CHAPTER 6

Pregnancy Complications in Singleton Pregnancies with Isolated Fetal Heart Defects


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ABSTRACT

Introduction
As the prenatal detection rates of congenital heart defects (CHDs) increase, obstetricians are more frequently faced with pregnancies complicated by a fetal CHD. Congenital anomalies in general are associated with preterm birth and fetal demise. The aim of this study was to gain insight into the prevalence of preterm birth and fetal demise in singleton pregnancies with fetuses with isolated CHDs.

Material and Methods
A geographical cohort study was performed in a large region in the Netherlands. Fetuses and infants from singleton pregnancies diagnosed with severe isolated CHD, born between 1 January 2002 and 1 January 2012, were included. All cases in the CHD cohort were assessed for preterm birth or fetal demise. The proportions of preterm birth and fetal demise were compared to a control group and odds ratios were calculated.

Results
The proportion of preterm births in the CHD cohort (n=1013) was 9.1% [95% confidence interval 7.3-10.9] compared to 5.6% [95% CI 5.4-5.8] in the control group, with an odds ratio of 1.7 [95% CI 1.4-2.1]. The preterm birth started spontaneously in 49.5% and 38.4% were induced. In 15 cases fetal demise occurred (1.5% [95% CI 0.8-2.2]), compared to 0.7% [95% CI 0.6-0.8] in the control group, odds ratio 2.0 [95% CI 1.2-3.4].

Conclusions
Higher rates of preterm birth and fetal demise occur in fetuses with isolated CHD compared to the general population. Prenatal specialists should be vigilant for signs of heart failure, premature closure of the foramen ovale or fetal distress in fetuses with isolated CHDs.
INTRODUCTION

Congenital heart defects (CHDs) affect 6 to 11 per 1000 newborns. 20-30% of CHDs are severe. 1-3 Prenatal detection rates are rising and are presently around 50%. 4-9 Thus, obstetricians are increasingly faced with healthy women, pregnant with a fetus with a severe CHD. A prenatal diagnosis of CHDs contributes significantly to an optimal outcome for the affected infant. It allows for the planning of the delivery in a center with pediatric cardiology and neonatology facilities and assures the appropriate management of the neonate after delivery. 5;10;11 In addition, a diagnosis during pregnancy provides the opportunity to detect additional congenital anomalies and to perform chromosomal analysis. Once all essential information is collected, the parents can be counselled appropriately and, when the diagnosis is made timely, they have the opportunity to decide on the continuation of the pregnancy in severe cases. 10;11 Little is known regarding possible associated obstetric morbidity in cases of fetal CHD. These pregnancies generally develop physiologically due to the presence of the fetal shunts (ductus arteriosus and foramen ovale), and obstetric morbidity is assumed to occur with the same prevalence as in pregnancies without fetal heart defects. 12;13 A preterm birth, however, may cause significant problems in the neonatal period, as surgery has to be postponed until the neonate has an acceptable weight. 13;14 Neonates with severe CHDs born prematurely have higher mortality rates than children born at term. 15-17 If a neonate is preterm and, as a consequence, has a lower birthweight, a lethal situation may arise for some heart defects that would have had a good outcome if the child had been born at term. Even an early term birth between 37 to 38 weeks’ gestation is associated with worse outcomes after neonatal cardiac surgery. 18 It is known that in few cases of fetal heart defects (such as Ebstein’s anomaly, premature closure of the foramen ovale in hypoplastic left heart syndrome 12;19;20) fetal cardiac failure and demise can occur. The overall risk for fetal demise related to isolated CHDs in general, is not known. The knowledge of the prevalence of obstetric complications in pregnancies complicated by fetal CHD is important in the obstetric management and counselling of parents. The primary aim of this study is to gain insight into the prevalence of preterm birth and fetal demise in singleton pregnancies with fetuses with isolated CHDs. A secondary aim is to evaluate whether the preterm birth was spontaneous or iatrogenic.

MATERIAL AND METHODS

From a previously described geographical cohort in the North-West Netherlands 9, including 1,912 fetuses and infants born between 2002 and 2012 with severe CHDs, we selected the singleton pregnancies with isolated fetal CHDs. Prenatal detection rates
in this cohort were 47% for all CHD combined and 34% for isolated CHD. In 404 cases (51% of the cases with a prenatal diagnosis) the pregnancy was terminated on request of the parents, these cases were excluded. Multiple pregnancies (n=85) were excluded, since in that group a relation to preterm delivery and fetal death is evident. The CHD was isolated in 1,013 of the 1,423 remaining cases. The pregnancy outcome was known in all cases. The cardiac defect was known at the time of birth in 26.4% of the 1,013 cases. All included types of CHD are listed in the legend of Table 1. Data were originally collected from prospectively entered cases in the prenatal ultrasound databases and pediatric cardiology databases. Data concerning the obstetric parameters and, where applicable, post-mortem reports were collected via assessment of the obstetric medical records and pathology databases. We searched all pathology databases in this region for fetal or neonatal cases without a prenatal diagnosis of malformations that turned out to have a CHD. Follow-up of all cases was one year after birth. Approval from the Medical Ethical Committee of the VU University Medical Centre was obtained for this study. (Date of approval: 7 November 2012, reference number 2012/396.)

Severe CHDs were defined as CHDs that required surgery or therapeutic catheterization or caused death within 1 year after birth. As we focused on structural heart defects, we excluded cases with cardiomyopathy or arrhythmia without an underlying structural heart defect. Cases with isolated patent ductus arteriosus or patent foramen ovale were not included in this cohort. All CHD included in this study are listed in the legend of Table 1. Isolated CHDs were defined as CHDs without any additional chromosomal or genetic anomalies or extracardiac malformations (except for single umbilical artery). From this cohort, we assessed all cases with preterm birth or fetal demise. The gestational age was determined by first trimester ultrasound biometry. Preterm birth was defined as a delivery before a gestational age of 37+0 weeks. We subcategorized preterm birth into birth below 28 weeks, between 28 and 32 weeks and between 32 and 37 weeks of gestation. Inclusion of cases started from a gestational age of 19+0 weeks. Term birth was defined as a delivery after 37 completed weeks. In 0.9% of the cases the exact duration of the pregnancy was unknown. These were all postnatally diagnosed cases with a (atrio)ventricular septal defect that underwent surgery several months after birth. In their files there was nothing stated on prematurity or special circumstances around the birth. They were therefore considered as term and included in the analysis. Spontaneous preterm birth was defined as a delivery following spontaneous onset of labor irrespective if labor was subsequently augmented or resulted in a caesarean section in case of failure to progress or fetal distress. Fetal distress was defined as hypoxic changes in the cardiotocogram and/or abnormalities in Doppler velocimetry of the umbilical artery and/or median cerebral artery. Iatrogenic preterm birth was
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defined as a primary caesarean section in the absence of any signs of spontaneous labor or as medical induction of labor. The reasons for medically induced preterm birth were categorized into fetal, maternal and a combination of fetal and maternal indications. Fetal demise was defined as the intra-uterine death of a fetus and were included after a gestational age of at least 19+0 weeks.

The control group consisted of all singleton deliveries (n=68,190) in the year 2010 of women living in the same region (selected by postal code) as the cases. Data on the number of live births at different gestational ages (ranging from 19+0 weeks to 43+0 weeks), fetal demise and neonatal mortality were provided by ‘The Netherlands Perinatal Registry’. This is a national medical registry of all deliveries and perinatal mortality in the Netherlands.

Comparisons were made between the CHD cohort and the control group and between cases in the CHD cohort with and without a prenatal diagnosis. Information and data were collected and analyzed using SPSS version 20.0. Odds ratios (ORs) and their associated confidence intervals (CIs) were calculated. The chi-square test was used to test for associations between categorical variables. A p-value below 0.05 was considered as statistically significant, all tests were two-sided.

RESULTS

Preterm birth in isolated CHD

Of the 1,013 singleton pregnancies with isolated CHD, 9.0% resulted in a preterm birth. If cases with fetal demise were excluded, the proportion of preterm births in isolated CHD was 9.1% [95% CI 7.3-10.9] compared to 5.6% [95% CI 5.4-5.8] in the control group. The odds ratio for preterm birth (<37+0 weeks) in isolated CHD was 1.7 [95% CI 1.4-2.1]. The odds ratio for birth below 28 weeks, between 28 and 32 weeks and between 32 and 37 weeks of gestation in fetuses with isolated CHD was respectively 2.0, 2.3 and 1.6 compared to the control population (Table 2). The mortality in the first year of life after a preterm birth was 22% (50% in the group born before 32 weeks of gestation), of which 70% was pre-surgery mortality (78% in the group before 32 weeks).

The size of the cohort allowed us to assess the prevalence of preterm births per type of CHD (Table 1). Valve abnormalities, septal defects and complex heart defects with atrial isomerism showed the highest rates of live preterm birth.

No difference in preterm birth rate was found between the cases in the CHD cohort with a prenatal diagnosis compared to the cases without a prenatal diagnosis (9.7% compared to 9.0% p=0.746).
### Table 1 Preterm birth per type of CHD

<table>
<thead>
<tr>
<th>CHD categories</th>
<th>N</th>
<th>Preterm birth</th>
<th>Compared to controls OR [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Septal defects</td>
<td>158</td>
<td>18 (11.4)</td>
<td>2.2 [1.3-3.6]</td>
</tr>
<tr>
<td>2. Valve abnormalities in biventricular hearts</td>
<td>101</td>
<td>17 (16.8)</td>
<td>3.4 [2.0-5.8]</td>
</tr>
<tr>
<td>3. Pulmonary or systemic venous return abnormalities</td>
<td>40</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>4. Aortic arch anomalies</td>
<td>155</td>
<td>13 (8.4)</td>
<td>1.6 [0.9-2.7]</td>
</tr>
<tr>
<td>5. Conotruncal anomalies</td>
<td>318</td>
<td>26 (8.2)</td>
<td>1.5 [1.0-2.3]</td>
</tr>
<tr>
<td>6. Hypoplastic right heart syndrome</td>
<td>20</td>
<td>2 (10.0)</td>
<td>1.9 [0.4-8.1]</td>
</tr>
<tr>
<td>7. Hypoplastic left heart syndrome</td>
<td>65</td>
<td>2 (3.1)</td>
<td>0.5 [0.1-2.2]</td>
</tr>
<tr>
<td>8. Other univentricular heart defects</td>
<td>78</td>
<td>6 (7.7)</td>
<td>1.4 [0.6-3.2]</td>
</tr>
<tr>
<td>9. Complex heart defects with atrial isomerism</td>
<td>28</td>
<td>4 (14.3)</td>
<td>2.8 [1.0-8.1]</td>
</tr>
<tr>
<td>10. Miscellaneous</td>
<td>25</td>
<td>3 (12.0)</td>
<td>2.3 [0.7-7.7]</td>
</tr>
<tr>
<td>Total</td>
<td>998</td>
<td>91 (9.1)</td>
<td>1.7 [1.3-2.1]</td>
</tr>
</tbody>
</table>

Categories consist of:
1. Ventricular septal defect(s) (VSD), balanced atrioventricular septal defect (AVSD)
2. Pulmonary (PS) or aortic valve stenosis, mitral stenosis, Ebstein’s anomaly, tricuspid dysplasia, tricuspid or mitral regurgitation
3. Total or partial abnormal pulmonary venous return, giant eustachian valve/cor triatriatum dexter or sinister
4. Aortic coarctation, hypoplastic or interrupted aortic arch, multiple level left heart obstruction, double aortic arch
5. Tetralogy of Fallot, double outlet right ventricle (DORV)-Fallot type with VSD and/or pulmonary stenosis, simple transposition of great arteries (without significant VSD), complex TGA (with significant VSD and/or PS), DORV- Taussig Bing (= TGA type), truncus arteriosus, pulmonary atresia with VSD, congenitally corrected TGA, absent pulmonary valve syndrome, aortopulmonary window, hemitruncus
6. Pulmonary atresia with intact ventricular septum, critical pulmonary valve stenosis with right ventricular hypoplasia
7. Aortic valve atresia, critical aortic valve stenosis with left ventricular hypoplasia
8. Double inlet left ventricle, tricuspid valve atresia, absent left A-V connection, unbalanced AVSD, TGA with right ventricular (RV) hypoplasia and straddling tricuspid valve, criss-cross, DORV with mitral valve and left ventricular (LV) hypoplasia, congenitally corrected TGA with RV hypoplasia, isolated atrio-ventricular (AV) discordance with hypoplastic RV and VSD
9. Left or right atrial isomerism, heterotaxy syndromes
10. Polyvalvular disease, isolated double chambered right ventricle, right atrial aneurysm

### Table 2 Preterm birth in isolated fetal CHD compared to controls

<table>
<thead>
<tr>
<th>Birth</th>
<th>Isolated fetal CHD</th>
<th>Control cases</th>
<th>OR [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before 28+0 weeks</td>
<td>7 (0.7)</td>
<td>231 (0.3)</td>
<td>2.0 [1.0-4.4]</td>
</tr>
<tr>
<td>From 28+0 to 31+6 weeks</td>
<td>11 (1.1)</td>
<td>320 (0.5)</td>
<td>2.3 [1.3-4.3]</td>
</tr>
<tr>
<td>From 32+0 to 36+6 weeks</td>
<td>73 (7.3)</td>
<td>3197 (4.8)</td>
<td>1.6 [1.3-2.0]</td>
</tr>
<tr>
<td>Overall preterm birth</td>
<td>91 (9.1)</td>
<td>3748 (5.6)</td>
<td>1.7 [1.3-2.1]</td>
</tr>
<tr>
<td>Total live births</td>
<td>998</td>
<td>67204</td>
<td></td>
</tr>
</tbody>
</table>
Spontaneous versus induced preterm birth

Within the group of preterm born infants (n=91), spontaneous onset of delivery was reported in 49.5% and iatrogenic in 38.4% of the cases. In the remaining 12.1% this information was unavailable because the infant could not be linked to a pregnancy file (cases without a prenatal diagnosis).

The indications for preterm induction of the delivery are shown in Figure 1. The most frequent indications were fetal distress and intra-uterine growth restriction (IUGR), either or not in combination with a maternal hypertensive disorder. There was only one pregnancy in which the reason for induction of the delivery was the heart defect itself. The diagnosis was a prematurely closed foramen ovale in a fetus with a small left ventricle leading to heart failure.

The proportion of medically induced and total preterm births was comparable between the group with a prenatal diagnosis (3.1% and 9.7% resp.) and the group with a postnatal diagnosis ((3.5% and 9.0% resp.) p=0.746).

Figure 1 Medically induced preterm births (n=35). The numbers in the figure represent percentages.

Indications for induction of delivery

- fetal hydrops
- intra-uterine growth restriction
- fetal distress
- hypertensive disorder
- abnormal blood loss
- hypertensive complication combined with fetal distress or IUGR
Fetal demise in isolated CHD

There were 15 cases of fetal demise in the CHD cohort (1.5% [95% CI 0.8-2.2]). Compared to the control group (fetal demise rate of 0.7% [95% CI 0.6-0.8]) this resulted in an odds ratio of 2.0 [95% CI 1.2-3.4]. The fifteen cases are described in Table 3. We found a higher percentage of fetal demises in the CHD cases with a prenatal diagnosis compared to the CHD cases without a prenatal diagnosis (5.0% versus 0.3%) (p< 0.001).

DISCUSSION

In an unselected population of over a thousand pregnancies with isolated fetal CHDs an increased risk for preterm birth and fetal demise was found compared to the control population. The odds for a preterm birth were higher in all subcategories. Most preterm births started spontaneously. If induction was performed before 37 completed weeks of gestation, the most common reasons were fetal distress and/or IUGR either or not in combination with a maternal hypertensive disorder.

Seven of the 15 cases (47%) with fetal demise could be explained by intra-uterine cardiac failure – due to the CHD. The other eight demise cases (53%) could not be attributed to hemodynamic changes caused by the CHD. The presence of the fetal shunts and the higher pressure in the right ventricle make most CHDs compatible with fetal life. 12;13 There is no evident pattern within this group related to type of defect or gestational age at which the demise occurred, however the cases where cardiac failure was present show common denominators of valvular dysplasia and/or venous obstruction.

Previous reported rates of preterm birth of infants with a CHD vary between 11.5-20.5% with reported corresponding odds ratios of 1.7-2.6. 21-23 The most plausible explanation for the higher rates found, is that previous studies also included cases with non-isolated CHDs 22;23, whereas we excluded non-isolated cases. The proportion of induced preterm birth in those cohorts was not reported. Chromosomal anomalies frequently associated with CHD such as trisomy 13 or 18, are mostly accompanied by severe IUGR and consequently could be a significant cause for the higher rate of preterm deliveries in those studies. The cohort described by Laas et al. did differentiate between isolated and non-isolated CHDs, and the outcomes of that study are the closest to ours. The numbers they presented per type of CHD, however, included cases with multiple extracardiac and/or chromosomal anomalies. 21 Our study is the first study that provides the prevalence of preterm birth per type of CHD in isolated cases and shows that the prevalence is increased, but not to the extent that had been reported previously. This knowledge is useful for counselling parents after genetic analysis has shown no abnormalities.
### Table 3 Cases of fetal demise

<table>
<thead>
<tr>
<th>Cardiac diagnosis</th>
<th>Number of cases</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ebstein’s anomaly with significant tricuspid regurgitation</td>
<td>3</td>
<td>On prenatal scan observed cardiac failure, fetal demise between 25 and 29 weeks of gestational age. Diagnosis confirmed at post-mortem examination in 2 cases, in the third case the post-mortem examination was declined.</td>
</tr>
</tbody>
</table>
| Hypoplastic aortic arch                                | 3               | 1 case with severe maternal preeclampsia with placental abruption at 34 weeks  
1 case of fetal demise at 35 weeks. Post-mortem examination showed an hypoplastic aortic arch, the size of the LV within normal range, with premature closure of foramen ovale, maternal hyperglycemia, insulin dependent diabetes  
1 case in combination with persistent left superior caval vein, no extracardiac anomalies found on ultrasound, karyotyping and post-mortem declined, no explanation found for demise * |
| Aortic coarctation                                      | 2               | Both cases were not prenatally diagnosed. Post-mortem findings: 1 case demise at 31 weeks with premature closure of foramen ovale, second case* demise at 37 weeks, no other anomalies found |
| Truncus arteriosus (TA)                                | 2               | Same mother in both cases. First case on prenatal scan truncal valve regurgitation and cardiac failure, normal karyotype, fetal demise at 29 weeks. Second case on prenatal scan small truncal valve and interrupted aortic arch, normal karyotype, development of cardiac failure, fetal demise at 29 weeks, post-mortem: TA type 2, VSD, quadricuspid dysplastic truncal valve, and patent arterial duct |
| Tetralogy of Fallot                                     | 1               | Prenatally detected, normal karyotype. Fetal demise at 39 weeks*, post-mortem diagnosis confirmed, no other abnormalities, except for extremely low placental weight |
| Complex transposition of great arteries                 | 1               | Prenatally detected, fetal demise at 41 weeks*, post-mortem examination confirmed diagnosis: TGA, bicuspid dysplastic pulmonary valve, and dysplastic mitral valve. Hypertrophic right ventricle with a narrow infundibulum. Chorioamnionitis of the placenta |
| Tricuspid valve atresia                                 | 1               | Fetal demise at 19 weeks*. Not prenatally diagnosed. Diagnosis at post-mortem examination: Atresia of the tricuspid valve with hypoplastic right ventricle, hypoplastic pulmonary trunk and dilated right atrium |
| Left atrial isomerism                                    | 1               | Fetal demise at 19 weeks, at 13 weeks on prenatal scan: fetal heart block and failure, normal karyotype. Diagnosis at post-mortem examination: left isomerism, situs ambiguous atria, ambiguous AV connection, concordant VA connection, persistent left superior caval vein, AVSD, hypoplastic aortic arch, polyvalvular disease. |
| Double outlet ventricle                                  | 1               | Prenatal diagnosis: DORV with aortic and pulmonary valve stenosis, VSD, narrow isthmus of the aortic arch, normal karyotype. Fetal demise at 28 weeks*, post-mortem examination declined |

**Legend**

All cases had a prenatal diagnosis of the heart defect, except for the cases with aortic coarctation and the case with tricuspid valve atresia, which were identified in the pathology databases.  
* no hemodynamic explanation for demise
Similar to preterm birth, fetal demise occurs more frequently in fetuses with isolated CHDs compared to the control population. Previous studies report demise rates in fetuses with a CHD from 2.7% to 12%. Most of the studies, however, report demises in a population including cases with associated extracardiac and chromosomal abnormalities. More importantly, most studies describe cohorts of prenatally diagnosed cases with CHDs, leaving out cases in which the CHD were missed prenatally. This inevitably produces a selection bias towards the more severe heart defects. The reports by Levi et al. and ours are the only studies that focus on isolated CHDs and include fetal demise cases in which the diagnosis was made postnatally by post-mortem examination. The slightly lower proportion of fetal demise found in our study could be explained by the fact that we excluded multiple pregnancies. The higher percentage of demise cases in the group with a prenatal diagnosis can be explained by the fact that more severe CHD usually have higher prenatal detection rates.

Our report is the first that describes the fetal demise cases with the cardiac diagnosis in detail. Only 47% of the cases in our study could be explained by intra-uterine cardiac failure related to the CHD. The cases with a premature closure of the foramen ovale underline the importance of a prenatal diagnosis and prenatal follow-up, especially in CHDs that are known to be at risk. Timely intervention in these cases may prevent fetal demise, with the disadvantage of an induced preterm birth with accompanying risks. Although a part of the pregnancy complications found can be explained by the CHD itself, the reasons for the increased risk for preterm birth and fetal demise in pregnancies with isolated fetal CHD partly remain unclear. A part may be attributed to rhythm disturbances, as it is known that some types of CHD are associated with this complication. Furthermore, genetic and environmental influences may play a role. Mutated genes and environmental influences may affect vascular development in the placenta as well. The altered vascular development of the placenta may explain some fetal demise cases. Furthermore a significant association between IUGR and fetal CHDs has been described, potentially explaining some of the inductions of labor because of fetal distress. It is also known that fetuses with cardiac defects carry a higher risk of genetic syndromes. These syndromes could remain undetected in fetal demise cases were a post-mortem examination was declined by parents or due to the difficulty in detection of mild dysmorphic features in macerated fetuses. It is possible that undiagnosed syndromes could underlie some of the fetal demise cases. These hypotheses do not explain preterm births in neonates with a normal birthweight who had an uneventful long-term outcome. As the cause of spontaneous preterm birth is accepted to be multifactorial, it is most likely that preterm birth in fetuses with CHDs has a multifactorial (maybe partly common) cause as well.
Our study describes a cohort with a representative number of severe isolated fetal CHDs in singleton pregnancies diagnosed prenatally as well as after birth. We included cases from pathology databases in the study region in which the diagnosis of the CHD was made by post-mortem examination and we could provide a detailed description of the fetal demise cases. We compared fetuses with isolated CHDs to a control group with singleton pregnancies from the same referral area as the affected fetuses. Missing data regarding gestational age at birth was only 0.9%.

A limitation in our study is that we were unable to correct for all possible risk factors, except for multiple pregnancies. To minimize the effect of possible confounders we chose a control population from the same region and time period to minimize bias on socio-demographic characteristics. Cases with CHDs or other congenital anomalies could not be excluded from the control group, because The Netherlands Perinatal Registry could not provide full coverage of this type of data. This may account for around 2% of the births in the control group. If the control group had only contained cases without congenital anomalies, the odds ratio for the outcomes of this study could possibly have been higher.

We were able to produce the prevalence of preterm birth per type of CHD, but the limited sample size still results in wide confidence intervals. Even if a CHD is isolated, higher rates of preterm birth and fetal demise compared to the general population are present. The risks in singleton pregnancies with isolated fetal CHDs are, however, lower than most rates published earlier. For accurate and valid counselling of parents who are expecting a child with a CHD, the prevalence of those complications in singleton pregnancies with isolated CHDs is relevant information. Especially in this modern era, when chromosome analysis including micro-array are offered to parents as standard care, and many significant associated anomalies can be ruled out prenatally, the remaining risk of obstetric complications is essential. Prenatal specialists should be aware of the conditions for a functional fetal circulation: a well-functioning placenta, a patent single ventricular inflow, a patent single ventricular outflow, competent inflow and outflow valves and at least one ventricle that fills normally and can eject sufficiently to sustain the equivalent of the combined cardiac output. When one or more of these is not present, fetal cardiovascular compromise including evolution of heart failure or sudden fetal demise may occur.
REFERENCE LIST


