Clinical Features, Management, and Outcome of Children With Fetal and Postnatal Diagnoses of Isomerism Syndromes

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Background—Isomerism is associated with a complex spectrum of anomalies. There is paucity of data on prenatally detected cases.

Methods and Results—Between January 1990 and February 2004, 83 of 166 cases (50%) had a prenatal diagnosis of left isomerism (LAI; 52 of 97) or right isomerism (RAI; 31 of 69) at our institution. The spectrum of anomalies, management, and outcomes was compared for fetal and postnatal diagnoses of LAI and RAI. RAI more often than LAI was associated with AV septal defect (90% versus 56%; \( P < 0.0001 \)), pulmonary outflow obstruction (91% versus 37%; \( P < 0.0001 \)), total anomalous pulmonary venous drainage (73% versus 13%; \( P < 0.0001 \)), and abnormal VA connections (68% versus 33%; \( P < 0.0001 \)), whereas inferior vena cava interruption (3% versus 93%; \( P < 0.0001 \)), complete AV block (0% versus 13%; \( P = 0.004 \)), aortic obstruction (6% versus 33%; \( P < 0.0001 \)), and extracardiac defects (5% versus 25%; \( P = 0.006 \)) were less common. The spectrum of lesions was comparable for fetal and postnatal cases, except for AV block (fetal, 25%; postnatal, 0%; \( P = 0.0002 \)) and AV septal defect (fetal, 67%; postnatal, 42%; \( P = 0.023 \)) in LAI. Fetal demise was due mainly to pregnancy termination (LAI, 42%; RAI, 45%). Survival of actively managed children with LAI was significantly better than for those with RAI (\( P < 0.0001 \)) but did not differ with regard to fetal versus postnatal diagnosis. Most LAI cases required no intervention or underwent successful biventricular cardiac surgery (65%), unlike RAI cases (13%; \( P < 0.0001 \)).

Conclusions—Prenatal diagnosis did not affect overall survival despite facilitated care. The prognosis of RAI was worse compared with LAI because of more complex associated cardiac defects and the inability to perform successful surgical procedures. (Circulation. 2005;112:2454-2461.)

Key Words: echocardiography • fetus • heart defects, congenital • isomerism • outcome

The concept of atrial isomerism refers to the similar appearance of the atrial appendages and the disposition of the pectinate muscles to the AV orifice that permits a distinction to be made between bilateral appendages of right or left morphology.1,2 Left isomerism (LAI) or right isomerism (RAI) is diagnosed in 0.4% to 2% of all infants with congenital heart disease but account for at least 6% of the cardiac defects detected in utero.3–6 There is a wide spectrum among the 2 forms.7–13 Although it is well established that these anomalies contribute to important morbidity and mortality, it is unknown whether the spectrum of disease and outcome differs among cases with fetal versus postnatal diagnosis of LAI or RAI. Although antenatal diagnosis often represents a more severe spectrum of cardiovascular disease,14 fetal diagnosis may permit more options, including termination of pregnancy or more tailored neonatal treatment.15–20

We sought to assess the impact of prenatal diagnosis on management and outcome in a large cohort of cases with a diagnosis of either LAI or RAI.

Methods

The outcomes of all cases with a diagnosis of isomerism at the Hospital for Sick Children between January 1990 and February 2004 were reviewed. Our facility provides the only fetal and pediatric cardiac tertiary care for a population of >7 million, with ~80,000 live births per year. Referrals from other centers for surgical interventions but not ongoing care were excluded (n=12). The Institutional Research Ethics Board approved this study.

Medical charts and imaging data were studied to determine the spectrum of anomalies. Collected information included patient age at diagnosis, pregnancy and postnatal management, morbidity, and outcome. If the outcome was unsure, the referring and/or treating physician was approached to ascertain complete follow-up data.

The diagnosis of cardiovascular anomalies was based on ultrasound findings using established diagnostic criteria.5,11 When applicable, diagnostic accuracy was further substantiated by autopsy.
Left Isomerism (n=97)

Referral Patterns and Perinatal Management

Fetal Series

Fifty-two pregnancies were referred between 14 and 37 gestational weeks (median 20 weeks), mainly for suspected cardiac defects (n=42), a noncardiac fetal anomaly (n=2), or a previous child with congenital heart disease (n=5). Of 37 pregnancies diagnosed before 24 weeks’ gestation, 20 (54%) were terminated, including 9 with complete fetal AV block. Two fetuses with AV block died spontaneously. Of 30 live-born cases, all but 2 were referred as neonates (range, 0 to 154 days of life).

Postnatal Series

Forty-five cases had a postnatal diagnosis of LAI at a median of 41 days (range, 0 to 361 days) of life. Only 18 (35%) were referred as neonates, presenting with cyanosis (n=15), cardiovascular collapse (n=1), or biliary atresia (n=2). Cases referred later presented with cyanosis (n=8), heart failure (n=8), and/or extracardiac symptoms (n=8).

Clinical Features

Table 1 compares the anomalies among fetal and postnatal LAI. The diagnosis was confirmed in 71 cases and was probable in 22 fetal and postnatal cases, except for AV septal defects and complete AV block. Fourteen cases (6 fetal, 8 postnatal) had no clinically relevant cardiac abnormalities. Extracardiac lesions included biliary atresia (n=5), intestinal malrotation (n=5), duodenal atresia (n=1), tracheoesophageal fistula (n=1), cleft palate (n=1), limb anomalies (n=2), and central nervous system anomalies (n=2).

Postnatal Management and Outcome

Figures 2 and 3 detail the management and survival of all cases with LAI.

Fetal Series

Of the 30 live-born cases, 22 children were alive at a median follow-up of 5.4 years (range, 0.2 to 12 years). This includes 11 of 13 (85%) after biventricular repair and 6 of 7 (86%) after single-ventricle palliation, including 3 with a completed Fontan operation. Arrhythmias after birth included complete AV block after surgery (n=1), sick sinus syndrome (n=2), and supraventricular (n=2) or ventricular (n=2) tachycardia.

Postnatal Series

Of 45 cases, 28 children are alive at a median follow-up of 7.5 years (range, 0.3 to 15.1 years). This includes 10 of 19 (53%) with biventricular repair and 7 of 8 (88%) with palliative cardiac surgery, including 4 with a Fontan operation. Noncardiac surgery included portojejunostomy (n=3) or liver transplant (n=2) for biliary atresia, Ladd’s procedure for intestinal malrotation (n=2), tracheoesophageal fistula repair (n=1), ventriculo-peritoneal shunt for hydrocephaalus with encephalocele (n=1), and cleft lip repair (n=1). One child each developed sick sinus syndrome and ventricular tachycardia.
Factors Associated With Mortality of Actively Managed Cases With LAI
Kaplan-Meier survival for actively managed cases (n=64) was 95% (95% CI, 90 to 100) at 1 month, 86% (95% CI, 77 to 94) at 1 year, 75% (95% CI, 63 to 87) at 5 years, and 73% (95% CI, 60 to 85) at 10 years after birth (Figure 3). Those with a fetal diagnosis had surgery earlier than postnatal cases, with no difference in outcome (Figures 3 and 4). Aortic obstruction and dextrocardia were independent risk factors for increased mortality (Tables 2 and 3).

Right Isomerism (n=69)

Referral Patterns and Prenatal Management

Fetal Series
Thirty-one pregnancies were referred between 19 and 39 gestational weeks (median, 20 weeks) because of suspected fetal cardiac anomalies (n=30) or a previous sibling with RAI (n=1). Of 22 diagnosed before 24 weeks' gestation, 14 (64%) were terminated. Of 17 live-born cases, 16 were referred at 1 day (range, 0 to 57 days) of age.

Postnatal Series
Thirty-eight cases had a postnatal diagnosis of RAI at 2 (0-48) days of life, with all but 4 being referred as neonates. The main findings at presentation included cyanosis and heart murmur (n=35), cardiac failure (n=2), and duodenal atresia (n=1).

Clinical Features
Table 1 compares the findings among fetal and postnatal RAI. The diagnosis was confirmed in 46 cases and probable in 18 fetal and 5 neonatal cases. One child each had duodenal atresia with chromosome 11p+ translocation and hiatus hernia. Supraventricular tachycardia occurred in 3 postnatal cases.

Postnatal Management and Outcome
Figures 3 and 5 illustrate the outcome and management of RAI cases.
Fetal Series
Of 17 live-born cases, 10 (59%) had surgery. Only 2 remain alive after modified Glenn and Fontan procedures at a median follow-up of 5.3 years (range, 2.3 to 8.4 years).

Postnatal Series
Cardiac surgery was performed in 32 of 38 children (84%). One child with balanced circulation has thus far required no intervention. Eleven cases are currently alive at a median follow-up of 6.4 years (range, 1 to 11.6 years), including 3 after a modified Glenn procedure, 6 after a Fontan operation, and 1 after a heart transplant.

Factors Associated With Mortality of Actively Managed Cases With RAI
Kaplan-Meier estimates for survival of actively managed cases (n=43) was 83% (95% CI, 71 to 94) at 1 month, 42% (95% CI, 27 to 57) at 1 year, and 29% (95% CI, 14 to 44) at 5 years after birth (Figure 3). The cohort of prenatally diagnosed live-born cases with RAI had a significantly worse outcome compared with those with a postnatal diagnosis because of a higher rate of nonintervention and failed biventricular repair in the fetal series (Figure 5 and Table 2). If active treatment was chosen, fetal RAI cases underwent...
surgery significantly earlier than those with a postnatal diagnosis. Patient age at initial surgery was an independent risk factor for mortality. In contrast, the finding of an unbalanced AV septal defect was associated with a reduced risk of death (Tables 2 and 3).

**Discussion**

To the best of our knowledge, this is the first study to compare the clinical features, management, and outcomes of fetuses and children with LAI and RAI.

**Prenatal Detection**

The Hospital for Sick Children Fetal Cardiac Program has undertaken substantial efforts to improve fetal cardiac screening by obstetricians, most importantly by introducing an educational outreach program. As a result, the prenatal detection rate of isomerism syndromes has nearly doubled during the course of the last decade, with >60% of affected cases currently diagnosed in utero in the greater Toronto area.

Currently, most cardiovascular anomalies can be delineated with considerable accuracy by the experienced fetal echocardiographer, a conclusion that is reinforced by our study findings. In contrast, important extracardiac anomalies such as biliary atresia may not be detectable even by targeted fetal ultrasound scanning. This limitation in detecting extracardiac anomalies should be emphasized during prenatal counseling. Major extracardiac issues requiring treatment were particularly common with LAI, with at least 25% of live births in this study being affected. An even higher incidence of extracardiac lesions has been reported from autopsy series, although the significance of many of these findings may be debatable.

Unlike cardiac and extracardiac lesions, the incidence of known chromosomal disorders is low in isomerism syndromes; therefore, an amniocentesis is probably not justified. Still, we did observe siblings with RAI and a child with a translocation anomaly on chromosome 11. Similar examples of familial occurrences of RAI suggesting an increased recurrence risk for some parents have been reported.

**Management**

Most fetal cases were diagnosed before 24 gestational weeks, which represents an acceptable age limit for pregnancy termination in Ontario. This timely fetal anomaly diagnosis resulted in equally high pregnancy termination rates among LAI (54%) and RAI (64%) compared with the largest previously published fetal series on these lesions. This finding may be surprising because in general LAI has a far better long-term prognosis than RAI. However, a significant proportion (25%) of our fetal LAI cases presented with heart

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**Figure 4.** Competing-risks analyses for the event of surgery or death without surgery for the cohorts of actively managed live-born cases with fetal and postnatal diagnosis of LAI or RAI. Comparisons were made for the event of surgery among RAI and LAI (P=0.0012) and among fetal and postnatal diagnoses (P=0.0028). Competing-risks analysis is used when a patient is simultaneously at risk for ≥2 time-related events—in this case, surgery or death without surgery. The methodology uses parametric modeling of the multivariable hazard function for each event and combines the hazards to give the actual proportion of subjects at any given time point who have experienced that event. Thus, although the proportion of patients who have not experienced an event decreases, the proportion of patients who experience each event increases in a manner reflective of the time-related risk for that particular event. At any given time point, the proportion of patients in each of the 3 states sums to 100%. The graphs depict the multivariable prediction for fetal vs postnatal diagnosis of LAI vs RAI. Confidence limits are not provided for the sake of clarity.
in association with other malformations. Because this combination of findings usually leads to spontaneous fetal or neonatal demise,\textsuperscript{32,33} most parents preferred not to pursue active management. In the absence of heart block, spontaneous intrauterine demise has been a rare event for both forms of isomerism.\textsuperscript{6,22,23}

Apart from complete AV block in LAI, the incidence of cardiovascular features at a fetal or postnatal diagnosis of either LAI or RAI was largely comparable. However, as a result of pregnancy termination and stillbirths, the cohort of live-born cases with either a fetal or postnatal diagnosis of LAI or RAI ended up with a comparable pattern of cardiac pathology at birth (data not shown). In our patient population, LAI was predominant both before (63%) and after (54%) delivery, with live-birth incidences for LAI of 0.67 and for RAI of 0.49 per 10 000 live births. This is comparable to published population-based data that isomerism occurs in 1 to 1.44 in each 10 000 live births.\textsuperscript{4,28,34}

One might expect that the timing of pathology detection also influences postnatal care. Indeed, children with a fetal diagnosis of LAI or RAI were referred and operated on at a significantly younger age compared with postnatal patients. Still, 41% of all parents preferred nonintervention over active postnatal care if RAI was discovered in utero, which is in firm contrast to the 13% nonintervention rate after a postnatal diagnosis ($P < 0.033$). Unfortunately, the retrospective design of the present study does not allow us to examine parental decision making in more detail. Nevertheless, the detection of severe cardiac anomalies only after birth often requires parents to immediately choose between proactive care and nonintervention, whereas a prenatal diagnosis offers more time for an informed decision.

**Outcomes**

Our results emphasize that the outcome of actively managed children with isomerism syndromes is not influenced by fetal or postnatal diagnosis but differs between LAI and RAI. Complex anomalies of pulmonary venous connections and intracardiac anatomy make long-term palliation or repair difficult despite the ongoing development of promising surgical techniques addressing these abnormalities.\textsuperscript{15,19,35–38} In LAI, single-ventricle repair, coarctation of the aorta, heart block, and gastrointestinal anomalies have been reported to unfavorably influence surgical outcome and attrition.\textsuperscript{5} In our

| Table 2: Univariate Estimates (Cox Proportional-Hazards Modeling) of Hazard Ratio for Time-Related Death of the Cohort of Actively Managed Cases With LAI or RAI |
|-----------------|--------|-----------------|--------|
| Variables       | LAI    | RAI             |
| Demographic     |        |                 |
| Male gender     | 0.78   | 0.45            |
| Fetal diagnosis | 0.29   | 0.32            |
| Cardiac         |        |                 |
| Anomalous PV connection | 0.4   | 0.19            |
| Obstructed pulmonary veins | 0.15 | 0.19            |
| AV septal defect | 0.34 | 0.19            |
| Unbalanced AV septal defect | 0.48 | 0.03            |
| Single ventricle | 0.19 | 0.19            |
| Discordant VA connections | 0.7  | 0.7             |
| Double-outlet right ventricle | 0.87 | 0.2             |
| Aortic obstruction | 0.009 | 0.006          |
| Pulmonary artery obstruction | 0.19 | 0.2             |
| Dextrocardia or mesocardia | 0.02 | 0.29            |
| Intervention    |        |                 |
| No surgery      | 0.37   | 0.43            |
| Biventricular repair | 0.12 | 0.066           |
| Single-ventricle palliation | 0.35 | 0.43            |
| Age at first surgery* | 0.3  | 0.001           |

HR indicates hazard ratio; PV, pulmonary veins.

*Logarithmic estimates.

| Table 3: Independent Factors Associated With Time-Related Mortality |
|----------------|----------------|
| Relative HR (95% CI) | P |
| LAI             |        |
| Aortic obstruction | 3.21 | 0.03 |
| Dextrocardia     | 2.77   | 0.04 |
| RAI             |        |
| Unbalanced AV septal defect | 0.27 | 0.005 |
| Age at surgery <1 mo of age | 3.9 | 0.002 |

HR indicates hazard ratio.
study, aortic stenosis and an abnormal cardiac position were the only independent hazard risks for actively treated children. Interestingly, after exclusion of "normal" hearts in the analysis, mortality tended to be lower with palliative Kawashima and Fontan operations (13%) compared with the larger number of patients who underwent biventricular surgical repair attempts (35%). Similar favorable results with the Fontan operation have been reported. Similar favorable results with the Fontan operation have been reported.37 Still, compared with a previous 28-year institutional review,5 the 5-year survival of all children with LAI has only slightly improved, from 59% to 64% in this study.

Survival of the overwhelming majority of individuals with RAI requires extensive palliative surgery or heart transplantation rather than biventricular repair.12,15,16,20,39–41 In fact, in our contemporary study experience, there is not a single patient with a biventricular repair for RAI who is alive. RAI-associated independent risk factors for decreased time to death were reported previously and included patient age at initial surgery,12,42 small or obstructed pulmonary veins,12,43–45 the presence43 or absence12 of pulmonary outflow tract obstruction, major AV valve anomalies,12 and a functional single ventricle.44 In our study, 18 of 42 operated RAI patients underwent repair of total anomalous pulmonary venous connections, with relief of obstructed veins in half of them, more recently with sutureless surgical techniques.19,38 Neither the presence of totally anomalous pulmonary venous connection with and without obstruction nor its repair emerged as a definite risk factor for death. In contrast, patient age at initial surgery was an independent risk factor for death, whereas survival was improved in the presence of an unbalanced AV septal defect. The latter finding, although surprising, may be explained by the collectively poor outcome after biventricular repair attempts, whereas some functional univentricular hearts were more effectively palliated. Yet, in our experience, even palliative surgery is associated with a poor 5-year survival rate of only 35%. This is far worse than one would expect on the basis of a reported 15% to 20% mortality risk in the small subset of cases with completion of their Fontan connection.12,37 Unfortunately, most candidates for single-ventricle palliation will never proceed to a Fontan operation for various RAI-related reasons.12 Comparison with a previous 26-year institutional review for the years between 1970 and 1996 showed that the overall 5-year survival with RAI has decreased from 35% to 22% since 1990. When parents opted for an active management, 5-year survival improved slightly to 29%. Although a direct comparison with previously published data may be problematic, the findings illustrate the persistently somber perspectives associated with RAI.

Study Limitations

Several limitations need to be addressed. Outcome data based on the numerous clinical and anatomical variables would require significantly larger numbers of affected fetuses and children with this entity. Extracardiac anomalies were reported as they related to morbidity and mortality. Detailed descriptions of the full anomaly spectrum have been provided previously.5,9,12 We also did not try to include cases with solely a postmortem diagnosis of isomerism because they may be considered a failure of prenatal and postnatal diagnoses. Based on the study of Gilljam et al,5 a postmortem diagnosis was made in 9% of LAI cases between 1970 and 1998. Because their study included an extended era when cross-sectional echocardiography was not available, we assumed that the number of missed cases would be substantially lower nowadays.

In summary, our study demonstrates a significant impact of prenatal isomerism diagnosis on live-birth rates and neonatal management although the overall outcome is not changed for the better. Postnatal survival among those with RAI is reduced compared with cases with LAI as a result of more complex associated cardiac defects and an inability to perform successful surgical palliation or correction. None of the survivors with RAI underwent a successful biventricular
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