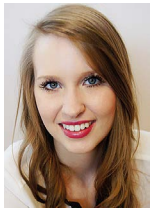
Prenat Cardio 2022; 12(1): 25-30
DOI: https://doi.org/10.5114/pcard.2023.126182
Received: 20.01.2023
Accepted: 14.03.2023

Prenatal Cardiology
www.termedia.pl/Journal/Prenatal_Cardiology

Case report

Prenatal diagnosis of hypoplastic left heart syndrome with PAPVC and FO restriction and pulmonary hypertension – coexisting factors suggesting poor prognosis due to pulmonary hypertension with histopathological confirmation



Aleksandra Nowakowska[1], Michał Krekora[2], Tomasz Talar[3], Marek Kopala[4], Hanna Romanowicz[5], Maria Respondek-Liberska[1,6]

[1]Department for Prenatal Cardiology, Polish Mother's Memorial Hospital Research Institute, Lodz, Poland
[2]Department of Obstetrics and Gynaecology, Polish Mother's Memorial Hospital Research Institute, Lodz, Poland
[3]Department of Neonatology, Polish Mother's Memorial Hospital Research Institute, Lodz, Poland
[4]Department of Cardiac Surgery, Polish Mother's Memorial Hospital Research Institute, Lodz, Poland
[5]Department of Pathology, Polish Mother's Memorial Hospital Research Institute, Lodz, Poland
[6]Department for the Diagnosis and Prevention of Fetal Malformations, Medical University of Lodz, Poland

Abstract

Prenatal hypoplastic left heart syndrome (HLHS) is widely described in the literature as a congenital heart defect with underdevelopment of the left side of the heart. There are many well-known risk factors that comprise a poor prognosis, such as coexisting genetic syndrome, or extra-cardiac malformations like diaphragmatic hernia, premature delivery, low birth weight, etc. Herein we present an isolated case of HLHS, with echocardiographic data from the third trimester, after in utero transfer, born at term in a tertiary centre with an obstetrics, cardiology, and cardiac surgery department within the same research institute, with Prostin administration without delay, Norwood procedure planned relatively early, but despite all efforts – neonatal demise. We believe that the main cause of death was pulmonary hypertension, and such an observation was never published before.

Key words: pulmonary hypertension, Norwood operation, HLHS, partial anomalous pulmonary venous connections, restriction foramen ovale.

Corresponding author:
Aleksandra Nowakowska
Department for Prenatal Cardiology
Polish Mother's Memorial Hospital Research Institute
Rzgowska 281/289
93-338 Lodz
e-mail: aaleksandra.nowakowska@gmail.com

Introduction

Hypoplastic left heart syndrome (HLHS) is one of the most common, prenatally diagnosed congenital heart diseases (CHD) [1-3]. In this CHD, the right ventricle serves as the main pump supplying blood to both pulmonary and systemic circulation, while the left ventricle has almost no haemodynamic function.

The outcome of patients with HLHS has improved over the years because of prenatal diagnosis, perinatal care, trans-

fer in utero, early intra-venous Prostin administration, surgical techniques, and perioperative care. Neonatal HLHS is usually referred for planned cardiac surgery, but despite the development of neonatal cardiac surgery, some coexisting additional factors make the outcome poor [4-5]. Our retrospective analysis of the presented case has suggested paying attention to pulmonary hypertension as a new coexisting factor and prediction of poor prognosis.

Case report

A 29-year-old woman (gravida 2 para 2) was referred to our tertiary centre (Prenatal Cardiology, Obstetrical Department, Paediatric Cardiac Surgery Department in the same hospital) for fetal echocardiography examination at 27 weeks of gestation due to suspicion of hypoplastic left heart syndrome (detected at 20 weeks of gestation). She did not provide an ultrasound examination from the first trimester of pregnancy. At an initial echocardiographic examination in our centre, left heart syndrome with mitral and aortic valve atresia was confirmed. There was also fibroelastosis of the left ventricle. In pulmonary venous flow there was high velocity with reversal flow (Figure 1), but with low risk of restriction foramen ovale (FO) (velocity time integral – VTI f/r = 8). Next examination was at 32 weeks, without significant progression.

At 33 weeks, in addition to previous findings, partial anomalous pulmonary venous return was diagnosed. The left pulmonary veins formed a common collector, which went behind the left atrium intracardially, because the left atrium was not completely filled with blood despite power angio Doppler with low flow velocity, so it was an indirect sign not published before (Figure 2). An oxygen test was performed during the study, without pulmonary vein reaction.

At 35 weeks the velocity of blood flow in the foramen ovale was around 120 cm/s and VTI f/r = 5, so high risk of restrictive foramen ovale was diagnosed (Figure 3).

The last fetal echo examination was at 36 weeks with the following final conclusions: HLHS + mitral and aortic valve atresia, fibroelastosis, partial anomalous pulmonary venous return with reversal flow in pulmonary veins, restrictive foramen ovale (in the 36th week VTI f/r = 3) (Table 1), and dilatation of the pulmonary trunk (Figure 4).

At 38 weeks, a female newborn was born by elective caesarean section with birth weight 3200 g and Apgar score 9/9. Neonatal echocardiographic examination confirmed the prenatal diagnosis: partial anomalous pulmonary venous return (intracardially) with preserved communication and leak in IAS.

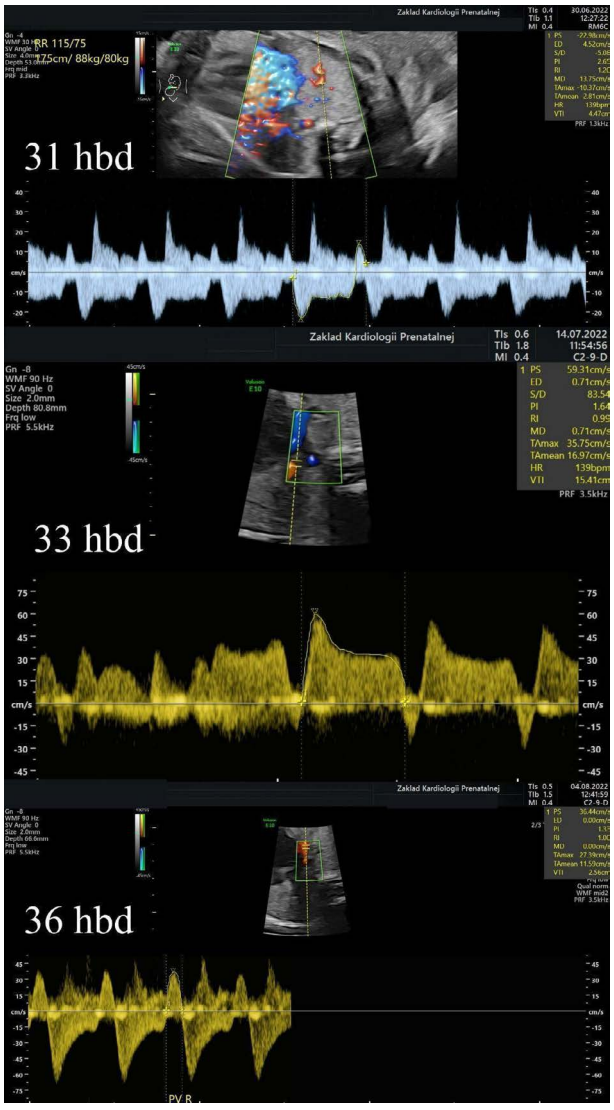


Figure 1. Pulmonary veins blood flow at 31, 33, and 36 weeks of gestation with moderate reversal flow without significant progression

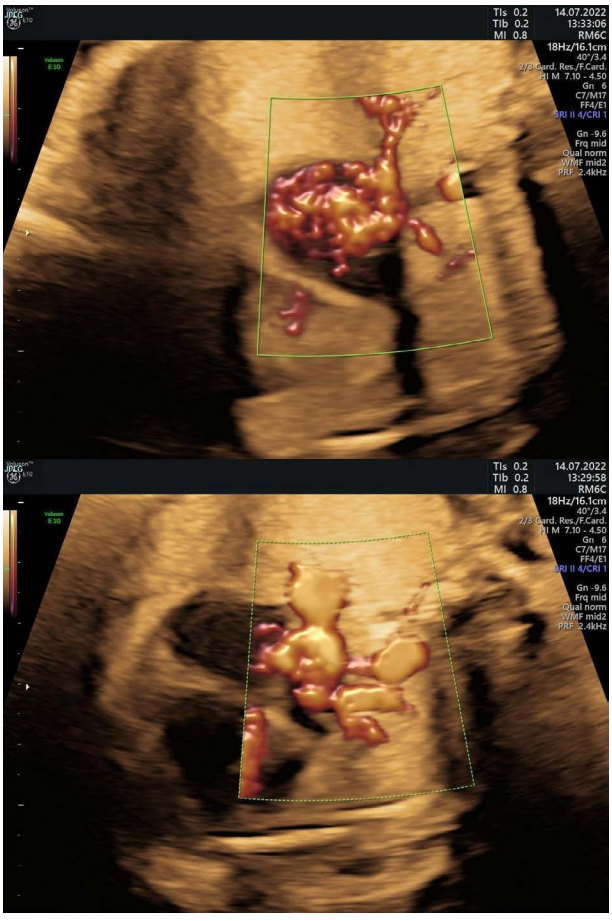


Figure 2. Abnormal blood filling of the left atrium, which suggested partial anomalous pulmonary venous connections

Despite IV Prostin infusion, several hours later there was peripheral and central cyanosis with saturation around 60-80%.

On the 7th day of postnatal life the Norwood operation was performed. Part of the Norwood procedure is an excision of interatrial septum II, normally creating large communication between left and right atrium. In this patient there was an intracardiac type of partial anomalous pulmonary vein return. After surgical removal of IAS II, additional relief of pulmonary vein inflow was not needed.

Postoperative examination revealed neoAo regurgitation (72 cm/s), narrow pulmonary branches, good inflow systolic function in RV, but impaired outflow contractility. Due to hypotension, scanty diuresis on infusion of catecholamines, pericardial effusion, and poor general condition, the newborn was qualified for ECMO procedure. Despite initial improvement, on the 17th day her death was announced. Based on an autopsy and histopathology findings, concentric thickening of smaller and larger intrapulmonary vessels were revealed as features of pulmonary hypertension (Figure 5).

Discussion

Despite the development of reconstructive surgery in the early 1980s, a considerable number of infants with HLHS remain at high risk of mortality (Table 2) [6-8]. One of the most critical risk factors includes restrictive FO with secondary left atrial (LA) hypertension [9-12]. Restrictive FO causes obstructed blood flow from the left to the right atrium, and blood pressure in the left atrium increases, leading to passive lung congestion and haemodynamic instability. In newborns with a highly restrictive FO or intact atrial septum, even if the surgical procedure is performed immediately after delivery, the prognosis is worse (mortality 50%) than in newborns with unobstructed inter-atrial communication (mortality 23%) [7, 8]. One of the methods for assessing restricted FO is the evaluation

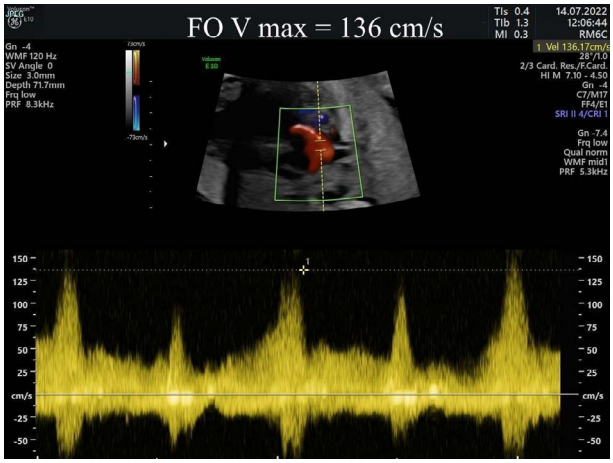


Figure 3. Restriction of blood flow left-right at the foramen ovale after 35th week of gestational age

of the ratio of the forward blood flow to the reversal flow (VTI f/r) in the pulmonary veins, using the spectral Doppler [13]. The greater the narrowing of the FO, the greater the reversal of blood flow. The ultrasound criterion of non-restricted FO is a VTI f/r ratio > 5 [14]. A forward to reversal VTI ratio of less than 5 and greater than 3 is associated with moderate FO restriction, whereas a VTI f/r of less than 3 is present in severe FO restriction and intact atrial septum cases [15-17].

Also, a maternal hyperoxygenation (MHO) test may be also useful in fetuses with HLHS. Żalińska *et al.*, in their latest review, described the potential benefits of performing MHO during pregnancy [18]. Because of oxygen delivery to the fetus, pulmonary blood flow increases, and increased venous return to the left heart is caused by an increased pulmonary blood flow after MHO with substantial improvement in the left ventricular filling, which causes more blood pumping to the aorta and stimulates its growth. This phenomenon may play a signifi-

Table 1. Longitudinal echocardiographic examination in the presented fetus with HLHS in the Prenatal Cardiology Department

Parameter	Week of gestation – LMP					Comment
	27.6	32.1	33.5	35.5	36.5	
Fetal estimated growth [g]	1143 ±167	1636 ±239	2274 ±332	3088 ±451	3297 ±438	Normal biometry
Cardiac basic anatomy	HLHS Mitral valve atresia Aorta atresia Fibroelastosis	HLHS Mitral valve atresia Aorta atresia Fibroelastosis	HLHS Mitral valve atresia Aorta atresia Fibroelastosis	HLHS Mitral valve atresia Aorta atresia Fibroelastosis	HLHS Mitral valve atresia Aorta atresia Fibroelastosis	No change
Cardiac detailed anatomy with intracardiac blood flow assessment			Pulm. vein. return anomaly LSVC	Pulm. vein. return anomaly LSVC FO restriction	Pulm. vein. return anomaly LSVC FO restriction	PAPVC FO restriction
Assessment of pulmonary venous flow	Reversal flow in pulmonary veins	Reversal flow in pulmonary veins	Reversal flow in pulmonary veins	Reversal flow in pulmonary veins	Reversal flow in pulmonary veins	No progression
MPA with [mm]	8.6 (Z-score +4.18)	10 (Z-score +4.12)	12 (Z-score +5.09)	12 (Z-score +4.4)	13 (Z- score +4.64)	Progression
Risk of restrictive FO by VTI f/r	VTI f/r 9.8	VTI f/r 9.8	VTI f/r 13	VTI f/r 5-7	VTI f/r 3.5-3.8	Progression

LMP – last menstrual period, HLHS – hypoplastic left heart syndrome, LSVC – left superior vena cava, FO – foramen ovale, PAPVC – partial anomalous pulmonary venous connections, VTI f/r – velocity time integral.

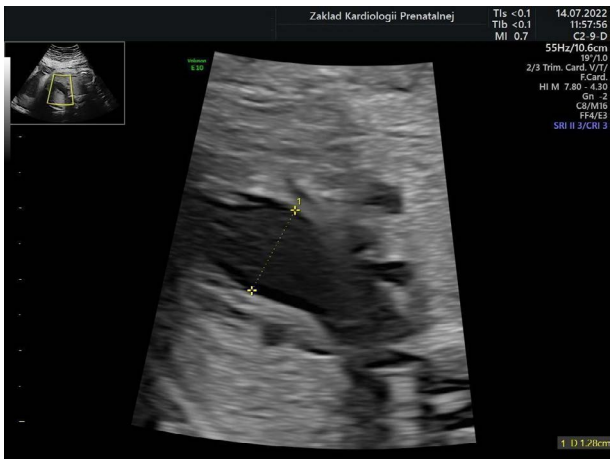


Figure 4. Main pulmonary artery dilatation – 12.8 mm at 36 weeks of gestation

cant role in fetuses with HLHS, because of the small left ventricle and narrowing aorta. Other publications also concluded that MHO in fetuses with HLHS could be useful in predicting emergent atrial septoplasty after birth [19-22].

In the present case, foramen ovale restriction was seen but relatively late – from the 35th week of gestation, so it was not considered as long lasting or predictive of poor neonatal condition just after birth [13]. The Norwood operation was planned and performed on the 7th day of postnatal life (in our centre the mean day for the Norwood procedure in 2020-2021 was on the 9-10th day). This surgical method is defined as the creation of an aortopulmonary connection and neoaortic arch construction resulting univentricular physiology and the creation of a source of pulmonary blood flow with a calibrated systemic-to-pulmonary artery shunt (connection of right ventricle to pulmonary artery) [23-25].

Jadczak *et al.* concluded that earlier development and longer presence of FO restriction in HLHS is associated with higher short-term mortality, regardless of the degree of restriction [13]. In this case, despite late diagnosis of FO restriction, early, planned operation, the newborn still had symptoms of cardiopulmonary failure.

An important additional poor prognostic factor was dilated pulmonary trunk seen prenatally, suggesting abnormal lung development, which correlated with pulmonary hypertension [26].

The next important prenatal finding in the presented case was partial anomalous pulmonary venous connections (PAPVC). This prenatal anomaly is rarely described in the literature [27, 28]. Total anomalous pulmonary venous connections (TAPVC)

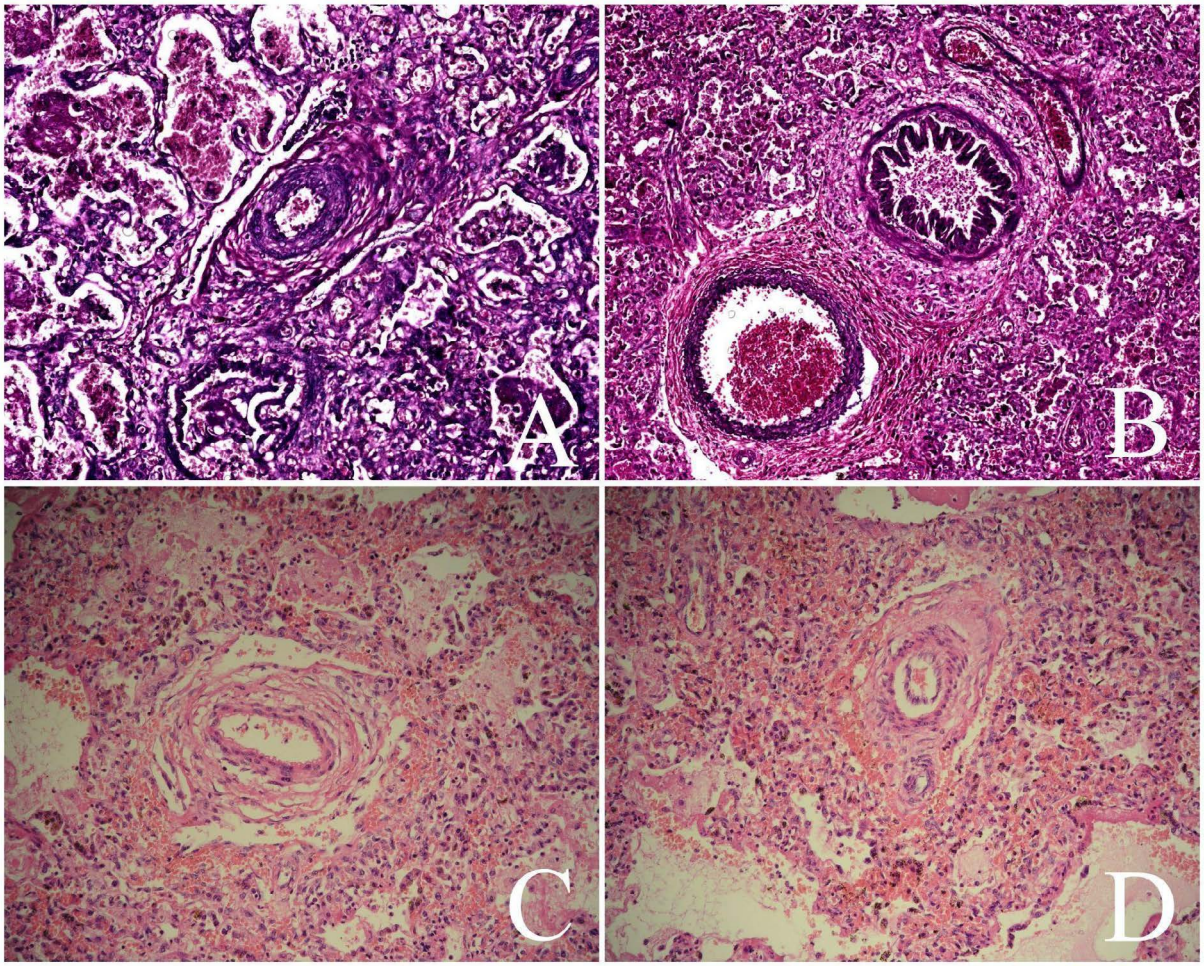


Figure 5. Characteristics of pulmonary hypertension in histopathology. **A** – Concentric thickening of the intrapulmonary arteriole with fibril proliferation. **B** – Concentric thickening of intrapulmonary arterioles and veins with proliferation of elastic fibres. **C** – Concentric thickening of the intrapulmonary arterioles. **D** – Concentric thickening of intrapulmonary arterioles and veins

Table 2. Fetal sonographic risk factors for fetuses with HLHS based on current literature [2, 12-16, 20, 22]

Risk factor based on prenatal ultrasound	Year of publication	Authors
Pulmonary venous flow patterns	2005	Michelfelder *et al.*
Mitral insufficiency	2010	Rogers *et al.*
Restriction of FO	2011 2018 2020	Divanovic *et al.* Gellis *et al.* Jadczak *et al.* Sokołowski *et al.*
Main pulmonary artery dilatation	2021	Murlewska *et al.*
Abnormal pulmonary veins connection LS pulm. vein to innominate vein	2013 2022	Góra *et al.* Di Pasquale *et al.*
Coexisting diaphragmatic hernia	2022	Kanade *et al.*

FO – foramen ovale, LS – left superior.

and PAPVC represent rare anomalies, accounting for 1-3% of all cardiac malformations detected after birth, and supracardiac or infracardiac anomalous pulmonary venous connections are much better described than intracardiac [29].

In the presented case, PAPVC was first detected in the 3rd trimester, at 33 weeks of gestation, because only part of the left atrium was fulfilled by Doppler slow colour blood flow. It was assumed that this was due to abnormal connection of veins and was confirmed after birth during neonatal echocardiography as intracardial PAVC. This observation, as partial filling of left atrium by fetal blood in the case of PAVC, is reported for the first time. As far as we are concerned, it was not observed before.

Total and partial anomalous venous connection comprises a wide spectrum of congenital cardiovascular malformations in which one or more pulmonary veins returns to the right atrium or systemic venous circulation instead of draining directly into the left atrium [29]. Góra *et al.* [30] published 3 cases with HLHS + TAPVC and concluded that these complex heart defects, despite echocardiographic supervision and deliveries in the main obstetric centre, caused quick haemodynamic deterioration and the demise of newborns even before surgery. But histopathology of neonatal lungs was not possible in every case.

What is known, in fetuses with HLHS, severe restriction of FO, and premature closure of the atrial septum leads to left atrial hypertension and remodeling of the pulmonary vasculature, which can severely worsen the prognosis. In our case, in combination with restrictive FO, partial abnormal flow of pulmonary veins with abnormal flow contributed to the increase in features of pulmonary hypertension, which led to the most serious consequences. We were wondering – due to numerous unfavourable prognostic factors in the presented case (including PAPVC + restrictive FO + dilated main pulmonary artery) – whether earlier surgical intervention would be a better choice, perhaps in the first 24 hours of life.

Jayakumar *et al.* [27] described a rare situation in which the 2 right-sided and 2 left-sided pulmonary veins each formed a confluence and drained into the left atrium. It was similar to our case in which veins formed a common collector. The newborn developed progressive pulmonary venous congestion and severe acidosis. Because of dismal clinical outcomes in view of her comorbidities, including prematurity, severe IUGR, and obstructed pulmonary veins with recognized pulmonary vascular disease, surgical intervention was not performed in that case.

In the Washington centre, in fetuses with prenatal restriction of FO, the Rashkind procedure was performed in the first minute after birth in the delivery room [31]. The survival rate of the HLHS group with a highly restrictive FO or intact atrial septum, after the Rashkind procedure and the first stage of cardiac surgery, was 33-48%.

In the Boston centre, in-utero surgical treatment was performed, and the 6-month survival rate of patients treated *in utero* was significantly greater than for those in whom FO balloon septostomy was only performed after birth (69% vs. 38%, respectively) [32]. These two observations make us think that early intervention in the most difficult cases of HLHS may be a chance for these newborns to prolong their survival, and prenatal echocardiography and early diagnosis is a clue to further management.

In the presented case, on the first neonatal echo, restriction of the foramen ovale was not seen, and despite complex HLHS the neonatal condition was stable, and there were no clinical symptoms of pulmonary hypertension.

Conclusions

Partial anomaly pulmonary venous return, wide main pulmonary artery, and restrictive foramen ovale were unfavourable risk factors in our case of HLHS, and despite relatively early surgical intervention, there was a poor outcome with autopsy-histopathology findings of pulmonary hypertension.

Conflict of interest

The authors declare no conflict of interest.

REFERENCES

1. Kordjalik P, Respondek-Liberska M. HLHS on the basis of nationwide registry of fetal cardiac pathology www.orpkp.pl. Prenat Cardio 2013; 3: 18-21.
2. Tulzer A, Huhta JC, Hochpoechler J, Holzer K, Karas T, Kielmayer D, et al. Hypoplastic left heart syndrome: is there a role for fetal therapy? Front Pediatr 2022; 10: 944813.

3. Kanade R, Shazly S, Ruano R. Interventions and neonatal outcomes of fetuses with hypoplastic left heart syndrome and congenital diaphragmatic hernia: a systematic review. J Matern Fetal Neonatal Med 2022; 35: 4184-4189.
4. Ono M, Kido T, Wallner M, Burri M, Lemmer J, Ewert P, et al. Preoperative risk factors influencing inter-stage mortality after the Norwood procedure. Interact Cardiovasc Thorac Surg 2021; 33: 218-226.
5. Respondek-Liberska M. Classification of congenital heart defects in prenatal cardiology in the third trimester and before delivery in congenital heart defects – diagnosis and treatment. PZWL, Warsaw 2022.
6. Goldberg CS, Gomez CA. Hypoplastic left heart syndrome: new developments and current controversies. Semin Neonatol 2003; 8: 461-468.
7. Yabrodi M, Mastropietro CW. Hypoplastic left heart syndrome: from comfort care to long-term survival. Pediatr Res 2017; 81: 142-149.
8. Rogers L, Peterson A, Rychik J. Aortic outflow hypoplasia with dilated left ventricle and severe mitral insufficiency: the mitral valve dysplasia syndrome. Ultrasound Obstet Gynecol 2010; 36: 198.
9. Taketazu M, Barrea C, Smallhorn JF, Wilson GJ, Hornberger LK. Intrauterine pulmonary venous flow and restrictive foramen ovale in fetal hypoplastic left heart syndrome. J Am Coll Cardiol 2004; 43: 1902-1907.
10. Tulzer A, Arzt W, Prandstetter C, Tulzer G. Atrial septum stenting in a foetus with hypoplastic left heart syndrome and restrictive foramen ovale: an alternative to emergency atrioseptectomy in the newborn – a case report. Eur Heart J Case Rep 2020; 4: 1-4.
11. Zhang A, Luo G, Sun Y, Chen T, Pan S. Creation of high position fetal balloon atrial septoplasty for hypoplastic left heart syndrome and highly restrictive atrial septum: a case report and literature review. J Interv Med 2020; 3: 55-57.
12. Glatz JA, Tabbutt S, Gaynor JW, Rome JJ, Montenegro L, Spray TL, et al. Hypoplastic left heart syndrome with atrial level restriction in the era of prenatal diagnosis. Ann Thorac Surg 2007; 84:1633-1638.
13. Jadczak A, Respondek-Liberska M, Sokołowski Ł, Chrzanowski J, Rizzo G, Araujo Júnior E, et al. International Prenatal Cardiology Collaboration Group. Hypoplastic left heart syndrome with prenatally diagnosed foramen ovale restriction: diagnosis, management and outcome. J Matern Fetal Neonatal Med 2022; 35: 291-298.
14. Sokolowski Ł, Respondek-Liberska M, Pietryga M, Slodki M. Prenatally diagnosed foramen ovale restriction in fetuses with hypoplastic left heart syndrome may be a predictor of longer hospitalization, but not of a need for an urgent rashkind procedure. Ginekol Pol 2019; 90: 31-38.
15. Divanović A, Hor K, Cnota J, Hirsch R, Kinsel-Ziter M, Michelfelder E. Prediction and perinatal management of severely restrictive atrial septum in fetuses with critical left heart obstruction: clinical experience using pulmonary venous Doppler analysis. J Thorac Cardiovasc Surg 2011; 141: 988-994.
16. Gellis L, Drogosz M, Lu M, Sleeper LA, Cheng H, Allan C, et al. Echocardiographic predictors of neonatal illness severity in fetuses with critical left heart obstruction with intact or restrictive atrial septum. Prenat Diagn 2018; 38: 788-794.
17. Michelfelder E, Gomez C, Border W, Gottliebson W, Franklin C. Predictive value of fetal pulmonary venous flow patterns in identifying the need for atrial septoplasty in the newborn with hypoplastic left ventricle. Circulation 2005; 112: 2974-2979.
18. Zalinska A, Respondek-Liberska M, Slodki M. Maternal hyperoxygenation during pregnancy as a tool in fetal disease diagnosis and treatment. J Clin Ultrasound 2023; 51: 273-282.
19. Respondek-Liberska M, Donofrio M. Maternal hyperoxygenation in prenatal ultrasound and fetal echocardiography – literature review 2020. Prenat Cardio 2021; 1: 5-12.
20. Szwast A, Tian Z, McCann M, Donaghue D, Rychik J. Vasoreactive response to maternal hyperoxygenation in the fetus with hypoplastic left heart syndrome. Circ Cardiovasc Imaging 2010; 3: 172-178.
21. Channing A, Szwast A, Natarajan S, Degenhardt K, Tian Z, Rychik J. Maternal hyperoxygenation improves left heart filling in fetuses with atrial septal aneurysm causing impediment to left ventricular inflow. Ultrasound Obstet Gynecol 2015; 45: 664-669.
22. Enzensberger C, Axt-Fliedner R, Degenhardt J, Kawecki A, Tenzer A, Kohl T, et al. Pulmonary vasoreactivity to materno-fetal hyperoxygenation testing in fetuses with hypoplastic left heart. Ultraschall Med 2016; 37: 195-200.
23. Goldberg CS, Gaynor JW, Mahle WT, Ravishankar C, Frommelt P, Ilardi D, et al. Pediatric Heart Network Investigators. The pediatric heart network's study on long-term outcomes of children with HLHS and the impact of Norwood Shunt type in the single ventricle reconstruction trial cohort (SVRIII): design and adaptations. Am Heart J 2022; 254: 216-227.
24. Jacobs JP. Hypoplastic left heart syndrome: definition, morphology, and classification. World J Pediatr Congenit Heart Surg 2022; 13: 559-564.
25. Mroczek T. HLHS: complex anatomic surgical considerations during treatment pathway. World J Pediatr Congenit Heart Surg 2022; 13: 600-608.
26. Murlewska J, Sylwestrzak O, Respondek-Liberska M. Unfavorable postnatal outcome with significant dilation of the fetal main pulmonary artery near term. Birth Defects Res 2021; 113: 55-62.
27. Jayakumar KA, Tilak G, Das BB. Reports of 2 rare associations of hypoplastic left heart syndrome. JACC Case Rep 2019; 1: 526-531.
28. Di Pasquale L, Cesnjevar R, Jäger O, Dave H. Surgical correction of partial anomalous left superior pulmonary venous connection to the innominate vein. Multimed Man Cardiothorac Surg 2022. doi: 10.1510/mmcts.2022.065.
29. Paladini D, Pistorio A, Wu LH, Meccariello G, Lei T, Tuo G, et al. Prenatal diagnosis of total and partial anomalous pulmonary venous connection: multicenter cohort study and meta-analysis. Ultrasound Obstet Gynecol 2018; 52: 24-34.
30. Góra E, Moczulska H, Janiak K, Słodki M, Respondek-Liberska M. Anomalous pulmonary venous return with stenosis in complex left heart defect – lethal anomaly – 3 case report. Prenat Cardio 2013; 3: 22-27.
31. Sanapo L, Pruetz JD, Słodki M, Goens MB, Moon-Grady AJ, Donofrio MT. Fetal echocardiography for planning perinatal and delivery room care of neonates with congenital heart disease. Echocardiography 2017; 34: 1804-1821.
32. Vida VL, Bacha EA, Larrazabal A, Gauvreau K, Thiagaragan R, Fynn-Thompson F, et al. Hypoplastic left heart syndrome with intact or highly restrictive atrial septum: surgical experience from a single center. Ann Thorac Surg 2007; 84: 581-585.

Division of work:
Aleksandra Nowakowska (ORCID: 0000-0003-3228-5533): data analysis and interpretation, writing the article.
Michał Krekora (ORCID: 0000-0002-5496-4556): collection and/or assembly of data.
Tomasz Talar (ORCID: 0000-0002-1192-1601): collection and/or assembly of data
Marek Kopala (ORCID: 0000-0003-1222-192X): collection and/or assembly of data.
Hanna Romanowicz (ORCID: 0000-0003-3898-4861): collection and/or assembly of data.
Maria Respondek-Liberska (ORCID: 0000-0003-0238-2172): research concept and design, data analysis and interpretation, critical revision of the article, final approval of the article.