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Congenital heart defects: from a prenatal perspective

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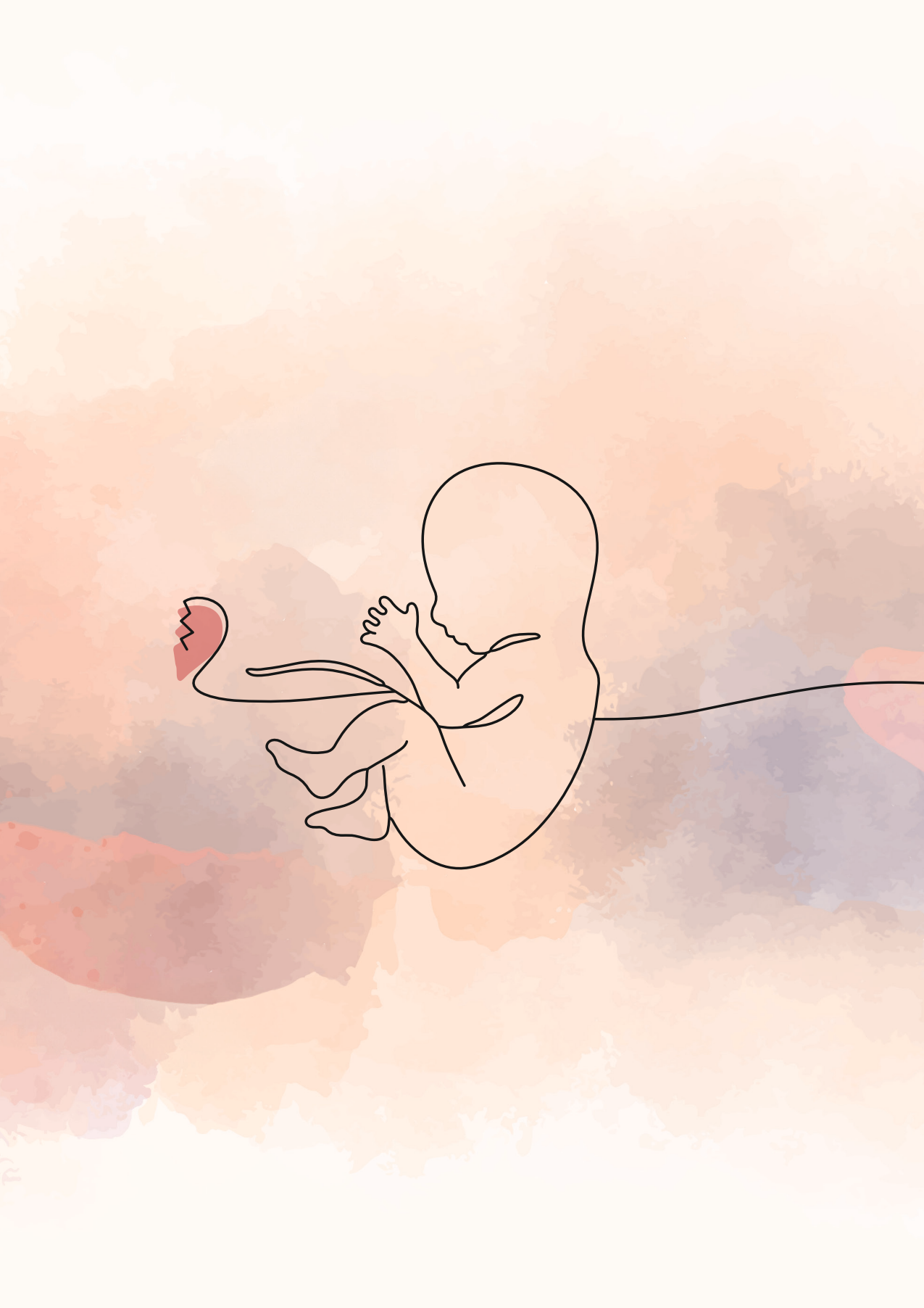
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CHAPTER 8

The aorto-left ventricular tunnel from a fetal perspective

Original case series and literature review

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ABSTRACT

Introduction

Aorto-left ventricular tunnel (ALVT) accounts for <0.1% of congenital heart defects. Evidence on the prognosis from a fetal perspective is limited. With this retrospective international case series, we provide information on the outcome of fetuses with ALVT.

Methods

All members of the Association for European Paediatric and Congenital Cardiology's (AEPC) Fetal Working Group and fetal medicine units worldwide were invited for participation. We observed antenatal parameters, neonatal outcome and postnatal follow-up. Additionally, a systematic search of the literature was performed.

Results

Twenty fetuses with ALVT were identified in 10 participating centers (2001-2019). Fetal echocardiographic characteristics of ALVT included an increased cardiac-thorax ratio (95%), left-ventricular end-diastolic diameter (90%) and a dysplastic aortic valve (90%). Extracardiac malformations were rare (5%). Eight fetuses died at a median gestational age (GA) of 21+6 weeks (range, 19-24): all showed signs of hydrops prior to 24 weeks or at autopsy. All others (60%, 12/2) were live-born (median GA 38+4, range 37-40), underwent surgery and were alive at last follow up (median 3.2 years, range 0.1-17). The literature reported 22 ALVT fetuses with similar outcome.

Conclusions

In the absence of fetal hydrops, ALVT carries a good prognosis. Fetuses who survive to 24 weeks without hydrops are likely to have a good outcome.

INTRODUCTION

Although the exact incidence of an aorto-left ventricular tunnel (ALVT) is unknown, it is estimated between 0.001% and 0.1% of all congenital heart defects.^{1, 2} This defect is characterized by an abnormal connection between the ascending aorta and left ventricle that bypasses the aortic valve (AoV). This 'tunnel' provides a site for diastolic run-off from ascending aorta to the left ventricle, similar to significant aortic regurgitation, which may cause left ventricular (LV) dysfunction and congestive heart failure (CHF) as a result of the LV volume overload.¹

Over the past 20 years, the introduction of an accessible and well-organized prenatal screening programs has considerably improved prenatal detection rates of CHDs in general from 23% to 59.5%^{3, 4}, with a pooled estimate of 45.1% for all isolated CHDs in unselected populations⁵. This development has likely improved the prenatal detection rate of ALVTs as well. Especially the most severely affected cases will be referred to fetal cardiology units, because of the enlarged left ventricle with an abnormal appearing left ventricular outflow tract. Due to the rarity of this heart defect, correctly diagnosing the cause of these ultrasonographic features remains a challenge, as well as estimating the risk of intrauterine decompensation following a correct diagnosis.

The few case reports on fetal ALVT focus on the characteristics of the diagnosis rather than outcomes beyond surgery.^{6, 7} Conversely, postnatal studies focus on the prognosis of ALVT following a diagnosis in the neonatal period or in childhood.⁸⁻¹¹ As the age at diagnosis is related to the severity of heart defects in general, it can be expected that the prognosis of antenatal cases is worse, compared to ALVT cases detected in early infancy.¹² On the other hand, a prenatal diagnosis of ALVT might improve the prognosis, if cases benefit from timely intervention to mitigate deterioration after birth.¹³

Severe paravalvular regurgitation and signs of LV failure are critical conditions in utero and may potentially be important predictors of fetal death or neonatal death shortly after birth in ALVT cases.¹² However, the onset, severity and progression of congestive heart failure can vary significantly between patients.¹ To enable proper prenatal counselling for this condition, studies that describe the natural history and prenatal predictors at presentation in relation to outcome, are essential. With this study we aimed to gather up-to-date information on the outcome of a relatively large cohort of prenatally diagnosed ALVT cases worldwide. In addition, we systematically reviewed the literature for risk factors of intrauterine demise and neonatal outcome in fetuses with ALVT.

METHODS

We invited all members of the Association for European Paediatric and Congenital Cardiology's (AEPC) Fetal Cardiology Working Group and other fetal medicine units worldwide to participate in this retrospective multi-centre case series. Electronic databases or fetal registries were searched for patients with a prenatal diagnosis of ALVT. ALVT was defined as the presence of paravalvular aortic-left ventricular regurgitation that was visible on prenatal ultrasound and confirmation of the diagnosis on postnatal echocardiography amongst those that were liveborn. The Medical Ethics Committee of the Leiden University Medical Center approved this study.

Participating centres reviewed the patient charts and databases. Prenatal characteristics and course of disease after diagnosis were recorded using a pre-defined case record form (CRF). This CRF included the following antenatal parameters: gestational age at diagnosis, LV function (fractional shortening or ejection fraction) and cardiac biometry at diagnosis, Doppler flow velocimetry waveforms (umbilical artery (UA), middle cerebral artery (MCA), umbilical vein (UV) and ductus venosus (DV)), signs of fetal hydrops, cardiovascular profile score (CVPS), the presence of significant additional (extra-)cardiac malformations, the use of transplacental pharmacological treatment and pregnancy outcome. We supplemented an illustration indicating how the cardiothoracic ratio by circumference (CTR)^{14, 15}, left ventricular end-diastolic diameter (LVEDD)¹⁶, aortic valve annulus¹⁶, ascending aorta¹⁶ and Doppler measurements¹⁷⁻¹⁹ should be measured to minimize measurement error (Appendix 1). The left ventricular myocardial performance index (MPI), with a reported normal range from 0.35 ± 0.03 to 0.40 ± 0.05 with advancing gestation²⁰⁻²², was calculated as reported by Tei *et al.*²³. The formula by Huhta *et al.*²⁴ was used to calculate the CVPS. The fetal heart was considered enlarged (cardiomegaly), if the CTR was greater than 0.5¹⁵, by measurement or recorded as such at time of examination. The left ventricle, aortic valve annulus or ascending aorta was reported to be enlarged, if the specific measurement did not fall within the normal range (2 standard deviations above the mean for its gestational age).¹⁶ Fetal LV function was defined abnormal, based on the normal range for left ventricular fractional shortening (LV-FS) or ejection fraction (LV-EF) for its respective gestational age.²⁵ Fetal hydrops was defined as the presence of at least 2 symptoms, including ascites, pleural effusion, pericardial effusion, skin edema or polyhydramnios.

In addition, we recorded interventions to prevent fetal demise (including premature delivery), the occurrence of fetal death, gestational age at birth, birth weight, Apgar scores at 1, 5 and 10 minutes and admission to the neonatal intensive care unit. We furthermore collected data on postnatal status: postnatal cardiac measurements,

age at (corrective) surgery, site of ALVT closure, presence of a residual shunt, surgical complications, postoperative cardiac function and hospital stay, morbidity, mortality and age at last follow-up visit.

The development of fetal hydrops was chosen as our primary outcome, because a considerable number of reported fetuses with ALVT demise before a viable age is reached^{2,26}, whereas those that do make it to term generally have a good postoperative prognosis^{6, 7, 27-33}. To evaluate potential prognostic factors, we assessed the association between the prenatal characteristics of ALVT at diagnosis and the risk of demise, as well as postnatal outcome for those that survived until birth. Although this is the first study that describes a relatively large series of fetuses with this rare diagnosis, these numbers remain small for extensive statistical analysis. Descriptive statistics, including the median \pm range and proportions, were therefore used to report on prenatal characteristics, postnatal outcome and potential associations.

Literature review

We systematically searched the electronic PubMed, Embase, Web of Science, Cochrane Library and Emcare databases from database inception to December 2 2021, using search terms related to “aorto-left ventricular tunnel” and “prenatal diagnosis”, to identify reported cases with a prenatal diagnosis of ALVT in the literature (Appendix 2). Research results are reported in agreement with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Screening for relevant articles by title and abstract was performed by one reviewer (A. van Nisselrooij). If relevant, full-text was retrieved and selected articles were cross-referenced (Figure 2). The following data were collected from the included articles: year of publication, first author, time of diagnosis, cardiac features at prenatal diagnosis, presence of fetal hydrops, gestational age at birth, (age at) surgery and follow-up.

RESULTS

Prenatal diagnosis

Fifty-six percent of the approached centres (10/18) were able to contribute cases to this study. We included 20 cases with a prenatal diagnosis of ALVT from 10 fetal cardiology units worldwide over a period of 20 years (2000-2019), that had not been previously reported in the literature. Prenatal diagnoses were made in the second trimester in 75% (15/20) of cases with a median gestational age at diagnosis of 21+2 [range: 14+4 - 38+1]. The diagnosis of ALVT had been confirmed on autopsy (88%, 6/7 fetal demised cases) or postnatal transthoracic echocardiography (all liveborn cases).

Characteristics of the patients with ALVT on fetal echocardiography involved an increased CTR in 95% (19/20), LV dilatation (90%, 18/20) and increased diameter of the ascending aorta (100%, 20/20) (Figure 1). The majority of cases presented with LV dysfunction (70%, 14/20) and a dysplastic aortic valve (90%, 18/20). Abnormal mitral valve (dysplasia/accessory tissue) was encountered in 10% (2/20). Significant extracardiac malformations were found in only one case, in which a 3p14.1 microdeletion was diagnosed (Table 1).

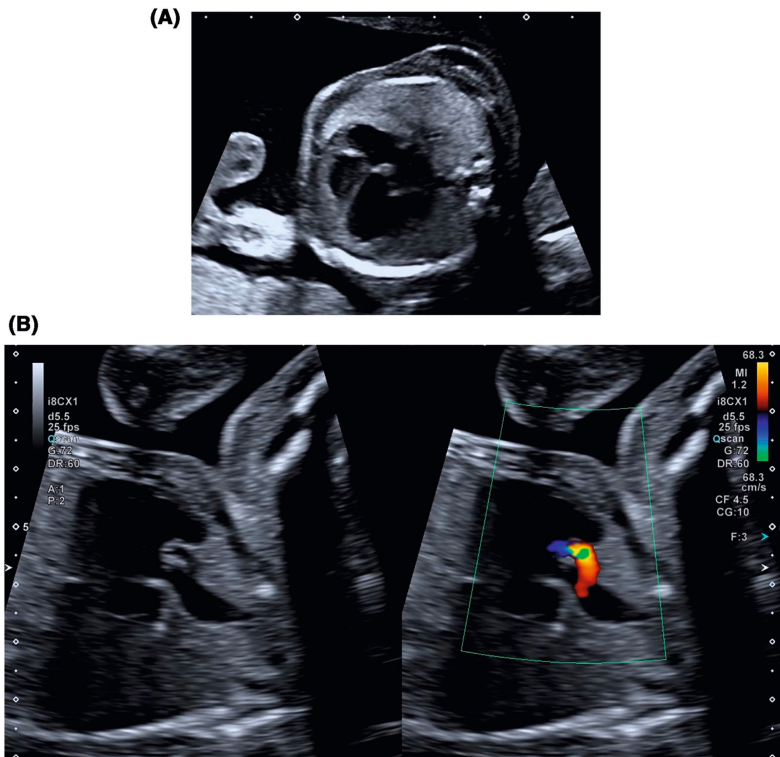


Figure 1.

(A) Four chamber view clearly showing cardiomegaly with left ventricular (LV) dilatation.
 (B) LV outflow tract view in diastole. The flow through the tunnel that bypasses the aortic valve is clearly visible

Table 1. Prenatal characteristics at diagnosis

Number of cases		20	
GA at diagnosis	Median (weeks + days)	21 + 2	[14 + 4 - 38 + 1]
Diagnosis in second trimester		16	(80.0%)
Cardiac features at first presentation			
Cardiomegaly (CTR>0.5) ¹⁵		19	(95.0%)
CTR		59%	[43 - 81%]
LVEDD ¹⁶	enlarged	18	(90.0%)
LV aspect	hypertrophic	11	(55.0%)
LV function	dysfunction	14	(70.0%)
	fractional shortening	25.0%	[11 - 40%]

Table 1. (continued)

	ejection fraction	48.6%	[28 - 57%]
AoV annulus ¹⁶	enlarged	11	(57.9%)
AoV aspect	dysplastic	18	(90.0%)
AoV function	insufficiency	7	(38.9%)
Asc. Aorta diameter ¹⁶	enlarged	20	(100.0%)
ALVT	size (mm)	3.4	[1.5 - 8.0]
Other structural cardiac malformations		2	(10.5%)
	extracardiac	1	(5.3%)

Data are given as n (%) or median [range]. Data on the size and function of the aortic valve were missing in 1 and 2 cases, respectively.

The fetal heart, left ventricle, aortic valve annulus and ascending aorta were 'enlarged', if: (1) the specific measurement did not fall within the normal range with respect to the gestational age^{15, 16} or (2) the exact size had not been measured, but the size appeared evidently increased according to the cardiac expert involved in the treatment for that particular case.

Abbreviations: Asc, aorta ascending aorta; ALVT, aorto-left ventricular tunnel; AoV aortic valve; CTR, cardiothoracic ratio; GA, gestational age; LV, left ventricular; LVEDD, left ventricular end-diastolic diameter.

Outcome

Forty percent (8/20) of cases showed signs of fetal hydrops, including skin edema, ascites and pleural or pericardial effusion at diagnosis or autopsy. The pregnancy was terminated on request of the parents before 24 weeks of gestation in 20% (4/20) of cases and spontaneous fetal death occurred in 3 cases (15%; 3/20), all of whom showed hydrops at time of diagnosis (<24 weeks GA). The remaining 65% (13/20) of cases resulted in a liveborn term neonate (median birth weight: 3420 gram; 92% ≥ 50th centile). The Apgar score at 5 minutes was ≥7 in all but one newborn (case 8), who eventually died (5%, 1/20). This case was diagnosed at 31 weeks of gestation, showing severe LV dysfunction and fetal hydrops, and quickly deteriorated after birth, requiring mechanical ventilation and inotropic support. Postnatal echocardiography, as well as MRI, were performed, displaying signs of a non-compaction cardiomyopathy with severe systolic dysfunction and mitral valve dysplasia. As extracorporeal membrane oxygenation (ECMO) was not yet available at the time in this facility (2010), it was decided not to intervene and the neonate died the 8th day of life due to progression of CHF.

All other liveborn neonates (60%, 12/20) underwent corrective surgery at a median age of 16 days [range: 1-44 days] and were discharged home after 22 days [median, range: 9-45 days]. In the majority of cases the tunnel was closed at the aortic site (75%, 9/12), whereas in 25% (3/12) of cases both sites were closed. The origin of the

left (LCA) and right coronary artery (RCA) were normal in 83% (10/12). In two cases (case 10 and 15) the RCA had to be separated from the tunnel. A residual paravalvar leak was described in three neonates (25%, 3/12) and surgery-related complications were encountered in one neonate (8%, 1/12). The latter involved a case that presented with clinical seizures requiring antiepileptic treatment the day after surgery, associated with hypoxic-ischemic brain injury, which was confirmed on MRI. Although the epileptic activity appeared transient, mild unilateral spastic cerebral palsy (Gross Motor Function Classification System (GMFCS), level 1) and delayed language development was reported on neurological follow-up (case 14). Altogether, 60% (12/20) of fetuses with a prenatal diagnosis of ALVT were alive at time of our analysis. The majority of patients are free of morbidity (58%; 7/12) at a median follow-up time of 3.2 years (range, 16 days - 17 years). In the remaining, aortic stenosis was present in three (25%, 3/12), CHF with reduced left and right ventricular function in one (8%, 1/12) and neurological symptoms in one case (8%, 1/12) (Table 2).

Table 2. Prenatal features in relation to outcome

Case description		Characteristics at presentation					Peripheral Dopplers				Outcome			
Nr	GA dx	ALVT (mm)	LVH	AoV size	LV function	Fetal hydrops	UV flow	DV a-wavet	UA EDFt	MCA EDFt	IUT	Pregnancy outcome	Surg-ery	Mort-ality
1	21+3	2.6	+	enlarged	dysfunction	+	-	-	-	-	no	TOP	21+6	+
2	18+2	3.0	+	enlarged	dysfunction	+	-	-	-	-	no	TOP	20+1	+
3	18+4	2.5	+	enlarged	normal	+	-	-	-	-	no	TOP	19+5	+
4	21+1	1.9	+	enlarged	dysfunction	+	normal	normal	normal	normal	no	TOP	21+5	+
5	23+0	3.3	-	normal	dysfunction	+	pulsatile	abnormal	abnormal	normal	no	FD	N.A.	+
6	20+3	4.5	-	normal	dysfunction	+	-	abnormal	abnormal	-	-	FD	24+0	+
7	20+0	8.0	-	enlarged	dysfunction	+‡	pulsatile	abnormal	abnormal	abnormal	yes	FD	23+0	+
8	31+3	6.0	+	enlarged	dysfunction	+	-	-	-	-	no	Livebirth	37+6	-
9	19+0	1.5	-	normal	normal	-	normal	-	normal	-	no	Livebirth	38+6	+
10	29+1	-	+	-	dysfunction	-	-	-	-	-	-	Livebirth	38+2	+
11	38+1	5.0	+	enlarged	dysfunction	-	-	-	-	-	no	Livebirth	38+0	+
12	14+4	5.5	+	enlarged	normal	-	normal	normal	normal	normal	no	Livebirth	39+4	+
13	23+0	2.8	-	normal	dysfunction	-	normal	normal	normal	normal	no	Livebirth	39+6	+
14	20+4	3.5	-	enlarged	normal	-	normal	normal	normal	abnormal	-	Livebirth	37+0	+
15	20+5	3.0	+	normal	normal	-	normal	normal	abnormal	abnormal	yes	Livebirth	38+0	+
16	20+6	1.5	-	normal	normal	-	normal	normal	normal	normal	no	Livebirth	38+0	+
17	22+3	4.0	+	enlarged	dysfunction	-	normal	normal	normal	abnormal	yes	Livebirth	40+0	+
18	32+3	-	-	normal	dysfunction	-	-	-	-	-	-	Livebirth	38+2	+
19	23+0	4.0	-	normal	dysfunction	-	pulsatile	normal	-	-	no	Livebirth	39+4	+

Table 2. (Continued)

Case description		Characteristics at presentation				Peripheral Dopplers				Outcome				
Nr	GA dx (mm)	ALVT (mm)	LVH	AoV size	LV function	Fetal hydrops	UV flow	DV a-wave†	UA EDF†	MCA EDF†	IUT	Pregnancy outcome	Surgery	Mortality
20	30+4	4.2	+	enlarged	dysfunction	-	normal	normal	abnormal	abnormal	yes	Livebirth	40+0	+
Risk of mortality														
														40%
			33.3%	25.0%	16.7%	7.7%	11.1%	11.1%	14.3%	40.0%	50.0%			
			45.5%	54.5%	50.0%	100.0%	66.7%	100.0%	60.0%	20.0%	25.0%			
			1.7	3.6 (0.5 - 26.4)	5.0 (0.5 - 54.5)	n.a.	16 (0.7 - 383.0)	n.a.	9.0 (0.6 - 143.9)	0.4 (0.02 - 6.3)	0.3 (0.03 - 4.2)			

Abbreviation: ALVT, aorto-left ventricular tunnel; AoV, aortic valve; CHF, congestive heart failure; CI, confidence interval; DV, ductus venosus; EDF, end-diastolic flow; FD, fetal death (spontaneous); GA, dx gestational age at diagnosis; IUT, intra-uterine (pharmacological) treatment; LV, left ventricular; LVH, left ventricular hypertrophy; MCA, middle cerebral artery; OR odds ratio, TOP, termination of pregnancy; UA, umbilical artery; UV, umbilical vein.
 † abnormal, if end-diastolic flow was absent or reversed, ‡ fetal hydrops was present at autopsy.

Prognostic factors

If the ALVT had been diagnosed in the second trimester (75%, 15/20) and signs of hydrops did not occur before 24 weeks of gestation (8/15), the fetal condition remained stable during the course of pregnancy and all survived to surgery. However, all fetuses with signs of fetal hydrops before 24 weeks of gestation (7/20) resulted in elective or spontaneous termination of pregnancy. The presence of fetal hydrops appeared equally important in cases with a prenatal diagnosis in the third trimester, as all without signs of fetal hydrops survived (4/4), whereas the one presenting with hydrops at first evaluation died in the neonatal period (1/1).

Although LV-FS or -EF could only be obtained in 60% (12/20) of cases, the degree of LV dysfunction at presentation seemed related to the presence of fetal hydrops. We found a LV-FS \leq 25% [range: 11 – 25%] or -EF \leq 51% [range: 28 - 51%] at presentation in 87.5% of cases (7/8) that developed fetal hydrops during the course of pregnancy. Decreased LV-FS or EF, on the other hand, was never found amongst survivors (FS range: 27 - 40%; EF range: 40 – 57%). Other factors associated with an increased mortality risk included an enlarged aortic valve diameter (54.5% vs 25%, in those with normal aortic valve diameter) or left ventricular hypertrophy (LVH) at presentation (45.5% vs 33.3%, in absence of LVH).

Furthermore, evaluation of abnormal flow patterns on pulsed wave Doppler velocimetry can potentially aid to the differentiation between ALVT fetuses with a high mortality risk and those with a better chance of survival, based on the presence of absent or reversed end-diastolic flow in the UA (mortality: 60.0% vs 14.3%, if UA flow was normal), pulsatile flow in the UV (mortality: 66.7% vs 11.1%, if UV was not pulsatile) or a reverse a-wave in the ductus venosus (DV) (mortality: 100.0% vs 11.1%, if DV flow was normal).

Although the proportion of fetuses with aortic valve insufficiency tended to increase with advancing gestation (39% at presentation vs 82% shortly after birth), this was not associated with mortality. A correlation between mortality and abnormal flow in the middle cerebral artery (MCA) did not seem evident either. Unfortunately, we were unable to assess the potential predictive value of the MPI or CVPS, as these could not be calculated in 65% (13/20) and 60% (12/20) of the cases, respectively. Only a few fetuses received transplacental pharmacological treatment with digoxin alone or a combination of digoxin and metoprolol following a prenatal diagnosis of ALVT (20%, 4/20). Although there was no progression of CHF in treated fetuses, this impedes us to reliably assess this potential effect on the risk of mortality as well (Table 3).

Table 3. Postoperative outcome & follow-up of all surviving ALVT cases

Case	Postnatal course				General well-being			
	Age at surgery†	LV dysfunction	Residual shunt	Complications	Discharge home (days)	Follow-up	Reinterventions	Morbidity
9	42	no	-	NEC, residual AoS	16	Alive (17 yr.)	2 Surgical valve repair, AoV replacement (14 + 16.5 yr)	Alive and healthy
10	44	no	no	-	N.A.	Alive (10 yr.)	1 Commissurotomy AoV + PV (7 mo)	AoS (mild-abnormal)
11	10	no	-	-	45	Alive (13 yr.)	1 Bentall procedure (13 yr)	AoS (abnormal), AoI, AoAsc aneurysm
12	1	no	no	unknown	10	Alive (9 yr.)	0	AoS (mild)
13	1	yes	-	-	22	Alive (10 yr.)	0	CHF (LV+RV dysfunction)
14	5	yes	-	hypoxic-ischemic brain injury <i>po.</i>	21	Alive (4 yr.)	0	Spastic cerebral palsy (GMFCS I), AoI, residual aneurysm ALVT‡
15	25	yes	yes	-	34	Alive (2 yr.)	0	Alive and healthy
16	1	yes	no	SVT*	19	Alive (16 mo.)	0	Alive and healthy
17	29	no	yes	-	22	Alive (1.5 mo.)	0	Alive and healthy
18	4	-	yes	-	16	Alive (16 days)	0	Alive and healthy
19	25	yes	-	-	9	Alive (3.5 wks)	0	Alive and healthy
20	21	no	no	unknown	30	Alive (1.5 mo.)	0	Alive and healthy

Data are given as median or proportion of cases with complete information.

Abbreviations: ALVT, aorto-left ventricular tunnel; AoAsc, ascending aorta; AoS, aortic stenosis; AoV, aortic valve; CHF, congestive heart failure; GMFCS, I Gross Motor Function Classification System grade I; LV, left ventricular; mo, months; NEC, necrotizing enterocolitis; *po.*, postoperative; PV, pulmonary valve; RV, right ventricular; SVT, supraventricular tachycardia; wks, weeks; yr, years.

† Age at surgery in days. ‡ Supraventricular tachycardia requiring medication



Literature review

The literature search yielded 42 articles. After screening of the title and abstract and reviewing of the full-text, 17 articles were found eligible for inclusion. These articles together reported on 22 fetuses prenatally diagnosed with an ALVT (1996-2021).^{2, 6, 7, 12, 26-38} Patient characteristics and outcome of the reported fetuses are summarized in Table 4. Overall, 65% (15/23) were alive and thriving at the end of the follow-up period. Fetal hydrops was reported in 6/15 (33%) fetuses with a prenatal diagnosis in the second trimester, of which four resulted in fetal or postnatal demise (68%). On the other hand, fetal hydrops was never reported in those diagnosed in the third trimester, and only one case diagnosed in the third trimester demised (14%).

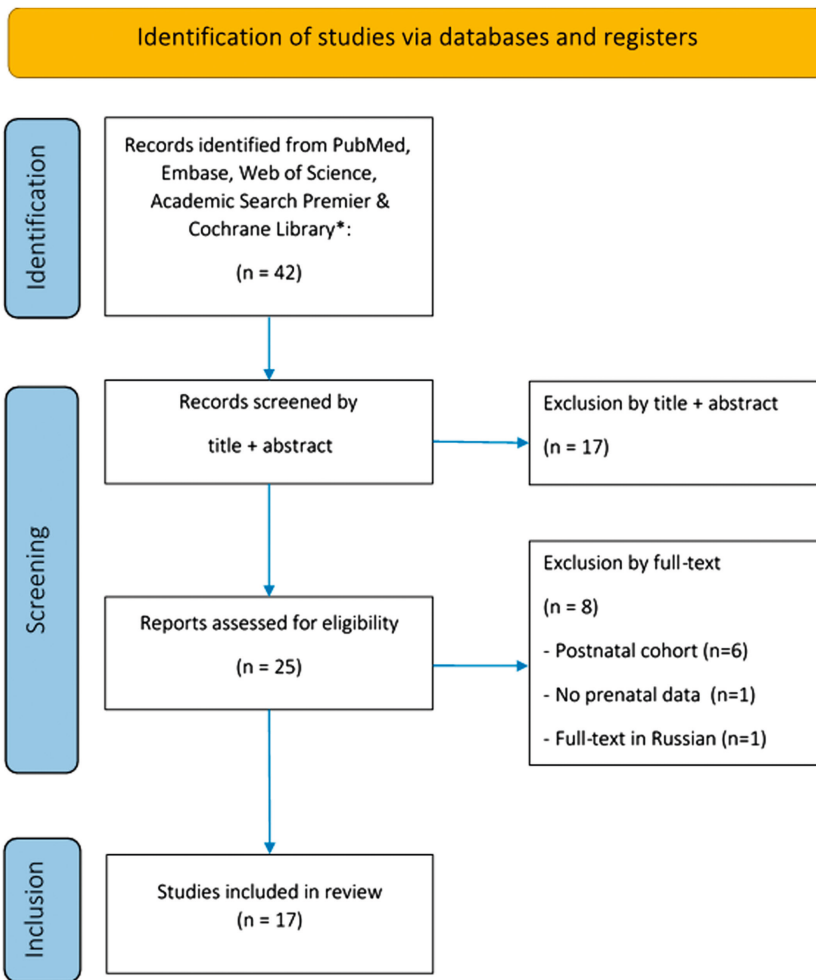


Figure 2. Identification of eligible studies in the literature, according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines

Table 4. Summary of fetuses diagnosed with ALVT reported in the literature (n=2238)

Prenatal diagnosis in second trimester								
Case	Year	Author	Time of diagnosis	Cardiac features at prenatal diagnosis	Fetal hydriops	GA at birth	Surgery (age, days)	Follow-up
1	1995	Cook ²	22 GA	LV dilatation and hypertrophy, turbulent flow through ALVT	<i>unknown</i>	-	-	Termination of pregnancy
2	1996	Sousa-Uva ²⁶	22-24 GA	severe LV dysfunction and dilatation, dysplastic aortic cusps, paravalvular aortoventricular reflux	yes	-	-	Termination of pregnancy
3	1996	Sousa-Uva ²⁶	22-24 GA	severe LV dysfunction, myocardial hypertrophy, dysplastic regurgitant aortic cusps	yes	-	-	Spontaneous fetal demise (27 wks of gestation)
4	2013	Terry ¹²	21 GA	Severe LV dilation/hypertrophy, poor contractility, reverse LV outflow adjacent to aortic valve. Endocardial fibrosis	yes	-	-	Spontaneous fetal demise (30 wks of gestation)
5	2007	Pascoli ³⁴	26 GA	LV dilatation and hypertrophy, enlarged aortic root, displastic AoV and aortic regurgitation	no	39	Yes (-)	Neonatal death (day 10), due to persistent ischemic failure of extremities
6	2011	Singh ⁶	20 GA	-	yes	37	Yes (2)	Postnatal demise (5 wks), due to multisystem failure
7	2005	Biffanti ³³	22 GA	LV dilatation and dysfunction, ALVT	yes	35	Yes (2)	Alive and thriving at discharge, FU 9 weeks postoperatively

Table 4. (Continued)

Prenatal diagnosis in second trimester								
Case	Year	Author	Time of diagnosis	Cardiac features at prenatal diagnosis	Fetal hydrops	GA at birth	Surgery (age, days)	Follow-up
8	2007	Kenny ⁷	26 GA	significant eccentric jet of aortic regurgitation wit LV dilatation, large ALVT	<i>unknown</i>	40	Yes (11)	Alive, FU on postoperative course unknown
9	2008	Henaine ²⁹	22 GA	enlarged LV, abnormal systolic-diastolic flow in the ascending aorta	<i>unknown</i>	term	Yes (6)	Alive and thriving, FU 2 years
10	2011	Singh ⁶	22 GA	-	no	38	Yes (1)	Alive and thriving, FU unknown
11	2011	Singh ⁶	20 GA	-	no	40	Yes (1)	Alive and thriving, FU unknown
12	2011	Singh ⁶	23 GA	-	no	40	Yes (1)	Alive and thriving, FU unknown
13	2014	Jone ³¹	25 GA	LV dilatation and dysfunction, dysplastic aortic cups, ascending aorta dilatation, ALVT	no	36	Yes (3)	Alive and thriving at 9 months FU
14	2016	Smith ³⁵	23 GA	left and right ventricular dilatation and dysfunction	no	term	Yes (3)	Alive and asymptomatic at 5 months FU
15	2020	Truong ³⁷	24 GA	LV dilatation, dysfunction, endocardial fibrosis and aortic regurgitation through a tunnel near the IVS	yes	term	yes (3)	Alive with normal LV function at 2 years FU

Table 4. (Continued)

Prenatal diagnosis beyond second trimester (or unknown)								
Case	Year	Author	Time of diagnosis	Cardiac features at prenatal diagnosis	Fetal hydrops	GA at birth	Surgery (age)	Follow-up
16	2017	Kosutic ³⁶	30 GA	LV and ascending aorta dilatation, separate ALVT	no	38	Yes (9 days)	Postnatal demise (8wks), due to peri-/postoperative complications
17	2000	Grab ²⁸	31 GA	LV and aortic root dilatation, large ALVT around the annulus	no	40	Yes (3 months)	Alive and thriving at 8 months FU
18	2005	Kolcz ³⁰	35 GA	enlargement/severe hypertrophy LV, aortic root dilatation, ALVT with paravalvular regurgitation	unknown	40	Yes (1 day)	Alive and thriving at 2 years FU
19	2015	Christmann ²⁷	35 GA	LV dilatation/hypertrophy, paravalvular regurgitation around the annulus	unknown	-	Yes (18 days)	Alive and asymptomatic at 5 year FU
20	2016	Nakamura ³²	31 GA	LV dilatation/dysfunction, dysplastic aortic valve, ALVT	no	37	Yes (1 hour)	Alive and thriving at 2 months FU
21	2021	Ito ³⁸	30 GA	LV dilatation, severe regurgitation through ALVT	unknown	36	yes (1)	Alive, trivial aortic regurgitation at 1 month after surgery
22	2016	Smith ³⁵	unknown	-	unknown (CHF reported)	-	Yes (1 day)	Alive and thriving, mild cardiomyopathie at 12 years FU

Abbreviations: FU, follow-up; IVS, intraventricular septum; LVOT, left ventricular outflow tract.

DISCUSSION

This is the first study that reports on the fetal course of ALVT in relation to outcome in a contemporary cohort of prenatally diagnosed cases worldwide. Despite the significant risk of fetal or neonatal demise (40% of cases in our study), we found that in the absence of symptoms of fetal hydrops, all patients survived with good clinical outcome at a median age of 3.2 years (range, 1 month to 18 years).

This series shows that the key features leading to the fetal diagnosis of ALVT are cardiomegaly, LV dilatation, dilatation of the ascending aorta and paravalvular aorto-ventricular regurgitation. The retrograde flow that passes to the left ventricle beside the aortic valve, is the cornerstone of the diagnosis. With modern ultrasound systems the tunnel itself may even be visible (Figure 2). Majority of cases show an abnormal LV function at presentation, defined as an impaired LV-FS or -EF.²⁵ Impaired LV contractility may eventually lead to low cardiac output, elevated venous pressure, fetal hydrops and fetal or neonatal demise. ALVT usually presents as an isolated defect, though aortic valve abnormalities including bicuspid aortic valve may also be present.

Not surprisingly, fetal hydrops appears to be associated the most with adverse outcome. Prognosis of fetuses with symptoms of hydrops (including ascites, pleural effusion or skin edema) was very poor, as all cases died before a viable age was reached or surgery could be performed. However, if fetuses did not develop hydrops, all successfully received corrective surgery and the majority are free of morbidity at 3.2 years of age. Presence or absence of hydrops was described in 15/22 ALVT cases reported in the literature.^{6, 12, 26, 28, 32, 33, 36, 37} Six cases had signs of hydrops with similar outcome compared to this series, as the majority resulted in fetal or postnatal demise (68%).^{6, 26, 33} Similar to our experience, the literature review showed that in the absence of hydrops, fetal or neonatal mortality occurred in only 14% of cases.^{6, 28, 31, 32, 34-36} Our finding that stable non-hydropic fetuses with ALVT, despite the impressive cardiomegaly and impaired contractility, generally survive to term with good clinical outcome, is essential for prenatal counselling; it is important that the parents are aware that the prognosis in those who survive without hydrops to near term is better than prognosis if there is evolving hydrops in mid-gestation before they make decisions regarding the pregnancy.⁸

We encountered a strong relationship between abnormal peripheral Doppler measurements and perinatal death in fetuses with ALVT. In this study 100% of cases with a reverse a-wave in the DV died, compared to 13% if the a-wave remained positive. The risk of mortality was also considerably higher among fetuses with pulsatile flow

in the UV and absent or reversed end-diastolic flow in the UA. As abnormal venous Dopplers are a result of congestive heart failure²⁴, these parameters reflect on the condition of the fetus with development of fetal hydrops as an end-stage and do not influence the prognosis independently. This is in line with a previous study by Gudmundsson *et al.* stating that the presence of umbilical venous pulsations is the most useful predictor of perinatal death in cases with fetal hydrops.³⁹ However, it should be stressed that abnormal flow in the umbilical artery may be incorrectly interpreted as a sign of placental dysfunction, rather than a result of the presence and size of an ALVT. Finally, an enlarged aortic valve diameter at presentation also seemed associated with the development of fetal hydrops and adverse outcome.

Safe and effective treatment options for ALVT patients in fetal life have not been reported to date. Although some studies suggest that the use of intrauterine digoxin and beta-blocker therapy may improve CVPS with little risk to do potential harm, case numbers in our study were limited and current evidence is too scarce to suggest IUT as a fetal therapy in cases with fetal ALVT.

The majority of liveborn neonates (92%) received corrective surgery without significant postoperative complications. Neonatal death occurred in the only liveborn that had presented with hydrops in the third trimester and quickly deteriorated after birth. Although we did not observe postoperative deaths in this study, postoperative mortality has been reported in three cases in the literature.^{6, 34, 36} All demised due to rapid progressive deterioration perioperatively and/or postoperative complications. The age at surgery varied considerably amongst our original cases from a few hours after birth to 6 weeks of age. This is consistent with the literature, describing neonates that require surgery within the first days of life^{6, 30-32, 34, 35, 37}, as well as those in which surgery could be delayed up to 3 months or even 1 year of age^{6, 28}. This reflects the heterogeneity in clinical conditions in ALVT patients, as well as changing attitudes regarding and expertise with neonatal surgical interventions in general. Altogether, our results stress that close monitoring of these neonates is warranted, given the risk of rapid and sudden deterioration despite aggressive anti-congestive therapy and the unpredictability of postoperative recovery.

Overall survival in fetuses with ALVT was 60% with good clinical outcome in the survivors. Fifty-eight percent of these cases did not show signs of additional morbidity with a normal cardiac function at a median age of 3.2 years. The majority of cases remained asymptomatic until the end of primary school, after which cardiac signs, such as a mild to moderate aortic stenosis, became more apparent and surgical intervention involving replacement of the aortic valve was necessary. In this study three cases

needed aortic valve replacement at a median age of 14 years and 3/4 patients over age 10 has had additional surgery at the time of this writing.

Despite the international character of this study, with the aim to include a maximal number of available fetuses with this extremely rare heart defect, we were still underpowered to perform extensive statistical analyses. The retrospective character and broad time-period from which cases were retrieved, therewith precluded us to evaluate all potentially prognostic factors for adverse outcome, amongst which the presence of pathogenic variants after genetic testing. As a third, the considerable changes in the prenatal detection of CHDs in general, as well as care for these patients over the past decades may have resulted in the description of a selected population and the results may not be applicable to cases in the current period. To develop an accurate prediction model that aids prenatal counseling by truly discriminating those at risk of fetal or neonatal demise from those with a generally good clinical outcome, a global registry is necessary to obtain a larger study population with time.

In conclusion, evaluation of fetal hydrops and concomitant fetal Doppler anomalies before 24 weeks of gestation seem particularly useful to indicate cases of ALVT at risk for perinatal death. In the absence of signs of fetal hydrops, all cases reached term and were liveborn. Although close monitoring after birth is warranted, the vast majority will make it to surgery and survive with good clinical outcome. To improve our understanding of this disorder and the variability in clinical presentations, autopsy and genetic studies are necessary.

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