OBSTETRICS

Placental vascular malperfusion lesions in fetal congenital heart disease

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BACKGROUND: Fetuses with congenital heart disease are at increased risk of perinatal morbidity and mortality, which is highly influenced by their prenatal health. Placental function is vital for the health of the fetus, but increased rates of pathologic lesions of the placenta have been observed in pregnancies complicated by fetal congenital heart disease.

OBJECTIVE: This study aimed to determine the prevalence of both gross and histologic placental pathologies in a cohort of pregnancies complicated by fetal congenital heart disease vs healthy controls using the Amsterdam Placental Workshop Group Consensus Statement sampling and definitions of placental lesions.

STUDY DESIGN: This single-center retrospective cohort study included placental examinations from pregnancies diagnosed prenatally with fetal congenital heart disease between 2010 and 2019; moreover, control placentas were collected from pregnancies without maternal or fetal complications. Placentas were sampled and evaluated according to the Amsterdam Placental Workshop Group Consensus Statement and gross and histopathologic diagnoses determined.

RESULTS: Approximately 80% of fetuses diagnosed with congenital heart disease (n=305) had a placental examination for comparison with controls (n=40). Of note, 239 placentas (78%) in the group with fetal congenital heart disease had at least 1 gross or histopathologic lesion compared with 11 placentas (28%) in the control group ($P<.01$). One-third of placentas complicated by fetal congenital heart disease met the criteria for small for gestational age, and 48% of placentas had one or more chronic lesions, including maternal vascular malperfusion (23% vs 0%; $P<.01$), villitis of unknown etiology (22% vs 0%; $P<.01$), fetal vascular malperfusion (20% vs 0%; $P<.01$), and other chronic lesions (16% vs 0%; $P<.01$). Acute inflammation was equally present in both the group with fetal congenital heart disease and the control group (28% vs 28%; $P=1.00$). Although gestational age and birthweight z score were similar between the 2 groups, birth head circumference was 1.5 cm less in pregnancies complicated by fetal congenital heart disease with a significantly lower z score compared with the control group (-0.52 ± 1.22 vs 0.06 ± 0.69; $P<.01$).

CONCLUSION: Vascular malperfusion lesions and chronic forms of inflammation occur at markedly higher rates in placentas complicated by fetal congenital heart disease, which may contribute to the decreased head circumference at birth. Further work in neuroplacentology is needed to explore connections among cardiac defects, placental vascular malperfusion lesions, and fetal brain development.

Key words: cardiac neurodevelopment, chorangiosis, congenital heart defect, deciduitis, endothelial cushions, fetal brain, intrauterine, neuroplacentology, placental hemodynamics, placental histopathology, placental hypoplasia, placental inflammation, placental pathology, syncytial knots, villitis, villous edema, villous maturation

Introduction

Congenital heart disease (CHD) is a leading cause of childhood morbidity and mortality with an estimated incidence of 6 to 8 per 1000 live births.[1] The etiology of adverse outcomes is multifactorial with influence from surgical factors and a growing awareness of contributions from the prenatal environment. Birthweight and Apgar scores are both correlated with improved survival in neonates undergoing cardiac surgeries,[2,3] and these metrics are directly linked with placental function. Histopathologic examination of the placenta is not uniformly performed after delivery of infants with CHD but can provide important information about the intrauterine environment.[4,5]

Placentas from pregnancies complicated by fetal CHD are typically smaller[6] and have perfusion deficits by imaging in utero.[7,8] Studies of placental pathology after birth show high rates of thrombosis, infarction, chorangiosis, and hypomature villi in pregnancies complicated by fetal CHD.[9] Although informative, these descriptive studies lack healthy controls for comparison, and few studies follow the Amsterdam Placental Workshop Group Consensus Statement recommendations for placental sampling and definitions of pathologic lesions.[10] Overall, these factors contribute to the need for additional research into placental findings associated with fetal CHD.

This study aimed to determine the prevalence of both gross and histologic placental pathologies in a cohort of pregnancies complicated by fetal CHD compared with healthy controls using the Amsterdam Placental Workshop Group Consensus Statement recommendations and the earlier version from the Placental Pathology Practice Guideline Development Task Force of the College of American Pathologists.[11] We hypothesized that fetal CHD would be associated with higher rates of all chronic forms of placental pathology, particularly fetal vascular malperfusion (FVM), a lesion resulting from an obstruction in fetal blood flow to the placenta characterized by placental thrombosis, avascular villi, and/or

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AJOG at a Glance

Why was this study conducted?
Large-scale, rigorous, and controlled studies of placental pathology in pregnancies complicated by fetal congenital heart disease (CHD) are lacking.

Key findings
Fetal CHD was associated with high rates of chronic placental lesions, particularly maternal and fetal vascular malperfusion lesions and chronic inflammation.

What does this add to what is known?
Placental vascular malperfusion lesions may contribute to poor head growth in fetuses with heart defects.

villous stromal-vascular karyorrhexis. Subsequently, in exploratory analyses, we sought to determine the relative burden of placental pathologies in specific subgroups of CHD physiology.

Methods

Study subjects

This single-center retrospective cohort study included placental pathologic examinations in pregnancies diagnosed with fetal CHD spanning from 2010 to 2019. The study was approved by the institutional review board of The University of Texas Southwestern Medical Center. The inclusion criteria were singleton pregnancies complicated by moderate to severe CHD, defined as those expected to require surgical intervention before hospital discharge (group with CHD). For more specific analyses, the group with CHD that excluded those with genetic diagnoses, genetic variants of unknown significance, clinically diagnosed syndromes, and extracardiac anomalies was used to reduce the possibility of bias from these factors (group with isolated CHD). In addition, participants were only included if delivery occurred at one of our campus hospitals (Parkland Hospital or William P. Clements Jr. University Hospital) to ensure that the placentas were evaluated by the same team of placental pathologists, as previously described.[12,13] Control placentas were collected as part of a prospective study,[14] with inclusion criteria of gestational age of at least 37 weeks, singleton pregnancy, no evidence of fetal anomalies or fetal growth restriction, and absence of fetal asphyxia. Demographic information was collected for both the mother and infant, including maternal age, gestational age at birth, infant sex, race, and ethnicity. Maternal pregnancy complications, fetal diagnoses, and birth characteristics were collected, and percentiles were determined for anthropometric data.[15] Specific factors affecting the risk of placental pathology were collected, including maternal gravida status, maternal diabetes mellitus (DM; both gestational and pregestational), any form of maternal hypertension, and presence of placenta accreta spectrum disorder.

Placental pathology

Placentas from pregnancies complicated by fetal CHD are routinely sent for gross and histologic examinations by placental pathologists. Our standardized approach to placental pathology has been previously described.[12] Briefly, the initial gross examination included the evaluation of the umbilical cord, membranes, and placental disk. Trimmed placental weight was measured after removal of the umbilical cord, fetal membranes, and nonadherent blood clots. This trimmed weight was used for the calculation of the birthweight—to—placental weight ratio. Gross pathologies recorded for the study included those that were small for gestational age (SGA; <10th percentile) not accompanied by histologic abnormalities that would explain the small size, large for gestational age (LGA; >90th percentile), single umbilical artery, hypercoiled umbilical cord, abnormal cord insertion, and abnormal placental disk shape.

Placental disks were sectioned at 1- to 2-cm intervals to identify lesions within the parenchyma. Representative sections of the placental parenchyma, umbilical cord, and fetal membranes were examined. Moreover, abnormalities identified by sectioning were included in the histologic study. Only significant placental pathologies were recorded, per institutional standard and as previously described.[10] Those pathologies included acute inflammation, maternal vascular malperfusion (MVM), FVM, villitis of unknown etiology (VUE), and other lesions. Acute inflammation included acute chorioamnionitis with and without fetal vasculitis. MVM included diagnoses of infarct of >5% of parenchyma, maternal vascular lesions, increased syncytial knots, villous hypoplasia, and/or hemorrhage or hematoma. FVM included diagnoses of thrombosis, chorangiosis, avascular villi, diffuse fibrin, and/or endothelial cushions. VUE included those with low grade and high grade and villitis with avascular villi. Other lesions included those with delayed villous maturation and/or villous edema. Any lesion other than those involving acute inflammation was considered chronic for our analyses.

Statistical analyses

Maternal and infant characteristics and placental pathologies were compared using the chi-squared or Fisher exact test where appropriate. Mean differences between the 2 groups were compared using the *t* test, and medians were compared using the Mann-Whitney *U* test. In all analyses, both the group with CHD and the group with isolated CHD were compared with controls with statistical significance set at $P<.05$. For intragroup, hypothesis-generating analyses, we divided the cohort with CHD by physiology into those with hypoplastic left heart syndrome (HLHS), single ventricle (SV) with right-sided obstructive lesions (SV-RSOLs), other SV lesions, 2-ventricle (2V) lesions, and those with transposition of the great arteries (TGA).

Results

Study subjects

Between 2010 and 2019, a total of 387 patients with CHD met the inclusion criteria. Of these, 82 did not have a placenta sent for pathology and were excluded from the analysis, resulting in 305 placentas complicated by CHD included in the analysis. The decision regarding which placentas were sent for pathologic examination was provider specific. As controls were collected as part of a prospective study, placental pathology was available in all 40 control subjects. Study subjects with placental pathology in the cohort with CHD consisted of 71 with HLHS, 26 with SV-RSOLs, 19 with other SV lesions, 34 with TGA, and 155 with 2V lesions (composed primarily of tetralogy of Fallot [n=51], aortic coarctation [n=23], complete atrioventricular canal [n=20], double outlet right ventricle [n=11], and <10 each of aortic stenosis, absent pulmonary valve, double aortic arch, Ebstein anomaly, heterotaxy, interrupted aortic arch, pulmonic stenosis, total anomalous pulmonary venous return, tricuspid atresia, truncus arteriosus, vascular ring, and isolated ventricular septal defect).

Maternal characteristics were similar between the group with CHD and the control group with the exception that pregnancies with fetal CHD had higher rates of complications, including advanced maternal age (9% in the group with CHD vs 5% in controls; $P=.56$), hypertension (10% in the group with CHD vs 0% in controls; $P=.04$), DM (16% in the group with CHD vs 0% in controls; $P<.01$), and placenta accreta spectrum disease was diagnosed in 1 pregnancy complicated by CHD (Table 1). Fetal growth patterns were not available for many patients; therefore, fetal growth restriction was diagnosed in only 18 patients in the cohort with CHD and none in the control group. Inconsistent information was available regarding the use of assisted reproductive technologies, including in vitro fertilization (IVF) with only 2 confirmed IVF pregnancies in the cohort with CHD and none in controls. Diagnosis of clinical chorioamnionitis was absent in the control group with a median rupture of membranes (ROM) duration of 0.5 hours (n=40; interquartile range [IQR], 0–6) compared with 5 cases of clinical chorioamnionitis in the group with CHD with a median ROM duration of 1 hour (n=288; IQR, 0–5).

Infant characteristics between the control group and the group with CHD differed by gestational age at delivery (39 weeks [IQR, 38–39] in the group with

TABLE 1
Maternal and infant patient characteristics

Characteristic	Control (n=40)	CHD (n=387)
Maternal characteristics		
Age	28±5	29±6
Gravity	3 (2–4)	3 (2–4)
Parity	3 (1–3)	2 (1–3)
Cesarean delivery	20 (50)	163 (44)
Pregnancy complications		
Diabetes mellitus	0 (0)	63 (16)[a]
Hypertension	0 (0)	38 (10)[b]
Advanced maternal age	2 (5)	36 (9)
Placenta accreta spectrum disorder	0 (0)	1 (<1)
Infant characteristics		
Female sex	16 (40)	176 (46)
Race and ethnicity		
Black non-Hispanic	2 (5)	137 (35)[a]
White non-Hispanic	1 (3)	43 (11)[a]
Hispanic	37 (93)	173 (45)[a]
Other	0 (0)	34 (9)[a]
Gestational age at birth	39 (39–40)	39 (38–39)[a]
1-min Apgar score	8 (8–9)	8 (7–8)[a]
5-min Apgar score	9 (9–9)	9 (8–9)[a]
Birthweight (g)	3498 (3176–3676)	3060 (2710–3469)[a]
Birthweight percentile	0.46 (0.32–0.64)	0.35 (0.16–0.65)
SGA (<10th percentile)	2 (5)	60 (16)
AGA (10th–90th percentile)	33 (83)	293 (76)
LGA (>90th percentile)	5 (13)	34 (9)
Birthweight *z* score	−0.06±0.75	−0.28±1.08
Birth head circumference (cm)	35.0 (34.0–35.5)	33.5 (32.0–34.5)[a]
Birth head circumference percentile	0.56 (0.37–0.69)	0.29 (0.09–0.57)[a]
Birth head circumference *z* score	0.06±0.69	−0.52±1.22[a]

Number (percentage) data were compared using the chi-square or Fisher exact test, mean±standard deviation data were compared using the *t* test, and median (interquartile range) data were compared using the Mann-Whitney *U* test.

AGA, appropriate for gestational age; *CHD*, congenital heart disease; *LGA*, large for gestational age; *SGA*, small for gestational age.

[a] Statistically significant result at $P<.01$; [b] $P<.05$.

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CHD vs 39 weeks [IQR, 39−40] in controls; $P<.01$). Birthweight z score was not significantly different between the 2 groups (−0.28±1.08 in the group with CHD vs −0.06±0.75 in controls; $P=.09$), but birth head circumference differed by 1.5 cm (33.5 cm [IQR, 32.0−34.5] in the group with CHD vs 35.0 cm [IQR, 34.0−35.5] in controls; $P<.01$), and birth head circumference z score was significantly different (−0.52±1.22 in the group with CHD vs 0.06±0.69 in controls; $P<.01$) (Table 1). This difference in head circumference z score persisted when controls were compared with the group with isolated CHD (−0.42±1.15 in the group with isolated CHD [n=225] vs 0.06±0.69 in controls; $P=.01$), although the birthweight z score remained similar between the 2 groups (−0.17±1.02 in the group with isolated CHD [n=264] vs −0.06±0.75 in controls; $P=.51$]. Genetic testing was performed in 62% of those with CHD. There were a total of 44 patients with placental examination who had a diagnosed genetic condition (14% in the cohort with CHD), including 23 patients with Down syndrome, 9 with 22q11 deletion syndrome, and 6 with Turner syndrome. An additional 13 patients with CHD had a variant of uncertain significance detected in their genetic testing, and 21 patients with placental examination had one or more extracardiac anomalies without a specific genetic diagnosis. Those anomalies included 1 patient each with microcephaly, ventriculomegaly, esophageal atresia, horseshoe kidney, multicystic kidney, ureterocele, biliary atresia, fetal hydrops, trigonocephaly, tethered cord, Peter anomaly, and renal agenesis with hydrocolpos; 2 patients each with omphalocele and cleft palate; and 4 patients with situs inversus with or without asplenia. A total of 40 patients (13%) from the group with CHD were deceased at the time of medical record review, and 80% of those deaths occurred in the first year of life.

Gross placental pathology

In the cohort with CHD, 239 placentas (78%) had at least 1 gross or histopathologic lesion, compared with 11 placentas (28%) in the control group ($P<.01$). Similarly, gross placental pathologies were significantly more frequent in the group with CHD than in the control group (Table 2). There were 101 placentas (33%) complicated by CHD that met the weight criteria for SGA, whereas there were 36 placentas (12%) complicated by CHD that met the weight criteria for LGA. Only 4 placentas complicated by CHD had an abnormal shape. There were 58 placentas complicated by CHD (15%) with umbilical cord abnormalities, including 34 with a single umbilical artery, 20 with a hypercoiled cord, and 12 with an abnormal cord insertion. Average placental weights were 471±127 g with a birthweight−to−placental weight ratio of 6.70±1.29 in our cohort with CHD and 481±119 g with a birthweight−to−placental weight ratio of 6.74±1.31 in our cohort with isolated CHD.

Histologic placental pathology

All categories of microscopic placental pathology other than acute inflammation were significantly more frequent in the cohort with CHD (Table 3). Average ROM durations were 5.1±6.5 hours in placentas complicated by CHD with acute inflammation (n=75) and 6.8±5.7 hours in placentas in the control group (n=11) ($P=.40$). Chronic lesions were only found in the placentas complicated by CHD (48% in the group with CHD vs 0% in control; $P<.01$) (Table 4). Chronic inflammation manifesting as VUE was found in 66 placentas complicated by CHD (22%); most chronic inflammatory lesions manifesting as VUE were low grade (68%). High-grade villitis was found in 13 placentas complicated by CHD and associated with avascular villi in another 8 placentas complicated by CHD. Chronic MVM lesions occurred in 71 placentas complicated by CHD (23%) and none in control placentas ($P<.01$). These cases included 35 placentas with hypoplasia, 20 placentas with infarction of >5% of parenchyma, 6 placentas with maternal vascular lesions, 7 placentas with increased syncytial knots, 12 placentas with villous hypoplasia, and 23 placentas with hemorrhage or hematoma. FVM was found in 61 placentas complicated by CHD (20%) and none in control placentas ($P<.01$). Within the FVM category, chorangiosis was the primary etiology (38%), with smaller percentages of FVM lesions caused by thrombosis (30%), diffuse fibrin (23%), endothelial cushions (23%), and avascular villi not associated with villitis (14%). Compared with control placentas, placentas complicated by CHD had nearly 3 times the rate of multiple placental pathologies (121 of 305 [40%] in the group with CHD vs 6 of 40 [15%] in controls; $P<.01$). In the control

TABLE 2
Gross placental pathologies

Variable	Control (n=40)	CHD (n=387)	Isolated CHD (n=263)
Pathology report	40 (100)	305 (79)	204 (78)
SGA placenta	0 (0)	101 (33)[a]	64 (31)[a]
LGA placenta	0 (0)	36 (12)[a]	25 (12)[a]
Umbilical cord abnormalities	0 (0)	62 (20)[a]	39 (19)[a]
Single umbilical artery	—	34 (55)	22 (56)
Hypercoiled umbilical cord	—	20 (32)	12 (31)
Abnormal cord insertion	—	12 (19)	8 (21)
Abnormal placental shape	0 (0)	4 (1)	3 (1)

Number (percentage) data were compared using the chi-square or Fisher exact test.

CHD, congenital heart disease; *LGA*, large for gestational age; *SGA*, small for gestational age.

[a] Statistically significant result at $P<.01$.

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placentas, these were composed of only acute inflammatory lesions, but in the placentas complicated by CHD, 18% had multiple chronic lesions ($P<.01$), and 13% had both chronic and acute lesions combined ($P=.01$) (Table 4).

Exploratory analyses

For exploratory within-group analyses, we divided the group with CHD, as described, into those with HLHS, SV-RSOLs, other SV lesions, 2V lesions, and TGA (Table 5). We found significant differences in the rate of placentas of SGA fetuses with the highest prevalence in patients with 2V cardiac defects (41% in 2V lesions vs 27% in SV-RSOLs vs 26% in other SV lesions vs 24% in HLHS and TGA; $P=.047$). Differences in the rates of VUE between the 2 groups ranged from 15% in the group with SV-RSOLs to 29% in the group with TGA ($P=.69$). MVM was found in 35% of those with SV-RSOLs and 17% in those with HLHS, although the rates of MVM were 21% in those with other SV lesions, 26% in those with 2V lesions, and 18% in those with TGA ($P=.32$). Despite similar birthweights, the head circumference z score was the lowest in those with SV-RSOLs (-0.94 ± 0.88 in those with SV-RSOLs; -0.47 ± 0.98 in those with HLHS; -0.42 ± 1.16 in those with other SV lesions; -0.47 ± 1.39 in those with 2V lesions; -0.58 ± 1.08 in those with TGA; $P=.44$).

TABLE 3
Histopathologic placental lesions

Variable	Control (n=40)	CHD (n=305)	Isolated CHD (n=204)
Any pathology	11 (28)	239 (78)[a]	163 (80)[a]
Acute inflammation	11 (28)	84 (28)	56 (28)
Maternal inflammatory response (with or without fetal vasculitis)	11 (28)	82 (98)	55 (98)
Fetal inflammatory response	6 (15)	42 (50)	31 (55)
Villitis of unknown etiology	0 (0)	66 (22)[a]	45 (22)[a]
Low grade	—	45 (68)	33 (73)
High grade	—	13 (20)	9 (20)
With avascular villitis	—	8 (12)	3 (7)
Maternal vascular malperfusion	0 (0)	77 (25)[a]	59 (29)[a]
Placental hypoplasia	—	35 (49)	25 (42)
Infarct	—	20 (28)	15 (25)
Maternal vascular lesions	—	6 (8)	3 (5)
Increased syncytial knots	—	7 (10)	6 (10)
Villous hypoplasia	—	12 (17)	7 (12)
Hemorrhage or hematoma	—	23 (32)	21 (36)
Fetal vascular malperfusion	0 (0)	57 (19)[a]	40 (20)[a]
Thrombosis	—	18 (30)	15 (38)
Chorangiosis	—	23 (38)	16 (40)
Avascular villi	—	6 (10)	5 (13)
Diffuse fibrin	—	10 (16)	5 (13)
Endothelial cushions	—	10 (16)	5 (13)
Other lesions	0 (0)	65 (20)[a]	46 (23)[a]
Delayed villous maturation	—	13 (20)	7 (15)
Chronic deciduitis	—	48 (74)	36 (78)
Villous edema	—	11 (17)	7 (14)

Number (percentage) data were compared using the chi-square or Fisher exact test.

CHD, congenital heart disease.

[a] Statistically significant result at $P<.01$.

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Comment

Principal findings

In this retrospective cohort study, we found a remarkably high rate of pathologic placental lesions in pregnancies complicated by fetal CHD, totaling 78% of our cohort. Even when excluding patients with CHD with genetic diagnoses, variants of uncertain significance, and extracardiac anomalies, the rate of pathologic placental lesions was 83%. In comparison, our healthy control group had only a rate of pathologic placental lesions of 28%, all of which were acute inflammation. Vascular malperfusion lesions were common in our group with CHD: MVM was found in 25% of our cohort with CHD (29% in the group with isolated CHD), and 19% of placentas complicated by CHD (20% in the group with isolated CHD) were diagnosed with FVM. This was coupled with significantly smaller head circumference for gestational age in our groups with CHD and isolated CHD. Although our study was not powered to conclude differences between CHD subtypes, our exploratory analyses showed a nonsignificantly higher rate of MVM lesions in fetuses with SV-RSOLs (present in 35% of cases).

Results in the context of what is known

The placenta complicated by CHD is the focus of a growing body of literature that seeks to understand the many perinatal influences on both short- and long-term outcomes in this vulnerable population.[16–18] Suspicions regarding abnormal placental function in these pregnancies have been confirmed through advanced imaging studies[19] and separately through descriptive studies of

TABLE 4
Combined placental pathologies

Variable	Control (n=40)	CHD (n=305)	Isolated CHD (n=204)
Normal	29 (73)	66 (22)[a]	41 (20)[a]
Single pathology	5 (13)	118 (39)[a]	77 (38)[a]
Chronic pathology	0 (0)	147 (48)[a]	103 (51)[a]
Multiple pathologies	6 (15)	121 (40)[a]	86 (42)[a]
>2 chronic pathologies	0 (0)	56 (18)[a]	42 (21)[a]
Acute + chronic pathologies	0 (0)	39 (13)[a]	27 (13)[a]

Number (percentage) data were compared using the chi-square or Fisher exact test.

CHD, congenital heart disease.

[a] Statistically significant result at $P<.01$.

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placental pathology.[9,20,21] Our report was the largest cohort of placentas complicated by CHD studied to date using the Amsterdam Placental Workshop Group Consensus Statement placental pathology guidelines and the earlier version from the Placental Pathology Practice Guideline Development Task Force of the College of American Pathologists[11] and confirmed the findings of previous work in this area.[9]

The high rate of vascular malperfusion lesions in our cohort with CHD is particularly interesting considering the unclear etiology of CHD in most patients and the early multiorgan effects of severe forms of fetal CHD. The high prevalence of MVM in our cohort with CHD indicated a possible defect in early placentation involving inadequate spiral artery remodeling. This may explain why other studies have demonstrated an association between fetal CHD and preeclampsia, particularly early-onset preeclampsia.[22] However, we did not observe this increase in preeclampsia in our cohort with CHD as the rate of any type of hypertension (preexisting, gestational, and associated with preeclampsia) in this study was only 10%.

In addition to MVM, the rate of FVM in our cohort with CHD was significantly higher than in controls, affecting 19% of placentas complicated by CHD. These lesions result from an obstruction in fetal blood flow to the placenta, typically chronic partial obstruction, or intermittent complete obstruction, which can result from cardiac insufficiency among other causes.[23] This leads to histopathologic findings of placental thrombosis, avascular villi, and/or villous stromal-vascular karyorrhexis.[10] As fetal blood flow to the placenta mirrors other end-organ perfusions, the high rate of FVM in these placentas raises concerns for deleterious effects on other organ systems, including the brain. Interestingly, in our cohort with CHD, the overall head circumference was, on average, 1.5 cm smaller than controls with a significantly lower *z* score for gestational age. A total of 10% of the cohort with CHD had a birth head circumference <3rd percentile for gestational age, fitting a diagnosis of microcephaly.[24] Decreased head growth and delayed brain maturation in fetal CHD have been described in many previous studies,[25–27] even as early as the first trimester of pregnancy.[28] Although this may be attributable to genetic alterations in some patients with CHD, patients with isolated CHD showed similar differences in birth head circumference. This relationship between poor head growth and aberrant placental hemodynamics is the focus of ongoing exploration.[19]

TABLE 5
Details of placental pathology in the subgroup with fetal congenital heart disease

Variable	HLHS (n=87)	SV-RSOL (n=35)	Other SV lesions (n=19)	2V lesion (n=202)	TGA (n=44)
Placental pathology report	71 (82)	26 (74)	19 (100)	155 (77)	34 (77)
Birthweight: placental weight	6.74±1.31	6.73±1.73	6.63±0.83	6.56±1.25	7.03±1.17
SGA placenta	17 (24)	7 (27)	5 (26)	64 (41)	8 (24)
LGA placenta	6 (9)	3 (12)	2 (11)	23 (15)	2 (6)
Umbilical cord abnormality	14 (20)	6 (23)	4 (21)	34 (22)	4 (12)
Abnormal shape	2 (14)	0 (0)	0 (0)	1 (3)	1 (25)
Acute inflammation	20 (28)	9 (34)	6 (32)	40 (26)	9 (27)
VUE	16 (23)	4 (15)	3 (16)	33 (21)	10 (29)
MVM	12 (17)	9 (35)	4 (21)	40 (26)	6 (18)
FVM	13 (18)	4 (15)	4 (21)	31 (20)	9 (26)
Other lesions	14 (20)	5 (19)	2 (11)	19 (12)	8 (24)

2V, 2-ventricle lesion; *FVM*, fetal vascular malperfusion; *HLHS*, hypoplastic left heart syndrome; *LGA*, large for gestational age; *MVM*, maternal vascular malperfusion; *SGA*, small for gestational age; *SV-RSOL*, single ventricle with right-sided obstructive lesion; *TGA*, transposition of the great arteries; *VUE*, villitis of unknown etiology.

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Clinical implications

Other investigators have recently reported a connection between placental

FVM lesions and neurodevelopmental outcomes at 2 years in patients with severe fetal growth restriction.[29] With the mounting evidence of prenatal influences on neurodevelopmental outcomes in patients with CHD,[16] this connection among high rates of placental malperfusion lesions, abnormal head growth, and neurodevelopmental outcomes warrants further exploration. Another key finding of this study was the high rate of chronic inflammatory lesions in the placentas complicated by CHD, known as VUE. Although most villitis cases were low-grade VUE, there were a total of 29 placentas complicated by CHD (9.5%) with high-grade VUE or VUE associated with avascular villi. These placental lesions are associated with impaired fetoplacental circulation and can lead to adverse clinical outcomes in the fetus.[30] Overall, our cohort demonstrated that vascular malperfusion lesions and/or chronic inflammatory lesions were present in nearly half of all placentas complicated by CHD. This finding of an abundance of chronic placental lesions indicated early damage to the placenta and raised questions regarding the etiology and clinical significance of these abnormalities.

Research implications

In the analyses of the subgroup with CHD, we found a higher rate of MVM lesions in our group with SV-RSOLs (present in 35%). Although our sample size was not sufficient for this result to be statistically significant, it merits further investigation. Because most CHD diagnoses are not found to have an underlying genetic cause, these data may suggest a potential influence of early placentation in disrupted cardiogenesis, as has been postulated by other investigators.[21,31,32] Specifically, disturbances in the resistances of early placental vasculature may cause changes in cardiac preload during key developmental stages of the heart leading to some forms of CHD, such as RSOLs; as in utero, the right ventricle is the primary source of cardiac output. Alternatively, or in combination with the effects of vascular resistance, shared developmental pathways in the placenta and heart may drive both phenomena, and there is accumulating evidence of a multitude of genes that are commonly expressed by early fetal heart cells and placental endothelial cells and trophoblasts, cytotrophoblasts, and syncytiotrophoblasts.[33]

Strengths and limitations

The strengths of this study included our healthy control comparison group, the inclusion of information on maternal and infant characteristics, and our robust sample size that permitted exploratory subgroup analyses. In addition, some previous reports of histopathology in placentas complicated by CHD did not follow the most widely accepted and rigorous definitions for placental pathology known as the Amsterdam Placental Workshop Group Consensus Statement.[10,11] This statement resulted from an international conference that involved leading experts in placental pathology, and it describes a specific protocol for sampling the placenta and specific diagnostic criteria for each lesion. Our institutional adherence to these standards and the high rate of placental examination that totaled nearly 80% of our placentas complicated by CHD over a 10-year period contribute to the validity of our findings.

Although this study has a robust sample size and was built on previous investigations in the field, several limitations must be recognized. Our pathologists were not blinded to the fetal CHD diagnosis, and there were 20% of placentas complicated by CHD not examined, thus raising the possibility of bias affecting our results. Regarding the finding of differences in head circumference, unfortunately, we did not have longitudinal prenatal growth parameters to determine the timing and evolution of this finding. Another limitation of this study was the lack of genetic testing in a large number of our cohort with CHD and none of the healthy controls. With the approximate 30% rate of genetic conditions in patients with CHD,[34,35] recent clinical recommendations are to more readily send genetic testing for those with moderate or severe CHD.[36,37] However, as our cohort dated back to 2010, genetic testing practices varied during the time course of our study. Finally, our limited sample size for subgroup analyses prevented hypothesis testing with individual types of cardiac pathophysiology. Based on previous studies in this area,[25] we know that different subtypes of CHD are associated with functional differences in the placenta that are superimposed on similar rates of placental pathologies. Further characterization of placental function in specific forms of CHD will require multicenter data sharing to obtain adequate sample sizes for these analyses. Nevertheless, this report of placental data from a large number of patients with CHD along with a robust clinical characterization of our cohort has added to the existing literature and raised important questions regarding the role of early placentation on cardiac morphogenesis and the influence of chronic placental lesions on short- and long-term outcomes in patients with CHD.

Conclusions

In pregnancies complicated by fetal CHD, there is much we can learn about the prenatal environment from pathologic examination of placental tissue, particularly when using a standardized approach as described by the Amsterdam Placental Workshop Group Consensus Statement.[10] Thus, placental examination should be considered for all pregnancies complicated by fetal CHD. Both MVM and FVM lesions and chronic forms of inflammation are abundant in placentas complicated by fetal CHD. These chronic lesions may contribute to the decreased head circumference at birth observed in our cohort of neonates with CHD. Further research using early markers of placental function, such as advanced imaging,[19,38–40] is needed to delineate the etiology of placental lesions in fetal CHD and their influence on clinical outcomes. ■

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