Spectrum of congenital heart defects and extracardiac malformations associated with chromosomal abnormalities: results of a seven year necropsy study

C Tennstedt, R Chaoui, H Körner, M Dietel

Abstract

Objective—To analyse the spectrum of congenital heart malformations, the frequency of extracardiac malformations, and the proportion of chromosome aberrations among fetuses sent for necropsy.

Material—Necropsies were performed on 815 fetuses—448 induced abortions (55%), 220 spontaneous abortions (27%), and 147 stillbirths (18%)—during a seven year period (1991–97) in the department of pathology of the Charité Medical Centre in Berlin. A congenital heart defect was identified in 129 cases (16%). For all 129 fetuses, karyotyping and an ultrasound examination had been performed.

Results—Congenital heart defects were present in 22% of induced abortions (99 cases), 9% of spontaneous abortions (20 cases), and 7% of stillbirths (10 cases). The heart malformations were classified into 13 categories. A fetus with more than one defect was included only in the category of the most serious defect. The malformations in order of frequency were: ventricular septal defect (VSD) (28%), atrioventricular septal defect (AVSD) (16%), hypoplastic left heart (HLH) (16%), double outlet right ventricle (DORV) (12%), coarctation of the aorta (CoA) (6%), transposition of the great arteries (TGA) (4%), aortic valve stenosis (AoVS) (4%), tetralogy of Fallot (TOF) (3%), truncus arteriosus communis (TAC) (3%), pulmonary valve stenosis/pulmonary valve atresia (PaVS/PaVA) (3%), tricuspid atresia (TA) (3%), single ventricle (SV) (1.5%), and atrial septal defect (ASD) (0.5%). The most common congenital heart defects were VSD, AVSD, HLH, and DORV, which made up 72% of all the cases. In 11 cases the heart defect was isolated (no other cardiovascular or extracardiac malformations present), 85 cases (66%) were associated with additional cardiac malformations, 85 cases (66%) were associated with extracardiac malformations, and chromosome anomalies were detected in 43 cases (33%).

Conclusions—Fetal congenital heart malformations are common. These defects are often associated with other cardiovascular and extracardiac malformations, as well as with chromosome anomalies. Complex heart defects such as AVSD, HLH, and DORV are frequent in fetuses, as they often lead to spontaneous abortion or stillbirth or, after prenatal diagnosis, to deliberate termination of pregnancy.

Keywords: congenital heart defects; extracardiac malformations; chromosomal abnormalities; necropsy examination

Congenital heart defects, which make up about 1% of human malformations, are among the most common malformations in fetuses. Because of their poor prognosis they contribute significantly to infant mortality. Various epidemiological studies have shown that in liveborn infants the incidence of congenital heart defects is between four and eight per 1000; in stillborn infants the incidence is 10 times that of live births. The prenatal diagnosis of congenital heart defects is often difficult and can only be carried out competently at specialist centres.

For the past 10 years there has been a centre for prenatal diagnosis and treatment at the Charité Hospital, at which approximately 3000 women with high risk pregnancies are examined annually. About 60 heart defects are detected prenatally each year, including about 20 cases that are examined postmortem (induced and spontaneous abortions and stillbirths). Congenital heart defects are often associated with extracardiac malformations. In the Baltimore-Washington Infant Study (BWIS) the frequency of associated extracardiac anomalies in live births is given as 20%. Some of these cases are caused by chromosome abnormalities: 4.5% of all congenital heart defects in liveborn infants are part of a complex syndrome resulting from a chromosome anomaly, and considerably more in embryos and fetuses, since chromosome abnormalities often lead to death at an early gestational stage. In a prenatal study published by Chaoui et al., 22% of the fetuses with congenital heart defects had chromosome aberrations.

Not only is the rate of chromosome aberrations significantly higher in fetuses than in liveborn infants because of their reduced viability, but so also is the spectrum of congenital heart defects, as well as their association with extracardiac malformations.

Our goal in this paper is to analyse the spectrum of congenital heart malformations, to determine the frequency of extracardiac malformations and the proportion of chromosome...
Table 1 Incidence of congenital heart defects, other cardiovascular (CV) and extracardiac malformations, and cases with chromosome anomalies (1991-97)

<table>
<thead>
<tr>
<th>Diagnostic group</th>
<th>Total</th>
<th>No other CV or extracardiac malformations</th>
<th>With other CV malformations</th>
<th>Chromosome anomalies</th>
<th>Trisomy 21</th>
<th>Trisomy 18</th>
<th>Trisomy 13</th>
<th>Monosomy X</th>
<th>Triploidy N</th>
<th>Other structural anomalies</th>
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<tbody>
<tr>
<td>VSD</td>
<td>36 (28)</td>
<td>20</td>
<td>31</td>
<td>15</td>
<td>8</td>
<td>4</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>AVSD</td>
<td>21 (16)</td>
<td>–</td>
<td>17</td>
<td>17</td>
<td>13</td>
<td>9</td>
<td>3</td>
<td>–</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>HLH</td>
<td>21 (16)</td>
<td>8 (38)</td>
<td>7</td>
<td>8</td>
<td>2</td>
<td>–</td>
<td>1</td>
<td>1</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>DORV</td>
<td>15 (12)</td>
<td>–</td>
<td>14</td>
<td>11</td>
<td>5</td>
<td>–</td>
<td>3</td>
<td>2</td>
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<tr>
<td>CoA</td>
<td>7 (6)</td>
<td>2</td>
<td>7</td>
<td>3</td>
<td>1</td>
<td>–</td>
<td>2</td>
<td>–</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>TGA</td>
<td>5 (4)</td>
<td>2 (40)</td>
<td>4</td>
<td>1</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
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<td></td>
</tr>
<tr>
<td>AoVS</td>
<td>5 (4)</td>
<td>1 (20)</td>
<td>4</td>
<td>1</td>
<td>1</td>
<td>–</td>
<td>–</td>
<td>1</td>
<td>–</td>
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</tr>
<tr>
<td>TOF</td>
<td>4 (3)</td>
<td>2</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td>–</td>
<td>1</td>
<td>–</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>TAC</td>
<td>3 (2)</td>
<td>1</td>
<td>3</td>
<td>1</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>1</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>PaVS/PaVA</td>
<td>4 (3)</td>
<td>–</td>
<td>3</td>
<td>–</td>
<td>–</td>
<td>–</td>
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<tr>
<td>TA</td>
<td>4 (3)</td>
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<td>3</td>
<td>2</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>SV</td>
<td>2 (1.5)</td>
<td>–</td>
<td>2</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>ASD</td>
<td>1 (0.5)</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>129 (100)</td>
<td>11 (9)</td>
<td>85 (66)</td>
<td>85 (66)</td>
<td>43 (33)</td>
<td>19 (15)</td>
<td>11 (9)</td>
<td>6 (5)</td>
<td>3 (2)</td>
<td>2 (1.5)</td>
</tr>
</tbody>
</table>

Values are n or n (%).

AoVS, aortic valve stenosis; ASD, atrial septal defect; AVSD, ativoventricular septal defect; CoA, coarctation of the aorta; DORV, double outlet right ventricle; HLH, hypoplastic left heart; PaVS/PaVA, pulmonary valve stenosis/pulmonary valve atresia; SV, single ventricle; TA, tricuspid atresia; TAC, truncus arteriosus communis; TGA, transposition of the great arteries; TOF, tetralogy of Fallot; VSD, ventricular septal defect.

Methods

During a seven year period (1991 to 1997) necropsies were performed in the department of pathology at the Charité Medical Centre in Berlin on 815 fetuses between 11 and 41 weeks of gestation. These included 448 induced abortions (55%), 220 spontaneous abortions (27%), and 147 stillbirths (18%). In 129 cases (16%) a congenital heart defect was diagnosed (99 induced abortions, 20 spontaneous abortions, and 10 stillbirths). In all 129 cases prenatal diagnosis was carried out at the Centre for Prenatal Diagnostics and Therapy with high resolution ultrasound and a multidisciplinary approach was used.

The following equipment was used for the cardiac examinations: Toshiba SSA100A, Toshiba SSA270A (colour Doppler) (Toshiba, Tokyo, Japan), and Ultramark-9-HDI (Advanced Technology Laboratories, Bothell, Massachusetts, USA) (B image, PW-CW, and colour Doppler). In all cases fetal karyotyping was made using various fetal tissues. Prenatal cytogenetic analyses were performed on fetal cells obtained by chorion villus sampling, amniocentesis, and cordocentesis. Since 1996 molecular cytogenetic methods have been used primarily on suspicion of deletions in the CATCH22 region. The patients were given counselling by our multidisciplinary team. Pregnancy was terminated in case of complex cardiac anomalies or when the heart defect was associated with severe extracardiac malformations. In addition, tissue from aborted fetuses and stillbirths was investigated.

For evaluation 13 categories were established for the classification of congenital heart defects: ventricular septal defect, atrioventricular septal defect, hypoplastic left heart, double outlet right ventricle, coarctation of the aorta, transposition of the great arteries, pulmonary valve stenosis/pulmonary valve atresia, tetralogy of Fallot, aortic valve stenosis, truncus arteriosus communis, tricuspid atresia, single ventricle, and atrial septal defect (table 1), which were either isolated or combined with other cardiovascular anomalies. Hearts with more than one lesion were classified according to the more serious lesion. The frequency of extracardiac malformations and chromosomal abnormalities in cases with congenital heart defects was examined.

Results

INCIDENCE OF CONGENITAL HEART DEFECTS

A congenital heart defect was detected in 129 of the 815 fetuses examined (16%); 99 induced abortions (22%), 20 spontaneous abortions (9%), and 10 stillbirths (7%). For all 815 fetuses, prenatal ultrasound findings and the results of karyotyping were available. In 92% of the cases the prenatally diagnosed heart malformation was confirmed at necropsy examination.

In 10 cases (8%), necropsy showed additional cardiac anomalies that had not been identified prenatally. In two cases, a ventriculo-coronary communication was diagnosed prenatally in the 17th and 18th week of gestation using transvaginal and transabdominal colour Doppler sonography. The heart preparation showed additional ventriculo-coronary and intercoronary communications. In four cases, necropsy examination showed additional coarctation of the aorta. In three cases the necropsy examination showed a retroesophageal origin of the right subclavian artery from the descending part of the aorta. In the final case a partial anomalous pulmonary venous connection was detected at necropsy.

In eight cases prenatally diagnosed cardiac anomalies were not confirmed at necropsy (ventricular septal defect, atrioventricular septal defect, coarctation of the aorta, and hypoplastic aorta). But in all these cases the extracardiac findings which led to the termination of pregnancy were confirmed.

The following heart deformations were diagnosed at necropsy, in order of frequency: ventricular septal defect (36%), atrioventricular septal defect (21), hypoplastic left heart (21), double outlet right ventricle (15), coarctation of the aorta (7), transposition of the great
arteries (5), aortic valve stenosis (5), tetralogy of Fallot (4), truncus arteriosus communis (4), pulmonary valve stenosis/pulmonary valve atresia (4), tricuspid atresia (4), single ventricle (2), and atrial septal defect (1), with only the most significant defect being given in cases with more than one defect. Ventricular septal defect, atrioventricular septal defect, hypoplastic left heart, and double outlet right ventricle made up 72% of the heart defects (table 1). The ratio of males (73) to females (56) was 1.3:1.

ASSOCIATION WITH OTHER CARDIOVASCULAR MALFORMATIONS

The congenital heart malformations were isolated in only 11 cases (9%). In 66% of the cases further cardiovascular anomalies were observed. For example, ventricular septal defect occurred together with double outlet right ventricle, coarctation of the aorta, tetralogy of Fallot, tricuspid atresia, atrial septal defect, transposition of the great arteries, and truncus arteriosus communis.

ASSOCIATION WITH EXTRACARDIAC MALFORMATIONS

The congenital heart defects were associated with extracardiac anomalies in 85 cases (66%). The most frequent of these anomalies involved the central nervous system (31%), the kidneys, urinary tract, and genital system (26%), and the gastrointestinal system (24%). Anomalies of the respiratory system (11%) and the skeletal system (8%) were less common (table 2).

CHROMOSOMAL ABNORMALITIES

Chromosomal abnormalities were diagnosed in 43 cases (33%): there were 19 fetuses with trisomy 21, 11 with trisomy 18, six with trisomy 13, three with 45,X, two with triploidy, one with trisomy 22, and one with submicroscopic deletion at 22q11.2 (table 3).

The following cardiac abnormalities were found in the chromosomally abnormal fetuses: 13 of the 21 cases of atrioventricular septal defect (62%), 15 of the 36 cases of ventricular septal defect (42%), two of the four cases of tetralogy of Fallot, five of the 15 cases of double outlet right ventricle, three of the seven cases of coarctation of the aorta, one of the four cases of truncus arteriosus communis, one of the five cases of aortic valve stenosis, two of the 21 cases of hypoplastic left heart, and the single cases of atrial septal defect (table 1). In contrast, fetuses with transposition of the great arteries, pulmonary valve stenosis/pulmonary valve atresia, tricuspid atresia, and single ventricle had a normal karyotype. Atrioventricular septal defect was the commonest type of congenital heart defect in cases of chromosome anomaly: nine of these cases were associated with trisomy 21, three with trisomy 18, and one with trisomy 22.

Trisomy 21 and trisomy 18 were more often associated with atrioventricular septal defect or ventricular septal defect than with hypoplastic left heart, double outlet right ventricle, coarctation of the aorta, or tetralogy of Fallot. Obstruction of the left ventricular outflow tract was observed in three cases of X monosomy (45,X).

None of the 43 cases with chromosomal abnormalities had an isolated heart defect. In 56% of the cases the heart defects were accompanied by other cardiovascular anomalies and 98% were accompanied by extracardiac malformations.

Discussion

INCIDENCE OF CONGENITAL HEART DEFECTS

In these fetal necropsy cases there was a high incidence of severe congenital heart defects. There are two reasons for this: first, the centre for prenatal diagnosis and treatment at the Charité specialises in the detection of fetal congenital heart defects, such defects being diagnosed at a very early gestational stage (as early as the 11th or 12th week of pregnancy); second, fetuses with such defects often do not go to term.

The incidence of congenital heart defects in the 815 cases presenting for necropsy in this study was 16% (22% of induced abortions, 9% of spontaneous abortions, and 7% of stillbirths). In contrast, for live births the frequency of congenital heart defects in various epidemiological studies has ranged between four and eight per 1000.1–4 Necropsies on neonates (stillbirths and liveborn infants dying shortly after birth) have shown incidence rates for congenital heart defects varying between 6% and 13%.* 5–14

In our present study of aborted fetuses and stillbirths, ventricular septal defect was the most common defect (28%). In no case did it occur as an isolated lesion. In 56% it was associated with other cardiovascular anomalies (double outlet right ventricle, coarctation of the aorta, tetralogy of Fallot, tricuspid atresia,
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Ventricular septal defect has been reported to be the most frequent cardiac defect in various other necropsy studies of live births and stillbirths, and in those studies the proportion was higher than in ours (between 32% and 42%); this difference may reflect the composition of the case population, as the studies cited included not only stillbirths but also liveborn infants, among whom ventricular septal defect mainly occurs as an isolated lesion which may allow the infant to survive the first few days after birth. In prenatal ultrasound investigations by Hanna et al, ventricular septal defect was diagnosed in 38% of the cases (21/60). In the Baltimore-Washington Infant Study (BWIS), which is a nine year (1981 to 1989) epidemiological study of congenital heart defects in 4390 live births up to the end of the first year of life, ventricular septal defect made up a higher proportion of the defects (32%) than in the current study, with 81% of the cases occurring in isolation.

The spectrum and frequency of the individual lesions differ from those found in paediatric cardiology surveys. Severe heart defects such as atrioventricular septal defect, hypoplastic left heart, and double outlet right ventricle, which are usually lethal, made up 44% of the malformations in our necropsy population (of which 58% were induced abortions). In one study, severe congenital heart defects diagnosed at prenatal ultrasound examination—such as atrioventricular septal defect, hypoplastic left heart, and tetralogy of Fallot—comprised 33% of the cases. In contrast, in the BWIS, atrioventricular septal defect, hypoplastic left heart, and double outlet right ventricle comprised only 13% of the cases among liveborn infants. Our results show that complex heart defects more often lead to spontaneous abortion or to stillbirths. In addition, if highly specialised prenatal diagnosis is made before viability, termination of pregnancy can be offered.

The slightly higher proportion of males with congenital heart defects in our population agrees with the results of other necropsy studies. In contrast, in the BWIS only 27% of the congenital heart defects were associated with extracardiac anomalies, the most frequent being of the central nervous system, the eyes, the gastrointestinal system, and the kidneys, urinary tract and genital system, as well as of the abdominal wall. It was noted in the BWIS that the majority of cases of transposition of the great arteries and right and left sided obstructive defects were not associated with extracardiac anomalies, and in our study only one case of transposition of the great arteries was associated with an extracardiac malformation. For malformations of the outflow tract, Lurie et al gave a ratio of isolated extracardiac anomalies to combined extracardiac anomalies of 1:2.5.

Prenatal investigations have shown that heart defects often accompany defects in other organ systems. Copel et al and Greenwood et al observed heart defects in 30% of omphaloceles, in up to 20% of cases of duodenal atresia, in up to 30% of congenital diaphragmatic hernias, in between 5% and 15% of CNS malformations, and between 8% and 71% of the cases with defects of the kidneys, urinary tract, and genital system. These findings point to the need to investigate the heart in cases of extracardiac anomaly and to look for extracardiac anomalies when cardiovascular malformations have been diagnosed.

CHROMOSOME ABNORMALITIES

In our study, chromosomal abnormalities were associated with congenital heart defects in 43 of the fetuses (33%). Among liveborn infants with heart defects, around 5% have chromosome abnormalities, the proportion being as high as 12% in more recent studies. Prenatal investigations by Chaoui et al showed a higher rate of chromosomal abnormalities in fetuses with congenital heart defects (22%) than among live births. In an analysis of fetuses with heart defects, Gembruch et al found chromosomal abnormalities in 28%. The incidence of congenital heart defects and chromosome abnormalities in fetuses is higher than in liveborn infants or stillbirths as the fetuses often do not survive until birth and are therefore not included in statistical data collected by paediatric cardiologists.

ASSOCIATION WITH OTHER CARDIOVASCULAR MALFORMATIONS

Some 66% of the fetuses with congenital heart defects had more than one defect. In published reports, necropsy studies of live births and stillbirths showed that up to 52% of the cases had more than one cardiac anomaly. The proportion was higher in our population—which included cases in early fetal development—than in studies of stillbirths or live births, which suggests that multiple cardiovascular anomalies are responsible for early spontaneous abortions.
published reports, the frequency of chromosome abnormalities found after the discovery of a congenital heart defect varies between 16%28 and 50%.29 In a prenatal study of fetuses with congenital heart defects by Körner et al, the rate of chromosome anomalies was found to be 29%.29

In the current study ventricular septal defect, atrioventricular septal defect, hypoplastic left heart, and double outlet right ventricle were associated with the highest rates of chromosome abnormalities, in contrast to cases with simple vascular obstruction or malformations such as pulmonary valve stenosis/pulmonary valve atresia, tricuspid atresia, and transposition of the great arteries, where there was a low prevalence of chromosome anomalies.

Among the 43 chromosomally abnormal fetuses, the following abnormalities were detected: 19 with trisomy 21, 11 with trisomy 18, six with trisomy 13, three with monosomy X, two with triploidy, one with trisomy 22, and one with a submicroscopic deletion at chromosome 22q11.2. Atrioventricular septal defect was associated with the highest proportion of chromosomal abnormalities: 12 of the 21 fetuses (57%) with this defect had an aneuploidy, including nine with trisomy 21 and three with trisomy 18. In the BWIS, trisomy 21 was the most frequent abnormality associated with congenital heart defects, followed by trisomy 18, trisomy 13, and monosomy X (45,X).

In our present study the following association between chromosome abnormalities and cardiac defects was observed: 30% of cases of ventricular septal defect/atrioventricular septal defect were associated with trisomy 21; 12% of cases of ventricular septal defect/atrioventricular septal defect were associated with trisomy 18; and 29% of cases of anomaly of the aortic arch were associated with monosomy X. In a study of fetuses in the 11th to 16th week of gestation, Hyett et al also detected an association between atrioventricular septal defect/ventricular septal defect and trisomy 21, ventricular septal defect and trisomy 18, and severe narrowing of the aortic arch and 45,X.30 In a retrospective study of 272 children with Down’s syndrome who came to necropsy, Warkany et al found heart defects in 52% and in 64% of these the anomaly was an atrioventricular septal defect.30 In our study, seven fetuses (47%) with prenatally diagnosed trisomy 21 also had an atrioventricular septal defect. For this reason chromosome analysis is indicated for every prenatally diagnosed heart defect. Fetuses which have not been investigated prenatally should have postnatal cytogenetic investigation. If the karyotype is normal, more detailed investigations may need to be carried out (for possible exclusion of mosaicism or microdeletion), depending on the clinical findings.

Hyett et al observed increased thickness of nuchal translucency between the 11th and the 16th week of gestation in fetuses with trisomy 21, 18, and 13 and monosomy X (45,X) who also had an atrioventricular septal defect or a ventricular septal defect; they showed that the aortic isthmus was significantly narrower in these fetuses than in normal fetuses and postulated that this might explain the increased nuchal translucency in these four chromosome abnormalities.31

Cardiac development is regulated by complex mechanisms involving interaction between genetic and environmental factors. The etiology of the majority (70–80%) of congenital heart defects is still unexplained. With progress in molecular and developmental biology, our understanding of factors that influence cardiac development is likely to increase. In the last few years it has been shown, for example, that conotruncal heart defects such as tetralogy of Fallot, truncus arteriosus, double outlet right ventricle, and transposition of the great arteries, together with various types of ventricular septal defects, are associated with a microdeletion on chromosome 22.32–35 Raymond et al have described five cases with congenital heart defects which showed a deletion of 22q11.2 at prenatal diagnosis.35 The incidence of del(22) is reported to be 1/5000–10 000 births. In 106 fetuses with congenital heart defects and a normal karyotype, Lucy et al found two cases with a 22q11.2 deletion.36 In cases where conventional methods showed a normal karyotype, chromosome abnormalities (7q11.23, 10p13, and 8p deletions) were assumed by Lucy to be the cause of the cardiac anomalies. In one of our cases with a ventricular septal defect associated with coarctation of the aorta, it was possible to detect a deletion at chromosome 22 by molecular genetic investigations. Up to now aborted fetuses have not been included in investigations of the genetic basis of heart defects.36

In 10 of our cases (8%), necropsy showed additional cardiac anomalies that had not been diagnosed prenatally. In eight cases, prenatally diagnosed cardiac anomalies were not confirmed at necropsy (ventricular septal defect, atrioventricular septal defect, coarctation of the aorta, and hypoplastic aorta), but in all these cases the extracardiac findings, which led to termination were confirmed.

CONCLUSIONS

Specific prenatal ultrasound diagnosis and necropsy investigation, supported by molecular and cytogenetic investigations, can provide us with a good idea of the many factors that lead to congenital heart defects.37 In such cases systematic collection of data is necessary to provide an adequate basis for counselling families, as well as for the clinical or necropsy investigation of congenital heart defects, extracardiac malformations, and chromosomal abnormalities. Our future investigations will be devoted to the identification of the genes and modifying factors that play a role in congenital malformations of the heart, which may make it possible to estimate the risk for affected families.

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