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Prenatal diagnosis, associated findings and postnatal outcome of fetuses with double outlet right ventricle (DORV) in a single center

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Abstract

Objective: To assess the spectrum of associated anomalies, the intrauterine course, postnatal outcome and management of fetuses with double outlet right ventricle (DORV).

Methods: All cases of DORV diagnosed prenatally over a period of 8 years were retrospectively collected in a single tertiary referral center. All additional prenatal findings were assessed and correlated with the outcome. The accuracy of prenatal diagnosis was assessed.

Results: Forty-six cases of DORV were diagnosed prenatally. The mean gestational age at first diagnosis was 21+4 weeks (range, 13–37). A correct prenatal diagnosis of DORV was made in 96.3% of the cases. If the relation of the great arteries, the position of the ventricular septal defect (VSD) and additional cardiac anomalies are taken into account, the prenatal diagnosis was correct in 92.6% of the cases. One case was postnatally classified as transposition of the great arteries with subpulmonary VSD and was excluded from further analysis. A total of 41 (91.1%) fetuses with DORV had major additional cardiac

anomalies, 30 (66.7%) had extracardiac anomalies and 13 (28.9%) had chromosomal or syndromal anomalies. Due to their complex additional anomalies, five (11.1%) of our 45 fetuses had multiple malformations and were highly suspicious for non-chromosomal genetic syndromes, although molecular diagnosis could not be provided. Disorders of laterality occurred in 10 (22.2%) fetuses. There were 17 terminations of pregnancy (37.8%), two (4.4%) intrauterine and seven (15.6%) postnatal deaths. Nineteen of 22 (86.4%) live-born children with an intention to treat were alive at last follow-up. The mean follow-up among survivors was 32 months (range, 2–72). Of 21 children who had already undergone postnatal surgery, eight (38.1%) achieved biventricular repair and 13 (61.9%) received univentricular palliation. One recently born child is still waiting for surgery. All children predicted prenatally to need a single ventricle palliation, and all children predicted to achieve biventricular repair, ultimately received the predicted type of surgery. After surgery, 14 of 18 (77.8%) children were healthy without any impairment.

Conclusion: DORV is a rare and often complex cardiac anomaly that can be diagnosed prenatally with high precision. DORV is frequently associated with major additional anomalies, leading to a high intrauterine and postnatal loss rate due to terminations or declined postnatal therapy. Without additional anomalies, the prognosis is good, although approximately 60% of children will have single ventricle palliation.

Keywords: congenital heart defect; double outlet right ventricle; fetus; prenatal diagnosis.

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Introduction

Double outlet right ventricle (DORV) is a rare and complex conotruncal malformation representing less than 1% of all congenital heart defects [1, 2]. The first description by Witham defined DORV as both pulmonary artery and aorta originating from a morphological right ventricle [3]. Drainage of the left ventricle is commonly achieved

through a ventricular septal defect (VSD) at different locations and with varying relation to the pulmonary or aortal outflow tract [4]. Other authors defined DORV only by the type of ventriculo-arterial connection as one of the great arteries overriding the VSD by more than 50% [5–7].

To distinguish DORV from other conotruncal malformations, description of the relationship of the great arteries and the position of the VSD is crucial [8]. While DORV describes the type of ventriculo-arterial connection, tetralogy of Fallot (TOF) describes the infundibular morphology. Independent of any additional infundibular stenosis, the ventriculo-arterial connection of a case of TOF with more than 50% aortic overriding is unequivocally a DORV.

The postnatal physiology is mainly dependent on the location of the VSD in relation to the great arteries and the presence or absence of outflow tract obstructions. Severe pulmonary stenosis may lead to neonatal cyanosis whereas severe aortic stenosis or coarctation may necessitate prostaglandin E_1 treatment in order to maintain adequate systemic perfusion. Therefore, accurate prenatal echocardiographic diagnosis is mandatory in counseling parents with regard to prognosis and treatment options as well as planning for delivery and postnatal management [2, 9].

DORV is frequently associated with additional major cardiac and extracardiac anomalies with an incidence of up to 90% in pre- and postnatal series [1, 2, 4, 7, 9–14]. In addition to the complex abnormal cardiac morphology itself in some types of DORV, associated cardiac anomalies are left and right ventricular outflow tract obstructions (LVOTO and RVOTO), atrioventricular (AV)-valve stenosis and atresia, hypoplastic left ventricle (HLV), straddling of aortic valve and coronary artery anomalies. Associated chromosomal anomalies including trisomy 13, trisomy 18 and 22q11 microdeletion occur in 25.0% to 45.2% of fetuses; all fetuses had additional cardiac or extracardiac anomalies [2, 9, 15–18]. Those additional anomalies significantly contribute to the postnatal mortality and morbidity and may complicate the surgical course.

Without additional coexisting anomalies, the outcome is usually good. Whether the subtype of DORV significantly influences the outcome is yet unclear. However, DORV may require more extensive surgery due to the great variations in abnormal cardiac morphology in comparison with TOF [1, 19].

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

DORV including VSD position, relationship of the great arteries and outflow tract obstructions were assessed.

Materials and methods

All prenatally diagnosed DORV were retrospectively reviewed for intrauterine course and outcome in the perinatal database of one tertiary referral center for prenatal medicine and fetal echocardiography (University of Cologne, Germany). All fetuses with DORV were diagnosed between January 2010 and December 2017.

The anatomic survey and fetal echocardiography were performed in a standardized fashion. Fetal echocardiography was carried out by a segmental approach using standardized anatomical planes incorporating pulsed-wave and color Doppler imaging [20, 21]. Sector or curved array-probes of 5 MHz, 7.5 MHz or 9 MHz were used for all ultrasound examinations (ATL HDI 5000 and IU22 Philips, Hamburg, Germany; Voluson 730 Pro and Expert, E8 and E10, respectively, GE Healthcare, Solingen, Germany). A pediatric cardiologist attended at least one of the prenatal ultrasound examinations and subsequently counseled the patients. Following delivery and initial care by the attending neonatologist, all newborns were examined by a pediatric cardiologist within 12 h after birth. Conventional karyotyping was performed in all cases, predominantly prenatally, otherwise postnatally. In two cases with normal karyotype, clinical anomalies prompted a targeted mutation analysis postnatally (Cornelia-de-Lange syndrome and Johanson-Blizzard syndrome).

In this study, DORV was primarily defined by the type of ventriculo-arterial connection: the origin of 50% or more of the circumference of each great artery was above the morphological right ventricle. Cases with an aortic overriding of 50% and more and additional infundibular pulmonary stenosis were defined as the DORV Fallot type, whereas cases with infundibular stenosis and an aortic overriding of less than 50% were classified as TOF. All cases with a postnatal diagnosis of TOF or TGA instead of DORV were excluded from the study. Only for the assessment of diagnostic accuracy, all newborns were included in the cohort as examples of incorrect diagnoses.

We classified different types of DORV in accordance with the current classification of the Society of Thoracic Surgeons-European Association for Cardiothoracic Surgery (STS-EACTS) International Nomenclature and the Association for European Pediatric Cardiology (AEPC) which defined four types of DORV [7, 14]. Due to the high incidence of DORV in heterotaxy, we added a fifth type of DORV, the AVSD type in heterotaxy, as proposed by Lacour-Gayet [10].

(1) DORV, VSD type: normally related great arteries and aorta overriding the subaortic or doubly committed VSD by more than 50%. (2) DORV, Fallot type: VSD type with additional RVOTO. (3) DORV, TGA type (Taussig-Bing): side-by-side related great arteries with subpulmonary VSD and overriding pulmonary trunk. (4) DORV non-committed VSD type: any relationship of great arteries and non-committed (remote) VSD, mostly in hearts with AVSD. The VSD is far removed from both the aortic and pulmonary valves and is located within the inlet septum without perimembranous extension. (5) DORV, AVSD/heterotaxy type: DORV with AVSD and heterotaxy syndrome (either left or right isomerism).

The following variables were assessed, as far as retrospectively achievable: maternal age, gestational age at diagnosis, associated

cardiac, extracardiac and chromosomal or genetic abnormalities, DORV classification according to the relationship of the great arteries, position of the VSD and presence or absence of outflow tract obstructions. Minor anomalies like right aortic arch, persistent left superior vena cava and singular umbilical artery were documented, but not classified as associated cardiac and extracardiac anomalies, respectively.

All data were retrieved from medical files, stored ultrasound images and, if available, from ultrasound video recordings, and pre- and postnatal diagnoses of all live-born children were compared to assess the accuracy of prenatal diagnosis.

All cases were classified into five groups according to the pregnancy outcome: termination of pregnancy (TOP), intrauterine fetal (IUFD) or neonatal death (NND), death in infancy or childhood (CHD) and survivors. Neonatal death was defined as death within the first 28 days of life, and CHD 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.

Intergroup comparisons were made using the χ^2 test, Student's *t*-test or Fisher's exact test when appropriate. Values are given as mean $\pm$ standard deviation (SD) unless otherwise indicated. $P < 0.05$ was considered statistically significant. The Institutional Review Board of our center does not require formal approval for retrospective archive studies; therefore, ethical approval was not sought.

Results

During the study period, 46 cases of fetal DORV were diagnosed prenatally. The mean gestational age at first diagnosis was 21 + 4 weeks (range, 13–37).

One case was postnatally classified as TGA with VSD. This case was excluded from the outcome analysis. Only for the assessment of diagnostic accuracy, all 46 cases were included.

Two (4.4%) of the 45 fetuses had a prenatal diagnosis of VSD-type DORV, five (11.1%) had the Fallot type, 27 (60.0%) had the TGA type, three (6.7%) had the non-committed VSD type and eight (17.8%) had the AVSD type with heterotaxy.

Additional cardiac, extracardiac and genetic anomalies

Forty-one (91.9%) fetuses with DORV had major additional cardiac anomalies. The most common cardiac anomalies were RVOTO in 15 (33.3%) and LVOTO in 11 (24.4%) cases. The remaining fetuses had HLV with or without mitral valve atresia (MA) in 13 (28.9%) cases. Major extracardiac anomalies occurred in 30 (66.7%) fetuses, including skeletal or facial dysmorphias, facial clefts, cerebral

anomalies and bilateral renal agenesis. Disorders of laterality occurred in 10 (22.2%) cases, including five cases with left isomerism, four cases with right isomerism and one case with situs inversus totalis. Chromosomal or non-chromosomal syndromes occurred in 13 (28.9%) fetuses (trisomy 18 in six fetuses, trisomy 13, trisomy 17-mosaicism, triploidy, microdeletion 22q11, Kleeftstra syndrome, Cornelia de Lange syndrome and Johanson-Blizzard syndrome in one fetus each). Due to their complex additional anomalies, five (11.1%) other fetuses were highly suspicious for non-chromosomal genetic syndromes, but molecular diagnosis could not be provided.

Outcome

TOP was performed in 17 of the 45 (37.8%) cases (Table 1 and Figure 1). All of these fetuses had additional major anomalies including eight fetuses with chromosomal anomalies and three fetuses which were highly suspicious for genetic syndromes due to additional facial, cerebral and skeletal anomalies.

IUFD occurred in two (4.4%) fetuses with the AVSD-type DORV, left isomerism and complete heart block.

Twenty-six neonates (57.8%) were born alive. NND occurred in three (6.7%) cases, including one neonate with trisomy 18 and another one with a suspected genetic syndrome. Both neonates died after compassionate care. The third neonate died due to low cardiac output failure after cardiac surgery at the age of 15 days.

CHD occurred in four (8.9%) cases, including two cases with trisomy 17 mosaicism and Cornelia de Lange syndrome, respectively. Both received compassionate

Table 1: Outcome of 45 cases with DORV according to the associated condition.

	n	TOP	IUFD	NND	CHD	Alive
Trisomy 18	6	5		1		
Trisomy 13	1	1				
Trisomy 17 mosaicism	1					1
Triploidy 69XXX	1	1				
22q11 microdeletion	1	1				
Cornelia de Lange syndrome	1				1	
Kleeftstra syndrome	1					1
Johanson-Blizzard syndrome	1					1
Multiple malformation syndrome	7	5		1		1
Heterotaxy	10	2	2			6
Isolated	15	2		1	2	10
Total	45	17	2	3	4	19

TOP, termination of pregnancy; IUFD, intrauterine fetal death; NND, neonatal death; CHD, death in infancy or childhood.

Figure 1: Outcome of 46 cases with prenatally diagnosed double outlet right ventricle (DORV).

TOP, termination of pregnancy; IUFD, intrauterine fetal death; NND, neonatal death; CHD, death in infancy or childhood.

care. The third infant died because of global respiratory insufficiency after cardiac surgery at the age of 3 months and the fourth infant died because of renal and cardiac failure after the second step of Norwood palliation at the age of 11 months (Table 1).

Nineteen of the 45 children with a confirmed diagnosis of DORV were alive at the time of writing of the manuscript, resulting in an overall survival rate of 42.2%. After exclusion of TOP, IUFD and cases in which parents opted for compassionate care, the “intention-to-treat group” consisted of 22 fetuses, all were born alive (Table 2). Twenty-one of those infants already underwent surgery, three died and 18 survived. One infant is still awaiting surgery and facing univentricular palliation due to HLW and MA. Due to inadequate postnatal growth (5 kg body weight at the age of 7 months), repair of anomalous pulmonary venous connection and the first step of palliation were postponed. The mean follow-up of survivors was 32 months (range, 2–72).

The intention-to-treat survival rate was 86.4% (19/22). After surgery, 77.8% (14/18) were healthy without any impairment at the latest follow-up, 22.2% (4/18) were mildly impaired (Figure 2).

Postnatal cardiac surgery

The type of postnatal surgery was dependent on the complexity of the cardiac defect itself and the postnatal hemodynamic situation. If surgical risk appeared to be too high or if biventricular complete repair did not seem achievable, univentricular palliation was performed. Eight of 21 (38.1%) infants underwent biventricular repair and 13 of 21 (61.9%) received univentricular palliation (Table 2). All children predicted prenatally to need a single ventricle

palliation, and all children predicted to achieve biventricular repair, ultimately received the predicted type of surgery.

Within the biventricular repair group, infants received either one-stage complete repair or aorto-pulmonary (AP) shunting, right-ventricle-to-pulmonary-artery (RV-PA) conduit, VSD patch or VSD tunneling, aortic arch reconstruction, banding of pulmonary arteries or arterial switch operation, depending on their type of DORV and their postnatal hemodynamic situation. One of those eight infants had an additional coronary artery anomaly and died at the age of 15 days because of low cardiac output failure after aortic arch reconstruction and banding of pulmonary arteries. The other seven infants survived surgery, six were healthy without impairment and one infant was mildly impaired due to mild cardiac insufficiency (Table 2).

Univentricular palliation was performed in the presence of major additional cardiac anomalies, including MA, HLW, L-transposition of great arteries or severe obstruction of right and left ventricular outflow tract, respectively. Two of those 13 children died in childhood. The first child had complex DORV with MA, single right ventricle and interrupted aortic arch and died after the first step of Norwood palliation and aortic arch reconstruction because of global respiratory insufficiency at the age of 3 months. The second severely growth restricted child had TGA (Taussig-Bing)-type DORV with additional hypoplastic aortic arch and died at the age of 11 months after the second step of Norwood palliation because of pulmonary hypertension and renal and cardiac failure. The other 11 children survived, and eight were healthy without impairment. One child developed moderate pulmonary valve insufficiency and mild dyspnea, one child had autism-spectrum disorder and one child had concomitant Johanson-Blizzard syndrome (Table 2).

Table 2: Associated conditions and outcome in 22 live born children with an intention to treat (cases with compassionate care were excluded).

Type of DORV	Relation of great arteries	Location of VSD	Additional cardiac anomalies	Additional extracardiac anomalies	Karyotype/genetic diagnosis	Postnatal diagnosis	Outcome	Gestational age@death or last follow-up	Surgical aim	Surgery
1 TGA	Side-by-side	Sub-pulmonary	CoA	–	46 XY	DORV TGA type (d-TGA, Taussig-Bing), CoA, single coronary ostium	NND	Death@ day 15	Biventricular repair	Death after reconstruction of aortic arch and banding of pulmonary arteries because of low cardiac output failure
2 TGA	Side-by-side	Sub-pulmonary	MA, HLIV, IAA	–	46 XX	DORV TGA type (d-TGA), MA, HLIV, IAA	CHD	CHD@3 months	Univentricular palliation	Death after Norwood I and reconstruction of aortic arch because of global respiratory insufficiency
3 TGA	Side-by-side	Subpulmonary	Hypoplastic aortic arch, LPSVC	–	46 XX	DORV TGA type (d-TGA, Taussig-Bing), hypoplastic aortic arch, LPSVC, ASD	CHD	CHD@11 months	Univentricular palliation	Death after Norwood I+II and reconstruction of aortic arch because of renal and cardiac failure and pulmonary hypertension
4 TGA	Side-by-side	Sub-pulmonary	Hypoplastic aortic arch	–	46 XX	DORV TGA-type (d-TGA, Taussig-Bing), hypoplastic aort arch	Alive, no limitations	2 months	Biventricular repair	Arterial switch, VSD patch, reconstruction of aortic arch
5 TGA	Side-by-side	Sub-pulmonary	MA, HLIV, LPSVC, ARSA	Flat profile	Kleefstra syndrome	DORV TGA type (d-TGA), MA, HLIV, LPSVC, ARSA, PAPVR	Alive	7 months	Univentricular palliation	Still waiting for surgery
6 TGA	Side-by-side	Sub-pulmonary	MA, HLIV	–	46 XY	DORV TGA type (d-TGA), MA, HLIV, LPSVC, ARSA	Alive, no limitations	6 months	Univentricular palliation	Norwood I+II
7 TGA	Side-by-side	Sub-pulmonary	CoA	Pes equinovarus	46 XY	DORV TGA type (d-TGA, Taussig-Bing), CoA, bicuspid aort valve	Alive, mildly impaired, mild cardiac insufficiency	4 months	Biventricular repair	Rashkind, aortic isthmus stenting, banding of Pulmonary arteries, achilles tenotomy
8 AVSD (with heterotaxy)	Side-by-side	AVSD	Common atrium, LPSVC, aplasia of VCI, persistent azygos vein	Left isomerism, situs ambiguous, polysplenia	–	DORV AVSD/ heterotaxy type, AVSD, d-TGA, common atrium, aplasia VCI, persistent azygos vein, LPSVC	Alive, no limitations	8 months	Biventricular repair	Banding of Pulmonary arteries

Table 2 (continued)

Type of DORV	Relation of great arteries	Location of VSD	Additional cardiac anomalies	Additional extracardiac anomalies	Karyotype/genetic diagnosis	Postnatal diagnosis	Outcome	Gestational age@death or last follow-up	Surgical aim	Surgery
9 AVSD (with heterotaxy)	Side-by-side	AVSD	HLV, PS, TAPVR in RA	Right isomerism, ambiguous situs, asplenia, microcephaly	–	DORV AVSD/ heterotaxy type, AVSD, HLV, d-TGA, PS, TAPVR, LPSVC	Alive, mildly impaired, mild dyspnea	14 months	Univentricular palliation	Norwood I, commissurotomy of PV
10 AVSD (with heterotaxy)	Side-by-side	AVSD	Dextrocardia, PS, bilateral VCS, aplasia VCI, persistent azygos vein	Left isomerism, situs ambiguous, right sided spleen	46 XX	DORV, AVSD/ heterotaxy type, AVSD, d-TGA, dextrocardia, bilat. VCS, aplasia of VCI, persistent azygos vein	Alive, no limitations	18 months	Biventricular repair	AP shunt, shunt exchange
11 VSD	Normal	Subaortic	MA, HLV, hypoplastic aortic arch	Facial dysmorphism, cleft palate, finger/toe deformities, syndrome?	46 XX, syndrome?	DORV VSD type, MA, HLV, hypoplastic aortic arch	Alive, no limitations	21 months	Univentricular palliation	Norwood I+II
12 TGA	Side-by-side	Sub-pulmonary	HLV, mild PS, RAA, LPSVC	–	–	DORV TGA type (d-TGA), HLV, PS, RAA, LPSVC	Alive, no limitations	21 months	Univentricular palliation	Norwood I
13 TGA	Side-by-side	Sub-pulmonary	Criss cross heart, severe PS, RAA	Right isomerism, ambiguous situs, asplenia	–	DORV TGA type (d-TGA), criss cross, PS, RAA	Alive, no limitations	33 months	Univentricular palliation	Norwood I+II
14 Fallot	Normal	Subaortic	PS	Situs inversus totalis	46 XX	DORV Fallot type, PS	Alive, no limitations	33 months	Biventricular repair	Pulmonary valve repair, VSD patch
15 TGA	Side-by-side	Sub-pulmonary	Hypoplastic aortic arch, ISTA	–	–	DORV TGA type (d-TGA, Taussig-Bing), hypoplastic aortic arch, CoA	Alive, no limitations	35 months	Univentricular palliation	Norwood I–III, aortic arch stenting
16 AVSD (with heterotaxy)	Side-by-side	AVSD	MA, HLV, TAPVR in coronary sinus	Right isomerism, ambiguous situs, asplenia	–	DORV AVSD/ heterotaxy type, MA, HLV, AVSD, d-TGA, TAPVR in coronary sinus	Alive, no limitations	35 months	Univentricular palliation	Norwood I–III, unroofing procedure
17 TGA	Side-by-side	Sub-pulmonary	cc-TGA, l-TGA, subpulmonary VSD, PS, dextro-cardia, LPSVC	–	–	DORV TGA type (l-transposition), subpulmonary VSD, PS, LPSVC, dextrocardia	Alive, impaired, autism-spectrum-disorder	46 months	Univentricular palliation	Norwood I–III

Table 2 (continued)

Type of DORV	Relation of great arteries	Location of VSD	Additional cardiac anomalies	Additional extracardiac anomalies	Karyotype/genetic diagnosis	Postnatal diagnosis	Outcome	Gestational age@death or last follow-up	Surgical aim	Surgery
18 Non-committed with AVSD	Side-by-side	AVSD	HLV, severe PS, LPSVC	Absent nasal bone, dilated bowel	Johanson-Blizzard-Syndrome	DORV non-committed type, HLVD, AVSD, d-TGA, PS, LPSVC	Alive, impaired, syndrome	46 months	Univentricular palliation	Norwood I+II, colon segmental resection
19 TGA	Side-by-side	Sub-pulmonary	MA, HLVD, hypoplastic aortic arch	-	46 XX	DORV dGA type (d-TGA, Taussig-Bing), MA, HLVD, hypoplastic aortic arch	Alive, no limitations	52 months	Univentricular palliation	Norwood I-III, reconstruction of aortic arch
20 TGA	Side-by-side	Sub-pulmonary	PS	-	46 XY	DORV TGA type (d-TGA), PS	Alive, no limitations	52 months	Biventricular repair	RV-PA conduit, VSD patch, conduit exchange
21 TGA	Side-by-side	Sub-pulmonary	PS, muscular VSD	-	46 XY	DORV TGA type (d-TGA), subpulmonary VSD, muscular VSD, TGA, PS	Alive, no limitations	49 months	Biventricular repair	Rashkind, arterial switch operation, VSD patch, pulmonalis-patch dilatation
22 Non-committed VSD	Side-by-side	Remote (muscular VSD)	MA, HLVD, DIRV, hypoplastic aortic arch	-	46 XX	DORV non-committed VSD type, DIRV, MA, HLVD d-TGA, hypoplastic aortic arch	Alive, no limitations	72 months	Univentricular palliation	Norwood I-III

VSD, ventricular septal defect; AVSD, atrio-ventricular septal defect; IUGR, intrauterine growth restriction; NND, neonatal death; PS, pulmonary valve stenosis; DA, agenesis of arterial duct; RAA, right aortic arch; HLVD, hypoplastic left ventricle; MD, mitral valve dysplasia; CHD, childhood death; PS, pulmonary valve stenosis; LPSVC, left persistent superior vena cava; ARSA, aberrant right subclavian artery; PAPVR, partial anomalous pulmonary venous return; IAA, interrupted aortic arch; ASD, atrial septal defect; CoA, coarctation of the aorta; ccTGA, congenitally corrected TGA; l-TGA, levo-TGA; DIRV, double inlet right ventricle; RA, right atrium; PV, pulmonary valve; MA, atresia of mitral valve; RV-PA conduit, right ventricle-to-pulmonary-artery conduit; VCS, vena cava superior; VCI, vena cava inferior; AP shunt, aorto-pulmonary shunt.

Figure 2: Kaplan-Meier curve for observed survival of 46 cases with prenatally diagnosed double outlet right ventricle. The dotted line represents term.

Figure 3: DORV, VSD type, with subaortic VSD and overriding aorta. LV, left ventricle; RV, right ventricle; Ao, overriding aorta; *subaortic VSD.

Accuracy of prenatal ultrasound

To determine the accuracy of prenatal ultrasound, we only included the 27 liveborns with available postnatal confirmation of diagnosis. A correct prenatal diagnosis of DORV was made in 96.3% (all but one) of the cases. One case of prenatal diagnosis of TGA-type DORV was postnatally classified as d-TGA with subpulmonary VSD.

In another case with Kleefstra syndrome and DORV with MA, HLIV, d-TGA and subpulmonary VSD, additional partial anomalous pulmonary venous connection was missed at the prenatal ultrasound. Thus, the prenatal diagnosis was correct in 92.7% (all but two) of the cases, if the spatial relationship of the great arteries, position of the VSD and all additional cardiac anomalies are also taken into account.

Figure 4: DORV, TGA type, with subpulmonary VSD and overriding pulmonary trunk. LV, left ventricle; RV, right ventricle; TP, overriding pulmonary trunk; Ao, aorta; *subpulmonary VSD.

Among the 26 liveborns with a postnatally confirmed diagnosis of DORV, there were the following types of DORV: one (3.8%) VSD type, two (7.7%) Fallot type, 17 (65.4%) TGA type, two (7.7%) non-committed VSD and four (15.4%) AVSD type with heterotaxy (Figures 3 and 4).

Discussion

DORV occurs with a prevalence of 0.46–8.8% in prenatal series and decreases to 0.003–0.02% in live-born infants [2, 9, 11, 22–25]. However, only a few series of prenatally diagnosed DORV with small cohorts and only short postnatal follow-up periods have been published so far [2, 4, 9, 12, 19]. In addition, the number of survivors in these series was extremely low, due to the high rate of TOP, spontaneous intrauterine loss and considerable postsurgical mortality. Therefore, most information concerning the outcome of newborns with DORV is available from postnatal series. Our current study is one of the largest cohorts of prenatally diagnosed DORV with a larger number of survivors and therefore might improve the prenatal counseling of affected couples.

DORV was reported to be associated with additional cardiac, extracardiac and chromosomal anomalies in 90%, 38–58% and 25%, respectively [2, 7, 9, 10, 13, 14, 19, 22, 26–28]. Similarly, we also found a high prevalence of severe additional anomalies. All our fetuses (100%) had

additional cardiac anomalies, including severe RVOTO and LVOTO, HLIV, partial or total anomalous pulmonary venous connection or coronary anomalies. Right and left outflow tract obstructions and HLIV occurred with an incidence of 46%, 24% and 28%, respectively, which is in accordance with the reported incidence [2, 4, 9, 19]. Major extracardiac anomalies occurred in 66% of our fetuses and chromosomal anomalies or genetic syndromes in 28% of our fetuses. In another 11% of fetuses, we highly suspected a chromosomal aberration or genetic syndrome, although molecular diagnosis was inconclusive. Abnormalities of laterality occurred in 22%, including two cases with a lethal combination of left isomerism with AVSD and complete heart block. Previous series also reported the abnormalities of laterality in 25–35% of DORV [9, 11, 19]. In conclusion, a fetal diagnosis of DORV should trigger an extensive search for additional anomalies.

The rate of TOP in previously published cohorts of DORV varies considerably between 15.8% and 43.3% [2, 9, 16, 19]. This might be due to the fact that in some studies the diagnosis was made later in pregnancy and beyond the time period in which TOP would have been a legal option. In our cohort, the rate of TOP was 37%. Additionally, 9% of parents in our cohort chose compassionate postnatal care. Only half of all pregnancies with a prenatal diagnosis of DORV were continued with the intention of postnatal surgical treatment.

The importance of an accurate prenatal diagnosis in counseling parents with regard to prognosis and to predict the type of postnatal surgical approach is obvious. Our study confirms that DORV can be diagnosed prenatally with a high degree of accuracy. The correct diagnosis of DORV was made in 96% of the cases. Diagnosis was usually not made prior to 21 weeks of gestation, presumably due to the predominantly normal looking four-chamber view that conceals this defect from basic cardiac screening. As basic cardiac screening in Germany does not include the assessment of left and right long axis views, the detection rate of cardiac anomalies with a normal looking four-chamber view is low. If the relationship of the great arteries, the position of VSD and all cardiac anomalies were taken into account, an accurate diagnosis was achieved in 92% of the cases. This is in accordance with previously published studies with an overall accuracy between 59 and 88% [2, 9, 11, 12, 19]. Despite some inaccuracy in the exact diagnosis of all anatomic details of DORV, accurate counseling regarding the type of expected surgical approach and postoperative uni- or biventricular endpoint was possible in all cases. All children predicted prenatally to need a single ventricle palliation, and all children predicted to achieve biventricular repair, ultimately received the predicted

type of surgery. Except for Gelehrter et al., who achieved a correct prediction of surgical approach in 91% of cases, and Zidere et al., who achieved a correct prediction in all of their six cases, none of the previously published studies correlated the diagnostic accuracy with the prediction of postnatal surgery [11, 29].

Previously published data described a varying but overall poor prognosis of fetuses with DORV, with overall survival rates of only 21%–43% [4, 9, 12, 19]. Even after the exclusion of terminated pregnancies, the intention-to-treat survival rates did not exceed 50% in most cohorts and post-surgical mortality was high with up to 75% [2, 9, 15, 30]. Two other studies described significantly better intention-to-treat survival rates of 63% and 69% with lower post-surgical mortality rates of 31% [4, 19]. Our study confirms a better prognosis with an intention-to-treat survival rate of 86% and a much lower post-surgical mortality rate of 14% in our cohort. The discrepancy of survival rates may be explained by the small cohorts in all previously published studies with no more than 13 children who underwent surgery, but keeping in mind that outcome in our study was assessed at different stages of surgical repair or palliation. Not all included children had completed surgical repair or last step of palliation and postoperative follow-up periods differed significantly in our children. The majority of our survivors (62%) ended up having univentricular palliation, only 38% achieved biventricular repair. This is in accordance with previous reports in which up to 75% of survivors received univentricular palliation [2, 4, 9, 19].

Our study also confirms a better postsurgical health status. A total of 77.8% of our survivors were healthy without impairment after cardiac surgery at last follow-up. Among the four impaired children, one child was impaired because of non-cardiac problems due to a concomitant syndromal anomaly. Another child developed autism-spectrum disorder and the remaining two children were impaired only by mild dyspnea and mild cardiac insufficiency, respectively. The only previously published study that assessed the postsurgical health status reported 67% healthy survivors [4].

The strength of our single center study is that so far this is the largest published cohort of prenatally diagnosed DORV with 45 prenatally diagnosed cases, 26 cases with a postnatally confirmed diagnosis, 21 children who underwent surgery with known outcome and 18 survivors after surgery at last follow-up.

Our study also has a number of limitations. Despite our relatively large cohort, the number of newborns who underwent surgery is still small due to the rarity of the cardiac defect itself and the high percentage of TOP and

cases in which parents declined surgical intervention postnatally. The small size of our cohort did not allow for a detailed subgroup analysis and for identifying any predictors of outcome. In addition, not all children have yet completed their ultimate surgical repair or palliation and the outcome was assessed at different time points of surgical repair or palliation, and a long-term follow-up is lacking. A further limitation is its retrospective design, which limits the assessment of detailed spatial relationship of some cardiac structures.

In conclusion, the overall outcome strongly depends on the presence and severity of additional anomalies. In fetuses without lethal associated anomalies, the prognosis seems to be better than that previously reported with a survival rate of >80% and a good chance of healthy short-term survival without significant impairment, although 60% undergo univentricular palliation. In addition, postnatal type of surgical repair (uni- or biventricular) can be predicted with high accuracy on a prenatal ultrasound.

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