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ORIGINAL RESEARCH

Placental Vascular Malperfusion in Pregnancies With Congenital Heart Disease

A Prospective Comparative Study

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ABSTRACT

BACKGROUND Advances in congenital heart disease (CHD) management have improved survival rates, resulting in a growing population of women of childbearing age with CHD. These women face higher risk of obstetric and neonatal complications during pregnancy. While the underlying mechanisms remain unclear, previous studies have identified maternal vascular malperfusion (MVM) in their placentas.

OBJECTIVES This study aimed to compare the prevalence of MVM in pregnant women with CHD to those without CHD, assess its association with obstetric and neonatal outcomes, and explore potential risk factors for MVM.

METHODS In this prospective single-center study, we enrolled pregnant women with CHD who were followed from March 2021 to June 2023, along with a control group matched for age, parity, and body mass index. Placentas were analyzed for MVM using a scoring system based on the Amsterdam Placental Workshop Group Consensus guidelines. N-terminal pro b-type natriuretic peptide assays in the second trimester and echocardiography in the third trimester were performed to evaluate maternal cardiovascular health.

RESULTS Placentas from 39 CHD and 67 control women were analyzed. MVM prevalence was significantly higher in the CHD group compared to controls (56.4% vs 13.4%, $P < 0.001$). CHD pregnancies had a higher incidence of adverse obstetric and neonatal outcomes, which were independently associated with MVM (RR: 7.2, $P = 0.002$). No clinical or paraclinical factors were associated with MVM in CHD women.

CONCLUSIONS Women with CHD had a higher prevalence of MVM compared to controls, which was associated with adverse pregnancy outcomes. However, no clinical or paraclinical risk factors for MVM were identified. (JACC Adv. 2025;4:101592) © 2025 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

ACHD = adult congenital heart disease

ASD = atrial septal defect

CHD = congenital heart disease

ED = endothelial dysfunction

FGR = fetal growth restriction

HDPs = hypertensive disorders of pregnancy

LV = left ventricle

MVM = maternal vascular malperfusion

NT-proBNP = N-terminal pro-B-type natriuretic peptide

PIH = pregnancy-induced hypertension

RHI = reactive hyperemia index

RV = right ventricle

S/D = systolic/diastolic

TPL = threatened preterm labor

VSD = ventricular septal defect

Advances in the management of congenital heart disease (CHD) in the last decades have improved survival rates for patients, resulting in a growing population of childbearing women living with CHD.[1] These women face a higher risk of cardiac complications during pregnancy,[2,3] as well as obstetric and neonatal complications, such as preeclampsia, preterm delivery, and fetal growth restriction (FGR).[3,4]

Unlike maternal cardiac complications, these latter outcomes have been less investigated, and their underlying mechanisms remain poorly understood. Impaired placental function has emerged as a key hypothesis.[5-7] The placenta is a vital interface for the oxygen and nutrients supply to the fetus. An impaired placental development, potentially affected by maternal health, is associated with adverse fetal outcomes.[8-10] Retrospective histopathological studies have identified placental abnormalities in women with CHD, with vascular pathology, particularly maternal vascular malperfusion (MVM), being the most prevalent.[11,12] To date, only one study has compared placentas of women with CHD to those without, identifying MVM as the sole placental pathology significantly more frequent in the CHD group.[13]

Lesions characteristic of MVM, including villous maldevelopment, result from hypoxic/ischemic and oxidative damage to the placenta.[14,15] These hypoxic conditions are hypothesized to be more prevalent in CHD-affected pregnancies due to potential hemodynamic alterations that may compromise placental perfusion.

Nevertheless, studies on MVM in CHD-affected pregnancies remain scarce and require prospective validation. Consequently, in this prospective study, we first aimed to assess the prevalence of MVM in pregnant women with CHD compared with a control group. The secondary objectives were: 1) to investigate the association between MVM and adverse obstetric and neonatal outcomes; and 2) to explore potential clinical and paraclinical risk factors associated with MVM in CHD pregnancies.

METHODS

STUDY POPULATION. In this prospective study, all women ≥18 years of age with CHD who were pregnant between March 1, 2021, and June 1, 2023, were screened from the Adult Congenital Heart Disease (ACHD) Consultation at Cliniques Universitaires Saint-Luc. Women without CHD who were pregnant during the same period were recruited from the Cliniques Universitaires Saint-Luc obstetrics consultation. Women were included during the first trimester, between 6 weeks + 0 days and 13 weeks + 6 days of gestation.

High-risk pregnancies were excluded from both groups. This included women with chronic inflammatory or infectious diseases, immunosuppression, multiple gestations, or a history of preeclampsia, FGR, or preterm birth in previous pregnancies. Additionally, patients who smoked or consumed alcohol at any point during their pregnancy were excluded. To further homogenize the two groups of women with and without CHD in terms of risk factors influencing pregnancy outcomes, we matched them for age, parity, and body mass index.

The study protocol was approved by our Institutional Review Board (*Comité d'éthique hospitalo-facultaire Saint-Luc - UCL*, Reference: 2020/09DEC/612, Belgian Registration Number: BE4032020000120), and written informed consent was obtained from all participants.

PREGNANCY OUTCOMES. *Obstetric and neonatal outcomes* were defined as the occurrence of one of the following complications during pregnancy or postpartum: threatened preterm labor (TPL), defined as uterine contractions before 37 weeks of gestation requiring tocolysis; pregnancy-induced hypertension (PIH), defined as new-onset hypertension (blood pressure ≥140 mm Hg systolic or ≥90 mm Hg diastolic) without proteinuria after 20 weeks of gestation; preeclampsia, defined as PIH accompanied by at least one of the following criteria: ≥0.3 g protein in a 24-hour urine sample, maternal organ dysfunction, or FGR; placental abruption; preterm birth (<37 weeks' gestation); and small-for-gestational-age, defined as newborn weight <10th percentile. The term hypertensive disorders of pregnancy

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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(HDPs) were used to refer to the presence of PIH and/or preeclampsia.

ECHOCARDIOGRAPHY. All patients underwent third-trimester echocardiography (between 27 + 0 and 37 + 6 weeks' gestation) using ultrasound systems (Epiq system, Philips Healthcare). Examinations were performed by experienced sonographers, following the European Association of Cardiovascular Imaging guidelines.[16-18] Detailed echocardiographic methods, including measurement protocols for systolic function, ventricular dimensions, valvular assessment, and the classification of residual lesions in CHD patients, are provided in the Supplemental Appendix.

N-TERMINAL PRO B-TYPE NATRIURETIC PEPTIDE ASSAY. Blood samples were collected via venipuncture during the second trimester of pregnancy (between 19 and 27 week's gestation) for N-terminal pro-B-type natriuretic peptide (NT-proBNP) assay. We chose the second trimester for assays, as NT-proBNP levels measured at 20 weeks' gestation have been shown to predict cardiac events in pregnant women with CHD.[19] Details of the assay protocol can be found in the Supplemental Appendix.

UTEROPLACENTAL DOPPLER. Standardized uteroplacental Doppler flow measurements were performed in all patients between 20 and 24 weeks' gestation using an ultrasound system (General Electrics E10) by experienced obstetricians. The systolic/diastolic (S/D) ratios of the left and right uterine arteries, as well as the presence of an early diastolic notch, were recorded. An abnormal finding was defined as a mean S/D ratio—calculated as the average of the left and right uterine artery S/D ratios—greater than 3 and/or the persistence of an early diastolic notch after 26 weeks of gestation.

PLACENTAL PATHOLOGY. Placentas from both CHD and control women were collected after delivery. Details of the sampling and tissue processing methods are provided in the Supplemental Appendix. Evaluation of the slides was performed by an expert pathologist (P.B.), alongside a medical intern trained in histology, following the protocols outlined by the Amsterdam Placental Workshop Group Consensus Statement.[20] The CHD status of the mothers was concealed during the evaluation of the slides to mitigate bias. MVM was assessed through a scoring system that allocated points according to the presence and severity of MVM criteria as defined by the Amsterdam Consensus (Supplemental Table 1). This methodology has been previously applied in pathological studies of preeclamptic placentas.[21,22]

STATISTICAL ANALYSES. All analyses were conducted using R (R Core Team, 2020) and RStudio (Rstudio Team, 2020). Continuous variables were expressed as mean ± 1 SD for variables with symmetric distributions or as median (25th-75th percentiles) for variables with asymmetric distributions. The distribution of variables was assessed using histograms, Q-Q plots, boxplots, and complemented by measures of skewness and kurtosis. Categorical variables were expressed as counts (percentages). Group comparisons were performed using the Student's *t*-test or the Mann-Whitney test for continuous variables, and the chi-square test or Fisher's exact test for categorical variables, as appropriate. A 2 P value <0.05 was considered statistically significant. P values and CIs were not adjusted for multiple comparisons and should therefore be interpreted with caution.

To assess the association between MVM and pregnancy outcomes, patients were categorized based on MVM presence (defined as an MVM score >90th percentile of controls, ie, MVM score >1), and outcomes were compared between MVM and non-MVM groups. A multivariable Poisson regression model was used to adjust the association between MVM and pregnancy outcomes (dependent variable) for CHD status. This analysis was restricted to 2 covariates—MVM (primary independent variable) and CHD status—due to the limited number of events.

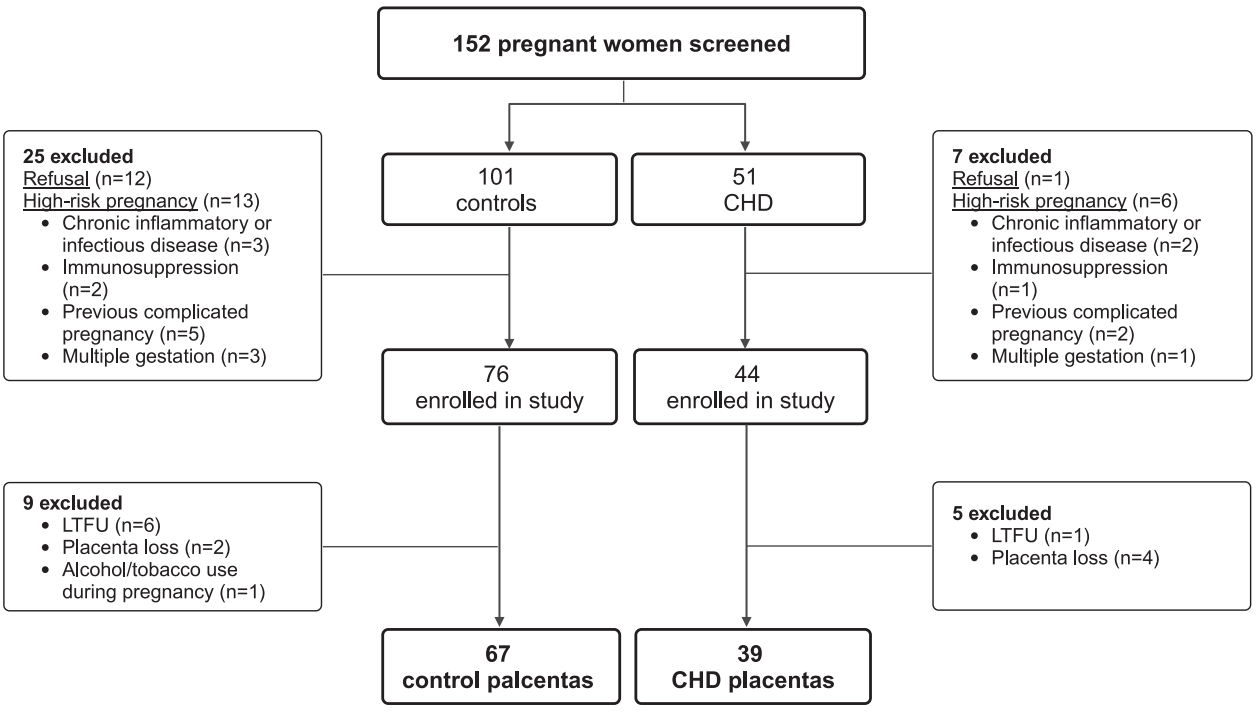
A univariable Poisson regression was used to explore risk factors associated with MVM in CHD patients. Pearson's or Spearman's correlation coefficients were used to examine variable relationships, depending on data distribution.

RESULTS

PATIENT BASELINE CHARACTERISTICS. A total of 152 women were initially screened, including 101 without CHD and 51 with CHD. After excluding 32 participants due to refusal or high-risk pregnancies (specific exclusion criteria detailed in Supplemental Table 2), and an additional 14 exclusions during the study, the final cohort consisted of 67 control women and 39 women with CHD, whose placentas were submitted for histopathological analysis (**Figure 1**). No previously undiagnosed CHD was found in the control group during third-trimester echocardiographic assessment.

The distribution of CHD lesions in our cohort is shown in **Figure 2**. Atrial septal defect (ASD), ventricular septal defect (VSD), and tetralogy of Fallot together accounted for over 50% of the CHD lesions. According to the European Society of Cardiology

FIGURE 1 Study Flowchart



Of the 152 women initially screened, 32 were excluded due to high-risk pregnancies or refusals. Among the 120 women enrolled in the study, 14 additional participants were excluded during pregnancy follow-up. The final cohort consisted of 67 controls and 39 women with CHD whose placentas were submitted for histopathological analysis. CHD = congenital heart disease; LTFU = lost to follow-up.

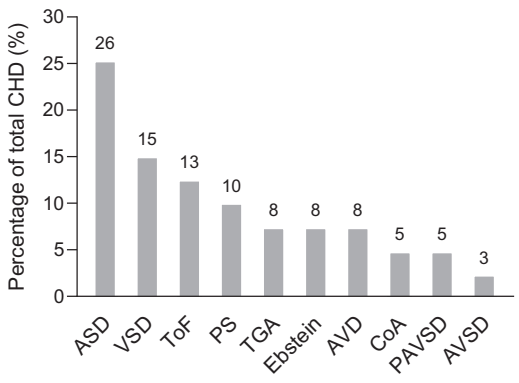
classification for CHD complexity,[23] the majority of CHDs were classified as mild (43.6%) or moderate CHD (51.3%), while only 5.1% were classified as severe. All cyanotic CHD (n = 11) were surgically repaired before pregnancy. Both patients with transposition of the great arteries underwent arterial switch correction.

The CHD and control groups exhibited comparable baseline characteristics (Table 1), with the exception of a significantly higher rate of in vitro fertilization in the CHD group ($P = 0.025$) and a higher prepregnancy smoking rate among CHD patients ($P = 0.003$), but without active smoking during pregnancy. Women with CHD presented a pregnancy risk profile similar to that of the control group, as evidenced by the absence of significant differences in pregnancy risk factors such as maternal age, gestational diabetes, and weight gain during pregnancy.

PREGNANCY DATA AND OUTCOMES. Second-trimester NT-proBNP levels, measured in 77 patients (25 CHD and 52 controls), were significantly higher in the CHD group compared to controls (70.4 [47-112] pg/mL vs 48.9 [30-70] pg/mL, $P = 0.012$). Uteroplacental Doppler measurements showed a similar mean S/D ratio between groups (2.18 ± 0.45 for CHD patients *vs* 2.10 ± 0.41 for controls, $P = 0.466$), with only one CHD and one control patient exhibiting a mean S/D ratio greater than 3. Table 2 shows echocardiographic data. Left and right heart chamber dimensions were increased in CHD patients, with all cases of left ventricle (LV) and right ventricle (RV) dilatation occurring in this group. Left ventricular ejection fraction and RV fractional area change were similar between groups. None of the control patients had valvular disease, compared to 36% of the CHD group ($P < 0.001$).

The pregnancy and delivery outcomes are summarized in Table 3. No differences were found in delivery mode, induced labor, instrumentation use, or epidural anesthesia between groups. CHD pregnancies had a significantly higher incidence of obstetric and neonatal events (30.8% vs 9.0%, $P = 0.009$), including increased rates of HDPs ($P = 0.010$) and TPL ($P = 0.049$). All preterm births occurred in the CHD group (n = 4, $P = 0.017$).

FIGURE 2 Distribution of Congenital Heart Disease Types Among Participants



The bar graph shows the distribution of CHD types among the study participants (n = 39). The most common types included ASD, VSD, and ToF. ASD = atrial septal defect (n = 10); AVD = aortic valve dysplasia (n = 3); AVSD = atrioventricular septal defect (n = 1); CoA = coarctation of the aorta (n = 2); Ebstein anomaly (n = 3); PAVSD = pulmonary atresia with ventricular septal defect (n = 2); PS = pulmonary stenosis (n = 4); TGA = transposition of the great arteries (n = 3); ToF = tetralogy of Fallot (n = 5); VSD = vventricular septal defect (n = 6); other abbreviation as in Figure 1.

TABLE 1 Baseline Characteristics of Patients

	All (N = 106)	Controls (n = 67)	CHD (n = 39)	*P* Value
Maternal age at pregnancy, y	29.5 ± 4.2	29.6 ± 3.9	29.5 ± 4.6	0.915
Primiparous	58 (54.7)	38 (56.7)	20 (51.3)	0.734
In vitro fertilization	6 (5.7)	1 (1.5)	5 (12.8)	**0.025**
Prepregnancy CVRF				
Hypertension	2 (1.8)	1 (1.4)	1 (2.6)	1.000
Diabetes	0 (0.0)	0 (0.0)	0 (0.0)	-
History of smoking	8 (7.5)	1 (1.4)	7 (17.9)	**0.003**
Obesity (BMI ≥30 kg/m^2)	15 (13.9)	8 (11.6)	7 (17.9)	0.530
Baseline clinical parameters[a]				
Heart rate, bpm	76.6 ± 11.2	76.6 ± 9.5	76.6 ± 14.4	0.996
Systolic blood pressure, mm Hg	119 ± 10.8	119 ± 10.0	118 ± 12.4	0.929
Diastolic blood pressure, mm Hg	71.6 ± 9.4	71.0 ± 9.1	73.0 ± 9.8	0.344
SpO2, %	98.5 ± 1.3	98.7 ± 1.2	98.2 ± 1.3	0.245
BMI, kg/m^2	24.9 ± 4.9	24.4 ± 4.4	25.8 ± 5.7	0.225
Pregnancy risk factors				
Age >35 y	9 (8.3)	6 (8.7)	3 (7.7)	1.000
Active smoking during pregnancy	0 (0.0)	0 (0.0)	0 (0.0)	-
Gestational diabetes	12 (11.1)	6 (8.7)	6 (15.4)	0.345
Total weight gain, kg	9.6 ± 5.1	9.7 ± 4.9	9.2 ± 5.6	0.678

Values are mean ± SD or n (%). Values in **bold** correspond to *P* values <0.05. [a]Parameters at first trimester of pregnancy (inclusion).
BMI = body mass index; CHD = congenital heart disease; CVRF = cardiovascular risk factors.

To further explore the factors associated with adverse outcomes, we compared patients with and without events across the entire cohort. This analysis confirmed a significantly higher proportion of CHD patients in the group with adverse events ($P = 0.009$) (Supplemental Table 3). Additionally, detailed comparisons of baseline characteristics, echocardiographic parameters, NT-proBNP levels, and uterine Doppler findings between these groups are presented in Supplemental Tables 3 to 6.

PATHOLOGICAL FINDINGS. Anatomical and pathological analysis of collected placentas is summarized in **Table 4**. We identified that 56.4% (n = 22) of placentas from CHD women exhibited MVM compared to 13.4% in the control group ($P < 0.001$). Additionally, the MVM score was significantly higher in the CHD group (2 [1-3] vs 0 [0-1], $P < 0.001$) (**Figure 3A**), and placentas with an MVM score >1 predominantly came from CHD patients (**Figure 3B**). Macroscopically, all placental infarcts were identified in CHD patients ($P = 0.006$). All microscopic lesions constituting MVM criteria were significantly more common in CHD placentas (**Table 4**). We did not find any significant differences in the incidence of other histological lesions, including chorioamnionitis, chronic villitis, chorangiosis, and delayed villous maturation.

ASSOCIATION BETWEEN MVM AND PREGNANCY OUTCOMES. Comparison between patients with MVM (n = 31) and without MVM (n = 75) revealed significantly higher rates of adverse obstetric and neonatal outcomes in the MVM group (45.2% vs 5.3%, $P < 0.001$) (Supplemental Table 7). The group with MVM experienced higher rates of HDPs, TPL, placental abruption, and small-for-gestational-age (**Figure 4**). Additionally, MVM score was negatively correlated with newborn weight ($r_s = -0.36$, $P < 0.001$). A trend toward a higher rate of preterm birth was also observed in the group with MVM ($P = 0.074$).

After adjustment for CHD, a significant association was still observed between MVM and obstetric and neonatal outcomes (RR: 7.2, $P = 0.002$) (Supplemental Table 8).

RISK FACTORS ASSOCIATED WITH MVM IN CHD PATIENTS. Univariable analysis showed that none of the clinical, biological, or echocardiographic parameters were significantly associated with MVM in CHD patients (**Figure 5**). Surprisingly, CHD complexity was also not associated with MVM. Indeed, when comparing the percentage of placentas with MVM across CHD complexity groups, no significant difference was found (Supplemental Table 9), underscoring the lack of correlation between CHD complexity and MVM severity score ($r_s = 0.09$, $P = 0.556$). Interestingly, even within the mild CHD group, 47.1% (n = 8)

TABLE 2 Third Trimester Echocardiography Data

	All (N = 106)	Controls (n = 67)	CHD (n = 39)	*P* Value
Left ventricle				
LVED diameter, cm	4.66 ± 0.49	4.49 ± 0.41	4.94 ± 0.49	**<0.001**
LVED volume, mL	105 ± 26.0	100 ± 20.2	112 ± 32.1	0.054
LVEF, %	59.5 ± 5.1	59.8 ± 4.9	59.1 ± 5.4	0.523
LV dilatation	3 (2.8)	0 (0.0)	3 (7.7)	0.053
E/A ratio	1.39 (1.22-1.61)	1.37 (1.22-1.57)	1.49 (1.18-1.66)	0.341
Right ventricle				
RVED area, cm^2	21.0 ± 4.5	20.0 ± 3.0	22.4 ± 5.9	**0.029**
FAC, %	47.6 ± 4.8	48.1 ± 5.2	46.8 ± 4.1	0.180
RV dilatation	4 (3.8)	0 (0.0)	4 (10.2)	**0.019**
TAPSE, cm	2.3 ± 0.5	2.4 ± 0.4	2.1 ± 0.5	**0.003**
S' wave, cm/s	12.0 ± 2.2	12.6 ± 1.8	10.9 ± 2.3	**0.001**
RV-RA gradient, mm Hg	17.6 ± 6.9	14.8 ± 4.8	20.7 ± 7.5	**0.001**
Left atrium				
LA dilatation	4 (3.8)	1 (1.5)	3 (7.7)	0.149
LA volume, mL	32.3 ± 10.6	30.2 ± 9.3	36.5 ± 11.7	**0.012**
Valvulopathy[a]	14 (13.2)	0 (0.0)	14 (35.9)	**<0.001**
Aortic regurgitation	2 (1.9)	0 (0.0)	2 (5.1)	0.143
Pulmonary regurgitation	5 (4.7)	0 (0.0)	6 (15.4)	**0.002**
Mitral regurgitation	0 (0.0)	0 (0.0)	0 (0.0)	-
Tricuspid regurgitation	3 (2.8)	0 (0.00)	3 (7.7)	0.051
Aortic stenosis	1 (0.9)	0 (0.00)	1 (2.6)	0.378
Pulmonary stenosis	3 (2.8)	0 (0.00)	3 (7.7)	0.051
Residual lesion	-	-	9 (23.1)	-
Severe valvulopathy	-	-	7 (17.9)	-
Residual shunt (Qp/Qs >1.5)	-	-	2 (5.1)	-
Systemic RV	-	-	0 (0.0)	-
PH	-	-	0 (0.0)	-

Values are mean ± SD, n (%), or median (25th-75th percentile). Values in **bold** correspond to *P* values <0.05.
[a]Moderate or severe valve regurgitation or stenosis.
ED = end-diastolic; FAC = fractional area change; LA = left atrium; LV = left ventricle; LVEF = left ventricular ejection fraction; PH = pulmonary hypertension; Qp = pulmonary outflow; Qs = systemic outflow; RA = right atrium; RV = right ventricle; TAPSE = tricuspid annular plane systolic excursion; other abbreviation as in Table 1.

TABLE 3 Pregnancy and Delivery Outcomes

	All (N = 106)	Controls (n = 67)	CHD (n = 39)	*P* Value
Time to delivery from enrollment, wk	26.8 (25.7-28.0)	26.9 (26.0-28.0)	26.2 (25.4-27.8)	0.087
Gestational age at delivery, wk	39.3 (38.5-40.2)	39.4 (38.6-40.2)	39.0 (38.1-39.6)	**0.006**
Newborn weight, g	3,295 ± 417	3,344 ± 427	3,211 ± 389	0.105
Type of delivery				
Cesarean	21 (19.8)	11 (16.4)	10 (25.6)	0.370
Induced labor	39 (36.8)	25 (37.3)	14 (35.9)	1.000
Instrumental delivery	12 (11.3)	9 (13.4)	3 (7.7)	0.529
Epidural anesthesia	93 (87.8)	60 (89.6)	33 (84.6)	0.753
Pregnancy outcomes	18 (17.0)	6 (9.0)	12 (30.8)	**0.009**
Threatened preterm labor	8 (7.5)	2 (3.0)	6 (15.4)	**0.049**
HDPs	7 (6.6)	1 (1.5)	6 (15.4)	**0.010**
Placental abruption	3 (2.8)	1 (1.5)	2 (5.1)	0.553
SGA	3 (2.8)	3 (4.5)	0 (0.0)	0.296
Preterm birth	4 (3.8)	0 (0.0)	4 (10.3)	**0.017**

Values are median (25th-75th percentile), mean ± SD, or n (%). Values in **bold** correspond to *P* values <0.05.
HDP = hypertensive disorder of pregnancy; SGA = small-for-gestational age; other abbreviation as in Table 1.

of placentas were affected by MVM. Details of the prevalence of MVM-affected placentas according to specific CHD lesions are provided in Supplemental Table 10.

Although women with CHD had a significantly higher history of smoking prior to pregnancy compared to controls, prepregnancy smoking was not associated with MVM. Only 2 of the 8 patients who smoked before pregnancy developed MVM. A sensitivity analysis excluding these 8 patients confirmed the significant difference in MVM rates between groups ($P < 0.001$) (Supplemental Table 11).

DISCUSSION

To our knowledge, this study represents the first prospective histopathological analysis of placentas from women with CHD compared with a control group. We found that more than one-half of the women with CHD had placental lesions indicative of MVM, with a rate four times higher than in the control group. The presence of MVM was associated with adverse obstetric and neonatal outcomes, independent of the presence of CHD. MVM was prevalent even in patients with mild CHD, with almost half affected. No clinical or paraclinical factors were associated with MVM in CHD women (**Central Illustration**).

PREVALENCE AND COMPARATIVE ANALYSIS OF MVM IN CHD-AFFECTED PREGNANCIES. In this study, we examined the placental pathology of 39 CHD-affected pregnancies, primarily of mild to moderate complexity, compared to 67 controls. We found that nearly two-thirds (56.4%) of placentas from women with CHD were affected by MVM, consistent with previous studies. In 2016, Lima et al[24] reported 50% of ischemic lesions in placentas from women with various heart diseases (acquired and congenital). More recent studies focusing specifically on CHD populations found 40% of placental vascular pathologies, including 27% MVM,[11] while another reported 53% MVM.[12] However, these retrospective studies may have overestimated MVM due to selection bias, as placentas were only examined in high-risk pregnancies with complications. Our study is the first to prospectively analyze the placentas from consecutive CHD pregnancies, confirming a high prevalence of MVM in this population.

Furthermore, we observed a significantly higher MVM rate and score in the CHD group compared with controls. To date, only one retrospective study has compared placentas from women with CHD to those from controls,[13] similarly showing higher rates of MVM-associated lesions in CHD placentas. However, this study had limitations due to its retrospective

design, lack of matching for comorbidities and pregnancy risk factors, and focus on only three MVM criteria (small placental disk, placental infarcts, and accelerated villous maturation). In our study, we ensured comparability between groups in terms of comorbidities, parity, and major pregnancy risk factors. Additionally, we used a scoring system to account for each MVM criterion, assigning points based on the presence and severity of lesions. This approach allowed us to standardize the evaluation of MVM and ensure a more objective comparison between groups, given the absence of a clear diagnostic threshold in current guidelines.

MVM AND PREGNANCY OUTCOMES. Pregnancy in women with CHD is well established to carry a higher risk of obstetric and neonatal complications compared to the general population.[3,4] Consistent with this, our CHD cohort demonstrated a significantly higher incidence of HDPs, TPL, and preterm birth when compared to the control group.

However, a significant gap remains in understanding the link between maternal CHD and adverse obstetric and neonatal events. Previous studies have suggested placental dysfunction as a potential mechanism.[5,6] Histopathological analyses of placentas from women with CHD have demonstrated the presence of MVM lesions,[11-13,25] however, they were unable to establish a relationship between these placental abnormalities and pregnancy outcomes. Our study identified a significant association between MVM and adverse obstetric and neonatal outcomes, with a notably higher incidence of complications in patients with MVM. Interestingly, this association was independent of the presence of CHD, indicating that it was not a group effect, but rather reflects the direct impact of placental dysfunction on pregnancy outcomes. Moreover, unlike Wu et al who found no relationship between placental vascular pathology and newborn birth weight, our study even demonstrated a significant negative correlation between MVM score and birth weight. These findings strengthen the hypothesis that placental dysfunction is a key mechanism driving adverse pregnancy outcomes in women with CHD.

PREDICTORS OF MVM AND EMERGING HYPOTHESES BEHIND PLACENTAL DYSFUNCTION IN CHD PATIENTS. While few studies have explored the link between maternal heart disease and placental dysfunction, existing research indicates that altered hemodynamics may contribute to impaired placental function in these patients.[5,6] Reduced systemic LV function, reduced cardiac output during pregnancy, and RV dysfunction have all been associated with altered uteroplacental circulation.[5,6,26-28] One hypothesis is that reduced maternal cardiac function impairs uteroplacental perfusion, leading to villous underdevelopment and ischemic placental changes.[7] However, in our study, none of the cardiac hemodynamic parameters measured by third-trimester echocardiography were associated with MVM in CHD patients. This may partly be due to the fact that our CHD patients had normal LV and RV function parameters, with no patients having an left ventricular ejection fraction <50% or RV fractional area change <35%, and no cases of heart failure identified during pregnancy. Additionally, all severe CHD lesions had been repaired. Similarly, although CHD patients had higher NT-proBNP levels than controls, NT-proBNP was not associated with MVM.

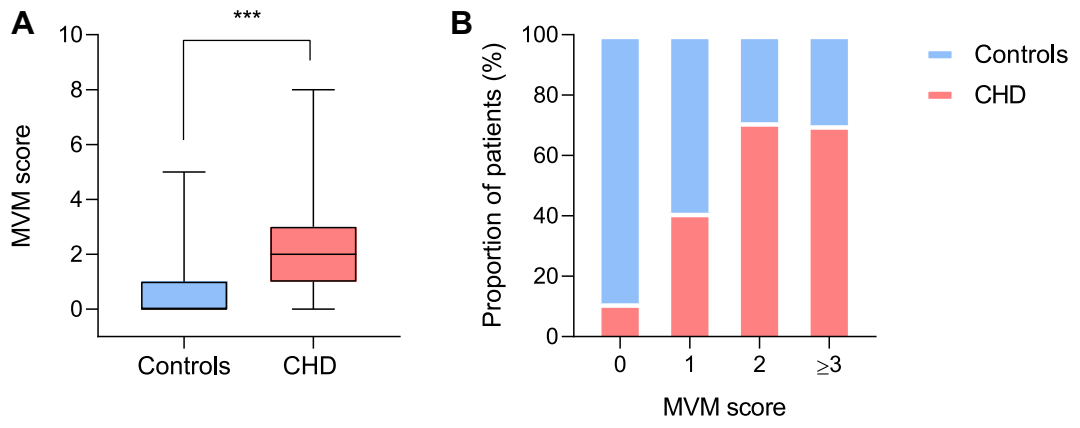
TABLE 4 Histopathological Results of Collected Placentas

	All (N = 106)	Controls (n = 67)	CHD (n = 39)	*P* Value
Placenta and cord anatomy				
Placental weight, g	433 ± 90.4	434 ± 92.7	433 ± 87.5	0.990
Large placenta[a]	3 (2.8)	2 (3.0)	1 (2.6)	1.000
Small placenta[b]	30 (28.3)	16 (23.9)	14 (35.9)	0.271
Single umbilical artery	1 (0.9)	0 (0.0)	1 (2.6)	0.368
VCI	2 (1.9)	1 (1.5)	1 (2.6)	1.000
Maternal vascular malperfusion	31 (29.2)	9 (13.4)	22 (56.4)	**<0.001**
Gross lesions				
Retroplacental hemorrhage	2 (1.9)	1 (1.4)	1 (2.6)	1.000
Placental hypoplasia[b]	30 (28.3)	16 (23.9)	14 (35.9)	0.271
Infarcts	5 (4.7)	0 (0.0)	5 (12.8)	**0.006**
Microscopic lesions				
AVM				**0.024**
Focal	9 (8.5)	3 (4.5)	6 (15.4)	
Diffuse	2 (1.9)	0 (0.0)	2 (5.1)	
DVH				**0.009**
Focal	8 (7.5)	3 (4.5)	5 (12.8)	
Diffuse	3 (2.8)	0 (0.0)	3 (7.7)	
Increased syncytial knots				**0.005**
Focal	11 (10.4)	4 (5.9)	7 (17.9)	
Diffuse	6 (5.7)	1 (1.5)	5 (12.8)	
Fibrin deposition				**<0.001**
Focal	41 (38.7)	14 (20.9)	27 (69.2)	
Diffuse	3 (2.8)	1 (1.5)	2 (5.1)	
Decidual vasculopathy	0 (0.0)	0 (0.0)	0 (0.0)	.
Other histological lesions				
Chorioamnionitis	24 (22.6)	18 (26.9)	6 (15.4)	0.262
With fetal response	8 (7.5)	7 (10.4)	1 (2.6)	
Without fetal response	16 (15.1)	11 (16.4)	5 (12.8)	
Villitis of unknown etiology	27 (25.5)	16 (23.9)	11 (28.2)	0.794
Low grade	24 (22 0.6)	13 (19.4)	11 (28.2)	
High grade	3 (2.8)	3 (4.5)	0 (0.0)	
Chorangiosis	8 (7.5)	5 (7.5)	3 (7.7)	1.000
Delayed villous maturation	9 (8.5)	6 (8.9)	3 (7.7)	1.000

Values are mean ± SD or n (%). Values in **bold** correspond to *P* values <0.05. [a]Placental weight >90th percentile. [b]Placental weight <10th percentile.

AVM = accelerated villous maturation; DVH = distal villous hypoplasia; VCI = velamentous cord insertion; other abbreviation as in Table 1.

FIGURE 3 Comparison of Maternal Vascular Malperfusion Scores Distribution Between Congenital Heart Disease and Controls Patients

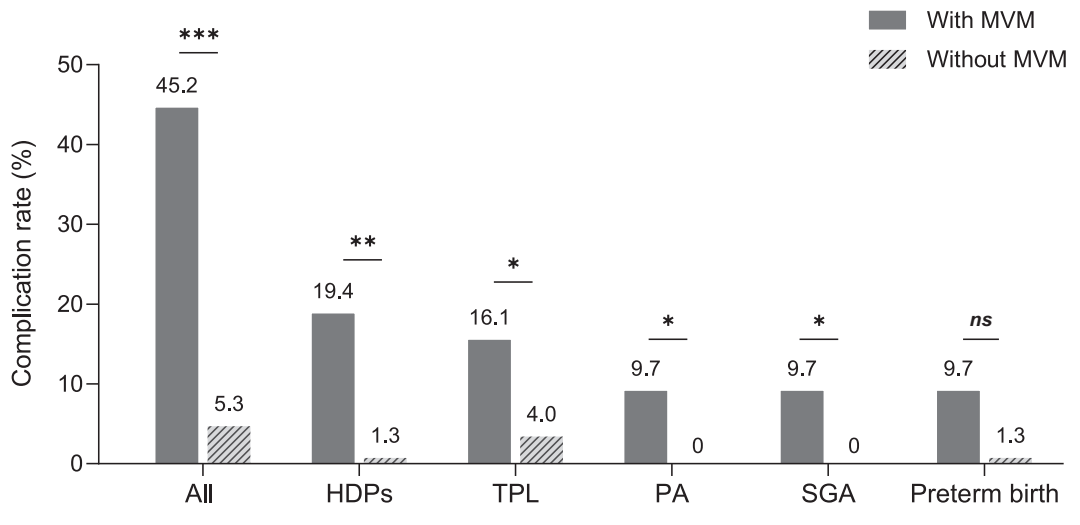


(A) MVM scores were significantly higher in CHD patients compared to controls, with a median score of 2 (1-3) in the CHD group vs 0 (0-1) in the control group (***$P < 0.001$). (B) Placentas with an MVM score >1 predominantly came from CHD patients. MVM = maternal vascular malperfusion; other abbreviation as in Figure 1.

Consistent with recent pathological studies,[11-13] we found no correlation between CHD complexity and MVM. Surprisingly, we observed a considerable rate of MVM (47.1%) even in mild CHDs, such as repaired ASDs. This suggests that the development of MVM in CHD pregnancies involves mechanisms beyond reduced cardiac output alone.

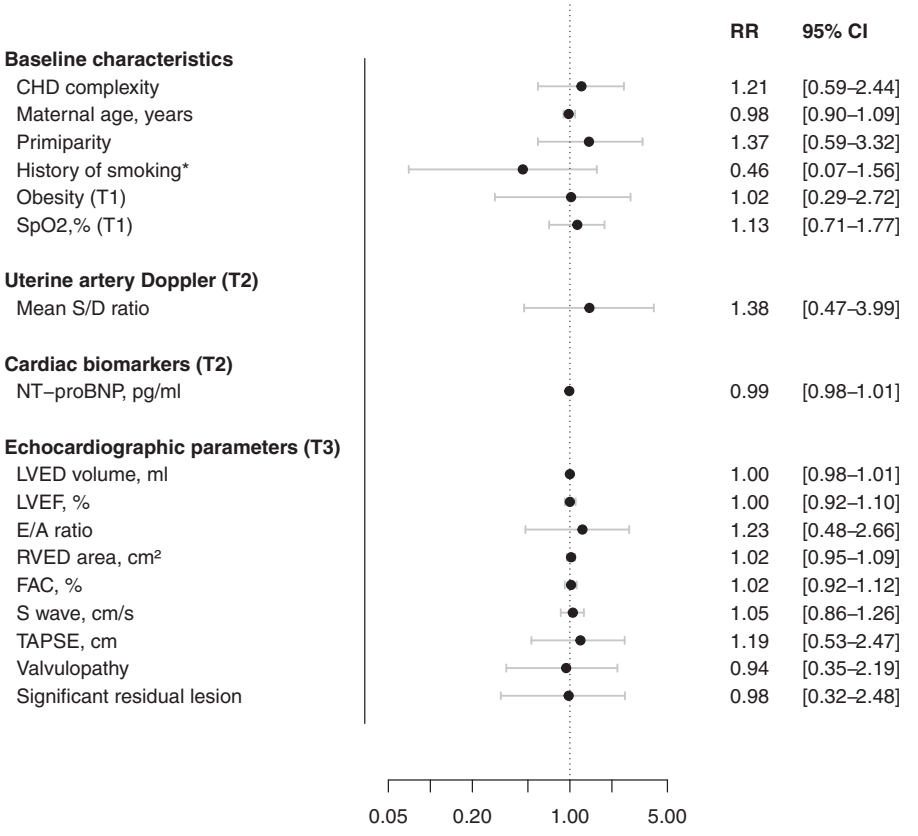
The absence of differences in uteroplacental Doppler flow between CHD and control patients, along with the lack of association between MVM and uterine artery S/D ratio, suggests normal placentation in our CHD cohort.[29-31] However, it is important to note that the predictive utility of uterine artery Doppler for placental dysfunction is not universally

FIGURE 4 Association Between Maternal Vascular Malperfusion and Adverse Pregnancy Outcomes



Patients with placental MVM had significantly higher rates of adverse pregnancy outcomes than those without. "All" refers to the overall complication rate, including all listed outcomes. *$P < 0.05$; **$P < 0.01$; ***$P < 0.001$. HDP = hypertensive disorder of pregnancy; PA = placental abruption; SGA = small-for-gestational-age; TPL = threatened preterm labor; other abbreviation as in Figure 3.

FIGURE 5 Univariable Analysis for Maternal Vascular Malperfusion Prediction in Congenital Heart Disease Patients



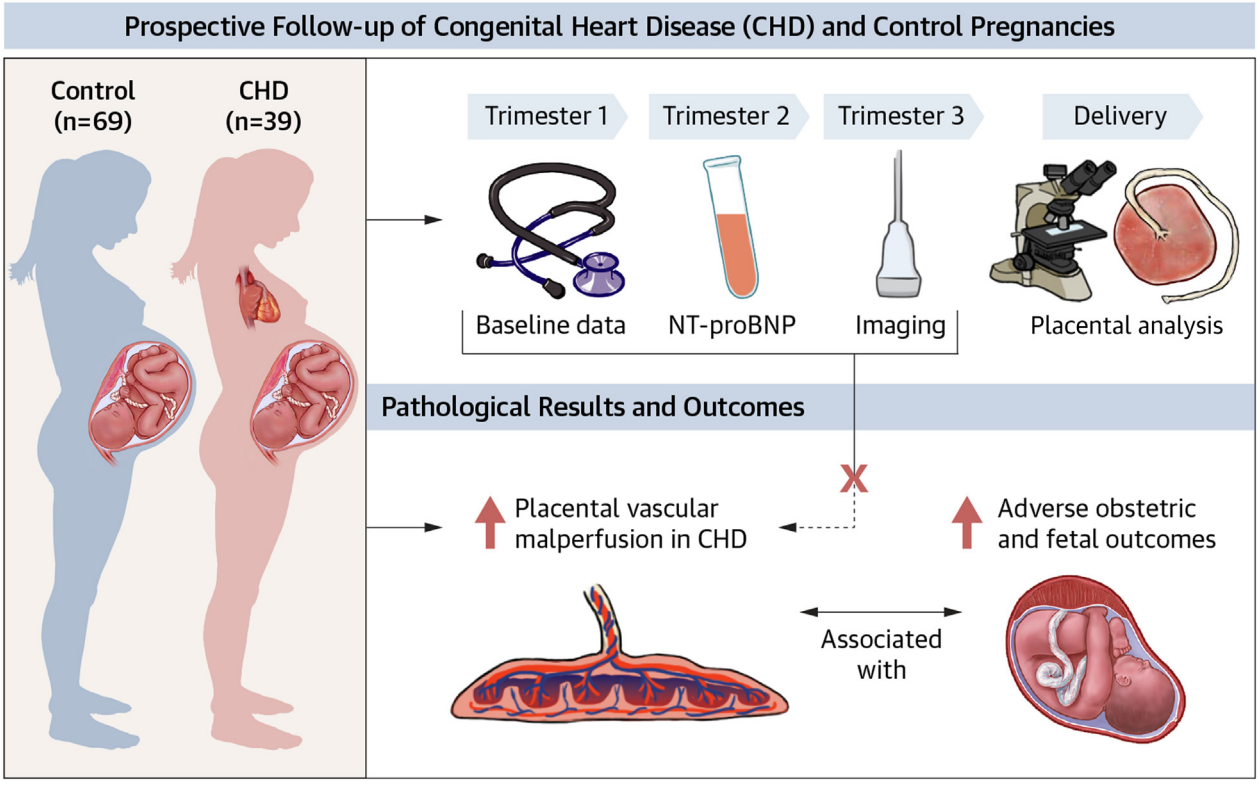
Univariable analysis shows that none of the clinical, biological, or echocardiographic parameters predicted MVM in CHD patients. The dotted line represents the relative risk (RR) threshold of 1, indicating no effect. The X-axis represents RRs with a 95% CI. *Before pregnancy. T1 = first trimester of pregnancy; T2 = second trimester of pregnancy; T3 third trimester of pregnancy; ED = end-diastolic; FAC = fractional area change; LV = left ventricle; LVEF = left ventricular ejection fraction; NT-proBNP = N-terminal pro b-type natriuretic peptide; RR = relative risk; RV = right ventricle; S/D = systolic/diastolic; TAPSE = tricuspid annular plane systolic excursion; other abbreviation as in **Figure 1**.

consistent, as normal Doppler findings do not always exclude underlying vascular abnormalities.[32,33] Furthermore, no cases of decidual vasculopathy were found in CHD placentas, supporting these findings. This is consistent with Soto et al[13] who found that MVM findings were not associated with a higher rate of decidual vasculopathy in CHD placentas.

Therefore, it seems appropriate to consider that endothelial dysfunction (ED) may contribute to placental dysfunction in this population. Indeed, studies have demonstrated the presence of ED in patients with CHD.[34-36] Odanaka et al[35] found that even young patients with repaired ASDs and VSDs had a significantly lower reactive hyperemia index (RHI), a validated tool for assessing ED, compared to controls. Similarly, Lin et al[34] reported higher endothelial microparticles levels, markers of endothelial damage, in patients with repaired ASDs and VSDs compared to controls, regardless of the presence of pulmonary hypertension.

In our study, although patients who smoked during pregnancy were excluded, the CHD group had a higher rate of prepregnancy smoking. However, this was not associated with MVM, and excluding patients with a smoking history did not alter the significantly higher MVM rate in the CHD group. While smoking is a known risk factor for ED, Odanaka et al[35] observed ED in their cohort of CHD patients, despite them being generally healthy adolescents without comorbidities typically associated with ED, such as heart failure, renal insufficiency, hypertension, or obesity. This suggests that CHD patients may exhibit ED independent of traditional risk factors. Additionally, no significant difference in RHI was found between different CHD subgroups, including complex conditions like the Fontan procedure and simpler, noncyanotic CHD,

CENTRAL ILLUSTRATION **Placental Vascular Malperfusion and Its Association With Adverse Obstetric and Fetal Outcomes in Congenital Heart Disease Pregnancies**



Rahnama N, et al. JACC Adv. 2025;4(3):101592.

Prospective assessment of placental vascular malperfusion and adverse outcomes in pregnancies with congenital heart disease compared to controls. Abbreviations as in Figure 5.

yet all exhibited a lower RHI compared to controls, indicating that any form of CHD, regardless of complexity, may be sufficient to lead to ED.

Given that ED disrupts vasodilation and increases oxidative stress, leading to reduced blood flow and tissue oxygenation,[37,38] we hypothesize that ED could lead to placental hypoxia and subsequent MVM in CHD pregnancies. The mechanism may be similar to that of late-onset preeclampsia, wherein pre-existing maternal microvascular dysfunction leads to placental hypoxia, resulting in a dysfunctional placenta despite normal placentation.[39-41] Further research is needed to investigate placental hypoxia and the molecular pathways involved in placental dysfunction in women with CHD.

STUDY LIMITATIONS

Our study has several limitations. First, the rarity of CHD pregnancies and the single-center design limited our sample size, potentially reducing statistical power for secondary outcomes and for identifying associations with MVM. Second, the study population, drawn from a tertiary care center, may have introduced bias due to more comprehensive prepregnancy counseling and follow-up compared to primary care. Lastly, the diversity of CHD types and the small sample size precluded subanalyses by heart defect or repair type, warranting a larger multicenter study.

CONCLUSIONS

Placentas from women with CHD exhibited a four-fold higher prevalence of MVM lesions (56.4%) than those from women without CHD. These lesions were associated with higher rates of adverse obstetric and neonatal outcomes. However, no clinical or paraclinical factors were associated with MVM in CHD women, particularly regarding the cardiac status and maternal hemodynamics. Notably, CHD complexity was not correlated with MVM, as nearly half (47.1%) of mild CHDs developed placental MVM. This

unexpected finding suggests that factors beyond those directly related to CHD contribute to placental dysfunction in these patients. Consequently, all CHD patients, regardless of the complexity of their condition, should be managed by a multidisciplinary team, including maternal-fetal medicine and ACHD specialists, to monitor and address potential placental dysfunction. Future research is needed to explore the underlying mechanisms of placental dysfunction in this specific population.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Placentas from women with CHD demonstrated a four-fold higher prevalence of MVM compared to controls. MVM was associated with adverse obstetric and neonatal outcomes, independent of CHD status. These findings suggest that placental dysfunction plays a crucial role in pregnancy complications in CHD patients, even in those with mild CHD.

TRANSLATIONAL OUTLOOK: Given the high prevalence of MVM in CHD pregnancies, even in mild cases, and the lack of identified risk factors, all women with CHD should be monitored by a multidisciplinary team, including maternal-fetal medicine and ACHD specialists, to address and manage potential placental dysfunction. Further research is needed to investigate the underlying mechanisms of placental dysfunction in this population and to determine effective strategies for reducing adverse pregnancy outcomes.

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KEY WORDS congenital heart disease, maternal vascular malperfusion, placenta, pregnancy

APPENDIX For a supplemental Methods section as well as supplemental tables, please see the online version of this paper.