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Perinatal Outcomes in Hypoplastic Left Heart Syndrome

Hipoplastik Sol Kalp Sendromunda Gebelik Sonuçları

AYSEGUL ATALAY [1] Orcid ID: 0000-0002-4494-9248
DİLEK ŞAHİN [2] Orcid ID: 0000-0001-8567-9048

[1] Ankara City Hospital, Department of Obstetrics and Gynecology, Division of Perinatology, Ankara, Turkey
[2] Ankara City Hospital, Department of Obstetrics and Gynecology, University of Health Sciences, Ankara, Turkey

ÖZ

Amaç: Prenatal olarak hipoplastik sol kalp sendromu (HLHS) tanısı konulan fetüslerdeki deneyimlerimizi gözden geçirmek.

Gereç ve Yöntem: Üçüncü basamak bir sevk merkezinde 2020-2022 yılları arasında prenatal olarak HLHS tanısı alan fetüslerin retrospektif çalışması.

Bulgular: 29 HLHS'li fetüs tespit edildi. 29 olgunun 13'ünde (%44,8) eşlik eden kardiyak anomaliler ve 8'inde (%27,5) eşlik eden ekstrakardiyak anomaliler vardı. Vakaların yalnızca küçük bir azınlığına (%20) invaziv tanı testleri uygulanmıştır ve bunların hepsinin karyotipi normaldir. Vakaların çoğu zamanında doğmuştur (%58,6), doğumdaki ortanca gebelik haftası 37 (dağılım, 34-39) ve ortalama standart sapma doğum ağırlığı 3099±455 gramdır. Ayrıca, HLHS erkek fetüslerde kız fetüslere göre daha yaygındı (%69'a vs %31). Tanı konulan 29 vakanın 4'ünde (%13,7) gebeliğin sonlandırılması seçilmiş ve ≤ 26. gebelik haftasından önce gerçekleştirilmiştir. Gebeliğin 23,29 ve 34. haftalarında 3 intrauterin fetal ölüm (IUFD) gerçekleşmiştir. 29 HLHS vakasının 22'si (%75,8) canlı doğmuştur. Canlı doğan 22 bebekten 3'ü uygun cerrahi adayları olmadıkları için tıbbi prosedürlerle tedavi edilmiş ve daha sonra postnatal 22., 23. ve 25. günlerde ölmüştür. Olguların 15'ine cerrahi uygulanmış olup bunlardan sadece biri halen hayattadır. Yenidoğan döneminin ilk üç ayındaki mortalite oranı %96.5 idi.

Sonuç: Fetal ekokardiyografi, ilk trimesterın sonlarından itibaren HLHS'nin kesin tanısının konulmasına olanak sağlamaktadır. Erken prenatal tespit ve postnatal cerrahi müdahalelere rağmen, merkezimizin son iki yıldaki bulguları, HLHS için kötü sonuçları yansıtmaktadır.

Anahtar Kelimeler: hipoplastik sol kalp sendromu; prenatal; postnatal; sonuç; fetüs

ABSTRACT

Aim: To review our experience in fetuses with prenatally diagnosed hypoplastic left heart syndrome (HLHS).

Materials and Method: Retrospective study of fetuses prenatally diagnosed with HLHS between 2020 and 2022 in a tertiary referral center.

Results: 29 fetuses with HLHS were identified. 13 of all 29 cases (44.8%) had associated cardiac abnormalities and 8 cases (27.5%) had coexisting extracardiac abnormalities. Only a small minority of cases underwent invasive diagnostic testing (20%), and all of which had a normal karyotype. Most cases were delivered at term (58.6%), median gestational week at delivery was 37 (range, 34-39), and the mean standard deviation (SD) birthweight was 3099±455 grams. In addition, HLHS was more common in male than in female fetuses (69% vs 31%). Termination of pregnancy (TOP) was selected in 4 (13.7%) of the diagnosed 29 cases and performed before at ≤ 26 weeks of pregnancy. There were 3 intrauterine fetal demise (IUFD) at 23,29, and 34 weeks of gestation. Among the 29 cases of HLHS, 22 (75.8%) were live born. 3 of 22 live born infants were managed by medical procedures as they were not appropriate surgical candidates and later died at 22nd, 23rd and 25th of postnatal day. Surgery was performed in 15 cases and only one of them is are still alive. Mortality rate in the first three months of neonatal period was 96.5%.

Conclusion: Fetal echocardiography allows an accurate diagnosis of HLHS, which is made even

in the late first trimester. Despite early prenatal detection and postnatal surgical interventions, the results from our center in last two years reflect poor outcomes for HLHS.

Keywords: hypoplastic left heart syndrome, prenatal, postnatal, outcome, fetus

Sorumlu Yazar/ Corresponding Author: Aysegul ATALAY
Adres: Ankara City Hospital, Department of Obstetrics and Gynecology, Division Perinatology, Bilkent blv. No.1 Cankaya, 06800, Ankara, Turkey
E-mail: draysegulatalay@gmail.com

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INTRODUCTION

Hypoplastic left heart syndrome (HLHS) is one of the most severe forms of congenital heart disease, one of the most difficult to treat, and incompatible with life if left untreated. The prevalence of HLHS in the United States is approximately 2 to 3 cases per 10,000 live births and accounts for 2 to 3 percent of all congenital heart diseases (1, 2). The reported incidence is most probably underestimated because the number of spontaneous abortions and terminations of affected fetuses is indeterminate. It is characterized by underdevelopment of the left-sided structures of the heart, which include the mitral valve, left ventricle, aortic valve, and aortic arch, resulting in inadequate support of systemic perfusion. However, the fetus diagnosed with HLHS is very stable, and death in utero is uncommon, but when it does occur, it is often associated with a genetic or chromosomal abnormality. In fetal HLHS, the developed right ventricle usually functions well, providing a combination of placental umbilical venous return and fetal systemic venous return via the fetoplacental circulation.

The vast majority of HLHS cases are detected prenatally by fetal echocardiography, which provides an opportunity for counseling and perinatal planning and also allows prenatal counseling of the family and preparatory planning for delivery and postnatal care by the obstetric and cardiology team. On fetal echocardiography, HLHS is typically characterized by hypoplasia of the left ventricle with mitral atresia or stenosis, aortic atresia or stenosis, and hypoplasia of the ascending aorta.

Despite prenatal diagnosis, counseling, and improved postnatal surgical and medical interventions, mortality and morbidity remain high in our country. Therefore, the aim of this study was to present our experience with prenatally diagnosed HLHS in terms of associated anomalies, neonatal outcomes, and mortality rates to gain experience for future fetal and neonatal interventions.

MATERIALS AND METHOD

We retrospectively analyzed all cases of HLHS diagnosed between 2020 and 2022 at our tertiary referral center for prenatal diagnosis and management of fetal and neonatal disorders during pregnancy. This retrospective study was approved by the local Institutional Review Board (E2-23-3488). We searched our computerized database for prenatally diagnosed HLHS and also performed a literature search to compare our data with those of previous series.

Ultrasound examinations were performed with a Voluson E10 system (GE Healthcare Medical Systems, Milwaukee, WI, USA) and included detailed assessment of cardiac and noncardiac structures according to the International Society of Ultrasound in Obstetrics and Gynecology guidelines (3). Fetal heart examinations were performed with conventional two-dimensional ultrasound and color and pulse-wave Doppler ultrasound by fetal cardiologists and obstetricians specializing in prenatal diagnosis and fetal echocardiography. Prenatal diagnoses were made with the constellation of anatomic findings for HLHS (diminutive LV, abnormal mitral and aortic valves, and a hypoplastic ascending aorta). The diagnoses were confirmed by postnatal echocardiography performed by experienced pediatric cardiologists in liveborn infants during neonatal stay or from autopsies in stillbirths or termination.

According to the definition of the International Nomenclature Society (4), hearts with hypoplasia of the left ventricle with transposition of great arteries (TGA) or double outlet right ventricle (DORV), or with a common atrioventricular septal defect (AVSD), should be excluded. In addition, examination of large series of hearts from pathology archives has confirmed that the integrity of the ventricular septum is one of the most obvious features of HLHS (5, 6). Therefore, we excluded the 9 cases including ventricular septal defect (VSD), and also hypoplastic left ventricle cases due to either transposition or double outlet right ventricle, or with a common atrioventricular junction were also excluded from our study. All pregnant women with early detected fetal HLHS were advised to undergo fetal karyotyping.

To perform this study, the following variables were evaluated: Maternal age, gravidity, parity, previous miscarriage, living child, gestational week at diagnosis, presence of associated cardiac and extracardiac abnormal findings, gestational age at delivery, neonatal sex, birth weight, Apgar scores at the first and fifth minutes, postnatal surgical and medical interventions and follow-up, mortality due to HLHS, and short-term outcomes.

Statistical analysis

Data were collected using an Excel 2007 spreadsheet (Microsoft Corp., Redmond, WA, USA). For statistical analysis, continuous variables were presented as mean and standard deviation (SD) or median and range values according to the normally distribution by using the Kolmogorov–Smirnov test. Categorical variables were presented as numbers and percentages.

RESULTS

During the 2-year period of the current study, 38 pregnancies were evaluated and of the 38 cases complicated by fetal HLHS during the study period, 9 cases were excluded from further analysis: 5 with a coexistent VSD, 2 DORV, 2 AVSD, because we suggest that lesions to be included in HLHS should have an intact ventricular septum. Finally, we included 29 cases in the study analysis.

The characteristics of the study population is presented in Table 1. The mean standard deviation (SD) of maternal age was 27.07±6.50 years and the median (min-max) gestational age at diagnosis of HLHS were 25 (14-38) weeks. Table 1 also outlines the associated cardiac and extracardiac abnormal findings of HLHS cases on the basis of prenatal sonographic appearance. 13 of all 29 cases (44.8%) had associated cardiac abnormalities and 8 cases (27.5%) had coexisting extracardiac abnormalities as detailed in Table 1. According to prenatal sonographic findings, isolated HLHS occurred in 14 (48%) of cases.

First trimester screening was performed in only 12/29 (41%), and 11 cases were reported as low combined risk. Although all pregnant women with early detected fetal HLHS were advised to undergo fetal karyotyping, only a small minority of cases underwent invasive diagnostic testing (20%), and all of which had a normal karyotype.

Table 1. Characteristics and ultrasound findings of 29 fetuses with a prenatal diagnosis of hypoplastic left heart syndrome (HLHS)

	HLHS (n=29)
Maternal age (mean, SD)	27.07±6.50
Gravidity (median, min-max)	2 (1-5)
Parity (median, min-max)	1 (0-3)
Previous miscarriage (median, min-max)	0 (0-2)
Living Child (median, min-max)	1 (0-3)
Gestational week at diagnosis (median, min-max)	25 (14-38)
Diagnosis before 24 weeks of pregnancy (n, %)	13 (44.8%)
Associated cardiac findings (n, %) • Atrial septal defect • Tricuspid regurgitation • Pericardial effusion • Persistent left superior vena cava • Partial anomalous pulmonary venous return • Right isomerism • Supraventricular tachycardia	13 (44.8%)

Table 2 and Table 3 summarize the fetal and neonatal outcomes of all cases with a prenatal diagnosis of HLHS. Most cases were delivered at term (58.6%), median gestational week at delivery was 37 (range, 34-39), and the mean standard deviation (SD) birthweight was 3099±455 grams. In addition, HLHS was more common in male than in female fetuses (69% vs 31%). Termination of pregnancy (TOP) was selected in 4 (13.7%) of the diagnosed 29 cases and performed before at ≤ 26 weeks of pregnancy (Table 3). There were 3 intrauterine fetal demise (IUFD) at 23,29, and 34 weeks of gestation (Table 3).

Table 2. Fetal and neonatal outcomes of fetuses with a prenatal diagnosis of HLHS

	HLHS (n=29)
GA at delivery (median, min-max)	37 (34-39)
Term delivery (n, %)	17 (58.6)
Preterm birth (n, %)	5 (17%)
Birth weight (grams) (mean, SD)	3099±455
Gender (n, %) Male Female	 20 (69%) 9 (31%)
Apgar at 1st minute (median, min-max)	6 (1-7)
Apgar at 5th minute (median, min-max)	8 (3-9)
Mode of delivery (n, %) • Caesarean section • Vaginal delivery	 18 (62%) 11 (38%)
Short term outcome (n, %) • Termination of pregnancy • Intrauterine fetal demise • Live Birth • Mortality	 4 (13.7%) 3 (10.3%) 22 (75.8%) 28 (96.5%)
Management of live births (22/29) • Death before surgery • Death after surgery • Alive after surgery • Not suitable for surgery (medical palliation)	 5/22 14/22 1/22 3/22

Table 3. Characteristics and outcomes of 29 fetuses with a prenatal diagnosis of HLHS

Case	GW at diagnosis	Associated cardiac findings	Associated extracardiac findings	Gender	GW at birth Birth weight	Perinatal outcome
1	37	ASD, TR	SGA	Female	38-2320	Live birth, PN day 12 ex after BAS, Norwood
2	37	-	-	Male	39-3200	Live birth, PN day 23 ex after PB
3	32	-	-	Female	36-3520	Live birth, PN day 0 ex
4	38	ASD, PE	-	Male	38-3680	Live birth, PN day 2 ex after Norwood
5	26	-	-	Male	37-2470	Live birth, PN day 71 ex after PB
6	21	TR	-	Male	24-560	TOP
7	32	TR, PLVCS	SUA, VM, CH	Female	34- 2050	IUFD
8	32	ASD, TR, PAPVR		Male	37-3360	Live birth, PN hour 12 ex after BAS
9	23	ASD	-	Female	39-3300	Live birth, PN day 12 ex after PB
10	32	-	-	Male	38-3140	Live birth, PN day 12 ex after BAS
11	24	-	-	Male	36-2400	Live birth, PN day 10 ex after PB
12	21	ASD, TR		Male	37-3230	Live birth, PN day 11 ex after Norwood
13	23	-	-	Female	39-3860	Live birth, PN day 0 ex
14	37	ASD, TR	-	Male	38-3600	Live birth, PN month 9 ex after Norwood Sano shunt
15	22	PLVCS	SGA	Male	38-2780	Live birth, PN day 2 ex after Norwood
16	22	-	-	Female	26-300	TOP
17	14	-	-	Male	38-3350	Live birth, **18 months alive after PB and Glenn**
18	22	-	SGA	Female	38-2465	Live birth, PN day 22 ex after medical palliation
19	26	-	-	Female	38-3100	Live birth, PN day 11 ex before surgery
20	23	ASD, PAPVR, SVT	Club foot	Male	37-3080	Live birth, PN day 11 ex before surgery
21	33	-	-	Male	36-3370	Live birth, PN day 7 ex after PB
22	34	-	-	Male	38-2480	Live birth, PN day 15 ex after PB
23	36	ASD	-	Female	36-3640	Live birth, PN day 23 ex after medical palliation
24	22	Right isomerism	CCA, VM	Male	26-1060	TOP
25	31	-	-	Male	38-3560	Live birth, PN day 25 ex after medical palliation
26	21	-	SGA	Male	39-2540	Live birth, PN day 5 ex after Norwood
27	26	-	-	Male	29-1300	IUFD
28	21	-	-	Male	22-260	TOP
29	21	TR	VM	Male	23-740	IUFD

ASD, atrial septal defect; TR, tricuspid regurgitation; GW, gestational week; HLHS, hypoplastic left heart syndrome; IUFD, intrauterine fetal demise; IUGR, intrauterine growth restriction; SGA ,small for gestational age; gr, grams; ex, exitus; PND, postnatal; BAS, balloon atrial septostomy, TOP, termination of pregnancy; PLVCS, persisted left vena cava superior; SUA, single umbilical artery; VM, ventriculomegaly; PAPVR, partial anomalous pulmonary venous return; pulmonary banding, PB; SVT, supraventricular tachycardia; CCA, corpus callosum agenesis; CH, cerebellar hypoplasia; PE, pericardial effusion

mong the 29 cases of HLHS, 22 (75.8%) were live born. 3 of 22 live born infants were managed by medical procedures as they were not appropriate surgical candidates and later died at 22nd, 23rd and 25th of postnatal day. Surgery was performed in 15 cases and only one of them is are still alive. He is 18 months old, and bilateral pulmonary banding and subsequent Glenn procedures was performed him. Mortality rate in the first three months of neonatal period was 96.5%.

DISCUSSION

The present study has shown that, unfortunately, our postnatal outcomes in last two years have been extremely poor and far from recent literature (7, 8), and HLHS seems to be the main cause of death, regardless of additional extracardiac, cardiac and chromosomal abnormalities. We have not included cases of HLHS associated with some complex cardiac anomalies (especially those with VSD) in the study to maintain a homogeneous group. Although there is no universal opinion on whether routine ultrasonography can alter outcome, fetal echocardiography allows early diagnosis of HLHS and gives clinicians the opportunity to triage this group depending on prenatal findings. Our data also suggest that HLHS is increasingly diagnosed in utero, in agreement with the literature (7). Although postnatal surgical outcomes in HLHS have steadily improved, significant morbidity and mortality are common (9). Through improvements in fetal diagnosis and innovations in interventional techniques, there is an increasing interest in surgical interventions for a variety of congenital diseases in utero, including spina bifida, congenital diaphragmatic hernia, tumors, and congenital heart disease (10). In some forms of HLHS, fetal aortic stenosis during gestation leads to endocardial fibroelastosis and in utero progression of aortic stenosis to HLHS. Fetal aortic balloon valvuloplasty increases blood flow through the left heart and decreases left

ventricle pressure load and prevents progression to HLHS (11, 12). Fetal cardiac interventions alter the disease progression and may potentially improve our postnatal outcomes. Therefore, future high-risk cohort studies are needed.

In our study, HLHS predominated in males (69% vs. 31%), which is consistent with most population-based and clinical studies (13, 14). A previous multicenter study between 2003 and 2014 showed that the presence of Turner, DiGeorge, and Down syndromes was associated with increased mortality and morbidity in infants with HLHS (15). However, although all the pregnant women with early detected fetal HLHS were recommended to undergo fetal karyotyping, only a small minority of cases (20%) underwent invasive diagnostic testing, and all of these women had a normal karyotype.

The presence of HLHS is often suspected or can be readily diagnosed by an obstetrician at the 20 weeks pregnancy obstetric ultrasound owing to the great distortion in the 4-chamber view whether or not the presence of associated cardiac, extracardiac and chromosomal abnormalities. However, in only 44% of cases, the diagnosis was made before the 24th week of pregnancy, which is lower than the observations of previous studies (16, 17). This is due to the fact that our clinic is a referral center, and not a primary follow-up.

In the present study, approximately 27.5% of associated extracardiac and 44.8% of cardiac defects were detected. Despite the frequency of extracardiac abnormalities in the literature ranges between 3% and 62% (7, 18, 19), our results are consistent with the majority of outcome studies(20). Song et al. reported in a multicenter study that isolated HLHS occurred in 62.8% of cases (21) . However, Tennstedt et al. reported that isolated HLHS was found only 38% of fetuses examined by autopsy (22), and Wojtowicz et al. reported 40% isolated HLHS (17), which is consistent with the present study, in which isolated HLHS occurred in 48% of our cases.

Our study has several limitations. The main limitations of the present study are the relatively small sample size and the retrospective design. Namely, we conducted an institutional rather than a population-based study that included a small number of fetuses with HLHS. In addition, as mentioned previously, large series from literature have confirmed that the integrity of the ventricular septum is one of the most obvious features of HLHS (5, 6). Therefore, because we also excluded the cases including VSD, our sample size was even smaller compared to studies with included (17).

CONCLUSION

Fetal echocardiography allows an accurate diagnosis of HLHS, which is made even in the late first trimester. Despite early prenatal detection and postnatal surgical interventions, the results from our center in last two years reflect poor postnatal outcomes for HLHS. To improve postnatal outcomes, we hope that our study will contribute to the more frequent use of fetal cardiac interventions in clinical practice than ever before.

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