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ORIGINAL RESEARCH

Prenatal and Postnatal Cardiac Development in Offspring of Hypertensive Pregnancies

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BACKGROUND: Pregnancy complications such as preterm birth and fetal growth restriction are associated with altered prenatal and postnatal cardiac development. We studied whether there were changes related specifically to pregnancy hypertension.

METHODS AND RESULTS: Left and right ventricular volumes, mass, and function were assessed at birth and 3 months of age by echocardiography in 134 term-born infants. Fifty-four had been born to mothers who had normotensive pregnancy and 80 had a diagnosis of preeclampsia or pregnancy-induced hypertension. Differences between groups were interpreted, taking into account severity of pregnancy disorder, sex, body size, and blood pressure. Left and right ventricular mass indexed to body surface area (LVMI and RVMI) were similar in both groups at birth (LVMI 20.9±3.7 versus 20.6±4.0 g/m^2, P=0.64, RVMI 17.5±3.7 versus 18.1±4.7 g/m^2, P=0.57). However, right ventricular end diastolic volume index was significantly smaller in those born to hypertensive pregnancy (16.8±5.3 versus 12.7±4.7 mL/m^2, P=0.001), persisting at 3 months of age (16.4±3.2 versus 14.4±4.8 mL/m^2, P=0.04). By 3 months of age these infants also had significantly greater LVMI and RVMI (LVMI 24.9±4.6 versus 26.8±4.9 g/m^2, P=0.04; RVMI 17.1±4.2 versus 21.1±3.9 g/m^2, P<0.001). Differences in RVMI and right ventricular end diastolic volume index at 3 months, but not left ventricular measures, correlated with severity of the hypertensive disorder. No differences in systolic or diastolic function were evident.

CONCLUSIONS: Infants born at term to a hypertensive pregnancy have evidence of both prenatal and postnatal differences in cardiac development, with right ventricular changes proportional to the severity of the pregnancy disorder. Whether differences persist long term as well as their underlying cause and relationship to increased cardiovascular risk requires further study.

Key Words: high blood pressure ■ hypertension ■ preeclampsia ■ pregnancy ■ ventricular

See Editorial by Thornburg et al.

Infants born to mothers who have had hypertensive disorders of pregnancy are at increased risk of cardiovascular events[1] and clinical hypertension[1,2] later in life. The rise in blood pressure is evident from childhood and increases into adulthood,[3] so that by 20 years of age up to 30% of young adults who have clinical hypertension have a background history of maternal pregnancy hypertension.[4]

The increased risk may in part relate to differences in vascular phenotype observed in the offspring. During the first few months of life, their vascular cells have reduced angiogenic function and the changes predict the efficiency of their postnatal microvascular development.[5–7] Differences are also evident in the pulmonary circulation with altered pulmonary vascular responses in later life.[8,9] Whether hypertensive pregnancy also relates to differences in offspring cardiac development is less clear. Most studies have been in adolescents, and focused on the left ventricle, with reports of no differences in mass[10,11] or hypertrophy proportional

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CLINICAL PERSPECTIVE

What Is New?

- We showed that at birth, term-born infants exposed to a hypertensive pregnancy had a significantly smaller right ventricular end diastolic volume.
- At 3 months of age, these infants also had significantly greater right and left ventricular mass indexed to body surface area.
- Changes in right ventricular mass and end diastolic volume between birth and 3 months correlated with severity of the hypertensive disorder.

What Are the Clinical Implications?

- Our findings of a disproportionate increase in cardiac mass in infants born to hypertensive pregnancies are consistent with some prior observations in older populations.
- This raises the possibility that differences in later life may be because of distinct trajectories for cardiovascular growth, which start in the first few months of life and precede the development of significant hypertension.
- Early postnatal life may represent a critical window for cardiac development, and optimization of perinatal care may reduce the long-term cardiovascular sequelae in this cohort.

Nonstandard Abbreviations and Acronyms

ASD	atrial septal defect
CCRF	Oxford Cardiovascular Clinical Research Facility
EDV	end diastolic volume
EPOCH	Effect of Preterm Birth and Pregnancy Hypertension on Offspring Cardiovascular Health
LV	left ventricular
LVMI	left ventricular mass index
NHS	National Health Service
PDA	patent ductus arteriosus
RV	right ventricular
RVMI	right ventricular mass index
RVEDVI	right ventricular end diastolic volume index
RVEDV	right ventricular end diastolic volume
sENG	soluble endoglin

to variation in blood pressure.[12] We have previously demonstrated an association between preterm birth and cardiac structure and function,[13,14] with differences emerging during early postnatal life.[15] This alteration in cardiac development was seen irrespective of whether the infant was born after hypertensive or normotensive pregnancy but there appeared to be a potential, additional impact of maternal hypertension on cardiac development.[15]

Therefore, we have now explored the specific association of maternal hypertension with prenatal and postnatal cardiac development, by studying term-born individuals, without other pregnancy complications, and before development of significant changes in blood pressure. We then explored whether particular clinical features of the maternal hypertensive disorder were associated with changes in cardiac structure or function. Our hypothesis was that maternal hypertension would be associated with unique cardiac remodeling in the offspring in the first 3 months of postnatal life compared with infants born to normotensive pregnancies.

METHODS

The data that support the findings of this study, including more detail on the Methods and Materials, are available in the Supplementary Materials or from the corresponding author upon reasonable request.

Study Overview

Between 2011 and 2015, mothers being cared for by the Oxford University Hospitals NHS Foundation Trust were identified by their clinical care team and invited to take part in 1 or more of a portfolio of studies coordinated by the Oxford Cardiovascular Clinical Research Facility. These studies were designed to investigate the impact of pregnancy complications on cardiovascular development during fetal and neonatal life. The EPOCH (Effect of Preterm Birth and Pregnancy Hypertension on Offspring Cardiovascular Health) study[5] was a prospective cohort study investigating the effects of prematurity and hypertensive disorders of pregnancy on the cardiovascular development of the offspring. Ethical approval was granted by the South Central Berkshire Research Ethics Committee (reference 11/SC/0006), and the trial registered with ClinicalTrials.gov (reference number NCT01888770). A stratified recruitment strategy was used so that the 5 study groups (normotensive term, normotensive preterm, preeclampsia term, pregnancy-induced hypertension term, and hypertensive preterm) had approximately equal numbers (Figure 1).

Inclusion and Exclusion Criteria

Singletons and multiplets were included. Mothers below the age of 16 years were excluded from the study as were those with chronic cardiovascular

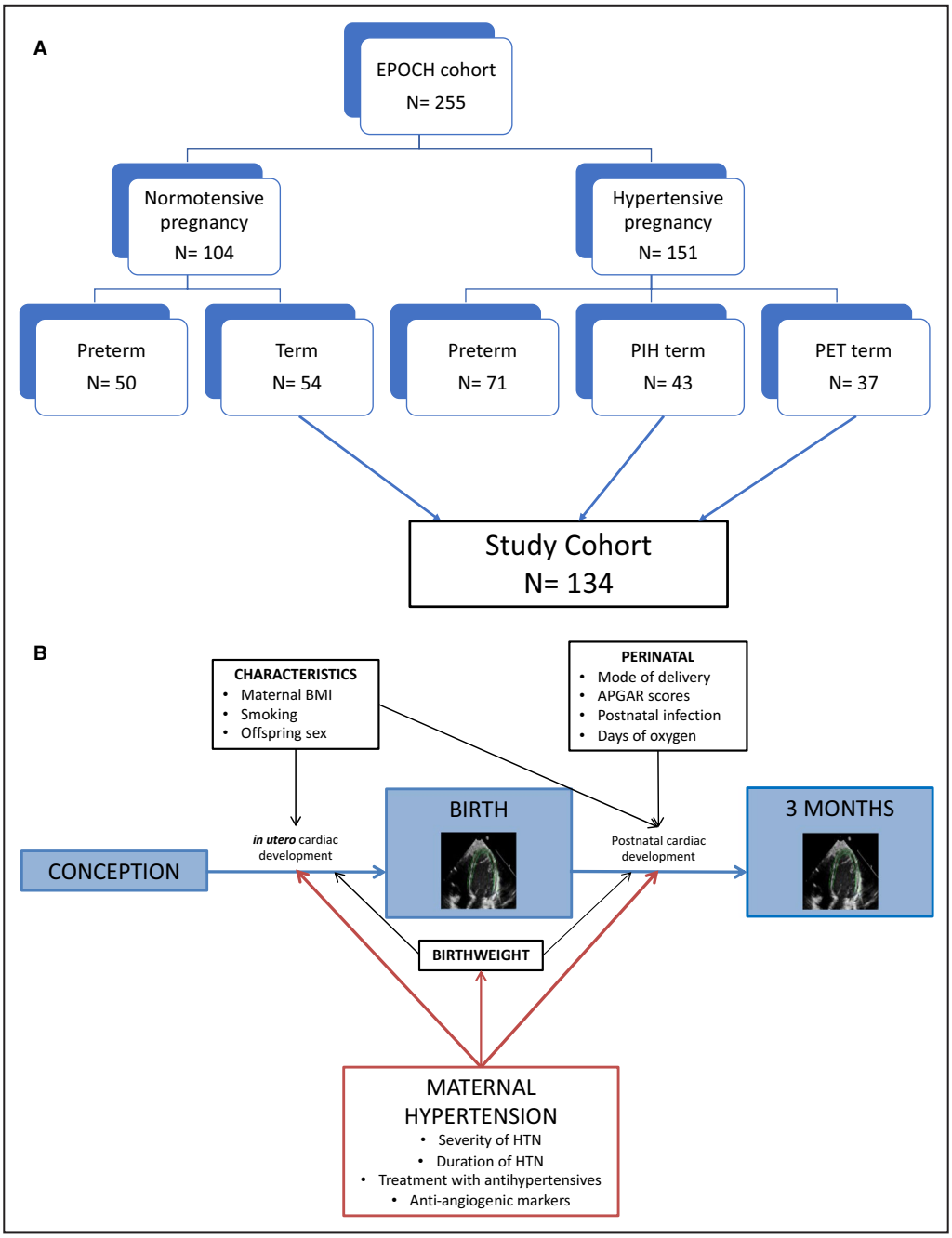

Figure 1. An overview of the study cohort and design.
A. An overview of the study cohort. **B**. Postnatal echocardiography was performed in the cohort of term infants at birth and 3 months of age in order to investigate the effects of maternal hypertension on cardiac structure and function and their association with other maternal and perinatal characteristics. BMI indicates body mass index; EPOCH, Effect of Preterm Birth and Pregnancy Hypertension on Offspring Cardiovascular Health; HTN, hypertension; and PET, preeclamptic.

conditions prenatally, including essential hypertension. Infants were excluded if they had evidence of any severe malformations, congenital cardiovascular disease, chromosomal abnormalities, or genetic disorders, but those with persistent features of a fetal circulation at birth (ie, patent ductus arteriosus (PDA) and/or atrial septal defect (ASD) were included.

Neonatal Cohort Selection and Imaging Assessments

This exploratory study was a secondary analysis to specifically look at the effect of exposure to a hypertensive pregnancy on term-born babies. Echocardiography data were used from

measurements at birth and 3 months of age in infants born after 37 weeks' gestation who participated in the EPOCH study.[5] All mothers gave written informed consent, and assent for involvement of their children, including permission to access maternal and offspring clinical records. Figure 1 outlines an overview of the study design. Inclusion and exclusion criteria as well as data collection methods and clinical characterization have been previously reported[5] and are reported briefly in Data S1. Definitions of preeclampsia and pregnancy-induced hypertension were based on standard definitions of the International Society for the Study of Hypertension in Pregnancy.[16] Those in the normotensive group were required to have had blood pressure <140/90 mm Hg at each pregnancy visit without a previous history of hypertension or hypertension in other pregnancies. Women with essential hypertension were excluded from the study.

Echocardiography

Imaging was performed with a S12-4 transducer attached to a Phillips CX50 at birth and a Philips iE33 at 3 months of age. At each time point, a 2-dimensional transthoracic echocardiography protocol that included acquisition of a 4-chamber view optimized for the left ventricle (LV) was performed according to standard guidelines.[17] Postnatal measures were performed in a temperature-controlled room, with the infant at rest in a semirecumbent position at 45°, either in the arms of their mother, or a crib. To optimize images for postprocessing sector width, gains and depth were altered to maximize frame rate and multiple images were acquired for offline selection of highest quality loops. We used TomTec Image Arena 4.6 to create automated volumetric estimates of LV mass based on endocardial and epicardial borders defined in multiple 4-chamber cine loops. An adaptation of the method was applied to the right ventricle (RV), as previously reported.[18] Images were deemed analyzable if the endo- and epicardial border of the ventricle could be seen clearly in its entirety during the whole cardiac cycle. Detailed methods and our laboratory inter- and intraobserver variability for measures are described in Data S1.

Statistical Analysis

Statistical analysis was performed using SPSS Version 22 (IBM, Armonk, NY) and GraphPad Prism 6.0 (La Jolla, CA,). To compare mean differences in cardiac size postnatally, a Student *t* test and Mann–Whitney *U* test were used as appropriate. Tests of associations were performed using a χ^2 test. Bonferroni corrections were used for multiple group comparisons. Simple linear regression models were performed between measures of cardiovascular structure and function and each of maternal, offspring, and pregnancy covariates. Those covariates that were significant at the 5% level were included in a multiple linear regression (maternal age was adjusted for regardless of statistical significance). When both systolic and diastolic blood pressure were significant in the bivariate regression models because of multicollinearity, only systolic blood pressure was used in the multiple regression. Values are presented as mean±SD unless stated otherwise. Bar charts are presented as mean±SEM. $P<0.05$ were considered statistically significant.

RESULTS

Study Population Characteristics

Maternal and offspring demographic and anthropometric characteristics in the normotensive and hypertensive groups are presented in Table 1. Mothers who experienced a hypertensive pregnancy had a higher bone mineral density and a higher systolic and diastolic blood pressure at their booking antenatal visit (usually between 8 and 12 weeks' gestation). The mean of the maximum blood pressure during pregnancy for mothers diagnosed with a hypertensive pregnancy was 158±12 mm Hg (systolic) and 99±7 mm Hg (diastolic). The mean gestational age at diagnosis was 37.3±3.1 weeks' gestation. Of the 80 hypertensive women, 57 required treatment with antihypertensive medication during pregnancy (36 were on labetalol alone, 3 on nifedipine alone, and 18 were on 2 different agents). Although babies born preterm were excluded, those born to hypertensive pregnancies were born on average 3 days earlier and had on average a 1-cm smaller head circumference at birth. Subgroup analysis demonstrated these differences related to being born to preeclamptic pregnancies and were not evident in those whose mothers had pregnancy-induced hypertension (Table S1). Infants from a preeclamptic pregnancy were also found to be lighter and had a lower birthweight *z*-score than those born to mothers with pregnancy-induced hypertension or normotensive pregnancies. Of note, there were no differences in blood pressure between groups either at birth or 3 months of age (Table 1 and Table S1). All 134 infants had echocardiography data from at least 1 time point. Images were deemed analyzable if the endo- and epicardial border of the ventricle could be seen clearly in its entirety during the whole cardiac cycle. Echocardiography was performed at birth in 122 infants, of which LV measures were possible in 117 (4 unanalyzable because of infant movement, 1 excluded because of subsequent diagnosis of Turner's syndrome). One hundred twenty attended for the scan at 3 months of age, of

Table 1. Cohort Characteristics

	Normotensive (n=54)	Hypertensive (n=80)
Maternal demographics & anthropometrics		
Maternal age at delivery, y	32.7±4.0	32.0±6.0
Body mass index at booking, kg/m^2	23.1±3.5	26.7±5.1§
Booking sBP, mmHg	107.9±9.0	120.0±12.0§
Booking dBP, mmHg	64.8±8.0	73.5±10.3§
Smokers, n (%)	2 (4)	2 (3)
Gestational diabetes mellitus, n (%)	3 (6)	5 (6)
Offspring demographics & anthropometrics		
Birth		
Gestational age at delivery, wk	39.8±1.3	39.3±1.3†
Males, n (%)	29 (54)	30 (38)
Birth order*	1 (1)	1 (1)
Cesarean section, n (%)	14 (26)	22 (28)
Age at assessment, d	5.3±7.6	3.2±3.1
Birthweight, g	3433±529	3250±568
Birthweight z-score	0.28±1.0	0.10±1.2
Head circumference, cm	35.0±1.5	34.2±1.7‡
sBP, mmHg	82.6±13.8	81.1±13.1
dBP, mmHg	44.7±9.3	45.3±9.6
3mo		
Age at assessment, d	99.6±14.8	96.7±13.1
Weight, g	6180±816	5974±937
Head circumference, cm	41.1±1.6	40.7±1.7
sBP, mmHg	96.3±11.7	97.6±12.6
dBP, mmHg	52.7±12.0	55.9±12.4

Booking blood pressure indicates the measurement taken during the first antenatal appointment in the first trimester of pregnancy; dBP, diastolic blood pressure; and sBP, systolic blood pressure.

*Median±interquartile range.

†P<0.05.

‡P<0.01.

§P<0.001.

which 110 had analyzable images. Image acquisition was optimized for LV assessment but, of the available scans at birth, 76 had analyzable RV views with 75 infants having measures at follow-up.

LV and RV Structure and Function at Birth and 3 Months of Age

Infants born to a hypertensive pregnancy had a similar LV mass at birth, compared with those born to normotensive pregnancies, with no differences in LV mass indexed to body surface area or EDV. LV EDV was smaller but the difference was no longer significant when adjusted for body size and, at 3 months of age, no significant differences in LV volume were evident. However, LV mass indexed to either body size or ventricular volume was significantly increased in the group born to a hypertensive pregnancy at 3 months of age. This was not correlated with infant blood pressure either at birth or at 3 months of age. No differences in LV function were observed either at birth or 3 months of age (Figure 2A, Table S2). Infants born to a hypertensive pregnancy had similar RV mass indexed to body surface area at birth. However, RV EDV was smaller at birth in this group and this persisted when adjusted for body size. As a result, RV mass indexed to EDV was also higher (Figure 2B, Table S2). At 3 months of age both RV mass indexed to body surface area and indexed to EDV were significantly greater and RV volume remained significantly smaller (Figure 2B, Table S2). No differences in RV function were observed at either time point (Table S2).

Associations Between Maternal Pregnancy Characteristics and Infant Cardiac Changes

Body surface area at birth and at 3 months of age calculated using the Boyd formula[19] was not associated with RV mass change over this time period. Body surface area at 3 months of age was also not associated with LV mass change over the first 3 months of life. However, body surface area at birth was negatively correlated with LV mass change (P<0.001). This was independent of the presence of maternal hypertension. A similar relationship was seen between birthweight z-score and LV mass change (P<0.001). However, birthweight z-score was not associated with an increased LV mass indexed to body surface area at 3 months of age (P=0.37). This would suggest that babies that are smaller at birth show an accelerated growth postnatally but with a proportionately normal heart.

No other maternal, offspring, perinatal, or pregnancy factors were found to predict LV volume or mass differences during the first 3 months of life (Table S3) including infant sex. In bivariate analysis, the reduced RV volume at birth was associated with several different factors related to severity of hypertensive pregnancy disorder including need for antihypertensive treatment, classification of hypertensive disorder (Figure 3A), higher maximum maternal blood pressure, higher maternal soluble endoglin (sENG) levels at birth, and a lower birthweight z-score (Table S4) with associations between duration of treatment in the 57 women who required antihypertensive medication not reaching significance (P=0.18). Associations between RV end diastolic volume index and the use of labetalol (P=0.48) or the number of antihypertensive medications taken (P=0.08) were also not significant, although there was a nonsignificant negative trend with use of nifedipine (B coefficient −3.29 mL/m^2, P=0.05 with no nifedipine being the reference). In a multivariable

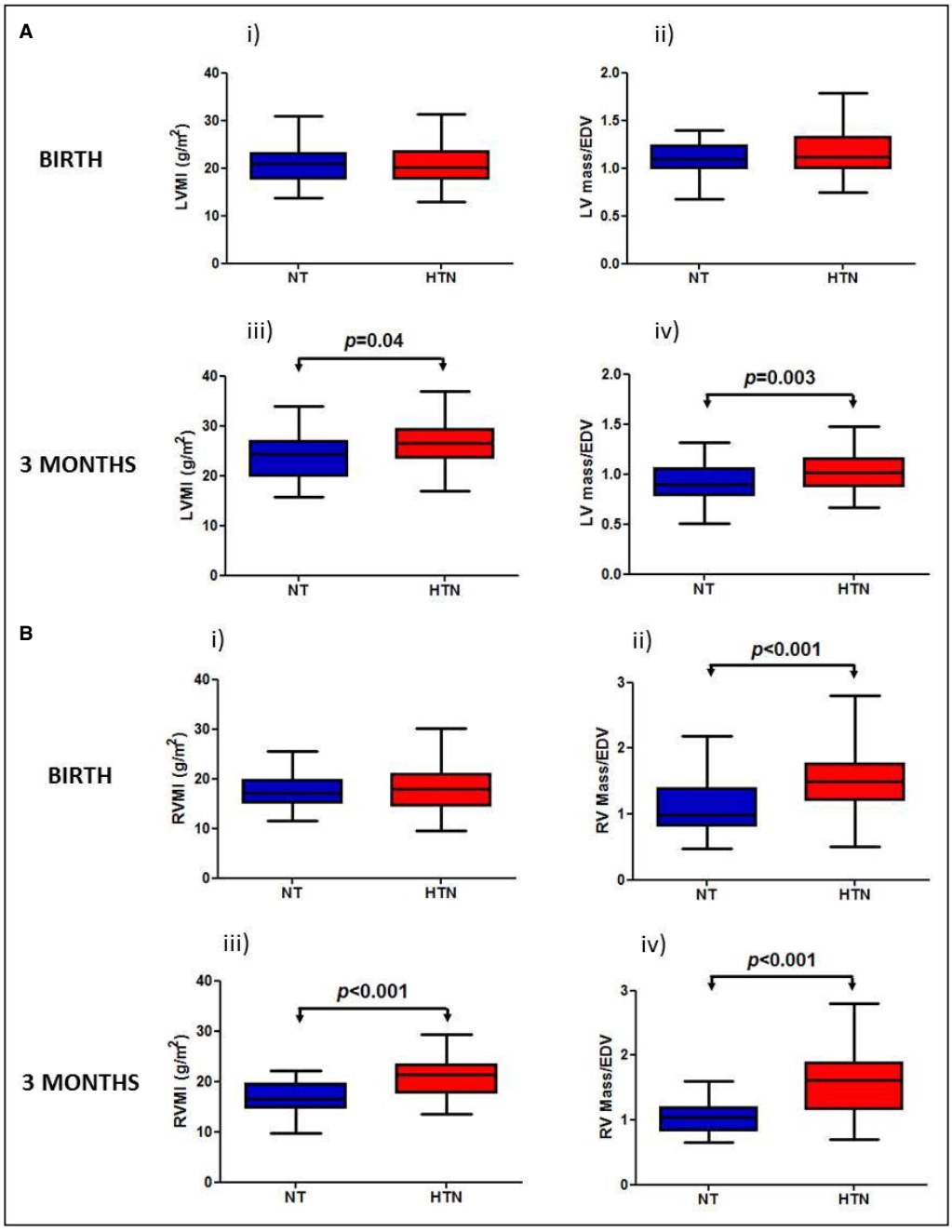

Figure 2. A, Tukey boxplots demonstrating (i) LVMI and (ii) LVM /EDV at birth and (iii) LVMI and (iv) LVM/EDV at 3 months in term offspring born to normotensive and hypertensive pregnancies. EDV indicates end diastolic volume; HTN, hypertensive pregnancy; LV left ventricle; LVMI, left ventricular mass index; and NT normotensive pregnancy. **B**, Tukey boxplots demonstrating (i) RVMI and (ii) RVM/EDV at birth and (iii) RVMI and (iv) RVM/EDV at 3 months in term offspring born to normotensive and hypertensive pregnancies. EDV indicates end diastolic volume; HTN, hypertensive pregnancy; NT, normotensive pregnancy; RV, right ventricle; and RVMI, right ventricular mass index.

model, only maximum systolic blood pressure remained an independent predictor (Table 2). Increased RV mass at 3 months of age was also associated with factors related to the severity of hypertensive disease including higher booking blood pressure, higher maximum blood pressure, longer duration of hypertension, treatment with antihypertensives, and higher levels of sENG in the maternal circulation at birth (Table 3). However, the correlation with duration of antihypertensive treatment and RV mass index at 3 months did not reach significance (P=0.07). There was also no association with the use of labetalol (P=0.12), nifedipine

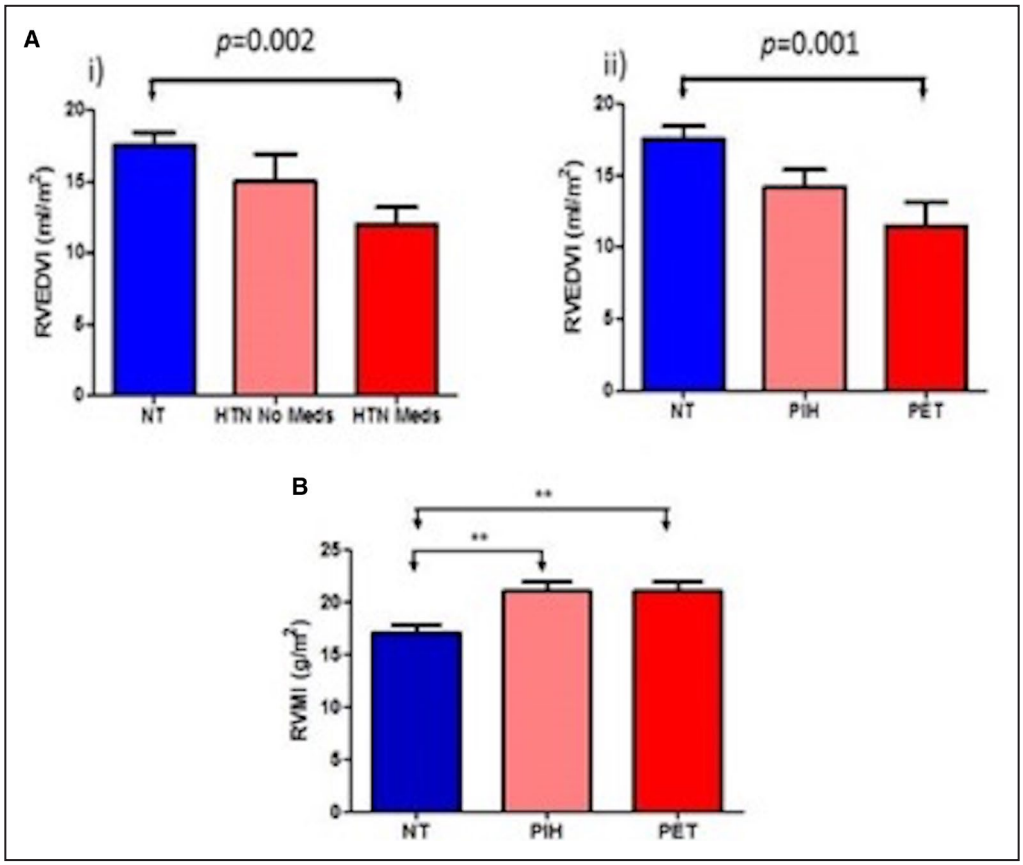

Figure 3. A, Bar charts show a significant association between a reduction in right ventricular end diastolic volumes at birth and (i) severity or (ii) classification of the hypertensive disorder in the mother.

P values are presented as 1-way ANOVA test between groups. HTN indicates meds hypertensive-treated pregnancy; HTN, no meds untreated hypertensive; NT, normotensive; PET, preeclamptic; PIH, pregnancy-induced hypertension; and RVEDVI, right ventricular end diastolic volume index. **B**, Bar chart demonstrates increased right ventricular mass index at 3 months in offspring born to a pregnancy complicated by pregnancy-induced hypertension and preeclamptic pregnancies compared with those from normotensive pregnancies. NT indicates normotensive; PIH, pregnancy-induced hypertension; PET preeclamptic; and RVMI, right ventricular mass index. ***P*<0.01.

(*P*=0.57), or number of antihypertensive medications used (*P*=0.96). Delivery by cesarean section and a higher diastolic blood pressure in the offspring at 3 months were also correlated with increased RV mass (Table S3). In a multivariable model of RV mass index at 3 months with pregnancy characteristics, levels of sENG and mode of delivery remained independent predictors of RV mass index, accounting for 43% of the variance (Table 4). Associations between pregnancy factors and RV structure and function were similar in groups born to pregnancy-induced hypertension and preeclampsia (Figure 3B).

DISCUSSION

This study shows that infants born at term, after late-onset hypertensive pregnancy disorders, without significant growth restriction, have altered RV structure at birth and go on to have a disproportionate increase in both LV and RV mass over the first 3 months of life, which are not associated with blood pressure changes. The changes in the RV, both at birth and 3 months of age, are predicted by maternal features that describe the severity of the hypertensive disorder during pregnancy.

Increases in cardiac mass are seen early in the pathogenesis of hypertensive heart disease[20–22] and can precede diagnosis of hypertension in children and adults who are at high risk because of a family history of high blood pressure.[23–26] Pregnancy hypertension is considered a factor that places mothers and their offspring at high risk for hypertension,[1–4,27] and in experimental models of pregnancy-induced hypertension, the offspring display adverse changes to LV structure and function.[28] However, human observational studies have been inconclusive and it has been difficult to disentangle the relative contribution of high blood pressure in the individual versus the history of

Table 2. Multivariable Linear Regression of Right Ventricular End Diastolic Volume Index at Birth With Maternal, Offspring, and Pregnancy Characteristics

	RVEDVI Birth		
	B	95% CI	*P* Value
Maternal age at delivery, y	0.10	−0.20 to 0.40	0.51
Maximum sBP, mm Hg	−0.15	−0.29 to −0.01	0.03*
Treatment with antihypertensives			
No	Reference		
Yes	−1.67	−7.67 to 4.34	0.58
sENG levels, ng/mL	0.01	−0.29 to 0.31	0.93
Birthweight *z*-score	0.19	−1.56 to 1.93	0.83
TVD change, %	−0.01	−0.13 to 0.10	0.82

sENG indicates soluble endoglin; RVEDVI, right ventricular end diastolic volume index; sBP, systolic blood pressure; and TVD, total vessel density.
*$P<0.05$.

hypertensive pregnancy, or other pregnancy complications, to any differences identified. In 1 study, no differences in LV mass were evident in children born to hypertensive pregnancies compared with normotensive pregnancies,[10] but the study sample had a broad range of ages during adolescence, when there is significant physiological variability in rate of increases in LV mass related to growth.[29] A study focused on early adolescent children at age 12 years found those born to a hypertensive pregnancy had an increased cardiac mass but changes in LV mass were proportional to

Table 3. Bivariate Linear Regression Coefficients of RVMI at 3 Months With Characteristics of Hypertensive Disease

	RVMI 3 months		
	B	95% CI	*P* Value
Severity of hypertension			
Booking sBP, mmHg	0.12	−0.04 to 0.20	0.005*
Booking dBP, mmHg	0.15	0.05–0.24	0.003*
Maximum sBP, mmHg	0.09	0.04–0.13	<0.001*
Maximum dBP, mmHg	0.12	0.05–0.20	0.001*
Duration of hypertension, wk	0.64	0.10–1.17	0.02*
Treatment with antihypertensives			
No	Reference		
Yes	2.23	0.15–4.30	0.04*
sFlt-1 levels, pg/mL	0.001	0.00–0.002	0.12
sENG levels, ng/mL	0.30	0.17–0.43	<0.001*
PlGF levels, pg/mL	0.05	−0.02 to 0.11	0.15
VEGF levels, pg/mL	−0.003	−0.03 to 0.03	0.83
sFlt-1/PlGF ratio	0.11	−0.002 to 0.024	0.08

dBP indicates diastolic blood pressure; PlGF, placental growth factor; RVMI, right ventricular mass index; sBP, systolic blood pressure; sENG, soluble endoglin; sFlt-1, soluble fms-like tyrosine kinase-1; and VEGF, vascular endothelial growth factor.
*$P<0.05$.

Table 4. Multivariable Linear Regression Coefficients of RVMI at 3 Months With Pregnancy Characteristics

	RVMI 3 months		
	B	95% CI	*P* Value
Maternal age at delivery, y	−0.67	−0.27 to 0.14	0.52
Booking sBP, mm Hg	−0.03	−0.3 to 0.07	0.57
Maximum sBP, mm Hg	0.06	−0.03 to 0.16	0.17
Duration of hypertension, wk	0.44	−0.14 to 1.01	0.13
Treatment with antihypertensives			
No	Reference		
Yes	−0.67	−3.99 to 2.66	0.69
sENG levels, ng/mL	0.19	0.02–0.36	0.03*
Cesarean section			
No	Reference		
Yes	3.40	0.99–5.90	0.007*

RVMI indicates right ventricular mass index; sBP, systolic blood pressure; and sENG, soluble endoglin.
*$P<0.05$.

blood pressure.[11] Our findings of changes in cardiac mass in infants born to hypertensive pregnancies are therefore consistent with some prior observations and raise the possibility that differences in later life may be caused by distinct trajectories for changes in cardiac mass, which start in the first few months of life and precede the development of significant hypertension.

Few studies have investigated RV changes, and we found the most significant and consistent differences were evident in this ventricle. The finding of a small right ventricular end diastolic volume at birth, which persists during infancy, raises the possibility that hypertension during pregnancy has a disproportionately greater impact on RV development. In utero there is a RV-dominant circulation and therefore there may be relatively greater exposure of the RV to any adverse in utero hemodynamic changes. Preeclampsia is characterized by a poorly invaded placenta, which is likely to alter both fetal preload and afterload, and an altered systemic state with inflammation and oxidative stress.[30,31] Such factors could induce RV fibrosis, limiting ventricular growth or altering fetal vascular tone. Additionally, adverse exposures during a critical late fetal and perinatal period[32] in both animal and human studies[33,34] are able to alter pulmonary vascular development, via an epigenetic-dependent pathway.[9] Adolescent offspring of preeclamptic pregnancies living at high altitudes have 30% higher pulmonary artery pressures[8] as well as increased markers for oxidative stress. Their siblings born to normotensive pregnancies had normal vascular function, supporting a specific impact of pregnancy hypertension on the developing vasculature. We did not have measures of pulmonary pressure, or placental vascular resistance, in our study group, which is a potential limitation.

Recently, a novel noninvasive index using echocardiography in children has been developed that measures RV coupling with the pulmonary vasculature.[35] However, because there is variability in pulmonary hemodynamics over the first few months of life because of postnatal transition, estimates of these measures using echocardiography may not have been reliable at follow-up.[36] Nevertheless, the presence of pulmonary vascular changes in combination with altered myocardial efficiency, because of reduced RV end diastolic volumes, might account for the postnatal increase in RV mass after the opening of the pulmonary circulation. Further longitudinal follow-up of this cohort, which would include detailed multimodality assessment of cardiovascular structure including atrial size and the pulmonary vasculature, is warranted. We, and others, have previously demonstrated that the systemic microvasculature differs in offspring of hypertensive pregnancies,[5,6] which is likely to alter LV afterload, and could explain the parallel increases in postnatal LV mass observed in the study group.

To further test whether pregnancy hypertension was associated with cardiac development, we studied whether there were graded associations between severity of hypertension in pregnancy and the changes in the offspring at birth, taking into account other factors such as gestational age and birthweight. Indeed, RV volume reductions at birth were more severe in those born following preeclampsia than pregnancy-induced hypertension, but this classification did not predict differences in mass. This may be because although preeclampsia and pregnancy-induced hypertension have a different underlying pathophysiology, it can often be difficult in a clinical situation to distinguish the two.[37] Therefore, we opted to use continuous measures of pregnancy severity including maximum blood pressure level and circulating sENG across the cohort for our analyses. When these were used, cardiac changes were proportional to markers of disease severity, with associations extending to RV measures at 3 months of age. In multivariable models, other associations, such as mode of delivery, appeared to be because of their co-association with pregnancy disorder, rather than reflecting an independent influence.

Because preeclampsia is often associated with a host of changes in the offspring including suppression of fetal growth in addition to a maternal antiangiogenic profile,[37] our findings may suggest it has greater influence on offspring cardiac remodeling compared with pregnancy-induced hypertension. However, increased rates of hypertrophy and reduced function are reported in mothers after all types of hypertensive pregnancies.[38] Our hypothesis was that an antiangiogenic profile in the maternal circulation did not directly cause changes in the fetus, merely that it was a surrogate marker for a hostile, in utero environment that may subsequently lead to adverse changes in the fetus. In support of this, Zafer et al. found correlation between maternal serum but not amniotic fluid levels of anti-angiogenic markers and uterine artery dopplers measured using ultrasound.[39] The association between sENG and fetal cardiovascular measures is intriguing. We have previously shown links between the maternal antiangiogenic profile and vascular development in the offspring postnatally,[5] and it may be that an additional prenatal impact on placental development alters fetal vascular load resulting in distinct patterns of myocardial development, as previously shown in animal physiology.[40] There are also strong maternal–offspring correlations in LV mass,[41] and a shared, familial, cardiovascular phenotype between mother and offspring may explain some of these findings. In addition, both preeclampsia and pregnancy-induced hypertension have been shown to affect uterine blood flow, which may be a possible common pathway for the 2 conditions resulting in fetal cardiac remodeling.[42]

Another potential limitation is our use of semi-automated software to derive measures from single 4-chamber views. Neonatal echocardiography is technically challenging, so our use of a single plane increased data capture and allowed standardized, repeated measures during postnatal life. Assumptions about ventricular geometry in the analysis means absolute mass measures should be interpreted cautiously but, because similar assumptions were made across the cohort, with good reproducibility, between-group differences are likely to be present. The complex shape of the RV makes it difficult to analyze but single-plane measurements have been reported[18] and, as there are limited reports of RV changes, our findings add novel data to the literature. The images were optimized for the LV and we were not able to acquire RV measurements in the whole cohort, which may have introduced a degree of bias. Therefore, replication of our findings in other cohorts will be of value. However, the repeatability of our RV measurements was high (Data S1) so it is unlikely our results are attributable to chance based on the magnitude of the differences.

In summary, we have demonstrated differences in ventricular structure at birth in term-born offspring of hypertensive pregnancies, which is most pronounced for the RV. These structural differences precede a disproportionate increase in both RV and LV mass over the first 3 months of life. Further work will be of value to establish whether differences persist into later life and whether they impact physical or respiratory function, as well as later cardiac risk. The RV changes were proportional to the severity of the hypertensive disease, and to what extent hypertensive pregnancy management plans or interventions to control blood pressure

during pregnancy can mitigate cardiac changes in the offspring requires further investigation.

ARTICLE INFORMATION

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Disclosures

None.

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SUPPLEMENTAL MATERIAL

Data S1.

Cohort selection

A stratified recruitment approach to ensure balanced representation of preterm and term birth as well as hypertensive and normotensive pregnancies was employed through the EPOCH (Effect of Preterm birth and pregnancy Hypertension on Offspring Cardiovascular Health) study (South Central Berkshire Research Ethics Committee ref. 11/SC/0006, UKCRN/clinical trials ref. NCT01888770)[5]. On designated days of the week, consecutive women who had delivered preterm and/or who had experienced a hypertensive pregnancy were approached to take part in the study. A subgroup of women who had experienced a term, normotensive pregnancy delivering on the same day were also approached. In total 255 infants were recruited and underwent echocardiography soon after birth and at three months of age. Of these, 134 were born at term (after 37 weeks gestation) and form the cohort used for this study.

Inclusion and exclusion criteria

Singletons and multiplets were included. Mothers below the age of 16 years were excluded from the study as were those with chronic cardiovascular conditions prenatally, including essential hypertension. Infants were excluded if they had evidence of any severe malformations, congenital cardiovascular disease, chromosomal abnormalities or genetic disorders but those with persistent features of a fetal circulation at birth i.e. Patent Ductus Arteriosus (PDA) and/or Atrial Septal Defect (ASD)) were included.

Clinical data collection and study measures

Characterisation of pregnancy complications and perinatal data related to the clinical care of the infant was extracted from medical records retrospectively in a standardised way across studies. Gestational age at time of measurements was calculated relative to gestational age

defined at first trimester ultrasound and preterm birth was defined as any birth before 37 weeks gestation. Hypertensive pregnancy diagnosis (pregnancy induced hypertension, preeclampsia) was defined according to ISSHP guidelines[16]. Women with essential hypertension were excluded from the study. At both the birth and three month assessments, weight was measured using digital scales (Charder Model MS4200) to the nearest 0.01kg with the infant fully naked. Z-scores for weight were calculated using the International Standard size at birth reference charts from the INTERGROWTH-21st Project[36, 37] using their online application (https://intergrowth21.tghn.org/global-perinatal-package/intergrowth-21st-comparison-application/). At birth and three months, three blood pressure measurements were recorded on the right calf, known to be comparable to arm measurements in neonates,[38] with an automated digital monitor (Dinamap technology® V100) using appropriate sized cuffs and were averaged for analysis. Investigators performing the assessments were not blinded to participant group, but those involved in image analysis were.

Quantification of cardiac mass and volume - Cineloops were acquired with ECG tracing for gating. Mass and volume estimates were obtained by manual contouring of the endo and epicardium using TomTec Image Arena 4.6 from the apical four chamber view for fetal, neonatal and infant echocardiography. The end diastolic frame was manually selected using the point of mitral valve closure as the marker and contours manually set at the inner endocardial edge and outer epicardial edge within the onset of the pericardium. To maximise reproducibility, the entirety of the septum was contoured for both LV and right ventricular (RV) measurements. Ventricular mass and volumes were adjusted for body size based on estimated body surface area (BSA), using the Boyd formula [39] and these values are reported as mass, or volume, index. To assess inter and intraobserver variability for measures, 10 datasets were selected at random (i.e. not selected for image quality) from neonatal datasets and reanalysed using the same set of selected cardiac cycles. Intraclass Correlation

Coefficients (ICC) for single measures with 95% confidence intervals for intra and inter-observer variability yielded 1.00 (0.98-1.00) and 0.97 (0.83-0.99) for postnatal LV mass and 0.96 (0.84-0.99) and 0.81 (0.41-0.95) for postnatal RV mass respectively.

Quantification of Ventricular Systolic and Diastolic Function - LV systolic parameters including ejection fraction, stroke volume and cardiac output were captured from automated tracking of the contours of the endocardium using TomTec Image Arena 4.6 as above. Manual adjustments of the contours were made, as required, throughout the cardiac cycle to ensure appropriate tracking of all segments and excluded if this was not possible due to image quality. RV systolic function was quantified by taking an M-Mode slice through the tricuspid annulus using the cursor in real time to measure the tricuspid annular plane systolic excursion (TAPSE), analysed offline using Philips Xcelera 3.3. At birth and three month follow up, routine diastolic function parameters were assessed. Pulsed wave Doppler was measured from the mitral valve tips to assess early and late diastolic inflow and the ratio of these flows were characterised as E/A ratio using Philips Xcelera 3.3. Further Doppler interrogation of the lateral mitral valve annulus using Tissue Doppler Imaging was measured in early diastole (E') and was utilised in the ratio of early diastolic flow to early diastolic tissue velocity (E/E') to assess myocardial relaxation in relation to the filling velocities. 10 datasets were again selected at random and the ICC for single measures with 95% confidence intervals for intra and inter-observer variability were as follows: 0.99 (0.95-1.00) and 0.98 (0.94-1.00) for E/A ratio; 1.00 (1.00-1.00) and 0.93 (0.97-1.00) for lateral E'; 0.97 (0.87-0.99) and 0.90 (0.64-0.97) for TAPSE.

Angiogenic marker quantification - Blood samples were collected from the mother postnatally, centrifuged and separated within 30 minutes for storage at -80^{o}C pending analysis. Plasma circulating vascular endothelial growth factor A (VEGF-A or $VEGF_{165}$), soluble fms-like tyrosine kinase-1 (sFlt-1), placental growth factor (PlGF), and soluble

endoglin (sENG) concentrations were quantified with commercial enzyme-linked immunosorbent assays (ELISAs) (Quantikine, R&D Systems Europe, Abingdon, UK). All samples, standards, and controls were plated in duplicate. Optical density of each well was measured at 450nm using a FLUOstar Omega microplate reader (BMG Labtech, KBioScience, USA). Data was analyzed using Omega Data Analysis software. Duplicate readings for each standard, control, and sample were averaged, and the average zero standard optical density was subtracted. Standard curves were created by generating a four-parameter logistic curve-fit. A coefficient of variation between duplicates <15% was considered acceptable.

Table S1. Subgroup Cohort Characteristics.

	Normotensive (n=54)	PIH (n=43)	PET (n=37)
Maternal Demographics & Anthropometrics			
Maternal age at delivery, years	32.7±4.0	32.6±5.3	31.4±6.6
Body Mass Index at booking, kg/m^2	23.1±3.5	27.4±5.1[#]	25.9±5.0[§]
Booking sBP, mmHg	108±9	122±11[#]	117±13[#]
Booking dBP, mmHg	65±8	74±9[#]	73±11[#]
Smokers, n (%)	2(4)	1(2)	1(3)
Gestational Diabetes, n (%)	3 (6)	3 (7)	2 (5)
Offspring Demographics & Anthropometrics			
Birth			
Gestational age at delivery, weeks	39.8±1.3	39.7±1.1	38.8±1.3[†#]
Males, n (%)	29(54)	12(28)[§]	18(49)
Birth order[**]	1(1)	1(1)	1(1)
Caesarean section, n (%)	14(26)	11(26)	11(30)
APGARS at 5 minutes	10±0.19	10±0.21	10±0.62
Age at assessment, days	5.3±7.6	3.3±4.1	2.9±1.5
Birthweight, grams	3433±529	3443±554	3025±504[†#]
Birthweight z-score	0.28±1.0	0.43±1.2	-0.29±1.0*[§]
Head circumference, cms	35.0±1.5	34.9±1.6	33.5±1.5[‡#]
sBP, mmHg	82.6±13.8	81.8±13.2	80.3±13.1
dBP, mmHg	44.7±9.3	44.8±9.6	45.9±9.8

3 Months			
Age at assessment, days	99.6±14.8	95.3±13.9	98.2±12.2
Weight, grams	6180±816	6063±958	5873±918
Head circumference, cms	41.1±1.6	40.9±1.6	40.5±1.7
sBP, mmHg	96.3±11.7	95.6±12.5	99.8±12.5
dBP, mmHg	52.7±12.0	54.4±12.9	57.6±11.7

Comparison of PIH and PET group *$p<0.05$; †$p<0.01$; ‡$p<0.001$

Comparison to NT group §$p<0.05$; ‖$p<0.01$; #$p<0.001$

**Median (interquartile range)

sBP indicated systolic blood pressure; dBP diastolic blood pressure; PIH pregnancy induced hypertension; PET preeclampsia.

Table S2. Cardiac Structure and Function.

	Birth			Follow Up		
	NT	**HTN**	***p*-value**	**NT**	**HTN**	***p*-value**
Left Ventricle	n=48	n=69		n=48	n=62	
Volumes						
EDV (ml)	4.6±1.2	4.0±1.2	**0.02**	9.6±2.0	9.0±2.0	0.11
EDV Index (ml/m^2)	19.4±4.5	17.9±4.1	0.06	27.5±4.6	26.4±5.2	0.25
Mass						
Mass (g)	4.9±1.2	4.6±1.2	0.18	8.7±1.6	9.1±1.9	0.17
Mass Index (g/m^2)	20.9±3.7	20.6±4.0	0.64	24.9±4.6	26.8±4.9	**0.04**
Mass/EDV	1.1±0.2	1.2±0.3	0.11	0.9±0.2	1.0±0.2	**0.003**
Function						
Systolic Function						
Ejection fraction (%)	62.2±9.4	64.8±7.6	0.13	59.1±7.2	60.0±8.8	0.65
Stroke Volume (ml)	2.8±0.7	2.6±0.7	0.27	5.8±1.3	6.9±8.0	0.49
Diastolic Function						
EA	1.0±0.3	1.1±0.3	0.83	1.0±0.2	1.0±0.2	0.40
Lateral E’	6.8±1.5	6.5±1.8	0.49	10.2±2.0	10.3±2.2	0.77
Lateral E/E’ ratio	8.0±2.3	7.8±2.7	0.69	8.3±3.0	8.0±2.3	0.84
Right Ventricle	n=32	n=44		n=34	n=41	
Volumes						
EDV (ml)	3.9±1.5	2.9±1.2	**0.001**	5.8±1.4	5.1±1.9	0.06
EDV Index (ml/m^2)	16.8±5.3	12.7±4.7	**0.001**	16.4±3.2	14.4±4.8	**0.04**
Mass						
Mass (g)	4.1±1.0	4.1±1.3	0.86	6.1±1.6	7.4±1.7	**0.001**

Mass Index (g/m^2)	17.5±3.7	18.1±4.7	0.57	17.1±4.2	21.1±3.9	**<0.001**
Mass/EDV	1.1±0.5	1.5±0.4	**<0.001**	1.1±0.3	1.6±0.7	**<0.001**
Function						
TAPSE	0.89±0.2	0.86±0.2	0.36	1.5±0.3	1.5±0.3	0.65

EDV indicates end diastolic volume; TAPSE tricuspid annular plane systolic excursion; NT normotensive pregnancy; HTN hypertensive pregnancy.

Table S3. Bivariate Linear Regression Coefficients of Right and Left Ventricular Mass Index at 3 months with Maternal, Offspring and Pregnancy Characteristics.

	LVMI 3months			RVMI 3 months		
	B	**95% CI**	***p*-value**	**B**	**95% CI**	***p*-value**
Maternal factors						
Maternal BMI, (kg/m^2)	0.06	-0.13-0.26	0.53	0.17	-0.04-0.38	0.11
Severity of HTN						
Booking sBP,mmHg	0.004	-0.08-0.08	0.92	0.12	-0.04-0.20	**0.005**
Booking dBP, mmHg	0.06	-0.03-0.15	0.19	0.15	0.05-0.24	**0.003**
Maximum sBP, mmHg	0.04	-0.001-0.09	0.06	0.09	0.04-0.13	**<0.001**
Maximum dBP, mmHg	0.05	-0.02-0.11	0.17	0.12	0.05-0.20	**0.001**
Duration of HTN, weeks	0.27	-0.12-0.66	0.18	0.64	0.10-1.17	**0.02**
Treatment with anti-hypertensives						
No	Reference					
Yes	1.57	-0.29-3.43	0.10	2.23	0.15-4.30	**0.04**
sFlt-1 levels, pg/mL	$-9.84E^{-005}$	-0.001-0.001	0.83	0.001	0.00-0.002	0.12
sENG levels, ng/mL	0.07	-0.11-0.24	0.43	0.30	0.17-0.43	**<0.001**
PlGF levels, pg/mL	0.003	-0.08-0.09	0.94	0.05	-0.02-0.11	0.15
VEGF levels, pg/mL	0.008	-0.02-0.04	0.63	-0.003	-0.03-0.03	0.83
sFlt-1/PlGF ratio	-0.006	-0.23-0.010	0.46	0.11	-0.002-0.024	0.08
Perinatal factors						
Caesarean section						
No	Reference					
Yes	1.36	0.63-3.35	0.18	4.33	2.25-6.42	**<0.001**

Sex	-0.56	-2.41-1.29	0.55	1.38	-0.69-3.44	0.19
Male	Reference					
Female	-0.56	-2.41-1.29	0.55	1.38	-0.69-3.44	0.19
Birthweight z-score	-0.37	-1.17-0.43	0.37	-0.09	-1.08-0.90	0.85
APGARS at 5 mins	-1.96	-5.08-1.16	0.22	-1.17	-4.14-1.80	0.43
Infections	-1.26	-6.17-3.64	0.61	2.58	-3.85-9.01	0.43
No	Reference					
Yes	-1.26	-6.17-3.64	0.61	2.58	-3.85-9.01	0.43
Days of oxygen	1.52	-1.40-4.44	0.31	-1.03	-3.90-1.84	0.48
TVD change (%)	-0.06	-0.12- -0.003	**0.04**	-0.04	-0.10-0.02	0.22
Vascular measures						
sBP at birth, mmHg	0.002	-0.07-0.07	0.96	-0.01	-0.09-0.07	0.76
dBP at birth, mmHg	0.02	-0.08-0.11	0.72	-0.01	-0.12-0.10	0.86
sBP at 3 months, mmHg	0.009	-0.07-0.09	0.82	0.07	-0.02-0.16	0.13
dBP at 3 months, mmHg	-0.03	-0.11-0.05	0.44	0.09	0.007-0.18	**0.04**
PWV at birth, m/sec	0.06	-0.39-0.51	0.79	-0.18	-0.64-0.29	0.45
PWV at 3 months, m/sec	-0.21	-0.76-0.33	0.44	0.24	-0.31-0.79	0.39

BMI indicates body mass index; sBP systolic blood pressure, dBP diastolic blood pressure; HTN hypertension; sFlt-1soluble fms-like tyrosine kinase-1; sENG soluble endoglin, PlGF placental growth factor, VEGF vascular endothelial growth factor; TVD total vessel density; PWV pulse wave velocity, LVMI left ventricular mass index; RVMI right ventricular mass index; CI confidence interval.

Table S4. Bivariate Linear Regression Coefficients for Right Ventricular End Diastolic Volume Index at birth with Maternal, Offspring and Pregnancy Characteristics.

	RVEDVI Birth		
	B	**95% CI**	***p*-value**
Maternal factors			
Maternal BMI, kg/m^2	-0.07	-0.35-0.22	0.64
Severity of HTN			
Booking sBP, mmHg	-0.07	-0.20-0.05	0.25
Booking dBP, mmHg	-0.04	-0.19-0.10	0.53
Maximum sBP, mmHg	-0.09	-0.15- -0.02	**0.009**
Maximum dBP, mmHg	-0.20	-0.30- -0.09	**<0.001**
Duration of HTN, weeks	-0.60	-1.38-0.19	0.13
Treatment with anti-hypertensives			
No	Reference		
Yes	-4.94	-7.74- -2.15	**0.001**
sFlt-1 levels, pg/mL	0.00	-0.002-0.001	0.83
sENG levels, ng/mL	-0.30	-0.55- -0.05	**0.02**
PlGF levels, pg/mL	0.11	-0.24-0.46	0.52
VEGF levels, pg/mL	-0.009	-0.05-0.04	0.68
sFlt-1/PlGF ratio	-0.005	-0.031-0.021	0.72
Perinatal factors			
Caesarean section			

No	Reference		
Yes	-0.97	-4.47-2.53	0.58
Sex	-0.71	-3.74-2.33	0.64
Male	Reference		
Female	-0.71	-3.74-2.33	0.64
Birthweight z-score	1.92	0.58-3.27	**0.006**
Apgars at 5 mins	0.24	-3.82-4.30	0.91
Postnatal infections			
No	Reference		
Yes	4.51	-3.30-12.32	0.25
Need for oxygen			
No	Reference		
Yes	0.08	-11.00-11.17	0.99
TVD change, %	0.11	0.02-0.19	**0.02**
Vascular measures			
sBP at birth, mmHg	0.004	-0.11-0.12	0.94
dBP at birth, mmHg	-0.04	-0.21-0.12	0.60
sBP at 3 months, mmHg	-0.02	-0.13-0.10	0.80
dBP at 3 months, mmHg	-0.02	-0.15-0.11	0.76
PWV at birth, m/s	-0.30	-0.97-0.36	0.36
PWV at 3 months, m/s	-0.42	-1.23-0.38	0.29

BMI indicates body mass index; sBP systolic blood pressure, dBP diastolic blood pressure; HTN hypertension; sFlt-1soluble fms-like tyrosine kinase-1; sENG soluble endoglin, PlGF placental growth factor, VEGF vascular endothelial growth factor; TVD total vessel density; PWV pulse wave

velocity, RVEDVI right ventricular end diastolic volume index; CI confidence interval.