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# Impact of birth weight to placental weight ratio and other perinatal risk factors on left ventricular dimensions in newborns: a prospective cohort analysis

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## Abstract

**Objectives:** To investigate the association between birth weight to placental weight (BW/PW) ratio, and echocardiographic left ventricle (LV) morphology at birth, while accounting for other relevant perinatal factors.

**Methods:** A prospective cohort study was conducted on neonates at NewYork-Presbyterian Brooklyn Methodist Hospital from 2014 to 2018, categorized by their BW/PW percentile. Missing data were imputed with principal component analysis. Chi-squared and one-way analysis of variance were used to compare BW/PW groups and the best regression model was selected using a genetic and backward stepwise algorithm.

**Results:** We analyzed 827 neonates in three BW/PW groups: small (n=16), normal (n=488), and large (n=323). Placental thickness and smallest diameter were positively correlated with several LV parameters, including inter-ventricular septal thickness during diastole (IVSd) (p=0.002, p<0.001) and systole (IVSs) (p=0.001, p<0.001), LV posterior wall thickness at end of diastole (LVPWd) (p=0.003, p<0.001) and systole (LVPWs) (p<0.001, p<0.001), LV mass (p=0.017, p<0.001), and LV mass/volume (p=0.011, p<0.001). The BW/PW ratio correlated

with an increased shortening fraction (estimate=0.29, 95 % CI 0.03–0.55, p=0.027). PW correlated with IVSs (p=0.019), while the longest placental diameter was linked to a decrease in LV internal dimension during diastole (LVIDD) (estimate=-0.07, p=0.039), LV mass (estimate=-0.11, p=0.024), and LV mass/volume (estimate=-0.55, p=0.005).

**Conclusions:** This study found that several placental factors, including the BW/PW ratio, can independently affect LV dimension and morphology, highlighting the importance of fetal growth and placental health in the physiological adaptation of the fetal heart. More research is needed to establish causation and inform newborn prevention strategies.

**Keywords:** placental dimensions; echocardiography; left ventricular dimensions; placental efficacy; birth weight to placental weight ratio; congenital heart diseases

## Introduction

The placenta is crucial for fetal development, serving not just as a regulator of nutrient transport but also as a factor in fetal programming and long-term health outcomes. Its weight is a key determinant of both fetal growth and birth weight (BW), particularly as it shows a positive correlation near term [1, 2]. This holds particular importance as both abnormally low and high placental sizes have been associated with adverse neonatal outcomes [3, 4]. Additionally, the ratio of BW to placental weight (BW/PW) serves as a valuable measure of placental efficiency in nutrient supply. Elevated ratios indicate more efficient nutrient transfer to the fetus, whereas reduced ratios are often linked to suboptimal nutrient delivery, contributing to increased risks of pregnancy complications and conditions such as fetal growth restriction and small-for-gestational-age (SGA) infants, especially earlier in gestation (6, 7, 8).

The left ventricle (LV) serves as a vital predictor of cardiac health in neonates. Alterations in LV dimensions or mass, potentially due to fetal programming, can pose a

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significant risk to cardiovascular health both immediately and in the long term [5]. Studies have shown that alterations in placental function and structure may lead to cardiovascular changes in the fetus, including the LV [6]. Studies have evaluated various anthropometric measures, such as height, weight, and body surface area (BSA), as determinants of cardiovascular structure size in children including the LV [7]. Among these, BSA has been identified as the primary predictive variable for cardiac parameters. It is commonly used to calculate z-scores for cardiac structures in neonates and infants [8, 9]. In our previous study, we have observed that BW is also a significant predictor of LV dimensions in SGA infants [10].

PW has been identified as the factor with the most influence on the BW. When examined in isolation, PW accounts for 48 % of the variability in BW [11]. Furthermore, after adjusting for relevant maternal and neonatal characteristics, the combined placental measurements account for a substantial 74 % of its variability [11]. This interrelationship suggests that placental metrics can serve as effective predictors of neonatal LV dimensions. Numerous factors such as maternal health, gestational age (GA), and environmental conditions are known to influence BW/PW ratio and, subsequently, neonatal outcomes [12]. However, the specific mechanisms by which the BW/PW ratio affects LV measurements remain less well understood. This has led to a research gap, warranting further investigation into the correlation between BW/PW ratio and neonatal cardiac health, particularly in the context of LV measurements.

Understanding the relationship between BW/PW ratio and LV dimensions may not only offer insights into immediate neonatal care but also into long-term cardiovascular health, as early cardiac changes have been linked to increased susceptibility to cardiovascular diseases in later life [13]. The primary aim of this study is to elucidate the association between the BW/PW ratio and LV dimensions in neonates, thereby contributing to a more nuanced understanding of factors influencing neonatal cardiac structure that may have implications for cardiovascular health into later life. The secondary objectives of this study are to investigate the associations between additional placental, maternal, and neonatal factors and their influence on LV parameters.

## Subjects and methods

### Study design and setting

This single-center prospective cohort study investigated the impact of key parameters, including placental factors, on echocardiographic LV

dimensions and morphology in newborns. The primary objective of the study was to evaluate the relationship between the BW/PW ratio and different LV dimensions in newborns while considering other neonatal, maternal, and placental factors. Echo evaluations were conducted within 48–72 h after delivery and before hospital discharge. The study was conducted at NewYork-Presbyterian Brooklyn Methodist Hospital's nursery ward and neonatal intensive care unit (NICU) from 2014 to 2018, adhering to the Helsinki Declaration and approved by the hospital's Institutional Review Board (IRB). Data security was maintained by appointing distinct identification numbers to each participant and keeping the data securely in a protected repository. Reporting followed the strengthening the reporting of observational studies in epidemiology (STROBE) guidelines [14].

### Eligibility criteria

This study included neonates who underwent echocardiographic evaluations at the hospital mostly for murmur evaluation as part of routine screening. Neonates below the 10<sup>th</sup> percentile or above the 90<sup>th</sup> percentile on the Fenton growth chart were selected for routine screening echocardiography [15]. Neonates with major cardiac pathology, significant congenital abnormalities, hypoxic respiratory failure, severe sepsis/shock, low 5 min APGAR score, genetic diagnosis, perinatal depression, or born before the 35<sup>th</sup> week of pregnancy were excluded. Significant cardiac pathologies, as exclusion criteria in our study, encompass any structural anomalies detected via echocardiography, irrespective of the clinical presentation. This includes, but is not limited to, congenital heart diseases such as septal defects, complex cyanotic heart conditions, and outflow tract obstructions, as well as valvular disorders like severe stenosis or regurgitation. Symptomatic newborns with conditions such as persistent pulmonary hypertension of the newborn and cardiac dysfunctions that lead to clinical instability were also excluded from the study. Conversely, neonates with trivial cardiac findings, which do not impact hemodynamics – like a patent ductus arteriosus that presents with minimal shunting or a patent foramen ovale measuring less than 3 mm – were not excluded and therefore participated in the study. These minor conditions are typically not associated with significant clinical consequences and are often considered normal variants in neonates. Parental consent was not obtained as echocardiography scans were part of routine screening protocols for newborns. Following echocardiography testing and discharge, no further follow-up was done for the included neonates.

### Predictor variables

We used neonatal, maternal, and placental factors as predictor variables. The included population was divided into three categories based on their BW/PW ratio using reference ranges provided by the study conducted by Flatley et al. (2022) [16]. These reference ranges were adjusted for GA, sex, and parity. The three groups were categorized as follows: small BW/PW (less than the 10<sup>th</sup> percentile), normal BW/PW (between the 10<sup>th</sup> and 90<sup>th</sup> percentiles), and large BW/PW (more than the 90<sup>th</sup> percentile). Utilizing the same percentiles cutoff, we categorized the population into three size groups: SGA, appropriate for gestational age (AGA), and large for gestational age (LGA) based on Fenton charts [15].

Neonatal variables included sex, GA, birth weight, height, head circumference, chest circumference, size category, ponderal index,

APGAR scores at 1 and 5 min, blood pressure (BP) measurements (diastolic, systolic, and mean PB), and NICU admissions. Maternal covariates included gravidity, parity, maternal age, body mass index (BMI), mode of delivery, gestational diabetes mellitus (GDM) diagnosis and management, ethnicity, and preeclampsia. GDM diagnosis followed the criteria set by the American Diabetes Association (ADA) collected from medical records at the time of delivery [17], and its management was divided into diet/lifestyle, medication, or insulin. The diagnosis of preeclampsia in our study was extracted from medical records at the time of delivery, which was primarily made using the criteria established by the American Congress of Obstetricians and Gynecologists (ACOG) during the study period, while BP readings and BMI (using height and weight) were extracted at the time of delivery by our institution nurses. Placental factors considered were PW, BW/PW ratio, BW/PW category, placental dimensions (largest and smallest), and placental thickness. Relevant maternal medical history was obtained from electronic medical records, while neonatal and placental information was collected after birth.

### Outcome variables

The dependent variables included inter-ventricular septal thickness during diastole (IVSd) and systole (IVSs), left ventricular internal dimension during diastole (LVIDd) and systole (LVIDs), left ventricular posterior wall thickness at end of diastole (LVPWd) and systole (LVPWs), shortening fraction (FS), left ventricular mass (LVmass), left ventricular mass to volume ratio (LVmass/vol), and asymmetrical septal hypertrophy (ASH). The only binary variable, ASH, was derived from the IVSd to LVPWd ratio, while all other variables were continuous and either measured directly or estimated using echocardiography. LV morphology was evaluated using the 2D method for structural assessment and the M-mode method for functional evaluation. Echocardiography was conducted by a single board-certified cardiologist. In cases where the cardiologist is not available, the echo study is conducted by a technician and is subsequently re-reviewed and interpreted by the cardiologist. Most LV dimensions measures were conducted using the short-axis view, while some were done using the parasternal long-axis view. All echo LV dimensions measured were done in one single cycle. A Philips 5500 ECHO (Philips, Andover, MA, USA) device was used for examining the heart by echocardiography.

### Data analysis

We utilized multiple imputations to handle missing data in two sub-datasets – one for numerical variables and another for categorical variables. For numerical variables, we normalized the data using a logarithm transformation and then utilized a technique called multiple imputations with principal component analysis (MIPCA) with PCA to fill in missing values, creating a complete dataset [18]. For categorical variables, we employed MIPCA with multiple correspondence analysis (MCA) [18, 19]. This approach has advantages in managing large datasets with missing values, accurately estimating missing values, reducing dataset complexity, and effectively analyzing categorical data [19].

Then, we compared the characteristics of three BW/PW categories at baseline using different statistical tests. For categorical variables, the Chi-squared test was used, while for continuous variables, a one-way analysis of variance (ANOVA) was employed [20]. For

statistical modeling, a genetic algorithm was used for model selection based on the lowest Akaike information criterion (AIC) [21, 22]. The genetic algorithm iteratively searches for the optimal variable combination based on fitness criteria, inspired by natural selection and genetics. Afterward, a backward stepwise algorithm based on the F-test was applied to refine the model, retaining only significant variables at a 5% significance level [23]. The backward stepwise algorithm starts with all the variables selected by the genetic algorithm and removes non-significant ones based on the F-test [23].

Baseline characteristics were analyzed and presented in tables with frequencies, percentages, mean, and standard deviations. Regression model results were also presented in tables, showing estimates, standard errors, 95% confidence intervals (CI), and p-values for each predictor variable. Statistical significance was determined using a p-value threshold of less than 0.05. The model fit evaluation included R-squared ( $R^2$ ) and log-likelihood. Statistical analyses for Chi-squared and one-way ANOVA tests were conducted using Stata software (version 16.0, StataCorp LLC, College Station, TX). The missMDA package was used for imputing missing values, and the glmulti package was utilized for model selection using the genetic algorithm in RStudio Build 446 [18, 19, 22].

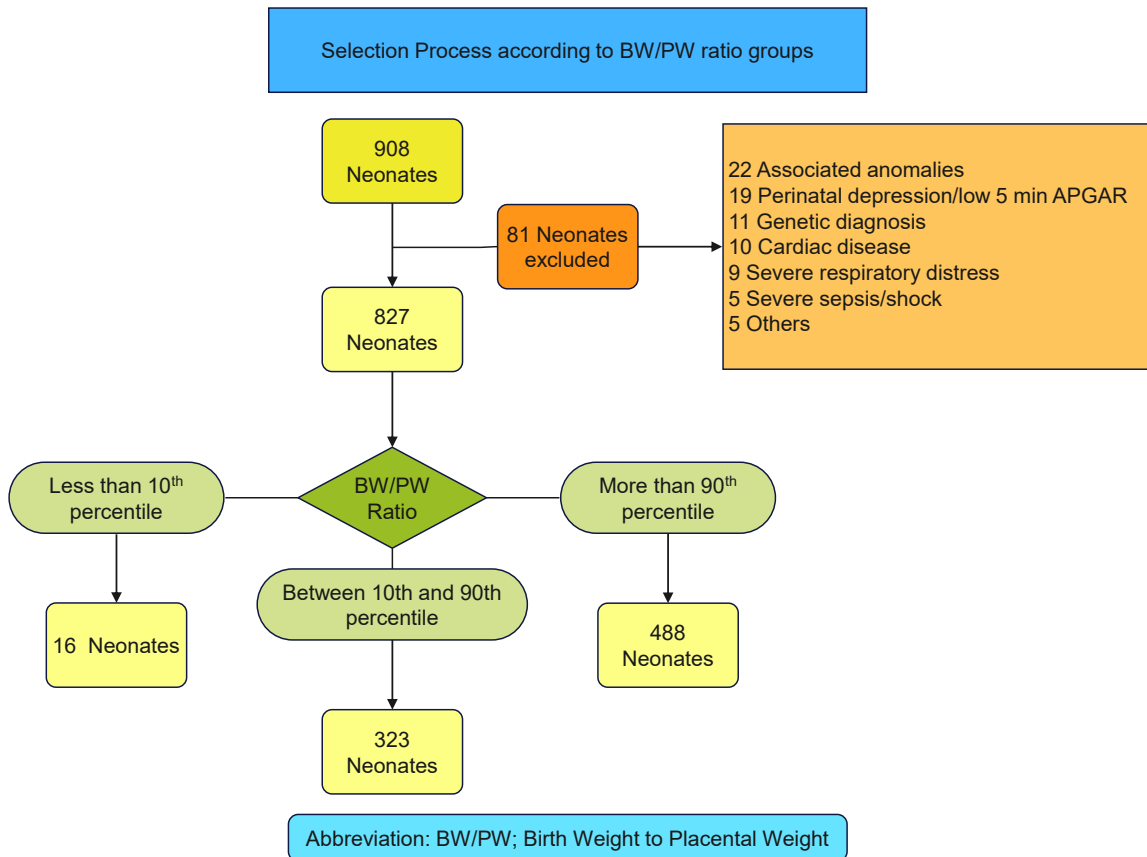
## Results

### Selection and inclusion process

Figure 1 presents an overview of the selection and inclusion process used in our study. Within the study period, a total of 908 neonates were admitted to the hospital. After excluding 81 neonates based on the selection criteria (reasons outlined in Figure 1), we included 827 neonates in our final analysis. Among these neonates, 16 were classified in the small BW/PW group (with BW/PW ratio less than the 10<sup>th</sup> percentile), 488 were in the large BW/PW group (with BW/PW ratio above the 90<sup>th</sup> percentile), and the remaining 323 neonates were categorized in the normal BW/PW group.

### Baseline characteristics

Table 1 presents the baseline characteristics of the neonates categorized based on their BW/PW ratio groups. The comparison of categorical variables among the groups revealed no statistically significant differences in sex, birth weight category, APGAR scores at 1 and 5 min, NICU admission, mode of delivery, gravidity, parity, preeclampsia, GDM status, GDM management, and ethnicity. Maternal insulin use for GDM was documented in 37 cases, while medication use was found in 66 cases (65 using glyburide and one using metformin). Notably, there were no significant variations in the distribution of these variables across the different BW/PW ratio groups.



**Figure 1:** Overview of the selection process of neonates according to BW/PW ratio groups in our study.

Table 2 presents the differences in baseline characteristics between the BW/PW ratio groups in continuous variables. Neonates in the small BW/PW ratio group had significantly lower birth weight, birth height, head circumference, chest circumference, and higher PW compared to those in the normal and large BW/PW ratio groups as shown in Table 2. Conversely, GA was significantly lower in the large BW/PW ratio group compared to the other groups. However, there were no significant differences in the ponderal index, maternal age, maternal BMI, maternal BP (systolic, diastolic, mean), placental diameter 1 (largest diameter), placental diameter 2 (smallest diameter), and placental thickness among the BW/PW ratio groups. Table 3 presents the differences in LV parameters between the BW/PW ratio groups. Upon analysis, no significant differences were observed in most of the LV parameters among the groups, including IVSd, IVSs, LVIDd, LVIDs, LVPWd, LVPWs, FS, LVmass, and LVmass/

vol. The presence of ASH showed no significant difference among the BW/PW ratio groups as well ( $p=0.664$ ).

## Regression results

Table 4 presents the regression analysis results, revealing significant associations between neonatal and maternal factors with various LV parameters. The IVSd model shows a strong fit with an  $R^2$  of 0.341 and an adjusted  $R^2$  of 0.333, explaining approximately 34.1% of its variance. Its log-likelihood is  $-974.455$ , indicating a good model fit. IVSs also has a robust fit ( $R^2=0.302$ , adjusted  $R^2=0.295$ ), while LVIDd has a slightly lower but still significant  $R^2$  of 0.266. In contrast, LVIDs and FS exhibit weaker fits with  $R^2$  values of 0.154 and 0.050, respectively. Notably, LVmass has the highest  $R^2$  at 0.406, indicating a strong relationship with the model, while

**Table 1:** Differences in baseline characteristics between BW/PW ratio groups in categorical variables.

	Small BW/PW ratio n=16		Normal BW/PW ratio n=323		Large BW/PW ratio n=488		Total n=827	
	n	%	n	%	n	%	n	%
Sex								
Male	9	56.25	186	57.59	267	54.71	462	55.86
Female	7	43.75	137	42.41	221	45.29	365	44.14
Birth weight category								
SGA	2	12.5	54	16.72	73	14.96	129	15.6
AGA	11	68.75	210	65.02	303	62.09	524	63.36
LGA	3	18.75	59	18.27	112	22.95	174	21.04
APGAR at 1 min								
Normal	16	100	278	86.07	432	88.52	726	87.79
Moderately depressed	0	0	31	9.6	32	6.56	63	7.62
Severely depressed	0	0	14	4.33	24	4.92	38	4.59
APGAR at 5 min								
Normal	16	100	304	94.12	462	94.67	782	94.56
Moderately depressed	0	0	19	5.88	26	5.33	45	5.44
NICU admission								
No	10	62.5	169	52.32	258	52.87	437	52.84
Yes	6	37.5	154	47.68	230	47.13	390	47.16
Mode of delivery								
Vaginal delivery	8	50	161	49.85	214	43.85	383	46.31
Cesarean section	8	50	162	50.15	274	56.15	444	53.69
Gravidity								
Primigravida	3	18.75	89	27.55	114	23.36	206	24.91
Multigravida	13	81.25	234	72.45	374	76.64	621	75.09
Parity								
Nulliparous	13	81.25	219	67.8	336	68.85	568	68.68
Multiparous	3	18.75	104	32.2	152	31.15	259	31.32
Preeclampsia								
No	15	93.75	292	90.4	439	89.96	746	90.21
Yes	1	6.25	31	9.6	49	10.04	81	9.79
GDM								
No	14	87.5	216	66.87	315	64.55	545	65.9
Yes	2	12.5	107	33.13	173	35.45	282	34.1
GDM management								
Diet or untreated	16	100	282	87.31	426	87.3	724	87.54
Medical	0	0	24	7.43	42	8.61	66	7.98
Insulin	0	0	17	5.26	20	4.1	37	4.47
Ethnicity								
White	10	62.5	202	62.54	290	59.43	502	60.7
African American	4	25	81	25.08	140	28.69	225	27.21
Asian	1	6.25	11	3.41	7	1.43	19	2.3
Hispanic	0	0	9	2.79	25	5.12	34	4.11
Others	1	6.25	20	6.19	26	5.33	47	5.68

NICU, neonatal intensive care unit; GDM, gestational diabetes mellitus; SGA, small for gestational age; AGA, appropriate for gestational age; LGA, large for gestational age; BW/PW, birth weight to placental weight.

ASH, though lacking an  $R^2$  value, shows an association with the model through a log-likelihood of  $-475.797$ .

GA displayed strong correlations with multiple LV dimensions, showing significant relationships with IVSd ( $p=0.011$ ), IVSs ( $p<0.001$ ), LVIDd ( $p<0.001$ ), LVIDs ( $p<0.001$ ), LVPWd ( $p<0.001$ ), LVPWs ( $p<0.001$ ), LVmass ( $p<0.001$ ), and LVmass/volume ratio ( $p=0.047$ ). Neonatal size factors, including size category, BW, ponderal index, and chest circumference, also influenced LV parameters. Additionally, male sex, NICU admission, and APGAR scores were associated with specific LV dimensions.

Among maternal factors, primiparity showed associations with decreased IVSd (estimate  $= -0.15$ ,  $p=0.016$ ), LVmass (estimate  $= -0.62$ ,  $p=0.005$ ), and LVmass/volume ratio (estimate  $= -1.84$ ,  $p=0.032$ ). GDM exhibited a significant increase in IVSs ( $p=0.010$ ), while insulin use was positively correlated with IVSd ( $p<0.001$ ). Maternal BMI was linked to decreased LVID during diastole ( $p=0.002$ ) and systole ( $p=0.005$ ), whereas maternal age was associated with increased LVPWd ( $p=0.036$ ). Furthermore, White and Hispanic ethnicities related to increased ASH.

Among the placental factors analyzed, placental thickness and smallest diameter exhibited significant associations with increased LV dimensions. Placental thickness was linked to substantial increases in IVSd ( $p=0.002$ ), IVSs ( $p=0.001$ ), LVPWd ( $p=0.003$ ), LVPWs ( $p<0.001$ ), LVmass ( $p=0.017$ ), and LVmass/volume ( $p=0.011$ ). Similarly, the shortest diameter of the placenta displayed significant positive correlations with IVSd ( $p<0.001$ ), IVSs ( $p<0.001$ ), LVIDd ( $p<0.001$ ), LVIDs ( $p=0.016$ ), LVPWd ( $p<0.001$ ), LVPWs ( $p<0.001$ ), LVmass ( $p<0.001$ ), and LVmass/volume ( $p<0.001$ ). Moreover, the BW/PW ratio was associated with an increase in FS, with an estimated coefficient of 0.29 (95% CI 0.03–0.55,  $p=0.027$ ). Additionally, PW showed a significant correlation with IVSs ( $p=0.019$ ), while the longest diameter of the placenta was associated with a decrease in LVIDd (estimate  $= -0.07$ ,  $p=0.039$ ), LVmass (estimate  $= -0.11$ ,  $p=0.024$ ), and LVmass/volume (estimate  $= -0.55$ ,  $p=0.005$ ).

## Discussion

The primary objective of this prospective cohort study was to investigate the relationship between the BW/PW ratio and LV dimensions in newborns while considering other neonatal, maternal, and placental factors. Our study found several significant associations between neonatal and maternal factors with various LV parameters. In our study,

**Table 2:** Differences in baseline characteristics between BW/PW ratio groups in continuous variables.

	Small BW/PW ratio n=16		Normal BW/PW ratio n=323		Large BW/PW ratio n=488		Total n=827	
	Mean	Std. Dev.	Mean	Std. Dev.	Mean	Std. Dev.	Mean	Std. Dev.
Birth weight, g	2,220.31	734.73	3,335.80	771.93	3,504.78	677.52	3,413.93	740.00
Birth height, cm	43.62	3.98	48.98	3.15	49.76	2.99	49.34	3.20
Birth HC, cm	31.31	1.63	34.19	1.99	34.34	2.16	34.22	2.13
Birth CC, cm	29.54	2.94	33.00	2.79	33.21	2.56	33.06	2.70
Ponderal index, g/cm <sup>3</sup>	2.63	0.38	2.81	0.41	2.83	0.38	2.81	0.39
Gestational age, weeks	38.63	1.75	38.82	1.44	38.32	1.52	38.52	1.51
Maternal age, years	32.04	4.84	31.76	6.01	31.58	5.55	31.66	5.72
Maternal BMI, kg/m <sup>2</sup>	31.48	7.13	32.84	7.13	32.05	6.50	32.35	6.77
Maternal SBP, mm Hg	128.78	17.99	124.61	14.81	123.55	14.09	124.07	14.46
Maternal DBP, mm Hg	78.30	11.43	74.31	11.91	74.72	10.41	74.63	11.04
Maternal MBP, mm Hg	97.23	10.55	90.54	11.02	90.55	10.36	90.68	10.65
Placental weight, g	603.36	184.05	577.59	136.70	482.16	102.10	521.78	127.75
Placental diameter 1, cm	19.75	2.80	18.34	2.67	18.18	2.66	18.27	2.68
Placental diameter 2, cm	16.37	2.06	15.83	1.96	15.83	2.00	15.84	1.98
Placental thickness, cm	2.48	0.91	2.43	0.60	2.49	0.66	2.46	0.64

Std. Dev., standard deviation; HC, head circumference; CC, chest circumference; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; MBP, mean blood pressure; BW/PW, birth weight to placental weight.

**Table 3:** Differences in LV parameters between BW/PW ratio groups.

	Small BW/PW ratio n=16		Normal BW/PW ratio n=323		Large BW/PW ratio n=488		Total n=827		p-Value
	Mean	Std. Dev.	Mean	Std. Dev.	Mean	Std. Dev.	Mean	Std. Dev.	
IVSd, mm	3.93	0.55	4.12	0.85	4.17	1.05	4.15	0.97	0.506
IVSs, mm	5.17	0.70	5.38	1.00	5.47	1.26	5.43	1.15	0.377
LVIDd, mm	18.56	1.76	18.51	2.04	18.43	2.18	18.47	2.11	0.863
LVIDs, mm	11.88	1.48	11.89	1.44	11.76	1.63	11.81	1.55	0.484
LVPWd, mm	3.49	0.59	3.52	0.61	3.55	0.69	3.54	0.66	0.849
LVPWs, mm	4.85	0.71	4.85	0.69	4.87	0.81	4.86	0.77	0.959
FS, %	35.33	3.01	35.40	4.05	35.99	4.43	35.75	4.27	0.148
LVmass, g	9.93	2.75	10.58	3.50	10.66	3.79	10.62	3.66	0.719
LVmass/vol, g/m <sup>2</sup>	49.01	10.88	50.80	12.80	50.66	12.03	50.69	12.31	0.849
Presence of ASH (n, %)	3	18.75 %	94	29.10 %	142	29.10 %	239	28.90 %	<sup>a</sup> 0.664

<sup>a</sup>Chi-squared p-value, LVmass, left ventricular mass; LVmass/vol, LVmass to volume ratio; IVSd, inter-ventricular septal thickness during diastole; IVSs, inter-ventricular septal thickness during systole; LVIDd, LV internal dimension during diastole; LVIDs, LV internal dimension during systole; LVPWd, LV posterior wall thickness at end of diastole; LVPWs, LV posterior wall thickness at end of systole; FS, shortening fraction; ASH, asymmetrical septal hypertrophy, Std. Dev., standard deviation; BW/PW, birth weight to placental weight.

GA correlated with multiple LV dimensions, suggesting prematurity or delayed gestational development affects cardiac function. This association between GA multiple LV

dimensions is well documented in the literature [24]. Neonatal factors (BW, ponderal index, chest circumference) were also linked in our study to specific LV dimensions,

Table 4: Regression models for LV parameters included.

LV parameter/predictor	Estimates	Standard error	CI	p	R <sup>2</sup> /R <sup>2</sup> adjusted	Log-likelihood
<b>IVSd<sup>a</sup></b>					0.341/0.333	-974.455
Gestational age	0.05	0.02	0.01–0.09	0.011		
Placental diameter 2, cm	0.08	0.02	0.04–0.11	<0.001		
Placental thickness, cm	0.14	0.05	0.05–0.23	0.002		
NICU admission	0.15	0.06	0.03–0.27	0.018		
LGA	0.78	0.08	0.62–0.94	<0.001		
SGA	-0.38	0.09	-0.56 to -0.21	<0.001		
Primiparity	-0.15	0.06	-0.27 to -0.03	0.016		
Insulin for GDM	0.65	0.16	0.35–0.96	<0.001		
<b>IVS</b>					0.302/0.295	-1,142.768
Gestational age	0.10	0.02	0.06–0.15	<0.001		
Ponderal index	0.20	0.09	0.02–0.39	0.033		
Placental weight	-0.00	0.00	-0.00 to -0.00	0.019		
Placental diameter 2, cm	0.08	0.02	0.04–0.12	<0.001		
Placental thickness, cm	0.18	0.06	0.08–0.29	0.001		
LGA	0.89	0.09	0.71–1.07	<0.001		
SGA	-0.54	0.10	-0.74 to -0.34	<0.001		
GDM	0.19	0.07	0.05–0.34	0.010		
<b>LVIDd<sup>b</sup></b>					0.266/0.255	-1,663.77
Gestational age	0.30	0.04	0.21–0.38	<0.001		
Chest circumference	0.07	0.02	0.02–0.12	0.004		
Maternal BMI	-0.03	0.01	-0.05 to -0.01	0.002		
Placental diameter 1, cm	-0.07	0.03	-0.13 to -0.00	0.039		
Placental diameter 2, cm	0.21	0.05	0.12–0.30	<0.001		
NICU admission	-0.36	0.15	-0.65 to -0.07	0.014		
Male	0.63	0.13	0.37–0.88	<0.001		
LGA	0.85	0.18	0.50–1.19	<0.001		
SGA	-1.29	0.21	-1.70 to -0.89	<0.001		
Normal APGAR 5	-0.90	0.35	-1.57 to -0.22	0.01		
<b>LVIDs</b>					0.154/0.145	-1,468.951
Gestational age	0.20	0.03	0.13–0.26	<0.001		
Chest circumference	0.05	0.02	0.02–0.09	0.006		
Maternal BMI	-0.02	0.01	-0.04 to -0.01	0.005		
Placental diameter 2, cm	0.07	0.03	0.01–0.13	0.016		
NICU admission	-0.38	0.11	-0.60 to -0.17	0.001		
Male	0.36	0.10	0.16–0.56	<0.001		
LGA	0.31	0.14	0.04–0.58	0.026		
SGA	-0.63	0.16	-0.94 to -0.31	<0.001		
<b>LVPWd<sup>c</sup></b>					0.300/0.292	-678.978
Gestational age	0.07	0.01	0.05–0.10	<0.001		
Maternal age	0.01	0.00	0.00–0.01	0.036		
Placental diameter 2, cm	0.07	0.01	0.05–0.09	<0.001		
Placental thickness, cm	0.1	0.03	0.03–0.16	0.003		
Male	0.08	0.04	0.00–0.16	0.044		
LGA	0.44	0.05	0.33–0.54	<0.001		
SGA	-0.22	0.06	-0.33 to -0.10	<0.001		
<b>LVPWs<sup>d</sup></b>					0.322/0.315	-792.304
Gestational age	0.06	0.02	0.03–0.09	<0.001		
Placental diameter 2, cm	0.08	0.01	0.05–0.11	<0.001		
Placental thickness, cm	0.14	0.04	0.07–0.22	<0.001		
LGA	0.49	0.06	0.37–0.61	<0.001		
SGA	-0.43	0.07	-0.57 to -0.30	<0.001		
Hispanic ethnicity	0.29	0.12	0.06–0.52	0.013		
<b>Lvmass<sup>e</sup></b>					0.406/0.398	-2030.394
Gestational age	0.44	0.07	0.30–0.57	<0.001		
Placental diameter 1, cm	-0.11	0.05	-0.21 to -0.02	0.024		
Placental diameter 2, cm	0.47	0.07	0.33–0.61	<0.001		

Table 4: (continued)

LV parameter/predictor	Estimates	Standard error	CI	p	R <sup>2</sup> /R <sup>2</sup> adjusted	Log-likelihood
Placental thickness, cm	0.40	0.17	0.07–0.73	0.017		
Male	0.70	0.20	0.30–1.10	0.001		
LGA	3.03	0.28	2.49–3.58	<0.001		
SGA	–1.89	0.31	–2.50 to –1.29	<0.001		
Primiparity	–0.62	0.22	–1.05 to –0.19	0.005		
Insulin for GDM	1.09	0.56	–0.00 to 2.18	0.051		
<b>LVmass/vol</b>					0.191/0.184	–3,161.363
Gestational age	0.53	0.27	0.01–1.06	0.047		
Placental diameter 1, cm	–0.55	0.20	–0.94 to –0.17	0.005		
Placental diameter 2, cm	1.53	0.28	0.98–2.08	<0.001		
Placental thickness, cm	1.63	0.64	0.37–2.89	0.011		
LGA	7.61	1.08	5.49–9.72	<0.001		
SGA	–2.83	1.17	–5.13 to –0.53	0.016		
Primiparity	–1.84	0.85	–3.52 to –0.16	0.032		
<b>FS</b>					0.050/0.047	–2,351.251
BW/PW ratio	0.29	0.13	0.03–0.55	0.027		
LGA	1.81	0.36	1.10–2.53	<0.001		
SGA	–1.00	0.41	–1.80 to –0.19	0.015		
<b>ASH<sup>f</sup></b>					0.054	–475.797
NICU admission	1.65	0.29	1.18–2.32	0.004		
LGA	1.62	0.32	1.10–2.38	0.015		
Hispanic ethnicity	0.31	0.14	0.12–0.73	0.011		
White ethnicity	0.50	0.09	0.35–0.70	<0.001		
Other ethnicity	0.45	0.17	0.20–0.92	0.038		

<sup>a</sup>Other variables controlled for in this model: GDM control (diet and medical treatment), <sup>b</sup>other variables controlled for in this model: APGAR1 (normal and severely depressed), <sup>c</sup>other variables controlled for in this model: GDM control (diet, medical and insulin treatment), <sup>d</sup>other variables controlled for in this model: Ethnicity (Asian, Whites and others), <sup>e</sup>other variables controlled for in this model: GDM control (diet and medical treatment), <sup>f</sup>other variables controlled for in this model: SGA category and Asian ethnicity, LVmass, left ventricular mass; LVmass/vol, LVmass to volume ratio; IVSd, inter-ventricular septal thickness during diastole; IVSs, inter-ventricular septal thickness during systole; LVIDd, LV internal dimension during diastole; LVIDs, LV internal dimension during systole; LVPWd, LV posterior wall thickness at end of diastole; LVPWs, LV posterior wall thickness at end of systole; IVS/LVPW, inter-ventricular septal thickness to LV posterior wall thickness ratio in diastole; FS, shortening fraction; ASH, asymmetrical septal hypertrophy; NICU, neonatal intensive care unit; BMI, body mass index; LGA, large for gestational age; SGA, small for gestational age; GDM, gestational diabetes mellitus; BW/PW, birth weight to placental weight.

highlighting fetal growth's influence on cardiac development. We have shown that primiparity is associated with decreased IVSd, LVmass, and LVmass/volume ratio, implying first-time mothers may impact a newborn's cardiac development. This could possibly be due to physiological adaptations, hemodynamic changes, structural adjustments, maternal age, and genetic/environmental factors influencing the cardiac parameters during the first pregnancy.

In our study, we used the 10<sup>th</sup> and 90<sup>th</sup> percentile as the cutoff for dividing our population based on the BW/PW ratio. One study aimed to investigate the correlation between the BW/PW ratio and major congenital anomalies in 735 singleton infants born at 34–41 weeks of gestation [25]. Of these infants, 15 % showed major congenital anomalies. The study found that the BW/PW ratio was not significantly associated with the presence or absence of major anomalies, and the distribution pattern of the BW/PW ratio varied

across different major anomaly subgroups [25]. However, major anomalies tended to aggregate in the 90<sup>th</sup> percentile of the BW/PW ratio [25]. Therefore, we recommend the use of such cutoffs in future research.

Neonates born to mothers with GDM are known to have larger LV dimensions compared to those born to non-diabetic mothers, indicating accelerated cardiac growth and temporary hypertrophy [26]. This is further compounded in cases of maternal type one or type two DM, where the risk of pathological ventricular hypertrophy in neonates is even higher [27]. These findings underscore the necessity of vigilant monitoring to manage perinatal complications. Studies have also shown that infants born to diabetic mothers have higher rates of ASH and increased IVS thickness, regardless of GA appropriateness [28]. In our research, we found that GDM significantly increased systolic IVS thickness ( $p=0.010$ ), and maternal insulin use was positively correlated with



diastolic IVS thickness ( $p < 0.001$ ). These results align with existing literature and highlight the impact of maternal diabetes and insulin use on neonatal cardiac development.

Many studies have attempted to identify the factors influencing LV parameters, and some neonatal factors have previously been linked to LV size and function. According to one research, LV dimensions can vary depending on age, sex, body size, and ethnicity [29]. A study found that low BW was associated with decreased left ventricular mass and increased wall stress in young adults [30]. It has also been reported that maternal age is significantly associated with poor LV function [31]. Another research group discovered that both maternal obesity and weight gain are linked to increased fetal LVmass [32]. Similarly, maternal ethnicity has been shown to influence fetal cardiovascular development, with South Asians being predisposed to altered heart structure and function [33]. One study examined 981 mother-offspring pairs from the Shanghai Birth Cohort to investigate the association between maternal gestational weight gain (GWG) and LV geometry and function in the offspring at four years of age [32]. The results showed that excessive maternal GWG, particularly in the second and third trimesters, was positively correlated with IVSd and LVmass. Additionally, excessive GWG during these trimesters increased the risk of LV eccentric and concentric hypertrophy in the offspring [32].

Interestingly in our paper, placental factors, such as placental thickness and smallest diameter, showed significant and independent associations with increased LV dimensions, indicating the potential role of placental health and efficiency in fetal cardiac development. The BW/PW ratio was associated with an increase in FS, which could imply a connection between placental efficiency and cardiac function. This might suggest that a more efficient placenta, as reflected in a lower BW/PW ratio, is associated with better cardiac function, possibly due to improved nutrient transfer during fetal development. However, PW had only a significant correlation with one LV parameter (IVSs), indicating that other placental measurements might have a more significant impact on cardiac development. Placental thickness and the shortest diameter of the placenta exhibited significant positive correlations with IVSd, IVSs, LVIDd, LVIDs, LVPWd, LVPWs, LV mass, and LV mass/volume, indicating substantial increases in these cardiac parameters. The notable associations between placental factors with increased LV dimensions raise intriguing questions about the impact of placental health and efficiency on cardiac development. The positive correlation between the BW/PW ratio and FS further supports the hypothesis that placental efficiency plays a role in fetal cardiac function.

It is well-known in the literature that the placenta plays an important role in the development of congenital heart

disease (CHD). One study analyzed placental pathology from singleton neonates prenatally diagnosed with CHD and delivered at term [34]. Placental abnormalities, such as smaller-than-expected size, chorangiosis, hypomature villi, thrombosis, and infarction, were common in CHD cases, with newborns with transposition of the great arteries exhibiting the most significant placental abnormality [34]. Another retrospective cohort study investigated the relationship between neonatal BW, head circumference, PW, and placental pathology in pregnancies affected by CHD [35]. Placental pathology was found in 37% of cases, and infants with CHD showed preserved BW and head circumferences despite small placentas and increased prevalence of placental pathology, indicating efficient placental function [35]. Abnormal placental growth may offer prenatal diagnostic value, and discordant placental and neonatal growth may suggest a vascular anomaly predisposing fetuses to CHD. One research group examined 6,975 men born in Helsinki between 1934 and 1944 to investigate the link between low BW and later risk of coronary heart disease [36]. Three different placental phenotypes were identified as predictors of the disease, depending on combinations of maternal height, BMI, and placental size [36]. Variations in three processes of normal placental development were hypothesized to lead to fetal malnutrition, possibly contributing to the increased risk of coronary heart disease in individuals with lower birth weights [36]. Based on our findings, we hypothesize that placental dimensions, thickness, and the BW/PW ratio may serve as potential indicators for the presence of CHD in newborns.

## Strength and limitations

This study exhibits several notable strengths that contribute to its scientific merit. Firstly, it adopts a prospective cohort design, allowing for the exploration of associations and reducing the potential for bias inherent in retrospective studies. The inclusion of neonates with echocardiographic evaluations conducted primarily for murmur evaluation as part of routine screening adds clinical relevance to the findings, making them more generalizable to clinical settings. Comprehensive consideration of neonatal, maternal, and placental factors provides a holistic understanding. Meticulous handling of missing data with MIPCA, coupled with genetic algorithm-based model selection followed by a backward stepwise algorithm, ensures comprehensive exploration and statistical validity in assessing predictor variables' impact on LV parameters.

Despite the valuable findings of this study, it is important to acknowledge its limitations. The single-center nature

of the study may limit generalizability of the results to other populations [37]. Additionally, the use of routine screening echocardiography may introduce selection bias, as neonates with major cardiac pathologies were excluded, potentially affecting the representation of certain LV dimensions in the study. The imputation technique used to handle missing data may introduce imprecision in the results, as using MIPCA for missing data has limitations. Efforts to address missing data through transformations and MIPCA may introduce biases. PCA for imputing missing data assumes a multivariate normal distribution, potentially misaligned with real-world datasets. It also assumes missing values occur at random, introducing bias, and may result in information loss or noise. Furthermore, due to the study's observational design, causality between the BW/PW ratio and LV dimensions cannot be established, and other confounding factors may influence the results.

In addition, the study has other limitations. The lack of long-term follow-up of participants after hospital discharge makes it challenging to assess the long-term outcomes of LV function and overall cardiovascular risk for SGA infants. Moreover, the incorporation of neonates undergoing echocardiography for murmurs, predominantly functional in nature, introduces a potential confounding factor, including the likelihood of detecting minor congenital heart defects. This complicates the derivation of clear conclusions and hinders generalizability to broader populations, thereby challenging the clinical applicability and utility of the findings. Ideally, the study should be conducted on a cohort of unselected and healthy children to enhance the robustness and relevance of the results. Therefore, caution must be taken when interpreting the findings of this study. The study design was not blinded, which could introduce bias in measurements and interpretation of the results. Additionally, important confounding variables like maternal smoking, a known risk factor for low birth weight and cardiac dysfunction, were not included in the analysis [38]. Another missing risk factor and a potential limitation of our study is the lack of records regarding pre-existing maternal type one and two diabetes, which is well-known to influence both neonatal size and increase the risk of CHDs. Moreover, our collected data lacks information on the timing of the diagnosis (preterm/term onset) and the severity of preeclampsia, potentially introducing bias into our results. Preeclampsia is a significant influencer of cardiac remodeling during development as it imposes strain on the placenta and, consequently, affects the size of the baby. This, in turn, can place a burden on the developing heart. Understanding the specific timing and severity of preeclampsia is crucial for a more comprehensive analysis of its impact on cardiac health in neonates, which was missing in our study. We also did not

have records of other medications used during pregnancy. Furthermore, the reliance solely on echocardiography to evaluate LV function has inherent limitations [39], and advanced imaging techniques for assessing LV morphology were not employed in the study. Lastly, it is worth noting that a single cardiologist conducted the echocardiographic evaluations, which may impact interobserver variability.

## Conclusions

This single-center prospective cohort study sheds light on the associations between neonatal, maternal, and placental factors with LV dimensions in newborns. We have shown that the BW/PW ratio can independently affect the LV dimensions and morphology. This study also underscores the significance of placental factors, such as placental thickness and smallest diameter, by revealing their correlations with increased LV dimensions, emphasizing the potential influence of placental health and efficiency on fetal cardiac growth. Additionally, significant relationships were observed between GA, neonatal size factors, maternal factors, and specific LV parameters, further highlighting the complex interplay of perinatal factors on cardiac development. Further research, including longitudinal and interventional multi-center studies, is required to fully understand the complex interplay between placental efficiency, maternal factors, and fetal cardiac development.

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**Informed consent:** Since echocardiography, a minimal risk procedure, was performed based on clinical indications, obtaining consent from the neonates' legal guardians was waived by NewYork-Presbyterian Brooklyn Methodist Hospital's IRB.

**Author contributions:** IE, DM and AG: formal analysis, data curation, methodology, validation, visualization, writing – original draft, writing – review & editing. AA: formal analysis, validation, writing – original draft, writing – review & editing. MC: conducted the echo studies. MH: supervised the data collection and organization of the data sheets. DH, DS, NR, BD,

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