

Heterotaxy Syndromes, A New Diagnostic Approach Highlighting The Value of D3-Dimensional Ultrasound and Doppler Angiography

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1. Abstract

1.1. Objective

To present a novel approach for the diagnosis of heterotaxy syndromes and highlight the value of 3D ultrasound and doppler angiography in their prenatal assessment.

1.2. Methods

A retrospective offline analysis of volume datasets of 6 fetuses diagnosed with heterotaxy syndromes by 3D ultrasound was conducted

1.3. Conclusion

Fetal parasagittal view is the key for diagnosis of heterotaxy syndromes, it is easy to obtain and interpret, offer a realistic anatomic image, needs no mental reconstruction of spatial relationships and is very beneficial mainly in detecting the situs and offers an added tool for the diagnosis of other anomalies and we recommended to obtain this view in all cases suspected of situs anomalies. Moreover, offline analysis of cardiovascular anomalies conferred significant diagnostic advantages over 2D ultrasound, we propose to use 3D ultrasound systematically in suspected cases of heterotaxy syndromes, and better understand and interpret fetal anatomy.

2. Introduction

Although the human body displays a bilaterally symmetrical exterior. Internally, however, there are striking asymmetries in the disposition and placement of internal organs. [1]. The latter phe-

nomenon being termed developmental chirality, left-right asymmetry, or laterality. [2].

At very early embryonic stages the embryo is bilaterally symmetrical with respect to the midline i.e. all major organ systems begin as midline structures with bilateral mirror-image symmetry with right-sidedness being the default state in all known species [3 ,4 , 5] On the other hand, left sidedness is induced by extensive cascades of asymmetric gene expression from the primitive node to the lateral plate mesoderm , which directs differentiation away from the default state on one side of the body and ultimately choreograph the correct positioning of organs along the L-R axis and are thereby characterized by sidedness (situs or handedness),[6 ,7, 8].

It has long been known that molecular left/right signals originate far before than the morphological asymmetry of visceral organs and is crucial to ensuring their proper position and function within the body [9].

The term situs solitus is used to describe the normal asymmetrical arrangement of the cardiac structures, as well as the remaining thoracoabdominal organs. [10].

In contrast, Situs inversus (SI) is a malformation in which the specification of LR asymmetry of the visceral organs is completely reversed. [11] and if associated with a right sided heart (dextrocardia) is referred to as situs inversus totalis [12]. Altered left-right asymmetry results in asymmetries in structure and placement of

organs occur stochastically, a condition termed heterotaxy, situs ambiguus, derived from the Greek heteros, “other” and taxis, meaning “arrangement” meaning other than the usual arrangement) allowing each organ to individually decide on its placement on the left or right side of the body [13, 14].

By convention, complete mirror image of normal (or situs inversus totalis) is not considered heterotaxy [10,15,16]. Historically, heterotaxy has been segregated based on splenic anatomy with patients being classified having asplenia or polysplenia [17]. This is now recognized as being less than ideal since splenic anatomy is not the best discriminator of the two subsets of heterotaxy [18, 19, 20]. In addition, a proportion of the patients of patients with heterotaxy have solitary spleens, moreover, the correlation between absence of the spleen, or multiple spleens, with findings in the other systems is far from perfect [21, 22]. This has led the somewhat nonsensical description of “asplenia with a solitary spleen [17].

Furthermore, the anatomic findings do not always correlate with function, as demonstrated by the fact that patients with either splenic anatomy, such as those with multiple spleens or even those with a solitary normally located spleen have been thought to have functional asplenia, increasing the risk of bacteremia and thrombosis [23, 24].

3. Materials and Methods

We present six cases diagnosed in our department in a period of 18 months. With these 6 cases and a review in the literature, we explore the definitions, controversies, diagnosis and characteristics of heterotaxy syndromes, and we study the role of 3D ultrasound, and we highlight the value of 3D and color doppler angiography in the diagnosis of ultrasound in the prenatal assessment of HS. We present a novel technique that facilitates the diagnosis of these syndromes.

Examinations were performed via Voluson 730 Pro (General Electric, Milwaukee, WI, USA) with a volumetric abdominal transducer (4–8 MHz). Stored cardiovascular volumes were prospectively and subsequently analyzed offline. Volume datasets were evaluated by an independent examiner who was not blinded to the previous diagnoses of cardiac anomalies per 2D ultrasound. Sonography images were then sent via the internet to a diagnosis reference center (Caen Teaching Hospital, France), and the initial prenatal diagnosis was confirmed or revised. A multidisciplinary team including a pediatric cardiologist, a neonatologist, and a pediatric cardiac surgeon provided comprehensive prenatal counseling to each expectant mother. Neonatal echocardiography was used to confirm the prenatal diagnosis in surviving fetuses.

4. Results

(Table 1) Summary clinical characteristics of and outcomes in the 6 patients

In our study, 5 patients had an interruption of the IVC, three of these patients had severe cardiac malformation and one of other

two patients had a persistent Left Superior Vena Cava (LPSVC), the other had a right umbilical vein, both had the stomach in the right side without congenital heart disease.

One of our patients had ultrasonographic signs for situs ambiguus with polysplenia (left isomerism) and the diagnosis was confirmed by fetopathological examination. (Case No. 1).

On the outcome of pregnancies, 5 had an unfavorable outcome 2 (pregnancy termination “hydrops foetalis” - 2 perinatal deaths and one IUFD). The fifth cases with no severe cardiac malformation delivered at 27+6 weeks’ gestation and child had psychomotor retardation which appears to be related to extreme prematurity. Our Case 6 is an example of this discrepancy between the atrial situs and visceral situs: Polysplenia, right atrial isomerism. (Figure 6 H, J). All karyotypes were normal, research 22q11 microdeletion was negative.

" Double vessel sign "was found in 3 cases with interruption of the IVC with azygos continuation -VCI. (Figure 4 A, 5C, D, 6 A, H). All our patients have benefited from the 3D ultrasound and color Doppler or Doppler energy; all volumes have been stored and processed offline. The 3D ultrasound has proven to be a valuable tool for the understanding of fetal anatomy heterotaxy syndromes especially fetal venous anatomy.

Using volumes, meticulous offline evaluation can be performed, enabling the operator to reconstruct fetal anatomy.

Parasagittal view of the abdomen and chest showing the heart and vessels connected to it was obtained in all cases. This sagittal view was obtained routinely in the vast majority of patients presenting to our unit to have experience and get accustomed to the anatomy of the heart and connecting vessels.

This view is obtained by orienting the scan plane along the true parasagittal plane of the fetal body immediately to the left of the midline, with slight adjustments to the probe's inclination the stomach can be seen in this view i.e., the stomach is to the left side. Grayscale facilitated the diagnosis of situs (Figure 1). Power Doppler imaging contributed primarily to prenatal diagnosis of vascular anomalies, and it was beneficial in detecting situs (Figure 2,3). Dextrocardia was confirmed by Doppler imaging following localization of the apex of the heart and axis of the left hepatic vein on opposite sides. From our experience, both left hepatic vein (LHV) and the apex of the heart are in the same side and point to the same direction i.e., downwards, the cardiac apex points to an opposite direction with respect to the spine i.e., away from the spine [25]. Any deviation from this relationship, using either Galss body mode or power Doppler or Doppler angiography would necessitate further evaluation (Figure: 2,3), for example, (Figure: 3 F, G) the cardiac apex and the LHV are in opposite directions and the cardiac apex points toward the spine, denoting an abnormal cardiac axis (Dextrocardia), thus using this parasagittal view, it is possible to diagnose dextrocardia using either Doppler angiogra-

phy with or without glass body mode.

We believe that this parasagittal view is easy to obtain and interpret, offer a realistic anatomic image, needs no mental reconstruction of spatial relationships and is very beneficial mainly in detecting the situs and offers an added tool for the diagnosis of other anomalies and we recommended to obtain this view, if not routinely, in all cases suspected of situs anomalies. This noble view confirms the presence of IVC, the presence IVC and aorta on both sides of the

vertebral column of as this view is obtainable only if this normal anatomical relationship is maintained, the presence of the stomach on the left side (F 2). In addition, it excludes dextrocardia (both left hepatic vein (LHV) and the apex of the heart are in the same side and point to the same direction i.e., downwards, the cardiac apex points to an opposite direction with respect to the spine i.e., away from the spine) and eliminates the presence of azygos vein.

Table 1 : Clinical characteristics of and outcomes for patients

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6
Heart position	Mesocardia	Levocardia	Levocardia	Levocardia	Dextrocardia	Dextrocardia
Stomach	Left	Right	Right	Right	Left	Right
IVC	Normal	Interruption	Interruption	Interruption	Interruption	Normal
Interruption of IVC with azygos continuation	No	Yes	Yes	Yes	Yes	No
Liver	Midline	Midline	Midline	Normal	Midline	Normal
Cardiac malformations	AVC-Single ventricle	LPSVC	AVC	AVC	Left isomerism	Right isomerism
	Right umbilical artery		Single ventricle	Interruption of the 4th aortic arch	Right umbilical vein	LPSVC
	Abnormal pulmonary venous return		Anomalies venous return	LPSVC	Total anomalous pulmonary venous return (TAPVR)	
			Hypoplasia of the ascendant aorta	Single atrium; right isomerism		Dextroposition of the aorta
			Direct venous return to atrium	Coarctation of the aorta	CAV	
Digestive anomalies	Intestinal malrotation		Midline liver	Midline liver	Midline liver	Polysplenia
			Polysplenia	Polysplenia	Polysplenia.	
				Intestinal malrotation	Intestinal malrotation	
			Appendix on the right side	Appendix on the right side	GB left side	
Caryotype	46 XX	46XY	46XY	46XX	46XX	46XY
Outcome	Pregnancy termination	Delivery at 27+6 weeks	Infant death at postnatal day 7	Pregnancy termination	Infant death at postnatal day12	IUFD

CAV : canal atrio-ventriculaire VCI : veine cave inférieure VDS : veine cave supérieure IUFD : Intrauterine fetal death. LPVC : Left persistent Superior vena cava UV : Umbilical vein

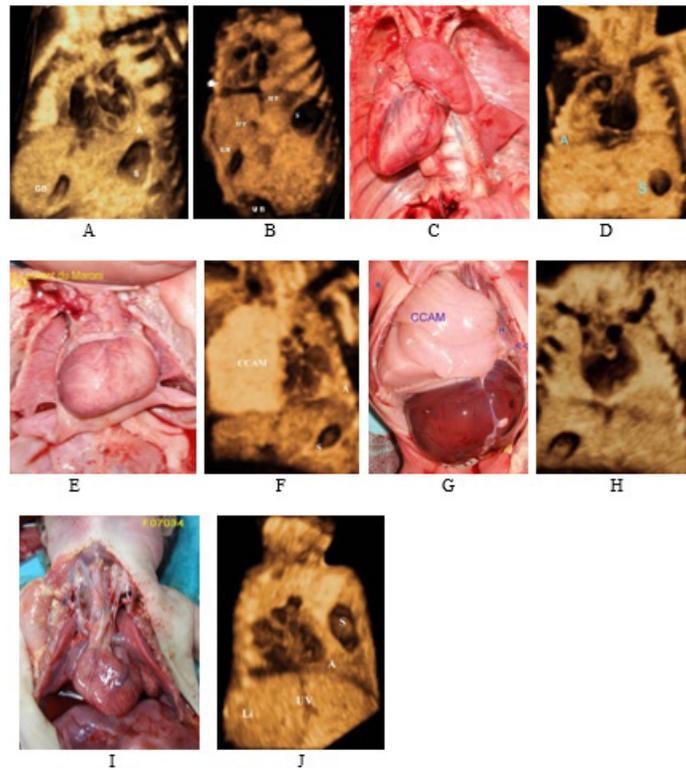


Figure 1: Situs determination.

(A) 3D volume of situs solitus. The heart and stomach are on the left; the gallbladder is on the right.

(B, C) Dextrocardia (echo-anatomic correlation). The heart is on the right thorax, the apex is on the right, the gall bladder is on the right, and the stomach is on the left.

(D, E) Dextrocardia (echo-anatomic correlation, the heart is on the normal position, the apex points to the right side).

(F, G) Levoposition of the heart to the left side due to (CCAM) Congenital cystic adenomatoid malformation – confirmed by fetopathological examination, cardiac apex is to the left (same side as stomach).

(H, I) Mesocardia (echo-anatomic correlation). The cardiac apex points to the midline.

(J) Dextroposition of the heart to the right side (left diaphragmatic hernia); cardiac apex is on the left (A).

Abbreviations: A: apex of the heart Stomach; VB: gallbladder; VCI: inferior vena cava. CCAM: Congenital cystic adenomatoid malformation . UV; umbilical vein. H; heart. UB; urinary bladder. Li: liver.

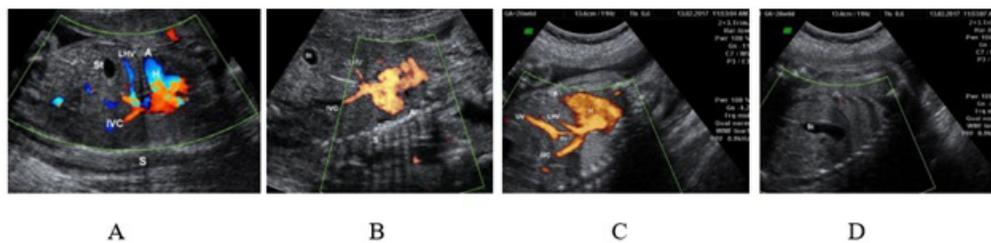


Figure 2

(A) Normal sagittal view to serve as a reference image for comparison with the subsequent drawings representing anomalies, apex of the heart (A) is on opposite direction to the spine (S). LHV, stomach (S) are to the same direction as A.

(B) sagittal view, dextrocardia, note that the, apex of the heart (A) is on the same direction to the spine (S). LHV, stomach (S) are to the same direction as A.

(C) Sagittal view obtained easily showing normal anatomy. (See text).

(D) by slight adjustments to the probe's inclination from the previous view the stomach is visible (latency 3 seconds).

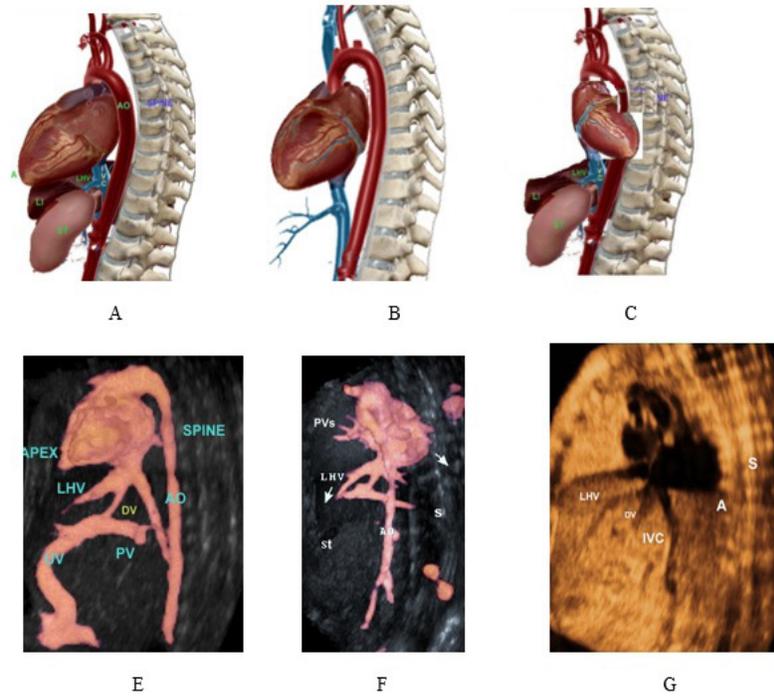


Figure 3

(A) A diagram showing abdominal vessels of the heart, the apex of the heart, and the left hepatic vein are on the same side, stomach (St) is on left side.
 (B) The apex of the heart and the left hepatic vein are on the same sides, cardiac apex points opposite to the spine, apex of the heart and LHV (arrows) are in the same direction,
 (C) Abdominal vessels of the heart that would be obtained if the heart is turned 180 c, i.e. dextrocardia notice that the apex of the heart, and the spine are on opposite sides (dextrocardia), stomach (St) is on left side. (This is not a real anatomic photo).
 (D) 3D power Doppler ultrasound showing normal abdominal vessels of the heart
 (E) 3D power Doppler ultrasound showing dextrocardia, the apex of the heart, and the spine are on opposite sides
 (F) Grey scale reconstruction showing dextrocardia, the apex of the heart, and the spine are on opposite sides

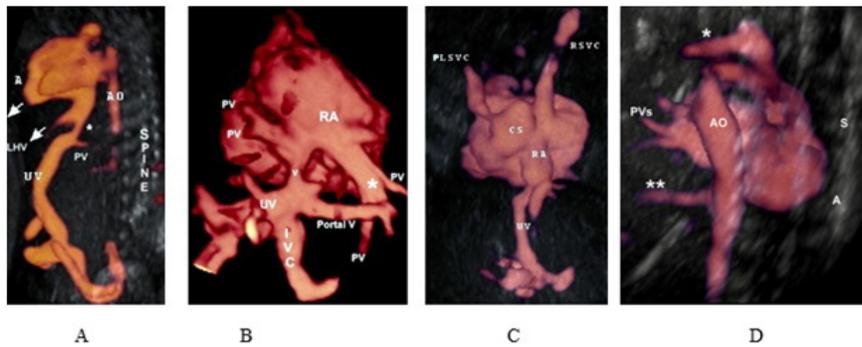


Figure 4: 3D power Doppler ultrasound.

(A) parasagittal view in a fetus with left isomerism and interrupted inferior vena cava with azygos continuity. The aorta (AO) and azygos vein (AZYG) are side by side, with different flow direction. The inferior vena cava is not identified (location marked by the “*” sign).
 (B) Doppler angiography showing total anomalous pulmonary venous connection with two left and two right pulmonary veins draining into a common vertical vein (V) which drains into infradiaphragmatic inferior vena cava.
 (C) Persistent left superior vena cava draining into the dilated coronary sinus and to the right atrium, the coronary sinus is aneurysmal
 (D) The apex of the heart is to the right, toward the spine, same case as Fig. 2 B (dextrocardia), an abnormal vessel along the left lateral margin of the aortic arch (*). This imaging finding is essentially diagnostic of either a left-sided superior vena cava (LP SVC) or an anomalous pulmonary vein, in this case (LPSVC). Note the presence of a confluent vessel (**) as a collecting vein behind the posterior atrium consistent with TAPVC, a common association with right isomerism.

Abbreviations: A: apex of the heart; AO: aorta; AZ: azygos vein; CS: coronary sinus; DV: ductus venosus; LHV: left hepatic vein; LSVC: left superior vena cava; PLSVC: persistent left superior vena cava; PV: portal vein; PVs: pulmonary veins; RA: right atrium; RSVC: right superior vena cava; SVC: superior, S : spine; St: stomach. T: thorax; UV: umbilical vein; IVC: inferior vena cava; TAPVC: total anomalous pulmonary venous return.

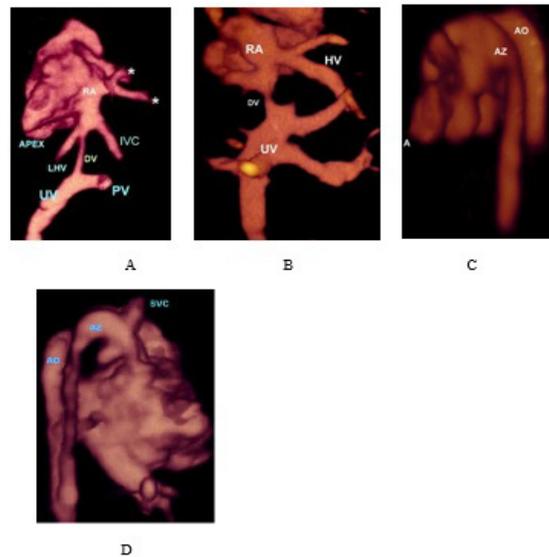


Figure 5

(A) Normal venous anatomy, the umbilical vein joins the IVC via ductus venosus and hepatic veins drain into the IVC, The IVC then enters the right atrium.

(B) Hepatic veins drain directly into the right atrium.

(C, D) Interrupted inferior vena cava with azygos continuation.

Abbreviations: A: apex of the heart; AO: aorta; AZ: azygos vein; CS: coronary sinus; DV: ductus venosus; LHV: left hepatic vein; LSVC: left superior vena cava; PLSVC: persistent left superior vena cava; PV: portal vein; PVs: pulmonary veins; RA: right atrium. TAPVC: total anomalous pulmonary venous return.

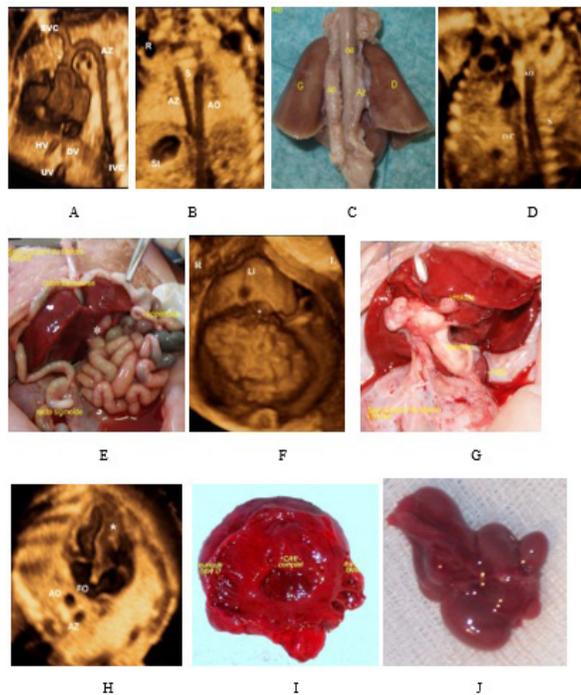


Figure 6

(A) Azygos continuation of the inferior vena cava and connection of the azygos vein to the superior vena cava (arrowhead), note the absence of IVC, hepatic veins drain directly into the right atrium.

(B) Coronal planes of the chest and abdomen in a fetus with left atrial isomerism and interrupted inferior vena cava showing the azygos vein (AzV) running parallel and posterior to the descending aorta (on both sides of the spine).

(C) Fetopathological examination showing azygos and aorta (case 1).

(D) The aorta and IVC are on the same side of the spine.

(E, F, G) Liver in the median position (echo-anatomic correlation), appendix and gall bladder (*) are on the left side, rectosigmoid is on the right side, note the presence of the all bladder and stomach on the same side G.

(H) Four chamber views showing a dilated azygos vein (Az) posterior to the descending aorta (Ao) "Double vessel sign."

(I, J) Fetopathological examination showing right atrial isomerism, note the presence of AVC, atrioventricular canal and Polysplenia. (case 4).

Abbreviations: A: apex of the heart; AO: aorta; AZ, azygos vein; DV: ductus venosus; LHV: left hepatic vein; LSVC, left superior vena cava; RA: right atrium. DV: Ductus venosus; UV: umbilical vein. St: stomach. S: spine; Li: liver. R: right; L:left. Arrowhead denotes superior vena cava, Asterisk denotes moderator band in E, gall bladder in F, G.

5. Discussion

The first 2 cases of congenital absence of the spleen in a normal heart, were observed in 1740 independently by Pohl and Jauch [26, 27]. Martin (1826) was the first to record a case of splenic agenesis associated with partial situs inversus and congenital cardiac malformation [27].

Biron Ivemark [18] in his landmark paper which included analyses of all cases in the published literature as well as his own 14 cases, published in *Acta Paediatrica* (1955), noted the association of spleen anomalies with some cardiac malformations, like atrioventricular canal defects and conotruncal anomalies, and his name is linked as "Ivemark's syndrome" with this constellation of anomalies.

Polhemus recognized that asplenia and polysplenia were associated with complex congenital heart disease [28].

Polysplenia was overlooked as a marker of HS until Moller and his colleagues in 1967 first fully documented the polysplenia syndrome, in their breakthrough paper, they correlated their own findings with the literature and showed the relation between polysplenia and bilateral left-sidedness syndrome. [29, 30].

Van Mierop et al. emphasized the association between asplenia and bilateral right sidedness. [31, 32].

Putschar and Mannion then indicated that "between the normal situs, which is asymmetrical, and the situs inversus, which is the asymmetrical mirror-image of normality, a symmetrical situs sometimes exists, exhibiting symmetrical rightness or leftness on both sides. [33].

Although terminology has evolved, this is probably the most eloquent description of isomerism, from the Greek "isos," meaning equal, and "meros," meaning part, in the historical literature.

Van Praagh regrouped these cardiac malformations into 2 groups, those that are more frequent with asplenia (right isomerism) and those that are more associated polysplenia (left isomerism). [34].

Van Mierop [31] described the concept of the left and right atrial isomerism that was not universally accepted. Van Praagh et al. [34] have pointed out that the concept of bilateral or two right atria and bilateral or two left atria is anatomically unrealistic because atrial chambers as a whole are not entirely isomeric

These assertions, however, were based on erroneous postulation that the atrial chambers as a whole were isomeric in these syndromes. [33]. So, this concept of atrial isomerism was refined to the right and left atrial appendage isomerism by McCartney and Anderson. [35]. Of note, true isomerism of the atrial appendages being distinguished according to the extent of the pectinate muscles relative to the atrioventricular junction has been demonstrated previously and confirmed by a recent study [36, 31].

Therefore, the concept of isomerism of the right and left atrial appendages are therefore more accurate as the atrial appendage is

known to be the most consistent feature of the atrial chambers. [37].

Distinguished authorities continue to deny the presence of such isomerism and argue in favor of description based on uncertainty, describing the arrangements in terms of "situs ambiguus. Van Praagh et al consider that the concept of atrial isomerism to be anatomically and conceptually inaccurate because partial mirror imaging does not meet the requirements for diagnosing isomerism [38].

Echocardiography remains the first line for the regular assessment of imaging congenital malformations of the heart. [39], therefore, it follows that it is also important to differentiate between right and left isomerism by echocardiographic interrogation of the appendages. [40]. Recently, a body of evidence has emerged indicating atrial appendages could be distinguished echocardiographically. [41, 42]. Nevertheless, in day-to-day clinical practice, assessment of atrial appendage morphology is difficult and time-consuming and not universally appreciated and not always indicative of bronchopulmonary or abdominal situs. [35]. Moreover, discordance between bronchopulmonary branching, atrial appendage arrangement, and splenic status was identified in >20% patients with heterotaxy, furthermore, atrial appendage morphology or the status of the spleen could not be classified in 15% of patients and 3.5% respectively. [43].

The main area of disagreement encompasses the concept of isomerism of the right and left atrial appendages and feasibility of the imaging techniques in assessment of atrial appendage morphology. A widely adopted school of teaching emphasizes that all cases of heterotaxy could be classified according to the morphology of the atrial appendages, which are the most constant feature in the setting of isomerism, these authors support the utility and feasibility of noninvasive imaging in living patients of distinguishing atrial appendages, thus about 80 % of cases would fall into this classification, right and left isomerism, exceptions do exist in the backscene, thus, classification of isomerism on this basis can allow for anticipation of, surveillance for, and counselling with regard to associated finding, thus they favour the concept of isomerism and in case of disharmony, each case can readily be described by paying specific attention to each series of organs. [17,20,31, 35,37,44]. Other authors deny or highlight the challenges in assigning atrial appendages as left or right, despite excellent in vivo imaging, pointing out that the diagnosis of heterotaxy based on these classifications is bleached in about 20 % of cases. [38, 43, 45]. Thus, the major point of disagreement on how to deal with these cases that break the rule, there is two important divergent positions. For these authors these exceptions to the syndromes dominate the scene, they point out that the presence of these exceptions do not guarantee the status of a specific atrial status, for them, each system of organs should be analyzed and described in independent fashion, then it is possible for clinicians to exclude any suggestion

of ambiguity and to provide accurate descriptions of the overall arrangement of the bodily organs

6. Conclusion

Assignment of laterality can be inherently difficult and affected by specific clinical biases which may result in some confusion of terminology and definition. Heterotaxy syndromes are diagnostically challenging due to complex spectrum of findings. Offline analysis of situs anomalies conferred significant diagnostic advantages over 2D ultrasound. We believe that parasagittal view demonstrating the heart and the abdominal vessels is easy to obtain and interpret, offer a realistic anatomic image, needs no mental reconstruction of spatial relationships and is extremely beneficial in detecting the situs and offers an added tool for the diagnosis of heterotaxy syndromes and other anomalies and we recommended to obtain this view routinely, especially in all cases suspected of situs anomalies. Being invaluable for the prenatal diagnosis of heterotaxy syndromes, we recommend using 3D ultrasound systematically in suspected cases of heterotaxy syndromes, to better understand and interpret fetal anatomy

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