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ORIGINAL RESEARCH

CARDIO-OBSTETRICS

Placental Findings in Pregnancies Complicated by Maternal Cardiovascular Disease

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ABSTRACT

BACKGROUND The incidence of pregnancy in women with cardiovascular disease (CVD) has increased, yet little is known about placental pathology in these women.

OBJECTIVES The objectives of this study were to describe placental pathology in pregnancies complicated by maternal CVD and to compare findings among categories of maternal CVD.

METHODS A retrospective, single-center study was conducted. Pathology reports for 264 placentas from pregnancies complicated by maternal CVD were reviewed for prespecified pathologic findings which were then compared against maternal characteristics.

RESULTS Placentas were from pregnancies associated with maternal congenital heart disease (n = 171), arrhythmia (n = 43), cardiomyopathy (n = 20), connective tissue disease (n = 20), and valvular heart disease (n = 10). Median maternal age at delivery was 32 years (range: 19-49). Median gestational age at delivery was 39 weeks (range: 25-41). Placental pathology was identified in 75% (199/264) of placentas. Anatomic pathology, primarily small placenta by weight, was present in 45% (119/264) of placentas. Vascular pathology, primarily maternal vascular malperfusion or fetal vascular malperfusion, was seen in 41% (107/264) of placentas. Acute chorioamnionitis and villitis of unknown etiology (VUE) were seen in 23% (61/264) and 11% (28/264) of placentas, respectively. Prevalence of VUE differed across CVD categories ($P = 0.008$) and was most common in maternal congenital heart disease; there were no differences in anatomic, infectious, and vascular pathologies across CVD categories.

CONCLUSIONS Pregnancies among women with CVD commonly demonstrate abnormal placental findings, especially anatomic and vascular pathology. Prevalence of VUE differed across CVD categories. Otherwise, the incidence of specific pathology findings did not differ based on maternal characteristics. (JACC Adv 2022;1:100008) © 2022 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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ABBREVIATIONS AND ACRONYMS

CHD = congenital heart disease

CVD = cardiovascular disease

HDP = hypertensive disorder of pregnancy

NICU = neonatal intensive care unit

NYHA = New York Heart Association

STORCC = Standardized Outcomes for Reproductive Cardiovascular Care

VUE = villitis of unknown etiology

Advances in the treatment of chronic diseases have led to a steady increase in the number of pregnancies complicated by maternal congenital heart disease (CHD), rheumatic heart disease, cardiomyopathy, and arrhythmias.[1,2] These conditions can predispose women and their offspring to adverse events throughout gestation and the postpartum period.[3-5]

The placenta is responsible for sustaining the health of the fetus, and abnormalities are associated with adverse fetal outcomes.[6-9] Placental development is also affected by maternal conditions, and placental pathology has been linked to both active maternal disease and the risk of future health problems.[10-12] While associations exist between placental health and maternal obesity, diabetes, and hypertension, there are very few studies examining the impact of other maternal cardiovascular diseases (CVDs) on the placenta. Such information could improve our understanding of the pathophysiologic mechanisms responsible for adverse fetal outcomes in women with CVD during pregnancy and in turn might inform patient counseling and guide surveillance during pregnancy.

In this study, we sought to describe the pathological profile of placentas from pregnancies in women with CVD and to look for associations between types of maternal CVD and different placental pathologies.

MATERIALS AND METHODS

The Standardized Outcomes for Reproductive Cardiovascular Care (STORCC) initiative, designed to establish a standardized protocol for the clinical evaluation and management of pregnant women with CVD, is a prospective cohort study that has been enrolling subjects receiving care at Brigham and Women's Hospital since September 2011.[13] For this study, we reviewed women who had enrolled in the STORCC through June 2019 with CHD, arrhythmia, cardiomyopathy, connective tissue disease, acquired valvular disease, ischemic heart disease, or vascular disease and included only those pregnancies for which the placenta was examined by subspecialty pathologists skilled in placental histopathology. Women who experienced a miscarriage before 20 weeks' gestation were excluded. Placentas from twin pregnancies were excluded due to inability to reliably link placental findings with the appropriate twin. The Institutional Review Boards of Brigham and Women's Hospital and Boston Children's Hospital approved this protocol (IRB-P00001248, approved 8/9/2011), and written informed consent was obtained from each patient.

Data were collected at each patient's first visit, including baseline demographics, type of CVD, comorbid conditions, medications, and certain parameters from the enrollment physical examination. Detailed cardiac, obstetric, fetal, and neonatal data were collected prospectively at each clinic visit, during all admissions, during the postpartum visit, and for up to 1 year following delivery as detailed in the original publication.[13]

Women were categorized into the following groups based on their underlying cardiac condition: CHD, arrhythmia, cardiomyopathy, connective tissue disease, acquired valvular disease, ischemic heart disease, and vascular disease. When an individual had multiple cardiac conditions from more than one category, they were categorized according to what was felt to be the most significant condition. Those women with CHD were additionally assigned an anatomic-physiologic classification as detailed in the 2018 American Heart Association/American College of Cardiology Guideline for the Management of Adults with Congenital Heart Disease.[14,15]

PLACENTAL PATHOLOGY REVIEW. Placentas from deliveries at Brigham and Women's Hospital are sent for pathologic examination at the discretion of the delivering obstetrician. We reviewed records of women enrolled in the STORCC initiative for the availability of placental pathology. These pathology reports were then reviewed by an experienced placental pathologist (B.J.Q.) according to a predetermined list of pathologic findings (**Table 1**) which were then categorized into anatomic, infectious, inflammatory, and vascular groups based on consensus criteria put forward by the Amsterdam Placental Workshop Group.[16] A random sample of 10% of the placentas were audited by B.J.Q. before data analysis to ensure interobserver reproducibility.

STATISTICAL METHODS. Patient characteristics and clinical data were summarized using frequencies and percentages for categorical variables and median [range] for continuous variables. Categorical variables were compared across CVD categories and between placental pathology groups using Fisher exact test. Continuous variables were compared between subgroups using the Wilcoxon rank-sum test. All data analyses were performed using SAS, version 9.4, for Windows (SAS Institute, Inc). Unless otherwise indicated, all tests of significance are 2-sided with statistical significance judged as $P \leq 0.05$.

RESULTS

MATERNAL DEMOGRAPHICS AND CLINICAL CHARACTERISTICS. There were 474 pregnancies enrolled in the STORCC initiative through June 2019. From those, we examined 278 placentas from pregnancies for which the placentas had been sent for pathologic examination. Comparing these 278 pregnancies to the 196 excluded, there was no significant difference in maternal age (32 [29-36] years vs 33 [29-35] years, $P = 0.25$) or maternal New York Heart Association (NYHA) Class at enrollment (97% vs 96% NYHA Class I, $P = 0.50$). Placentas that were sent for examination were associated with lower birth weight (3.0 [2.6-3.4] vs 3.2 [2.9-3.5] kg, $P < 0.001$), earlier gestational age (39 [37-39] vs 39 [38-39] weeks, $P < 0.001$), lower Apgar at 5 minutes (9 [8-9] vs 9 [9-9], $P < 0.001$), and greater likelihood of neonatal intensive care unit (NICU) admission (27 vs 11%, $P < 0.001$).

From the 278 placentas examined, we ultimately excluded the seven pregnancies that were complicated by ischemic heart disease (n = 4) and vascular disease (n = 3) due to the small number of cases in these categories. After excluding another seven twin pregnancies, there remained 264 pregnancies (55.7% of the total STORCC pregnancies) among 232 women. Twenty-eight women had placentas from 2 separate pregnancies and 2 women had placentas from three separate pregnancies included. The majority of placentas resulted from pregnancies complicated by maternal CHD (65%). The remaining 35% were from pregnancies complicated by maternal arrhythmia (16%), cardiomyopathy (8%), connective tissue disease (8%), and valvular heart disease (4%). Among the patients with cardiomyopathy, 7 (35%) had hypertrophic cardiomyopathy, 7 (35%) had a history of peripartum cardiomyopathy, 4 (20%) had nonischemic cardiomyopathy, 1 (5%) had ischemic cardiomyopathy, and 1 (5%) had arrhythmogenic right ventricular cardiomyopathy.

Maternal demographic and clinical characteristics are summarized in **Table 2** (women who were pregnant more than once may be represented multiple times). Median maternal age at delivery was 32 years and was similar across maternal heart disease categories. Median body mass index was toward the upper limit of normal. Median gravidity was 2 (range: 1-9).

Nearly all women were asymptomatic (NYHA class I) at the time of enrollment (n = 254 [96%]); no women exhibited NYHA Class IV symptoms. However, the women had relatively complex heart disease, with 85% of CHD being categorized as moderately or greatly complex (Supplemental Table 1). Maternal risk factors for adverse cardiac outcomes during pregnancy included left ventricular outflow tract peak gradient ≥30 mmHg in 21 cases (8%), systemic ejection fraction ≤40% in 7 cases (3%), and O_2 saturation ≤90% in 3 cases (1%).

TABLE 1 Placental Pathology Groupings

Pathology Group	Pathology Findings
Anatomic	Small placenta by weight (<10th percentile) Large placenta by weight (>90th percentile) Marginal cord insertion Membranous cord insertion Coiling abnormalities (hypercoiled [>3 coils/10 cm] or hypocoiled [<1 coil/10 cm]) Single umbilical artery Membranous vessels True umbilical cord knot Other umbilical cord abnormalities Circumvallate membranes Accessory placental lobe Abnormal implantation (placenta accreta spectrum disorders)
Infectious	Acute chorioamnionitis
Inflammatory	Villitis of unknown etiology Lymphoplasmacytic deciduitis Chronic histiocytic intervillositis
Vascular	Abruption, not otherwise specified Acute abruption Chronic abruption Fetal vascular malperfusion (including chorionic plate or stem villous thrombosis, villous stromal-vascular karyorrhexis, avascular villi) Intravillous thrombosis Subchorionic thrombosis Maternal vascular malperfusion (including placental infarction, decidual arteriopathy, and hypermaturational changes)

PLACENTAL PATHOLOGY. The frequencies of specific placental pathologies among the entire cohort and for each maternal heart disease group are shown in **Table 3**. Of the 264 placentas, some form of placental pathology was identified in 199 (75%).

Anatomic pathology was present in 45% of all placentas, with small placenta by weight being the most common anatomic pathological finding (27%). Large placenta by weight (8%), abnormal cord insertion (6%), and abnormal placental implantation (placenta accreta spectrum disorders) (5%) were less commonly seen. Large placenta by weight differed significantly across categories of CVD ($P = 0.003$) and was most common in women with cardiomyopathy (30%). The relationship between cardiomyopathy and large placenta by weight remained statistically significant after adjusting for birth weight using logistic regression. For the entire cohort, there was a strong association between large placenta and birth weight (3.5 kg in the presence of large placenta vs 3.0 kg in the absence of large placenta, $P < 0.001$) and between small placenta and birth weight (2.7 kg in the

TABLE 2 Maternal Characteristics

	Total (n = 264)	CHD (n = 171)	ARR (n = 43)	CMP (n = 20)	CTD (n = 20)	VALV (n = 10)
Age at delivery (years)	32 (19-49)	31 (19-43)	32 (20-49)	32 (28-42)	31 (20-39)	33 (21-38)
Gravidity	2 (1-9)	2 (1-9)	2 (1-8)	2 (1-8)	2 (1-5)	3 (1-5)
Parity	1 (0-3)	1 (0-3)	0 (0-3)	1 (0-2)	0 (0-3)	0 (0-1)
Previous terminated pregnancy	36 (14%)	20 (12%)	6 (14%)	4 (20%)	2 (10%)	4 (40%)
Previous spontaneous abortion	83 (32%)	55 (32%)	12 (28%)	8 (40%)	3 (15%)	5 (50%)
Assisted reproductive technology	23 (9%)	12 (7%)	3 (7%)	4 (20%)	3 (15%)	1 (10%)
Body mass index (kg/m^2)	24 (17-48)	24 (17-48)	25 (19-48)	25 (18-47)	23 (18-35)	23 (20-45)
NYHA class at enrollment (n = 270)						
I	254 (96%)	163 (96%)	42 (98%)	19 (95%)	20 (100%)	10 (100%)
II	7 (3%)	5 (3%)	1 (2%)	1 (5%)	0	0
III	2 (1%)	2 (1%)	0	0	0	0
Medications during pregnancy[a]						
Any β-blocker	78 (30%)	37 (22%)	21 (49%)	7 (35%)	10 (50%)	3 (30%)
Any calcium channel blocker	10 (4%)	4 (2%)	4 (9%)	1 (5%)	1 (5%)	0
Any diuretic	8 (3%)	6 (4%)	1 (2%)	1 (5%)	0	0
Any ASA	60 (23%)	41 (24%)	7 (16%)	6 (30%)	3 (15%)	3 (30%)
Any heparin	10 (4%)	4 (2%)	5 (12%)	0	0	1 (10%)
Any coumadin/warfarin	8 (3%)	4 (2%)	1 (2%)	1 (5%)	1 (5%)	1 (10%)
Any of the above	131 (50%)	70 (41%)	32 (74%)	11 (55%)	12 (60%)	6 (60%)
Any prenatal vitamin	237 (90%)	157 (92%)	34 (79%)	17 (85%)	20 (100%)	9 (90%)
Any progesterone	16 (6%)	11 (6%)	2 (5%)	0	3 (15%)	0
Any inhaled vasodilator	12 (5%)	9 (5%)	0	2 (10%)	1 (5%)	0
Any SSRI	32 (12%)	18 (11%)	7 (16%)	3 (15%)	2 (10%)	2 (20%)
Any thyroid hormone	12 (5%)	8 (5%)	2 (5%)	0	2 (10%)	0
Any other	104 (39%)	62 (36%)	22 (51%)	8 (40%)	7 (35%)	5 (50%)
Prior risk factors						
NYHA class II-IV	7 (3%)	6 (4%)	1 (2%)	0	0	0
O_2 saturation ≤90%	3 (1%)	3 (2%)	0	0	0	0
Systemic EF ≤40%	7 (3%)	2 (1%)	0	5 (25%)	0	0
LVOT peak gradient ≥30 mmHg	21 (8%)	16 (9%)	0	3 (15%)	0	2 (20%)
Maternal smoking	25 (9%)	18 (11%)	3 (7%)	2 (10%)	0	2 (20%)
Type 2 diabetes	4 (2%)	2 (1%)	1 (2%)	0	1 (5%)	0
Subpulmonary EF ≤40%	1 (<1%)	1 (1%)	0	0	0	0
Obstetric/fetal outcomes						
Gestational age at delivery (wks)	39 (25-41)	39 (25-41)	39 (36-41)	39 (35-41)	39 (28-41)	38 (32-41)
Hypertensive disorders of pregnancy	34 (13%)	26 (15%)	2 (5%)	2 (10%)	2 (10%)	2 (20%)
Female infant (n = 261)	149 (57%)	95 (57%)	23 (53%)	11 (55%)	14 (70%)	6 (60%)
Birth weight (kg) (n = 260)	3.0 (0.8-4.3)	3.0 (0.8-4.3)	3.1 (1.9-4.1)	3.2 (2.5-4.2)	2.9 (1.2-3.7)	3.0 (1.9-3.9)
Apgar score (n = 262)						
1 minute	8 (0-9)	8 (0-9)	8 (1-9)	8 (2-9)	8 (1-9)	8 (0-9)
5 minutes	9 (0-10)	9 (0-10)	9 (5-9)	9 (4-9)	9 (7-9)	9 (0-9)
NICU admission	69 (26%)	52 (30%)	4 (9%)	4 (20%)	7 (35%)	2 (20%)

Values are median (range) or n (%). [a]There was no angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker use during pregnancy.

ARR = arrhythmia; ASA = acetylsalicylic acid; CHD = congenital heart disease; CMP = cardiomyopathy; CTD = connective tissue disease; CVD = cardiovascular disease; EF = ejection fraction; LVOT = left ventricular outflow tract; NICU = neonatal intensive care unit; NYHA = New York Heart Association; SSRI = selective serotonin reuptake inhibitor; VALV = valvular heart disease.

presence of small placenta vs 3.1 kg in the absence of small placenta, $P < 0.001$).

No cases of chronic lymphoplasmacytic deciduitis or chronic histiocytic intervillositis were seen in this cohort. Villitis of unknown etiology (VUE) (**Figures 1A and 1B**) accounted for all inflammatory pathologies and was present in 11% of placentas; prevalence differed across categories of CVD ($P = 0.008$) and was most common in maternal CHD (15%). There was no significant correlation between previous history of maternal heart surgery and the presence of VUE (13% in cases with a history of maternal heart surgery vs 8% in cases without a history of maternal heart surgery, $P = 0.23$).

TABLE 3 Frequency of Placental Pathology Findings by Maternal CVD Category

	Total (n = 264)	CHD (n = 171)	ARR (n = 43)	CMP (n = 20)	CTD (n = 20)	VALV (n = 10)	*P* Value
Any anatomic pathology	119 (45%)	70 (41)	22 (51)	14 (70)	10 (50)	3 (30)	0.094
Small placenta	70 (27)	43 (25)	16 (37)	3 (15)	6 (30)	2 (20)	0.38
Large placenta	22 (8)	8 (5)	4 (9)	6 (30)	2 (10)	2 (20)	**0.003**
Marginal cord insertion	12 (5)	10 (6)	0	1 (5)	1 (5)	0	0.46
Membranous cord insertion	5 (2)	4 (2)	1 (2)	0	0	0	1.00
Coiling abnormalities	7 (3)	4 (2)	1 (2)	1 (5)	1 (5)	0	0.53
True umbilical cord knot	2 (1)	1 (1)	0	1 (5)	0	0	0.37
Other umbilical cord abnormalities	2 (1)	2 (1)	0	0	0	0	1.0
Circumvallate membranes	1 (<1)	1 (1)	0	0	0	0	1.0
Abnormal implantation	13 (5)	10 (6)	0	2 (10)	1 (5)	0	0.33
Infectious							
Acute chorioamnionitis	61 (23)	35 (20)	10 (23)	4 (20)	7 (35)	5 (50)	0.17
Inflammatory							
Villitis of unknown etiology	28 (11)	26 (15)	0	1 (5)	0	1 (10)	**0.008**
Vascular							
Any vascular pathology	107 (41)	73 (43)	14 (33)	9 (45)	8 (40)	3 (30)	0.74
Maternal vascular malperfusion	68 (26)	46 (27)	8 (19)	8 (40)	5 (25)	1 (10)	0.36
Acute abruption	17 (6)	10 (6)	1 (2)	1 (5)	4 (20)	1 (10)	0.11
Chronic abruption	11 (4)	10 (6)	1 (2)	0	0	0	0.79
Abruption, NOS	22 (8)	13 (8)	2 (5)	1 (5)	5 (25)	1 (10)	0.11
Fetal vascular malperfusion	28 (11)	20 (12)	6 (14)	0	1 (5)	1 (10)	0.47

Values are n (%). *P* values ≤0.05 are in **bold**.

ARR = arrhythmia; CHD = congenital heart disease; CMP = cardiomyopathy; CTD = connective tissue disease; CVD = cardiovascular disease; NOS = not otherwise specified; VALV = valvular heart disease.

Vascular pathology was seen in 41% of placentas, the most common type being maternal vascular malperfusion (26%), and at similar rates across maternal CVD categories.

Infectious pathology (ie, acute chorioamnionitis) was seen in 23% of placentas and did not differ significantly across CVD categories. Placentas with acute chorioamnionitis tended to come from lower gravidity ($P = 0.032$) and lower parity ($P < 0.001$) women.

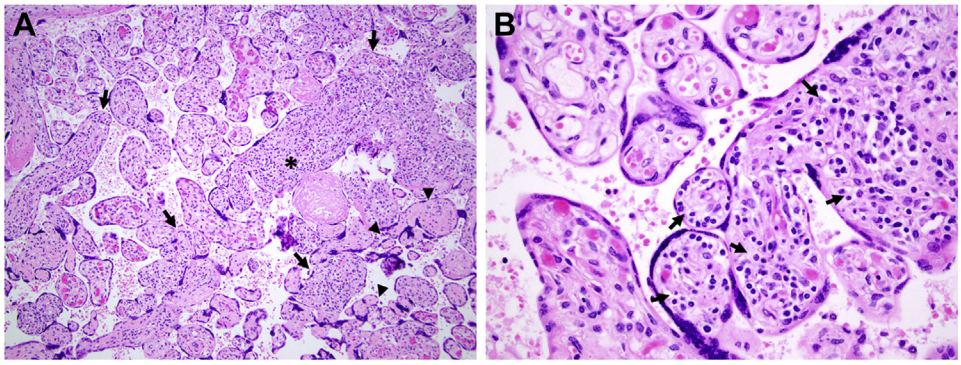
There was no association between gravidity, parity, or history of therapeutic or spontaneous abortion and inflammatory, anatomic, or vascular placental pathology (Table 4). Use of assisted reproductive technology was not associated with placental pathology, although this accounted for <10% of the included pregnancies. Among mothers with CHD, neither anatomic nor physiologic classification correlated with placental pathology.

The extent of subchorionic fibrin seen in placentas among maternal CVD categories is detailed in Table 5. Subchorionic fibrin plaques were observed and described as patchy, focal, or extensive in nearly half of all placentas. This was consistent across all maternal CVD categories. Extensive subchorionic fibrin was reported more commonly in maternal cardiomyopathy (20%) and CHD (18%) than in other maternal CVD categories. Extensive subchorionic fibrin was particularly common in placentas from mothers with Fontan physiology (50%) (Figures 2A and 2B), although they accounted for only a small percentage of the CHD cohort (n = 6 [3.5%]). The extent of subchorionic fibrin did not differ based on maternal aspirin or anticoagulant use during pregnancy among all subjects ($P = 0.23$) or within the maternal CHD cohort ($P = 0.70$).

MATERNAL AND NEONATAL OUTCOMES. Thirty-four (13%) of the 264 pregnancies were complicated by hypertensive disorders of pregnancy (HDPs) such as preeclampsia. The incidence of HDPs did not vary significantly between maternal CVD categories ($P = 0.34$). Placental pathology was not seen more frequently in pregnancies complicated by HDPs.

Median Apgar scores were 9 at 5 minutes across all maternal CVD categories (Table 2). Admission to the NICU was more frequent in our cohort than is reported in the general population (26% vs 7.8%).[17] Rates of NICU admission varied by maternal CVD category ($P = 0.036$). NICU admission was most common for neonates of mothers with CHD and connective tissue disease (30% and 35%, respectively), while neonates born to mothers with arrhythmia had the lowest rate of NICU admission (9%). The most common indication among the 69

FIGURE 1 Photomicrographs of One of the Placentas Showing Extensive Villitis of Unknown Etiology



(A and B) Photomicrographs of one of the placentas showing extensive villitis of unknown etiology characterized by numerous villi **(arrows)** expanded by chronic inflammatory infiltrate consisting of maternal lymphocytes and histiocytes with resultant obliteration of fetal capillaries. A stem villus **(*)** with obliterative fetal vasculopathy is readily seen with resultant adjacent avascular villi **(arrowheads)**. For comparison, adjacent noninflamed chorionic villi with open fetal capillaries filled with red blood cells are present (hematoxylin and eosin, 10×). On closer view, the chronic inflammatory cells **(arrows)** can be seen within the villi with loss of fetal capillaries in the inflamed areas. Adjacent normal chorionic villi with open fetal capillaries are observed (hematoxylin and eosin, 40×).

NICU admissions was prematurity (46%); other common indications were respiratory distress (29%), hypoglycemia (17%), CHD (13%), low Apgar score (13%), and small for gestational age (12%). In some cases, more than one indication for NICU admission was listed.

Anatomic pathology was associated with earlier delivery (38 weeks vs 39 weeks, $P = 0.046$) and lower birth weight (2.9 kg vs 3.1 kg, $P = 0.027$), although preterm birth (<37 weeks), specifically, was not a risk factor (22% vs 17%, $P = 0.43$). Acute chorioamnionitis was associated with higher birth weight (3.2 kg in cases with acute chorioamnionitis vs 3.0 kg in cases without acute chorioamnionitis, $P = 0.046$). No relationship was seen between VUE or vascular pathology and birth weight or gestational age at delivery.

DISCUSSION

We examined placentas in a cohort of women with CVD and correlated pathologic findings with heart disease subtypes. Gross anatomical abnormalities, inflammatory conditions, and infectious and vascular pathology were commonly seen, with 75% of the placentas showing some abnormal finding. Small placenta by weight, one of the chronic manifestations of uteroplacental insufficiency, was particularly common, as were pathologic features related to maternal vascular malperfusion. Placentas of women with CHD were significantly more likely to be affected by VUE than those of women with other forms of CVD.

The association between VUE and maternal CHD is not one that has been previously described. VUE has been considered a gestational analog of host-vs-graft immune reaction.[18,19] We know that compared to heart transplant in acquired heart disease, transplant in CHD is associated with an increased risk of rejection due to increased levels of human leukocyte antigen antibodies from prior blood transfusions and, for some, from homograft implants used in previous heart surgeries.[20] However, while it seems reasonable to postulate that VUE in maternal CHD is driven by the same mechanisms, we were unable to demonstrate a correlation between previous maternal heart surgery and VUE.

Although the placenta is primarily fetal in origin, placental development is influenced by both fetal and maternal factors during implantation (**Central Illustration**). A link between placental pathology and fetal CHD has been well demonstrated in recent studies.[21-23] One revealed a significant correlation between placental defects and heart, brain, and vascular maldevelopment. The findings suggest that molecular coregulatory or interdependent pathways during organogenesis exist between the placenta and these organ systems.[24]

The relationship between placental pathology and maternal CVD has been less well studied. Maternal CVD has been associated with adverse fetal outcomes and an increased risk of preeclampsia,[25-27] which is now understood to have an etiology rooted in the placenta. However, the impact of maternal CVD on the health of the placenta itself has been studied only

TABLE 4 Maternal/Fetal Characteristics by Placental Pathology Group

	Anatomic			Infectious			Inflammatory			Vascular		
Entire Cohort	**Abnormal (n = 119)**	**Normal (n = 145)**	***P* Value**	**Abnormal (n = 61)**	**Normal (n = 203)**	***P* Value**	**Abnormal (n = 28)**	**Normal (n = 236)**	***P* Value**	**Abnormal (n = 107)**	**Normal (n = 157)**	***P* Value**
Gravidity	2 (1-8)	2 (1-9)	0.88	2 (1-5)	2 (1-9)	**0.032**	2 (1-5)	2 (1-9)	0.52	2 (1-8)	2 (1-9)	0.58
Parity	1 (0-3)	1 (0-3)	0.93	0 (0-3)	1 (0-3)	**<0.001**	1 (0-3)	1 (0-3)	0.68	1 (0-3)	1 (0-3)	0.80
Previous terminated pregnancy	15 (13%)	21 (14%)	0.72	10 (16%)	26 (13%)	0.52	2 (7%)	34 (14%)	0.55	9 (8%)	27 (17%)	**0.045**
Previous spontaneous abortion	38 (32%)	45 (31%)	0.89	17 (28%)	66 (33%)	0.53	6 (22%)	77 (33%)	0.38	37 (35%)	46 (29%)	0.42
Assisted reproductive technology	12 (10%)	11 (8%)	0.52	6 (10%)	17 (8%)	0.80	4 (14%)	19 (8%)	0.28	10 (9%)	13 (8%)	0.83
Hypertensive disorder of pregnancy	14 (12%)	20 (14%)	0.71	7 (12%)	27 (13%)	0.83	4 (14%)	30 (13%)	0.77	15 (14%)	19 (12%)	0.71
Preterm birth (n = 263)	26 (22%)	25 (17%)	0.43	9 (15%)	42 (21%)	0.36	6 (21%)	45 (19%)	0.80	26 (25%)	25 (16%)	0.11
CHD Patients Only	**Abnormal (n = 70)**	**Normal (n = 101)**	***P* Value**	**Abnormal (n = 35)**	**Normal (n = 136)**	***P* Value**	**Abnormal (n = 26)**	**Normal (n = 145)**	***P* Value**	**Abnormal (n = 73)**	**Normal (n = 98)**	***P* Value**
Anatomic classification			0.46			0.17			0.28			0.62
I	10 (14%)	16 (16%)		6 (17%)	20 (15%)		6 (23%)	20 (14%)		9 (12%)	17 (17%)	
II	42 (60%)	67 (66%)		18 (51%)	91 (67%)		17 (65%)	92 (63%)		49 (67%)	60 (61%)	
III	18 (26%)	18 (18%)		11 (31%)	25 (18%)		3 (12%)	33 (23%)		15 (21%)	21 (21%)	
Physiologic classification			0.36			0.31			0.97			0.70
A	7 (10%)	13 (13%)		4 (11%)	16 (12%)		3 (12%)	17 (12%)		7 (10%)	13 (13%)	
B	19 (27%)	37 (37%)		16 (46%)	40 (29%)		8 (31%)	48 (33%)		22 (30%)	34 (35%)	
C	42 (60%)	50 (49%)		15 (43%)	77 (57%)		15 (58%)	77 (53%)		43 (59%)	49 (50%)	
D	2 (3%)	1 (1%)		0	3 (2%)		0	3 (2%)		1 (1%)	2 (2%)	

Values are as n (%). *P* values ≤0.05 are in **bold**.
CHD = congenital heart disease.

in a limited context. Several studies have focused on Doppler measures of uteroplacental blood flow, particularly indices of placental vascular resistance, as an indicator of placental health in women with CVD.[28-30] Abnormalities of placental development result in abnormal uteroplacental flow and resistance and correlate with maternal heart function and risk of preeclampsia, fetal growth restriction, and perinatal mortality.

One recent case series by Phillips et al.[31] has provided detailed evaluation of placental pathology in the setting of maternal CVD. Their analysis, which focused on 13 deliveries in seven women with complex CHD palliated to a Fontan circulation, found a high rate of premature birth and fetal growth restriction. Preeclampsia developed in 2 pregnancies. The primary pathologic finding reported in this series was prominent subchorionic fibrin deposition which was seen in all placentas. Circummargination of part of the fetal membrane insertion, a placental finding thought to reflect chronic abruption by some, was also noted in four placentas, and a variable degree of villous hypoplasia was present in four placentas as well. The authors speculated that the unusual subchorionic fibrin deposition was likely due to venous stasis from elevated vascular resistance and suggested a possible pathophysiologic mechanism whereby pronounced fibrin deposition impairs fetal perfusion through vascular compression. In our study, 4 of 6 placentas from our Fontan cohort showed prominent subchorionic fibrin, with 3 of these characterized as having extensive subchorionic fibrin.

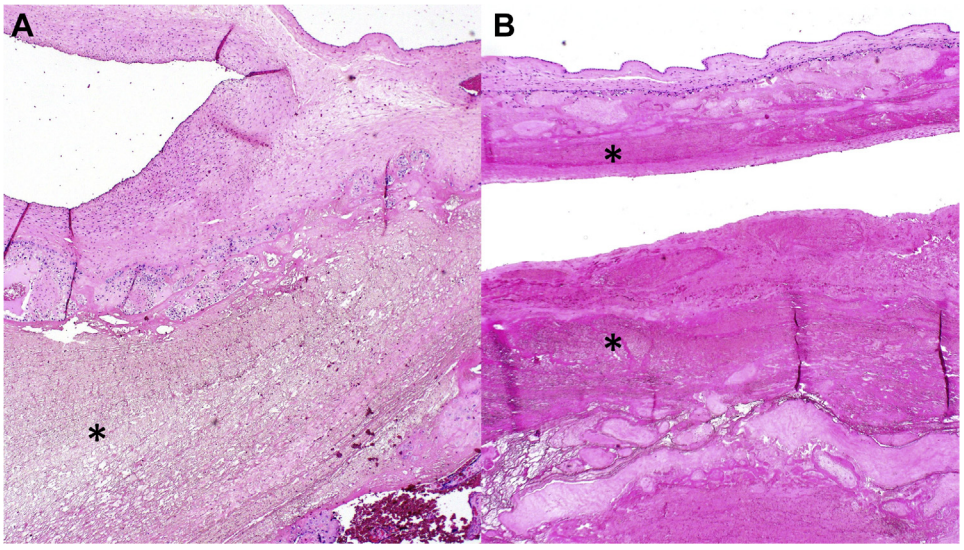
The findings of our group and of Phillips et al. justify further research into the relationship between maternal CVD and placental development. In 1997, the College of American Pathologists published guidelines for examining placentas in high-risk pregnancies.[32] Although "systemic disorders with

TABLE 5 Subchorionic Fibrin by Maternal CVD Category

		CHD					
	Total (n = 264)	**All CHD (n = 171)**	**Fontan Only (n = 6)**	**ARR (n = 43)**	**CMP (n = 20)**	**CTD (n = 20)**	**VALV (n = 10)**
Extensive	37 (14)	30 (18)	3 (50)	2 (5)	4 (20)	0	1 (10)
Patchy/focal	80 (30)	50 (29)	1 (17)	14 (33)	5 (25)	6 (30)	5 (50)
Normal/none/minimal	145 (55)	90 (53)	2 (33)	27 (63)	10 (50)	14 (70)	4 (40)
Unknown	2 (1)	1 (1)	0	0	1 (6)	0	0

Values are n (%).
ARR = arrhythmia; CHD = congenital heart disease; CMP = cardiomyopathy; CTD = connective tissue disease; VALV = valvular heart disease.

FIGURE 2 Representative Photomicrographs From Placentas of Two Mothers With Fontan Circulation Showing Prominent Subchorionic Fibrin Buildup (*)



(A and B) Placenta A came from a 30-year-old G4P2113 mother with L-transposition of the great arteries, pulmonary atresia, straddling tricuspid valve, and a hypoplastic right ventricle who had been palliated to a lateral tunnel Fontan. She delivered a healthy boy via spontaneous vaginal delivery at 37 weeks' gestation. Placenta B came from a 31-year-old G1P0101 mother with double-inlet left ventricle and pulmonary stenosis who had been palliated to a lateral tunnel Fontan. She presented to the emergency room at 28 weeks' gestation with hemodynamically unstable atrial fibrillation. In the course of cardioversion, persistent fetal bradycardia was observed, and an emergency cesarean section was performed (hematoxylin and eosin, 4×).

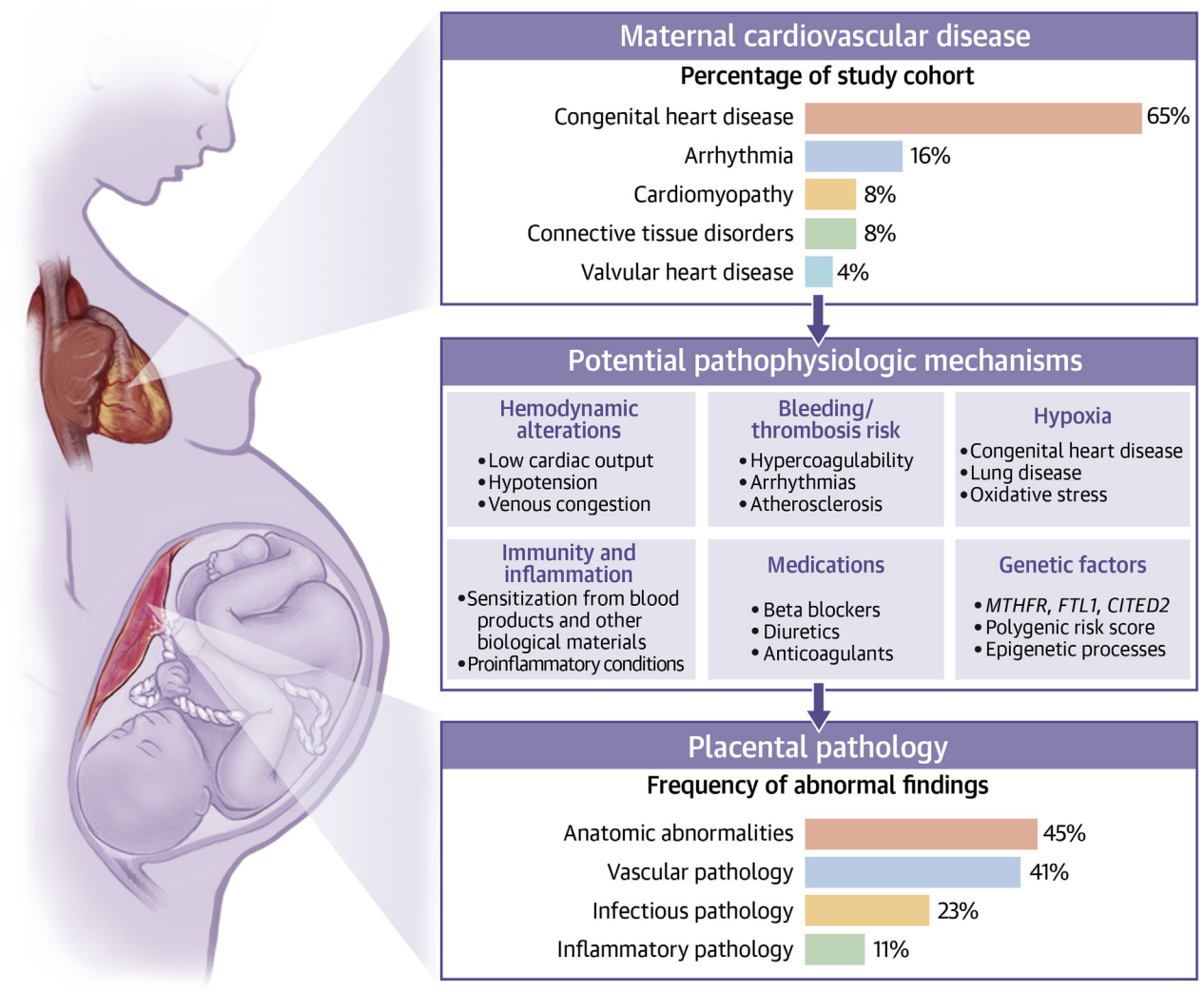
clinical concerns for mother or infant" is included as one indication for placental examination, it does not explicitly list maternal CVD as an example of such a disorder. We maintain that the presence of maternal CVD should be considered as an indication for automatic submission of the placenta for detailed histopathologic examination, especially given the rate of pathologic findings seen among our cohort of placentas.

STUDY LIMITATIONS. To the best of our knowledge, ours is the largest and most inclusive study of placental pathology in pregnancies complicated by maternal CVD to date. However, we recognize some notable limitations to our study. First, although the STORCC initiative is an ongoing, prospective effort, our analysis of placentas from the STORCC cohort was done using a retrospective design. Placentas were not submitted for pathologic examination in a standardized manner; therefore, this may result in a selection bias, with healthier women being less frequently represented. This may be compounded by our institution's role as a tertiary care center, resulting in a cohort of women with more complex heart disease than might be seen at other centers.

Second, our study does not include placentas from healthy controls. Although we were able to find one single-center review of placental pathology in term pregnancies with normal outcomes,[33] the absence of robust population data regarding placental pathology findings makes it difficult, if not impossible, to prove whether our findings represent an excess of pathology beyond that which would normally be expected.

Finally, the women in our cohort are largely made up of those with CHD. While we feel our cohort is a representative cross section of women with CVD who choose to get pregnant, this also means limited power in the analysis of the smaller CVD subgroups, most notably cardiomyopathy, connective tissue disease, and valvular disease. Atherosclerotic coronary artery disease and spontaneous coronary artery dissection were excluded from our analysis due to the very limited number of subjects with these diagnoses. However, as the risk profile of women choosing to become pregnant changes, these subpopulations may make up an increasingly important cohort that warrants further study. This highlights the need for a multicenter prospective study to improve representation from smaller subpopulations such as those identified previously.

CENTRAL ILLUSTRATION **Placental Pathology in Pregnancies Complicated by Maternal Cardiovascular Disease and Their Potential Pathophysiologic Mechanisms**



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CONCLUSIONS

In summary, we present a detailed assessment of placental pathology resulting from pregnancies complicated by maternal CVD. Gross anatomical abnormalities and vascular placental pathology were most common among our cohort as a whole, and a significantly higher rate of noninfectious inflammatory conditions in the form of VUE was seen among women with CHD than among women with other forms of CVD. In spite of these findings, maternal and fetal outcomes were generally favorable. Institutional policies to routinely submit placentas for pathologic examination in pregnancies complicated by maternal CVD would greatly improve our understanding of the relationship between maternal CVD and placental development. In addition, study of placentas from normal, uncomplicated deliveries is needed to better understand the significance of our aforementioned findings.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Placental development is influenced by both fetal and maternal factors during implantation, yet the influence of maternal CVD on the health of the placenta has only been studied to a limited degree. Abnormalities of placental development result in altered uteroplacental flow and resistance and correlate with risk of preeclampsia, fetal growth restriction, and perinatal mortality. This could be one mechanism by which maternal CVD leads to an increased rate of adverse pregnancy outcomes and may be a useful clinical indicator during routine obstetric evaluation.

TRANSLATIONAL OUTLOOK: Our findings justify further research into the relationship between maternal CVD and placental development. We believe that the presence of maternal CVD should be considered as an indication for routine submission of the placenta for detailed histopathologic examination, especially given how commonly pathologic findings were seen in our cohort of placentas.

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KEY WORDS adult congenital heart disease, cardio-obstetrics, histopathology, placentation, villitis of unknown etiology

APPENDIX For a supplemental table, please see the online version of this paper.