Research paper

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Hypoplastic left heart syndrome with mitral regurgitation: a new marker of poor fetal outcome

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HLHS; hypoplastic left heart syndrome; mitral regurgitation; tricuspid regurgitation; prenatal cardiology

Abstract

Aim: Hypoplastic left heart syndrome is a severe congenital heart defect that may be accompanied by tricuspid and mitral valve regurgitation. The aim of this paper is to identify a new ultrasound marker for evaluating the outcomes of fetuses with hypoplastic left heart syndrome. **Material and methods:** This was a single-center analysis of a group of fetuses who underwent fetal ultrasound examinations at our tertiary center between 2016 and 2023. This study included 80 fetuses with hypoplastic left heart syndrome. The gestational age of the studied fetuses ranged from 16.3 to 39.5 weeks. All anomalies and irregularities accompanying hypoplastic left heart syndrome were detected during the second and third trimesters of pregnancy. **Results:** Among fetuses with hypoplastic left heart syndrome with tricuspid regurgitation, the mortality rate was 0% (0/16) and the survival rate was 100% (16/16). In contrast, in fetuses with hypoplastic left heart syndrome with both tricuspid and mitral regurgitation, the mortality rate was 75% (3/4) and the survival rate was 25% (1/4). The incidence of death was significantly higher in the group of fetuses with hypoplastic left heart syndrome with both tricuspid and mitral regurgitation compared to the group with tricuspid regurgitation (Yates's chi-squared test: $p = 0.003$; Fisher's test: $p = 0.0035$). **Conclusions:** The coexistence of hypoplastic left heart syndrome with tricuspid and mitral regurgitation is significantly associated with the death of newborns even when treatment and/or surgery is performed. Therefore, the presence of mitral regurgitation in fetuses with hypoplastic left heart syndrome may serve as an additional ultrasound marker for poor neonatal outcome.

Introduction

Hypoplastic left heart syndrome (HLHS) is a severe congenital heart defect and one of the commonly diagnosed congenital heart defects (CHD) during prenatal life. Data collected from the Polish Nationwide Registry of Fetal Cardiac Pathology in the years 2004 to 2018 shows that HLHS accounted for 2.96% of the 9,542 CHDs diagnosed prenatally and published in the Registry[1,2]. Worldwide, HLHS constitutes 3% of all infants born with CHDs[3]. The potential survival of a neonate with HLHS depends on several factors, including a patent ductus arteriosus and good communication at the level of both atria. Therefore, post-birth management includes the administration of prostaglandin E1 (PGE1) to maintain ductus arteriosus patency. Newborns with HLHS have several treatment options, including the Norwood procedure, heart transplantation, or palliative care. One such option is hybrid treatment, dedicated especially for neonates with low birth weight and those born prematurely. Treatment is important because neonates demonstrate quite high pulmonary vascular resistance at birth. The problem is that after birth pulmonary resistance decreases, leading to increased blood flow through the pulmonary vessels and affecting systemic circulation. If the ductus arteriosus is not properly managed and closes, a reduction in systemic circulation is observed, quickly resulting in cardiovascular insufficiency. In general, the prognosis in HLHS is poor, with only two-thirds of children surviving up to five years of age. Moreover, approximately 33% of neonates die before undergoing any palliative surgical care, and 12.7% of neonates with a single ventricle have a greater risk for cardiac arrest, while 62.3% do not survive[3]. Recent advances in prenatal screening and diagnostic technologies have enabled healthcare providers to identify HLHS in fetuses and plan postnatal management in newborns. The aim of this study was to develop a new ultrasound marker for better prediction of fetal outcomes in cases of HLHS. HLHS may be accompanied by functional changes affecting the tricuspid and mitral valves. The mitral valve may be hypoplastic, with thickened leaflets that are barely movable, or it may have short chordae tendineae.

Sometimes, HLHS is characterized by tricuspid valve insufficiency (regurgitation), despite normal anatomy. The presence of tricuspid insufficiency is a sign of disfunction of the right ventricle. Since both mitral and tricuspid valve disfunctions may affect fetal and neonatal health, the presence of HLHS combined with regurgitation of the mitral and tricuspid valves may indicate a poor prognosis, leading to heart and pulmonary failure. Between 1999 and 2003, Respondek-Liberska M. analyzed 35 fetuses with prenatally diagnosed HLHS at the Prenatal Cardiology Department, showing that around 17% of newborns survived[5]. Prenatal echocardiography makes it possible to assess the severity of congenital heart defects and plan appropriate management and treatment for newborns, including a multidisciplinary team of obstetricians, neonatologists, cardiologists, and surgeons. Additional cardiovascular and extracardiac anomalies that accompany HLHS include ventricular septal defect, atrial septal defect, right aortic arch, single umbilical artery, persistent left superior vena cava, and agenesis of ductus venosus[6]. A recently proposed ultrasound marker for fetal outcomes in fetuses with HLHS is the longitudinal assessment of right ventricular function. Dysfunction of the right ventricle is associated with a poor prognosis in patients with HLHS. Ultrasound markers of right ventricular function include fractional area change (FAC) of the right ventricle and the tricuspid valve annular systolic excursion Z-score value (TAPSE)[7]. As a result, prenatal diagnosis of HLHS plays a key role in managing the condition, as early detection allows for proper medical planning and surgical intervention. Unfortunately, the fetal outcome may change if additional cardiac issues are found[8].

Materials and methods

This was a single-center analysis of a group of fetuses who underwent fetal ultrasound examinations at our tertiary center between 2016 and 2023. Data on HLHS were collected from the database of our unit (Fetal Pathology of the Medical University of Lodz) and the Polish Nationwide Registry of Fetal Cardiac Pathology (www.orpkp.pl) covering the years 2004 to 2023. The analysis included 80 fetuses with HLHS. Gestational age (GA) was calculated based on ultrasound biometry, involving the measurement of key parameters such as biparietal diameter, abdominal circumference, head circumference, femur length. The gestational age of the studied fetuses (n = 80) ranged from 16.3 to 39.5 weeks (average 29.3). All available ultrasound and echocardiographic examinations from multiple visits, up to three per fetus, were analyzed. All the anomalies and irregularities accompanying HLHS, which were the focus of this study, were detected during the second and third trimesters of pregnancy based on 2D ultrasound evaluation, where a disproportion between the left and right parts of the heart was visible, and color Doppler was used to observe the flow of blood through the structures of the left heart, including the left ventricle, aorta, aortic valve, and mitral valve. The measurements performed did not affect clinical management. The focus was solely on the analysis and interpretation of the collected data. This was a retrospective analysis of ultrasound and echocardiographic examinations retrieved from the facility's medical system. As a result, approval from the Ethics Committee was not required. All patients provided consent for the scientific analysis of their data at our center. The inclusion criteria included fetuses with HLHS combined with mitral and/or tricuspid regurgitation. In some cases, additional findings such as cardiomegaly, pericardial effusion, restrictive foramen ovale and/or abnormal flow through the foramen ovale were observed. In all cases, HLHS was characterized by a hypoplastic left ventricle. In the group of fetuses with HLHS combined with tricuspid and mitral valve regurgitation, there was one fetus with aortic arch hypoplasia. In cases with HLHS and mitral valve regurgitation, one fetus presented with mitral valve stenosis, and three cases involved aortic valve atresia. Also, a group of fetuses with HLHS but without mitral and/or tricuspid regurgitation was taken into consideration and presented in Fig. 1.

Exclusions

A total of 282 fetuses with HLHS were selected from the Polish Nationwide Registry of Fetal Cardiac Pathology (www.orpkp.pl) for the study. However, 202 cases were excluded due to lack of the follow-up of the newborns with HLHS. In these cases, either documentation

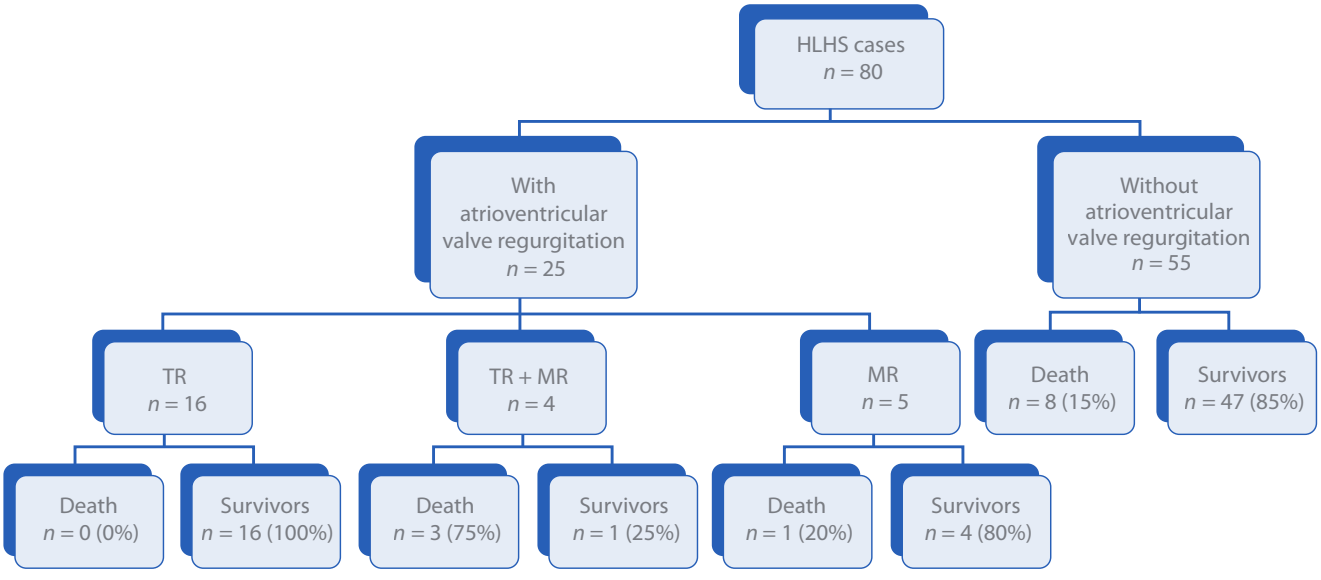

Fig. 1. *Prenatal and postnatal follow-up of respective HLHS groups*

was incomplete or information regarding postnatal management and neonatal outcomes was missing. As a result, 80 fetuses with complete data regarding postnatal follow-up were included in this study.

Fetal ultrasound examinations

Ultrasound examinations were performed using GE Voluson E8, GE Voluson E10, and Philips iU22 ultrasound machines with appropriate transabdominal transducers, and with both general abdominal programs and specialized heart-analysis programs integrated into these ultrasound machines.

Statistical analysis

Statistical analysis was performed using Statistica 13.3 and Excel 365 software. Percentages were calculated for nominal variables. Gestational age data followed a normal distribution according to the Shapiro-Wilk test (p >0.05). Nominal variables were compared using the Fisher test, while qualitative variables were calculated using the Yates's chi-squared test. An interaction graph and a histogram were created to compare mortality rates between fetuses presenting tricuspid insufficiency and those with both tricuspid insufficiency and mitral insufficiency. A p-value <0.05 was considered statistically significant.

Results

Eighty fetuses with HLHS were included in this study. Gestational age, calculated based on ultrasound biometry, ranged from 16.3 to 39.5 weeks (29.3 ± 6 weeks on average). The distribution of gestational age was normal according to the Shapiro-Wilk test (p = 0.056). The analyzed group of fetuses with HLHS (n = 80) was divided into four subgroups. The first subgroup included fetuses with HLHS without tricuspid (TR) or mitral regurgitation (MR) (n = 55, 69%) and without other abnormalities – the number of deaths was n = 8 (15%) and survivors n = 47 (85%). The second subgroup included fetuses with HLHS with tricuspid regurgitation (TR) (n = 16) but without other abnormalities – the number of deaths was n = 0 (0%) and survivors n = 16 (100%). The third subgroup included fetuses with HLHS and both tricuspid (TR) and mitral regurgitation (MR) (n = 4) but without other abnormalities – the number of deaths was n = 3 (75%) and survivors n = 1 (25%). The fourth subgroup included fetuses with HLHS and mitral regurgitation (MR) (n = 5) but without other abnormalities – the number of deaths was n = 1 (20%) and survivors n = 4 (80%) (Fig. 1). In the group of fetuses with HLHS combined with MR and TR (4 cases), the first case presented with a restrictive foramen and cardiomegaly; the second case showed abnormal flow through the foramen ovale; the third case had no other abnormalities; and the fourth case demonstrated pericardial effusion and cardiomegaly. In all four cases, both tricuspid and mitral regurgitation were classified as mild. Three fetuses with HLHS combined with TR and MR underwent the Norwood operation, while one had a stent implemented in the PDA in the second month of life due to bleeding to the central nervous system.

In the group of fetuses with HLHS with both TR and MR, the mortality rate was 75% (3/4) compared with the group of fetuses with HLHS with TR, where the mortality rate was 0% (0/16) and the survival rate was 100% (16/16). Among the fetuses with HLHS with both TR and MR who died, there was one case with aortic arch hypoplasia and one case with aortic stenosis. The incidence of death was significantly higher in the group of fetuses with HLHS with both tricuspid and mitral regurgitation than in the group with tricuspid regurgitation alone (Yates's chi-squared test p = 0.003; Fisher's test p = 0.0035). (Fig. 2, Fig. 3). There was no significant difference in the frequency of deaths between the group of fetuses with HLHS with tricuspid regurgitation and the group with HLHS with mitral regurgitation (Yates's chi-squared test p = 0.528; Fisher's test p = 0.24); however, this could be attributed to the small number of fetuses with HLHS with mitral regurgitation.

Discussion

The presence of mitral regurgitation in fetuses with HLHS seems to be an additional ultrasound marker for poor neonatal outcome. The findings of this study have significant implications for prenatal counselling and postnatal management. Prenatal evaluation is key

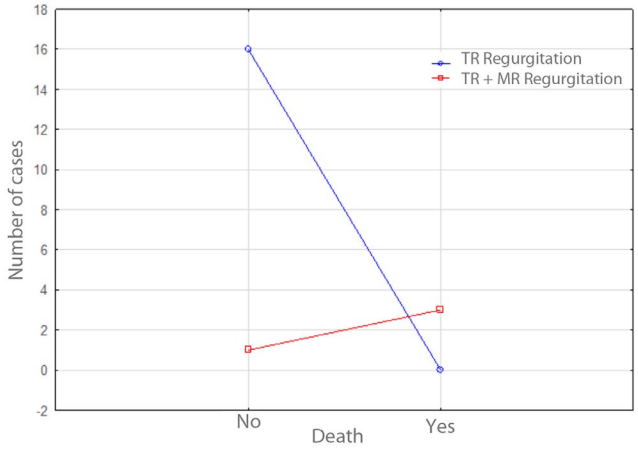

Fig. 2. *Graph illustrating interaction between fetuses with HLHS with TR and fetuses with HLHS with TR and MR*

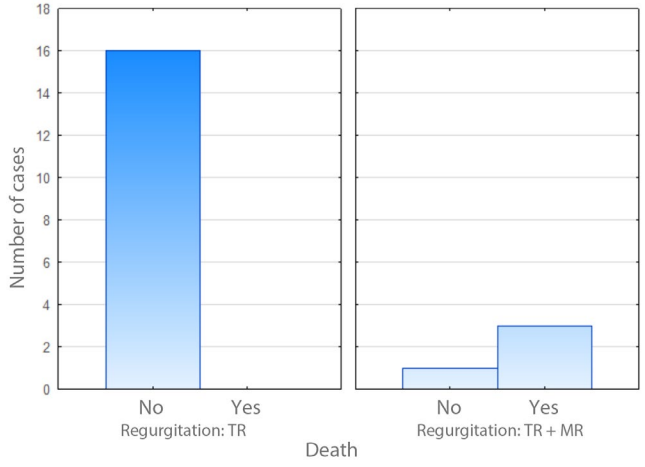

Fig. 3. *Graph illustrating the number of neonatal deaths in cases with prenatally diagnosed HLHS with TR (on the left) and with TR and MR (on the right)*

to detecting fetal abnormalities, including those affecting the heart. With advancements in technology, ultrasonographic prenatal diagnosis is expanding to provide the best possible care during pregnancy[9]. According to the classification elaborated by Respondek-Liberska and Słodki, HLHS is a congenital heart defect that can be treated but is often associated with many complications HLHS may be classified as a severe urgent defect or a severe planned defect depending on the presence of a restrictive foramen ovale or wide atrial communication, respectively[10,11]. It is a common finding that HLHS is accompanied by tricuspid regurgitation. However, according to our analysis, the fatality rate in such cases is very low despite the fact that TR is a known additional risk factor for poor prognosis[12]. Mitral regurgitation is a very rare finding in fetuses and newborns, but still such cases are diagnosed prenatally and must be addressed appropriately[13]. The widespread use of fetal echocardiographic monitoring[14–16], which is a first-line method for detecting HLHS, has made early diagnosis possible. Mitral regurgitation detected during prenatal echocardiographic examination in one of the cases with HLHS diagnosed at the Department of Prenatal Cardiology at the Institute of the Polish Mother's Memorial Hospital in Lodz is presented in Fig. 4. Advancements in prenatal echocardiography and postnatal care have contributed to survival rates for HLHS reaching 60–65%[17]. HLHS may be accompanied by abnormalities such as tricuspid regurgitation, restrictive foramen ovale, aortic valve atresia/stenosis, mitral valve atresia/stenosis, and pericardial effusion, which were also observed in some patients in this study. However, to date, the literature has not described any cases of HLHS combined with MR, nor has it presented any articles combination.

In the present study, tricuspid regurgitation was observed in 25% of patients with HLHS. Some studies have shown that TR is not a risk factor for early mortality[18–21], whereas other studies have demonstrated that TR may be a factor contributing to early mortality[22,23]. In the study by Barber *et al.*, 100 patients with HLHS and TR observed during echocardiographic examinations were analyzed. Of these, 37% had mild TR, 13% had moderate TR, and 3% had severe TR on their preoperative Doppler echocardiograms. The analysis showed that patients diagnosed with moderate or severe TR had a worse survival rate compared with patients without TR[24]. To sum up, TR is considered a significant risk factor for poor outcomes, especially in newborns with HLHS who develop TR at an earlier age. Despite these findings, our study showed that all patients with HLHS and TR had a survival rate of 100%, suggesting that early and continuous prenatal echocardiographic monitoring makes it possible to develop an optimal management plan for newborns with HLHS and facilitates cooperation among obstetricians, neonatologists, cardiac surgeons, and pediatric cardiologists. When it comes to MR in HLHS, the situation is quite different. In 3 out of 4 cases with HLHS and TR and MR, the survival rate was 25%, compared to cases with HLHS and TR, where the survival rate was 100%. This is a significant difference, which led to poor outcomes in newborns diagnosed with HLHS.

Due to the fact that no information about HLHS with MR is described in the literature, the authors proposed the following pathomechanism. The presence of mitral regurgitation leads to an overwhelming influx of blood into the left atrium. The overburdened left atrium undergoes remodeling and hypertrophy, with an increase in the strength of muscle contractions. With time, the left atrium becomes ineffective in generating a larger total stroke volume, which progresses to left ventricle disfunction. When the left atrium is not able to generate appropriate pressure, the left ventricle is underfilled with blood, causing more blood to accumulate in the left atrium. This results in the overloading of the pulmonary veins with blood and leads to reverse blood flow to the lungs, which become congested. As a result, pulmonary hypertension is observed,

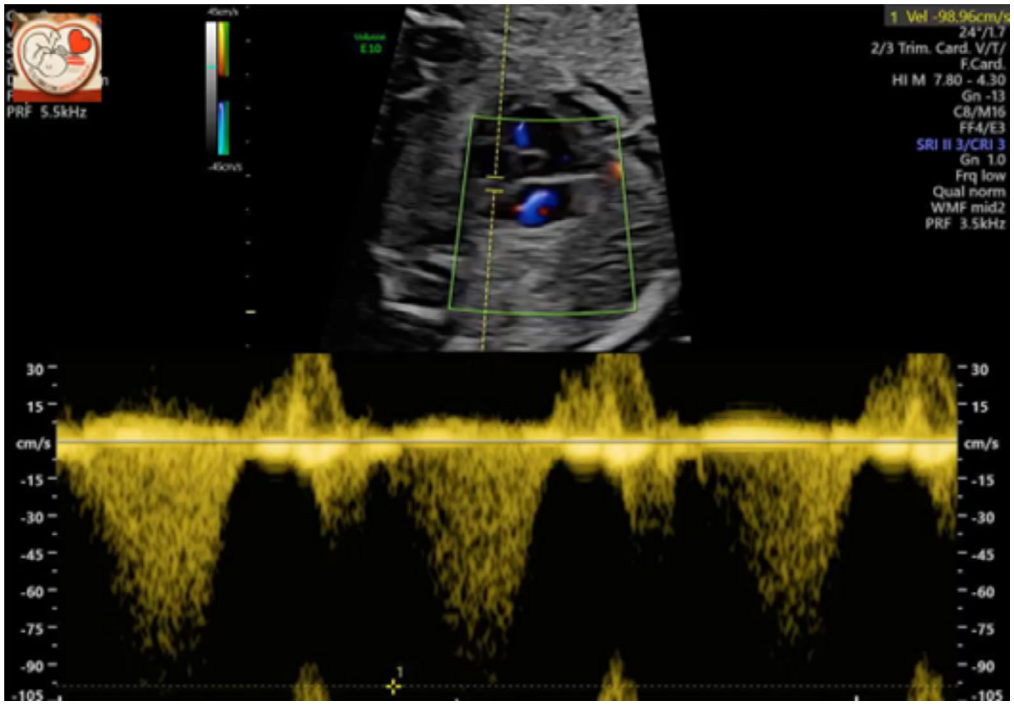

Fig. 4. *Fetus with HLHS with mitral regurgitation with a blood flow of 98.96 cm/s. Ultrasound image from the Prenatal Cardiology Department at the Institute of the Polish Mother's Memorial Hospital*

accompanied by left ventricle failure[25]. This is consistent with the post-mortem examination results of one case from this study. In that case, the autopsy results of a newborn with HLHS demonstrated pulmonary hypertension, atelectasis, and heart failure. These three abnormalities were the main findings leading directly to the poor neonatal outcome.

In one study on patients with HLHS, the function of the tricuspid valve and right ventricle was evaluated, concluding that after hybrid palliation for HLHS, patients with significant TR and/or RV dysfunction were at greater risk of death[26]. The combination of HLHS and TR can result in inadequate oxygenation of blood and overall decreased cardiac output. The severity of TR affects the prognosis for the fetus and/or neonate in different ways. Factors that must be taken into consideration include the degree of underdevelopment of the left side of the heart and the presence of additional cardiac abnormalities, such as a restrictive atrial septum[27–29]. Other factors that may affect the outcome in HLHS include race, ethnicity, socioeconomic status, and geography[30].

In general, major fetal congenital heart defects are related with a higher risk of pregnancy loss. According to a recent publication on a large cohort, in fetuses with HLHS, the risk of pregnancy loss was 10.7%. However, that study focused only on isolated HLHS[31]. Our study involved HLHS with and without MR and/or TR, which constitute additional risk factors for poor fetal and neonatal outcomes. It is worth noting that some conditions may progress to HLHS by the time of birth. A good example is critical aortic stenosis, which must also be taken into consideration for differentiation purposes[32]. Another important issue which must be analyzed during ultrasound examination is the observation of the foramen ovale. In HLHS, it is important to measure the diameter of the foramen ovale. In general, the foramen ovale is considered restrictive when its diameter is below 2.5 mm in fetuses with normal heart study and normal heart anatomy, whereas in fetuses with HLHS, the diameter of the foramen ovale below 4.0 mm is considered restrictive. If Doppler evaluation shows that the maximal blood flow velocity from the right to the left through the foramen ovale is higher than 40 cm/s, it is considered restrictive. According to available studies, HLHS accompanied by a restrictive foramen ovale has the highest mortality rate[33]. Another crucial factor to consider during echocardiographic examination is the presence of coronary artery abnormalities, which also occur in patients with HLHS and increase the risk of death[34]. In HLHS, the left heart is underdeveloped, which affects fetal hemodynamics. Parameters such as flow velocity, pressure, and wall shear stress are completely different than those in fetuses with normal heart structure and anatomy[33].

Managing fetuses with HLHS combined with mitral and/or tricuspid regurgitation typically requires a multidisciplinary approach, including cooperation between fetal medicine specialists, pediatric cardiologists, and cardiothoracic surgeons. The goal is to optimize prenatal care, plan for appropriate interventions, and provide comprehensive support to parents facing the challenges associated with the diagnosis.

The social aspect is also significant, as each case of a fetus with HLHS requires close collaboration between the medical team and the parents to provide guidance, support, and information throughout both the prenatal and postnatal periods. Emotional support for parents facing such a diagnosis is also crucial. According to an interview study, mothers of surviving children with HLHS had feelings of their guilt for the development of the condition in their fetuses. Some mothers also felt that the decisions regarding the pregnancy were mainly theirs, despite that fact that they had received support from their relatives. It is therefore essential for parents to recognize that they are not alone and that there are resources to support them. Receiving a diagnosis of HLHS during pregnancy or after birth can be emotionally overwhelming for parents[36]. In response to these challenges, many hospitals and support organizations offer counselling, support groups, and resources to assist families in managing the social and emotional aspects of caring for women with fetuses diagnosed with HLHS and, eventually, neonates, even in cases with poor outcomes.

In addition to the existing literature, our study identified another important risk factor in patients with HLHS: mitral and/or tricuspid valve re-gurgitation.

Our study has shown that the presence of mitral regurgitation in fetuses with HLHS may be a risk factor leading to poor neonatal outcomes. A key strength of the study is that it presents retrospective results from a relatively large population of fetuses, particularly given the fact that MR is a very rare finding, especially in patients with HLHS. To date, HLHS with MR has not been discussed in the literature, that is why our analysis may contribute to the adoption of early echocardiographic screening in every fetus, with a focus on the monitoring of both atrioventricular valves. Our findings are thus unique and not found even in the current specialized literature.

The prognosis and outcomes can be challenging in cases of complex congenital heart defects such as HLHS with accompanying mitral and tricuspid valve regurgitation. Close monitoring by a specialized medical team is crucial to determine the best course of action for the neonate[37]. However, our study has shown that the outcome for fetuses with HLHS associated with MR and TR is very poor.

The are several important clinical implications arising from our study. The aim of this analysis was to demonstrate the impact of mitral regurgitation on the outcome in patients diagnosed with HLHS. According to the study, MR is a strong risk factor for very poor neonatal outcomes due to heart failure. This was not observed in our cases of HLHS with tricuspid regurgitation. Therefore, the presence of MR in fetuses with HLHS should be considered an alarming sign of poor outcome. Such cases should be carefully analyzed by a group of specialists, including prenatal cardiologists, pediatric cardiologists, interventional cardiologists, cardiac surgeons, obstetricians, and neonatologists. These data are of great importance and have significant implications for prenatal counselling and postnatal management.

A limitation of our study is the small number of fetuses with HLHS and MR. The number of cases could have been larger, however, the authors decided to analyze only those cases with complete prenatal and postnatal examinations, including follow-up. In some cases, MR was observed in only one ultrasound examination. Therefore, the study included only those cases in which MR was consistently observed across all examinations during fetal echocardiographic monitoring. This limited the number of patients studied. It must be noted that while fetal echocardiography is highly valuable in diagnosing congenital heart defects, it may not detect all abnormalities. Moreover, this study lacks geographical and demographic diversity

to increase the representativeness and generalizability of the results. Therefore, further studies with larger, more diverse cohorts should be performed in the future to strengthen these findings.

Conclusions

The presence of hypoplastic left heart syndrome with tricuspid and mitral regurgitation is significantly associated with neonatal mortality, even when treatment and/or surgery is performed. The presence of mitral regurgitation in fetuses with hypoplastic left heart syndrome seems to be an additional ultrasound marker indicating poor neonatal outcomes. Our study has important implications for prenatal counselling and postnatal management.

Institutional review board statement

Ethical review and approval were waived for this study due to the fact that it was a retrospective analysis of fetal ultrasound documentation and the study was not a medical experiment or clinical research on patients.

Informed consent statement

Informed consent was obtained from all subjects involved in this study.

Data availability statement

Data are available on request due to privacy reasons.

Conflict of interest

The authors do not report any financial or personal connections with other persons or organizations which might negatively affect the contents of this publication and/or claim authorship rights to this publication.

Author contributions

Original concept of study: MRL. Writing of manuscript: SW. Analysis and interpretation of data: SW. Final acceptation of manuscript: MRL. Collection, recording and/or compilation of data: SW. Critical review of manuscript: IS.

References

1. Kordjalik P, Respondek-Liberska M: HLHS on the basis of a nationwide registry of fetal cardiac pathology www.orpkp.pl. Prenatal Cardiology. 2013; 3: 18–21.
2. Sokolowski L, 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. doi: 10.5603/GP.2019.0005.
3. Kritzmire SM, Cossu AE: Hypoplastic Left Heart Syndrome. 2023 Apr 24. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 Jan–.
4. Metcalf MK, Rychik J: Outcomes in hypoplastic left heart syndrome. Pediatr Clin North Am 2020; 67: 945–962. doi: 10.1016/j.pcl.2020.06.008.
5. Respondek-Liberska M: Kardiologia prenatalna dla położników i kardiologów dziecięcych. Czelej, Lublin 2005.
6. Wojtowicz A, Raczka M, Kordon Z, Ochoda-Mazur A, Janowiec K, Huras H *et al.*: Hypoplastic left heart syndrome: from the prenatal to the postnatal period. Ginekol Pol 2021; 92: 289–299. doi: 10.5603/GP.a2020.0160.
7. Balasubramanian S, Smith SN, Srinivasan P, Tacy TA, Hanley FL, Chen S *et al.*: Longitudinal assessment of right ventricular function in hypoplastic left heart syndrome. Pediatr Cardiol 2021; 42: 1394–1404. doi: 10.1007/s00246-021-02624-y.
8. Respondek-Liberska M: Diagnostyka Prenatalna USG/ECHO. Zmiany czynnościowe w układzie krążenia. Wydawnictwo Lekarskie PZWL, 2019.
9. Granese R, Gulino FA, Incognito GG, Cianci S, Martinelli C, Ercoli A: Ultrasonographic prenatal diagnosis: unveiling the path to improved antenatal care. J Clin Med 2023; 12: 4450. doi: 10.3390/jcm12134450.
10. Respondek-Liberska M: ATLAS of prenatal heart defects – Selected examples and their clinical significance. ADI Publishers. (PL): 2011.
11. Słodki M: Opracowanie modelu opieki nad ciężarną z wrodzoną wadą serca u płodu na podstawie nowego prenatalnego podziału wad serca. Wydawnictwo Państwowej Wyższej Szkoły Zawodowej w Płocku, 2012
12. 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. doi: 10.1080/14767058.2020.1716717.
13. Ferrazzini G, Fasnacht M, Arbenz U, Seger R, Biedermann R, Simma B *et al.*: Neonatal lupus erythematosus with congenital heart block and severe heart failure due to myocarditis and endocarditis of the mitral valve. Intensive Care Med 1996; 22: 464–466. doi: 10.1007/BF01712168.
14. Sokołowski Ł, Fendler W, Tobota Z, Kordjalik P, Krekora M, Słodki M, Respondek-Liberska M: Detection screening and seasonality evaluation of hypoplastic left heart syndrome in the polish national registry for fetal cardiac anomalies from the years 2004 to 2016. Prenat Diagn 2020; 40: 698–704. doi: 10.1002/pd.5677.
15. Sokołowski Ł, Słodki M, Murlewska J, Strzelecka I, Kordjalik P, Blitek M *et al.*: Fetal echocardiography in the 3rd trimester of pregnancy as an essential element of modern prenatal diagnostics and perinatal care – recommendations of Polish Society of Prenatal Cardiology 2020. Prenatal Cardiology 2020; 1: 5–12. doi:10.5114/pcard.2020.102272.
16. Strzelecka I, Biedrzycka M, Karuga FF, Szmyd B, Batarowicz K, Respondek-Liberska M: Seasonality of hypoplastic left heart syndrome and single ventricle heart in poland in the context of air pollution. J Clin Med 2021; 10: 3207. doi: 10.3390/jcm10153207.
17. Wald RM, Mertens LL: Hypoplastic Left Heart Syndrome Across the Lifespan: Clinical Considerations for Care of the Fetus, Child, and Adult. Can J Cardiol 2022; 38: 930–945. doi: 10.1016/j.cjca.2022.04.028.
18. Ross CJ, Mir A, Burkhart HM, Holzapfel GA, Lee CH: Tricuspid valve regurgitation in hypoplastic left heart syndrome: current insights and future perspectives. J Cardiovasc Dev Dis 2023; 10: 111. doi: 10.3390/jcdd10030111.
19. Starnes VA, Griffin ML, Pitlick PT, Bernstein D, Baum D, Ivens K, Shumway NE: Current approach to hypoplastic left heart syndrome. Palliation, transplantation, or both? J Thorac Cardiovasc Surg 1992; 104: 189–194; discussion 194–195.
20. Hoshino K, Ogawa K, Hishitani T, Kitazawa R, Uehara R: Hypoplastic left heart syndrome: duration of survival without surgical intervention. Am Heart J 1999; 137: 535–542. doi: 10.1016/s0002-8703(99)70503-x.
21. Reyes A 2nd, Bove EL, Mosca RS, Kulik TJ, Ludomirsky A: Tricuspid valve repair in children with hypoplastic left heart syndrome during staged surgical reconstruction. Circulation 1997; 96(9 Suppl): II-341-3; discussion II-344-5.
22. Helton JG, Aglira BA, Chin AJ, Murphy JD, Pigott JD, Norwood WI: Analysis of potential anatomic or physiologic determinants of outcome of palliative surgery for hypoplastic left heart syndrome. Circulation 1986; 74(3 Pt 2): I70–76.
23. Hraska V, Nosál M, Sýkora P, Soják V, Sagát M, Kunovský P. Results of modified Norwood's operation for hypoplastic left heart syndrome. Eur J Cardiothorac Surg 2000; 18: 214–219. doi: 10.1016/s1010-7940(00)00483-8.
24. Barber G, Helton JG, Aglira BA, Chin AJ, Murphy JD, Pigott JD, Norwood WI: The significance of tricuspid regurgitation in hypoplastic left-heart syndrome. Am Heart J 1988; 116(6 Pt 1): 1563–1567. doi: 10.1016/0002-8703(88)90744-2.

25. Patel H, Desai M, Tuzcu EM, Griffin B, Kapadia S: Pulmonary hypertension in mitral regurgitation. J Am Heart Assoc 2014; 3: e000748. doi: 10.1161/JAHA.113.000748.
26. Carrillo SA, Texter KM, Phelps C, , Tan Y, McConnell PI, Galantowicz M: Tricuspid valve and right ventricular function throughout the hybrid palliation strategy for hypoplastic left heart syndrome and variants. World J Pediatr Congenit Heart Surg 2021; 12: 9–16. doi: 10.1177/2150135120947692.
27. Jiali Y, Dongmei L, Jiangli D, Shi Z, Ming Z, Ganqiong X: Prenatal diagnosis: Hypoplastic left heart syndrome in combination with ventriculo-coronary communication. Birth Defects Res 2023; 115: 1936–1940. doi: 10.1002/bdr2.2258.
28. Sanchez-Escobar IC, Giraldo-Pinto M, Quintero-Gomez A, Arias A, de la Peña A, García R *et al.*: Interatrial Septum Stenting for Hypoplastic Left Heart Syndrome in Ex Utero Intrapartum Therapy. World J Pediatr Congenit Heart Surg 2024; 15: 226–230. doi: 10.1177/21501351231196484.
29. Anderson RH, Spicer DE, Crucean A: Which phenotypes should we include in the hypoplastic left heart syndrome? World J Pediatr Congenit Heart Surg 2023; 14: 738–740. doi: 10.1177/21501351231181313.
30. Lopez KN, Morris SA, Krishnan A, Jacobs MB, Bhat AH, Chelliah A *et al.*; Fetal Heart Society Research Collaborative: Associations Between Maternal Sociodemographics and Hospital Mortality in Newborns With Prenatally Diagnosed Hypoplastic Left Heart Syndrome. Circulation. 2023 Jul 18;148(3):283–285. doi: 10.1161/CIRCULATIONAHA.123.064476.
31. Jepson BM, Metz TD, Miller TA, Son SL, Ou Z, Presson AP *et al.*: Pregnancy loss in major fetal congenital heart disease: incidence, risk factors and timing. Ultrasound Obstet Gynecol 2023; 62: 75–87. doi: 10.1002/uog.26231.
32. Wong HS, Li B, Tulzer A, Tulzer G, Yap CH: Fluid Mechanical Effects of Fetal Aortic Valvuloplasty for Cases of Critical Aortic Stenosis with Evolving Hypoplastic Left Heart Syndrome. Ann Biomed Eng 2023; 51: 1485–1498. doi: 10.1007/s10439-023-03152-x.
33. Vena F, Bartolone M, D'Alberti E, Vasta A, Mazza A, D'Ambrosio V *et al.*: Echocardiographic features and outcome of restrictive foramen ovale in fetuses with and without cardiac malformations: Literature review. J Clin Ultrasound 2023; 51: 240–248. doi: 10.1002/jcu.23304.
34. Rueda-de-Leon E, Killen SAS, Soslow JH, McHugh MK, Fuchs SR, Kavanaugh-McHugh A: Prenatally diagnosed coronary artery abnormalities in hypoplastic left heart syndrome are associated with a higher probability of heart transplantation. Prenat Diagn 2022; 42: 1458–1465. doi: 10.1002/pd.6227.
35. Salman HE, Kamal RY, Hijazi ZM, Yalcin HC: Hemodynamic and Structural Comparison of Human Fetal Heart Development Between Normally Growing and Hypoplastic Left Heart Syndrome-Diagnosed Hearts. Front Physiol 2022; 13: 856879. doi: 10.3389/fphys.2022.856879.
36. Bertaud S, Lloyd DFA, Sharland G, Razavi R, Bluebond-Langner M. The impact of prenatal counselling on mothers of surviving children with hypoplastic left heart syndrome: A qualitative interview study. Health Expect 2020; 23: 1224–1230. doi: 10.1111/hex.13103.
37. Nealon E, Phelps C, Krawczeski C, Alexander R, Stiver C, Ball MK *et al.*: Impact of Maternal-Fetal Environment on Outcomes Following the Hybrid Procedure in the Single Ventricle Population. Pediatr Cardiol 2024; 45: 1258–1266. doi: 10.1007/s00246-022-03063-z.