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Maartje C. Snoep, MD; Bo B. Bet, MD; Fleur Zwanenburg, MD; Ingmar Knobbe, MD; Ingeborg H. Linskens, MD, PhD; Eva Pajkrt, MD, PhD; Lieke Rozendaal, MD; Lotte E. Van der Meeren, MD, PhD; Sally-Ann Clur, MD, PhD; Monique C. Haak, MD, PhD

BACKGROUND: Congenital heart defects 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. Considering that abnormal placental development has been described in congenital heart disease, our hypothesis is that placental insufficiency may contribute to fetal death in congenital heart disease.

OBJECTIVE: This study aimed to assess cases with fetal congenital heart disease and intrauterine demise, and analyze factors that are related to the demise.

STUDY DESIGN: All congenital heart disease cases diagnosed prenatally during the period January 2002 to January 2021 were selected from the regional prospective congenital heart disease registry, PRECOR. Multiple pregnancies and pregnancies with fetal trisomy 13 or 18, triploidy, and Turner's syndrome were excluded from the analysis, because fetal demise is attributed to the chromosomal abnormality in these cases. Cases were categorized into 4 groups based on the possible cause of fetal death as follows: cardiac failure, additional (genetic) diagnosis, placental insufficiency, and a group in which no cause was found. A separate analysis was performed for isolated congenital heart disease 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 congenital heart disease, and in this group 21.2% was most likely related to placental insufficiency.

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

Key words: congenital heart disease, fetal demise, placenta, stillbirth

Introduction

Fetal demise in the third trimester occurs in 1% to 2% of all pregnancies worldwide.[1,2] The 3 most important factors related to fetal demise are the presence of a congenital anomaly, a genetic diagnosis, and placental insufficiency.[1−8] In 8% to 14%, the intrauterine fetal demise occurs concurrently with a congenital anomaly.[1,9] CHDs are the most common congenital anomaly, with an incidence of 5 to 8 per thousand livebirths.[10,11]

The incidence of CHD in cases with fetal demise is more than 10 times the incidence of CHD in the liveborn population.[9] In fetuses with CHD, intrauterine death is frequently attributed to cardiac failure, because 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 play an important role in fetal demise, resulting in fetal growth restriction (FGR), preeclampsia (PE) and pregnancy-induced hypertension (PIH).[1,17] Considering that CHD is associated with abnormal development of the placenta and FGR, PE, and PIH,[18−22,23] placental insufficiency may contribute to fetal demise in CHD as well.

This study aimed to gain more knowledge about the suspected cause of 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.

Materials and 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, including 2 academic hospitals (Amsterdam University Medical Center and Leiden University Medical Centre) from January 2002 to January 2022. Cases with fetal arrhythmia are not included. The methodology

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AJOG MFM at a Glance

Why was this study conducted?

Fetal demise is more common in fetal congenital heart disease (CHD) and frequently attributed to cardiac failure in these cases. Placental insufficiency is described in pregnancies with fetal CHD and may therefore be a cause of stillbirth in these cases as well.

Key findings

In addition to cardiac failure and other (genetic) diagnoses, placental insufficiency is identified as an important suspected cause of stillbirth in fetal CHD. This corresponds to the previously described impaired vascular placental development in fetal CHD.

What does this add to what is known?

Placental insufficiency is an important contributing factor to fetal demise in CHD. Physicians should be aware of this cause of stillbirth, especially in isolated CHD cases. Physicians should implement regular assessment of fetal growth and Doppler flows to monitor placental function in fetal CHD.

of the data collection for this registry has been described previously.[23]

Fetal demise was defined as intrauterine 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 syndrome were excluded, because 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,[24,25] the reason for that is not entirely clear. Unlike in trisomy 13, trisomy 18, triploidy and Turner 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, and obstetrical history), fetal characteristics (gender, fetal growth, extracardiac malformations, hydrops, Doppler indices during fetal ultrasound, and genetic test results), data on the course of pregnancy (gestational age of fetal death and pregnancy complications) and postmortem examinations (laboratory reports, autopsy reports, and placental pathology reports) were collected from electronic patient files. Fetal cardiac diagnoses were categorized as previously described.[26]

Cause of death in stillbirth can be classified following the American Medical Association,[1] 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 4 groups based on factors that might have contributed to the fetal death. Allocation into these groups were made by consensus of 3 authors (M.C.S., F.Z., and M.C.H.).

The first group consisted of patients with signs of cardiac decompensation, defined as the presence hydrops (an accumulation of fluid in at least 2 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 or 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 or 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 histologic 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 placental abnormalities that were related to the fetal demise were described in the placental histologic examination reports were included in this group. Placental pathologic examinations were performed according to the standardized Amsterdam Protocol.[30] If available, placental histology results were described in this group. Maternal vascular malperfusion was present in cases in which infarction(s) and/or ischemia were described. Fetal vascular malperfusion was present in cases 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 or genetic diagnoses, and/or placental insufficiency.

In addition, 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 extracardiac structural anomalies and additional genetic diagnosis are included.

Statistical analysis

Categorical data are presented as numbers and percentages. Fisher exact tests and independent sample *t* tests are used where appropriate. Missing data were described and analyzed. All statistical analyses were performed using IBM SPSS Statistics 25.0.0.2 (IBM Corp, Armonk, NY).

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 syndrome with hydrops in the early second trimester (Figure). 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.

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 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 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 2 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 polymerase chain reaction [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 histologic 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.

FIGURE
Flowchart of included cases with fetal demise

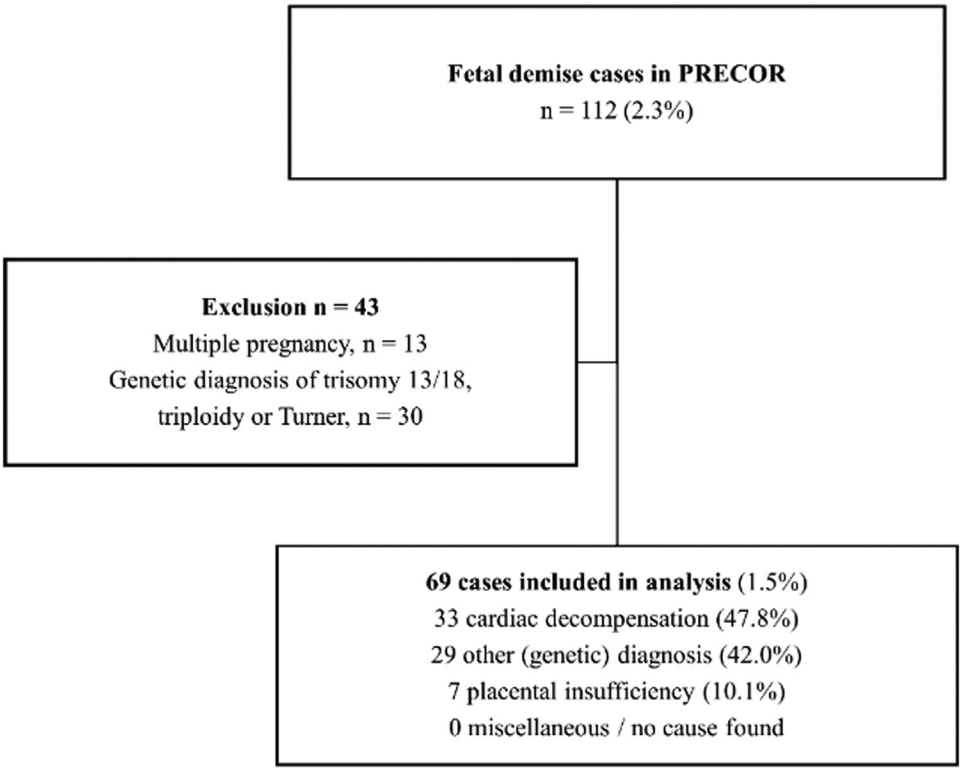

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TABLE 1
Baseline characteristics of included cases (N=69)

Characteristics	Fetal death related to cardiac decompensation, n=33, n (%)	Fetal death related to another (genetic) diagnosis, n=29, n (%)	Fetal death related to placental insufficiency, n=7, n (%),
Gestational age at time of fetal death			
16–24 wk	10 (30.3)	9 (31.0)	2 (33.3)
24–32 wk	14 (42.4)	10 (34.5)	4 (50.0)
32–40 wk	8 (24.2)	10 (34.5)	1 (16.7)
>40 wk	1 (3.0)	0 (0)	0 (0)
Estimated fetal weight or birthweight <10th 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 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)

AV, atrioventricular.

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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 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, and 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 syndrome and 6 cases (24.0%) had another genetic diagnosis (4 other chromosomal abnormalities and 2 gene mutations). In 19 cases (65.5%), there was an extracardiac diagnosis; and in 8 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 or genetic diagnosis, and were therefore allocated to the third group (Table 1). In 6 of 7 cases, extensive placental pathology reports were available, all indicating placental insufficiency (low placental weight, maternal/fetal vascular malperfusion, and inflammation) (Table 3). Two cases presented with preeclampsia. No cases in this group had preexistent maternal comorbidities nor hypertension and none of the cases had (gestational) diabetes. The 1 fetus without a placental pathology report had severe FGR and abnormal Dopplers and was therefore allocated to this group, because the severe FGR and abnormal Dopplers indicate placental insufficiency. In this group we encountered the following CHD: in 5 (71.4%) cases isolated VSD (3 muscular VSDs, 2 perimembranous VSDs), coarctation of the aorta in 1 (14.3%), and ToF in 1 (14.3%) (Table 2). Six fetuses (85.7%) in this group had an estimated fetal weight or birthweight below the 10th percentile. Considering that the cases were referred at different gestational age and because the gestational age at demise differed per case, we could not draw conclusions concerning growth patterns. The 4 cases with demise between 24 and 40 weeks had normal growth parameters between 20 and 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 because of the low number of cases. One fetus in this

TABLE 2
Cardiac diagnosis per group associated with fetal demise (N=69)

Characteristics	Signs of cardiac decompensation n=33, n (%)	Presence of another diagnosis n=29, n (%)	Signs of placental insufficiency n=7, n (%)
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[a]	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[b]	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)

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

[a] Including Ebstein's anomaly; [b] Transposition of the great arteries with significant VSD and/or DORV or pulmonary stenosis.

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group had a normal birthweight, was diagnosed with ToF without hydrops or AV regurgitation, and died at a gestational age of 25 weeks. This case was allocated to this group because 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), because 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 4). 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.

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. However, we identified, a new and important contributing factor to fetal demise in CHD, namely placental insufficiency, because 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[12] describe cardiac failure as a result of severe cardiac regurgitation as well, because 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 important contributors 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. Considering that 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.

TABLE 3
Placental pathology results

Patient	Placental weight <10th 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

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Though abnormal cardiac function is described in fetus with trisomy 21,[31] 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, because 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, and ToF). Strikingly, all isolated CHD cases without signs of cardiac failure did have signs of abnormal placental function and/or histologic 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 with the overall population.[9,12] In the Netherlands, the incidence of fetal demise after a gestational age of 22 weeks is 0.44%,[32] whereas the incidence of fetal demise in our CHD population, excluding fetal trisomy 13, trisomy 18, triploidy, and Turner syndrome was 1.4% (69 per 4806 cases). The fact that we identified a relatively high percentage of fetal demise related to placental 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.[22,23,33] This supports our hypothesis that common embryologic or environmental factors could affect the development of both the fetal heart and the placenta. Considering that CHD is known to be associated with impaired vascular placental development, we hypothesize that impaired placental function is an important contributor to adverse outcomes in fetal CHD.[22]

TABLE 4
Pregnancy outcomes in isolated congenital heart defects

Characteristics	N=33, n (%)
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 wk	11 (33.3)
24–32 wk	15 (45.5)
32–40 wk	6 (18.2)
>40 wk	1 (3.0)
Presence of hydrops	19 (57.6)
Presence of AV regurgitation	12 (36.4)
Estimated fetal weight or birthweight <10th percentile	13/29 (44.8)

AV, atrioventricular.

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Clinical implications

Considering that 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. Given that placental insufficiency can play a role, histologic 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 noninvasive examinations, especially in isolated cases with an unknown cause of death. In addition, it is important to distinguish between maternal or fetal malperfusion in placental pathology

examinations to get a better understanding of the placental function and the cause of the demise. Information on placental function in pregnancies with fetal demise is moreover important for future pregnancies, because 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) to monitor placental function in cases with fetal CHD.

Research implications

To assess the effect of abnormal placental 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. Furthermore, it is 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, because 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 placental pathology evaluation were not always available. Placental pathology reports were available in only 25 of 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, pathologic examination reports on the demised fetus was present in only 3 (4.3%) of the cases. As previously stated, histologic placental examination after birth and pathologic 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 the time entry of the cases in the database, some of the data were retrieved from 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 long 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), WES was not performed in most cases. WES is a technique that identifies single-gene abnormalities and was introduced rapidly in recent years; therefore, it was only performed in 6 of 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, because 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. However,all the remaining cases, have signs of abnormal placental function and/or histology. Placental 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 placental function on pregnancy outcomes and fetal demise. ■

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Author and article information

From the Department of Obstetrics and Fetal Medicine, Leiden University Medical Center, Leiden, The Netherlands (Drs. Snoep, Drs. Zwanenburg, and Prof. Haak); Department of Obstetrics and Fetal Medicine, Amsterdam University Medical Center, Amsterdam, The Netherlands (Drs. Bet, Drs. Linskens, and Prof. Pajkrt); Department of Pediatric Cardiology, Leiden University Medical Center, Leiden, The Netherlands (Drs. Knobbe and Drs. Rozendaal); Department of Pathology, Leiden University Medical Center, Leiden, The Netherlands (Drs. Van der Meeren); Department of Pathology, Erasmus Medical Center, Rotterdam, The Netherlands (Drs. Van der Meeren); Department of Pediatric Cardiology, Amsterdam University Medical Center, Amsterdam, The Netherlands (Drs. Clur).

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In addition to cardiac failure and other (genetic) diagnoses, placental factors play an important role in fetal demise in congenital heart disease.

Corresponding author: Maartje C. Snoep, MD. M.C.Snoep@lumc.nl