Aegean Journal of Obstetrics and Gynecology

Original Article

Pregnancy follow-up and outcomes of patients diagnosed with hypoplastic left heart syndrome

Özge Yücel Çelik [a], Osman Yılmaz [b], Mehmet Obut [a, †], Ayşe Keleş [a], Mine Gültekin Çalık [c], Aykan Yücel [a], Dilek Şahin [a]

[a] *Perinatology Department, University of Health Sciences Etlik Zübeyde Hanım Women's Health Care, Training and Research Hospital, Ankara, Turkey*

[b] *Pediatric Cardiology Department, University of Health Sciences Etlik Zübeyde Hanım Women's Health Care, Training and Research Hospital, Ankara, Turkey*

[c] *Obstetrics and Gynecology Department, Vm Medical Park Hospital, Ankara, Turkey*

A B S T R A C T

Objective: The study aimed to evaluate the follow-up and outcomes of patients diagnosed with fetal hypoplastic left heart syndrome in the prenatal period.

Material and methods: Between January 2017 and June 2019 the data of 36 patients diagnosed with fetal hypoplastic left heart syndrome (HLHS) in Etlik Zübeyde Hanım Woman's Health Care Training and Research Hospital (EZH) were evaluated retrospectively. All patients who suspected for any fetal or cardiac anomaly were evaluated in detailed ultrasound by two senior perinatologists and a pediatric cardiologist for a detailed cardiac evaluation. The demographic characteristics, pregnancy follow-up and maternal and fetal outcomes of patients were evaluated.

Results: During the study period fetal echocardiography was performed for 10377 patients. A totally 382 (3.7%) fetuses were diagnosed with congenital heart diseases and 36 (9.4%) of them were diagnosed with hypoplastic left heart syndrome. Additional extracardiac anomalies were detected in 13 (36.1%) fetuses. Concomitant fetal cardiac anomalies were detected in 15 fetuses and ventricular septal defect (n: 11) and double outlet right ventricle (n:8) were the most common anomalies among them. Eight pregnancies with fetal HLHS were terminated. The data of 10 patients' newborns were obtained and none of them lived up to a year.

Conclusion: The study revealed that the majority of patients with fetal HLHS are in the low-risk population group, thus, routine fetal cardiac evaluation is of great importance. The prognosis and outcome of the pregnancies diagnosed with fetal HLHS are poor. The option of pregnancy termination should be considered.

Keywords: congenital; heart defects; hypoplastic left heart syndrome; prenatal diagnosis

A R T I C L E I N F O

Doi: 10.46328/aejog.v2i2.47

Article history:

Received: 24 July 2020

Revision received 8 August 2020

Accepted 12 August 2020

Introduction

Hypoplastic left heart syndrome (HLHS) is one of the most frequently diagnosed congenital heart disease in the prenatal period. It is characterized by left ventricular hypoplasia, aortic and/or mitral atresia, and stenosis or hypoplasia of the ascending aorta [1, 2]. HLHS constitutes 2-3% of congenital heart diseases (CHD) and it is seen as 2-3 per 10,000 live births [3, 4]. The true incidence is unknown due to abortions and elective pregnancy terminations. The prevalence is more common among male fetuses [5]. Although HLHS can be detected in all trimesters of pregnancy, the second trimester especially between 18 and 24 weeks of pregnancy is the best time fort fetal cardiac evaluation. Recently, there has been a great advance in the quality of ultrasonography devices and the experience of ultrasonographers in the field of echocardiography. Accordingly, the rate of diagnosis of the fetus with HLHS in the first trimester is increased. Typical findings of HLHS are left ventricular dysfunction and narrowing of the left ventricle. Fibroelastosis is a common finding of HLHS though not present in all cases.

Fetal transcatheter interventions in some centers have become a therapeutic option for fetuses diagnosed with HLHS in the prenatal period but these centers are not common and few patients have the chance to access [6].

The most of fetuses diagnosed with HLHS are operated right after birth. HLHS accounts for 25% of the cardiac causes in early neonatal deaths [7]. Even though there has been some increases in the survival rate owing to postnatal surgery and medical interventions for these cases, mortality rates are still high and 5-year survival rate after surgical correction is remaining as 65% [8].

The aim of this study is to evaluate demographic data, follow up and outcomes of patients diagnosed with fetal HLHS in the prenatal period and outcomes of the newborns diagnosed with HLHS.

Material and methods

Data of patients diagnosed with fetal HLHS in the prenatal period between January 2017 and June 2019 in Etlik Zübeyde Hanım Woman's Health Care Training and Research Hospital (EZH), where have an average of 13.000 births per year, were collected retrospectively.

† Corresponding author.
E-mail: drmehmetobut@hotmail.com
ORCID ID: 0000-0002-6925-4784

The local ethical committee approved the study. During the pregnancy period, all patients are evaluated via ultrasonography at least four times in our hospital. As a result of these evaluations if there was any suspicion suggesting a fetal anomaly, the patients were referred to the perinatology council where at least two senior perinatologists were available and both evaluate the patient in detail via ultrasonography.

The detailed ultrasonographic evaluations were performed with the Voluson E6 device (GE Healthcare Austria GmbH & Co OG). For fetal echocardiographic evaluation in addition to two senior perinatologists, a pediatric cardiologist evaluated the patients with 4C probe on Vivid S6 ultrasound device (GE Medical Systems, Horten, Norway). All patients diagnosed with fetal HLHS were informed in detail about the course and prognosis of the disease. Because of the poor outcomes of this fetal cardiac anomaly, the parents informed about option of the pregnancy termination routinely. Our hospital is an maternity hospital, but there is no pediatric cardiovascular surgeon available. Due to the need for medical or surgical interventions after birth, parents who refused to terminate their pregnancy, were advised to give birth at a tertiary medical center with a cardiovascular surgery department and with the additional necessary consultation departments available.

Information related to birth and follow up in the postpartum period were obtained from patients' hospital records. For the study; maternal age, gravidity, parity, body mass index, educational status, cigarette smoking, residence, nationality, week of diagnosis, pregnancy outcome (termination or birth), pregnancy complications, additional fetal findings, amniocentesis/ chorion villus sampling result's (if present), prenatal screening tests, birth method and follow up after birth were evaluated.

Statistical analysis

Variables were analyzed by SPSS ("IBM SPSS Statistics version 21.0 for Windows"; Statistics, 2013, Chicago, IBM, USA). Descriptive analyses and categorical variables were defined as numbers and percentages. Numerical variables were defined as median (interval) or mean ± standard deviation.

Results

During the study period, fetal echocardiography was performed for 10377 patients. A total of 382 (3.7%) were diagnosed with congenital heart diseases and 36 (9.4%) of them with HLHS were included in this study. There were no multifetal gestations. Mean maternal age was 29.7 ± 6.6 years and one-fourth of the patients were primigravida. Mean gestational age at the time of diagnosis was 21.6 ± 4.9 weeks. One case of a diabetic mother had a history of a stillbirth due to HLHS. Maternal demographical characteristics are summarized in Table 1. Concomitant cardiac anomalies were detected in 15 patients during fetal echocardiographic evaluation. Ventricular septal defect (VSD) (n:11) and double outlet right ventricle (DORV) (n:8) were the most common concomitant cardiac anomalies (Table 2). The most frequent valvular anomaly was mitral valve atresia accompanied by aortic valve atresia (Table 3). Additional fetal anomalies were detected in 13 patients (36.1%). Of these, holoprosencephaly (Cleft lip-palate, multicyctic dysplastic kidney, increased intestinal echogenicity; cleft lip, single umbilical artery), single umbilical artery, pelviectasia (>7mm) and hydrops fetalis (pelviectasia; clench hand) were the most common accompanying anomalies (Table 4).

Table 1. Demographical and clinical features of the patients

Age [a]	29.7± 6.6
Gravidity [a]	2.8± 1.8
Living children [a]	1.4 ± 1.6
Body Mass Index [b]	24.5 (19-31)
Educational status[c]	
Primary school[c]	14(%38.9)
Elementary school[c]	5(%13.9)
High school[c]	3 (%8.3)
University[c]	14 (%38.9)
Nationality [b]	
Turkish Republic[c]	34(%94.4)
Syria and Uzbekistan[c]	2(%5.6)
Accomodation [c]	
Town/ Village[c]	3 (%8.3)
City[c]	33(%91.7)
Previous pregnancy with CHD [b]	1(%2.8)
Smoking [b]	4(%11)
Gestational age at diagnosis [a]	23.4 ± 5.1

[a] Data are expressed as mean±standard deviation
[b] Data are expressed as median (minimum-maximum)
[c] Data are listed as numbers and percentages

Eight pregnancies diagnosed with fetal HLHS were terminated (Table 4). Mean gestational age at termination were 21.6± 5.4 weeks. Four pregnancies were terminated after performing amniocentesis. The amniocentesis results were reported as the normal for 3 fetuses and as 46, XX, del(11) t(3;11) (p23;q24) for one fetus who have additional anomaly (holoprosencephaly, cleft lip-palate, multicystic dysplastic kidneys).

Table 2. Hypoplastic left heart syndrome and concomitant congenital heart diseases

Cardiac anomaly	n:36	Frequency (%)
HLHS	20	55,6
HLHS+ VSD	6	16,7
HLHS+ DORV	2	5,6
HLHS+DORV+VSD	5	13,9
HLHS+DORV+PVRA	1	2,8
HLHS+Interrupted Aorta	2	5,6

HLHS: Hypoplastic left heart syndrome, VSD: Ventricular septal defect, DORV: Double outlet right ventricle, PVRA: Pulmonary venous return anomaly

Information related to pregnancy outcomes of 18 patients could not be reached as they were referred to a tertiary center for delivery after diagnosed with fetal HLHS in our center. Four of 10 patients whose delivery information was reached had intrauterine growth retardation (IUGR) and 1 had polyhydramnios additionally.

Three neonates were died in the first week of life following medical treatment, before surgical interventions could be performed, and seven newborns died on mean day 37.2 (4-112) after medical and surgical treatments. The sex of 20 fetuses could be determined of which 11 were females and 9 were males (Table 4).

Table 3. Valvular anomalies seen with hypoplastic left heart syndrome

HLHS Valvular Anomalies[1]	n:26	Frequency (%)
Mitral and aortic valve atresia	14	53.9
Mitral and aortic valve hypoplasia	6	23
Mitral valve atresia and aortic valve hypoplasia	5	19.2
Mitral valve hypoplasia and aortic valve atresia	1	1

[1]Excluding patients with double outlet right ventricle, pulmonary venous return anomaly and interrupted aorta

Discussion

Prenatal diagnosis of pregnancies with fetal HLHS has great importance because the prognosis and outcomes of pregnancies with fetal HLHS are poor and many parents may choose to terminate the pregnancy. Additionally, for parents who want to continue their pregnancy, the diagnosis gives the chance to counselling parents and planning the delivery in a tertiary center where a pediatric cardiovascular unit experienced in the care of neonates with HLHS is available and where the required surgery can be performed [5]. In this study, the HLHS forms 9.4% of CHDs. Chitra et al. reported this rate as 15% [9].

Table 4. Features of patients whose pregnancy outcomes are known

	Gestational age at diagnosis	Additional sonographic findings	Prenatal screening	Cardiac anomaly	Birth method	Birth week	Sex	Days survived	Treatment method
Birth (n:10)	20	None	Combined and triple tests low risk	HLHS+VSD	NVD	41	F	7	Surgical
	22	Cleft lip-palate	Patient did not have the tests done	HLHS	C/S	37	F	31	Surgical
	35	None	Combined and triple tests low risk	HLHS	C/S	36	F	112	Surgical
	30	None	Triple test high risk	HLHS	NVD	39	F	78	Surgical
	20	None	Combined and triple tests low risk	HLHS	C/S	39	M	1	Medical
	20	Thymic hypoplasia	Triple test high risk	HLHS	C/S	39	F	4	Surgical
	20	Cerebellar hypoplasia, clench hands	Combined and triple tests high risk	HLHS	C/S	36	F	2	Medical
	37	None	Combined and triple tests low risk	HLHS	NVD	37	M	10	Surgical
	28	None	Combined test high risk	HLHS +DORV+VSD	C/S	37	F	1	Medical
	22	Ventriculomegaly, pes equinavarus, nuchal fold 18mm	Combined test high risk	HLHS+DORV+ VSD	NVD	39	F	18	Surgical
TOP (n:8)	20	None	Combined and triple tests low risk	HLHS + Interrupted aorta		21	M		
	23	Nuchal fold 8 mm	Combined and triple tests low risk	HLHS		24	M		
	22	None	N/A	HLHS	Hysterotomy	23	M		
	23	None	N/A	HLHS		24	M		
	19	Holoprosencephaly, cleft lip-palate, Increased intestinal echogenity, multicystic dysplastic kidneys	Combined test low risk	HLHS +VSD		21	F		
	23	Diaphragmatic hernia	Patient did not have the tests done	HLHS+ DORV+PVRA		24	F		
	20	None	Triple test low risk	HLHS		21	F		
	23	Multicystic dysplastic kidneys	Combined and triple tests low risk	HLHS+DORV		24	F		

HLHS: Hypoplastic left heart syndrome, VSD: Ventricular septal defect, DORV: Double outlet right ventricle, PVRA: Pulmonary venous return anomaly, C/S: Cesarean section, NVD: Normal vaginal delivery, TOP: Termination of pregnancy, F: Female, M: Male

This difference may result from that our centre does not have a pediatric cardiovascular unit which could have great importance for newborn survival after birth and this condition might affect parents' preference for choosing the centre for delivery. Despite the advances in surgical interventions and medical treatments, the mortality rates for patients with HLHS are still high [7]. A considerable number of chromosomal, cardiac and extracardiac anomalies accompany with HLHS. İn our clinical routine if a fetus diagnosed with HLHS, prenatal invasive testing and detailed fetal ultrasonography are offered to parents. Due to the poor outcomes of pregnancies with fetal HLHS, all parents are informed about the option of pregnancy termination. For parents who choose to terminate their pregnancy because of fetal HLHS, the earlier diagnosis causes less psychological stress [10]. İn this study, 8 of 20 patients whose pregnancy outcomes had been known were terminated.

The mean week of diagnosis for pregnancies with fetal HLHS was 21.6±4.9 weeks, while the mean week for pregnancy termination was 23.4±5.1.

The time gap between diagnosing to pregnancy termination was resulted from difficulty for parents in making a decision for pregnancy termination and for some parents who wanted to receive the result of invasive testing.

Extracardiac anomalies related to syndromes like Turner, Holt-Oram and Noonan are observed in 25% of HLHS patients [11, 12]. Cases accompanied by many extracardiac anomalies like hydrops fetalis, agenesis of the corpus callosum, cleft lip and palate were also reported [13]. In our study, additional anomalies were detected in 34% of the patients.

Concomitant cardiac anomalies such as atrial isomerism, double outlet right ventricle, total anomalous pulmonary venous return were reported with fetal HLHS [14]. The best-known accompanying cardiac anomaly for HLHS is double outlet right ventricle (DORV). Macedo et al. reported that mitral atresia was detected in 4 of 11 patients with DORV [15]. Similarly, in this study, DORV found in 8 of 36 fetuses diagnosed with fetal HLHS.

However, the most concomitant isolated cardiac anomaly was VSD which was detected in 11 of the cases.

HLHS is related to chromosomal anomalies and microdeletion syndromes with a rate of 4-5% [2, 16, 17]. Some cases were found to have single-gene disorders [18]. In this study, the chromosomal analysis of most fetuses is unknown because only 25% of patients accepted amniocentesis. İn one patient 46, XX, der(11) t(3;11) (p23;q24) was detected and preimplantation genetic diagnosis and in vitro fertilization was recommended for the subsequent pregnancy of the patient. Intrauterine growth retardation (İUGR) which is caused by a decrease in cardiac output is common [19]. In this study, IUGR was detected in on thirds of the pregnancies in patients who decided to continue of the pregnancy. Heart transplantation and providing comfort without surgery is a treatment option for patients with HLHS. [20].

Surgical interventions were performed for all newborns except the ones who died in the second days of life. Recent studies reported that 3 to 6-year survival rates for infants who went through the first stage of surgery successfully is raised to 60 to 70 per cent [8, 21]. Despite this, all the infants in our study whose postnatal data are available and the infants who underwent surgery were lost in the first four months of life. Neurodevelopmental status of the surviving infants is not yet clear, though psychomotor and mental development of patients who underwent transplantation was found to be below average [22]. Independent from the type of surgery, IQ (intelligence quotient) was observed to be 86±14, which is below the normal value [23]. Unfortunately, no surviving patients could be reached in our study group.

The weaknesses of the study are that genetic tests could not be performed in most cases, the data of most cases who continued with the pregnancy and newborns also were lost.

The strengths of this study are that all patients in the study were evaluated in the same center with two senior perinatologists and a pediatric cardiologist. The additional fetal anomalies and concomitant fetal cardiac anomalies are well defined.

Conclusion

The outcomes of pregnancy diagnosed with fetal HLHS are poor and the rates of newborn's mortality are high. Although reported studies have an idea that there are trends in the rise of newborn's survival we could not show in this study.

The termination of the pregnancy should be offered as an option to parents because of poor prognosis of the pregnancy with diagnosed with fetal HLHS.

Disclosure

Authors have no potential conflicts of interest to disclose.

References

1.Tchervenkov CI, Jacobs ML, Tahta SA. Congenital Heart Surgery Nomenclature and Database Project: hypoplastic left heart syndrome. Ann Thorac Surg. 2000;69(4 Suppl):S170-S179. doi:10.1016/s0003-4975(99)01283-7

2. Kritzmire SM, Cossu AE. Hypoplastic Left Heart Syndrome. In: StatPearls. Treasure Island (FL): StatPearls Publishing; January 30, 2020.

3.Gordon BM, Rodriguez S, Lee M, Chang RK. Decreasing number of deaths of infants with hypoplastic left heart syndrome. J Pediatr. 2008;153(3):354-358. doi:10.1016/j.jpeds.2008.03.009

4.Reller MD, Strickland MJ, Riehle-Colarusso T, Mahle WT, Correa A. Prevalence of congenital heart defects in metropolitan Atlanta, 1998-2005. J Pediatr. 2008;153(6):807-813. doi:10.1016/j.jpeds.2008.05.059

5.Morris SA, Ethen MK, Penny DJ, Mark A Canfield, Charles G Minard, David E. et al. Prenatal diagnosis, birth location, surgical center, and neonatal mortality in infants with hypoplastic left heart syndrome. Circulation. 2014;129(3):285-292. doi:10.1161/CIRCULATIONAHA.113.003711

6.Mäkikallio K, McElhinney DB, Levine JC, Gerald R Marx, Steven D Colan, Audrey C. et al. Fetal aortic valve stenosis and the evolution of hypoplastic left heart syndrome: patient selection for fetal intervention. Circulation. 2006;113(11):1401-1405. doi:10.1161/CIRCULATIONAHA.105.588194

7. Galindo A, Nieto O, Villagrá S, Grañeras A, Herraiz I, Mendoza A. Hypoplastic left heart syndrome diagnosed in fetal life: associated findings, pregnancy outcome and results of palliative surgery. Ultrasound Obstet Gynecol. 2009;33(5):560-566. doi:10.1002/uog.6355

8.Newburger JW, Sleeper LA, Gaynor JW, Danielle Hollenbeck-Pringle , Peter C Frommelt , Jennifer S Li. et al. Transplant-Free Survival and Interventions at 6 Years in the SVR Trial. Circulation. 2018;137(21):2246-2253. doi:10.1161/CIRCULATIONAHA.117.029375

9.Chitra N, Vijayalakshmi IB. Fetal echocardiography for early detection of congenital heart diseases. J Echocardiogr.

2017;15(1):13-17. doi:10.1007/s12574-016-0308-2
10.Jicinska H, Vlasin P, Jicinsky M, Ilga Grochova , Viktor Tomek , Julia Volaufova. et al. Does First-Trimester Screening Modify the Natural History of Congenital Heart Disease? Analysis of Outcome of Regional Cardiac Screening at 2 Different Time Periods. Circulation. 2017;135(11):1045-1055. doi:10.1161/CIRCULATIONAHA.115.020864
11. Song MS, Hu A, Dyamenahalli U, et al. Extracardiac lesions and chromosomal abnormalities associated with major fetal heart defects: comparison of intrauterine, postnatal and postmortem diagnoses [published correction appears in Ultrasound Obstet Gynecol. 2010 Mar;35(3):376. Dyhamenahali, U [corrected to Dyamenahalli, U]]. Ultrasound Obstet Gynecol. 2009;33(5):552-559. doi:10.1002/uog.6309
12. Connor JA, Thiagarajan R. Hypoplastic left heart syndrome. Orphanet J Rare Dis. 2007;2:23. Published 2007 May 11. doi:10.1186/1750-1172-2-23
13.Brackley KJ, Kilby MD, Wright JG, B Sethia, O Stumper, R Holder. et al. Outcome after prenatal diagnosis of hypoplastic left-heart syndrome: a case series. Lancet. 2000;356(9236):1143-1147. doi:10.1016/s0140-6736(00)02756-2
14. Rasiah SV, Ewer AK, Miller P, J G Wright, D J Barron, W J Brawn.et al. Antenatal perspective of hypoplastic left heart syndrome: 5 years on. Arch Dis Child Fetal Neonatal Ed. 2008;93(3):F192-F197. doi:10.1136/adc.2006.112482
15. Macedo A, Pinto E, Ramos S, M J Brito, M M Costa, I Serrano. et al. Alterações estruturais dos vasos pulmonares e artérias coronárias na síndrome do coração esquerdo hipoplásico [Structural changes in pulmonary vessels and coronary arteries in hypoplastic left heart syndrome]. Acta Med Port. 1991;4(5):253-256.
16. Raymond FL, Simpson JM, Sharland GK, Ogilvie Mackie CM. Fetal echocardiography as a predictor of chromosomal abnormality. Lancet. 1997;350(9082):930. doi:10.1016/s0140-6736(05)63265-5
17. Hinton RB, Martin LJ, Rame-Gowda S, Tabangin ME, Cripe LH, Benson DW. Hypoplastic left heart syndrome links to chromosomes 10q and 6q and is genetically related to bicuspid aortic valve. J Am Coll Cardiol. 2009;53(12):1065-1071. doi:10.1016/j.jacc.2008.12.023
18. McElhinney DB, Geiger E, Blinder J, Benson DW, Goldmuntz E. NKX2.5 mutations in patients with congenital heart disease. J Am Coll Cardiol. 2003;42(9):1650-1655. doi:10.1016/j.jacc.2003.05.004
19. Rosenthal GL. Patterns of prenatal growth among infants with cardiovascular malformations: possible fetal hemodynamic effects [published correction appears in Am J Epidemiol 1996 May 15;143(10):1079]. Am J Epidemiol. 1996;143(5):505-513. doi:10.1093/oxfordjournals.aje.a008771
20. Prsa M, Holly CD, Carnevale FA, Justino H, Rohlicek CV. Attitudes and practices of cardiologists and surgeons who manage HLHS. Pediatrics. 2010;125(3):e625-e630. doi:10.1542/peds.2009-1678
21. Scheurer MA, Salvin JW, Vida VL, Emile A Bacha, Frank A Pigula, John E Mayer Jr. et al. Survival and clinical course at Fontan after stage one palliation with either a modified Blalock-Taussig shunt or a right ventricle to pulmonary artery conduit [published correction appears in J Am Coll Cardiol. 2008 Jul 29;52(5):399]. J Am Coll Cardiol. 2008;52(1):52-59. doi:10.1016/j.jacc.2008.03.034
22. Newburger JW, Sleeper LA, Bellinger DC, Caren S Goldberg, Sarah Tabbutt, Minmin Lu. et al. Early developmental outcome in children with hypoplastic left heart syndrome and related anomalies: the single ventricle reconstruction trial. Circulation. 2012;125(17):2081-2091. doi:10.1161/CIRCULATIONAHA.111.064113
23. Mahle WT, Visconti KJ, Freier MC, Stephen M Kanne, William G Hamilton, Angela M Sharkey. et al. Relationship of surgical approach to neurodevelopmental outcomes in hypoplastic left heart syndrome. Pediatrics. 2006;117(1):e90-e97. doi:10.1542/peds.2005-0575