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ORIGINAL ARTICLE

Perinatal outcome and five-year survival in children with prenatal diagnosis of hypoplastic left heart syndrome

Evolución perinatal y sobrevida a cinco años en niños con diagnóstico prenatal de síndrome de hipoplasia de ventrículo izquierdo

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What do we know about the subject matter of this study?

Hypoplastic Left Heart Syndrome (HLHS) is a congenital heart disease of low prevalence and high lethality, which can be diagnosed prenatally. In Chile, there are few reports of series that include prenatal diagnosis and long term follow-up.

What does this study contribute to what is already known?

This prospective cohort study report the perinatal evolution and survival at one and five years of fetuses with a prenatal diagnosis of HLHS in a national referral center for congenital heart disease over 10 years. Approximately, half of the patients underwent surgery and 1 out of 5 fetuses survive at one and five years.

Abstract

Hypoplastic left heart syndrome (HLHS) is a congenital heart disease of low prevalence and high lethality. **Objective:** to determine the perinatal outcome and survival at one and five years of fetuses with a prenatal diagnosis of HLHS. **Patients and Method:** Prospective cohort study of all the fetuses with HLHS from the Perinatal Reference Center (CERPO) born between January 2008 and December 2017. Demographic and clinical perinatal data were obtained from the CERPO database. At one and five years of age, a telephone survey was conducted to determine the surgical treatment and survival. **Results:** 1,573 patients were admitted to the CERPO, 899 with congenital heart diseases (CHD), confirming the prenatal diagnosis of HLHS in 7% (110/1,573). The mean gestational age at diagnosis and the median at admission were 26+3 and 32+3 weeks, respectively. 89% were born alive, 90% at term, and 57% delivered by cesarean section. The median birth weight was 3,128 grams. 89% survive the prenatal period, 50% the early neonatal period, 33% the late neonatal period, 19% the first year, and 17% at 5 years. **Conclusions:** In this center, the one-year and five-year survival of fetuses with prenatal diagnosis of HLHS was 19% and 17%, respectively. It is important for prenatal counseling to consider publications based on local casuistry, that include patients with prenatal and postnatal diagnoses and those who underwent surgery, in order to provide more precise information to parents.

Keywords:
Hypoplastic Left Heart Syndrome;
Congenital Heart Disease;
Survival;
Mortality

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Introduction

Congenital heart disease (CHD) is the most common congenital malformation diagnosed in the prenatal period. Hypoplastic left heart syndrome (HLHS) is a complex CHD susceptible to diagnosis in this period. HLHS includes a broad group of congenital cardiovascular malformations, ranging from mitral atresia with aortic atresia, in which the left ventricle (LV) is virtual, to mitral stenosis or mitral hypoplasia with aortic atresia or aortic stenosis, in which the LV is hypoplastic. The common feature of all these conditions is the inability of the LV to perfuse systemically[1]. The pulmonary artery is enlarged, and the right ventricle is dilated and hypertrophied[2]. Without surgical intervention, HLHS is lethal[1,3]. 95% of newborns die in the first month of life when the ductus arteriosus closes, being the leading cause of neonatal mortality due to CHD[4].

The HLHS was described by Lev in 1952[5] and presented an estimated incidence of 6 to 8 per 1,000 live births[1,6]. The prevalence of HLHS is 2.6 per 10,000 births but only 1.6 per 10,000 live births[7], accounting for 23% of all cardiac deaths in the first week of life[8]. Most of these deaths occur before the first surgical stage[9] and 12% between the later stages[10], with a survival rate of 50 to 69% reported at five years of age[11]. Despite the low prevalence, HLHS accounts for 4 to 8% of all CHD[6,12]. In our country, Urcelay et al. reported a surgical survival for HLHS at one and five years of life of 64% and 57%, respectively[4], and Cubillos et al reported 47% of survival at one year[13].

Since it is not possible to create a left ventricle, surgical management is not curative and consists of palliative surgeries in 3 stages[14] and/or transplantation which is not yet performed in Chile in newborns.

Some patients with foramen ovale or restrictive atrial septal defect require the use of a catheter or interatrial stent before the first surgery, favoring the mixing of blood at the atrial level[1]. The surgical stages consist of Stage 1: Norwood procedure (first week of life) allows to increase systemic oxygen supply and organ perfusion. To establish pulmonary blood flow, the Blalock-Taussig shunt (modified Norwood procedure) or Sano shunt (Norwood-Sano) is used, and other patients will require another surgical option known as hybrid[1]; Stage 2: superior cavopulmonary connection or bidirectional Glenn procedure (3rd-6th month) or the hemi-Fontan procedure, which partially divides pulmonary and systemic venous blood flow; Stage 3: total cavopulmonary connection or Fontan procedure (18th month-4 years), allows total separation of the systemic and pulmonary circulation[1]; Stage 4: heart transplantation[15]. The details of these interventions and indications are not the purpose of this study.

Given their complexity, all these interventions are subject to morbidity and mortality. Palliative care is offered in cases where the cardiac surgical team considers that the possibility of survival is very low because of anatomical characteristics, mitral-aortic atresia with foramen ovale or restrictive atrial septal defect, ventricular dysfunction, significant right atrioventricular valve insufficiency, genetic alterations or aneuploidy, severe intrauterine growth restriction and/or premature delivery and/or associated malformations.

Mortality, morbidity, and use of financial resources make HLHS a challenge for pediatric cardiology and pediatric cardiac surgery centers[14]. In other countries, parents with children with HLHS or other CHDs may opt for the termination of pregnancy[16]. In a Danish study, between 1996 and 2013, it was observed that 18% of pregnancies were terminated due to severe CHD, however, if the diagnosis of major CHD was made prenatally, termination increased to 58%, reaching up to 87 % in patients with fetuses with univentricular heart in 2013[17]. In Chile, Law 21,030 on voluntary termination of pregnancy (VTP) does not include CHD with surgical possibilities as a cause for termination of pregnancy[18]. Likewise, Law 19,966 on Explicit Health Guarantees (GES) includes the CHD that can underwent surgery in persons under 15 years of age, among which the HLHS is included[19]. In the Clinical Guide for operable CHD, prenatal diagnosis guarantees access to surgery for these newborns[20].

The objective of this study was to describe the perinatal evolution and survival at 1 and 5 years of age of fetuses with a prenatal diagnosis of HLHS in a CHD referral center over 10 years.

Patients and Method

Prospective cohort study of patients diagnosed with HLHS admitted to the *Centro de Referencia Perinatal Oriente* (CERPO), Faculty of Medicine, *Universidad de Chile*, born between January 1, 2008, and December 31, 2017.

Patients were referred from some of the following Health Services corresponding to the different regions of the country: *Antofagasta*, *Viña del Mar*, *Ñuble*, *Concepción*, *Talcahuano*, *Bío-Bío*, *Arauco*, *Araucanía Norte*, *Araucanía Sur*, *Valdivia*, *Osorno*, *Aysén*, *Magallanes*, and *Metropolitano Oriente*. Once the CHD was confirmed, they were admitted to the CERPO, where the patient or legal guardian signed an informed consent approved by the Adult Scientific Ethics Committee, Eastern Metropolitan Health Service, which authorized the use of the information for research purposes.

In the CERPO electronic database (FileMaker Pro 7.0v2), demographic, personal, and parental data were

recorded as well as morbidity, obstetric, and family history. The gestational age at diagnosis and admission to the unit and previous ultrasound scans were recorded. Once admitted, they underwent multidisciplinary management that included: morphological ultrasound, and fetal echocardiography at CERPO and the *Hospital Dr. Luis Calvo Mackenna* (HLCM), a pediatric hospital and heart surgery referral center. Genetic study (amniocentesis or cordocentesis) was offered to patients who had another associated malformation. In addition, other complementary studies were performed (neurosonography, MRI, and study of transplacental infections) if appropriate due to clinical suspicion. All patients received counseling, accompaniment, and psychological support.

In stillbirths, date, weight, gestational age, and route of delivery were recorded and in live births, birth date, route of delivery, Apgar score at 1 minute and 5 minutes, weight, sex, and postnatal evolution were recorded.

Prospective follow-up at one year was carried out through a telephone survey by the CERPO medical team, psychologist, or midwife, recording the evolution of the newborn, whether she/he underwent surgery, dates of surgery if appropriate, type of surgeries, and survival at one year of life. In the case of death, the date of death was recorded and, according to this, it was classified as early neonatal mortality, late neonatal mortality, or postneonatal mortality. A second telephone survey was performed in the fifth year, recording survival according to chronological age.

A search was made of patients entered into the database using the following words and acronyms: left ventricular hypoplasia, LVH, left ventricular hypoplasia syndrome, HLHS, and fibroelastosis. All patients with a confirmed diagnosis in the unit and followed-up during this period were included. Patients referred with an initial diagnosis of HLHS, which was ruled out during pregnancy or in the early postnatal period, were excluded. The main variable of interest was survival at one and five years of age in patients diagnosed during the prenatal period.

Definitions

HLHS was defined as the underdevelopment of the left-sided structures of the heart, which includes the mitral valve, left ventricle, aortic valve, and aortic arch.

Stillbirth corresponded to a fetus that died in utero after 20 weeks and/or weighed more than 500 grams before delivery; early neonatal mortality (ENM) corresponded to a newborn who died between birth and 6 days of life; late neonatal mortality (LNM) corresponded to an infant who died between 7 and < 28 days of life, and postneonatal mortality (PNM) when death occurred between 28 days and < 1 year[21].

Statistical analysis: Categorical variables were described as absolute and percentage frequencies, and continuous variables as mean and standard deviation or median and interquartile range (IQR) according to the parametric or nonparametric distribution of the data. Statistical analysis was performed with GraphPad Prism 6 statistical software (USA).

A value of $p<0.05$ was considered significant.

Results

1573 patients were admitted to the CERPO, delivered between January 1, 2008, and December 31, 2017. 899 of them had CHD and of these, 118 had the initial diagnosis of HLHS. In 5 patients, the diagnosis was ruled out in subsequent prenatal check-ups and in 3 cases at birth, so they were excluded, confirming the prenatal diagnosis of HLHS in 7% (110/1573) of the admitted patients.

a) Characteristics of pregnant women and newborns with confirmed prenatal diagnosis of HLHS (n = 110)

The average gestational age at diagnosis at their place of origin was 26+3 weeks, however, referral was approximately 6 weeks later (Table 1). 6% had a family history and 2.7% had children with CHD. 89% of the fetuses were born alive and at a median of 38+1 weeks (IQR: 37+1-39+3). In 57% of deliveries, the route was cesarean section and 51% of the newborns were male. The median birth weight was 3,128 grams (IQR: 2,566-3,490). 11% of the live births had an Apgar score < 7 at five minutes and 83% of them died in the first week.

Of the total number of patients with HLHS, 34% (38/110) underwent a genetic study prenatally or at birth. 42% (16/38) of the fetuses studied were euploid fetuses and trisomy 18 was the most frequently found aneuploidy in 26% (10/38) of the cases studied, corresponding to 9% (10/110) of the sample.

24% (26/110) of the patients were referred from Santiago and 76% (84/110) from other regions of the country; however, 88% (97/110) were delivered in Santiago, mainly at the *Hospital Santiago Oriente "Dr. Luis Tisné Brousse"* and 12% (13/110) at their hospitals of origin.

In 50% of the cases (55/110), HLHS occurred as a single diagnosis, not related to other extracardiac structural malformations or other obstetric pathologies. 33% (36/110) were associated with other extracardiac structural malformations and 26% (29/110) were associated with intrauterine growth restriction.

b) Survival of fetuses and children with prenatal HLHS diagnosis

Figure 1 shows the survival from the fetal period to 5 years of follow-up.

Table 1. Characteristics of pregnant women and newborns with confirmed prenatal diagnosis of hypoplastic left heart syndrome (HLHS) (n = 110)

Pregnant women	
Maternal age (median;IQR)	29 (25-36)
Primiparous (%;n)	32% (35)
Gestational age at diagnosis in weeks (mean; SD)	26 ± 3
Gestational age at admission to CERPO (median;IQR)	32+3 (29+1-35+5)
History of previous child with heart disease (%;n)	2.7% (3)
Family history of heart disease (%;n)	6% (7)
Fetal male sex (%;n)	51% (56)
Newborns	
Live newborns (%;n)	89% (98)
Gestational age at delivery in weeks (median;IQR)	38+1 (37+1- 39+3)
Preterm births before 37 weeks (%;n)	10% (11)
Caesarean section (%;n)	57% (63)
Birth weight in grams (median;IQR)	3128 (2566-3490)
Apgar ≤ 7 at 5 minutes (%;n)	11% (12)

*IQR (interquartile range); CERPO: Centro de Referencia Perinatal Oriente.

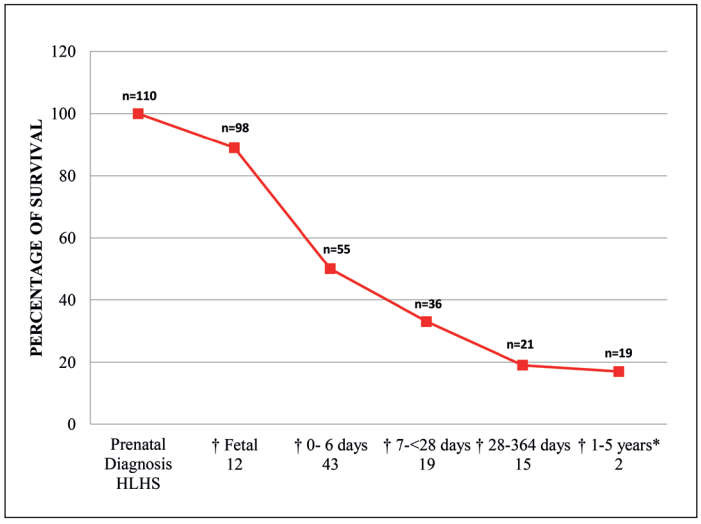

Figure 1. Survival of 110 fetuses and infants with prenatal diagnosis of hypoplastic left heart syndrome (HLHS). (†): Death by period. (*): This period considers 3 living children who have not yet reached 5 years of age.

89% (98/110) survive the prenatal period, 50% (55/110) survive the early neonatal period, 33% (36/110) survive the late neonatal period, 19% (21/110) the first year, and 17% (19/110) at 5 years of age, considering in this period, 3 live children who have not yet turned 5 years of age.

Of the newborns who died during the first week of life, 33% (14/43) died because they were classified out of surgical possibilities, 28% (12/43) died during surgery or due to complications, 23% (10/43) due to association with aneuploidy, and 16% (7/43) due to growth restriction, premature delivery, or other malformations.

c) Management of patients with prenatal diagnosis of HLHS and mortality of surgical treatment

In the 10 years of follow-up, between 2 (2016) and 7 patients (2008 and 2015) underwent surgery annually, with a median survival each year of 46.5% and a range from 0% between 2011-2012 to 75% between 2013-2017 (IQR: 15-61.5).

98 patients who were born alive, 50% (49/98) underwent surgery and 49% (48/98) were excluded from the surgical scope due to genetic alterations or aneuploidy, mitral-aortic atresia, other associated malformations, severe intrauterine growth restriction, and/or premature delivery (Table 2). Of patients undergoing surgery, 10% (5/49) presented associated extracardiac malformations and 8% (4/49) were born with intrauterine growth restriction. There were no patients undergoing surgery with aneuploidy or preterm delivery less than 36 weeks.

Of surgical patients, 61% (30/49) survived the first month after surgery, 43% (21/49) survived at one year, and 38% (19/49) survived at 5 years, considering 3 children in this group who are in follow-up and have not yet turned 5 years of age.

There was one patient whose treatment details were

not known; however, we did have the evolution and survival data, and therefore he was considered in the data analysis.

When analyzing the group of patients who underwent surgery and those who remain out of surgical scope, it is observed that there are several common conditions and/or pathologies, such as mitral-aortic atresia, growth restriction, tricuspid regurgitation, and even associated extracardiac malformations. Only the presence of aneuploidy such as trisomy 13 and trisomy 18 and premature delivery less than 36 weeks were not considered to be likely to undergo surgery.

Of the 49 operated patients, compared with the 48 non-operated patients, 86% (42/49) of the patients had no associated malformations. In the group of non-surgical patients, 54% (26/48) had no associated malformations (p= 0.001).

Table 2. Management of patients with prenatal diagnosis of hypoplastic left heart syndrome (HLHS) (n = 98) and mortality of patients with surgical treatment (n = 49)

	Nº	%
Out of surgical scope	48	49
Patient underwent surgery	49	50
Early Neonatal Mortality	10	20
Late Neonatal Mortality	9	18
Postneonatal mortality	9	18
Survival at one year of age*	21	43
Unknown treatment**	1	1
Total	98	100%

*At 5 years, the survival rate was 38% (19/49) of the patients who underwent surgery. **Patient with known evolution and postnatal survival, type of treatment unknown (surgical or non-surgical).

Discussion

HLHS is a congenital heart disease of relatively low prevalence, characterized by high lethality. In this study, 11% (12/110) of the cases died in utero, 39% (43/110) died within the first week of life, half of the cases underwent surgical treatment, and approximately one in five fetuses with prenatal diagnosis of HLHS survives to one year of life, a figure that practically remains stable until the fifth year of life, as same as reported in other publications[22,23].

In the report by Lee et al.[24], the mean age at diagnosis of CHD was 27+1 (± 5+6) and, in this study, it was 26+3. Likewise, they found a 10% incidence of aneuploidy in fetuses with prenatal chromosomal study. In contrast to these data, our study showed that 48% of the patients with prenatal genetic study had chromosomal alterations which could be related to the karyogram that was only performed in patients with a high suspicion of aneuploidy.

Most patients were referred to the CERPO after 30 weeks of pregnancy. Although the international literature is controversial as to whether early prenatal diagnosis is a determinant of a better postnatal outcome[4,16,15,25,26], in Chile, the 4 heart surgery centers are located in Santiago, therefore, early diagnosis is relevant for timely referral and delivery with expedited access to heart surgery centers in order to improve perinatal coordination and allowing a complete study with continuous psychological support to the parents.

The high cesarean section rate (57%; 63/110) could be related to the need to have a coordinated delivery with the neonatal and heart surgical team, to improve perinatal care and provide the best possibilities for the newborn.

49% of patients with HLHS did not underwent surgical treatment. This percentage could be explained by the severity of HLHS, association with other congenital malformations, chromosomal alterations, growth restriction, and premature delivery. This result is similar to that described by Idorn et al. where 50% of the patients died without surgery because they were out of surgical scope or because they died before surgery[27].

In the group of patients undergoing surgery, the association with malformations was significantly lower compared with those who did not undergo surgery. There are conditions shared by surgical and non-surgical patients, but the ones that left the HLHS carriers out of surgical scope were trisomy 13 and 18 and preterm delivery before 36 weeks.

The publication by Siffel et al. of 212 patients with non-syndromic HLHS reported an overall survival rate of 24% between 1979 and 2005, but this group showed a marked improvement over time, with 0% between 1979-1984 and 42% between 1999-2005[23]. In this study, although the number of cases is too small to show a significant trend, no improvement in survival was observed during the period of time studied (2008 to 2017).

In this series, survival of patients who underwent surgery reached 43% at 1 year and 38% at 5 years, similar to that reported by Fixler et al. who reported 42% and 38%, respectively[22], and the overall survival of patients diagnosed with HLHS at one year is 19%, comparable with the 22% survival reported by Cleves et al. in 2003[28].

The lethality around the first surgery was 39% (19/49), comparable with the one reported by Cubillos et al., where in their publication of 19 cases, they

report a lethality of 31% (4/13) in relation to the first surgery[13].

From the prenatal period, total mortality at 5 years of life was 81%, which was mainly concentrated in the postnatal period. The results of this series consider all patients with prenatal diagnosis of HLHS and included fetuses with aortic and mitral atresia, accentuated tricuspid regurgitation, right ventricular failure, associated malformations, aneuploidies, premature deliveries, and fetuses with intrauterine growth restriction, The results are less favorable, because being more severe cases, they have a higher probability of being diagnosed in the prenatal period, selecting a group of newborns that are out of surgical scope due to the severity of their CHD and associated conditions.

The results presented in this study reflect the 10-year experience of a National Reference Center for Fetal Heart Disease with fetuses diagnosed with HLHS, where the concordance between pre- and postnatal diagnosis is 97% given that HLHS was ruled out in only 3 cases out of 113 patients initially diagnosed, higher than the 90% concordance reported in 2013 by the same group[29].

This report considered prenatal diagnosis, pre- and post-natal evolution, and follow-up at 1 and 5 years. Cleves et al. report 40% neonatal survival and 22% survival at one year in patients with HLHS, comparable to the 36% neonatal survival (<28 days) and 19% survival at one year found in our study. Both cases include patients who die in the postnatal stage, even before referral to the heart surgery center, demonstrating the high lethality of this heart disease[28].

Among the limitations of this report, it should be considered that HLHS is a complex malformation, evolving over time, whose final diagnosis is postnatal. This study was done from the perspective of a perinatal referral center, so access to surgical indication, surgical protocols, management, and complications was limited. The information on pediatric follow-up at one and five years for patients with HLHS was made through telephone contact, usually provided by parents or direct relatives. Details of the treatment of one patient were not obtained, however, his evolution and survival were known and considered in the data analysis.

Conclusions

HLHS is a complex CHD and without surgical treatment it is lethal. The current therapeutic alternative is a surgical treatment in three stages, however and despite all the medical and surgical advances, our series presented a survival rate of 19% at one year of life and 17% at 5 years, but the survival rate of operated patients reached 43% at one year and 38% at 5 years, similar to the results described in national[13] and international reports[22]. It is important that prenatal counseling considers the results of the local reality, with groups of patients diagnosed with HLHS in the prenatal and postnatal period and those who undergo surgery.

The only conditions that excluded patients with HLHS from the surgical scope were the association with aneuploidy 13 or 18 and premature delivery of less than 36 weeks. This allows us to conclude that HLHS is a pathology whose definitive diagnosis is made in the postnatal period and the surgical indication is evaluated on a case-by-case basis.

Chile has made an important effort to guarantee timely and complete care for all operable CHD in children under 15 years of age. Recognizing the limitations of prenatal diagnosis, it is possible to progress in optimizing the identification of newborns with HLHS, timely referral to referral centers, and improving prenatal study techniques such as echocardiography, genetic study, and other tests to favor the identification of newborns with HLHS, who will have the option of surgical treatment in specialized heart surgery centers, to improve survival. HLHS is one of the most complex congenital heart diseases, with a high lethality, which is why it continues to be a multidisciplinary challenge for national and international maternal-fetal, neonatal, pediatric cardiology, and surgical medicine.

Ethical Responsibilities

Human Beings and animals protection: Disclosure the authors state that the procedures were followed according to the Declaration of Helsinki and the World Medical Association regarding human experimentation developed for the medical community.

Data confidentiality: The authors state that they have followed the protocols of their Center and Local regulations on the publication of patient data.

Rights to privacy and informed consent: The authors have obtained the informed consent of the patients and/or subjects referred to in the article. This document is in the possession of the correspondence author.

Conflicts of Interest

Authors declare no conflict of interest regarding the present study.

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