JACC: ADVANCES VOL. 2, NO. 4, 2023

ORIGINAL RESEARCH

CONGENITAL HEART DISEASE

Prenatal Congenital Heart Disease and Placental Phenotypes

Preserved Neonatal Weight Despite Small Placentas

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ABSTRACT

BACKGROUND Congenital heart disease (CHD) affects 8 in 1,000 live births with significant postnatal implications including growth failure, neurodevelopmental delay, and mortality. The placenta develops concomitantly with the fetal heart. High rates of placental pathology and discordant growth in pregnancies affected by CHD highlight the significance of the fetal-placental-cardiac axis.

OBJECTIVES This study aimed to characterize the relationship between neonatal birthweight (BW), head circumference, placental weight (PW), and placental pathology in pregnancies affected by CHD. PW:BW provides a surrogate to assess placental efficiency, or nutrient exchange and delivery by the placenta, across CHD phenotypes.

METHODS Retrospective cohort of 139 live-born singletons with postnatally confirmed CHD with placental pathology. Placental examination, infant BW, head circumference, and CHD categories (septal defects, right-sided defects, left-sided defects, conotruncal anomalies, and others) were included. Chi-square, Fisher's exact, or Kruskall-Wallis tests and multinomial logistic regressions, as appropriate.

RESULTS Median birthweight and head circumference percentile was 33 and 35, respectively. Placental pathology was documented in 37% of cases. PW to BW ratios were <10th percentile for 78% and <3rd percentile for 54% of the cohort, with no difference between CHD categories ($P = 0.39$ and $P = 0.56$, respectively).

CONCLUSIONS Infants with CHD have preserved BW and head circumferences in the setting of small placentas and increased prevalence of placental pathology, suggesting placental efficiency. Detection of abnormal placental growth could add prenatal diagnostic value. Placental and neonatal discordant growth may allude to a vascular anomaly predisposing fetuses to developing CHD. Further studies are needed to explore fetal nutrient delivery and utilization efficiency. (JACC Adv 2023;2:100383) © 2023 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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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.

Manuscript received September 15, 2022; revised manuscript received March 3, 2023, accepted March 31, 2023.

ISSN 2772-963X https://doi.org/10.1016/j.jacadv.2023.100383

ABBREVIATIONS AND ACRONYMS

CHD = congenital heart disease

DM = diabetes mellitus

HTN = hypertension

PW:BW = placental weight to birthweight

SGA = small for gestational age

Congenital heart disease (CHD) is the leading cause of major birth defects affecting approximately 8 per 1,000 live births.[1] Despite significant advancements in prenatal diagnostics and postnatal care, CHD remains a leading cause of infant morbidity and mortality, with studies showing one per 814 deaths attributable to CHD.[2] Many children with CHD are subsequently diagnosed with deficits in various domains of neurodevelopment.

The development of CHD is multifactorial and remains poorly understood. Etiologies likely extend beyond described genetic, epigenetic, and environmental factors. Recent insights demonstrate a plausibility of concomitant placental anomalies.[3,4] The placenta is a major vascular organ that significantly influences fetal organogenesis, development, and growth.[5] The fetal heart and maternal placenta develop concurrently by formation of a tubular heart and a primitive placental villous tree by 21 days of gestation.[6-8] Shared regulatory and signaling pathways exist in the development of the fetal heart and placenta.[9]

A body of literature suggests a link between vasculogenesis and angiogenesis in the fetal heart and placenta.[10] Placental vascular abnormalities have been detected at high rates in pregnancies affected by CHD. In particular, fetal vascular malperfusion and maternal vascular malperfusion lesions were found in 20% and 23% of placentas from pregnancies affected by fetal CHD, respectively, while they were not found in any control pregnancies.[11] Umbilical venous flow, a measure of fetal placental blood flow and a surrogate for placental function, has been shown to be lower in fetuses with CHD compared to controls.[12]

The placenta, the exclusive source of nutrients and oxygen to the developing fetus, is instrumental in prenatal growth and development. A large placenta is not necessarily indicative of adequate fetal growth since placental pathology (infarction, thrombosis, chorangiosis), blood flow resistance, and nutrient exchange and utilization are also influential. These factors are aberrant in the setting of CHD.

Placental weight to birthweight (PW:BW) ratios have been studied and correlated with short- and long-term outcomes for infants. In the perinatal period, high PW:BW correlates with increased admission rate to the neonatal intensive care unit, lower Apgar scores, and higher cesarean births.[13] In adulthood, high PW:BW is associated with risk of hypertension and death from cardiovascular causes.[14,15]

Infants born with CHD are more commonly small for gestational age (SGA) compared to those without CHD.[13] In a large database investigation for infants born in California, 16.3% of infants with CHD were SGA, compared to 8.1% of infants without CHD.[16] Infants born with CHD have demonstrated decreased growth velocity, particularly brain growth velocity, in the third trimester.[17] A fetal imaging study revealed a 13% reduction in brain volume in fetuses with CHD compared to controls.[18]

Despite existing literature on placental to birthweight ratios, there are few studies of placental to birthweight ratios in pregnancies affected by CHD and none include preterm births. The dynamic, intricate fetal-placental-cardiac axis of circulation in the context of CHD remains poorly understood. This study aims to characterize the relationship between neonatal growth and placental size and pathology in pregnancies affected by CHD and to assess placental efficiency in this population.

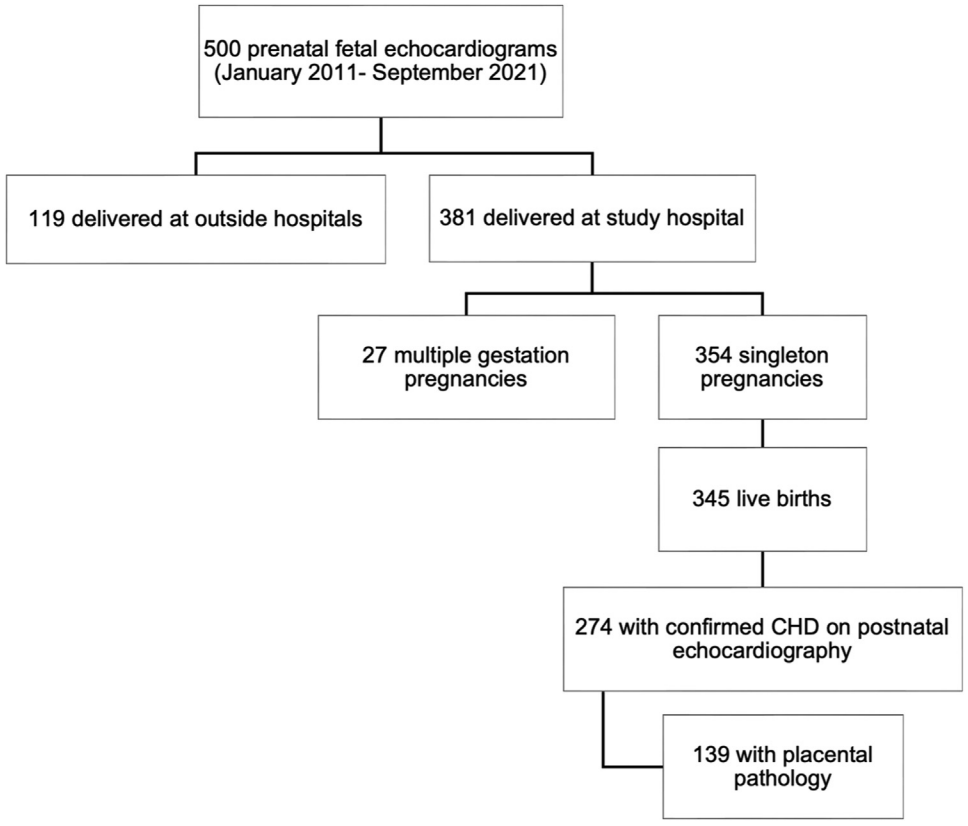
METHODS

This was a retrospective cohort study that examined all pregnancies that underwent prenatal echocardiography with pediatric cardiology at the University of California-Los Angeles (UCLA) for suspected CHD after screening ultrasonography and were referred for suspected CHD between January 2011 and September 2021. All singleton pregnancies delivered at UCLA (Ronald Reagan UCLA Medical Center or UCLA Santa Monica Medical Center) that resulted in a live birth with confirmed CHD on postnatal echocardiography and had placental pathology collected at delivery were included. Institutional Review Board approval was obtained (UCLA IRB #19-001754) and informed consent was waived given the retrospective nature of the study.

Chart review was conducted to obtain maternal demographic information and comorbidities, placental weight and pathology, neonatal birthweight, and postnatal CHD diagnosis. Risk factors and maternal comorbidities collected include hypertensive diseases of pregnancies, pre-eclampsia, diabetes, teratogenic exposure, and family history of CHD.[19,20]

Placentas were sent to pathology for gross and microscopic histopathologic examination at the time of birth. Gynecologic and perinatal pathologists at UCLA performed histologic examination. The placental size was measured, and the trimmed weight was recorded. All placentas were fixed in 10% buffered formalin. Sections submitted included 2 sections of umbilical cord, 2 sections of membrane, 3 full

FIGURE 1 Study Population



CHD = congenital heart disease.

thickness sections of grossly normal appearing placenta from the chorionic plate to the basal plate, and additional submitted sections of any grossly abnormal placenta. Sections underwent routine processing, were paraffin-embedded, sectioned at 3 to 5 μm, and stained with hematoxylin and eosin. The pathologists categorized the histopathologic lesions according to the Amsterdam criteria after the consensus statement was published.[21] Placental pathology reports were reviewed to extract placental weight and presence of the following pathologies: thrombosis, infarction, chorangiosis, and villous hypomaturation. Placental weight percentiles were assigned based on sex and gestational age from established nomograms.

Birthweight percentiles were assigned based on gestational age at birth using the World Health Organization and Fenton growth curves, for term and preterm (<37 weeks' gestational age) infants, respectively. SGA was assigned if the birthweight percentile was <the 10th percentile on the appropriate growth curve. CHD diagnoses were determined by postnatal echocardiography reports. Each diagnosis was then classified as one of the following: septal defects, right-sided heart defects, left-sided heart defects, conotruncal anomalies, or other (total anomalous pulmonary venous return, situs inversus, heterotaxy, dilated cardiomyopathy, multiple anomalies not fitting any one category).

PW:BW ratios were calculated and percentiles were assigned based on established nomograms.[22] All abstracted information was stored in a de-identified research database.

All maternal and neonatal variables were summarized with frequencies or median (IQR). Chi-square test (or Fisher's exact test if appropriate) was used to analyze categorical variables and Kruskal-Wallis test was used to analyze and compare continuous variables across the 5 CHD diagnoses. We also checked for associations between PW:BW ratio with the maternal variables with a Kruskal-Wallis test, and then ran a multinomial logistic regression of PW:BW

TABLE 1 Maternal Demographics and Clinical Characteristics

	All (N = 139,100%)	Septal Defect (n = 27,19%)	Right Heart Defect (n = 13,9%)	Left Heart Defect (n = 38,27%)	Conotruncal Anomalies (n = 41,29%)	Other Anomalies[a] (n = 20,14%)	*P* Value
Age, y	32 (27-36)	34 (29-40)	35 (25-39)	30 (27-35)	32 (26-36)	31 (25-35)	0.156[b]
Race/ethnicity							0.498[c]
Non-white	96 (69)	21 (78)	7 (54)	28 (74)	26 (63)	14 (70)	
White	43 (31)	6 (22)	6 (46)	10 (26)	15 (37)	6 (30)	
Comorbidities							
Diabetes mellitus	12 (9)	2 (7)	1 (8)	2 (5)	4 (10)	3 (15)	0.797[c]
Gestational diabetes	23 (17)	7 (26)	4 (31)	3 (8)	8 (20)	1 (5)	0.082[c]
Chronic hypertension	14 (10)	4 (15)	2 (15)	3 (8)	2 (5)	3 (15)	0.445[c]
Gestational hypertension	26 (19)	8 (30)	1 (8)	7 (18)	7 (17)	3 (15)	0.492[c]
Category of pregnancy induced hypertension							0.395[c]
Gestational hypertension	4 (15)	0 (0)	0 (0)	2 (29)	2 (29)	0 (0)	
Pre-eclampsia/Eclampsia	21 (81)	8 (100)	1 (100)	4 (57)	5 (71)	3 (100)	
HELLP	1 (4)	0 (0)	0 (0)	1 (14)	0 (0)	0 (0)	
Family history of CHD	16 (11)	2 (7)	2 (15)	4 (11)	5 (12)	3 (15)	0.909[c]
Assisted reproductive technology	3 (2)	1 (4)	1 (8)	0 (0)	0 (0)	1 (5)	0.092[c]
Medication/teratogen exposure	4 (3)	0 (0)	0 (0)	1 (3)	1 (2)	2 (10)	0.457[c]
Substance abuse							0.446[c]
Smoking	3 (2)	0 (0)	1 (8)	0 (0)	1 (2)	1 (5)	
Alcohol	2 (1)	1 (4)	0 (0)	0 (0)	1 (2)	0 (0)	
None	134 (96)	26 (96)	12 (92)	38 (100)	39 (96)	19 (95)	

Values are median (IQR) or n (%). [a]Other includes total anomalous pulmonary venous return, situs inversus, heterotaxy, dilated cardiomyopathy, multiple anomalies not fitting any one category. [b]Kruskal-Wallis. [c]Fisher's exact.

CHD = congenital heart disease; HELLP = hemolysis, elevated liver enzymes, low platelets.

ratio on the 5 CHD diagnoses, controlling for the following covariates: maternal DM, maternal gestational DM, maternal chronic hypertension (HTN), pregnancy induced HTN (none, gestational HTN, pre-eclampsia, hemolysis, elevated liver enzymes, low platelets), family history of CHD, and assisted reproductive technology. In post hoc analyses, we compared the same variables between single ventricle vs double ventricle physiology, and between left sided vs non-left-sided defects, and ran a logistic regression for each comparison with the same covariates as the multinomial logistic regression. Additionally, we compared placental weight percentile between placental infarction vs without infarction. We separately stratified the cohort by SGA status to compare across CHD diagnoses to explore potential interactions with SGA status. We also compared our study population with published reports for several maternal characteristics.

RESULTS

A total of 500 pregnant people had prenatal echocardiograms for a suspected fetal CHD at the institution between January 2011 and September 2021 (Figure 1), of which 139 met criteria for our study (live, singleton births, delivery at a study hospital, available placental pathology). Table 1 displays the spectrum of CHD diagnostic categories in this population. The most common lesions were conotruncal anomalies and left-sided heart defects, composing 29% and 27% of the cohort, respectively.

MATERNAL DEMOGRAPHICS AND CLINICAL CHARACTERISTICS. Maternal demographic and clinical risk factors for our cohort are summarized in Table 1 and compared to the general pregnant population in Table 2. The median maternal age was 32 years old, which is significantly higher than average age at delivery of first pregnancy.[23] Family history of CHD was identified in 11% of cases. DM or gestational diabetes affected 25% of pregnancies, which is significantly higher than the general pregnant population.[28] Hypertensive diseases of pregnancy were present in 19% of the cohort, of which 81% were categorized as pre-eclampsia or eclampsia. No statistically significant differences were detected between CHD groups.

BIRTHWEIGHT AND PLACENTAL PATHOLOGY. Table 3 displays neonatal and placental characteristics across CHD groups. The median gestational age at delivery for the entire cohort was 38 weeks, with no

significant difference between CHD groups. The median birthweight was 2,920 g and median birthweight percentile was 33 based on gestational age. The median head circumference was 33 cm and median head circumference percentile was 35 based on gestational age. Twenty-seven percent of the infants studied with CHD were SGA (**Table 3**), which is significantly higher than 11% in the general population.[27] Birthweight, SGA diagnosis, and head circumference were not significantly different between CHD diagnostic cohorts or in the post hoc sub analyses comparing single ventricle vs double ventricle physiology and left-sided defects vs non-left-sided defects (Supplemental Tables 1 and 2, respectively).

Median placental weight was 407 g, which is <3rd percentile for males or females born at 38 weeks' gestational age. Over half of the infants in our study had placental weights <3rd percentile and over two-thirds had placental weights <10th percentile based on sex and gestational age (**Table 3**). Infants with left-sided heart defects had the lowest median placental weight at 384 g; however, there was no statistically significant difference in placental weight across CHD categories. The majority (89%) of infants in our cohort who were SGA had placental weights <3rd percentile compared to less than one-half (47%) in the non-SGA cohort of our population (**Table 4**). There was no significant difference in distribution of placental weight percentiles across CHD diagnostic categories or when infants with left-sided defects were compared to those without left-sided defects or those with single ventricle were compared to those with double ventricle physiology (**Table 3**, Supplemental Tables 1 and 2, respectively). Within our non-SGA cohort, those with left-sided defects had a higher frequency of placental weights ≤3rd percentile (54%) compared to those without left-sided defects (44%) (**Table 4**).

PW to BW ratios were <3rd percentile for over half of the cohort and <10th percentile for almost 80% of the cohort, with no significant difference between CHD category ($P = 0.39$ and $P = 0.56$, respectively) (**Table 3**) or between those with single ventricle and double ventricle physiology ($P = 0.88$ and $P = 0.50$, respectively) (Supplemental Table 1). Comparing infants with left-sided heart defects to those without, those with left-sided heart defects tended to have PW:BW ratio <3rd percentile more commonly than those without (66% vs 50%, $P = 0.09$) (Supplemental Table 2).

In the bivariate analysis with PW:BW ratio, only family history of CHD was significantly associated with PW:BW ratio where those with a history had smaller ratios ($P = 0.02$). The other variables were not significantly associated ($P = 0.08$-0.96). However, in multivariate analysis, neither PW:BW ratio nor the other covariates were associated with defect category ($P = 0.70$ for PW:BW and 0.89 for family history), single vs double ventricle ($P = 0.63$ and $P = 0.14$), or left vs non-left-sided defect ($P = 0.82$ and $P = 0.80$) (data not shown).

The most common placental pathology in this population was infarction, which was diagnosed in 20% of all CHD cases. Placental thrombosis and chorangiosis were present in 7% and 6% of the cohort, respectively (**Table 3**). There was no significant difference in the incidence of placental pathology between CHD diagnostic groups. When we looked at placental weights and PW:BW in those with placental infarction vs those without infarction, we found no significant difference (Supplemental Table 3).

TABLE 2 Comparison of Our Study Population to General Pregnant Population

	Our Study Population	General Pregnant Population	*P* Value
Maternal age, y	31.5 ± 6.5	27.1 ± 6.5[23]	**<0.0001**
Assisted reproductive technology	2.2%	1.6%[24]	0.4904[a]
Substance abuse			
Smoking	2.2%	7.2%[25]	**0.0215**
Alcohol	1.4%	13.5%[26]	**<0.0001**
SGA	27%	11%[27]	**<0.0001**
Comorbidities			
Diabetes mellitus	8.6%	1.3%[28]	**<0.0001**[a]
Gestational diabetes	16.6%	7.6%[28]	**<0.0001**
Chronic hypertension	10.1%	0.9%-1.5%[29]	
Hypertensive disorders of pregnancy	18.7%	4-8%[30]	
Category of pregnancy induced hypertension			
Gestational hypertension	2.9%	3%[31]	
Pre-eclampsia	15.1%	2%-8%[32]	
Eclampsia	0%	0.82%[31]	
HELLP	0.7%	0.9%[33]	

Values are mean ± SD or %. **Bold** values indicate significant as defined by $P < 0.05$. [a]Fisher's exact.
HELLP = hemolysis, elevated liver enzymes, low platelets; SD = standard deviation; SGA = small for gestational age.

DISCUSSION

Despite an increased incidence of placental pathology in our cohort of pregnancies complicated by fetal CHD, we demonstrate small placentas regardless of lesion type in comparison to neonatal birthweight and head circumference, suggesting increased placental efficiency (**Central Illustration**). At first glance, our population of neonates with CHD had normal in-utero growth exemplified by a median birthweight percentile of 33. However, 27% of our population was SGA, which is a significantly higher rate than stated in prior studies examining fetal

TABLE 3 Birth Characteristics for Infants With CHD and Corresponding Placental Findings

	Total (N = 139)	Septal Defect (n = 27)	Right Heart Defect (n = 13)	Left Heart Defect (n = 38)	Conotruncal Anomalies (n = 41)	Other Anomalies (n = 20)	*P* Value
Gestational weeks at delivery	38 (37-39)	38 (36-39)	38 (37-39)	38 (37-39)	39 (37-39)	38 (37-39)	0.453[a]
Birthweight (g)	2,920 (2,400-3,418)	2,830 (2,415-3,220)	3,320 (2,582-3,440)	2,800 (2,405-3,279)	3,015 (2,550-3,435)	2,840 (2,405-3,328)	0.597[a]
Birthweight percentile	33 (8-65)	26 (4-71)	58 (21-65)	32 (5-65)	30 (8-60)	34 (11-75)	0.679[a]
SGA	38 (27)	8 (30)	2 (15)	12 (32)	11 (27)	5 (25)	0.842[b]
Head circumference (cm)	33.0 (32.0-34.5)	32.5 (31.0-34.0)	33.5 (32.5-36.0)	33.0 (31.4-34.1)	33.1 (32.0-34.5)	33.1 (32.0-36.0)	0.616[a]
Head circumference percentile	35.3 (5.6-75.5)	34.6 (5.6-82.0)	37.4 (12.5-96.3)	26.6 (3.5-61.5)	35.9 (4.4, 66.3)	22.7 (12.3-89.0)	0.563[a]
Placental characteristics							
Placental weight	407 (336-514)	401 (308-504)	427 (385-543)	384 (348-451)	423 (307-510)	430 (374-518)	0.601[a]
Placental weight percentile							0.491[b]
<3	81 (58)	16 (59)	7 (54)	25 (66)	25 (61)	8 (40)	
<10	14 (10)	3 (11)	0 (0)	2 (5)	5 (12)	4 (20)	
25/50/75/>90	44 (32)	8 (30)	6 (46)	11 (29)	11 (27)	8 (40)	
Placental weight to birthweight ratio	0.14 (0.12-0.16)	0.14 (0.13-0.18)	0.15 (0.14-0.16)	0.14 (0.12-0.16)	0.14 (0.12-0.16)	0.15 (0.14-0.16)	0.295[a]
Placental weight to birthweight percentile							
<3	75 (54)	14 (52)	5 (38)	25 (66)	22 (54)	9 (45)	0.394[b]
<10	109 (78)	21 (78)	10 (77)	32 (84)	33 (80)	13 (65)	0.556[b]
Thrombosis	10 (7)	1 (4)	2 (15)	2 (5)	4 (10)	1 (5)	0.680[b]
Infarction	28 (20)	6 (22)	2 (15)	7 (18)	8 (20)	5 (25)	0.960[b]
Chorangiosis	8 (6)	0 (0)	1 (8)	4 (11)	1 (2)	2 (10)	0.236[b]
Villus: hypomature	5 (4)	2 (7)	1 (8)	2 (5)	0 (0)	0 (0)	0.239[b]

Values are median (IQR) or n (%). [a]Kruskal-Wallis. [b]Fisher's exact.
CHD = congenital heart disease; SGA = small for gestational age.

growth in the setting of CHD and higher than the general population average of 11%.

We found that 37% of the placentas in our cohort had pathology, an incidence higher than 26% to 28% cited in all pregnancies, but lower than 57% to 78% cited in pregnancies affected by fetal CHD.[11,34,35] The frequency of infarction (20%) in our cohort is similar to other studies that found evidence of placental infarction in 17 to 28% of CHD pregnancies.[35,36] Surprisingly, we did not find significantly lower birthweights for infants from pregnancies with placental infarction. In the context of increased pathology, we then examined the relationship between placental size and fetal growth in our cohort.

The PW:BW ratio is inversely proportional to placental efficiency.[37] In other words, a low PW:BW

TABLE 4 Placental Weight Percentiles Categorized by CHD Defect Stratified by Infant SGA Status

	Total (N = 139)	Septal Defect (n = 27)	Right Heart Defect (n = 13)	Left Heart Defect (n = 38)	Conotruncal Anomalies (n = 41)	Other Anomalies (n = 20)
Non-SGA infants (n = 101)						
Placental weight percentile <3	47 (47)	9 (47)	5 (45)	14 (54)	15 (50)	4 (27)
Placental weight percentile <10	12 (12)	2 (11)	0 (0)	2 (8)	4 (13)	4 (27)
Placental weight percentile 25/50/75	39 (39)	8 (42)	6 (55)	8 (31)	11 (37)	6 (40)
Placental weight percentile 90	3 (3)	0 (0)	0 (0)	2 (8)	0 (0)	1 (7)
SGA infants (n = 38)						
Placental weight percentile <3	34 (89)	7 (88)	2 (100)	11 (92)	10 (92)	4 (80)
Placental weight percentile <10	2 (5)	1 (13)	0 (0)	0 (0)	1 (9)	0 (0)
Placental weight percentile 25/50/75	2 (5)	0 (0)	0 (0)	1 (8)	0 (0)	1 (20)
Placental weight percentile 90	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

Values are n (%).

CENTRAL ILLUSTRATION **Small, Efficient Placentas in Fetal CHD Pregnancies**

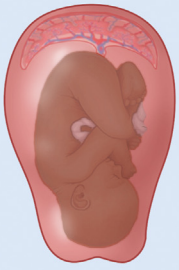
Study of Pregnancies Affected by Fetal CHD (N = 139)

27% CHD infants were small for gestational age vs. 11% in non-CHD population ($P < 0.001$)

Placental pathology in fetal CHD:
- Thrombosis: 7%
- Infarction: 20%
- Chorangiosis: 6%

Birth Characteristics for Infants with CHD and Corresponding Placental Findings

Median birthweight (BW)	33rd percentile
Median head circumference	35th percentile
Placenta weight (PW)	58% <3rd percentile, 68% <10th percentile
Placenta weight:birthweight	54% <3rd percentile, 78% <10th percentile



	CHD Cohort	Non-CHD Pregnancies
Placenta weight	407 g	644 g
Birthweight	2,920 g	3,248 g
PW:BW	0.14	0.20

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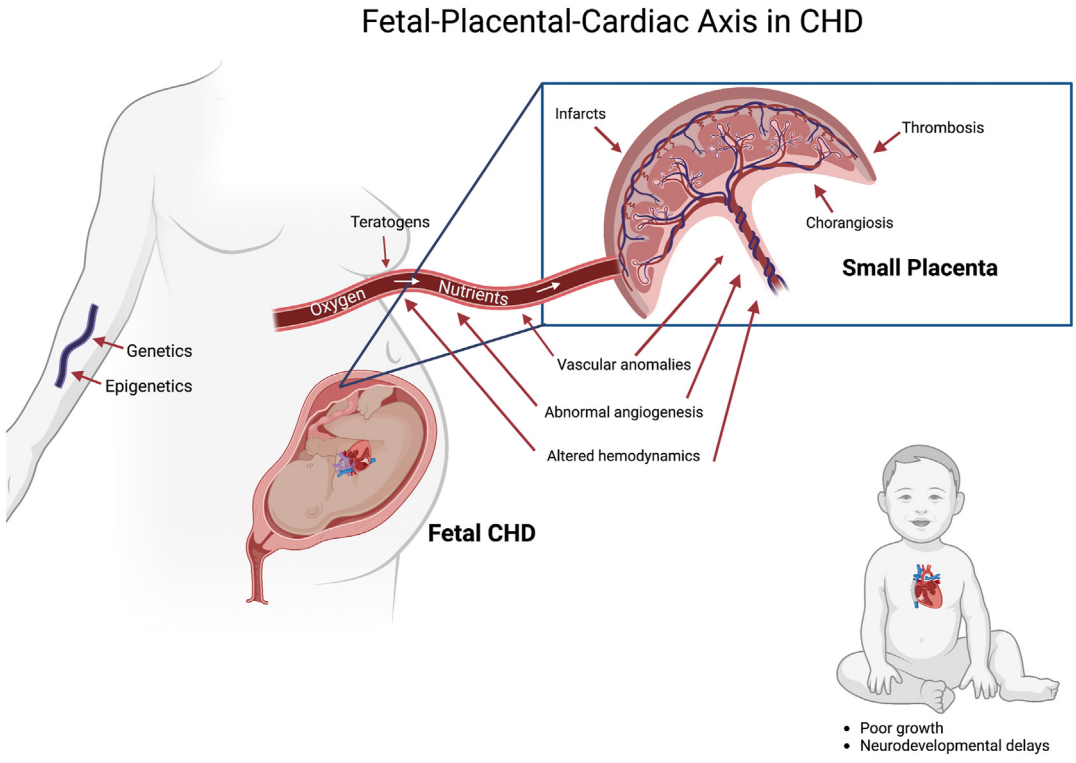
may correspond to higher placental efficiency or nutrient extraction from the fetus. We found that 78% of the cohort we studied had PW:BW ratios <10th percentile; furthermore, 54% had ratios <3rd percentile. These are quite comparable to findings in a smaller study that found 77% of PW:BW <3rd percentile and 49% of PW:BW <10th percentile in CHD pregnancies.[36] This suggests that despite small placental size, the developing fetuses receive enough oxygen and nutrients to grow, as exemplified by disproportionately higher birthweight percentiles. The placenta may adapt to deliver nutrients in a more efficient way to the developing fetus with CHD, even in the setting of increased placental pathology. An alternative explanation is that the developing fetus with CHD adjusts to extract or utilize nutrients more effectively (**Figure 2**). Further studies are needed to determine whether the placental transfer of oxygen and nutrients in CHD is enhanced and how it accomplishes this favorable phenotype.

Previous imaging studies in CHD pregnancies have shown that despite normal fetal estimated size and weight, brain size can be disproportionately low.[9] It is hypothesized that this is a result of longstanding decreased cerebral perfusion secondary to prolonged hypoxia. This is in opposition to the acute or subacute insufficiency seen with gestational hypertension leading to the well-documented brain sparing physiology. In our population of infants with CHD, we found median head circumference percentile to be

FIGURE 2 Plausible Mechanisms for the Fetal-Placental-Cardiac Axis in CHD



CHD = congenital heart disease.

35th percentile, which is close to the 33rd percentile we found for weight, suggesting proportional head and total body growth. For those with left-sided heart defects, head circumference tended to be smaller (27th percentile compared to birthweight of 32nd percentile) (**Central Illustration**).

The strengths of our study include a diverse, large sample size that included preterm and term deliveries. Our population encompassed a heterogeneous and comprehensive very complex group of CHD diagnoses.

STUDY LIMITATIONS. Despite several strengths, our study had limitations. Namely, this stems from the retrospective nature of the study design. Here in, we investigated maternal-fetal dyads from a single, high-volume quaternary care center that is a catchment area for pregnancies affected by complex CHD. All cases had prenatally diagnosed CHD. We excluded 119 out of 500, or roughly 1 in 4, on basis of delivery at a different institution, which introduces selection bias; however, it selects for the most high-risk lesions. Lower risk CHD lesions were able to deliver in the community. Our study population likely includes pregnancies complicated by more critical and ductal dependent lesions. Excluding dyads that did not have placentas sent for pathology introduces another source of selection bias. We examined the 135 dyads who were excluded based on not having placental pathology and report delivery dates and distribution of fetal cardiac anomalies in Supplemental Table 4. The ineligible group had more right-sided defects and conotruncal defects compared to our study population. Prior to the Amsterdam criteria, there was less standardization of placental pathology analysis.

Furthermore, we did not analyze any in utero placental imaging, quantitative, or qualitative analysis; we used the post-birth placental pathology as a surrogate. We chose to use separate growth curves for preterm and term infants in our study and this likely detected a higher incidence of SGA and smaller head circumferences than we would have if we had chosen to use the Fenton growth curve for all infants. This choice impacts the results comparing SGA to non-SGA infants. We did not study or control for nutritional status during pregnancy, which could impact BW:PW.

Finally, our small sample size has the potential to introduce type II errors. Clinically important differences, such as median birth weight of those with left-sided heart defects being 520 g less than those with right-sided heart defects, did not meet statistical significance.

CONCLUSIONS

We demonstrate low placental weights in pregnancies complicated by CHD with disproportionately low PW:BW ratios, suggesting that fetal growth was not as compromised as one would expect. The etiology of this phenomenon is not yet well understood but may provide invaluable insight into the development CHD. An abnormal maternal blood flow pattern could contribute to a vascular phenotype leading to abnormal placental growth and pathology, predisposing fetuses to developing CHD. Plausibly, early detection of abnormal placental growth could add prenatal diagnostic value. More so, antenatal fetal surveillance and delivery planning for fetal growth restriction (FGR) with CHD vs without CHD should be considered and a consideration for a more personalized approach to FGR in the setting of CHD, in place of grouping this cohort with all FGR antenatal management.

While we demonstrate preservation of total birthweight, the head circumference was proportional, suggesting a lack of head sparing, a likely result of chronic hypoxia throughout gestation vs a later hit, possibly predisposing these neonates to decreased growth trajectory and neurodevelopmental delays in childhood. Further studies investigating placental growth during pregnancy and following the growth of infants and children with a history of abnormal placental size and pathology over time will be important.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

Dr Desmond is supported by the T15L013976 (AD) National Library Of Medicine of the National Institutes of Health under Award Number T15LM013976. Dr Afshar has served as a consultant to Mirview; and is supported by the National Institute of Health K12HD000849 awarded to the Reproductive Scientist Development Program by the Eunice Kennedy Shriver National Institute of Child Health and Human Development. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Understanding the implications of placental pathology on fetal growth in-utero and development in the setting of CHD allows for personalized patient-centered care for a uniquely poised and vulnerable population. Our study demonstrates low placental to birthweight ratios in pregnancies affected by CHD. We do not yet know whether maternal factors or altered fetal hemodynamics are responsible for the placental changes.

TRANSLATIONAL OUTLOOK: In utero imaging to trend placental and fetal growth through gestation in pregnancies affected by CHD would be useful and could influence antenatal surveillance, monitoring, and delivery planning. Future studies looking at underlying molecular mechanisms that preserve growth and early developmental hallmarks of the fetal-placenta-cardiac axis are needed to understand disease etiology, interventions, and prevention of CHD.

REFERENCES

1. Donofrio MT, Moon-Grady AJ, Hornberger LK, et al. Diagnosis and treatment of fetal cardiac disease. *Circulation*. 2014;129(21):2183-2242. https://doi.org/10.1161/01.cir.0000437597.44550.5d

2. Lopez KN, Morris SA, Sexson Tejtel SK, Espaillat A, Salemi JL. US mortality attributable to congenital heart disease across the lifespan from 1999 through 2017 exposes persistent racial/ethnic disparities. *Circulation*. 2020;142(12):1132-1147.

3. Camm EJ, Botting KJ, Sferruzzi-Perri AN. Near to one's heart: the intimate relationship between the placenta and fetal heart. *Front Physiol*. 2018;9:629.

4. Perez-Garcia V, Fineberg E, Wilson R, et al. Placentation defects are highly prevalent in embryonic lethal mouse mutants. *Nature*. 2018;555(7697):463. https://doi.org/10.1038/nature26002

5. Burton GJ, Jauniaux E. Pathophysiology of placental-derived fetal growth restriction. *Am J Obstet Gynecol*. 2018;218(2):S745-S761. https://doi.org/10.1016/j.ajog.2017.11.577

6. Courtney JA, Cnota JF, Jones HN. The role of abnormal placentation in congenital heart disease; cause, correlate, or consequence? *Front Physiol*. 2018;9:1045.

7. Burton GJ, Jauniaux E. Development of the human placenta and fetal heart: synergic or independent? *Front Physiol*. 2018;9:373.

8. Huhta J, Linask KK. Environmental origins of congenital heart disease: the heart-placenta connection. *Semin Fetal Neonatal Med*. 2013;18(5):245-250. https://doi.org/10.1016/j.siny.2013.05.003

9. Al Nafisi B, van Amerom JF, Forsey J, et al. Fetal circulation in left-sided congenital heart disease measured by cardiovascular magnetic resonance: a case-control study. *J Cardiovasc Magn Reson*. 2013;15(1):65. https://doi.org/10.1186/1532-429X-15-65

10. Llurba E, Sánchez O, Ferrer Q, et al. Maternal and foetal angiogenic imbalance in congenital heart defects. *Eur Heart J*. 2014;35(11):701-707. https://doi.org/10.1093/eurheartj/eht389

11. Leon RL, Sharma K, Mir IN, et al. Placental vascular malperfusion lesions in fetal congenital

heart disease. *Am J Obstet Gynecol*. 2022;227(4):620.e1-620.e8. https://doi.org/10.1016/j.ajog.2022.05.038

12. Ho DY, Josowitz R, Katcoff H, et al. Midgestational fetal placental blood flow is diminished in the fetus with congenital heart disease. *Prenat Diagn*. 2020;40(11):1432-1438. https://doi.org/10.1002/pd.5791

13. Shehata F, Levin I, Shrim A, et al. Placenta/birthweight ratio and perinatal outcome: a retrospective cohort analysis. *BJOG Int J Obstet Gynaecol*. 2011;118(6):741-747. https://doi.org/10.1111/j.1471-0528.2011.02892.x

14. The relationship between birth weight and blood pressure amplifies from childhood to adulthood. Accessed August 3, 2022. https://oce.ovid.com/article/00004872-199917070-00003/HTML

15. Risnes KR, Romundstad PR, Nilsen TI, Eskild A, Vatten LJ. Placental weight relative to birth weight and long-term cardiovascular mortality: findings from a cohort of 31,307 men and women. *Am J Epidemiol*. 2009;170(5):622-631.

16. Steurer MA, Peyvandi S, Baer RJ, et al. Impaired fetal environment and gestational age: what is driving mortality in neonates with critical congenital heart disease? *J Am Heart Assoc*. 2019;8(22):e013194. https://doi.org/10.1161/JAHA.119.013194

17. Limperopoulos C, Tworetzky W, McElhinney DB, et al. Brain volume and metabolism in fetuses with congenital heart disease: evaluation with quantitative magnetic resonance imaging and spectroscopy. *Circulation*. 2010;121(1):26-33. https://doi.org/10.1161/CIRCULATIONAHA.109.865568

18. Sun L, Macgowan CK, Sled JG, et al. Reduced fetal cerebral oxygen consumption is associated with smaller brain size in fetuses with congenital heart disease. *Circulation*. 2015;131(15):1313-1323. https://doi.org/10.1161/CIRCULATIONAHA.114.013051

19. Auger N, Fraser WD, Healy-Profitós J, Arbour L. Association between preeclampsia and congenital heart defects. *JAMA*. 2015;314(15):1588-1598. https://doi.org/10.1001/jama.2015.12505

20. Fung A, Manlhiot C, Naik S, et al. Impact of prenatal risk factors on congenital heart disease in the current era. *J Am Heart Assoc*. 2013;2(3):e000064. https://doi.org/10.1161/JAHA.113.000064

21. Khong TY, Mooney EE, Ariel I, et al. Sampling and definitions of placental lesions: Amsterdam Placental Workshop Group consensus statement. *Arch Pathol Lab Med*. 2016;140(7):698-713. https://doi.org/10.5858/arpa.2015-0225-CC

22. Almog B, Shehata F, Aljabri S, Levin I, Shalom-Paz E, Shrim A. Placenta weight percentile curves for singleton and twins deliveries. *Placenta*. 2011;32(1):58-62. https://doi.org/10.1016/j.placenta.2010.10.008

23. Osterman M, Hamilton B, Martin JA, Driscoll AK, Valenzuela CP. Births: final data for 2020. *Natl Vital Stat Rep*. 2021;70(17):1-50.

24. Perinatal risks associated with assisted reproductive technology. Accessed November 9, 2022. https://www.acog.org/en/clinical/clinical-guidance/committee-opinion/articles/2016/09/perinatal-risks-associated-with-assisted-reproductive-technology

25. Drake P, Driscoll AK, Mathews TJ. Cigarette smoking during pregnancy: United States, 2016. *NCHS Data Brief*. 2018:1-8.

26. Gosdin LK, Deputy NP, Kim SY, Dang EP, Denny CH. Alcohol consumption and binge drinking during pregnancy among adults aged 18-49 years — United States, 2018-2020. *Morb Mortal Wkly Rep*. 2022;71(1):10-13. https://doi.org/10.15585/mmwr.mm7101a2

27. Osuchukwu OO, Reed DJ. Small for gestational age. In: *StatPearls*. StatPearls Publishing; 2022.

28. Gestational diabetes mellitus. Accessed December 5, 2022. https://www.acog.org/en/clinical/clinical-guidance/practice-bulletin/articles/2018/02/gestational-diabetes-mellitus

29. ACOG Practice Bulletin No. 190: gestational diabetes mellitus. *Obstet Gynecol*. 2018;131(2):e49. https://doi.org/10.1097/AOG.0000000000002501

30. Booker WA. Hypertensive disorders of pregnancy. *Clin Perinatol*. 2020;47(4):817-833. https://doi.org/10.1016/j.clp.2020.08.011

31. Wallis AB, Saftlas AF, Hsia J, Atrash HK. Secular trends in the rates of preeclampsia, eclampsia, and gestational hypertension, United States, 1987-2004. *Am J Hypertens*. 2008;21(5):521-526. https://doi.org/10.1038/ajh.2008.20

32. Ives CW, Sinkey R, Rajapreyar I, Tita ATN, Oparil S. Preeclampsia—pathophysiology and clinical presentations: JACC state-of-the-art review. *J Am Coll Cardiol*. 2020;76(14):1690-1702. https://doi.org/10.1016/j.jacc.2020.08.014

33. Aloizos S, Seretis C, Liakos N, et al. HELLP syndrome: understanding and management of a pregnancy-specific disease. *J Obstet Gynaecol*. 2013;33(4):331-337. https://doi.org/10.3109/01443615.2013.775231

34. Frontiers | pregnancy complications, correlation with placental pathology and neonatal outcomes | clinical diabetes and healthcare. Accessed May 16, 2022. https://www.frontiersin.org/articles/10.3389/fcdhc.2021.807192/full

35. Schlatterer SD, Murnick J, Jacobs M, White L, Donofrio MT, Limperopoulos C. Placental pathology and neuroimaging correlates in neonates with congenital heart disease. *Sci Rep*. 2019;9:4137. https://doi.org/10.1038/s41598-019-40894-y

36. Rychik J, Goff D, McKay E, et al. Characterization of the placenta in the newborn with congenital heart disease: distinctions based on type of cardiac malformation. *Pediatr Cardiol*. 2018;39(6):1165-1171. https://doi.org/10.1007/s00246-018-1876-x

37. Hayward CE, Lean S, Sibley CP, et al. Placental adaptation: what can we learn from birthweight: placental weight ratio? *Front Physiol*. 2016;7:28.

KEY WORDS cardiac, congenital heart disease, fetal, obstetrics, pathology, placenta, pregnancy

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