Pregnancy Hypertension 17 (2019) 104–108

Contents lists available at ScienceDirect

Pregnancy Hypertension

journal homepage: www.elsevier.com/locate/preghy

Cardiac remodeling in morbidly obese women and its association with adverse perinatal outcomes

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ARTICLE INFO

Keywords:
Cardiac remodeling
Echocardiography
Gestational hypertension
Hypertensive disorders of pregnancy
Obesity
Preeclampsia

ABSTRACT

Objectives: To determine the association of cardiac remodeling in early pregnancy and adverse perinatal outcomes among women with BMI ≥ 40 kg/m^2.

Study design: We performed a retrospective cohort study including women with BMI ≥ 40 kg/m^2 without known cardiac disease. Women who underwent screening transthoracic echocardiography prior to gestational age 24 weeks were included. Women were analyzed by group with normal or abnormal geometry, including concentric remodeling, eccentric hypertrophy, and concentric hypertrophy. Multivariable logistic regression was used to assess the association of abnormal geometry with perinatal outcomes. We had 80% power with alpha 0.05 to detect a 3.0-fold increase in the primary outcome among women with abnormal geometry.

Main outcome measures: Our primary outcome was a composite of adverse perinatal outcomes including any 1 of the following: preterm birth (< 37 weeks), low birth weight (< 2500 g), or hypertensive disorders of pregnancy, including gestational hypertension, preeclampsia, and chronic hypertension with superimposed preeclampsia.

Results: Of 140 women, 53 (37.9%) had abnormal geometry. The average BMI was similar between those with normal and abnormal geometry (44.7 vs. 44.2 kg/m^2, p = 0.53). The primary outcome occurred in 20.7% with normal geometry and 30.2% with abnormal geometry (p = 0.20). After adjustment for parity, chronic hypertension, and tobacco use, abnormal cardiac geometry was not associated with the composite primary outcome (adjusted OR 2.01 [95% CI 0.84–4.78]) but was associated with hypertensive disorders of pregnancy (adjusted OR 2.82 [95% CI 1.03–7.78]).

Conclusions: Cardiac remodeling early in pregnancy is associated with hypertensive disorders of pregnancy.

1. Introduction

More than half of women giving birth in the United States are overweight or obese [1], with an increasing proportion of reproductive-age women having class III obesity (BMI 40 kg/m^2 or greater) [2]. Risks of preterm birth, preeclampsia, stillbirth, cesarean delivery, and infectious morbidity are increased among obese women compared to normal-weight women, and women with class III obesity appear to be at highest risk [3–6]. Outside of pregnancy, long-standing obesity impairs both the structure and function of the heart [7].

Normal pregnancy is associated with significant hemodynamic alterations that lead to reversible structural cardiac changes, including increased left ventricular mass and concentric remodeling [8,9]. The degree of cardiac remodeling is directly related to maternal body habitus and is greater among overweight women compared to normal weight women [9]. Pregnancy-induced cardiac remodeling in otherwise healthy women is typically physiologic and resolves postpartum [9,10]. However, there is evidence that abnormal cardiac remodeling occurs during hypertensive pregnancy [10,11]. Abnormal cardiac remodeling, including left ventricular hypertrophy, is associated with increased

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https://doi.org/10.1016/j.preghy.2019.05.018
Received 25 February 2019; Received in revised form 5 May 2019; Accepted 23 May 2019
Available online 23 May 2019

morbidity in pregnancy [11].

Women with class III obesity are at risk of both abnormal cardiac remodeling and adverse pregnancy outcomes, such as preeclampsia and preterm birth, even in the absence of chronic hypertension. However, the effect of cardiac remodeling on pregnancy and perinatal outcomes among morbidly obese pregnant women has not yet been closely examined. We hypothesized that cardiac remodeling in women with class III obesity early in pregnancy is associated with adverse pregnancy outcomes after controlling for hypertension.

2. Methods

We performed a retrospective cohort study including women with documented BMI ≥ 40 kg/m^2 at the initiation of prenatal care at our institution who underwent screening transthoracic echocardiography during pregnancy as part of a clinical risk-assessment protocol. The screening protocol was offered to women with BMI greater than or equal to 40 kg/m^2 regardless of additional comorbidities and included echocardiography, thyroid stimulating hormone, vitamin D, and hemoglobin A1c. We included women who had a screening echocardiogram performed prior to 24 weeks at the University of Michigan Health System between December 2005 and October 2013. The gestational age cut-off of 24 weeks was selected because cardiac indices including relative wall thickness (RWT) and left ventricular mass begin to increase in normotensive pregnancies between 22 and 28 weeks [10]. All echocardiograms were read by faculty cardiologists in the Department of Cardiology at the University of Michigan. Among patients who underwent more than one echocardiogram during their pregnancy, the results from the earliest test were used. Women who had a clinically-indicated echocardiogram due to preexisting cardiac disease or symptoms were excluded. Demographic and obstetric characteristics, echocardiography, and pregnancy outcomes were abstracted from the electronic medical record. This study was approved by the institutional review board at the University of Michigan Medical Center, and informed consent was waived.

The cohort of obese women was divided into 2 groups for analysis and comparison: normal and abnormal geometry. The abnormal geometry group included women with (1) concentric remodeling, (2) eccentric hypertrophy, and (3) concentric hypertrophy defined according to the 2015 American Society of Echocardiography guidelines [12]. Patients were categorized into each group based on their RWT and left ventricular mass index (LVMI), which is a function of left ventricular mass indexed to body surface area. Normal geometry was defined as RWT ≤ 0.42 and LVMI ≤ 95 g/m^2. Concentric remodeling was defined as RWT > 0.42 with LVMI ≤ 95 g/m^2. Eccentric hypertrophy was defined as RWT ≤ 0.42 with LVMI > 95 g/m^2. Concentric hypertrophy was defined as RWT > 0.42 with LVMI > 95 g/m^2.

Our primary outcome was a composite of adverse perinatal outcomes including 1 or more of the following: preterm birth < 37 weeks (both medically indicated and spontaneous preterm birth), low birth weight (< 2500 g), and hypertensive disorders of pregnancy (HDP). HDP included gestational hypertension, preeclampsia with or without severe features, and chronic hypertension with superimposed preeclampsia as defined by current guidelines from the American College of Obstetricians and Gynecologist Hypertension Task Force [13]. Secondary outcomes included the individual components of the primary outcome, early preterm birth (< 34 weeks), neonatal intensive care admission, and cesarean delivery.

A power calculation was performed for the primary outcome based on the fixed sample size of 140 women: 87 with normal geometry and 53 with abnormal geometry. There is limited data on perinatal outcomes in relation to cardiac remodeling, however we assumed 10% incidence of the composite outcome among women with normal geometry. Therefore, using an alpha of 0.05, we would have 80% power to detect a 3.0-fold increased risk in the group with abnormal geometry.

Normality of variables was assessed by the Shapiro-Wilk test. Comparisons between remodeling groups were analyzed using Chi square test, Fisher's exact test, Student's *t*-test, and Wilcoxon Rank-Sum tests where appropriate. Multivariable logistic regression models were created to examine the association of abnormal cardiac geometry on the primary outcome after adjusting for chronic hypertension, nulliparity, and tobacco use. These variables were included in the model after bivariate analysis demonstrated $p < 0.20$. Crude and adjusted odds ratios with 95% confidence intervals (CI) were calculated. Analyses were performed using StataIC 15 (StataCorp, College Station, TX). A p-value < 0.05 was considered statistically significant.

3. Results

There were 211 women with BMI ≥ 40 kg/m^2 who had any echocardiogram performed during pregnancy. Women with preexisting cardiac disease were excluded (n = 9). One-hundred forty women underwent screening echocardiogram per the clinical protocol prior to 24 weeks and were included in the study (Fig. 1). The median gestational age at time of screening echocardiogram was 13.6 weeks (interquartile range 10.6–18.5 weeks). At the time of screening echocardiogram, 53 women (37.9%) had abnormal geometry with concentric remodeling being the most common abnormality. Eccentric hypertrophy and concentric hypertrophy occurred in 2.1% and 3.6% of women, respectively. Only 1 woman had a left ventricular ejection fraction (LVEF) < 50%. There was no difference in LVEF between women with normal and abnormal geometry ($p = 0.23$) with the median in both groups 65%.

Demographic and obstetric characteristics of the study population are shown in Table 1. Mean maternal age was 31.8 ± 5.9 years. Chronic hypertension was a common comorbidity and was observed more often among women with abnormal geometry (37.7% vs. 21.8%, $p = 0.04$). There were no significant differences between groups in age, BMI, nulliparity, pre-gestational diabetes, obstructive sleep apnea, or tobacco use.

The composite primary outcome of preterm birth, low birth weight, and HDP occurred in 20.7% of women with normal geometry and 30.2% of women with abnormal geometry ($p = 0.20$). There were no differences between groups among the individual components of the primary outcome (Table 2). Women with abnormal remodeling delivered earlier than women with normal geometry (38.9 vs. 39.1 weeks, $p = 0.02$) although this is not a clinically relevant difference. There were no differences between groups in birthweight, early preterm birth, neonatal intensive care admission, or cesarean delivery.

After adjustment for nulliparity, chronic hypertension, and tobacco use, abnormal cardiac geometry was not associated with the composite primary outcome (Table 3). However, when evaluating the individual components of the primary outcome, abnormal geometry was associated with increased odds of developing HDP (adjusted OR 2.82 [95% CI 1.03–7.78]). A sensitivity analysis was performed after excluding women with chronic hypertension because chronic hypertension is associated with abnormal geometry and the primary outcome. When limiting the analysis to women without chronic hypertension, there were 33 women with abnormal geometry. In this group, abnormal geometry was not associated with the primary outcome (adjusted OR 2.39 [95% CI 0.81–7.08]) or HDP (adjusted OR 2.82 [95% CI 0.77–10.26]).

4. Discussion

In this study of 140 women with class III obesity, more than a third of women had abnormal cardiac geometry on screening echocardiogram although eccentric hypertrophy, concentric hypertrophy, and depressed systolic function occurred rarely. While abnormal remodeling was not associated with the composite primary outcome, adjusted analyses demonstrated an association with HDP. This association was no longer present when excluding women with chronic

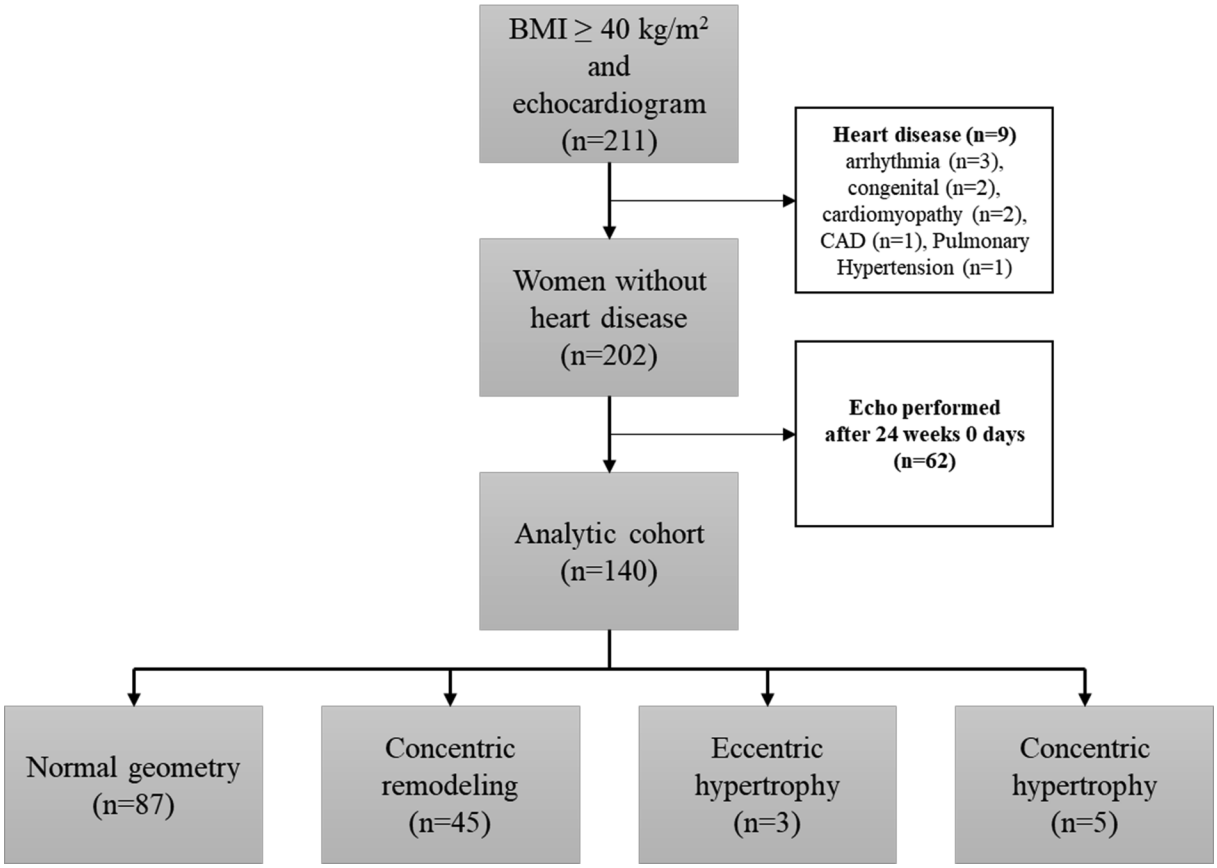

Fig. 1. Study population.

Table 1
Maternal demographic and obstetric characteristics.

Maternal variables	Normal geometry (n = 87)	Abnormal geometry (n = 53)	p-value
Age, y	31.4 ± 5.7	32.4 ± 6.2	0.31
Race/Ethnicity			0.51
White	53 (60.9)	34 (64.2)	
Black	25 (28.7)	17 (32.1)	
Hispanic	4 (4.6)	0 (0.0)	
Other	5 (5.8)	2 (3.8)	
BMI, kg/m²	44.7 (41.8, 48.9)	44.2 (41.9, 50.6)	0.53
BMI category			0.21
BMI 40–49.9	71 (81.6)	38 (71.7)	
BMI ≥ 50	16 (18.4)	15 (28.3)	
Nulliparity	34 (39.1)	13 (24.5)	0.08
Chronic hypertension	19 (21.8)	20 (37.7)	0.04
Pre-gestational diabetes	7 (8.1)	5 (9.4)	0.77
Obstructive sleep apnea	9 (10.3)	9 (17.0)	0.30
Tobacco use	4 (4.6)	7 (13.2)	0.10

Data presented as mean ± standard deviation, n (%), or median (interquartile range) as appropriate. BMI, body mass index.

hypertension although that is likely due to the small sample size.

Obesity drives cardiac remodeling via multiple mechanisms including increased cardiac output, increased workload, effects of sleep disordered breathing, suboptimal blood pressure, and neuro-hormonal influences [14]. Concentric remodeling was present in a significant proportion of our population, which is consistent with the literature in non-pregnant obese adults [14,15]. Despite previous theories that obesity is primarily associated with eccentric hypertrophy [14], there is growing evidence that concentric remodeling is more common and that there is a dose-response of obesity with concentric remodeling [14–16].

Physiologic adaptation to the increased blood volume in pregnancy results in some degree of cardiac remodeling [10]. Cardiac remodeling in pregnancy has primarily been studied amongst healthy nulliparous women or those with hypertensive disorders [10,17–20]. Melchiorre et al. [18] found that 6% of healthy nulliparous women had concentric hypertrophy between 11 and 23 weeks, which is similar to the 4% of women in our study with that degree of abnormality. Other studies have found much higher prevalence of eccentric hypertrophy among normotensive and hypertensive women (14–67%), although those studies were performed in the late second to early third trimester, limiting comparison [19,20].

Ambia et al. [11] described a cohort of women with treated chronic hypertension who underwent screening echocardiographic evaluation in the first half of pregnancy. In that study, concentric remodeling, eccentric hypertrophy, and concentric hypertrophy were all associated with adverse outcomes. The authors posited that the end organ damage present early in pregnancy marked women at high risk for superimposed preeclampsia and subsequent adverse perinatal outcomes. Our results also suggest that abnormal cardiac geometry in early pregnancy is associated with hypertensive disease in later pregnancy. That we did not find an association of abnormal geometry and composite adverse outcomes is likely driven by sample size and the lower incidence of preterm birth and low birth weight among women with obesity compared to women with treated hypertension.

The strengths of our study include a standardized method for defining cardiac remodeling to allow comparison within the literature. The echocardiograms were also performed early in pregnancy in an attempt to isolate the impact of obesity versus adaptation to pregnancy. We are limited in our conclusions by the small number of women with left ventricular hypertrophy; it is possible that by combining all classes of remodeling we have attenuated the impact of hypertrophic changes. The study was also performed at a single academic hospital where the

Table 2
Perinatal outcomes by cardiac geometry.

Perinatal outcomes	Normal geometry (n = 87)	Abnormal geometry (n = 53)	p-value
Gestational age at delivery, weeks	39.1 (38.0, 40.0)	38.9 (37.6, 39.3)	0.02
Birth weight, g	3330 (3010, 3725)	3408 (3115, 3970)	0.55
Composite adverse perinatal outcome	18 (20.7)	16 (30.2)	0.20
Preterm birth (< 37 weeks)	7 (8.1)	8 (15.1)	0.19
Low birth weight (< 2500 g)	4 (4.6)	5 (9.4)	0.30
HDP	12 (13.8)	13 (24.5)	0.11
Early preterm birth (< 34 weeks)	3 (3.5)	2 (3.8)	1.00
Neonatal intensive care	5 (5.8)	6 (11.3)	0.33
Cesarean delivery	43 (49.4)	28 (52.8)	0.70

Data are presented as n (%) or median (interquartile range) as appropriate. HDP, hypertensive disorders of pregnancy.

Table 3
Crude and adjusted odds ratio for adverse outcomes with abnormal geometry.

Perinatal outcomes	Crude odds ratio[1]	Adjusted odds ratio[2]	p-value[3]
Composite adverse perinatal outcome	1.66 (0.76–3.63)	2.01 (0.84–4.78)	0.12
Preterm birth (< 37 weeks)	2.03 (0.69–5.97)	1.63 (0.53–5.04)	0.39
Low birth weight (< 2500 g)	2.16 (0.55–8.44)	1.63 (0.37–7.08)	0.52
HDP	2.03 (0.85–4.87)	2.82 (1.03–7.78)	0.04

Data are presented as odds ratio (95% confidence interval). HDP, hypertensive disorders of pregnancy.
1. Odds ratio present for abnormal versus normal geometry.
2. Adjusted for nulliparity, chronic hypertension, and tobacco use with normal geometry as referent.
3. P-value is for the adjusted model.

majority of patients were non-Hispanic white limiting generalizability to other populations.

Given the growing proportion of reproductive aged women who are morbidly obese, and the abundant research demonstrating the long-term health implications of abnormal cardiac remodeling, this is an area of research that has the potential to significantly impact maternal and neonatal health. Screening echocardiograms are important for diagnosing true cardiac dysfunction, which is a known risk among obese women. However, given our findings that left ventricular systolic function is preserved and remodeling was not associated with composite adverse outcomes, we did not find evidence that routine screening echocardiograms improves obstetric care at this time. Our findings do highlight a potential association between cardiac remodeling earlier in pregnancy and HDP regardless of chronic hypertension. In order to better assess whether subclinical cardiac disease or cardiac remodeling predict HDP, larger, prospective, longitudinal studies are needed. Additional studies with attention to first trimester screening and postpartum follow-up are also needed to determine if there is utility in screening echocardiograms for the purposes of lifelong cardiovascular risk modification.

5. Conclusions

Cardiac remodeling is common among morbidly obese pregnant women. Abnormal geometry was associated with HDP and merits further study in a larger cohort.

6. Author statements

I, Jourdan Triebwasser, declare that I participated in the study design, data collection/analysis/interpretation, and drafting of the manuscript, and that I have seen and approved the final version. I have the following conflicts of interest: none.

I, Nayla Kazzi, declare that I participated in the study design, data collection/analysis/interpretation, and drafting of the manuscript, and that I have seen and approved the final version. I have the following conflicts of interest: none.

I, Melinda Davis, declare that I participated in the study design, data interpretation, and drafting of the manuscript, and that I have seen and approved the final version. I have the following conflicts of interest: none.

I, Emily Kobernik, declare that I participated in the study design, data interpretation, and drafting of the manuscript, and that I have seen and approved the final version. I have the following conflicts of interest: none.

I, Lisa Levine, declare that I participated in the study design, data interpretation, and drafting of the manuscript, and that I have seen and approved the final version. I have the following conflicts of interest: none.

I, Elizabeth Langen, declare that I participated in the study design, data collection/analysis/interpretation, and drafting of the manuscript, and that I have seen and approved the final version. I have the following conflicts of interest: none.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Declaration of Competing Interest

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.preghy.2019.05.018.

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