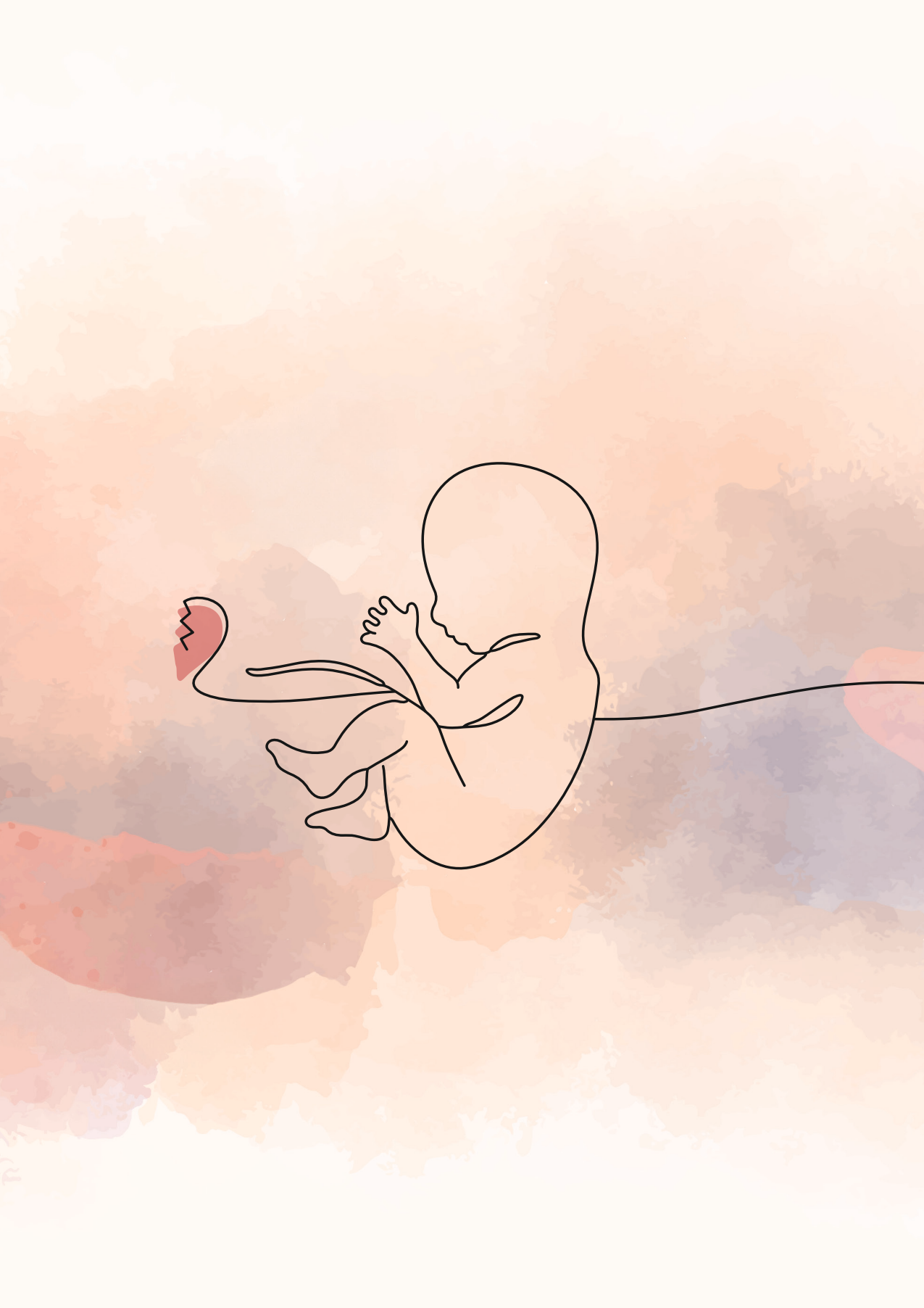
Congenital heart defects: from a prenatal perspective

Nisselrooij, A.E.L. van



CHAPTER 7

The prognosis of common arterial trunk from a fetal perspective

A prenatal cohort study and systematic literature review

Amber E.L. van Nisselrooij, Lotta Herling, Sally-Ann Clur, Ingeborg H. Linskens, Eva Pajkrt, Lukas A. Rammeloo, Arend D.J. ten Harkel, Mark G. Hazekamp, Nico A. Blom, Monique C. Haak

Prenat Diagn. 2021 May;41(6):754-765.

ABSTRACT

Objective

The limited number of large fetal cohort studies on common arterial trunk (CAT) impedes prenatal counselling at mid-gestation. This study evaluates the prognosis of CAT from a fetal perspective.

Method

Fetuses with a prenatally diagnosed CAT were extracted from the PRECOR registry (2002-2016). We evaluated fetal and postnatal survival and the presence of additional morbidity at last follow-up. Literature databases were searched systematically for additional cases.

Results

Thirty-eight cases with a prenatal diagnosis of CAT were identified in our registry, of which 18/38 (47%) opted for pregnancy termination (TOP). Two cases resulted in spontaneous intra-uterine demise (10%, 2/20), six cases demised postnatally (33%, 6/18), leaving 60% (12/20) alive, after exclusion of TOP, at a mean age of six (range: 2-10 yr.).

Additional morbidity was found in 42% (5/12) of survivors, including 22q11.2 deletion syndrome, Adams-Oliver syndrome and intestinal atresia, whereas 8% (1/12) had developmental delay. The remaining 50% (6/12, and 30% of ongoing pregnancies) of survivors appeared isolated with normal development. All of whom required replacement of the initial right ventricle to pulmonary artery conduit.

Additionally, we reviewed 197 literature cases on short-term outcome.

Conclusion

The risk of fetal and neonatal demise, as well as significant morbidity amongst survivors, should be included in prenatal counselling for CAT.

INTRODUCTION

Common arterial trunk (CAT), also known as truncus arteriosus, is a rare congenital heart defect (CHD) that accounts for approximately 1% of fetuses diagnosed with a CHD.[1] It is characterized by a single arterial trunk, overriding the interventricular septum, which provides blood to the systemic and pulmonary circulation and coronary arteries. To describe the anatomical variations between CAT cases, three classification systems have been reported to date.[2-4]

Prenatal detection rates for conotruncal anomalies, including CAT, have increased substantially over the past years.[5-8] A prenatal diagnosis provides the opportunity for genetic analysis and advanced ultrasound examination, given its association with genetic syndromes and (extra-) cardiac malformations.[9-11] This is essential, as it enables parents to make an informed decision whether to continue the pregnancy and provides the opportunity for delivery in a specialized facility. Despite these clear benefits, evidence stating that a prenatal diagnosis would influence neonatal mortality and morbidity, is scarce.[12-17]

Parental counselling for fetuses with a CAT is, however, primarily based on postnatal cohort studies, due to the lack of large studies on prenatally detected cases. The majority of these postnatal cohorts focus on postoperative results or neonatal outcome, which may only reflect a selected population of CAT cases.[18-20] To provide evidence on the prognosis of CAT from a fetal perspective and improve prenatal counselling at mid-gestation, this study will focus on outcome of *fetuses* with a prenatal diagnosis of CAT. A systematic analysis of the literature is performed to assemble evidence from currently available studies.

METHODS

All fetuses and neonates with a diagnosis of a congenital heart defect (CHD) in the region Amsterdam-Leiden (40.000 births/year) are referred to a tertiary care center. Since 2002 these centers have together collected all CHD cases in our population-based registry 'PRECOR'. Data collection for this registry has explicitly been described before.[21] We used this registry to identify all fetuses with a prenatal diagnosis of CAT from 2002 to 2016. The standard mid-trimester anomaly scan was introduced as part of the Dutch national screening program in 2007. Our cohort has reported one of the highest prenatal detection rates since, including a 85% prenatal detection rate for CAT[21], which has only increased over time. As the majority of prenatally detected cases in this cohort originate from 2007-2016, we expect that our cohort is representative for all fetuses with CAT.

Postnatal echocardiography and post-mortem reports were assessed to ascertain the diagnosis in all cases. If pregnancy was terminated or spontaneous intra-uterine fetal demise occurred without parental consent for autopsy, cases were not excluded to avoid selection bias.

The fetal ultrasound databases were evaluated for data on structural malformations, genetic testing and pregnancy outcome. Patient records were studied to assess postnatal mortality, (age at) surgery, neurodevelopment at post-surgical outpatient consultations and verify the extracardiac malformations (ECMs) detected with prenatal ultrasound.

Patient characteristics and respective outcome parameters will be presented for each case individually. This study has been approved by the Leiden University's medical ethics committee.

Systematic review

Our systematic review of the literature is reported following the PRISMA statement[22] and has been submitted for registration in the PROSPERO database on 11 September 2019. We explored the PubMed, Embase, Web of Science, Academic Search Premier and Cochrane Library databases for articles on outcome of fetal CAT in September 2019. The entire search strategy is enclosed as supplementary material (Supplemental material S1).

Criteria for inclusion in the systematic review were; (1) case series (≥ 3 cases minimum) ór cohort studies (any number of CAT cases) that report on (2) pregnancy or postnatal

outcome of (3) prenatally diagnosed case(s) with CAT. Fetal studies focusing on cohorts with 22q11.2 deletion syndrome (DS) were not considered eligible for inclusion to avoid a potential selection bias. If information on pregnancy outcome was missing from the abstract or full-text, authors were contacted for additional information to enable inclusion of these studies in the review.

Two researchers [AvN, LH] independently screened the literature search results for eligible articles. Discordances were discussed and, if necessary, a third reviewer [MH] was consulted. The same authors [AvN, LH] studied the full-text of selected articles to extract data on pregnancy and postnatal outcome in fetuses with a prenatal diagnosis of CAT. Pregnancy outcome was considered our primary outcome, as most studies focused on perinatal parameters. Secondary parameters included: neonatal surgery, neonatal mortality (<28 days of age), survival at the end of the study period and the presence of a genetic diagnosis or additional malformations. If multiple studies reported on the same cases, the most eligible study was chosen.

The Quality in Prognostic Studies (QUIPS) tool[23] was used to evaluate the quality of selected articles was evaluated [AvN and LH, independently] and identify major risks of bias. This assessment was merely used for interpretation of results and did not determine inclusion in the review.

Descriptive statistics were used to display the results of all included articles separately, with regard to pregnancy outcome, postnatal course and the presence of additional morbidity. To estimate the prognosis of fetal CAT in a large cohort of prenatally diagnosed fetuses, we attempted to summarize the raw data from all included articles and combine these with our own original data, when possible.

RESULTS

We identified 43 fetuses with a prenatal diagnosis of CAT in the PRECOR registry. Consent for autopsy was obtained in 30% (6/20) of demised fetuses, which all confirmed the prenatal diagnosis. Postnatal echocardiography confirmed the diagnosis in 78% (18/23) of liveborn cases, resulting in an 83% (24/29) overall diagnostic accuracy. After exclusion of these five misdiagnosed cases with pulmonary atresia and a ventricular septal defect (PA-VSD), 38 cases were included in this study. The majority of fetuses originated from 2007-2016 (87%, 33/38).

Structural malformations

Fetuses with CAT had additional morbidity in 61% (23/38) of the cases, involving genetic syndromes (39%, 15/38) and/or structural extracardiac malformations (ECMs) (53%, 20/38). Karyotyping or aneuploidy testing was performed in all cases (38/38), whereas some received additional testing for genetic syndromes as well: 39% (15/38) FISH for 22q11.2 DS, 39% (15/38) chromosome microarray analysis and 18% (7/38) exome sequencing, respectively. Although 22q11.2 deletion syndrome (21%, 8/38) was diagnosed particularly often, less common syndromes, such as CHARGE, Adams-Oliver and Cri-du-Chat syndrome, were also found in a significant proportion of fetuses (18%, 7/38). The ECMs diagnosed on prenatal ultrasound were all confirmed postnatally, and none of the fetuses that appeared isolated on prenatal ultrasound showed ECMs after birth.

Additional cardiac anomalies were present prenatally in 37% (14/38) of all fetuses with CAT. These mainly comprised truncal valve regurgitation (moderate to severe) or stenosis (21%, 8/38) and interruption of the aortic arch (IAoA; 8%, 3/38). Other significant CHDs, including polyvalvular disease (3%, 1/38), anomalous pulmonary venous return (3%, 1/38), mitral valve stenosis (3%, 1/38) and unroofed coronary sinus (3%, 1/38), occurred in non-isolated cases only (Table 1).

Isolated CAT cases (39%, 15/38), without a (prenatally suspected) genetic diagnosis or ECMs, presented with significant prenatal truncal valve regurgitation or stenosis in 33% (5/15) or an interrupted aortic arch in 7% of cases (1/15), respectively. However, the majority (60%, 9/15) did not show other significant cardiac anomalies (right aortic arch or aberrant right subclavian artery not considered) (Table 1).

Termination of pregnancy

Parents opted for pregnancy termination (TOP) in 47% (18/38) of cases with a prenatally diagnosed CAT, of which 5% (2/38) comprised selective multifetal pregnancy reductions. The majority of terminated cases had additional morbidity (72%, 13/18) or significant truncal valve regurgitation (11%, 2/18) and only 17% (3/18) appeared isolated. The proportion of TOPs for CAT decreased over time: from 57% in 2002-2009 to 41% in 2010-2016.

Mortality

Intra-uterine fetal demise (IUFD) occurred in 10% (2/20) of continuing pregnancies. The remaining 90% (18/20) resulted in a liveborn neonate at a median gestational age of 39 weeks (Table 1). Four neonates (22%, 4/18 liveborns) died within the first week of life. Two had spontaneous pre-term pre-labor rupture of membranes (PPROM) and were not actively treated after birth. Both of whom had a very poor prognosis and expected quality of life, based on the combination of (extreme) prematurity and significant additional morbidity (case 22 and 24). The remaining two were actively treated, but died either pre- or postoperatively. The first (case 23) comprised a case with CHARGE syndrome and multiple congenital anomalies that was delivered at 34 weeks of gestation due to PPROM. She died the first day despite ventilation and intubation. The second case (case 21) with 22q11.2 deletion syndrome and IAoA underwent surgery at day 7, but died the same day due to severe postoperative complications.

We encountered two infant deaths (11%, 2/18 liveborns) at 5 and 18 months of age. One infant (case 25) was born dysmature at 31 weeks of gestation and had a complex CAT with an atrioventricular septal defect, severe left atrioventricular valve incompetence and mild-to-moderate truncal valve regurgitation. She underwent banding of the pulmonary arteries at three weeks of age (body weight: 1900 gram) and presented with poor right ventricular function at 5 months of age. Although corrective surgery was planned immediately, a cardiac arrest occurred during preoperative preparations and she eventually died of multi-organ failure. The second case (case 26) with CAT type 2, complicated by bilateral pulmonary artery stenosis, received corrective surgery and replacement of the Gore-Tex patch with a pulmonary homograft at 16 months of age. Two months later, the child suddenly deteriorated at home and a cardiac arrest followed shortly after, most likely provoked by a respiratory tract infection causing increased right ventricular pressures.

Table 1. Outcome and associated anomalies in 38 cases with a prenatal diagnosis of CAT

Case	Sex	GA dx	Birth year	CAT conf.	Outcome				Associated anomalies		
					Pregnancy	*GA at birth*	*Age at surgery*	*Devel. delay*	*Cardiac, prenatal*	*Extra-cardiac, prenatal*	*Genetic diagnosis*
1	F	19+0	2003	-	TOP	-	-	-	0	Cleft lip	22q11.2 DS
2	M	20+5	2006	+	TOP	-	-	-	0	MCA[1]	0
3	M	20+3	2006	+	TOP	-	-	-	0	0	22q11.2 DS
4	M	18+3	2006	-	TOP	-	-	-	0	MCA[2]	MODY type 3
5	M	20+4	2007	-	TOP	-	-	-	0	0	0
6	F	19+6	2007	-	TOP	-	-	-	RAA, PLSVC, ARSA	MCA[3]	0
7	F	21+5	2008	+	TOP	-	-	-	0	MCA[4]	0
8	M	20+1	2008	-	TOP	-	-	-	RAA	Cleft lip-palate	0
9	M	19+6	2008	-	TOP	-	-	-	Truncal valve regurg.	0	22q11.2 DS
10	M	19+5	2009	+	TOP	-	-	-	0	0	0
11	F	21+5	2009	-	TOP	-	-	-	0	0	0
12	F	20+6	2010	+	TOP	-	-	-	Truncal valve regurg., fibroelastosis	MCA[5]	Trisomy 9 mosaicism
13	M	19+1	2010	-	TOP	-	-	-	Polyvalvular disease	Cerebellar hypoplasia, Rocker bottom feet	Trisomy 13
14	F	20+0	2014	-	TOP	-	-	-	Truncal valve regurg./stenosis	0	0
15	F	21+0	2015	-	TOP	-	-	-	Truncal valve stenosis	0	22q11.2 DS

Table 1. *(Continued)*

Case	Sex	GA dx	Birth year	CAT conf.	Outcome				Associated anomalies		
					Pregnancy	***GA at birth***	***Age at surgery***	***Devel. delay***	***Cardiac, prenatal***	***Extra-cardiac, prenatal***	***Genetic diagnosis***
16	M	20+2	2016	-	TOP	-	-	-	Truncal valve regurg.	0	0
17	F	19+4	2009	-	MFPR	-	-	-	0	Abnormal aspect kidney + Urethral dilatation	PTHSL1
18	M	18+3	2014	-	MFPR	-	-	-	0	sIUGR (gratacos 3), SUA	0
19	M	20+3	2008	-	IUFD (29+0)		-	-	Truncal valve regurg.	Fetal hydrops	0
20	F	17+5	2009	+	IUFD (29+5)		-	-	Truncal valve regurg., IAoA	Fetal hydrops	0
21	M	20+5	2005	+	NND (day 7)	40+3	7	-	IAoA type B *[RAA]*	0	22q11.2 DS
22	M	21+0	2007	+	NND (day 1)	35+3 (PPROM)	-	-	0	IUGR	Cri-du-Chat syndrome
23	F	19+1	2011	+	NND (day 1)	34+1 (PPROM)	-	-	APVR	MCA[6]	CHARGE syndrome
24	F	17+1	2014	+	NND (day 4)	28+4 (PPROM)	-	-	MS, PLSVC, enlarged CS	IUGR	0
25	F	16+5	2016	+	InfD (5 mo.)	31+5	22	-	RAA *[AVSD]*	MCA[7]	0
26	M	20+5	2015	+	InfD (1.5 yr)	39+6	8	+	0	0	0

Table 1. *(Continued)*

Case	Sex	GA dx	Birth year	CAT conf.	Outcome				Associated anomalies		
					Pregnancy	*GA at birth*	*Age at surgery*	*Devel. delay*	*Cardiac, prenatal*	*Extra-cardiac, prenatal*	*Genetic diagnosis*
27	F	21+0	2007	+	Alive (4 yr.)	39+2	14	+	0	0	22q11.2 DS
28	F	34+1	2008	+	Alive (10 yr.)	38+1	96	0	0 *[RAA]*	MCA[8]	Adams-Oliver syndrome
29	M	20+2	2009	+	Alive (9 yr.)	40+1	16	+	*0*	MCA[9]	22q11.2 DS
30	M	21+1	2009	+	Alive (9 yr.)	39+1	13	0	0	0	0
31	F	22+3	2009	+	Alive (8 yr.)	39+3	18	0	RAA	0	0
32	F	20+4	2011	+	Alive (8 yr.)	37+0	11	0	IAoA type B	0	0
33	F	20+5	2011	+	Alive (7 yr.)	39+6	22	0	RAA	0	0
34	M	22+1	2012	+	Alive (6 yr.)	39+0	36	+	0	Bilateral hydronephrosis	22q11.2 DS
35	M	20+4	2014	+	Alive (4 yr.)	41+3	9	+	RAA	0	0
36	M	26+3	2015	+	Alive (4 yr.)	37+2	13	0	Truncal valve stenosis	0	0
37	M	19+1	2016	+	Alive (2 yr.)	37+2	125	0	Unroofed CS, PLSVC	Intestinal atresia	0
38	M	20+2	2016	+	Alive (3 yr.)	41+0	14	0	0	0	0

Table 1. *(Continued)*
Data presented between '[ ]' include associated anomalies that were not detected before birth. Outcome is assessed at last follow-up visit. Age at surgery reported in days. Devel. delay developmental delay (present at last follow-up visit), TOP termination of pregnancy, MFPR multifetal pregnancy reduction, IUFD intrauterine fetal demise, NND neonatal death (<28 days), InfD Infant death, 22q11.2 DS 22q11.2 deletion syndrome PTHSL1 Pitt-Hopkins-like syndrome-1, MODY Maturity-Onset Diabetes of the Young, RAA right aortic arch, regurg. Regurgitation, PLSVC persistent left superior vena cava, ARSA aberrant right subclavian artery (arteria lusoria), VSDs ventricular septal defects, IAoA interrupted aortic arch, APVR anomalous pulmonary venous return, MS mitral valve stenosis, CS coronary sinus, PPROM preterm pre-labor rupture of membranes, MCA multiple congenital anomalies, IUGR intrauterine growth restriction, sIUGR selective IUGR, + = present, 0 = not present, - = no information, yr. year, mo. Months
Cases with multiple congenital anomalies (MCA):
1. cheilognathopalatoschisis, diaphragmatic hernia, radial aplasia with ulnar shortening right, bilateral flexion contracture of the wrist, bilateral oligodactylia (two fingers and one thumb right hand, absent right foot), rocker-bottom foot left, thoracic kyphosis, hypospadias, possibly a diaphragmatic hernia with short ribs
2. holoprosencephaly, bilateral renal agenesis, single umbilical artery, oligohydramnios
3. multicystic dysplastic unilateral kidney, abdominal cyst, single umbilical artery, (uncertainty on diaphragmatic hernia)
4. abnormal sacral spine, dislocated/abnormal location kidneys, single umbilical artery, (oligohydramnios)
5. spina bifida (L3/L4 to sacrum), hydrochephaly, unilateral renal agenesis, unilateral foot deformity (or deviation), single umbilical artery, signs of fetal decompensation
6. unilateral schisis, unilateral renal agenesis, single umbilical artery
7. hemivertebra, rib malformation, polydactyly, unilateral club foot, single umbilical artery, absent growth at 31+5 due to maternal factors (preeclampsia, HELLP, placental insufficiency with abnormal peripheral Dopplers)
8. bilateral asymmetric dysplasia of feet with unilateral equinovarus deformity, bilateral flexion contracture wrist, IUGR with brain-sparing (increased end-diastolic flow MCA)
9. abnormal head shape, abnormal shape ear

Prenatal counselling

The classification by Collett & Edwards[2] was used to describe the type of CAT in 75% of cases (15/20). The CAT was classified type I in 27% (4/15) and type II in 73% (11/15) of fetuses. Fetuses with CAT type I and II showed a relatively similar survival rate (75%, 3/4 vs 63%, 7/11) and probability to present with additional malformations (75%, 3/4 vs 73%, 8/11).

Fetuses with additional morbidity (non-isolated) showed a 50% (5/10) mortality risk (TOPs not included), including all early neonatal deaths (40%, 4/10) and one infant death (10%, 1/10). All of whom had significant other cardiac anomalies, whereas none of the non-isolated survivors did.

Isolated cases had a 30% (3/10) probability of fetal (20%, 2/10) or postnatal demise (10%, 1/10). Significant truncal valve regurgitation was found in both IUFD fetuses, but in none of the survivors. The presence of an IAoA alone, apart from prenatal truncal valve regurgitation, was not associated with fetal or neonatal mortality. All isolated CAT survivors required replacement of the initial right ventricle to pulmonary artery (RV-PA) conduit (6/7) or RV-PA patch (1/7) and 43% (3/7) up to four surgical re-interventions, due to pulmonary stenosis or insufficiency (cardiac catheterizations not considered).

After exclusion of pregnancy terminations, 60% of fetuses with CAT (12/20) were alive at last follow-up visit (mean: 6 years, range: 2-10). Half of these survivors had a genetic diagnosis, significant ECMs or developmental delay, leaving 50% (6/12) isolated with normal development. This means that only 30% (6/20) of continuing pregnancies and a prenatal diagnosis of CAT were alive without additional morbidity or signs of developmental delay at 6 years of age (Figure 1).

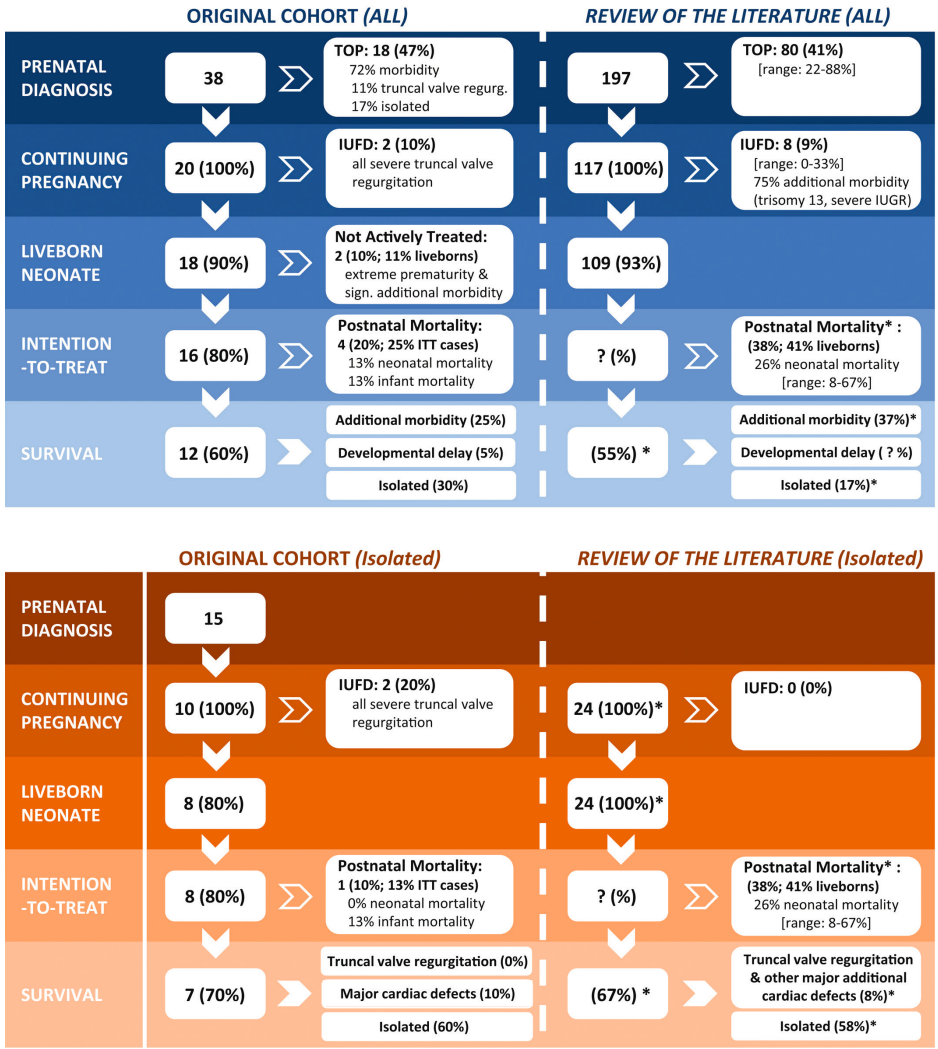


Figure 1. Outcome of (isolated) fetuses after a prenatal diagnosis of CAT

TOP termination of pregnancy, IUFD intrauterine fetal death, ITT Intention-to-treat, IUGR intrauterine growth restriction, Truncal valve regurg. Truncal valve regurgitation (> mild).
* Not all studies report on survival or the presence of additional morbidity

Systematic review

Our literature search identified 546 potentially relevant articles, of which 70 were assessed for eligibility based on title and abstract and 13 eventually met the inclusion criteria (Figure 2).[5-7, 24-33] Five studies focuses on CAT specifically[6, 7, 24, 30, 31], whereas the remaining 8 included other cardiac defects as well[5, 25-29, 32, 33]. Altogether, these studies described 197 fetuses with a prenatal diagnosis of CAT.

Figure 2. Flowchart systematic review of the literature

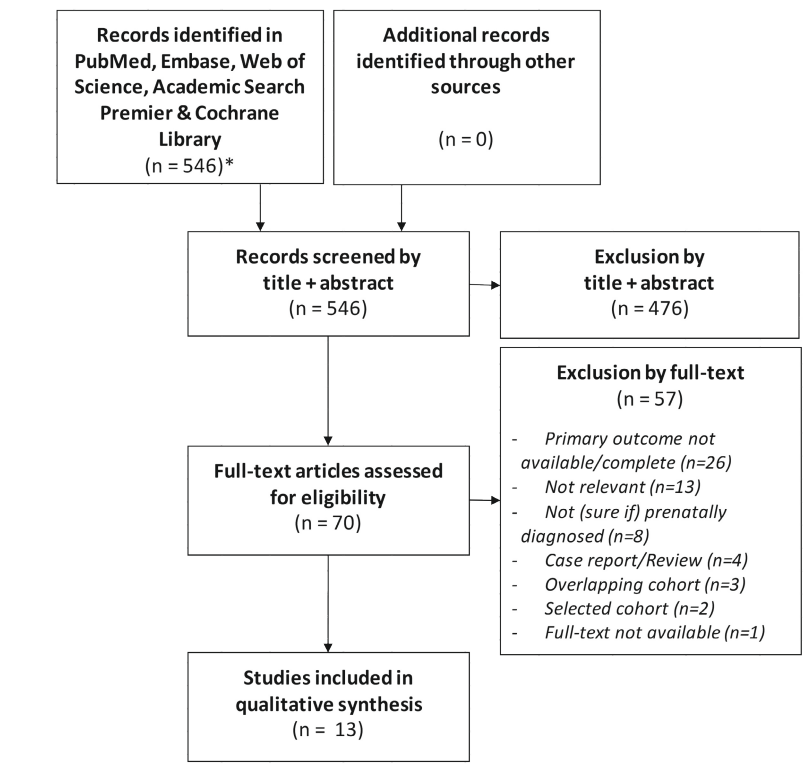


Figure 2. Flowchart systematic review of the literature

Additional morbidity

The available data on outcome and presence of additional morbidity in fetuses with CAT is reported for each study separately, and combined, in Table 2. A genetic syndrome was found in 30% (44/148) of all fetuses with CAT, which varied between 13% and 39% in large cohorts. Structural ECMs, such as holoprosencephaly, cleft lip, renal agenesis and esophageal or duodenal atresia, were present in 36% (61/170) of CAT cases. Associated cardiac anomalies were reported in five studies (39% of cases, 37/95)[7, 28, 30, 32, 33].

Table 2. Review of results on pregnancy outcome, postnatal course and additional mortality derived from included articles

Author, Year	Time	N.	Confirmation of diagnosis	Pregnancy outcome			Neonatal outcome		Survival		Associated anomalies		
				TOP	IUFD	Livebirth	Surgery	NND	All	*TOP excl.*	Genetic diagnosis	N Tested	Structural anomalies
Allan *et al.*,[30] 1984	< 1984	1	Yes (100%)	0% (0/1)	0% (0/1)	100% (1/1)	-	0% (0/1)	0% (0/1) alive; (1 InfD at 4 mo.)	0% (0/1) alive	0% (0/1)	-	0% (0/1) ECMs
Paladini *et al.*,[36] 1996	1990 - 1994	6	Yes (100%)	50% (3/6)	0% (0/6)	50% (3/6)	33% (1/3); (1 awaiting)	67% (2/3) (1 NNDpr, 1 NNDpo)	17% (1/6) alive and awaiting surgery;	33% (1/3)	17% (1/6): Trisomy 18	100% (6/6); karyo	17% (1/6) ECMs 0% (0/6) associated CVAs
Hafner *et al.*,[33] 1998	1992 - 1996	3	Yes	67% (2/3)	0% (0/3)	33% (1/3)	-	-	-	-	33% (1/3): Aneuploidy (47+fragment)	100% (3/3); karyo	33% (1/3) ECMs: spina bifida; *unknown for aneuploidy case*
Tometzki *et al.*,[22] 1999	1985 - 1997	3	Yes (100%)	33% (1/3)	33% (1/3)	33% (1/3)	100% (1/1)	0% (0/1)	33% (1/3) survival > 28 days;	50% (1/2)	67% (2/3): Trisomy 13, CHARGE syndrome	-	33% (1/3) ECMs: bilateral anophthalmos; *unknown for T13/ CHARGE cases*
Duke *et al.*,[21] 2001	1990 - 1999	17	Yes (100%)	24% (4/17)	0% (0/17)	76% (13/17)	62% (8/13)	54% (7/13) (5 NNDpr, 2 NNDpo)	29% (5/17) alive; (1 InfD > 3 mo.)	38% (5/13)	18% (3/17): 22q11.2 DS (3)	71% karyo, 59% 22q11.2 (FISH)	24% (4/17) ECMs: 1 hydrocephaly, 3 MCA
Volpe *et al.*,[8] 2003	1993 - 2002	23	Yes (100%)	35% (8/23)	9% (2/23)	57% (13/23)	62% (8/13) (2 awaiting)	- (3 prD, 2 poD¶)	35% (8/23) alive; (2 awaiting surgery)	53% (8/15)	35% (8/23): 22q11.2 DS (6), Trisomy 13, Trisomy 22	96% karyo, 83% 22q11.2 (FISH)	43% (10/23) ECMs: 4/10 MCA 30% (7/23) associated CVAs

Table 2. *(Continued)*

Author, Year	Time	N.	Confirmation of diagnosis	Pregnancy outcome			Neonatal outcome		Survival		Associated anomalies		
				TOP	IUFD	Livebirth	Surgery	NND	All	*TOP excl.*	Genetic diagnosis	N Tested	Structural anomalies
Galindo *et al.,*[6] 2009	1990 - 2005	13†	Yes (100%)	38% (5/13)	0% (0/13)	62% (8/13)	75% (6/8)	38% (3/8); (2 NNDpr, 1 NNDpo)	23% (3/13) alive; (2 InfDpo)	38% (3/8)	31% (4/13): Trisomy 13 (2), 22q11.2 DS (2)	-	54% (7/13) ECMs
Swanson *et al.,*[7] 2009	1992 - 2007	38	Yes, partly (only livebirths)	45% (17/38)	5% (2/38)	50% (19/38)	89% (17/19)	11% (2/19) (2 NNDpr, 4 poD¶)	34% (13/38) alive to 60 days;	62% (13/21)	-	-	32% (12/38) ECMs
Bourdial *et al.,*[31] 2012	2002 - 2007	16	Yes (not all fetal deaths)	88% (14/16)	0% (0/16)	22% (2/16)	-	-	-	-	25% (4/16): 22q11.2 DS (4)	-	-
Lee *et al.,*[34] 2013	2003 - 2012	12‡	Yes (100%)	33% (4/12)	0% (0/12);	67% (8/12)	88% (7/8)	25% (2/8) (1 NNDpr, 1 NNDpo)	50% (6/12) alive after surgery;	75% (6/8)	17% (2/12): unbalanced translocation, inversion	100% karyo, 75% 22q11.2 (FISH)	17% (2/12) ECMs 67% (8/12) associated CVAs
Traisrisilp *et al.,*[37] 2015	2004 - 2013	8§	Yes (100%)	75% (6/8)	0% (0/8)	25% (2/8)	-	-	-	-	13% (1/8): Trisomy 13	88% karyo	25% (2/8) ECMs 75% (6/8) associated CVAs
Gómez *et al.,*[32] 2016	2006 - 2013	8	Yes (100%)	88% (7/8);	0% (0/8)	12% (1/8);	100% (1/1)	0% (0/1)	13% (1/8) alive at 10 MoL.	100% (1/1)	38% (3/8): Trisomy 13 (2), Triploïdy	100% karyo / FISH for 22q11	50% (4/8) ECMs: 1 holoprosencephaly, 3 MCA 25% (2/8) associated CVAs
Morgan *et al.,*[35] 2019	1990 - 2014	49	Uncertain	22% (11/49)	2% (1/49)	76% (37/49)	*73% (27/37) primary BVR*	-	-	-	-	-	-

Table 2. *(Continued)*

Author, Year	Time	N.	Confirmation of diagnosis	Pregnancy outcome			Neonatal outcome		Survival		Associated anomalies		
				TOP	IUFD	Livebirth	Surgery	NND	All	*TOP excl.*	Genetic diagnosis	N Tested	Structural anomalies
Original data *This study*	2002 - 2016	38	Yes (63%)	47% (18/38)	5% (2/38)	47% (18/38)	83% (15/18)	22% (4/18) (3 NNDpr, 1 NNDpo)	32% (12/38) alive after surgery (2 InfDpo at 5 & 18 mo.)	60% (12/20)	39% (15/38): 22q11.2 DS (8), Aneuploidy (2), other genetic diagnosis (5)	100% karyo / FISH for 22q11	45% (17/38) ECMs 37% (14/38) associated CVAs
All included studies		**235**		**43%** (100/235) *[22-88%]*	**3%** (8/235) *[0-33%]*	**54%** (127/235) *[22-76%]*	**76%** (64/84) *[62-89%]*	**28%** (20/72) *[11-67%]*	**31%** (50/159) *[17-50%]*		**30%** (44/148) *[17-67%]*		**36%** (61/170) ECMs **39%** (37/95) associated CVAs
All included studies (TOP excl.)		**135**			6% (8/135) [0-50%]	94% (127/135) [50-100%]	70% (64/91) [53%-88%]	26% (20/77) [8-67%]		**55%** (50/91) *[33-75%]*			

Data are presented as % (n) or % (n) or % (n) [range]. Proportions reported for individual studies that are based on n=1, are not taken into account in the range.
TOP termination of pregnancy, IUFD intrauterine fetal demise, NND neonatal death (<28 days of life), BVR biventricular repair, pr preoperatively, po postoperatively, prD preoperative death (age at time of death unknown), poD postoperative death (age at time of death unknown), InfD infant death, mo. months of age, CVAs cardiovascular anomalies, ECMs extracardiac malformations, MCA multiple congenital anomalies, Karyo karyotyping, 22q11.2 DS 22q11.2 microdeletion syndrome.

† assessment of (neonatal) outcome/associated defects related to all CAT with definitive postnatal diagnosis (including those with different prenatal dx)
‡ assessment of associated defects related to postnatal confirmed CAT cases (excluding 2 fetal deaths without autopsy: 1 TOP, 1 IUFD)
§ only CAT type II and III was eligible for inclusion in this study
¶ not stated whether there were neonatal deaths amongst the cases that died pre- or postoperatively (Volpe. 2003), only that it happened <30 days after surgery (Swanson. 2009)

Outcome

Forty-three percent of pregnancies (100/235, range 22-88%) was terminated. IUFD occurred in 6% of continuing pregnancies (8/135, range 0-13% in larger cohorts), which means 94% (127/135) resulted in a liveborn neonate.

The probability of neonatal death, reported in 9 of the 14 available cohorts (including ours), appeared 28% (20/72) in liveborn neonates. Surgery was performed in 76% (63/83) of neonates, because 20% (17/83) died pre-operatively and 4% (3/83) were awaiting surgery. The study by Morgan *et al.*[31] only described the proportion of cases that underwent primary biventricular repair, which is the preferable surgical option for the correction of CAT in the majority of cases. As they did not specify the proportion of cases that died pre-operatively, were awaiting surgery or received alternative surgery, these cases were not included in the calculated proportion of cases that underwent surgery in all studies together. After exclusion of pregnancy terminations, 55% (50/91) of CAT fetuses were alive at the time each study was reported, based on the 10 studies that described survival.

Prenatal counselling

In 7 studies mortality was related to the presence of additional morbidity.[6, 8, 21, 22, 32, 34, 35] Genetic syndromes or ECMs were found in 75% of deceased cases (IUFD or neonatal death) versus 31% of surviving cases. Four studies reported on mortality for isolated CAT and its relation to associated cardiac anomalies.[7, 24, 28, 30] These studies together showed a postnatal mortality of 33% (8/24) (all with intention-to-treat). Prenatal truncal valve regurgitation or major additional cardiac defects were present in 63% (5/8) of demised cases compared to 13% (2/16) of survivors (data not presented). If data from our cohort were included as well, this was 64% (7/11) in non-survivors and 9% (2/23) in survivors, respectively.

To conclude, 54% (36/67) of CAT fetuses with complete data survived, of which 37% (25/67) occurred isolated and 17% (11/67) had additional morbidity (mainly genetic syndromes) (Figure 1, Supplemental material S2).

Quality assessment

The QUIPS tool[23] was used to identify major risks of bias for each of the 13 studies (Supplemental material S3). Most studies (10/13) scored low to moderate risk of bias on all six domains. Hafner *et al.*[29] scored high risk of bias on 'outcome measurement', because outcome was not clearly defined, not measured similarly in all patients and incomplete for pregnancy outcome. However, after we had contacted the authors, they supplied us with complementary data. Lee *et al.*[30] and Traisrisilp *et al.*[33] scored

high risk of bias on 'study attrition', because a significant proportion of cases were lost-to-follow-up or the number of cases excluded due to incomplete postnatal follow-up was not stated.

DISCUSSION

Our study shows a considerable risk of mortality in fetuses diagnosed with CAT. Demise mainly occurs during pregnancy or shortly after birth in cases with truncal valve incompetence or complications as a result of a genetic syndrome, in particular when delivered prematurely. Sixty percent of continuing pregnancies with intention-to-treat, calculated from mid-gestation, were alive after surgery and only 30% of cases showed no signs of additional morbidity or developmental delay at the age of six.

This is the first large cohort study that evaluates postnatal outcome, with regard to additional morbidity and neurodevelopment, in fetuses diagnosed with CAT. A systematic analysis of the literature to assemble evidence from currently available studies has to our knowledge never been performed either. First of all, we encountered a 10% IUFD risk in continuing pregnancies, which was slightly higher compared to the literature. This might be due to an underrepresentation of IUFD cases in reported studies, as some studies merely focus on cases with confirmation of the diagnosis on postnatal echocardiography or autopsy[5, 24, 28, 30], which can often not be performed after fetal demise. We expect that our findings approach the true risk of IUFD, as comparable results have been reported by two similar cohort studies.[6, 7]

Although the vast majority of continuing pregnancies appeared to result in a liveborn neonate, there remained a considerable risk of postnatal mortality (30%). Half of these cases did not undergo surgery, which all involved complex CAT cases with (extreme) prematurity. Active treatment after birth was not initiated in the majority of these preoperative deaths, as the prenatally expected prognosis and quality of life was poor. The postnatal mortality rate in all included studies combined appeared slightly higher, but still comparable.[5-7, 24, 30, 32] Unfortunately most of these cohorts merely mention case-specific, rather than general, causes for postnatal mortality and did not focus on potential prognostic factors apart from truncal valve pathology. Large postnatal cohorts that describe the outcome of CAT often solely include cases that underwent surgery.[9, 10, 34-37] This is important for prenatal counselling, because this selection explains why postnatal cohort studies overestimate the overall survival; these studies report 1-year survival rates between 79% and 89%, which is comparable to the 1-year postoperative survival of 87% in our cohort. From a fetal perspective, however, only 60% of reported fetuses with CAT were alive six years after surgery.

The presence of additional morbidity has shown to be an important predictor for mortality, as genetic syndromes or ECMs were found in 75% of non-survivors (IUFD and neonatal deaths) compared to 31% of survivors. Premature birth, which occurred only

in cases with additional morbidity, appeared equally important, as none of those that delivered prematurely survived until corrective surgery could be performed. In term neonates, the risk of postnatal mortality was still slightly higher in those with genetic syndromes or significant ECMs compared to those with isolated CAT and favorable cardiac anatomy. As it is likely that additional morbidity is directly related to preterm birth, and might reflect the more severely affected cases, we believe both aspects should be considered to estimate the prognosis. In isolated cases the presence of prenatal truncal valve regurgitation (greater than mild) was particularly associated with fetal and postnatal mortality. The finding that major additional cardiac anomalies (other than IAoA), beside truncal valve regurgitation, are a risk factor for postnatal mortality in isolated CAT, was not confirmed in our cohort.[7, 24, 30] Thus, despite the fact that most postnatal cohorts solely report on the need for truncal valve repair or additional cardiac defects as risk factors for mortality[9, 35, 36], these data show that genetic syndromes and significant ECMs are also important to consider.

The prognosis of fetal CAT is, however, not only influenced by the considerable risk of postnatal mortality, but significant morbidity among survivors as well. Genetic syndromes associated with neurodevelopmental delay or (postoperative) complications, such as 22q11.2 deletion and Adams-Oliver syndrome, were found in a third of fetuses that survived and have a significantly negative impact on the quality of life of these children. If advanced techniques, such as exome sequencing, are applied to rule out these genetic syndromes, counselling regarding the prognosis can be more specific and more optimistic, especially in isolated cases. This is important, as the proportion of isolated cases at mid-gestation increased over time, due to advances in prenatal detection of CAT. Accurate diagnosis of CAT at mid-gestation has, however, proven to remain a challenge, as a small proportion appeared to have a PA-VSD after birth.[5-7, 24]

An important limitation of the literature review is the fact that prenatally diagnosed cases with CAT originated from a long time-period (1990-2016) and studies mainly focused on short-term perinatal outcome. This complicates objective comparison of outcome data, as prenatal detection rates, surgical techniques and postnatal care management have changed significantly over time. Besides that, previous studies barely report on postnatal outcome beyond the neonatal period nor the presence of significant morbidity or developmental delay amongst survivors. In 4 of the 13 included studies[27, 29, 31, 33], data on postnatal course or survival were not even complete for all cases, which represent 32% of reported fetuses. As the vast majority originated from the large cohort by Morgan *et al.*[31], the authors were contacted and verified that all available data had been reported. Additionally, most studies did not perform genetic testing in all CAT cases[7, 24, 33] or did not report the proportion tested[6, 25-27, 29, 31, 32]. Lastly,

the presence of additional morbidity could not always be directly related to outcome, because it had either been described for all CAT cases together[6, 32] or the article lacked information on the postnatal course entirely[27, 29, 33]. Although this restricted our systematic review almost exclusively to short-term neonatal parameters, such an overview has never been presented before. Furthermore, it stresses the importance of large cohort studies with sufficient data on outcome and prognosis from a fetal perspective to improve prenatal counselling for CAT.

CONCLUSION

The survival rate for prenatally diagnosed CAT is low and depends highly on the presence of additional morbidity and occurrence of premature birth. As genetic syndromes, ECMs and developmental delay are present in half of the cases that do survive, microarray analysis with sequential exome sequencing should be considered in these cases. Large prospective cohort studies, that include extensive genetic testing for all cases, are needed to assess the prognosis with morbidity-free survival more precisely.

ACKNOWLEDGEMENTS

We would like to thank Jan Schoones, a medical librarian at the Leiden University Medical Centre, for the assistance in the literature search.

REFERENCES

1. Allan LD, Sharland GK, Milburn A, et al. Prospective diagnosis of 1,006 consecutive cases of congenital heart disease in the fetus. J Am Coll Cardiol. 1994;23(6):1452-8.
2. Collett RW, Edwards JE. Persistent truncus arteriosus; a classification according to anatomic types. Surg Clin North Am. 1949;29(4):1245-70.
3. Russell HM, Jacobs ML, Anderson RH, et al. A simplified categorization for common arterial trunk. J Thorac Cardiovasc Surg. 2011;141(3):645-53.
4. Van Praagh R, Van Praagh S. The anatomy of common aorticopulmonary trunk (truncus arteriosus communis) and its embryologic implications. A study of 57 necropsy cases. Am J Cardiol. 1965;16(3):406-25.
5. Galindo A, Mendoza A, Arbues J, et al. Conotruncal anomalies in fetal life: accuracy of diagnosis, associated defects and outcome. Eur J Obstet Gynecol Reprod Biol. 2009;146(1):55-60.
6. Swanson TM, Selamet Tierney ES, Tworetzky W, et al. Truncus arteriosus: diagnostic accuracy, outcomes, and impact of prenatal diagnosis. Pediatr Cardiol. 2009;30(3):256-61.
7. Volpe P, Paladini D, Marasini M, et al. Common arterial trunk in the fetus: characteristics, associations, and outcome in a multicentre series of 23 cases. Heart. 2003;89(12):1437-41.
8. Vesel S, Rollings S, Jones A, et al. Prenatally diagnosed pulmonary atresia with ventricular septal defect: echocardiography, genetics, associated anomalies and outcome. Heart. 2006;92(10):1501-5.
9. Naimo PS, Fricke TA, Yong MS, et al. Outcomes of Truncus Arteriosus Repair in Children: 35 Years of Experience From a Single Institution. Semin Thorac Cardiovasc Surg. 2016;28(2):500-11.
10. Martin BJ, Ross DB, Alton GY, et al. Clinical and Functional Developmental Outcomes in Neonates Undergoing Truncus Arteriosus Repair: A Cohort Study. Ann Thorac Surg. 2016;101(5):1827-33.
11. O'Byrne ML, Mercer-Rosa L, Zhao H, et al. Morbidity in children and adolescents after surgical correction of truncus arteriosus communis. Am Heart J. 2013;166(3):512-8.
12. Bonnet D, Coltri A, Butera G, et al. Detection of transposition of the great arteries in fetuses reduces neonatal morbidity and mortality. Circulation. 1999;99(7):916-8.
13. Mahle WT, Clancy RR, McGaurn SP, et al. Impact of prenatal diagnosis on survival and early neurologic morbidity in neonates with the hypoplastic left heart syndrome. Pediatrics. 2001;107(6):1277-82.
14. Tworetzky W, McElhinney DB, Reddy VM, et al. Improved surgical outcome after fetal diagnosis of hypoplastic left heart syndrome. Circulation. 2001;103(9):1269-73.
15. Cohen MS, Schultz AH, Tian ZY, et al. Heterotaxy syndrome with functional single ventricle: does prenatal diagnosis improve survival? Ann Thorac Surg. 2006;82(5):1629-36.
16. Daubeney PE, Sharland GK, Cook AC, et al. Pulmonary atresia with intact ventricular septum: impact of fetal echocardiography on incidence at birth and postnatal outcome. UK and Eire Collaborative Study of Pulmonary Atresia with Intact Ventricular Septum. Circulation. 1998;98(6):562-6.
17. McElhinney DB, Salvin JW, Colan SD, et al. Improving outcomes in fetuses and neonates with congenital displacement (Ebstein's malformation) or dysplasia of the tricuspid valve. Am J Cardiol. 2005;96(4):582-6.

18. Imamura M, Drummond-Webb JJ, Sarris GE, Mee RB. Improving early and intermediate results of truncus arteriosus repair: a new technique of truncal valve repair. Ann Thorac Surg. 1999;67(4):1142-6.
19. Kalavrouziotis G, Purohit M, Ciotti G, et al. Truncus arteriosus communis: early and midterm results of early primary repair. Ann Thorac Surg. 2006;82(6):2200-6.
20. Thompson LD, McElhinney DB, Reddy M, et al. Neonatal repair of truncus arteriosus: continuing improvement in outcomes. Ann Thorac Surg. 2001;72(2):391-5.
21. van Velzen CL, Clur SA, Rijlaarsdam ME, et al. Prenatal detection of congenital heart disease--results of a national screening programme. BJOG. 2016;123(3):400-7.
22. Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. BMJ. 2009;339:b2535.
23. Hayden JA, van der Windt DA, Cartwright JL, et al. Assessing bias in studies of prognostic factors. Ann Intern Med. 2013;158(4):280-6.
24. Duke C, Sharland GK, Jones AM, Simpson JM. Echocardiographic features and outcome of truncus arteriosus diagnosed during fetal life. Am J Cardiol. 2001;88(12):1379-84.
25. Tometzki AJ, Suda K, Kohl T, et al. Accuracy of prenatal echocardiographic diagnosis and prognosis of fetuses with conotruncal anomalies. J Am Coll Cardiol. 1999;33(6):1696-701.
26. Allan LD, Crawford DC, Anderson RH, Tynan MJ. Echocardiographic and anatomical correlations in fetal congenital heart disease. Br Heart J. 1984;52(5):542-8.
27. Bourdial H, Jamal-Bey K, Edmar A, et al. Congenital heart defects in La Reunion Island: a 6-year survey within a EUROCAT-affiliated congenital anomalies registry. Cardiol Young. 2012;22(5):547-57.
28. Gomez O, Soveral I, Bennasar M, et al. Accuracy of Fetal Echocardiography in the Differential Diagnosis between Truncus Arteriosus and Pulmonary Atresia with Ventricular Septal Defect. Fetal Diagn Ther. 2016;39(2):90-9.
29. Hafner E, Scholler J, Schuchter K, et al. Detection of fetal congenital heart disease in a low-risk population. Prenat Diagn. 1998;18(8):808-15.
30. Lee MY, Won HS, Lee BS, et al. Prenatal diagnosis of common arterial trunk: a single-center's experience. Fetal Diagn Ther. 2013;34(3):152-7.
31. Morgan CT, Tang A, Fan CP, et al. Contemporary Outcomes and Factors Associated With Mortality After a Fetal or Postnatal Diagnosis of Common Arterial Trunk. Can J Cardiol. 2019;35(4):446-52.
32. Paladini D, Rustico M, Todros T, et al. Conotruncal anomalies in prenatal life. Ultrasound Obstet Gynecol. 1996;8(4):241-6.
33. Traisrisilp K, Tongprasert F, Srisupundit K, et al. Prenatal differentiation between truncus arteriosus (Types II and III) and pulmonary atresia with ventricular septal defect. Ultrasound Obstet Gynecol. 2015;46(5):564-70.
34. Asagai S, Inai K, Shinohara T, et al. Long-term Outcomes after Truncus Arteriosus Repair: A Single-center Experience for More than 40 Years. Congenit Heart Dis. 2016;11(6):672-7.
35. Chen Q, Gao H, Hua Z, et al. Outcomes of Surgical Repair for Persistent Truncus Arteriosus from Neonates to Adults: A Single Center's Experience. PLoS One. 2016;11(1):e0146800.
36. Russell HM, Pasquali SK, Jacobs JP, et al. Outcomes of repair of common arterial trunk with truncal valve surgery: a review of the society of thoracic surgeons congenital heart surgery database. Ann Thorac Surg. 2012;93(1):164-9; discussion 9.
37. Sojak V, Lugo J, Koolbergen D, Hazekamp M. Surgery for truncus arteriosus. Multimed Man Cardiothorac Surg. 2012;2012:mms011.

SUPPLEMENTAL MATERIAL

Appendix S1. Search strategy systematic analysis of the literature

Access date: 1-9-2019

Pubmed

((“Prognosis”[Mesh] OR “prognosis”[tw] OR prognos*[tw] OR “Pregnancy Outcome”[Mesh] OR “outcome”[tw] OR “outcomes”[tw] OR “long-term”[tw] OR “longterm”[tw] OR “Follow-Up Studies”[Mesh] OR “Follow-Up”[tw] OR “Followup”[tw] OR “pregnancy outcome”[tw] OR outcome*[tw] OR “Live birth”[Mesh] OR “livebirth”[tw] OR “live birth”[tw] OR “livebirths”[tw] OR “live births”[tw] OR “Abortion, Induced”[Mesh] OR “abortion”[tw] OR “termination of pregnancy”[tw] OR “pregnancy termination”[tw] OR “demise”[tw] OR “Death”[Mesh] OR “Fetal Death”[mesh] OR “fetal death”[tw] OR “fetal deaths”[tw] OR “foetal death”[tw] OR “foetal deaths”[tw] OR “intrauterine death”[tw] OR “intrauterine deaths”[tw] OR “intra-uterine death”[tw] OR “intra-uterine deaths”[tw] OR “death”[tw] OR “deaths”[tw] OR “Mortality”[Mesh] OR “mortality”[Subheading] OR “mortality”[tw] OR “Fatal Outcome”[Mesh] OR “Morbidity”[Mesh] OR “morbidity”[tw] OR “Growth and Development”[Mesh] OR “growth and development”[Subheading] OR “development”[tw] OR “Neurobehavioral manifestations”[Mesh] OR “neurologic disorder”[tw] OR “nervous system disorder”[tw] OR “Nervous System Diseases”[Mesh] OR “nervous system disease”[tw] OR “neurologic disorders”[tw] OR “nervous system disorders”[tw] OR “nervous system diseases”[tw] OR “neurologic disease”[tw] OR “neurologic diseases”[tw] OR “neurodevelopment”[tw] OR neurodevelopment*[tw] OR “disability”[tw] OR “disabilities”[tw] OR “impaired”[tw] OR “impairment”[tw] OR “Quality of Life”[Mesh] OR “quality of life”[tw] OR “life quality”[tw] OR “HRQOL”[tw] OR “Genetic Diseases, Inborn”[Mesh] OR “genetic disease”[tw] OR “genetic diseases”[tw] OR “genetic disorder”[tw] OR “genetic disorders”[tw] OR “hereditary disease”[tw] OR “genetic defect”[tw] OR “gene defect”[tw] OR “hereditary diseases”[tw] OR “genetic defects”[tw] OR “gene defects”[tw] OR “Syndrome”[Mesh] OR “syndrome”[tw] OR “Treatment Outcome”[tw] OR “Therapeutic Index”[tw] OR “Treatment Failure”[tw] OR “Outcome Assessment (Health Care)”[Mesh] OR “birth”[tw] OR “ births”[tw] OR “growth”[tw] OR “lifespan”[tw] OR “Comparative Study”[Publication Type] OR compar*[tw]) **AND** (“Fetus”[Mesh] OR “fetus”[tw] OR “fetuses”[tw] OR “foetus”[tw] OR “foetuses”[tw] OR “fetal”[tw] OR “foetal”[tw] OR “Prenatal Diagnosis”[Mesh] OR “prenatal diagnosis”[tw] OR Prenatal Diagnos*[tw] OR “Intrauterine Diagnosis”[tw] OR “Intra-uterine Diagnosis”[tw] OR Intrauterine Diagnos*[tw] OR Intra-uterine Diagnos*[tw] OR “Antenatal diagnosis”[tw] OR Antenatal Diagnos*[tw] OR “Prenatal Screening”[tw] OR Prenatal Screen*[tw] OR “Antenatal Screening”[tw] OR Antenatal Screen*[tw] OR “Ultrasonography, Prenatal”[Mesh] OR Prenatal Ultraso*[tw] OR Prenatal echogra*[tw] OR Antenatal Ultraso*[tw] OR “prenatal detection”[tw] OR “antenatal detection”[tw] OR antenatal*[tw] OR prenatal*[tw]) **AND** (“Truncus arteriosus”[Mesh] OR “Truncus arteriosus, persistent”[Mesh] OR “truncus arteriosus”[tw] OR “common arterial trunk”[tw] OR “persistent truncus arteriosus”[tw] OR “common truncus arteriosus”[tw] OR “common trunk”[tw] OR “persistent truncus”[tw] OR “truncus communis”[tw] OR truncus commun*[tw] OR “common trunc”[tw] OR “common truncal valve”[tw] OR “common truncus”[tw] OR “common trunks”[tw] OR “conotruncal anomaly”[tw] OR “cono truncal anomaly”[tw] OR “conotruncal anomalies”[tw] OR “cono truncal anomalies”[tw] OR “conotruncal malformation”[tw] OR “cono truncal malformation”[tw] OR “conotruncal malformations”[tw] OR “cono truncal malformations”[tw] OR “fetal congenital heart disease”[tw] OR “fetal congenital heart diseases”[tw] OR “foetal congenital heart disease”[tw] OR “foetal congenital heart diseases”[tw] OR ((“congenital heart disease”[ti] OR “congenital heart diseases”[ti]) AND (“fetus”[ti] OR “foetus”[ti])))) **NOT** (“Animals”[mesh] NOT “Humans”[mesh]) AND (english[la] OR dutch[la] OR “swedish”[la]))

Embase, Web of Science, Cochrane Library & Academic Search Premier

Similar to the one used in Pubmed

Appendix S2. Associated anomalies in survivors and non-survivors reported in the studies that described outcome & additional morbidity

	Survivors (TOP excl.)				Deceased, IUFD (TOP excl.)				Deceased, Neonatal death (Liveborns)			
	%	Isolated	Additional morbidity		%	Isolated	Additional morbidity		%	Isolated	Additional morbidity	
Allan *et al.*,1984	100% (1/1)	100% (1/1)	0% (0/1)		-	-	-	-	-	-	-	-
Tometzki *et al.*,1999	50% (1/2)	0% (0/2)	50% (1/2)	1 CHARGE syndrome	50% (1/2)	0% (0/2)	50% (1/2)	1 Trisomy 13	-	-	-	-
Duke *et al.*,2001	38% (5/13)	23% (3/13)	15% (2/13)	1 22q11.2 DS 1 Pierre Robin sequence, hemivertebrae, cleft palate	-	-	-	-	54% (7/13)	31% (4/13)	23% (3/13)	1 22q11.2 DS 1 MCA 1 Hydrocephaly
Volpe *et al.*,2003	53% (8/15)	47% (7/15)	7% (1/15)	1 22q11.2 DS, unilateral renal agenesis	13% (2/15)	7% (1/15)	7% (1/15)	1 Severe IUGR	-	-	-	-
Galindo *et al.*,2009	38% (3/8)	25% (2/8)	13% (1/8)	1 not specified	-	-	-	-	23% (3/8)	25% (2/8)	13% (1/8)	1 *not specified*
Lee *et al.*,2013	75% (6/8)	63% (5/8)	13% (1/8)	1 22q11.2 DS	-	-	-	-	25% (2/8)	13% (1/8)	13% (1/8)	1 congenital diaphragmatic hernia
Gómez *et al.*,2016	100% (1/1)	100% (1/1)	0% (0/1)		-	-	-	-	-	-	-	-
Morgan *et al.*,2013	-	-	-	-	3% (1/38)	0% (0/38)	3% (1/38)	1 Trisomy 13	-	-	-	-

Appendix S2. *(continued)*

	Survivors (TOP excl.)				Deceased, IUFD (TOP excl.)				Deceased, Neonatal death (Liveborns)			
	%	**Isolated**	**Additional morbidity**		*%*	**Isolated**	**Additional morbidity**		*%*	**Isolated**	**Additional morbidity**	
Original data *This study*	60% (12/20)	35% (7/20)	25% (5/20)	3 22q11.2 DS 1 Adams-Oliver syndrome 1 Intestinal atresia	10% (2/20)	10% (2/20)	0% (0/20)	*2 Severe truncal valve regurgitation*	22% (4/18)	0% (0/18)	22% (4/18)	1 22q11.2 DS 1 CHARGE syndrome 1 Cri-du-Chat syndrome 1 IUGR
Total		**70% (26/37)**	**30% (11/37)**	**73% (8/11) genetic diagnosis 18% (2/11) ECM only 9% (1/11) *not specified***		**50% (3/6)**	**50% (3/6)**	**67% (2/3) genetic diagnosis 33% (1/3) ECM only**		**25% (8/32)**	**75% (14/32)**	**44% (4/9) genetic diagnosis 44% (4/9) ECM only 11% (1/9) *not specified***
Total (*Infant death not reported*)	**54% (37/68)**	**37% (25/68)**	**17% (11/68)**		**8% (6/75)**	**4% (3/75)**	**4% (3/75)**		**17% (16/92)**	**8% (7/92)**	**10% (9/92)**	

TOP termination of pregnancy, IUFD intra-uterine fetal death, 22q11.2 DS 22q11.2 deletion syndrome, MCA multiple congenital anomalies, IUGR intra-uterine growth restriction, ECM extracardiac malformation

Appendix S3. Quality assessment of included studies to assess risk of bias; QUIPs (Quality in Prognosis Studies) tool23

	Study Participation	Study Attrition	Prognostic Factor Measurement	Outcome Measurement	Study Confounders	Statistical Analysis & Reporting
Allan *et al.*,1984	Moderate	Low	Low	Moderate	Moderate	Low
Paladini *et al.*,1996	Low	Low	Low	Low	Low	Low
Hafner *et al.*,1998	Low	Low	Low	High	Low	Moderate
Tometzki *et al.*,1999	Moderate	Moderate	Low	Moderate	Moderate	Moderate
Duke *et al.*,2001	Low	Low	Low	Low	Low	Low
Volpe *et al.*,2003	Low	Low	Low	Low	Low	Low
Galindo *et al.*,2009	Low	Moderate	Low	Low	Low	Low
Swanson *et al.*,2009	Low	Low	Low	Low	Moderate	Low
Bourdial *et al.*, 2012	Low	Low	Moderate	Moderate	Moderate	High
Lee *et al.*,2013	Low	High	Low	Low	Low	Low
Gómez *et al.*,2016	Low	Low	Low	Low	Low	Low
Morgan *et al.*,2019	Low	Low	Low	Low	Moderate	Moderate
Traisrisilp *et al.*,2015	Low	High	Low	Low	Low	Low

Low: low risk of bias, Moderate: moderate risk of bias, High: high risk of bias.