the dilated azygos or hemiazygos and the aorta side-by-side in left isomerism as the “double-vessel sign”. In the current study, it was a useful sign that enabled the suspicion of this diagnosis. Furthermore, the persistence of an azygos vein can be confirmed by colour Doppler in a longitudinal view of the descending aorta, as in the present case (Figure 3).

Congenital anomalies of the IVC are uncommon, accounting for up to 8.7% of the population, including anomalies of the left renal vein. The IVC develops at 6 to 8 weeks of gestation, and the complexity of its ontogeny can lead to a wide variety of anomalous venous return from the abdomen and lower limbs. The absence or agenesis of the intrahepatic IVC (‘interrupted IVC’) is classically associated with other congenital anomalies (atrial isomerism and heterotaxy syndromes) and is a risk factor for venous thrombosis of lower limbs, especially in young adults [10].

In conclusion, a prenatal ultrasound diagnosis of left isomerism with no other associated cardiac abnormalities, although associated with persistent bradycardia, was of critical importance in guiding an appropriate parental counselling concerning a potential favourable prognosis perinatally, and a thorough fetal echocardiogram could exclude complete heart block as well as an heterotaxy syndrome (cardiosplenic syndrome).

## Conflict of interest

The authors declare no conflict of interest.

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### Division of work:

**Pedro Pires** (ORCID: 0000-0002-1970-5321): research concept and design.

**Sandra Silva Mattos** (ORCID: 0000-0003-0896-3568): collection and/or assembly of data.

**Sônia Cristina Hinrichsen** (ORCID: 0000-0002-1927-1308): data analysis and interpretation.

**Nathalie Jeanne Bravo-Valenzuela** (ORCID: 0000-0003-1491-4877): writing the article.

**Gabriele Tonni** (ORCID: 0000-0002-2620-7486): critical revision of the article.

**Edward Araujo Júnior** (ORCID: 0000-0002-6145-2532): critical revision of the article.