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Fetal and neonatal mortality in patients with isolated congenital heart diseases and heart conditions associated with extracardiac abnormalities

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ABSTRACT

Congenital malformations are a known cause of intrauterine death; of them, congenital heart diseases (CHDs) are accountable for the highest fetal and neonatal mortality rates. They are strongly associated with other extracardiac malformations and an early fetal mortality. Two hundred and twenty fives cases of CHDs are presented. Of them, 155 were isolated CHDs (group A) and 70 were associated with extracardiac malformations, chromosomal disorders, or genetic syndromes (group B). The overall mortality in group B was higher than that observed in group A ($p < 0.01$). Prenatal mortality was similar in both groups: A: 8.4% (13 out of 155); B: 15.7% (11 out of 70). Postnatal mortality was A: 16.8% (26 out of 155) ($p < 0.01$), OR: 0.52 (95% CI: 0.16-1.7); B: 32.9% (23 out of 70) ($p < 0.01$), OR: 0.41 (95% CI: 0.20-0.83). Heart diseases associated with extracardiac abnormalities had a higher mortality rate than isolated congenital heart diseases in the period up to 60 weeks of postmenstrual age (140 days post-term). No differences were observed between both groups of patients in terms of prenatal mortality.

Key words: *survival, prenatal diagnosis, fetal mortality, congenital heart diseases.*

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INTRODUCTION

Congenital malformations are a known cause of intrauterine death.[1] Of them, congenital heart diseases (CHDs) are accountable for most cases of fetal and neonatal mortality.[2]

CHDs are greatly associated with other extracardiac malformations and, according to published data, they lead to a high fetal mortality rate;[5-8] for this reason, we were interested in studying whether the presence of these findings modified prenatal and postnatal development.

The study objective was to assess prenatal and postnatal mortality caused by isolated heart diseases or when associated with other extracardiac malformations, from prenatal diagnosis up to 60 weeks of postmenstrual age (140 days post-term).

MATERIAL AND METHODS

This was an observational, prospective, cohort study. Between March 2003 and July 2009, all fetuses of pregnant patients aged 18-44 years old, referred to the Fetal Medicine Unit (FMU) of Hospital Italiano de Buenos Aires, at 18-38 weeks of gestation were examined. Subjects included were pregnant women with a suspected alteration in the four-chamber and three-vessel view of the fetal heart during the routine fetal ultrasound examination, or with a history of CHD risk (pregnant women with a metabolic condition, severe obesity, connective tissue disease, exposure to a teratogenic agent, suspected chromosomal abnormality or extracardiac malformation, family history of CHDs, fetal infection, oligohydramnios-polihydramnios, and multiple pregnancy). A pediatric cardiologist performed a Doppler echocardiogram on the fetuses of these patients in order to confirm or rule out the presence of a heart condition. A real time General Electric Vingmed Vivid V ultrasound device with 1.5-3.6 mHz and 4.4-10 mHz cardiac transducers was used.

Pregnant women at risk of being lost to follow-up during the study and those with an inadequate ultrasound window during obstetric or fetal cardiac ultrasounds were excluded.

The suspicion of a genetic syndrome was confirmed or ruled out during the neonatal period by the hospital's Genetic Medicine

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Department, or postmortem by the Anatomic Pathology Service.

In order to calculate the sample size, a mortality difference over 20% with a 95% confidence interval and an 80% power was estimated, with a minimum of 70 patients per group.

The sample was divided into two groups: group A, patients with isolated CHDs; group B, patients with CHDs associated with other extracardiac malformations, chromosomal abnormalities or genetic syndromes. Survival and mortality were analyzed in the period between the prenatal diagnosis and up to 60 weeks of postmenstrual age (140 days post-term) or the time of death.

Data were analyzed using the χ^2 test for dichotomous outcome measures, and expressed using odds ratios with 95% confidence intervals.

Survival over time was analyzed using the Kaplan-Meier test.

RESULTS

A total of 1658 fetuses were examined at the FMU using a fetal echocardiogram; CHDs were detected in 225 of them.

Groups were as follows: group A, patients with isolated CHDs (n= 155); group B, patients with CHDs associated with other extracardiac malformations, chromosomal abnormalities or genetic syndromes (n= 70). Overall mortality in group B was higher, with a significant difference (p< 0.01) from group A *(Table 1)*. When prenatal mortality was assessed, it was similar between both groups *(Table 1)*: 8.4% (13 out of 155) in group A and 15.7% (11 out of 70) in group B. Postnatal mortality was 16.8% (26 out of 155) in group A (p <0.01), OR: 0.52 (95% CI: 0.16-1.7) and 32.9% (23 out of 70) in group B (p <0.01), OR: 0.41 (95% CI: 0.20-0.83).

Tables 2 and *3* describe CHDs found in the deceased fetuses and newborn infants of groups A and B, respectively, and their extracardiac abnormalities and causes of death.

TABLE 1. *Overall prenatal and postnatal mortality in groups A and B*

	Group A *n* (%) *n*= 155	**Group B *n* (%) *n*= 70**	***p***	**OR (IC 95%)**
Overall mortality	39 (25.2%)	34 (48.6%)	<0.01	2.24 (126-3.98)
Prenatal mortality	13 (8.4%)	10 (14.2%)	<0.01	0.47 (0.14-1.5)
Postnatal mortality	26 (16.8%)	23 (32.9%)	<0.01	0.41 (0.20-0.83)

Table 2. Isolated congenital heart diseases. Mortality

Group A	**Isolated congenital heart disease**		
Patients n: 155	**Congenital heart disease**	**Surgery**	**Causes of death**
13	**Prenatal death**		
1	Tricuspid atresia	No	Restrictive foramen ovale
1	Tetralogy of Fallot with severe pulmonary stenosis	No	Unknown
8	Hypoplastic left heart syndrome	No	Pregnancy termination and sudden death
2	Ebstein's anomaly	No	Suddendeath
1	Shone's syndrome	No	Suddendeath
26	**Postnatal death**		
8	Hypoplastic left heart syndrome	No	Sepsis and heartfailure
5	Hypoplastic left heart syndrome	Yes	Post-operativeperiod
4	Ebstein's anomaly	No	Heart failure and pulmonary hypertension
3	Transposition of the great vessels	Yes	Low output and sepsis
1	Tetralogy of Fallot + pulmonary valve agenesis	Yes	Necrotizing enterocolitis
1	Tetralogy of Fallot + pulmonary valve agenesis	No	Sepsis
3	Dilated cardiomyopathy	No	Prematurity and heart failure
1	Shone's syndrome	Yes	Arrhythmia during the postoperative period

The analysis of postnatal mortality in group A indicated that 26 newborn infants died; 10 out of 155 (6.5%) during the postoperative period, and 16 out of 155 (10%) who had not undergone a heart surgery either due to their severity or because of the absence of a surgical indication. These data and the causes of death are detailed in *Table 2*: 8 patients had hypoplastic left heart syndrome (HLHS) and could not undergo surgery due to their critical status; 4 patients had severe Ebstein's anomaly and died due to heart failure and pulmonary hypertension with no response to medical treatment, 2 of them were preterm newborn infants. One patient with tetralogy of Fallot and pulmonary valve agenesis died due to sepsis.

This series presents the association of different chromosomal abnormalities and congenital heart diseases, which are detailed in *Table 4*. In group B, an association was found with an abnormal kariotype in 11 out of 34 cases (32.3%) and with non-chromosomal genetic syndromes in 4 out of 34 cases (8.8%). Chromosomal abnormalities were trisomy 18 and 21, with 4 cases each. In addition, 1 trisomy 8 case and 2 trisomy 13 cases were found. In relation to non-chromosomal genetic syndromes, there were 4 cases presented: in 1 of the cases DiGeorge syndrome was diagnosed, and 3 could not be included in any known syndrome.

Extracardiac abnormalities were related to the central nervous system (CNS) in 8 out of 34 cases (23%), followed by digestive tract malformations in 5 out of 34 cases.

DISCUSSION

In this cohort, the survival rate of patients with isolated CHDs was significantly higher than that of patients with CHDs associated with an extracardiac abnormality: 74.8% (116 out of 155) versus 51.4% (36 out of 70).

The association with extracardiac abnormalities was one of the factors with an impact on mortality, either due to the overall severity of the patient's condition or because a long-term prognosis was contradictory to invasive treatment. There were no significant differences in terms of CHD type, frequency and severity; therefore, we assumed that group B was made up of CHDs that should have similar results to group A in relation to their survival.

Although the association with extracardiac malformations casts a shadow over the prognosis, it is known that this is not the only outcome measure to be taken into consideration. It should be noted that prematurity and low birth weight were not analyzed in this study, and it is believed that they could have had a significant influence on morbidity and mortality, as well as on the final outcome.

In this series, no significant differences were observed in prenatal mortality (24.1%), including both groups. The rate was lower than that described by some large European studies,[5,9,10] where pregnancy termination is a common practice, unlike the situation in Argentine.

It is interesting to note that in group B, 10 out of 70 fetuses died in the prenatal stage; all of them had a normal karyotype, but 3 were carriers of an unidentified genetic syndrome, and their death was because of heart failure. One case was associated with a situs ambiguous and an arrhythmia that could not be treated pharmacologically; the other case was an atrioventricular canal defect with severe regurgitation of the common AV valve.

The rate of postnatal mortality in group B (48.6%) was similar to that observed in the studies made by Eronen[1]and Boldt,[3] who described a mortality rate close to 44%. These authors attribute this high mortality rate to the complexity of the heart disease, but also to its association with extracardiac and chromosomal malformations.

As a result, we believe that pregnant women and their unborn children should be timely referred to a facility with a higher level of care where they can be managed by a multidisciplinary team of professionals, taking into account that the best incubator for such babies is their mother's womb.

When analyzing extracardiac abnormalities frequency and characteristics, the most common were chromosomal abnormalities, followed by multiple extracardiac malformations and, to a lesser extent, non-chromosomal genetic syndromes. The incidence of chromosomal abnormalities among the deceased cases in group B was 29%; in other studies, such incidence ranged between 28% and 66%.[3-6,12-15]

We agree with most authors that CNS abnormalities are the ones most commonly associated with CHDs; in our series, the agenesis of the corpus callosum was the most common abnormality, but other studies have found that anencephaly, hydrocephaly,and spina bifida were the most common findings.[8,15]

TABLE 3. *Congenital heart diseases associated with extracardiac malformations, chromosomal abnormalities or genetic syndromes in deceased patients from group B*

Group B Patients (*n*= 70)	CHDs associated with other abnormalities Congenital heart diseases	Extra cardiac abnormalities	Karyotype	Genetic disorder	Cause of death
10	**Prenatal death**				
1	Hypoplastic left heart syndrome	Brachycephaly, esophageal atresia, hypotelorism, low ear implantation, dysplastic nails	Normal	Undetermined	Sudden death
1	Hypoplastic left heart syndrome	Agenesis of the corpus callosum, hydrocephaly	Normal		Sudden death
1	Hypoplastic left heart syndrome	Renal polycystosis	Normal		Hydrops fetalis due to restrictive foramen ovale
1	AVCD	Cystic hygroma, outer ear abnormalities	Normal	Undetermined	Hydrops fetalis due to severe atrioventricular valve regurgitation
1	Severe aortic stenosis	Severe hydropsfetalis+ renal polycystosis	Normal		Heart failure
3	Dilated cardiomyopathy	Twin-to-twin transfusion syndrome: acephaly and upper limb malformation	Normal		Heart failure
1	DORV + AVCD	Polydactyly, kidney malformation + hydropsfetalis	Trisomy 13		Heart failure
1	Situs ambiguous + DORV + anomalous pulmonary venous return	Asplenia, esophageal atresia	Normal	Undetermined	Arrhythmia uncontrolled with drug treatment
24	**Postnatal death**				
4	Hypoplastic left heart syndrome	Left diaphragmatic hernia	Normal		Pulmonary hypoplasia + pulmonary hypertension
1	DORV + pulmonary stenosis	Encephalopathy, brachycephaly, micrognathism, agenesis of the corpus callosum, hypotelorism, cleft lip and palate	Trisomy 8		Encephalopathy
1	DORV + PA + TAPVR	Clinodactyly, hemivertebra, agenesis of the corpus callosum, agenesis of cerebellar vermis, hydrocephaly, Dandy-Walker malformation	Trisomy 18		Severe CNS abnormality
1	Aorta coarctation + VSD + PDA	Agenesis of left kidney and upper limbs	Normal		Kidney failure
3	VSD	Different CNS, kidney and gastroduodenal malformations	Normal		Non cardiac
3	VSD	Digestive tract malformation	Trisomy 21	Down's	Sepsis-prematurity
1	PA + VSD	Mega cystocele	Normal		Sepsis
1	AVCD	Esophageal atresia	Trisomy 21		Mediastinitis
1	AVCD	Duodenal atresia	Trisomy 13		Sudden death
1	AVCD	Agenesis of the corpus callosum, hydrocephaly	Trisomy 18		CNS abnormality
1	VSD + PDA	Agenesis of the corpus callosum	Trisomy 18		
1	TAPVR	Severetrachealstenosis	Normal		Not capable of receiving ventilation
1	Tetralogy of Fallot	Cleftlip and palate	Normal	DiGeorge	Sepsis
1	Tetralogy of Fallot	Renal agenesis	Trisomy 18		
1	Tetralogy of Fallot + ASD	Hydrocephaly	Normal		Severe hydrocephaly
1	ASD+VSD + PDA	Outer ear dysplasia, syndactyly	Normal		Sepsis
1	VSD	Severe hydrops fetalis+ vein of Galen aneurysm	Normal		Heart failure that cannot be treated

AVCD: atrioventricular canal defect; DORV: double outlet right ventricle; PA: pulmonary atresia; TAPVR: total anomalous pulmonary venous return; VSD: ventricular septal defect; PDA: patent ductusarteriosus; ASD: atrial septal defect.

TABLE 4. *Congenital heart diseases associated with chromosomal disorders*

Congenital heart diseases	Chromosomal disorders			
	Trisomy 8	Trisomy 13	Trisomy 18	Trisomy 21
DORV + PA	**1**			
Tetralogy of Fallot			1	
AVCD		1	1	1
VSD + PDA			1	
VSD				3
DORV + AVCD		1		
DORV + PA + TAPVR			1	

DORV: double outlet right ventricle; PA: pulmonary atresia; AVCD: atrioventricular canal defect;
VSD: ventricular septal defect. PDA: patent ductusarteriosus; TAPVR: total anomalous pulmonary venous return.

CONCLUSIONS

In this study, heart diseases associated with extracardiac abnormalities had a higher morbidity and mortality rate than isolated congenital heart diseases in the period up to 60 weeks of postmenstrual age (140 days post-term).No differences were observed in prenatal mortality when comparing both groups of patients.■

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