Article published online: 2022-07-01

Prenatal Diagnosis, Associated Findings, and Postnatal Outcome in Fetuses with Double Inlet Ventricle (DIV)

Pränatale Diagnose, Begleitbefunde und postnataler Ausgang bei Feten mit doppeltem Einlassventrikel

OPEN ACCESS

Authors

Paul Böckenhoff[1], Astrid Hellmund[1], Ingo Gottschalk[2], Christoph Berg[2], Ulrike Herberg[3], Annegret Geipel[1], Ulrich Gembruch[1]

Affiliations

1 Department of Obstetrics and Prenatal Medicine, University Hospital Bonn, Bonn, Germany
2 Department of Prenatal Medicine und Gynecological Sonography, University Hospital Cologne, Cologne, Germany
3 Department of Pediatric Cardiology, University Hospital Bonn, Bonn, Germany

Key words

Echocardiography, Fetal cardiology, Pediatric cardiology, Double inlet ventricle, Prenatal diagnosis

Schlüsselwörter

Echokardiografie, Fetale Kardiologie, Pädiatrische Kardiologie, Double inlet ventricle, Pränatale Diagnostik

received 05.01.2022
accepted 29.04.2022
published online 01.07.2022

Bibliography

Ultraschall in Med 2023; 44: e226–e240
DOI 10.1055/a-1866-4538
ISSN 0172-4614

© 2022. The Author(s).

This is an open access article published by Thieme under the terms of the Creative Commons Attribution-NonDerivative-NonCommercial-License, permitting copying and reproduction so long as the original work is given appropriate credit. Contents may not be used for commercial purposes, or adapted, remixed, transformed or built upon. (https://creativecommons.org/licenses/by-nc-nd/4.0/).

Georg Thieme Verlag KG, Rüdigerstraße 14, 70469 Stuttgart, Germany

Correspondence

Prof. Ulrich Gembruch
University Hospital Bonn
Department of Obstetrics and Prenatal Medicine, Venusberg Campus 1, 53127 Bonn, Germany
ulrich.gembruch@ukbonn.de

ABSTRACT

Purpose To assess the spectrum of associated cardiac anomalies, the intrauterine course, and postnatal outcome of fetuses with double inlet ventricle (DIV).

Methods Retrospective analysis of prenatal ultrasound of 35 patients with DIV diagnosed between 2003 and 2021 in two tertiary referral centers in Germany. All fetuses underwent fetal echocardiography and a detailed anomaly scan. Postnatal outcome and follow-up data were retrieved from pediatric reports.

Results 33 cases of DIV were correctly diagnosed prenatally. 24 fetuses (72.7 %) had a double inlet ventricle with dominant left (DILV), 7 (21.2 %) with dominant right ventricular morphology (DIRV), and 2 cases (6 %) with indeterminate morphology (DIIV). 4 (16.6 %) were Holmes hearts. 5 of the 7 fetuses (71.4 %) with DIRV had a double outlet right ventricle (DORV). Malposition of the great arteries was present in 84.8 %. Chromosomal abnormalities were absent. Termination of pregnancy was performed in 8 cases (24.2 %). 24 fetuses (72.7 %) were live-born. 5 (20.8 %) were female and 19 (79.2 %) were male. The median gestational age at birth was 38 + 2.5 weeks. All but one child received univentricular palliation. The median follow-up time was 5.83 years with an adjusted survival rate of 91.6 % (22 of 24 live-born children). There was one case of Fontan failure at 15.7 years.

Conclusion DIV remains a major cardiac malformation although both prenatal diagnostics and cardiac surgery have improved over the years. The course of pregnancy is commonly uneventful. All children need univentricular palliation. The children are slightly physically limited, develop a normal intellect, and attend school regularly.

ZUSAMMENFASSUNG

Ziel Beurteilung der assoziierten kardialen Anomalien, des intrauterinen und postnatalen Verlaufs von Feten mit doppeltem Einlassventrikel (DIV).

Methoden Retrospektive Analyse der pränatalen Befunde von 35 Patienten mit DIV zwischen 2003 und 2021 in 2 tertiären Referenzzentren in Deutschland. Bei allen Feten wurden eine fetale Echokardiografie und eine Feindiagnostik durchgeführt.

Postnatale Follow-up-Daten wurden aus pädiatrischen Berichten entnommen.

Ergebnisse 33 Fälle von DIV wurden pränatal korrekt diagnostiziert. 24 Feten (72,7 %) hatten einen DIV mit dominanter linker (DILV), 7 (21,2 %) mit dominanter rechtsventrikulärer (DIRV) und 2 Fälle (6 %) mit unbestimmter Morphologie (DIIV). 4 (16,6 %) waren Holmes-Herzen. 5 der 7 Feten (71,4 %) mit DIRV hatten einen DORV. Eine Malposition der großen Arterien lag in 84,8 % vor. Aneuploidien waren nicht vorhanden. Ein Abbruch wurde in 8 Fällen (24,2 %) durchgeführt. 24 Feten (72,7 %) wurden lebend geboren, davon waren 5 (20,8 %) weiblich und 19 (79,2 %) männlich. Medianes Gestationsalter bei der Geburt betrug 38 + 2,5 Wochen. Bis auf ein Kind erhielten alle eine univentrikuläre Palliation. Das mediane Follow-up betrug 5,83 Jahre mit einer adjustierten Überlebensrate von 91,6 % (22 von 24 Lebendgeborenen). Ein Fall von Fontan-Versagen mit 15,7 Jahren.

Schlussfolgerung DIV bleibt ein schwerer Herzfehler, auch wenn sich die pränatale Diagnostik und kardiochirurgische Palliation im Laufe der Jahre verbessert haben. Der Verlauf der Schwangerschaft ist meist problemlos. Alle Kinder erwartet eine univentrikuläre Palliation. Die Kinder sind körperlich leicht eingeschränkt, bei normalem Intellekt und gehen regelmäßig zur Schule.

Introduction

Double inlet ventricle (DIV) is present when both atria drain into the same ventricle via a right and left atrioventricular valve. DIV has a prevalence of less than 1 per 10,000 live births and accounts for about 1 % of all congenital heart defects [1, 2]. Maternal pregestational diabetes is associated with an increased risk of DIV [3]. DIV, considered the most common form of univentricular atrioventricular junction, can be complex. The nomenclature of univentricular hearts is still controversial. First described by van Praagh as a single ventricular heart [4], it is now clear that DIV has a big and a second small incomplete chamber within the ventricular mass. In normal hearts, there is a single left ventricle coexisting with a single right ventricle with each containing three segments: inlet, apex, and outlet with the muscular ventricular septum interposing between the right and left ventricular apical component carrying the atrioventricular conduction axis [5, 6]. In double inlet ventricular hearts, one chamber is incomplete, meaning it no longer possesses all of its components. These hearts are differentiated into three types: left ventricle type with incomplete right ventricle (DILV, most common), right ventricle type with incomplete left chamber (DIRV, sometimes), and solitary ventricle of indeterminate morphology (DIIV, rare). The latter type is frequently seen in association with heterotaxy (mostly right isomerism). DIRV is often associated with DORV. The interventricular communication between the dominant and the incomplete chamber (rudimentary outlet chamber) is often through a ventricular septal defect formerly known as the bulboventricular foramen [6]. A discordant ventriculoarterial connection (malposition of the great arteries (MGA)) and obstruction of the outflow tracts are common. The more uncommon case of a DILV with concordant ventriculoarterial connection is called Holmes heart [7, 8].

Differential diagnosis of DIV and DILV include tricuspid atresia (TA), hypoplastic left heart and unbalanced atrioventricular septal defect (AVSD).

The aim of this study was to assess the spectrum of associated cardiac anomalies, the intrauterine course, and postnatal outcome of fetuses with DIV. The morphological variants and the accuracy of prenatal echocardiographic diagnosis of DIV were assessed.

Patients and Methods

All prenatally diagnosed cases of DIV between 2003 and 2021 in two tertiary referral centers were retrospectively reviewed with regard to intrauterine course and outcome. 35 pregnant women were enrolled in this study. Two cases had to be excluded because DILV was not confirmed postnatally; instead TA was present.

All fetuses underwent a full anatomic scan and echocardiography in a standardized fashion including color and pulsed wave Doppler examinations. Ultrasound examinations were carried out with 5-MHz, 7.5-MHz or 9-MHz probes (IU 22 and EPIQ7, Philips, Hamburg, Germany; Aplio i900 Canon, Tokyo, Japan; Voluson E8 and E10, GE Healthcare, Solingen, Germany). All patients received consultation from a pediatric cardiologist at least once. If the patient decided to continue with the pregnancy, repeated sonographic scans were scheduled. In the early postnatal period, all patients underwent echocardiography performed by a pediatric cardiologist.

As far as retrospectively achievable, prenatal databases were analyzed regarding the type of double inlet ventricle (DILV/DIRV/DIIV), the great arteries, the incomplete outlet chamber, the patency of both atrioventricular valves, the presence of outflow tract obstructions, and additional cardiac and extracardiac anomalies. The following variables were assessed: maternal age, gestational age at diagnosis and at delivery, mode of delivery, birth weight, and Apgar score. Karyotype analysis including 22q11 was evaluated when available. Pediatric charts and autopsy results were analyzed and compared to prenatal findings. All data were retrieved from medical files, stored images, and video recordings. Structured telephone interviews were conducted with each family regarding quality of life (QOL). Pre- and postnatal diagnoses of all live-born children were compared to assess the accuracy of prenatal diagnosis. There was no autopsy conducted in six cases of termination of pregnancy due to refusal of the parents.

In this study DIV was defined by the presence of a dominant and an incomplete chamber based on the respective morphological appearance and presence or absence of the inlet, apex, and outlet component. Cases of TA where the atretic tricuspid valve is in communication with the dominant chamber were defined as DIV with TA. Cases in which the atretic AV valve belongs to the

incomplete ventricle were defined as true TA. In addition, we defined cases with AVSD as DIV with AVSD if more than 2/3 of the common AV valve drained into the dominant chamber.

All cases were classified into five groups according to the pregnancy outcome: termination of pregnancy (TOP), neonatal death (NND), death in infancy (INFD), and survivors. Neonatal death was defined as death within the first 28 days of life, and INFD as any death after 28 days of life. Postnatal medical files of echocardiography, cardiac catheterization, surgery, or autopsy were available for confirmation of the prenatal diagnosis in all live-born children.

Data analyses were performed using the Statistical Package for Social Sciences (SPSS 20.0 INC. Chicago, III USA) but were limited to descriptive analysis.

Approval from the ethics committee was obtained.

Results

Between 2003 and 2021, 33 cases of DIV were diagnosed at our centers with two pregnancies currently ongoing. The median gestational age at first presentation in our clinic was 23 + 3 weeks (range: 14–37) (▶ **Table 1**).

Cardiac anomalies

24 of the 33 fetuses (72.7 %) had a DILV, 7 (21.2 %) had a DIRV, and 2 (6 %) had a DIV of indeterminate type. Of the 24 cases with DILV, one (4 %) had a double outlet left ventricle (DOLV) and four (16.6 %) had a Holmes heart. In addition, normal position of the great vessels was present in two further cases. In one of the cases, there was pulmonary atresia (PA), while the aorta was normally coming from the left ventricle (LV) and in the other case, DIRV was present. 71.4 % of cases of DIRV (5/7) had a double outlet right ventricle (DORV). There were no cases of DIV with TA or with AVSD.

With regard to the position of the great arteries, there was malposition in 28 cases (84.8 %), 16 cases of dextro-MGA (57.1 %), 10 cases of levo-MGA (35.7 %). Two fetuses (7.1 %) had an undefined malposition, including one case of DILV with mirror image dextrocardia. In this case, the outflow was left-sided via a rudimentary outlet chamber into the aorta and a hypoplastic pulmonary trunk right parallel to the aorta. There were no cases of isomerism (left or right) in our cohort, but one child showed an interrupted inferior caval vein and azygos continuation. Pulmonary outflow tract obstruction was present in 13 cases (39.4 %), of which 8 were pulmonary stenosis (PS) (61.5 %) and 5 were pulmonary atresia (PA) (38.5 %). Anomalies of the aortic arch were seen in 36.4 % (12/33). These include right aortic arch (25 %), hypoplastic aortic arch (16.7 %), and aortic coarctation (CoA) (58.3 %); CoA was severe in 71.4 % (5/7). Three fetuses had a left persistent superior caval vein and one had an aberrant left subclavian artery. One fetus with DILV had third-degree AV block.

▶ **Table 1** Patient population.

Total cases	33
Lost to follow-up	3 % (1/33)
Termination of pregnancy	24.2 % (8/33)
Live birth	72.7 % (24/33)
Overall survival rate	66.6 % (22/33)
Adjusted survival rate (live births)	91.6 % (22/24)
Neonatal death (NND)	4.1 % (1/24)
Infant death (INFD)	4.1 % (1/24)
Median maternal age at first presentation	30 years (20–43)
Median gestational age at first presentation in our clinic	23 + 3 weeks (14–27)
Median gestational age (GA) at delivery	38 + 2.5 weeks (34–41)
Fetal sex live born	5 female (20.8 %)
	19 male (79.2 %)
Median birth weight	3220 g
Median follow-up time	5.83 years (1 day to 15.7 years)

Genetic testing and additional extracardiac anomalies

Chromosomal analysis was offered to all patients and was carried out at the patient's request in 19 cases (57.6 %) all having a euploid karyotype. In addition, analysis for microdeletion syndrome 22q11 was performed in 15 cases. All showed normal results.

Extracardiac anomalies were present in 6 of 33 cases (18.2 %) including three cases with a single umbilical artery, and one case each with a left-sided renal agenesis, azygos continuation, and gallbladder duplication.

Outcome

In 8 of 33 cases (24.2 %), the parents-to-be opted for TOP. One case was lost to follow-up (3 %); lastly this patient considered TOP. There was no IUFD. Overall 24.2 % (8/33) were female and 75.8 % (25/33) were male. 24 neonates (72.7 %) were live-born of which 5 (20.8 %) were female and 19 (79.2 %) male. 11 (45.8 %) of 24 pregnancies were delivered vaginally. In 13 cases (54.2 %), a caesarean delivery (CD) was performed due to obstetrical indications, with 30 % being unplanned. The median gestational age at birth was 38 + 2.5 weeks (range: 34–41). One fetus had CD at 34 + 0 weeks due to a pathological CTG during induction of labor after preterm premature rupture of membranes. The median birth weight was 3220 g (range: 1980–4570 g). IUGR was not present. The median 5-minute Apgar score was 9 (range: 5–10).

NND and INFD occurred in one of 24 cases each. One neonate who received Norwood I on day 13 of life with the Damus-Kaye-Stansel procedure, Sano shunt, and aortic arch reconstruction by patch-plasty died three days after surgery due to heart and acute renal failure on ECMO therapy. The other neonate underwent a modified Norwood procedure with patch extension of the aortic arch into the descending aorta, a BT shunt to the right pulmonary artery, and an atrioseptectomy on day 20 and died at 3 months of age on ECMO therapy prior to bidirectional Glenn (PCPC) also due to heart failure after a BT shunt closure.

The remaining 22 children were alive (5 patients > 10 years of age included) at the time this manuscript was written, resulting in

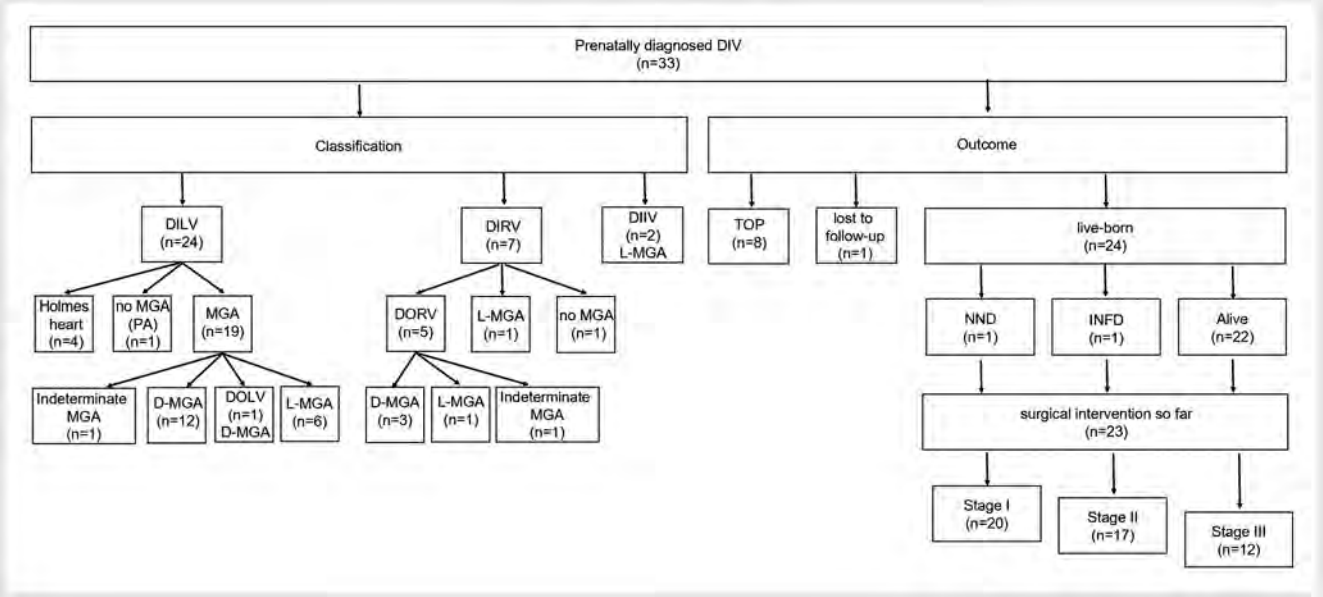
an adjusted survival rate of 91.6 %. Follow-up was available between 1 day and 15.7 years after birth. The median follow-up time was 5.83 years (▶ **Fig. 1**).

Postnatal cardiac surgery

All but one child underwent surgery with the aim of univentricular palliation. This 11-month-old child has a DILV with PA with centrally located small pulmonary arteries and multiple aorto-pulmonary collaterals. In this case, the central pulmonary arteries were too small for a Fontan circulation, so compassionate care was requested by the parents. Excluding this case, 86.9 % (20 of 23) of the neonates received a first stage of univentricular palliation in the form of a (modified) Norwood (-Sano) procedure, BT (Blalock-Taussig) shunt, DKS (Damus-Kaye-Stansel procedure), pulmonary artery banding (PAB), and/or atrioseptectomy with a mean age at the time of operation of 0.65 months with 16 of 18 (88.9 %) being performed within the first three weeks of life. Minus the two cases of NND and INFD, respectively, the bidirectional Glenn procedure (stage II; PCPC) was performed in 94.4 % (17/18) of cases (mean age at operation 6.76 months), including one Kawashima procedure due to an interrupted inferior caval vein with azygos vein continuity into the superior caval vein. The Fontan procedure (stage III; TCPC) was performed in 12 of 20 children (60 %). The mean age at Fontan completion was 39 months (3 3/12 years). At this point, it should be considered that, at the time the manuscript was written, seven children were younger than three years. Univentricular palliation is the common final course of action in all children of our collective. 5 of 22 children (22.7 %) received PAB. Four children (18.2 %) had a pacemaker implanted. The reason for this was a third-degree atrioventricular block in two cases (in one case congenitally, in the other postoperatively) and postoperative sinus bradycardia in two cases. Postoperative diaphragmatic paresis was seen three times. Failing Fontan occurred once (8.3 %) after 15.7 years. None of our patients underwent heart transplantation (▶ **Table 2**).

Quality of life

Structured telephone interview analysis with each family showed that on average, a satisfactory overall quality of life can be recorded over a period of more than 15 years. According to the parents, the children attend school regularly and have an age-appropriate intellect. One child started school one year late. Another child had delayed language development (parents are deaf). Furthermore, all children participate normally in social life. The majority enjoy sports, but almost all children have limited physical capacity. All children were checked by pediatric cardiologists every 6 months. Of the children aged 4 years and older (13 children), current height and weight values were available in 10 cases. In terms of length growth, 5 of the 10 children were below the 14th percentile and one of them below the 3 rd percentile. Here, pubertal development has not yet occurred. This is the oldest child in our cohort (15.7 years), who currently appears to be developing a failing Fontan. One child has an asymptomatic spherocytosis, another child has attention deficit hyperactivity disorder, and two children have had an asymptomatic SARS-CoV-2 infection. Antiaggregative or anticoagulant therapy had to be continued in 8 cases. Five of these were treated with phenprocoumon and three with acetylsalicylic acid. Antihypertensive or vasodilator therapy was continued in 7 of the children.



▶ **Fig. 1** Classification and outcome: Abbreviations: DIIV: double inlet indeterminate ventricle; DILV: double inlet left ventricle; DIRV: double inlet right ventricle; DIV: double inlet ventricle; D-MGA: dextro-malposition of the great arteries; DOLV: double outlet left ventricle; DORV: double outlet right ventricle; INFD: infant death; L-MGA: levo-malposition of the great arteries; NND: neonatal death; PA: pulmonary atresia; TOP: termination of pregnancy.

▶ **Table 2** Prenatal findings and outcome.

	GA at first presentation w+d	Type of DIV	Malposition of the great arteries	Outflow tract obstruction	Outlet chamber/position	Additional cardiac anomalies	Additional extracardiac anomalies	Diagnosis/ obduction	Delivery	GA at birth w+d	Birth weight (g)	Percentile weight/ length	Outcome	Surgery	Age at death or last follow-up (years/ months)	Long-term outcome
1	16 + 3	DILV	D-MGA	PS	RV/right	CoA	–	DILV, D-MGA, peripheral PS, preductal CoA	VB	18 + 4	–		TOP	–	–	–
2	24 + 5	DIRV	D-MGA	PS	DORV/ right	Severe CoA	–	DIRV+DORV, D-MGA, PS, subpulmonary VSD, aortic arch atresia	VB	26 + 0	–		TOP	–	–	–
3	21 + 6	DIRV	L-MGA	–	DORV/ right	–	–	DIRV +DORV, L-MGA	VB	23 + 5	–		TOP	–	–	–
4	14 + 1	DILV	no	–	RV/right	–	Left-sided renal agenesis	DILV – Holmes heart, left-sided renal agenesis	VB	17 + 2	–		TOP	–	–	–
5	20 + 1	DILV	L-MGA	–	LV/left anterior	Narrow aortic arch	–	DILV, L-MGA, narrow aortic arch	VB	20 + 2	–		TOP	–	–	–
6	18 + 4	DIRV	L-MGA	valv. PS	LV/left	LPSCV	–	DIRV, L-MGA, valv. PS, LPSCV	VB	19 + 4	–		TOP	–	–	–
7	18 + 1	DIRV	D-MGA	–	DORV/ right	–	–	DIRV+DORV, D-MGA	VB	21 + 1	–		TOP	–	–	–
8	26 + 1	DILV	no	PA	RV/right	–	SUA	DILV – Holmes heart, PA	VB	28 + 1	–		TOP	–	–	–

▶ **Table 2** (Continuation)

	GA at first presentation w+d	Type of DIV	Malposition of the great arteries	Outflow tract obstruction	Outlet chamber/position	Additional cardiac anomalies	Additional extracardiac anomalies	Diagnosis/ obduction	Delivery	GA at birth w+d	Birth weight (g)	Percentile weight/ length	Outcome	Surgery	Age at death or last follow-up (years/ months)	Long-term outcome
9	29 + 2	DILV	D-MGA (not side-by-side)	PS	DOLV/left	–	–	DILV+DOLV, D-MGA, PS	–	–	–	–	Lost to follow-up	–	–	–
10	22 + 5	DILV	D-MGA	–	RV/right	–	–	DILV, D-MGA	VB	39 + 3	4260	95/64	NND	Mod. Norwood (aortic arch reconstruction by patch-plasty, DKS, Sano-shunt)	16 days	
11	20 + 5	DILV	L-MGA	–	RV/left anterior	Hypoplastic aortic arch	–	DILV, L-MGA, hypo-plastic aortic arch	VB	36 + 5	3180	65/38	INFD	Mod. Norwood with patch extension of the aortic arch into the desc. Ao, BT shunt to the RPA, atrioseptectomy	3 months	
12	28 + 0	DIIV	L-MGA	–	Left	–	–	DIIV with L-MGA, mild subaortic obstruction	CD	38 + 0	2900	26/27	Alive	BT shunt, atrioseptectomy, ligation of DA, DDD-PM	0 3/12	Postoperative AV block III; next check-up in 2 weeks
13	22 + 1	DIRV	no	–	LV/left	–	–	DIRV with normally related great arteries	CD	35 + 4	3900	> 97/ 93	Alive	BT shunt	0 4/12	70 cm, 7,4kg; PCPC planned

▶ **Table 2** (Continuation)

	GA at first presentation w+d	Type of DIV	Malposition of the great arteries	Outflow tract obstruction	Outlet chamber/position	Additional cardiac anomalies	Additional extracardiac anomalies	Diagnosis/ obduction	Delivery	GA at birth w+d	Birth weight (g)	Percentile weight/ length	Outcome	Surgery	Age at death or last follow-up (years/ months)	Long-term outcome
14	27 + 4	DILV	no	–	RV/right	LPSCV	Gallbladder duplication	DILV – Holmes heart – with narrow (antegrade) TP from the rud. outlet chamber	CD	39 + 3	3534	50/79	Alive	Bilateral PAB, epimyocardial PM	0 4/12	63 cm, 5,6kg; post-interventional sinusbradycardia; next check-up in 4 weeks
15	23 + 5	DILV	MGA	PA	Left	Dextrocardia with mirror imaging	DCDA twins, SUA	Mirror image dextrocardia; DILV; outflow tract lying on left via rud. outlet chamber into aorta; PA with hypopl. TP right parallel to aorta; native Pa's and MAPCAs	VB	38 + 4	2315	7/22	Alive	None so far	0 11/12	52 cm, 3kg; central pulmonary arteries too small for Fontan circulation, so compassionate care requested by parents
16	30 + 5	DILV	D-MGA	PS	Right	–	SUA	DILV, D-MGA, PS, right AV insufficiency	CD	38 + 1	3130	32/62	Alive	AV valve reconstruction, PAB, PCPC	1 1/12	82 cm, 11,4 kg, BMI 17, normal development, no signs of cardiac insufficiency
17	25 + 6	DILV	L-MGA	–	RV/left anterior	–	–	DILV- L-MGA	CD	38 + 5	3100	32/52	Alive	Norwood-Sano, DKS, PCPC	1 3/12	74 cm, 11 kg, BMI 20
18	28 + 1	DILV	L-MGA	–	RV/left anterior	–	–	DILV- L-MGA	VB	39 + 3	3500	46/64	Alive	Norwood-Sano, DKS; atrioseptectomy, PCPC	1 7/12	Lean nutritional condition, no signs of cardiac insufficiency

▶ **Table 2** (Continuation)

	GA at first presentation w+d	Type of DIV	Malposition of the great arteries	Outflow tract obstruction	Outlet chamber/position	Additional cardiac anomalies	Additional extracardiac anomalies	Diagnosis/ obduction	Delivery	GA at birth w+d	Birth weight (g)	Percentile weight/ length	Outcome	Surgery	Age at death or last follow-up (years/ months)	Long-term outcome
19	25 + 6	DIIV	L-MGA	PA	Left	–	Azygos continuation, interrupted ICV	DIIV, L-MGA, PA, Azygos continuation, interrupted ICV	CD	39 + 3	3050	20/60	Alive	BT shunt, Kawashima	1 10/12	85 cm, 10,8 kg, BMI 15, good development. Heterotaxy excluded. She is thriving, runs freely, and speaks well
20	24 + 2	DILV	D-MGA	–	RV/right anterior	Severe CoA, AV block III	–	DILV, D-MGA, severe CoA, AV block III	CD	38 + 0	3150	36/18	Alive	Norwood-Sano, PAB; atrioseptectomy, PM implantation	1 11/12	84 cm, 11 kg, BMI 15,6, normal development, no signs of cardiac insufficiency
21	25 + 4	DILV	D-MGA	–	RV/right	CoA	–	DILV, D-MGA, CoA	VB	40 + 0	3910	74/86	Alive	Norwood-Sano with aortic arch reconstruction and atrioseptectomy, PCPC	4 8/12	104 cm (44. Perc), 16 kg, BMI 14.8; age-appropriate resilience; poor tooth status; Fontan planned, after dental restoration
22	21 + 6	DILV	D-MGA	–	RV/right anterior	Hypoplastic aortic arch, LPSCV	–	DILV, D-MGA, hypoplastic aortic arch, LPSCV	VB	37 + 2	3650	91/40	Alive	Norwood-Sano, atrioseptectomy, PCPC + ligation of LPSCV, TCPC	5 0/12	109 cm (31. Perc), 18.6kg; BMI 15.7; slight physical limitations, speech development delay
23	22 + 6	DILV	D-MGA	PA	RV/left anterior	RAA, ALSA	–	DILV, D-MGA, PA, MAPCAs, RAA, ALSA	VB	37 + 0	3210	59/83	Alive	Modif. BT shunt, PCPC, TCPC	6 8/12	121 cm (49. Perc), 21 kg, BMI 15.71, no physical limitations, asymptomatic SarsCoV2 infection

▶ **Table 2** (Continuation)

	GA at first presentation w+d	Type of DIV	Malposition of the great arteries	Outflow tract obstruction	Outlet chamber/position	Additional cardiac anomalies	Additional extracardiac anomalies	Diagnosis/ obduction	Delivery	GA at birth w+d	Birth weight (g)	Percentile weight/ length	Outcome	Surgery	Age at death or last follow-up (years/ months)	Long-term outcome
24	25 + 1	DILV	D-MGA	–	RV/right anterior	Severe CoA	–	DILV, D-MGA, severe CoA	CD	38 + 1	2820	12/8	Alive	Modif. BT shunt, PCPC, TCPC	8 1/12	Normal development, slight physical limitations
25	20 + 1	DILV	L-MGA	–	RV/right anterior	Severe CoA	–	DILV, L-MGA, severe CoA	VB	39 + 2	3450	43/39	Alive	Modif. Norwood + BT shunt, PAB, PCPC, TCPC, DDD-PM	8 6/12	122 cm (7. Perc), 29 kg, BMI 19,5, AV block III, likes to go to school, slight physical limitations
26	36 + 4	DIRV	MGA	–	DORV/ right	Mitral dysplasia	–	DIRV+DORV, MGA	CD	38 + 5	3400	60/34	Alive	Norwood-Sano, DKS, PCPC, TCPC	8 9/12	142 cm (86. Perc), 35.1kg; BMI 17.4; started school 1 year later, now in 2nd grade primary school, almost normal everyday resilience, ADHD
27	22 + 0	DILV	No	–	RV/right	–	–	DILV – Holmes heart	CD	34 + 0	1980	20/92	Alive	PCPC, TCPC	9 4/12	132 cm (13. Perc), 28.9kg; BMI 16.6, normal intelligence, slight physical limitations
28	22 + 0	DILV	D-MGA	PS	RV/right anterior	RAA	–	DILV, D-MGA, PS, RAA	CD	38 + 1	3080	39/6	Alive	PCPC, TCPC	9 10/12	The basic development, including the school situation (high school), is positive; slight physical limitations

Thieme

▶ **Table 2** (Continuation)

	GA at first presentation w+d	Type of DIV	Malposition of the great arteries	Outflow tract obstruction	Outlet chamber/position	Additional cardiac anomalies	Additional extracardiac anomalies	Diagnosis/ obduction	Delivery	GA at birth w+d	Birth weight (g)	Percentile weight/ length	Outcome	Surgery	Age at death or last follow-up (years/ months)	Long-term outcome
29	23 + 1	DILV	D-MGA	–	RV/right anterior	RAA, ALSA	–	DILV, L-MGA, PS	CD	37 + 5	3420	65/36	Alive	BT shunt, PAB, PCPC, TCPC	10 1/12	134 cm (12. Perc), 25kg; BMI 13.9, asymptomatic SarsCov2 infection, normal intelligence, slight physical limitations, delayed speech development (his parents are both deaf)
30	20 + 1	DILV	D-MGA	PA	RV/left anterior	Dextrocardia	–	DILV, D-MGA, PA, dextrocardia in situs solitus, MAPCA	CD	38 + 0	3220	14/71	Alive	BT shunt, closure of MAPCA, PCPC, TCPC with atrial PM	12 3/12	32.7 kg, sinus bradycardia after PCPC; slight physical limitations, 7th grade secondary school, hereditary spherocytosis (asymptomatic)
31	26 + 5	DILV	L-MGA	valv. PS	RV/left anterior	Dextrocardia	–	DILV with anterior outlet chamber, dextrocardia, L-MGA, valvular PS, hypoplastic IVC	VB	38 + 6	3220	29/< 3	Alive	BT shunt, PAB, atrioseptectomy, PCPC, TCPC	13 2/12	148 cm (9. Perc.), 50.8 kg, BMI 23.19, bilateral diaphragm paresis, slight physical limitations, 7th grade secondary school

▶ **Table 2** (Continuation)

	GA at first presentation w+d	Type of DIV	Malposition of the great arteries	Outflow tract obstruction	Outlet chamber/position	Additional cardiac anomalies	Additional extracardiac anomalies	Diagnosis/ obduction	Delivery	GA at birth w+d	Birth weight (g)	Percentile weight/ length	Outcome	Surgery	Age at death or last follow-up (years/ months)	Long-term outcome
32	23 + 0	DIRV	D-MGA	valv. PS	DORV/ right	–	–	DIRV+DORV, D-MGA, valv. PS	VB	40 + 6	4570	>97/ 80	Alive	PCPC, TCPC	14 0/12	164 cm (36. Perc), 55 kg, BMI 20.4, is now in 8th grade, dyslexia, IQ129, depressive episode with school refusal during Covid pandemic, physically well
33	31 + 3	DILV	D-MGA	–	RV/left anterior	Severe CoA	–	DILV, D-MGA, severe CoA	VB	39 + 2	3630	60/72	Alive	Norwood-Sano, PCPC, TCPC	15 8/12	152 cm (< 3. Perc), 37 kg, BMI 16; behind in growth, slight physical limitations, no pubertal development so far, currently probably failing Fontan with progressive edema

Abbreviations: ALSA: aberrant left subclavian artery; BTshunt: Blalock-Taussig shunt; CoA: aortic coarctation; CD: caesarean delivery; DCDA twins: dichorionic diamniotic twins; DILV: double inlet left ventricle; DIRV: double inlet right ventricle; DIIV: double inlet indeterminate ventricle; DKS: Damus-Kaye-Stansel procedure; D-MGA: dextro-malposition of the great arteries; INFD: infant death; ICV: interrupted inferior caval vein; IVC: interventricular communication; L-MGA: levo-malposition of the great arteries; LPSCV: left persistent superior caval vein; LV: left ventricle; MAPCA: major aorto-pulmonary collateral artery; NND: neonatal death; Pa: pulmonary artery; PA: pulmonary atresia; PAB: pulmonary artery banding; PCPC: partial cavo-pulmonary connection; PM: pacemaker; RAA: right aortic arch; RPA: right pulmonary artery; RV: right ventricle; SUA: single umbilical artery; TCPC: total cavo-pulmonary connection; TOP: termination of pregnancy; TP: pulmonary trunk; VB: vaginal birth; valv. PS: valvular pulmonary stenosis

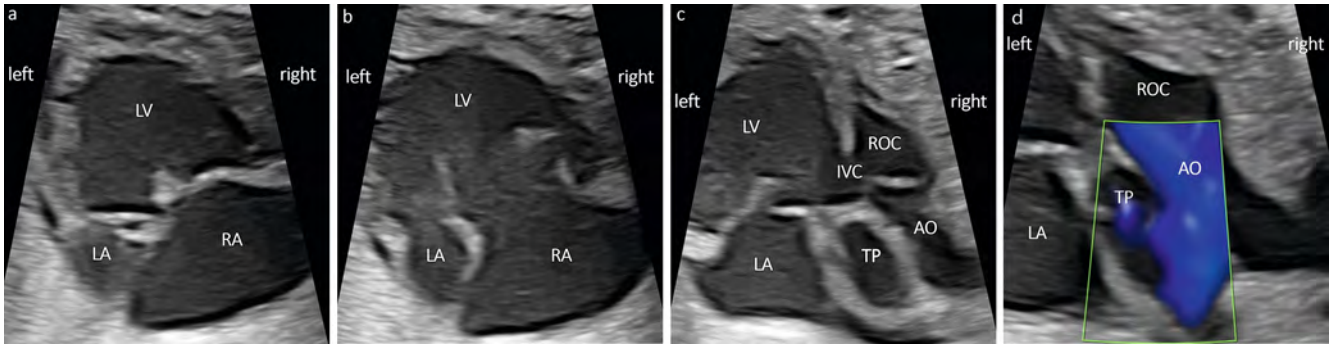
Thieme

Discussion

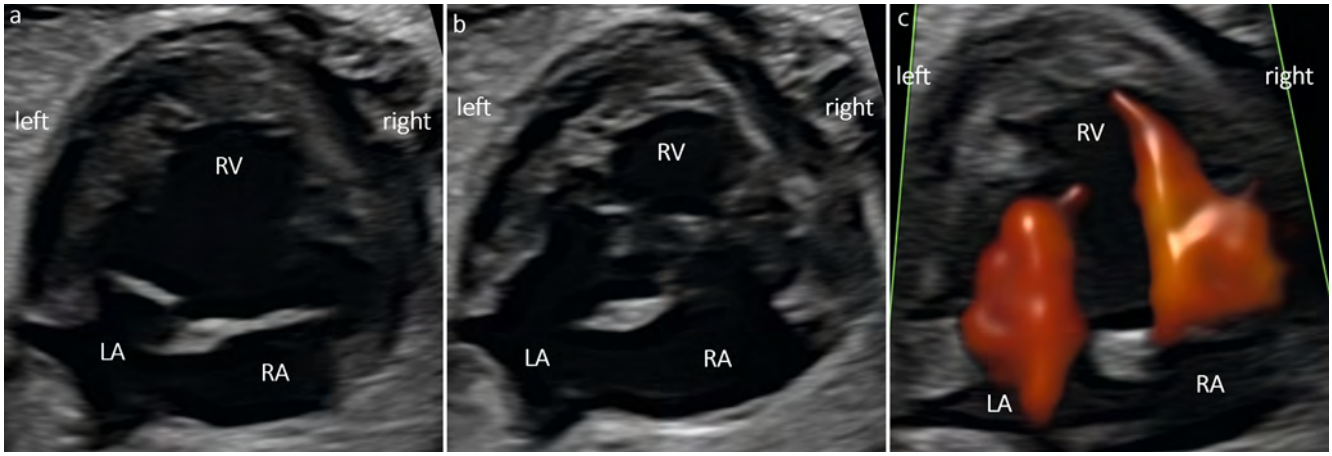
Prenatal diagnosis has improved over the last few years. The four-chamber view (4CV) shows only one ventricle without a ventricular septum. So, the connection between two atria and a single ventricle is mandatory for the diagnosis of DIV. The small, incomplete chamber typically cannot be visualized in the 4CV, as is usually possible in the hypoplastic left or right heart, but in a more cranial plane on the left or right side of the dominant ventricle (▶ **Fig. 2**). In cases of a dominant LV, the rudimentary outlet chamber is usually located antero-superiorly to the right of the dominant ventricle, whereas in a dominant right ventricle it is mainly located postero-inferiorly to the left side of the dominant ventricle [9]. Recognizing the dominant ventricle in terms of its morphological nature can be difficult prenatally. Histoanatomically, this differentiation is usually quite possible. Here, attention should be paid to the apical trabeculation (left ventricle with fine crisscross, right ventricle with coarse trabeculations). However, both fine and coarse trabeculation can be visualized sonographically (▶ **Fig. 3**). Furthermore, in DILV, both valves usually resemble mitral valves, where both of them are not in contact with the antero-superiorly located ventricular septum (septophobic), whereas in DIRV, the valves seem to be truly tricuspid (septophilic) and mitral valves [9]. However, such a prenatal distinction is often not possible due to the difficult to delineate attachment of the papillary muscles to the rudimentary outlet chamber.

Usually there is a malposition of the great vessels (MGA). In our collective this was true in 90 % of the cases, with two thirds being D-MGA and one third L-MGA (▶ **Fig. 2c** and ▶ **Fig. 4**). A small series of eight cases of DILV described L-MGA in all cases [10]. The frequency of a Holmes heart is given in the literature as 15 % [11]. In our collective, this variant was seen in 16.6 %.

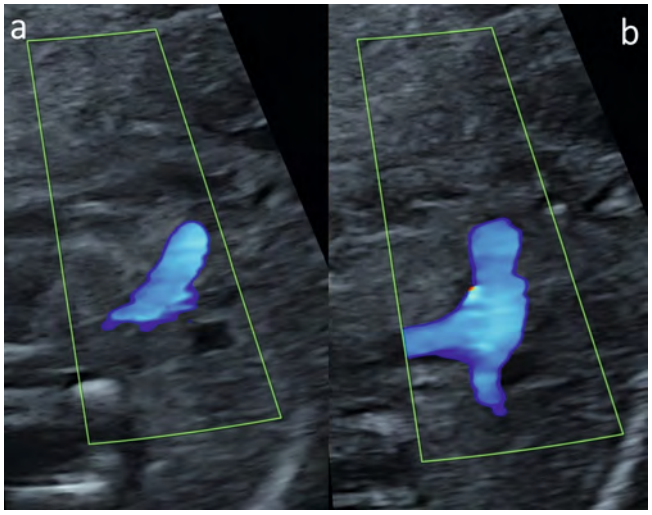
Color Doppler provides information about the patency of the AV valves, restriction of flow across the interventricular communication, and outflow tract obstruction. If the aorta arises from the rudimentary outlet chamber, the size of the interventricular communication can be responsible for the degree of aortic arch stenosis. The smaller the interventricular communication, the smaller the aortic arch (CoA, interrupted aortic arch, rare).



▶ **Fig. 2** **a** DILV (30 + 5 weeks): a) Four-chamber view (4CV) in systole with left and right atrium (LA, RA) and the dominant (left) ventricle (LV). **b** 4CV in diastole showing both AV valves opening into the same ventricle; note the unusual difference in size regarding the two atria. After birth, the AV valve had to be reconstructed due to a tricuspid insufficiency. **c** More cranial plane showing the interventricular communication (IVC) to the rudimentary outlet chamber (ROC) on the right side and the aorta (Ao) coming from the ROC in dextro-malposition. **d** Color Doppler in systole with the pulmonary trunk (TP) originating from the LV and the aorta coming from the ROC.



▶ **Fig. 3** **a** DIRV (30 + 1 weeks). An interventricular septum (IVS) is missing. Note the coarse apical trabeculations. Grayscale a) systole. **b** diastole. **c** Color Doppler ventricular inflow during diastole.



▶ **Fig. 4** DILV with L-MGA (20 + 1 weeks). Color Doppler in systole with the narrow aorta coming from the rudimentary outlet chamber in levo-malposition (**a**) and the pulmonary trunk (TP) originating from the LV (**b**). Because of different levels, both outflow tracts cannot be visualized on the same plane.

Differential diagnoses

In the case of an absent AV connection, the prenatal distinction between imperforate and atretic AV connection is difficult since both have the same pathophysiological effect. Especially TA and DILV with atresia of the right AV valve present quite similarly in fetal echocardiography. Here, knowing the exact position of the atretic tricuspid valve is relevant. If it is above the rudimentary outlet chamber, there is TA. However, if the atretic tricuspid valve is in communication with the dominant LV, DILV with TA is present. Even though both entities require Fontan palliation, it is useful to differentiate between them, as they seem to differ in outcome. Therefore, Lan et al. reviewed the outcomes of 164 consecutive pediatric patients with DILV (n = 105) or TA with transposed great arteries (n = 35; lost to follow-up n = 24) who underwent surgical palliation and showed patients with DILV having a significantly lower mortality rate than patients with TA with TGA [12]. Thus, while in the case of a right-sided imperforate or absent AV connection there is a TA, it is usually referred to as mitral atresia when this is the case on the left side. DIV can occur with any atrial arrangement and prenatal morphological differentiation between mitral and tricuspid valve is commonly not possible [9]. In our study, we had to exclude 2 cases because the prenatal suspicion of DILV was not confirmed. These patients had TA postnatally. In contrast to DIV, in association with TA, chromosomal anomalies may be present, in up to 10 % of cases in one series [13].

Another differential diagnosis is the unbalanced AVSD, where the common AV valve is skewed more to one side. It is called AVSD with DIV if more than two-thirds drain into the dominant ventricle. This, however, is often difficult to distinguish prenatally and the terminology is soft. In our collective, there were no such cases.

With regard to the position of the great vessels and the univentricular situation, ccTGA [14, 15] and hypoplasia of the left ventricle [16] are also included as differential diagnostic considerations.

Outcome

For patients with a functionally univentricular heart, Fontan palliation has become established in the course. To date, only a few studies describe the outcome of patients with DIV. Most data in this regard come from subgroup analyses of larger collectives of univentricular hearts and there is hardly any data regarding the quality of life which can be crucial for prenatal counseling.

In 2015, Beroukhim et al. described the perinatal outcome after prenatal diagnosis of single-ventricle defects (hypoplastic left heart syndrome, TA, DILV, PA with intact ventricular septum). The prenatal outcome of cases with single-ventricle cardiac defects was similar between those with a dominant RV and those with a dominant LV. However, postnatal intermediate-term survival favored those with a dominant LV [17]. Consistent with these findings, in 2016, Wolter et al. published a retrospective analysis of 155 patients with a prenatally diagnosed functionally univentricular heart between 2008 and 2015, including 103 with a dominant RV and 52 with a dominant LV. Outcome after surgery reached 93.7 % with higher survival rates for patients with dominant LV than patients with dominant RV [18].

The outcome has so far been studied mainly in relation to the main group of univentricular hearts. However, in 2005, Earing et al. analyzed 225 patients with DILV who all had Fontan operations from 1974 to 2001. The median age at Fontan operation was 9 years. During a median follow-up period of 12 years, there were 22 deaths (9.8 %), all within 30 days after the Fontan operation. The survival for the remaining 203 patients at 5, 10, 15, and 20 years was 91 %, 80 %, 73 %, and 69 %, respectively [19]. In 2008, Tham et al. examined the outcome of 171 patients with DILV from 1990 to 2004. Transplant-free survival was 88 %, 82 %, 79 %, and 76 % at 1 month, 1 year, 5 years, and 10 years, respectively. Prenatal diagnosis was made in 65 cases, with 43 being born alive. The proportion of prenatally diagnosed patients increased significantly during the study period. However, survival did not improve with prenatal diagnosis [20]. In 2017, Alsoufi et al. described the results of single ventricle palliation in 58 patients with DILV with an overall survival rate of 94 % and 87 % at 1 and 10 years, respectively [21].

In 2011, Gidvani et al. described 8 cases of DILV focusing of prenatal course and outcome. The mean gestational age at diagnosis was 24.7 weeks. All had L-MGA. Four fetuses (50 %) had PA. One fetus (12.5 %) also had TA and CoA and died at 17 months of age. Complete heart block was present in one fetus (12.5 %), who died shortly after birth. Six (75 %) infants are alive, the oldest one at 41 months of age [10]. The results of this small case series agree in parts with ours. We had L-MGA in only 35.7 % (10/28). Pulmonary outflow tract obstruction was present in 13 cases (39.4 %). In our cohort, no deterioration could be recorded antenatally. There were no signs of cardiac insufficiency. Doppler sonographic examinations of the ductus venosus (DV) were unremarkable in all pregnancies. We too did not find chromosomal abnormalities.

The earliest diagnosis in our cohort was made at 14 + 1 weeks of gestation. As DIV is characterized by an abnormal four-chamber view, there is the potential for diagnosis in early pregnancy. Recently, a 14-year retrospective study of 26,805 transvaginal ultrasound screening examinations between 14 and 16 weeks of gestation was performed. 14 cases of DILV were diagnosed [22]. As with other cardiac heart defects that are readily diagnosable in the four-chamber view, the timing of diagnosis depends on the timing of the first detailed fetal anomaly scan in the respective population.

The question of whether it is morphologically a left or a right ventricle might be prognostically relevant. It seems logical that the right ventricle was not created to maintain the systemic circulation after Fontan procedure. However, there is not much robust data for this. Julsrud et al. showed in their retrospective study that right ventricular morphology is associated with a worse short-term outcome (up to 6 months) [20]. One study showed better survival in cases with a dominant left ventricle (DILV, TA, PA with intact ventricular septum) compared to HLHS [17]. Differences in myofiber architecture were analyzed through cardiac magnetic resonance imaging and could in part explain these results. The RV adapts suboptimally as a solitary pumping chamber in the Fontan circulation as compared with the LV. Therefore, it seems that single right ventricles have a higher end-systolic wall and fiber stress, a higher rate of ventricular dilation, lower circumferential fiber shortening, and similar longitudinal shortening than single left ventricles [23]. We, however, could not confirm these results in our cohort. Of the 7 cases of right ventricular morphology in our collective, 4 were terminated and 3 are alive.

The development of pulmonary hypertension remains a feared complication of circulatory conversion. PAB is designed to reduce pulmonary blood flow to prevent pulmonary hypertension after birth. As primary surgical correction is the goal nowadays, PAB is performed less frequently, but remains a useful tool, especially in cases where PS is absent [24]. In our collective PAB was performed in 22.7 % (5 of 22 neonates).

Probably because of direct injury to the sinus node or its vascular supply, the development of arrhythmias after Fontan procedure has been reported in 4–16 %. Sometimes, antiarrhythmic or pacemaker therapy is indicated [25]. In our cohort there were four children who required pacemaker therapy (18.2 %).

Despite the undeniable improvement in survival after Fontan palliation, one of these patients, now almost 16 years old, developed a failing Fontan with progressive edema in relation to protein-losing enteropathy, a complication seen after Fontan operation in about 3–15 % [25].

Conclusion

The course of pregnancy is commonly uneventful for most affected fetuses. Chromosomal or associated extracardiac anomalies are usually absent. However, serial follow-up scans are required for detection of worsening of outflow tract obstructions or insufficiency of atrioventricular valves. In order to determine the type of DIV, the ventricular muscular structure should be inspected closely. The most common form is DILV, followed by DIRV and very rarely DIIV. When there is DIRV, DORV is usually present. Special attention should be paid to the interventricular communication, especially if the aorta arises from the incomplete ventricle, as the smaller its size the higher the chance of CoA or interrupted aortic arch. In addition, the presence or absence of pulmonary obstruction indicates the need for postnatal PAB. From an obstetric point of view, the affected fetuses can be delivered vaginally. Fontan palliation remains the common final course of action. The majority received a first stage of univentricular palliation within the first three weeks of life followed by PCPC on average at 6–7 months and lastly TCPC at the age of roughly three years with high survival rates. The assessment of quality of life, of course, is determined on an individual basis. However, it might be assessed as positive overall. All children have to undergo major surgical procedures and need to adhere to the prescribed regular, long-term check-ups as well as possible drug therapies. This can put a lot of strain on the individual and also the whole family. If all recommendations are implemented and there are no postoperative complications, these children can go to school regularly and are of normal intelligence. They tend to show physical growth differences and slight physical limitations. However, these interpretations are limited as it is a small group of cases (9/22 under 2 years).

The results of this study may contribute to better counseling for affected families in the future.

Conflict of Interest

The authors declare that they have no conflict of interest.

References

[1] Morris JK, Springett AL, Greenlees R et al. Trends in congenital anomalies in Europe from 1980 to 2012. PLoS One 2018; 13 (4): e0194986. doi:10.1371/journal.pone.0194986

[2] Samánek M, Voríšková M. Congenital heart disease among 815,569 children born between 1980 and 1990 and their 15-year survival: a prospective Bohemia survival study. Pediatr Cardiol 1999; 20 (6): 411–417. doi:10.1007/s002469900502

[3] Paige SL, Yang W, Priest JR et al. Risk factors associated with the development of double-inlet ventricle congenital heart disease. Birth Defects Res 2019; 111 (11): 640–648. doi:10.1002/bdr2.1501

[4] van Praagh R, Ongley PA, Swan HJ. Anatomic types of single or common ventricle in man. Am J Cardiol 1964; 13 (3): 367–386

[5] Anderson RH, Franklin RCG, Spicer DE. Anatomy of the functionally univentricular heart. World J Pediatr Congenit Heart Surg 2018; 9 (6): 677–684. doi:10.1177/2150135118800694

[6] Cook AC, Anderson RH. The anatomy of hearts with double inlet ventricle. Cardiol Young 2006; 16: 22–6. doi:10.1017/S1047951105002283

[7] Dobell AR, van Praagh R. The Holmes heart: historic associations and pathologic anatomy. Am Heart J 1996; 132 (2): 437–445. doi:10.1016/s0002-8703(96)90443-3

[8] Holmes WF. Case of malformation of the heart. Trans Med Chir Soc Edin 1824 (1): 252–9

[9] Penny DJ, Anderson RH. Other forms of functionally univentricular hearts. In: Anderson RH, Baker EJ, Penny DJ, Redington AN, Rigby ML, Wernovsky G, (eds.) Paediatric cardiology (3rd edition). Philadelphia, PA: Churchill Livingstone; 2010: 665–686

[10] Gidvani M, Ramin K, Gessford E et al. Prenatal diagnosis and outcome of fetuses with double-inlet left ventricle. Am J Perinatol Rep 2011; 1 (2): 123–128

[11] Weichert J, Axt-Fliedner R, Gembruch U et al. Holmes heart – a simple antenatal diagnosis of a complex cardiac anomaly? Fetal echocardiographic findings and review. Congenit Heart Dis 2013; 8 (6): 579–84. doi:10.1111/j.1747-0803.2011.00621.x

[12] Lan Y-T, Chang R-K, Laks H. Outcome of patients with double-inlet left ventricle or tricuspid atresia with transposed great arteries. J Am Coll Cardiol 2004; 43 (1): 113–119. doi:10.1016/j.jacc.2003.07.035

[13] Berg C, Lachmann R, Kaiser C et al. Prenatal diagnosis of tricuspid atresia: intrauterine course and outcome. Ultrasound Obstet Gynecol 2010; 35 (2): 183–190. doi:10.1002/uog.7499

[14] Vorisek CN, Enzensberger C, Willomeit S et al. Prenatal diagnosis and outcome of congenital corrected transposition of the great arteries – a multicenter report of 69 cases. Ultraschall in Med 2021; 42 (3): 291–296. doi:10.1055/a-1069-7698

[15] Krummholz A, Gottschalk I, Geipel A et al. Prenatal diagnosis, associated findings and postnatal outcome in fetuses with congenitally corrected transposition of the great arteries. Arch Gynecol Obstet 2021; 303 (6): 1469–1481. doi:10.1007/s00404-020-05886-8

[16] Vorisek CN, Bischofsberger L, Kurkevych A et al. Fetal echocardiography in predicting postnatal outcome in borderline left ventricle. Ultraschall in Med 2021. doi:10.1055/a-1530-5240.

[17] Beroukhim RS, Gauvreau K, Benavidez OJ et al. Perinatal outcome after prenatal diagnosis of single-ventricle cardiac defects. Ultrasound Obstet Gynecol 2015; 45 (6): 657–663. doi:10.1002/uog.14634

[18] Wolter A, Nosbüsch S, Kawecki A et al. Prenatal diagnosis of functionally univentricular heart, associations and perinatal outcomes. Prenat Diagn 2016; 36 (6): 545–554. doi:10.1002/pd.4821

[19] Earing MG, Cetta F, Driscoll DJ et al. Long-term results of the Fontan operation for double-inlet left ventricle. Am J Cardiol 2005; 96 (2): 291–298. doi:10.1016/j.amjcard.2005.03.061

[20] Tham EBC, Wald R, McElhinney DB et al. Outcome of fetuses and infants with double inlet single left ventricle. Am J Cardiol 2008; 101 (11): 1652–1656. doi:10.1016/j.amjcard.2008.01.048

[21] Alsoufi B, McCracken C, Kanter K et al. Current results of single ventricle palliation of patients with ouble inlet left ventricle. Ann Thorac Surg 2017; 104 (6): 2064–2071

[22] Khatib N, Bronshtein M, Beloosesky R et al. Early prenatal diagnosis of double inlet left ventricle. J Matern Fetal Neonatal Med 2021: 1–5. doi:10.1080/14767058.2021.1974385

[23] Ghelani SJ, Colan SD, Azcue N et al. Impact of ventricular morphology on fiber stress and strain in Fontan patients. Circ Cardiovasc Imaging 2018; 11 (7): e006738. doi:10.1161/CIRCIMAGING.117.006738

[24] Rao PS. Management of congenital heart disease: state of the art-part II-cyanotic heart defects. Children (Basel) 2019; 6 (4). doi:10.3390/children6040054

[25] Rychik J, Cohen MI. Long-term outcome and complications of patients with single ventricle. Prog Pediatr Cardiol 2002; 16 (1): 89–103