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RESEARCH

Medium-term Outcome of Prenatally Diagnosed Hypoplastic Left-Heart Syndrome and Impact of a Restrictive Atrial Septum Diagnosed in-utero

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Abstract

Objective: Surgical outcome data differs from overall outcomes of prenatally diagnosed fetuses with hypoplastic left heart syndrome (HLHS). Our aim was to describe outcome of prenatally diagnosed fetuses with this anomaly. Methods: Retrospective review of prenatally diagnosed classical HLHS at a tertiary hospital over a 13-year period, estimated due dates 01/08/2006 to 31/12/2019. HLHS-variants and ventricular disproportion were excluded. Results: 203 fetuses were identified with outcome information available for 201. There were extra-cardiac abnormalities in 8% (16/203), with genetic variants in 14% of those tested (17/122). There were 55 (27%) terminations of pregnancy, 5 (2%) intrauterine deaths and 10 (5%) babies had prenatally planned compassionate care. There was intention to treat (ITT) in the remaining 131/201(65%). Of these, there were 8 neonatal deaths before intervention, two patients had surgery in other centers. Of the other 121 patients, Norwood procedure performed in 113 (93%), initial hybrid in 7 (6%), and 1 had palliative coarctation stenting. Survival for the ITT group from birth at 6-months, 1-year and 5-years was 70%, 65%, 62% respectively. Altogether of the initial 201 prenatally diagnosed fetuses, 80 patients (40%) are currently alive. A restrictive atrial septum (RAS) is an important sub-category associated with death, HR 2.61, 95%CI 1.34–5.05, p = 0.005, with only 5/29 patients still alive. Conclusion: Medium-term outcomes of prenatally diagnosed HLHS have improved however it should be noted that almost 40% do not get to surgical palliation, which is vital to those doing fetal counselling. There remains significant mortality particularly in fetuses with in-utero diagnosed RAS.

- **What is already known on this topic**:
- Most patients with hypoplastic left heart syndrome are diagnosed prenatally in the UK.
- Survival for staged univentricular palliation including for HLHS is reported annually by the National Institute for Cardiovascular Outcomes Research.
- **What this study adds**:
- This study describes mortality between fetal diagnosis and surgical intervention.
- **How this study might affect practice**:
- This data helps with counselling a pregnant woman expecting a fetus with hypoplastic left heart syndrome, giving clearer outcome data than using surgical survival alone.

Keywords Fetal · Hypoplastic Left Heart Syndrome · Norwood · Fontan

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Introduction

Hypoplastic left heart syndrome (HLHS) is a relatively heterogeneous group of congenital heart malformations with a vestigial left ventricle, mitral and aortic valve stenosis/atresia and in some cases hypoplasia of the aortic arch [1] It has one of the highest rates of prenatal detection [2], [3], [4]. To be able to offer parents appropriate counselling, it is essential to have current outcome information for prenatally diagnosed fetuses and identify prenatal factors which are predictive of poor outcome. Counselling should cover not just survival but potential long-term morbidities and the likelihood of their child completing the Fontan circulation [5].

During fetal counselling there is a tendency to discuss surgical data and outcomes, however only a subgroup of fetuses will undergo surgery [6], [7]. The surgical literature excludes those fetuses that have suffered Intra-Uterine Death (IUD), neonatal death, or received comfort care. Surgical outcomes and survival, does not reflect the true outcome of a 20-week fetus with HLHS [8]·[9]·[10]. In fact, historical data from our institution between 2000 and 2004 has shown only 47% overall survival of the intention-to-treat group (ITT) from fetal diagnosis to the end of the five-year study period [7]. This is significantly lower when compared to the UK National Congenital Heart Diseases Audit for 2000–2015 showing 77.1%, 96.4% and 98.8% in-hospital survival from the Norwood/Hybrid, Cavo-Pulmonary Shunt (CPS), and Fontan completion surgeries, respectively [11].

We aimed to investigate outcome for prenatally diagnosed classical HLHS from diagnosis and identify prenatal risk factors associated with poor outcome.

Methods

West Midlands Regional Practice

The NHS Fetal-Anomaly-Screening-Program includes fetal structural abnormality screening between 18:20 + 6 weeks [3]·[4]. The Fetal Medicine Centre in Birmingham Women's Hospital (BWH) offers specialist fetal cardiology service to pregnant women from the West Midlands Region (population:5,961,900), and a supra-regional service to many areas of the UK [12]. All women referred to our unit undergo fetal echocardiography by a fetal/pediatric cardiologist and a detailed anomaly scan is performed by a fetal medicine specialist to assess for extra-cardiac defects (Siemens HELX 2000/3000 Evolution ultrasound system; GE Voluson E9). When a diagnosis of HLHS is confirmed, a multi-disciplinary team counsel the parents. The options of surgical palliation, termination of pregnancy and comfort care are discussed. Prenatal genetic testing is offered to all women. Non-invasive prenatal testing (NIPT) and whole-exome sequencing was not routinely available for the majority of the study period. Sequential fetal echocardiography is offered in ongoing pregnancies at 28-weeks and 34-weeks gestation where fetal growth and wellbeing are assessed. If parents opt for palliative cardiac surgery, delivery in a level 3 neonatal unit is recommended. Our unit does not perform fetal cardiac intervention on the atrial septum.

Newborns are transferred to the cardiac surgical unit at Birmingham Children's Hospital (BCH) where the Norwood procedure, is performed. Since March 2002, BCH has preferred the Sano modification of the Norwood procedure using a right ventricular to pulmonary artery conduit rather than a Blalock-Taussig shunt [13]. The Norwood is the initial procedure performed unless there are additional high risk factors for cardiopulmonary bypass (CPB) including restrictive atrial septum (RAS), prematurity, very-low-birth-weight (< 2 kg), or if CPB is contraindicated (intra-cerebral bleed or active necrotizing enterocolitis). For this group of patients, a hybrid procedure tailored for each case (Balloon Atrial Septostomy +/- stenting/septectomy and bilateral pulmonary artery bands) may instead be performed, maintaining ductal patency with Prostaglandin infusion [14]. All cases following a hybrid procedure undergo conversion to a Norwood procedure after they have stabilized, reached their corrected term gestational age and gained adequate weight. CPS is usually performed at 4–6 months of life, and completion of Fontan aged 3–5 years.

Patient Cohort

We searched our fetal electronic database (Viewpoint,GE) to find all cases of HLHS diagnosed prenatally over a 13-year period (estimated due dates between 01/08/2006 to 01/01/2020). We only included fetuses with "classical" HLHS (mitral atresia/aortic atresia, mitral stenosis/aortic atresia, and mitral stenosis/aortic stenosis) in the presence of situs solitus with normally related great vessels. We excluded HLHS variants and ventricular disproportion where it was unclear whether a biventricular circulation would be achieved after birth.

Maternal and fetal demographic data and clinical details were obtained from Viewpoint database records, ultrasound, and fetal echocardiogram reports/images. Fetuses were matched to postnatal data. Follow up data was obtained from review of medical and surgical records, Heartsuite and SEND databases. Demographics Batch Service Bureau (DBSB) process, and hospital contacts/tracking was used to ascertain life status. Patients were followed up for at least one year, until 1st January 2021. Prenatal and postnatal variables collected are shown in Supplementary Table 1. Fetal

growth data across two trimesters was only reliably available from 2011 to 2019.

Prenatal diagnosis of a restrictive atrial septum was based on the subjective judgement of the fetal cardiologist performing the scan, as well as senior review (ANS) of the fetal scan images including pulmonary venous doppler pattern where available.

Ethics

This study was registered with the Institution's Research & Development office and in accordance with the UK National Research Ethics Service guidance, neither individual informed consent nor formal research ethics committee review was required as the study was undertaken by the direct clinical care team using information previously collected in the course of routine care.

Statistical Analysis

Summary statistics are presented as median and interquartile range for continuous variables; and as counts and percentages for categorical variables.

Cumulative mortality was estimated using Kaplan-Meier (KM) method and comparison between groups made using the logrank test. KM plots were used to show survival prenatally indicating the time when pregnancy failed to progress because of intrauterine death or termination of pregnancy.

Cox proportional hazards regression was used to estimate hazard ratios (along with 95% confidence-intervals) for patients born alive with ITT. Survival was ascertained from date of birth to last physical contact with the patients or the patient status after tracing via the DBSB process.

We assessed the proportional hazards assumption in the Cox models by evaluating the weighted Schoenfeld residuals, and no violations of concern were observed.

Variables included in the model were chosen a priori by the clinical team. These were based on existing literature and clinical knowledge, rather than deferring to statistical criteria.

Table 1 Prenatal variables collected

Prenatal Variables	%	N
Extra cardiac abnormalities	10.3	21
*Abnormal genetics	11.1	8
**Hydrops, Pleural or pericardial effusion	4.9	10
Restrictive atrial septum	14.2	29
Tricuspid valve regurgitation > moderate	5.4	11
Tricuspid valve regurgitation > mild	17.2	35
Fetal weight < 10% second trimester (n = 78)	3.8	3
Fetal weight < 10% third trimester (n = 78)	14.1	11

*Only 72 women had prenatal genetic testing

**Four also had RAS, 6 had tricuspid regurgitation

All analysis was carried out using R v4.10,[15] RStudio and the following packages: ggplot2, lubridate, rms, survival and tidyverse.

Results

Cohort

Over this thirteen-year period, 203 fetuses were diagnosed with HLHS. Outcome information was available for 201. There were 201 (99%) singleton pregnancies and two twin pregnancies. The median gestational age for our prenatal diagnosis was 22 + 0 weeks (IQR 20 + 6 to 24 + 5 weeks).

The frequency of prenatal variables is described in Table 1.

Pathway from Prenatal Diagnosis

Figure 1a shows the pathway of fetuses with antenatal diagnosis of HLHS. After counselling in 55 of 201 (27%) pregnancies, the parents opted for termination. Although direct reasons for termination are difficult to retrospectively delineate, adverse factors included abnormal genetics being present in 3, extracardiac abnormalities found in 9, and RAS in 8.

Of continuing pregnancies, five (3%) died in-utero; of which two developed hydrops fetalis. Parents chose compassionate care in 10 of the 141 continuing pregnancies (7%).

In the remaining 131 pregnancies there was ITT the baby after birth. Of these, there were 7 neonatal deaths (5%) before intervention, at median age 11 days (IQR 8–20 days); Of these 7, three were premature with low birth weight. In addition, one patient was initially ITT but changed pathway to compassionate care when postnatal investigations confirmed antenatal diagnosis of single pelvic kidney with worsening renal failure and RAS. This brought the number of compassionate care to 11 of 141 pregnancies (8%).

Overall, therefore, 92% (121/131) of ITT group underwent intervention (Fig. 1b). An initial Norwood procedure was performed in the majority: 113/121 (93%), an initial hybrid in 7(6%) and one had palliative coarctation stenting. All babies that did not have an initial Norwood procedure had either a genetic anomaly, RAS and/or low birth weight.

Survival Analysis

Two patients were transferred out of region for further surgical care and are not included in the outcome analysis. Survival for the prenatal ITT group from birth.

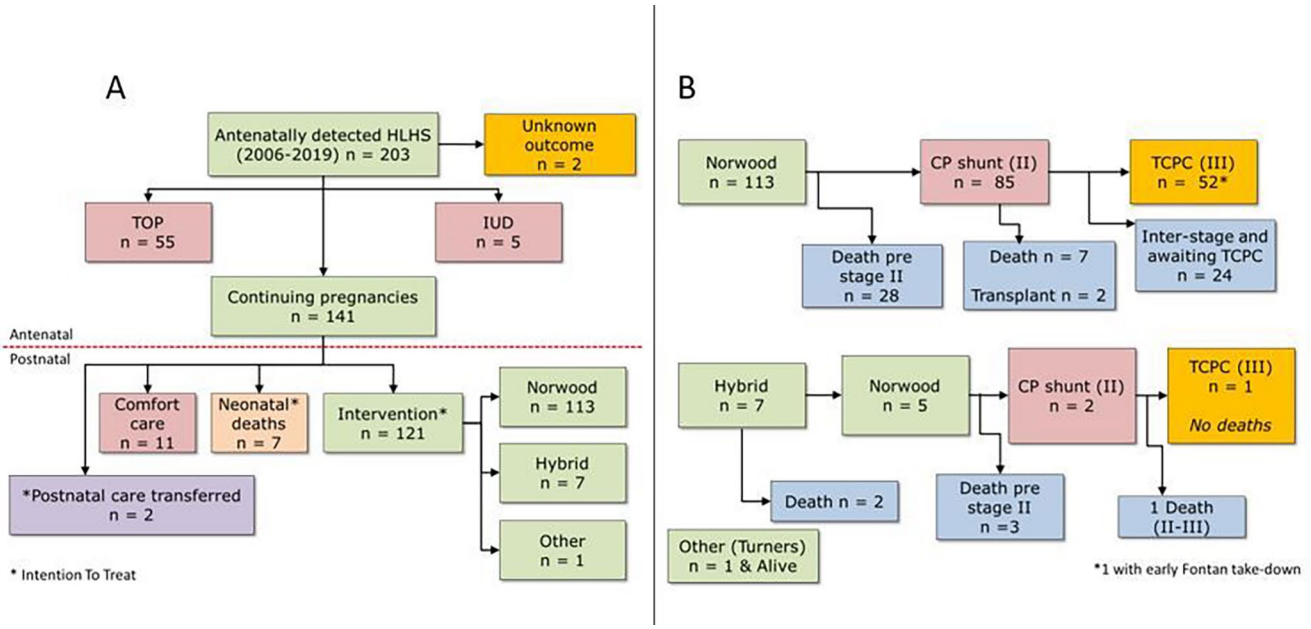

Fig. 1 Pathway of fetuses with antenatal diagnosis of HLHS

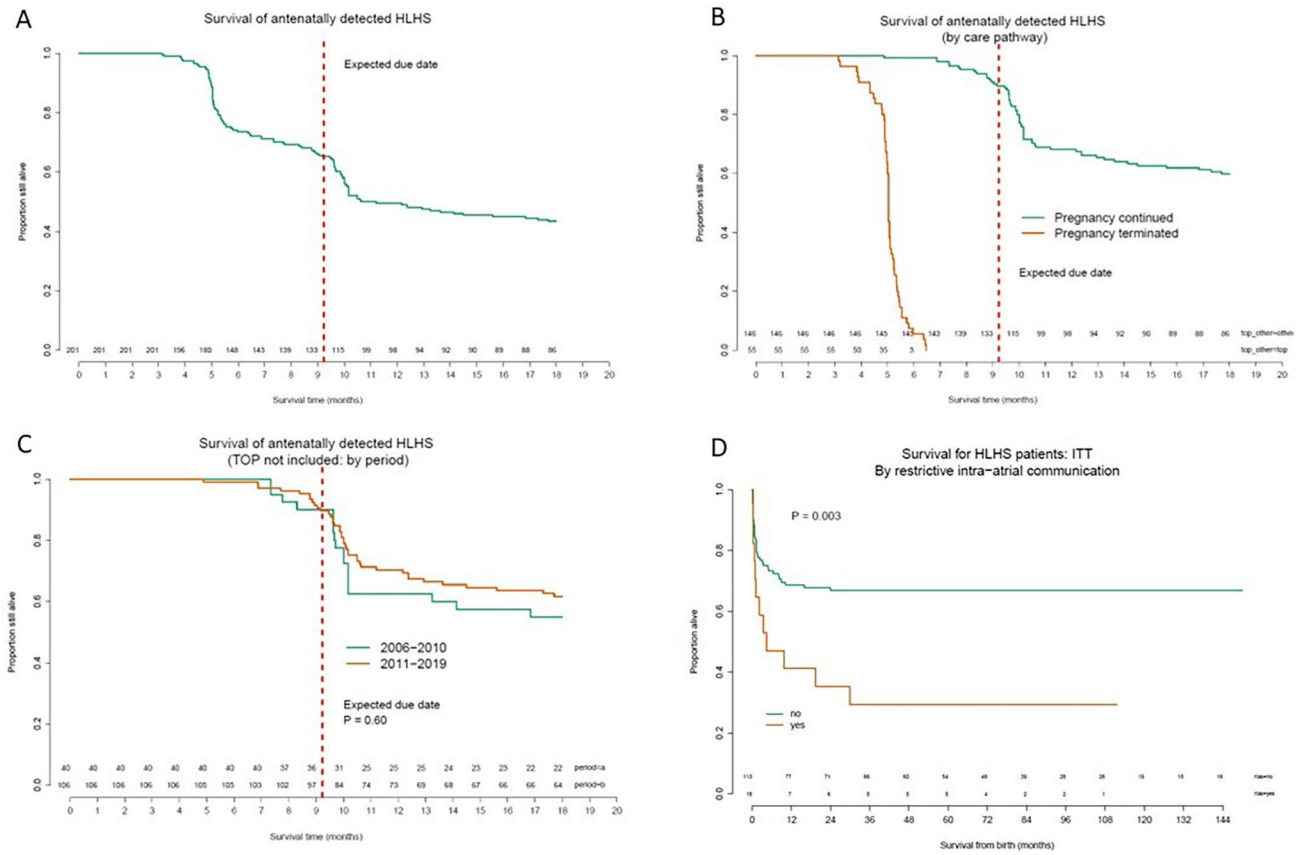

Fig. 2 Kaplan-Meier survival curve for antenatally detected HLHS from diagnosis (A), by care pathway (B), by era (C), and by presence of restrictive atrial septum (D)

(129 patients) at 6-months, 1-year and 5-years was 70%, 65%, 62% respectively.

For comparison, for the 121 that underwent intervention, survival from the initial procedure at 6-months, 1-year and 5-years was 74%, 69%, and 66% respectively.

For the intervention group, 80/121(66%) patients are alive at last follow-up. There were 39 deaths following surgery, with the majority(79%) following Norwood and before CPS. Two patients had transplantation following CPS.

Figure 2 shows a Kaplan-Meier survival curve for antenatally detected HLHS from diagnosis (a), by care pathway (b), by era (c), and by presence of RAS (d).

Assessing prenatal risk factors, Cox proportional hazards regression (Fig. 3) showed that RAS has a statistically significant association with an increased hazard of death HR 2.61 (95%CI 1.34 to 5.05 p = 0.005).

Both AA/MA subtype (HR 1.53, 95%CI 0.86 to 2.70, p = 0.15) and presence of tricuspid valve regurgitation (HR 1.52, 95%CI 0.79 to 2.93, p = 0.21) had a similar wide range of CI values which can correspond to either a small decrease in mortality or a large increase in mortality. The data is therefore overall, more consistent with an increase in hazard of death rather than a decrease.

We did not include fetal growth and abnormal genetics as a variable in the analysis as a large proportion of fetuses did not have this data available.

Genetic Testing and extra-cardiac Anomalies

Genetic testing was performed in 122 of the 203 (60%) fetuses diagnosed with HLHS. Seventy-two had this performed prenatally and 50 postnatally.

Genetic results were abnormal in 17 of 122 (14%) tested. Only eight of these were detected prenatally and 9 postnatally. Of the eight fetuses with abnormal genetics detected prenatally, five were liveborn with the remaining three undergoing termination (Trisomy 18, mosaic trisomy 7, 9q34.11 microdeletion).

Of the 14 liveborn patients with abnormal genetics, one had Turner syndrome (47,X) and therefore underwent palliative coarctation stenting, to avoid the known poor outcomes with Norwood and is still alive at six years of age. Two others had mosaic Turner and are still alive although one has not progressed to completion of Fontan. The genetic details and outcome of the remaining 11 patients are in Supplementary Table 2.

Prenatally detected extra-cardiac anomalies without known genetic anomalies were present in a further 16/203 (8%) fetuses. Nine of these pregnancies were discontinued, 2 died in-utero and another 2 died following neonatal comfort care. Only 3 of the 16 underwent cardiac surgery and all are alive (Supplementary Table 2).

Restrictive/ Intact Atrial Septum (RAS)

RAS was diagnosed prenatally in 29/203 (14%). Twenty-four had co-existing aortic atresia, 4 had aortic stenosis with the remaining 1 having undocumented aortic morphology. Nine of 29 (31%) had prenatal genetic testing with no variant detected in seven. Isolated pericardial effusion was present in 4/29 (14%), none had hydrops.

In 8/29 (28%) with RAS pregnancy was discontinued between 15 and 25 weeks gestational age, there was one intrauterine death. Two fetuses had planned comfort care following delivery, and a further baby with single kidney

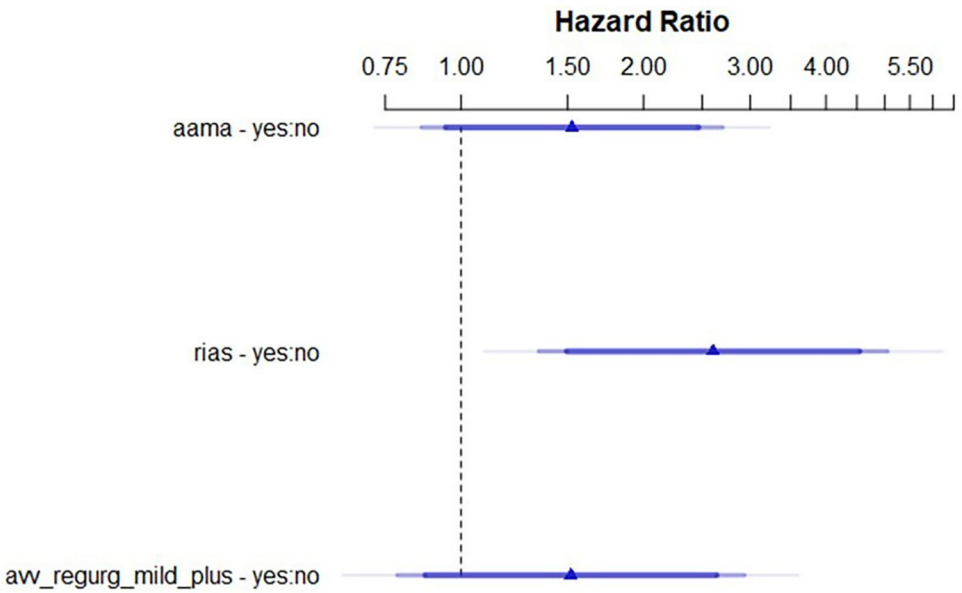

Fig. 3 Cox proportional hazards regression for prenatal risk factors in HLHS (aama: aortic atresia-mitral atresia, rias: restrictive interatrial septum, avv: atrioventricular valve)

was realigned to comfort care. One had care transferred to another center.

Sixteen underwent surgery, of which 7 (44%) survived the Norwood, and 5 (31%) are still alive. Three of these five have had Fontan completion, 1 is awaiting Fontan but with raised pulmonary arterial pressure, and the fifth patient has pulmonary lymphangiectasia and is not suitable for Fontan completion or transplantation. Of the 3 patients that have had Fontan completion, all are doing well but two are still on pulmonary hypertensive medication.

Tricuspid Valve Regurgitation

There was prenatal tricuspid regurgitation (TR) in 35/203 (17%). TR was graded as mild in 24, moderate in 8 and severe in 3. Six fetuses with TR developed pericardial effusion and/or hydrops.

Twenty-eight fetuses were liveborn, of which one underwent planned comfort care, and two died prior to surgery in the neonatal period. Of the remaining 25 fetuses, all had a Norwood procedure postnatally. Three did not have significant TR on initial postnatal echocardiogram, 16 had mild, 2 moderate and 3 had severe regurgitation. One had insufficient data to assess severity of regurgitation.

All three patients with severe TR had tricuspid valve repair at the time of Norwood, of which two died following Norwood, and the third is alive post Fontan. Three other patients who initially had mild TR, developed worsening TR post Norwood, and two of these underwent tricuspid valve repair at time of CPS. The third had tricuspid valve repair following CPS and then needed tricuspid valve replacement due to ongoing severe TR not amenable to further surgical repair.

Fetal Growth

Complete fetal growth data was available for only 78 fetuses, with only 3 (3.8%) meeting criteria for Intra-Uterine Growth Restriction (IUGR) in the 2nd trimester. However, in the third trimester, IUGR was more prevalent, being present in 11 fetuses (14%). There was also an overall 4% median centile reduction of estimated weight across these 78 fetuses between the 2nd and 3rd trimesters.

Discussion

In the current era, most cases of Hypoplastic left heart syndrome cases are diagnosed prenatally (53–88%).[2],[14],[16] There has been a significant increase in overall survival in the ITT group to 61% (80/131), in comparison with our previous series 32% (1994–1999) and 47% (2000–2004).[6],[7] This likely reflects improvement in surgical outcomes. At the same time, the decision to terminate pregnancy after counselling has fallen from 44% (1994–1999), to 25% (2000–2005), and is 27% in the current era (2006–2019).[6],[7] The low rate of TOP in our series is consistent with TOP rates in many similar surgical units world-wide [9], [10].

Birmingham has a very diverse population with Birmingham being the 7th most deprived local authority in England as well as being one of the few cities in England with more than half the population being from an ethnic minority [17], [18]. This may mean that more of our patients continue pregnancy because of their cultural, socioeconomic, and religious beliefs. However despite this, there has still been a change over time in our region suggesting that there are other important factors, including cultural changes, and a better publicized reputation for HLHS management with improving surgical outcomes.

There are also a significant number of fetuses (8%) that do not undergo intervention despite ITT. In our study 3% of fetuses had IUD, most of whom had prenatally detected additional problems. In addition, there was neonatal death in 5% of the ITT group, which was frequently associated with prematurity, low birth weight, and necrotizing enterocolitis. One patient had care re-aligned from ITT to compassionate when important comorbidities were found postnatally. Prematurity and low birth weight are known to increase the risk of neonatal death in congenital heart disease, with 100% mortality of premature HLHS patients in one series [14], [19]. Prenatal counselling must include these significant risks as outcome of pregnancy does not reflect that of the surgical intervention.

Mortality is an important consideration for counselling, and parents should be aware that even if the child survives the initial operation, there is still a 25% risk of death between the Norwood and CPS. This high mortality is reflected in the literature,[5] but we have also shown that some children get "stuck" between stages and cannot progress along the pathway with associated morbidity.

Reflecting the literature, we have shown RAS is an antenatal risk factor for mortality in our cohort, with 14% prevalence and only 10% of RAS patients reaching a Fontan circulation from fetal diagnosis [20], [21]. Antenatal diagnosis of a RAS can be difficult, usually reliant on pulmonary venous Doppler velocimetry traces.[20]. There are differing degrees of restriction and effects may vary depending when atrial restriction occurs in pregnancy. We suspect that restriction in the first/second trimester carries worse prognosis than late onset. RAS patients with aortic atresia and no outflow from the left heart may do worse compared to those with aortic stenosis where the left heart can be decompressed. Unfortunately, the numbers of patients with RAS in our study were too small for meaningful sub-analysis,

however future studies addressing such issues are critical in helping us to test these hypotheses and understand which groups are at risk. The dismal results in the longer term of some patients with an antenatally diagnosed RAS requires careful consideration as to whether we should offer them treatment at all using current techniques considering the poor quality of life, physical and psychological suffering they will undergo. In addition, if these patients develop failing Fontan circulation, they will likely be poor cardiac transplant candidates.

Some centers advocate fetal intervention when a restrictive atrial septum is found with either septal perforation/balloon dilation or atrial septal stent placement [22]. However, although this may aid stabilization of the neonate following delivery, the procedure in itself results in fetal death in 13%. [23] It is also not clear whether fetal intervention aids longer term survival, with survival to discharge no better in fetuses undergoing intervention vs. those without fetal intervention, according to the report from the International Fetal Cardiac Intervention Registry [23]. These fetal interventional procedures are typically performed at late gestation and are unlikely to reverse pulmonary vasculature changes occurring earlier in pregnancy. Pulmonary lymphangiectasia, usually secondary to severe RAS, has also been shown to be a risk factor for outcome but is poorly identified at present antenatally and not yet universal practiced [24]. Ongoing development of Fetal MRI may be better able to diagnose pulmonary lymphangiectasia as well as give better anatomical information on the developing fetal brain, enabling tailored counselling [21], [25], [26].

We found that tricuspid valve regurgitation may be an important factor for poor outcome. However similar to Liu et al. [27] we found very few fetuses had ≥ moderate severity of regurgitation, despite postnatal tricuspid regurgitation often being more prevalent.

Antenatal growth is also an important consideration in HLHS patients, with Triebwasser et al. showing no growth restriction prior to 26-weeks gestation but an overall deceleration in estimated weight and head circumference over the course of pregnancy [28]. However only 11% of this cohort met criteria for IUGR.[28] Our study showed similar findings with 4% overall median centile reduction for estimated weight over the later aspect of pregnancy, and only 14% meeting IUGR criteria. Significant growth restriction is likely to equate to low birth weight which is associated with increased risk of mortality and higher risk of neurodevelopmental impairment [28]. We suspect dropping across growth centiles is a risk factor for poor outcome, but this study was limited by incomplete data and warrants further study.

Limitations

We included only classical HLHS diagnosis as opposed to variants (e.g. unbalanced AVSD, DORV), to be consistent with our previously published analysis, and to identify risks factors in a homogenous population. This approach did limit numbers and may account for why we could not identify other prenatal risk factors. Cardiac morphology is important, and it is critical that not all univentricular hearts are counselled in the same way. Differences in outcome for different types of functionally univentricular hearts is becoming clear in postnatal interventional series [29].

Although growth data was available for the latter cohort of fetuses, in the earlier period this growth data was not commonly digitally documented and was not retrievable from older paper records.

We did not analyze morbidity, in particular neurological morbidity which has been shown to be a major component of poor outcome in recent publications.[21],[30],[31] Morbidity should be the focus of future study in our cohort, when combined with this survival data, will better shape prenatal counselling.

Conclusion

Medium-term outcomes of prenatally diagnosed HLHS have improved. However there remains a significant mortality often occurring before surgical intervention. Survival and Fontan completion is particularly unlikely in fetuses with in-utero RAS. Fetal growth, prenatal TR, and AA/MA may also be important prognostic factors. This data should aid future bespoke prenatal counselling.

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Declarations

Competing Interests Professor Kilby is a Principal Senior Clinical Medical Scientist in the Medical Research Group at Illumina, Cambridge, UK.

Disclosures Professor Kilby is a Principal Senior Clinical Medical

Scientist in the Medical Research Group at Illumina, Cambridge, UK.

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