Original Article

Right Atrial Isomerism – Preponderance in Asian Fetuses. Using the Stomach-distance ratio as a Possible Diagnostic Tool for Prediction of Right Atrial Isomerism

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Abstract

Introduction: To present the characteristics and spectrum of associated anomalies in right- and left-sided isomerism in our local population and to assess the possibility of using stomach-distance ratio (SDR) of less than 0.34 as a diagnostic tool to predict right atrial isomerism. Materials and Methods: This was a retrospective study of fetuses in our department over a period of 8 years with postnatally confirmed prenatal diagnosis of atrial isomerism. Results: In 22 cases, atrial isomerism was confirmed by post-mortem or postnatal echocardiography. Eighteen (81.8%) fetuses had right isomerism. Their main abnormal ultrasound findings were pulmonary stenosis or atresia (n = 9), atrioventricular septal defect (n = 10), right-sided stomach (n = 9), transposition of great arteries (n = 6), dextrocardia (n = 8), single ventricle (n = 4), juxtaposition of inferior vena cava and descending aorta (n = 5), ventricular septal defect (n = 2), interrupted inferior vena cava with azygous drainage (n = 2) and double outlet right ventricle (n = 3). Four (18.2%) fetuses had left isomerism. Their abnormal ultrasound findings were dextrocardia (n = 3), right-sided stomach (n = 3), atrioventricular septal defect (n = 2), double outlet ventricle (n = 2), ventricular septal defect (n = 1), pulmonary stenosis (n = 2) and interrupted inferior vena cava with azygous drainage (n = 1). 66.7% (12/18) of cases with right isomerism had SDR of less than 0.34 compared to 0% (0/4) of the cases with left isomerism ($P = 0.02$). Conclusion: Our study suggests an Asian predilection towards right isomerism compared to Western populations. We postulate that there may be racial differences in the expression of these 2 forms of isomerism. The ultrasound findings of complex heart disease and abnormal arrangement of great vessels in abdominal cavity, though important, are varied and non-specific evidence for either form of fetal atrial isomerism. There is a possibility of using the SDR <0.34 (representing stomach proximity to the fetal spine) as a possible diagnostic tool to predict right-sided atrial isomerism.

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Key words: Azygous vein, Cardiac defects, Dextrocardia, Heterotaxy syndrome, Stomach localisation, Stomach near spine, Visceral heterotaxy

Introduction

Atrial isomerism is a disorder of lateralisation characterised by symmetric development of normally asymmetric cardiac atria and organ systems. The synonyms for these defects include heterotaxy syndrome, polysplenic/asplenic syndrome, right/left isomerism, isomerism of the atrial appendages and situs ambiguous. Left isomerism and polysplenia syndrome refer to bilateral left-sidedness while right isomerism and asplenia syndrome refer to bilateral right-sidedness.

The pathology of atrial isomerism has been previously described by many authors.[1-11] Asplenia and polysplenia are the 2 most common associations of atrial isomerism. Typical features of right isomerism apart from bilateral morphological right atrial appendages and absent spleen, are cardiac defects especially atrioventricular septal defect, pulmonary stenosis/atresia and total anomalous pulmonary drainage, dextrocardia, bilateral trilobed lungs, visceral heterotaxy and same sidedness of descending aorta and inferior vena cava (IVC) in abdominal cavity. Typical features of left isomerism include bilateral morphological

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left atrial appendages, cardiac defects especially atrioventricular septal defect and complete heart block, dextrocardia, bilateral bilobed lungs, multiple splenules and interrupted IVC with azygous drainage.

The findings of right atrial isomerism in antenatal ultrasound include dextrocardia, complex heart disease such as complete atrioventricular septal defect, pulmonary stenosis/atresia and total abnormal pulmonary vein return, right-sided stomach, central gallbladder, juxtaposition of IVC and descending aorta. The findings of left atrial isomerism include dextrocardia, complete atrioventricular septal defect, complete heart block, right-side stomach, interrupted IVC with azygous or hemiazygous vein drainage.[11-20] The incidence of left atrial isomerism seems higher than the right during fetal stage in the English literature.[11,12-16,18,19,21]

The ultrasound features are not always typical to distinguish isomerism from non-isomerism cases especially those with right isomerism. Sometimes juxtaposition of IVC and descending aorta is not so easy to recognise. Stomach localisation can also be on either side of the abdominal cavity in both atrial isomerism.

The aim of this study was to present our experience in the prenatal diagnosis of anomalies of atrial isomerism and to assess a novel measurement method – the stomach-distance ratio (SDR) – in the prediction of right atrial isomerism.

Materials and Methods

This was a retrospective study carried out from 1998 to 2005. All the cases were from the Antenatal Diagnostic Centre (ADC) of KK Women's and Children's Hospital which is a tertiary maternal care hospital in Singapore. There were a total of 116,859 unselected patients scanned in the Antenatal Diagnostic Centre over the 8-year period. As this review conforms to the standards established by the NHMRC for ethical quality review,[22] ethics approval was not sought.

Evaluation of the fetal heart including cardiac position and apex direction, 4-chamber and outflow tract views, 3-vessel view with colour Doppler and aorto-pulmonary ratio, is part of the routine screening scan in our hospital. Once an abnormal finding is detected by our sonographers, the patient is re-scanned by a senior sonographer or doctor. The ultrasound machines used for this repeat high-risk scan are Acuson XP128/10, Acuson Aspen, Aloka 5500 and GE730 Expert.

A prenatal diagnosis of atrial isomerism was suspected by dextrocardia, complex cardiac anomalies such as atrioventricular septal defect and pulmonary stenosis, malpositioned stomach, juxtaposition of IVC and descending aorta, and interrupted IVC with azygous vein drainage. Juxtaposition of IVC and descending aorta was defined as both vessels occurring on the same side of the fetal body, with the IVC always anterior to the aorta. Interrupted IVC was identified on the basis of its sonographic absence and 2 closed vessels with different blood flow directions on the same side of the spine at the level just below the diaphragm. The final diagnosis was confirmed by post-mortem after termination of pregnancy (TOP), fetal or neonatal death, or postnatal echocardiography in cases of live births.

A novel method of measurement – the SDR – was used to assess stomach localisation by measuring the ratio of the distance of stomach bubble to spine (SS distance) and abdominal diameter on abdominal circumference (AC) level (Fig. 1). The following formula was used to calculate the ratio:

$$\frac{\textbf{Distance between centre of stomach and centre of spine}}{\textbf{0.5 (transverse diameter of AC + anterior-posterior diameter of AC)*}}$$

* This is the mean of the transverse and anterior-posterior diameters of the abdominal circumference.

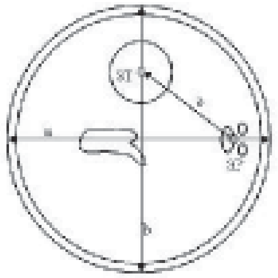
Ultrasound pictures of 100 normal fetuses were retrieved from the database, and stomach-spine (SS) distances as well as abdominal circumferences were measured and plotted against each other in a scatter graph (Fig. 2). A best-fit line was plotted with intercept at y = 0 and x = 0. The equation of this line was y = 0.4215x (correlation coefficient, R^2 = 0.6874). Mean SDR was taken to be 0.42 with a standard deviation of 0.04. Using 2 standard deviations (-0.08), a lower cut-off of 0.34 was used. A normally positioned stomach was defined as one with SDR of 0.34 or more (Fig. 3). The stomach was considered to be near the spine if SDR was less than 0.34 (Figs. 4-6).

The control group consisted of 28 cases of normal fetuses, isolated situs inversus, dextrocardia with other fetal abnormalities but not atrial isomerism, atrioventricular septal defect (AVSD), transposition of great arteries (TGA), double outlet right ventricle (DORV) and Fallot's tetralogy.

Results

There were 38 cases of suspected isomerism on prenatal echocardiography. Three resulting live births did not show atrial isomerism on postnatal examination. Nine cases had no post-mortem after TOP or fetal or neonatal death. Four cases were lost to follow-up. There were a total of 18 right-sided isomerism and 4 left-sided isomerism cases confirmed by post-mortem or postnatal echocardiography. These 22 cases were included in this study.

Table 1 shows the prenatal sonographic findings and postnatal diagnosis of the 18 right-sided atrial isomerism cases. All the cases had complex cardiac malformations



ST, stomach; SP, spine; a, anterior-posterior diameter of abdominal circumference; b, transverse diameter of abdominal circumference; c, distance between the centre of stomach and the centre of spine.

Fig. 1. Pictorial diagram for measurement of stomach-distance ratio (SDR)

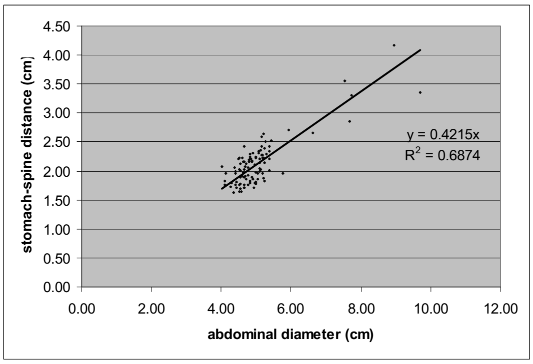
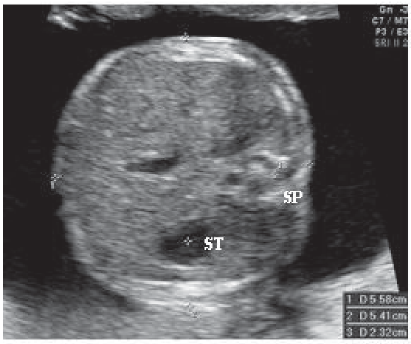
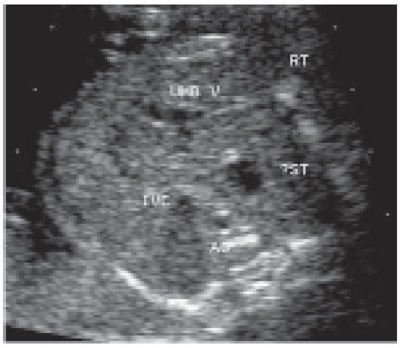


Fig. 2. Stomach-spine distance plotted against abdominal diameter stomach-spine distance (cm)



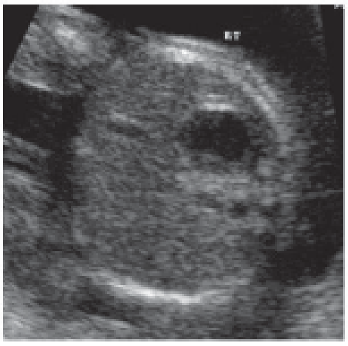
ST, stomach; SP, spine

Fig. 3. Normally positioned stomach, SDR 0.42



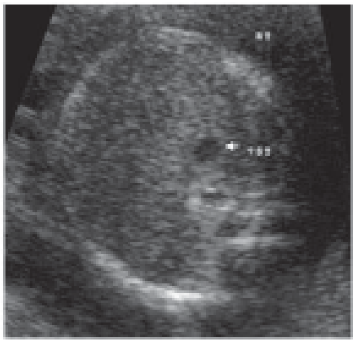
IVC, inferior vena cava; ?ST, stomach; AO, aorta; UMB V, umbilical vein; RT, right

Fig. 4. Stomach on right side of the abdomen and near spine, SDR 0.27 (case 2).



RT, right

Fig. 5. Stomach on right side of the abdomen and near spine, SDR 0.29 (case 5).



?ST, stomach; RT, right

Fig. 6. Stomach on the right side of the abdomen and near the spine, SDR 0.3. Postnatally the spleen was normal in size. This is a case of right isomerism (case 6).

including pulmonary stenosis or atresia (n = 9), atrioventricular septal defect (n = 10), transposition of great arteries (n = 6), single ventricle (n = 4), ventricular septal defect (n = 2) and double outlet right ventricle (n = 3). Dextrocardia was seen in 8 out of 18 cases. There were 9 cases with a right-sided stomach. Juxtaposition of IVC and descending aorta was found in 5 cases. Two cases had interrupted IVC with azygous drainage (cases 3 & 9). TOP was performed in 15 out of 18 cases. There were 3 livebirths. Karyotyping performed in 13 cases were all normal.

Table 2 shows the prenatal sonographic findings and postnatal diagnosis of the 4 left-sided atrial isomerism cases. All of them had complex heart abnormalities including atrioventricular septal defect (n = 2), ventricular septal defect (n = 1), pulmonary stenosis (n = 2) and double outlet ventricle (n = 2). Dextrocardia was noted in 3 of the 4 cases.

Table 1. Prenatal Sonography and Postnatal Findings in 18 Cases with Right Atrial Isomerism

Case	Gestation (weeks)	Prenatal sonographic findings	Post-mortem/Postnatal findings	Outcome of pregnancy
1	26+	dextrocardia, single V, large AO, right stomach, diaphragmatic hernia	dextrocardia, single A and V, absent DA, diaphragmatic hernia, bilateral trilobed lungs, asplenia, central liver	TOP, 46XY
2	20+	AVSD, DORV, PA (reverse flow), large AO, right stomach, left IVC and AO	AVSD, TGA, PA, TAPVR, left SVC, bilateral trilobed lungs, midline stomach, asplenia, malrotation of gut	TOP
3	20+	Single V, single OT, right stomach, absent IVC, dilated azygos vein	ASD, VSD, TGA, TAPVR, bilateral trilobed lungs, right stomach and pancreas, asplenia, absent IVC, dilated azygos vein, central liver	TOP, 46XY
4	20+	Dextrocardia, single V & OT, right IVC & AO	Dextrocardia, AVSD, truncus arteriosus, bilateral trilobed lungs, asplenia, malrotation of gut, fused adrenals	TOP, 46XX
5	20	AVSD, TGA, PS, PV not seen, right stomach, central GB	AVSD, PS, absent DA, TAPVR, bilateral trilobed lungs, asplenia, central liver & GB	TOP
6	19+	AVSD, DORV, right stomach, left IVC & AO	levocardia, AVSD, hypoplastic RV, TGA, PA, TAPVR, bilateral trilobed lungs, right stomach, malrotation of gut	TOP, 46XX
7	18+	Dextrocardia, AVSD, TGA, PS, absent stomach, left IVC	Both RA, ASD, VSD, IVC to LA, bilateral trilobed lungs, small stomach, asplenia, malrotation of gut	TOP, 46XX
8	21+	Dextrocardia, AVSD, TGA, PS, right stomach, left IVC	Dextrocardia, ASD, hypoplastic LV, TGA, PA, bilateral trilobed lungs, right stomach, right spleen, central liver, malrotation of gut	TOP, 46XY
9	20+	Dextrocardia, single V, TGA, absent IVC, dilated azygos vein	Dextrocardia, both RA, AVSD, absent DA, TAPVR, left SVC, bilateral 4-lobed lungs, small stomach, interrupted IVC, dilated azygos vein, asplenia, central liver	TOP, 46XX
10	23+	AVSD, single OT	ASD, single V & OT, PA, TAPVR, bilateral trilobed lungs, asplenia, central liver, left GB	TOP, 46XY
11	20+	Dextrocardia, AVSD, DORV, right stomach	Both RA, single V, CoA, TAPVR, left SVC, bilateral trilobed lungs, right stomach, right spleen, left liver	TOP, 46XY
12	19+	AVSD, single OT, PS	AVSD, PS, left SVC,bilateral trilobed lungs, hypoplastic spleen	TOP
13	20+	Hypoplastic LV, VSD, single OT, ventriculomegaly	Both RA, hypoplastic LV, VSD, DIRV, TGA, PS, TAPVR, left SVC, left IVC, bilateral trilobed lungs, asplenia, central liver, left GB	TOP, 46XY
14	22+	AVSD, TGA, PS, right stomach	Both RA, AVSD, TGA, PS, TAPVR, bilateral 4-lobed lungs, right stomach, asplenia, central liver, left GB, fused adrenals	TOP
15	21	Dextrocardia, VSD, DORV, PS, IVC to LA	Dextrocardia, AVSD, left SVC, bilateral trilobed lungs	TOP, 46XY
16	23+	Dextrocardia, AVSD, single A, DORV, PS, right IVC & AO, left GB	Dextrocardia, single A & V, PS, large AO, left SVC, APVR, asplenia, central liver	LB
17	33+	Central heart, hypoplastic LV, DORV, TAPVR, right stomach, left IVC & AO, central GB	Right isomerism, single V, hypoplastic LV, MA, DORV, PS, ASD, left SVC and IVC, right AO, normal spleen, right GB	LB, 46XX
18	33+	Single V, TGA, PS, diaphragmatic hernia, absent IVC	Right isomerism, DIRV, AVSD, TGA, PS, TAPVR, esophageal hernia, right stomach, asplenia	LB, 46XX

A: atrium; AO, aorta; ASD: atrial septal defect; AVSD: atrioventricular septal defect; DA: ductus arteriosus; DIRV: double inlet ventricle; DORV: double outlet right ventricle; GB: gall bladder; IVC: inferior vena cava; LA: left atrium; LV: left ventricle; MA: mitral atresia; OT: outflow tract; PA: pulmonary atresia; PS: pulmonary stenosis; PV: pulmonary vein; RA: right atrium; SVC: superior vena cava; TAPVR: total anomalous pulmonary venous return; TGA: transposition of great arteriosus; TOP, termination of pregnancy; V: ventricle; VSD: ventricular septal defect; LB: livebirth

There were 3 cases with a right-sided stomach. Interrupted IVC with azygous drainage was noted in only 1 case. TOP was performed in 3 cases. The remaining 1 died on the second postnatal day.

The stomach appeared near the spine in 12 of 18 right isomerism cases (SDR = 0.22-0.33). In 5 cases, the stomach appeared in the normal position (SDR = 0.34-0.53). There was 1 case (case 7) with absent stomach bubble. Post-mortem showed that the spleen was present in 1 case (case

Table 2. Prenatal Sonography and Postnatal Findings in 4 Cases with Left Atrial Isomerism

Case	Gestation (weeks)	Prenatal sonographic findings	Post-mortem/postnatal findings	Outcome of pregnancy
1	20+	Dextrocardia, AVSD, DOV, PS, right stomach, left IVC & AO, absent GB	Both LA appendages, single A, VSD, DORV, right stomach, polysplenia	TOP
2	21+	Dextrocardia, AS, multiple hemivertebra	Both LA appendages, enlarged RV, small AO, left SVC, bilateral bilobed lungs, hemivertebra	TOP
3	19+	Dextrocardia, VSD, DORV, PS, right stomach, horseshoe kidney, missing vertebra and ribs	Left isomerism, dextrocardia, ASD, DOLV, PS, right stomach, right spleen, central liver, fused kidney and adrenal	TOP
4	22+	AVSD, AS, right stomach, absent IVC, dilated azygos vein	AVSD, situs inversus, dilated azygos vein, left liver and GB	LB

A: atrium; AO: aorta; ASD: atrial septal defect; AVSD: atrioventricular septal defect; DOV: double outlet ventricle; DOLV: double outlet left ventricle; GB: gall bladder; IVC: inferior vena cava; LV: left ventricle; MA: mitral atresia; OT: outflow tract; PA: pulmonary atresia; PS: pulmonary stenosis; PV: pulmonary vein; RA: right atrium; RV: right ventricle, SVC: superior vena cava; TAPVR: total anomalous pulmonary venous return; TGA: transposition of great arteriosus; TOP: termination of pregnancy; V: ventricle; VSD: ventricular septal defect; LB: livebirth

Table 3. Stomach Localisation in Atrial Isomerism

		Antenatal finding			PM / postnatal finding	
Case	Isomerism	Stomach position	Stomach-distance ratio (SDR)	Stomach near spine	PM/LB	Spleen
1	Right	Right	0.23	Yes	PM	Asplenia
2	Right	Right	0.27	Yes	PM	Asplenia
3	Right	Right	0.29	Yes	PM	Asplenia
4	Right	Left	0.33	Yes	PM	Asplenia
5	Right	Right	0.29	Yes	PM	Asplenia
6	Right	Right	0.30	Yes	PM	Right
7	Right	Absent	–		PM	Asplenia
8	Right	Right	0.36	No	PM	Right
9	Right	Left	0.30	Yes	PM	Asplenia
10	Right	Left	0.30	Yes	PM	Asplenia
11	Right	Right	0.34	No	PM	Right
12	Right	Left	0.41	No	PM	Hypoplastic
13	Right	Left	0.27	Yes	PM	Asplenia
14	Right	Right	0.31	Yes	PM	Asplenia
15	Right	Left	0.47	No	PM	Left
16	Right	Left	0.28	Yes	LB	Asplenia
17	Right	Right	0.53	No	LB	Right
18	Right	Left	0.22	Yes	LB	Asplenia
19	Left	Right	0.44	No	PM	Polysplenia
20	Left	Left	0.46	No	PM	Left
21	Left	Right	0.41	No	PM	Right
22	Left	Right	0.46	No	LB	Right

LB: livebirth; PM: post-mortem

Table 4. Stomach Localisation in Non-atrial Isomerism

Case	Diagnosis	Stomach position	Stomach-distance ratio (SDR)	Stomach near spine
1	Normal	Left	0.38	No
2	Normal	Left	0.44	No
3	Normal	Left	0.40	No
4	Normal	Left	0.41	No
5	Normal	Left	0.49	No
6	Normal	Left	0.41	No
7	Normal	Left	0.44	No
8	Normal	Left	0.46	No
9	Normal	Left	0.44	No
10	Normal	Left	0.37	No
11	Isolated situs inversus	Right	0.32	Yes
12	Isolated situs inversus	Right	0.45	No
13	Isolated situs inversus	Right	0.40	No
14	Dextrocardia	Left	0.37	No
15	Dextrocardia	Left	0.37	No
16	Dextrocardia	Left	0.39	No
17	AVSD	Left	0.39	No
18	AVSD	Left	0.35	No
19	AVSD	Left	0.42	No
20	TGA or DORV	Left	0.44	No
21	TGA or DORV	Left	0.48	No
22	TGA or DORV	Left	0.38	No
23	TGA or DORV	Left	0.41	No
24	TGA or DORV	Left	0.36	No
25	TGA or DORV	Left	0.35	No
26	Fallot's tetralogy	Left	0.38	No
27	Fallot's tetralogy	Left	0.35	No
28	Fallot's tetralogy	Left	0.45	No

AVSD: atrioventricular septal defect; DORV: double outlet right ventricle; TGA: transposition of great arteriosus

6) with the stomach near the spine (Fig. 5) and absent in 1 case (case 4) with a normally positioned stomach. In contrast, the stomach appeared in the normal position in all 4 left isomerism cases (SDR = 0.41-0.46) (Table 3). This difference was statistically significant (*P* = 0.02).

In the control group, only 1 case had the stomach near the spine (SDR = 0.32). This was a case of isolated situs inversus. The SDR were above 0.33 in the remaining 27 control cases (SDR = 0.35-0.49) (Table 4).

Discussion

Our study concurs with previously reported findings showing the various associated cardiac anomalies in atrial isomerism.[11-13,15,16,18,19,21] Atrioventricular septal defect is most common in both right and left isomerism while single ventricle, pulmonary stenosis or atresia, transposition of great arteriosus and juxtaposition of IVC and descending aorta are more common in right isomerism. However, interrupted IVC with azygous drainage was seen only in 1 of 4 cases of left isomerism and in 2 of the 18 cases of right isomerism. This is different from the literature where most authors found this to be a very common finding in left isomerism.[12-14,17-21,23,24] Berg et al[20] had earlier reported 31 left isomerism cases, all of which had interrupted IVC with azygous drainage. Heart block is another common finding in left isomerism but there were none in our study group.

Table 5. Occurrence of Left Isomerism in Various Studies

Study	Country	Percentage of left isomerism
Ho SY, et al (1991)[19]	UK	67% (20/30)
Poon CK, et al (1996)[19]	USA	95% (36/38)
Sharland G, et al (1999)[11]	UK	68% (82/121)
Atkinson DE, et al (1998)[16]	USA	39% (5/13)
Lin JH, et al (2002)[18]	Taiwan	14% (4/29)
Berg C, et al (2003)[13]	USA	69% (22/32)
Berg C, et al (2005)[20]	USA	72% (18/25)
Taketazu M, et al (2006)[15]	Japan	68% (18/25)
Yan YL, et al (2007) – present study	Singapore	22% (4/18)

Previous studies have shown a preponderance of left atrial isomerism compared to right [11,13-15,16,18-20] (Table 5). An exception is 1 Taiwanese study by Lin et al[18] in which their ratio of left-to-right isomerism occurrence was only 14%. Our study shows a similar preponderance of right isomerism, with a ratio of 22% (4:18). Both Singapore and Taiwan are in Asia and its people are of similar race. We postulate that there may be a racial predisposition to the type of isomerism.

In comparison with the control group, the stomach bubble was found to be close to the spine more commonly in right isomerism (*P* = 0.001). This is regardless of whether the stomach was left- or right-sided. This could be due to both right-sided livers and an absent spleen in right isomerism which pushes the stomach to the centre of the body. This feature was not detected in left isomerism and can be explained by the fact that the position of the stomach is unlikely to be affected by the small left-sided liver and polysplenia.

This study has also attempted to use a novel method of predicting right atrial isomerism. There was a statistically significant difference between right isomerism and the control group when an SDR cut-off of 0.34 was used (*P*

<0.001). There was, however, no statistically significant difference between left isomerism and the control group. There was also a statistical difference in using the above cut-off to differentiate left and right atrial isomerism (P = 0.02). We acknowledge that the numbers in this study are small, and we hope that this study will generate interest among investigators to validate this formula in future studies.

Various authors[25,26] have shown that cardiac malformations are more complex in right isomerism than in left, and despite advancement in modern surgical techniques, outcome is also far worse in right isomerism, with one author[25] suggesting that right isomerism of the heart be considered as one of the worst forms of congenital cardiac disease. A recent study by Yildirim et al[27] found that overall mortality rate for those with right isomerism was greater than 50%, compared to only 23% for those with left isomerism. They also recommended vaccination against pneumococcal infections for patients with right isomerism, as these are more likely to have an absence of the spleen.

Prenatal diagnosis early in gestation will allow for appropriate counselling for families faced with such a difficult diagnosis, and planning for prompt treatment after birth. Practitioners need to identify and treat non-cardiac anomalies like non-functioning or absent spleen and malrotation of the gut.

Conclusion

There is geographical heterogeneity in the presentation of isomerism. Right isomerism is exceptionally common in our local population. We postulate that there may be a racial predisposition to the presentation of the type of isomerism.

The ultrasound findings of complex heart disease and abnormal arrangement of great vessels in the abdominal cavity are important evidences for the diagnosis of atrial isomerism. Besides these, we have attempted to predict right-sided atrial isomerism using a novel method – the SDR. There is also a possibility of using this method for differentiating left- and right-sided isomerism with a cut-off of 0.34, but more studies with larger numbers should be done to validate this finding.

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