



Universiteit
Leiden
The Netherlands

The placenta in fetal congenital heart disease

Snoep, M.C.

Citation

Snoep, M. C. (2025, September 23). *The placenta in fetal congenital heart disease*. Retrieved from <https://hdl.handle.net/1887/4262055>

Version: Publisher's Version

License: [Licence agreement concerning inclusion of doctoral thesis in the Institutional Repository of the University of Leiden](#)

Downloaded from: <https://hdl.handle.net/1887/4262055>

Note: To cite this publication please use the final published version (if applicable).



CHAPTER 6

Factors related to fetal demise in cases with congenital heart defects

Published AJOG MFM 2023 Aug;5(8):101023.

Maartje C. Snoep¹, Bo B. Bet², Fleur Zwanenburg¹, Ingmar Knobbe³,
Ingeborg H. Linskens², Eva Pajkrt², Lieke Rozendaal³,
Lotte E. van der Meeren^{4,5}, Sally-Ann Clur⁶, Monique C. Haak¹

¹ *Department of Obstetrics and Fetal Medicine, Leiden University Medical Center, Leiden, The Netherlands*

² *Department of Obstetrics and Fetal Medicine, Amsterdam University Medical Center, Amsterdam, The Netherlands*

³ *Department of Pediatric Cardiology, Leiden University Medical Center, Leiden, The Netherlands*

⁴ *Department of Pathology, Leiden University Medical Center, Leiden, The Netherlands*

⁵ *Department of Pathology, Erasmus Medical Center, Rotterdam, The Netherlands*

⁶ *Department of Pediatric Cardiology, Amsterdam University Medical Center, Amsterdam, The Netherlands*

ABSTRACT

Background

Congenital heart defects (CHD) are the most common congenital anomaly. Despite the increasing survival of these children, there is still an increased incidence of fetal demise, frequently attributed to cardiac failure. As abnormal placental development has been described in CHD, our hypothesis is that placenta insufficiency may contribute to fetal death in CHD.

Objectives

The aim of this study is to assess cases with fetal CHD and intra uterine demise, and analyze factors that are related to the demise.

Study design

All CHD cases diagnosed prenatally in the period January 2002– January 2021 were selected from the regional prospective CHD registry PRECOR. Multiple pregnancies and pregnancies with fetal trisomy 13/18, triploidy and Turner's syndrome were excluded from the analysis, as fetal demise is attributed to the chromosomal abnormality in these cases. Cases were categorized into four groups based on the possible cause of fetal death: cardiac failure, additional (genetic) diagnosis, placental insufficiency and a group in which no cause was found. A separate analysis was performed for isolated CHD cases.

Results

Of the 4806 cases in the PRECOR registry, 112 had fetal demise, of which 43 were excluded from the analysis (13 multiple pregnancies, 30 genetic). Of these, 47.8% were most likely related to cardiac failure, 42.0% to another (genetic) diagnosis and 10.1% to placental insufficiency. No cases were allocated to the group with an unknown cause. Only 47.8% of the cases had isolated CHD and in this group 21.2% was most likely related to placental insufficiency.

Conclusions

This study shows that in addition to cardiac failure and other (genetic) diagnoses, placental factors play an important role in fetal demise in CHD, especially in cases of isolated heart defects. Thus, these findings support the importance of regular ultrasonographic assessment of fetal growth and placental function in fetal CHD.

INTRODUCTION

Fetal demise in the third trimester occurs in 1-2% of all pregnancies worldwide.^{1,2} The three most important factors related to fetal demise are the presence of a congenital anomaly, a genetic diagnosis and placental insufficiency.¹⁻⁸ In 8-14% the intra-uterine fetal demise occurs concurrently with a congenital anomaly.^{1,9} Congenital heart defects (CHD) are the most common congenital anomaly, with an incidence of 5-8 per thousand livebirths.^{10,11}

The incidence of CHD in cases with fetal demise is more than ten times the incidence of CHD in the liveborn population.⁹ In fetuses with CHD, intra-uterine death is frequently attributed to cardiac failure, as in some major CHDs an imbalance in the fetal circulation can result in hydrops and demise.^{9,12-14} Atrioventricular septal defects (AVSD) and Ebstein's anomaly are CHDs known to cause atrioventricular (AV) regurgitation with subsequent development of hydrops and demise.^{9,12,15,16} However, fetal demise is also described in cardiac diagnosis such as small ventricular septal defects (VSD), where fetal cardiac failure is not expected.⁹

In addition to congenital defects, abnormal placental development plays an important role in fetal demise, resulting in fetal growth restriction (FGR), pre-eclampsia (PE) and pregnancy-induced hypertension (PIH).^{1,17} As CHD is associated with abnormal development of the placenta and FGR, PE and PIH^{18-22,24}, placental insufficiency may contribute to fetal demise in CHD as well.

The aim of this study is to gain more knowledge on the suspected cause fetal demise in CHD cases. We hypothesize that a significant amount of fetal demise in CHD cases can be attributed to cardiac failure or an underlying genetic abnormality. Based on the association between abnormal development of the placenta and CHD, we hypothesize that placental insufficiency might be a third important contributing factor to fetal demise in CHD.

METHODS

Patient selection

Cases with CHD and fetal demise were identified in the PRECOR-registry in The Netherlands. This registry prospectively includes all fetal and neonatal cases with severe CHD (defined as the need for surgery or therapeutic intervention in the first year of life) from the Center for Heart Abnormalities Amsterdam-Leiden (CAHAL), including two academic hospitals (Amsterdam University Medical Center and Leiden University Medical Centre) from January 2002-January 2022. Cases with fetal arrhythmia are not included. The methodology of the data collection for this registry has been described previously.²⁴

Fetal demise was defined as intra-uterine fetal death after 16+0 weeks of gestation. Multiple pregnancies were excluded. Fetuses with both hydrops in early second trimester and a diagnosis of trisomy 13, trisomy 18, triploidy or Turner's syndrome were excluded, as fetal demise is attributed to the chromosomal abnormality in these cases. Fetuses with other genetic diagnosis were included in this study.

Although it is known that fetal demise in trisomy 21 frequently occurs after a gestational age of 16 weeks^{25,26}, the reason for that is not entirely clear. Unlike in trisomy 13, trisomy 18, triploidy and Turner's syndrome, fetal demise in trisomy 21 is not per definition attributed to the chromosomal abnormality and the underlying CHD could play a role in the demise. Therefore, we included cases with trisomy 21 in our analysis.

Data collection

After identification of cases, additional data on cardiac diagnosis, maternal characteristics (age, parity, medical history, obstetric history), fetal characteristics (gender, fetal growth, extra-cardiac malformations, hydrops, Doppler indices during fetal ultrasound, genetic test results), data on the course of pregnancy (gestational age of fetal death, pregnancy complications) and post-mortem examinations (laboratory reports, autopsy reports, placental pathology reports) were collected from electronic patient files. Fetal cardiac diagnoses were categorized as previously described.²³

Cause of death in stillbirth can be classified following the American Medical Association¹, which is however too extensive for this cohort. We used and adapted this method to make a differentiation between genetic and structural causes of death. Therefore, we categorized our cases into four groups based on factors that might have contributed to the fetal death. Allocation into these groups were made by consensus (MS, FZ, MH).

The first group consisted of patients with signs of cardiac decompensation, defined as the presence hydrops (an accumulation of fluid in at least two fetal compartments) and/or Doppler examinations of the AV-valves suggesting cardiac failure based on severe AV-regurgitation (>50% regurgitant color jet).

The second group included cases in which an additional congenital/genetic anomaly was present, defined as the presence of a genetic abnormality and/or another severe extracardiac diagnosis that could lead to fetal demise. In cases in which cardiac decompensation and/or placental insufficiency was present related to an underlying (genetic) syndrome, the case was allocated to this group. In cases with a genetic syndrome, it is known that hydrops in the first trimester of pregnancy is often the result of abnormal lymphatic development rather than cardiac failure.²⁷⁻²⁹ In these fetuses, development of the lymphatic system is altered, causing delayed connection to the venous circulation, resulting in (nuchal) skin effusion and hydrops. Therefore, we

allocated these cases to the group of genetic/extracardiac diagnoses as the suspected cause of demise, especially because AV-regurgitation was absent.

The third group included cases with signs of placental insufficiency, defined as growth restriction with doppler abnormalities and/or histological placenta abnormalities. Cases allocated to this group showed either FGR (defined as estimated fetal weight or birthweight below the 10th percentile) AND the presence of Doppler flow velocity wave forms fitting with the diagnosis FGR (defined as a pulsatility index of the umbilical artery above the 95th percentile AND a cerebroplacental ratio below the 5th percentile). In addition, cases in which overt placenta abnormalities that were related to the fetal demise were described in the placental histological examination reports were included in this group. Placenta pathological examinations were performed according to the standardized Amsterdam Protocol³⁰. If available, placenta histology results were described in this group. Maternal vascular malperfusion was present in cases in which infarction(s) and/or ischemia was described. Fetal vascular malperfusion was present in cases in with fetal thrombosis. Inflammation was present in cases in which maternal inflammatory lesions were described.

The fourth group consisted of cases with a miscellaneous CHD and cases in which the fetal demise could not be attributed to cardiac failure, extracardiac malformations/genetic diagnoses and/or placental insufficiency.

Additionally, to exclude the effects of extracardiac and/or genetic abnormalities, a separate analysis was performed on pregnancy outcomes for isolated CHD cases. In this analysis, only cases without additional extra cardiac structural anomalies and additional genetic diagnosis are included.

Statistical analysis

Categorical data are presented as numbers and percentages (n,%). Fisher's exact tests and independent sample t-tests are used where appropriate. Missing data are described and analyzed. All statistical analyses were performed using IBM SPSS Statistics 25.0.0.2 (IBM, Armonk, NY, USA).

RESULTS

Case selection

In total, 112 cases with fetal demise between January 2002 and January 2022 were extracted from the PRECOR registry (n = 4806 cases). Forty-three cases were excluded: 13 multiples and 30 with a diagnosis of trisomy 13, trisomy 18, triploidy or Turner's syndrome with hydrops in the early second trimester (Figure 1). This resulted in 69 cases eligible for analysis, corresponding with an incidence of fetal demise of 1.5% for singleton CHD cases without the above described aneuploidies.

Table 1: Baseline characteristics of included cases (n=69)

n, %	Fetal death related to cardiac decompensation n = 33	Fetal death related to another (genetic) diagnosis n = 29	Fetal death related to placental insufficiency n = 7
Gestational age at time of fetal death			
16 – 24 weeks	10 (30.3)	9 (31.0)	2 (33.3)
24 – 32 weeks	14 (42.4)	10 (34.5)	4 (50.0)
32 – 40 weeks	8 (24.2)	10 (34.5)	1 (16.7)
> 40 weeks	1 (3.0)	0 (0)	0 (0)
Estimated fetal weight or birthweight <10 th percentile	8/31 (25.8)	15/27 (55.6)	6 (85.7)
Presence of extracardiac fetal diagnosis	7 (21.2)	19 (65.5)	0 (0)
Presence of genetic diagnosis	Genetic testing, n = 21	Genetic testing, n = 25	Genetic testing, n = 4
Trisomy 21	0 (0)	13 (52.0)	0 (0)
Noonan's syndrome	0 (0)	2 (8.0)	0 (0)
Other genetic diagnosis	0 (0)	6 (24.0)	0 (0)
Total	0 (0)	21 (84.0)	0 (0)
Presence of hydrops	22 (66.7)	8 (27.6)	0 (0)
Presence of AV-regurgitation	13 (39.4)	0 (0)	0 (0)

Characteristics of study subjects

Patient characteristics are shown in Table 1. In 33 (47.8%) cases, signs of cardiac decompensation were present: hydrops in 22 (66.7%) and/or AV-regurgitation in 13 (39.4%). The cardiac diagnoses in this group comprised of AVSD (n = 3, 9.1%, balanced, n = 4, 12.1% unbalanced), hypoplastic heart syndrome (HLHS) with AV-regurgitation (n = 4, 12.1%) and atrioventricular valve abnormalities (n = 9, 27.3%), including Ebstein's anomaly (n = 4, 12.1%), tricuspid valve dysplasia/stenosis (n = 2, 6.1%) and mitral valve dysplasia/stenosis (n = 3, 9.1%) (Table 2). The group with signs of cardiac failure included two cases with Tetralogy of Fallot (ToF) with hydrops from early in pregnancy onwards but without a genetic diagnosis. One of these had AV-regurgitation, in the absence of a chromosomal abnormality or signs of placental insufficiency. Genetic testing was performed in only 21 cases (63.6%) in the cardiac decompensation group, none had an abnormal genetic diagnosis (20 on quantitative fluorescence (QF)-PCR and single nucleotide polymorphism (SNP)-array, including Whole Exome Sequencing (WES)). Eight cases (25.8%) in the group with cardiac failure diagnoses had FGR, these cases did not show Doppler abnormalities and had normal histological placental examinations (where available). In the group with cardiac failure, 7 cases (21.2%) had minor extracardiac malformations, including minor congenital abnormalities of the urinary and/or genital tract and hemivertebrae.

Table 2: Cardiac diagnosis per group associated with fetal demise (n = 69)

n (%)	Signs of cardiac decompensation n = 33	Presence of another diagnosis n = 29	Signs of placental insufficiency n = 7
VSD	0 (0)	6 (20.7)	5 (71.4)
AVSD, balanced	3 (9.1)	4 (13.8)	0 (0)
Unbalanced AVSD	4 (12.1)	6 (20.7)	0 (0)
Pulmonary valve stenosis	1 (3.0)	1 (3.4)	0 (0)
Aortic valve stenosis	1 (3.0)	1 (3.4)	0 (0)
Atrioventricular valve dysplasia/stenosis/regurgitation‡	9 (27.3)	0 (0)	0 (0)
Totally/partially abnormal pulmonary venous return	0 (0)	0 (0)	0 (0)
Coarctation of aorta	1 (3.0)	1 (3.4)	1 (14.3)
HLHS	4 (12.1)	0 (0)	0 (0)
ToF	2 (6.1)	1 (3.4)	1 (14.3)
DORV (Fallot-type)	2 (6.1)	3 (10.3)	0 (0)
Transposition of the great arteries, simple	0 (0)	0 (0)	0 (0)
Transposition of the great arteries, complex†	0 (0)	1 (3.4)	0 (0)
Truncus arteriosus	2 (6.1)	0 (0)	0 (0)
Pulmonary atresia with VSD	1 (3.0)	1 (3.4)	0 (0)
Tricuspid valve atresia	2 (6.1)	0 (0)	0 (0)
Other complex anomaly	1 (3.0)	4 (13.8)	0 (0)

VSD = ventricular septal defect, AVSD = atrial ventricular septal defect, HLHS = hypoplastic left heart syndrome, ToF = Tetralogy of Fallot, DORV = double outlet right ventricle.

‡ Including Ebstein's anomaly

† Transposition of the great arteries with significant VSD and/or DORV or pulmonary stenosis

In 42.0% of the cases (n=29), the fetal demise was most likely related to another extracardiac diagnosis or a genetic diagnosis (other than trisomy 13, trisomy 18, triploidy and Turner's syndrome) (Table 1). Cardiac diagnoses in this group included VSD (n = 6, 20.7%), AVSD (n = 4, 13.8% balanced, n = 6, 20.7% unbalanced), double outlet right ventricle (DORV) (n = 3, 10.3%) and other complex heart defects in conjunction with the genetic syndrome (n = 4, 13.8%) (Table 2). Hydrops (mainly skin edema in early pregnancy) without AV-regurgitation was present in 8 cases (27.6%). In these cases, hydrops was attributed to the underlying (genetic) syndrome. As previously described, especially in the absence of AV-regurgitation, hydrops in the first trimester of pregnancies with a genetic syndrome is often a result of abnormal lymphatic development rather than cardiac failure.^{27,29} In the group of cases in which the fetal demise was most likely related to another diagnosis, 24 cases (86.2%) underwent genetic testing (13 QF-PCR,

6 QF-PCR + SNP-array, 5 expanded with WES), of which 21 (84.0%) were abnormal. The most common genetic diagnosis was trisomy 21 ($n = 13$, 52.0%), of which none showed AV-regurgitation after 16 weeks. Two cases (8.0%) had Noonan's syndrome and 6 cases (24.0%) had another genetic diagnosis (four other chromosomal abnormalities, two gene mutations). In 19 cases (65.5%), there was an extracardiac diagnosis and in eight cases (27.6%), there was no genetic diagnosis present and the fetal demise was most likely related to multiple extracardiac diagnoses, including intracranial abnormalities, spina bifida, large omphalocele and/or kidney abnormalities.

Seven cases (10.1%) of the total cohort had signs of placental insufficiency in the absence of cardiac failure and/or an extracardiac/genetic diagnosis, and were therefore allocated to the third group (Table 1). In six of seven cases, extensive placenta pathology reports were available, all indicating placenta insufficiency (low placenta weight, maternal/fetal vascular malperfusion, inflammation) (Table 4). Two cases presented with pre-eclampsia. No cases in this group had pre-existent maternal comorbidities nor hypertension and none of the cases had (gestational) diabetes. The one fetus without a placenta pathology report had severe FGR and abnormal Dopplers and was therefore allocated to this group, as the severe FGR and abnormal Dopplers indicate placenta insufficiency. In this group we encountered the following CHD: in 5 cases isolated VSD (71.4%) (3 muscular VSDs, 2 perimembranous VSDs), coarctation of the aorta in one (14.3%) and ToF in one (14.3%) (Table 2). Six fetuses (85.7%) in this group had an estimated fetal weight or birthweight below the 10th percentile. As the cases were referred at different gestational age and as the gestational age at demise differed per case, we could not draw conclusions concerning growth patterns. The 4 cases with demise between 24-40 weeks all had normal growth parameters between 20-23 weeks of gestation, indicating restriction of growth to occur later in pregnancy in these cases. The recognition of specific growth pattern is not possible due to the low number of cases. One fetus in this group had a normal birthweight, was diagnosed with ToF without hydrops or AV-regurgitation and demised at a gestational age of 25 weeks. This case was allocated to this group as extensive placental abnormalities were described in the placental pathology report, indicating severe placental insufficiency. Genetic testing (QF-PCR + SNP-array, no WES) was performed in 57.1% of the cases in this group and all results were normal (Table 1)

No cases were allocated to the fourth group (no identifying cause), as in all cases the fetal demise could be allocated to one of the above mentioned groups.

Isolated congenital heart defects

To exclude the effects of extracardiac and/or genetic abnormalities, we analyzed isolated CHD cases separately ($n = 33$) (Table 3). In isolated CHD, fetal death was most likely related to cardiac decompensation in 26 cases (78.8%) and to placental insufficiency in 7 cases (21.2%). In 19 (57.6%) isolated cases hydrops was present and 12 (36.4%) cases had AV-regurgitation.

Table 3: Pregnancy outcomes in isolated congenital heart defects

n, %	n = 33
Factors associated with fetal demise	
Signs of cardiac decompensation	26 (78.8)
Signs of placental insufficiency	7 (21.2)
Gestational age at time of fetal death	
16 – 24 weeks	11 (33.3)
24 – 32 weeks	15 (45.5)
32 – 40 weeks	6 (18.2)
> 40 weeks	1 (3.0)
Presence of hydrops	19 (57.6)
Presence of AV-regurgitation	12 (36.4)
Estimated fetal weight or birthweight <10 th percentile	13/29 (44.8)

Table 4: Placenta pathology results

Patient	Placenta weight <10 th percentile	Maternal vascular malperfusion	Fetal vascular malperfusion	Inflammation
1	Unknown	Yes	No	Yes
2	Yes	Yes	No	No
3	Yes	Yes	No	Yes
4	Unknown	Yes	No	Yes
5	Yes	Yes	No	No
6	Yes	Yes	Yes	No

DISCUSSION

Principal findings

This cohort study shows that cardiac failure or the presence of an underlying genetic syndrome are most likely the cause of demise in CHD fetuses. We identified, however, a new and important contributing factor to fetal demise in CHD, namely placental insufficiency, as 10.1% of our cases had signs of placental pathology in the absence of cardiac failure and an extracardiac diagnosis.

Results

The most important factor related to fetal death in our CHD cohort is, as expected, cardiac decompensation, as seen in 48% of the cases. The cardiac diagnoses were atrioventricular valve abnormalities, AVSD and HLHS, all in relation with AV-regurgitation and/or hydrops. Divanovic *et al.* describe cardiac failure as a result of severe cardiac regurgitation as well, as this was present in 27% of their CHD cases with fetal demise, similar to the 19% in our study population.¹²

Besides cardiac failure, concurrent (genetic) diagnoses are an important contributor to fetal demise in CHD. The cardiac defects in these group vary widely and included VSD, AVSD, DORV, pulmonary atresia, pulmonary stenosis and other complex heart anomalies, all in the absence of AV-regurgitation. As most of these diagnoses have no or minimal hemodynamic consequences in the fetal period, demise in these cases is mostly not the result of cardiac failure. None of our cases with trisomy 21 had AV-regurgitation and therefore the demise in these cases was not attributed to cardiac failure. Cardiac diagnoses in these cases were VSD, AVSD and DORV. Though abnormal cardiac function is described in fetus with trisomy 21³¹, the suspected cause of the demise was most likely related to the underlying syndrome and the additional developmental problems, such as extracardiac malformations and/or altered development of the lymphatic system causing fetal hydrops. Especially in trisomy 21, AV-regurgitation and abnormal peripheral Dopplers do not necessarily indicate heart failure as a cause of the demise.

Although decompensation and genetic syndromes were expected at the found rate, the number of cases with placental pathology was surprisingly high, as in 10.1% of all CHD cases with fetal demise and in 21.2% of the isolated CHD cases with fetal demise, signs of placental insufficiency were described. The cardiac diagnoses in this group had no association with cardiac failure (isolated VSD, coarctation, ToF). Strikingly, all *isolated* CHD cases without signs of cardiac failure did have signs of abnormal placental function and/or histological development. Fetal death in these cases is therefore most likely correlated with placental insufficiency.

This study furthermore confirms the earlier described increased prevalence of fetal demise in CHD compared to the overall population.^{9,12} In The Netherlands, the incidence of fetal demise after a gestational age of 22 weeks is 0.44%³², whilst the incidence of fetal demise in our CHD population, excluding fetal trisomy 13, trisomy 18, triploidy and Turner's syndrome, was 1.4% (69 per 4806 cases). The fact that we identified a relatively high percentage of fetal demise related to placenta insufficiency, fits with the finding that placenta-related complications are more common in cases with fetal CHD.^{18,20,22} The latter corresponds with previous studies, in which abnormal placentation, especially in terms of maternal and vascular malperfusion, is described.^{22,24,33} This supports our hypothesis that common embryological or environmental factors could affect the development of both the fetal heart and the placenta. As CHD is known to be associated with impaired vascular placental development, we hypothesize that impaired placenta function is an important contributor to adverse outcomes in fetal CHD.²²

Clinical implications

As fetal demise in CHD is not per definition related to the heart defect, it is important to systematically assess the cause of the demise, and not too easily attribute the demise to the heart defect in itself. As placenta insufficiency can play a role, histological placental examination is important for the identification of the cause of demise. Physicians should

emphasize the importance of placental pathology examinations and encourage parents to provide consent to these non-invasive examinations, especially in isolated cases with an unknown cause of death. In addition, it is important to distinguish between maternal or fetal malperfusion in placenta pathology examinations, in order to get a better understanding of the placenta function and the cause of the demise. Information on placenta function in pregnancies with fetal demise is moreover important for future pregnancies, as it may influence clinical management and monitoring for both the mother and subsequent fetuses. In addition, our results suggest an indication for regular assessment of fetal growth and Doppler flows (in particular of the umbilical artery), in order to monitor placental function in cases with fetal CHD.

Research implications

To assess the effect of abnormal placenta function on pregnancy outcomes and fetal demise, future studies should focus on placental (vascular) development in CHD cases. An association between fetal CHD, placental development, angiogenic expression and neurodevelopment has previously been suggested.²² To get a better understanding of this causal pathway, it is important to connect placental development to pregnancy outcomes and neurodevelopmental outcomes in CHD cases. It is furthermore important to distinguish whether the demise is related to the maternal side or the fetal side of the placenta.

Strengths and limitations

Strengths

The cases included in this study were retrieved from a large regional cohort, with prospective entry of all cases. A strength of this study is therefore the improbability of selection bias, as there are no missing cases. In addition, the cohort consists of a relatively large case series of demised fetuses.

Limitations

The first limitation of this study is that standardized fetal and maternal postmortem examination and a placenta pathology evaluation were not always available. Placental pathology reports were available in only 25/69 (36.2%) of the cases in our study and were especially missing in cases where clinicians attributed the fetal demise to cardiac decompensation or a genetic abnormality. In addition, pathological examination reports on the demised fetus was present in only three (4.3%) of the cases. As previously stated, histological placental examination after birth and pathological examination of the demised fetus is important for the identification of the cause of the fetal demise.

Although the PRECOR-registry is a prospective registry at time entry of the cases in the database, some of the data were retrieved of the patient charts, which is a second limitation of this study. Data on birthweight were frequently not reported in the registry

and the patient files ($n = 4$, 5.8%). In addition, the separate analysis on isolated CHD cases included a small group, with limited pathology examinations and genetic analysis. Another limitation of this study is that cases were included during a large period of time, in which genetic testing has greatly expanded. Although a SNP-array was performed in the majority of the cases with genetic testing ($n = 30$), Whole Exome Sequencing (WES) was not performed in most cases. WES is a technique that identifies single-gene abnormalities and was introduced rapidly in the last years, therefore, it was only performed in 6/69 (8.7%) of the cases in our study.^{34,35} It is therefore possible that cases included in this study that were considered as isolated CHD, may have actually had a single gene disorder. We expect that this did not influence the number of cases in which fetal demise was allocated to placental insufficiency, as each case in this group had evident signs of placental insufficiency on fetal ultrasound and/or placental pathology examinations.

Conclusions

Fetal demise in CHD is most frequently related to cardiac failure or the presence of a genetic syndrome. The remaining cases, however, all have signs of abnormal placental function and/or histology. Placenta insufficiency is therefore an important contributing factor to fetal demise in CHD cases. In cases with fetal CHD, physicians should implement regular assessment of fetal growth and Doppler flows to monitor placental function. Future research should focus on placental (vascular) development in CHD cases, to assess the effect of abnormal placenta function on pregnancy outcomes and fetal demise.

REFERENCES

- Stillbirth Collaborative Research Network Writing G. Causes of death among stillbirths. *JAMA* 2011;306(22):2459-68.
- Collaborators GBDCM. Global, regional, national, and selected subnational levels of stillbirths, neonatal, infant, and under-5 mortality, 1980-2015: a systematic analysis for the Global Burden of Disease Study 2015. *Lancet* 2016;388(10053):1725-74.
- Fretts RC, Boyd ME, Usher RH, Usher HA. The changing pattern of fetal death, 1961-1988. *Obstet Gynecol* 1992;79(1):35-9.
- Goldenberg RL, Kirby R, Culhane JF. Stillbirth: a review. *J Matern Fetal Neonatal Med* 2004;16(2):79-94.
- Pauli RM, Reiser CA, Lebovitz RM, Kirkpatrick SJ. Wisconsin Stillbirth Service Program: I. Establishment and assessment of a community-based program for etiologic investigation of intrauterine deaths. *Am J Med Genet* 1994;50(2):116-34.
- Petersson K, Bremme K, Bottinga R, *et al.* Diagnostic evaluation of intrauterine fetal deaths in Stockholm 1998-99. *Acta Obstet Gynecol Scand* 2002;81(4):284-92.
- Silver RM. Fetal death. *Obstet Gynecol* 2007;109(1):153-67.
- Varli IH, Petersson K, Bottinga R, *et al.* The Stockholm classification of stillbirth. *Acta Obstet Gynecol Scand* 2008;87(11):1202-12.
- Jorgensen M, McPherson E, Zaleski C, Shivaram P, Cold C. Stillbirth: the heart of the matter. *Am J Med Genet A* 2014;164A(3):691-9.
- Dolk H, Loane M, Garne E. The prevalence of congenital anomalies in Europe. *Adv Exp Med Biol* 2010;686:349-64.
- Hoffman JL, Kaplan S. The incidence of congenital heart disease. *J Am Coll Cardiol* 2002;39(12):1890-900.
- Divanovic A, Bowers K, Michelfelder E, *et al.* Intrauterine fetal demise after prenatal diagnosis of congenital heart disease: assessment of risk. *Prenat Diagn* 2016;36(2):142-7.
- Santo S, Mansour S, Thilaganathan B, Homfray T, Papageorgiou A, Calvert S, Bhide A. Prenatal diagnosis of non-immune hydrops fetalis: what do we tell the parents? *Prenat Diagn* 2011;31(2):186-95.
- Bellini C, Hennekam RC. Non-immune hydrops fetalis: a short review of etiology and pathophysiology. *Am J Med Genet A* 2012;158A(3):597-605.
- Freud LR, Escobar-Diaz MC, Kalish BT, *et al.* Outcomes and Predictors of Perinatal Mortality in Fetuses With Ebstein Anomaly or Tricuspid Valve Dysplasia in the Current Era: A Multi-center Study. *Circulation* 2015;132(6):481-9.
- Craig B. Atrioventricular septal defect: from fetus to adult. *Heart* 2006;92(12):1879-85.
- Korteweg FJ, Erwich J, Holm JP, Ravise JM, van der Meer J, Veeger N, Timmer A. Diverse placental pathologies as the main causes of fetal death. *Obstet Gynecol* 2009;114(4):809-17.
- Auger N, Fraser WD, Healy-Profitts J, Arbour L. Association Between Preeclampsia and Congenital Heart Defects. *JAMA* 2015;314(15):1588-98.
- Rosenthal GL. Patterns of prenatal growth among infants with cardiovascular malformations: possible fetal hemodynamic effects. *Am J Epidemiol* 1996;143(5):505-13.
- Boyd HA, Basit S, Behrens I, *et al.* Association Between Fetal Congenital Heart Defects and Maternal Risk of Hypertensive Disorders of Pregnancy in the Same Pregnancy and Across Pregnancies. *Circulation* 2017;136(1):39-48.
- Ghanchi A, Derridj N, Bonnet D, Bertille N, Salomon LJ, Khoshnood B. Children Born with Congenital Heart Defects and Growth Restriction at Birth: A Systematic Review and Meta-Analysis. *Int J Environ Res Public Health* 2020;17(9).
- Snoep MC, Aliasi M, van der Meeren LE, Jongbloed MRM, DeRuiter MC, Haak MC. Placenta morphology and biomarkers in pregnancies with congenital heart disease - A systematic review. *Placenta* 2021;112:189-96.
- 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.
- Mirembert H, Gindes L, Schreiber L, *et al.* The association between severe fetal congenital heart defects and placental vascular malperfusion lesions. *Prenat Diagn* 2019;39(11):962-7.
- Sparks TN, Griffin E, Page J, Pilliod R, Shaffer BL, Caughey AB. Down syndrome: perinatal mortality risks with each additional week of expectant management. *Prenat Diagn* 2016;36(4):368-74.
- Won RH, Currier RJ, Lorey F, Townner DR. The timing of demise in fetuses with trisomy 21 and trisomy 18. *Prenat Diagn* 2005;25(7):608-11.

27. Haak MC, Bartelings MM, Jackson DG, Webb S, van Vugt JM, Gittenberger-de Groot AC. Increased nuchal translucency is associated with jugular lymphatic distension. *Hum Reprod* 2002;17(4):1086-92.
28. Haak MC, Twisk JW, Bartelings MM, Gittenberger-de Groot AC, van Vugt JM. First-trimester fetuses with increased nuchal translucency do not show altered intracardiac flow velocities. *Ultrasound Obstet Gynecol* 2005;25(3):246-52.
29. Haak MC, van Vugt JM. Pathophysiology of increased nuchal translucency: a review of the literature. *Hum Reprod Update* 2003;9(2):175-84.
30. Khong TY, Mooney EE, Ariel I, *et al.* Sampling and Definitions of Placental Lesions: Amsterdam Placental Workshop Group Consensus Statement. *Arch Pathol Lab Med* 2016;140(7):698-713.
31. Clur SA, Oude Rengerink K, Ottenkamp J, Bilar-do CM. Cardiac function in trisomy 21 fetuses. *Ultrasound Obstet Gynecol* 2011;37(2):163-71.
32. Volksgezondheid. Sterfte rond de geboorte (2019). <https://www.vzinfo.nl/sterfte-rond-de-geboorte#:~:text=In%20dit%20onderwerp,-In%20het%20kort,van%2022%20weken%20of%20meer> 7 December 2022.
33. Leon RL, Sharma K, Mir IN, *et al.* Placental vascular malperfusion lesions in fetal congenital heart disease. *AJOG* 2022;227(4):620.e1-620.e8.
34. Sevim Bayrak C, Zhang P, Tristani-Firouzi M, Gelb BD, Itan Y. De novo variants in exomes of congenital heart disease patients identify risk genes and pathways. *Genome Med* 2020;12(1):9.
35. Homsy J, Zaidi S, Shen Y, *et al.* De novo mutations in congenital heart disease with neurodevelopmental and other congenital anomalies. *Science* 2015;350(6265):1262-6.

