RISK OF HYPERTENSION AND ABNORMAL BIOMARKERS IN THE FIRST YEAR POSTPARTUM ASSOCIATED WITH HYPERTENSIVE DISORDERS OF PREGNANCY AMONG OVERWEIGHT AND OBESE WOMEN

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Abstract

OBJECTIVES: Hypertension and obesity are common cardiometabolic risk factors in reproductive age women. The association of hypertensive disorders of pregnancy with later-life cardiovascular disease is well-established, however, it is unknown how obesity and hypertensive disorders of pregnancy converge to accelerate development of hypertension in the postpartum period. The aim of this study was to characterize rates of sustained hypertension at one year postpartum using the new American Heart Association /American College of Cardiology Guidelines among overweight and obese women with a normotensive pregnancy or hypertensive disorder of pregnancy.

STUDY DESIGN: 315 early pregnant women were enrolled prospectively and followed up to 12 months after delivery (mean 7.0 ± 1.8 months). At a postpartum research visit, we measured blood pressure and collected blood samples to measure cystatin C and high sensitivity C-reactive protein.

RESULTS: A total of 254 women had a normotensive pregnancy, 39 had gestational hypertension (12.4%) and 22 had preeclampsia (7.0%). 91 women had hypertension at the postpartum study

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CONFLICTS OF INTEREST: None

visit (28.9%). After adjustment for maternal age, BMI, lactation and time postpartum, preeclampsia was associated with an aOR 2.35 (95%CI 1.63–3.41) of development of sustained hypertension and an aOR 3.23 (95%CI 1.56–6.68) of hypertension with abnormal biomarkers compared to women with normotensive pregnancies.

CONCLUSIONS: We demonstrate a high prevalence of hypertension and abnormal biomarkers associated with hypertensive disorders of pregnancy among overweight and obese women. Our findings support the need for structured follow up and risk reduction in overweight and obese women with hypertensive disorders of pregnancy as early as the first year postpartum.

Keywords

INTRODUCTION

Cardiovascular disease (CVD) is the leading cause of death in women worldwide. There is a linear relationship between increasing body mass index (BMI) and risk of CVD.[1,2] Of particular concern, along with the increase in prevalence of obesity in the United States is the increasing rate of CVD mortality in younger women.[3] The association of hypertensive disorders of pregnancy (including preeclampsia and gestational hypertension) with later-life cardiovascular disease has been well established and replicated in diverse populations across multiple studies and these complications may provide a sex-specific window to susceptability.[4–7] The biologic plausibility of this relationship is reinforced by the observation that the risk is amplified in women with recurrent preeclampsia, more severe forms, or early-onset disease.[8–11] While many hypotheses have been generated to explain this association, our understanding of the underlying mechanisms is quite limited. At the time of diagnosis, women with preeclampsia have profound disruption of the endothelium, activation of the coagulation cascade and systemic inflammation.[12] This disruption is manifested in abnormalities in markers of inflammation and renal function, such as high sensitivity C-reactive protein (hsCRP) and cystatin C at the time of diagnosis.[13–16]

HsCRP is an inflammatory marker that has been associated with increased risk of CVD, and has been incorporated into risk estimates for cardiovascular events, including the Reynolds Risk Score.[17,18] Cystatin C is a protease inhibitor used as an indicator of renal function and glomerular filtration rate. Elevated concentrations are also associated with cardiovascular disease and cardiovascular mortality.[19–21] Among women with preeclampsia, maternal levels of cystatin C are elevated in the first trimester and at the time of delivery. This has prompted investigation of cystatin C as a possible first trimester marker for subsequent development of preeclampsia.[22,23]

Women with a hypertensive disorder of pregnancy are at increased risk of chronic hypertension compared to women with normotensive pregnancies. Chronic hypertension is well recognized as a risk factor for CVD. The prevalence of chronic hypertension after a hypertensive pregnancy varies depending on multiple factors including maternal age, severity of the hypertensive disorder of pregnancy, and follow up time postpartum.[24,25]

The American College of Cardiology (ACC) and the American Heart Association (AHA) recently revised the recommendations for the diagnosis of chronic hypertension in adults in the 2017 Task Force on Clinical Practice Guidelines.[26] Citing the strength of the evidence that incremental blood pressure increases impact the risk of clinical complications and death, the thresholds for the diagnosis of chronic hypertension were lowered to identify stage 1 hypertension as a systolic blood pressure between 130 mmHg and 139 mmHg or a diastolic blood pressure between 80 mmHg and 89 mmHg. However, these guidelines do not specifically address pregnancy or women with a history of hypertensive disorders of pregnancy. We sought to describe the rates of hypertension in overweight and obese women one year after delivery under the new ACC/AHA guidelines and to determine if pregnancy-associated hypertension is associated with an increased risk of abnormal biomarkers in the first year postpartum.

METHODS

The study population was derived from a cohort of women from the Prenatal Exposures & Preeclampsia Prevention (PEPP3) study, a prospective study of the impact of obesity on preeclampsia in women who received antepartum, delivery, and postpartum care at Magee-Womens Hospital of the University of Pittsburgh Medical Center. This study has been previously described in detail.[27] Women eligible for PEPP3 enrollment were 18–40 years of age and 6–16 weeks pregnant with a single fetus. Exclusion criteria included BMI <18 kg/m^2, pre-existing hypertension, diabetes, seizure disorders, collagen vascular disorder, drug or alcohol abuse, and liver, heart, or kidney disease. Women were also excluded from participation after diagnosis of a major fetal anomaly or fetal demise. To examine mechanisms linking obesity to preeclampsia and gestational hypertension, overweight and obese women (BMI ≥ $25kg/m^2$) were preferentially recruited to comprise 85% of the study population; a small group of normal weight women were enrolled for comparison. As part of the study protocol, women were asked to attend a postpartum visit at least 3 months after delivery.

For this analysis, we included women who were overweight or obese before pregnancy (BMI ≥ 25 kg/m^2) who attended a postpartum study follow-up visit within one year postpartum, who had not become pregnant in the interim and completed a blood draw at the postpartum visit. We compared women with hypertension at the postpartum study visit, as defined by the 2017 American College of Cardiology (ACC) and the American Heart Association (AHA) Task Force on Clinical Practice Guidelines as systolic blood pressure ≥ 130mmHg or diastolic BP ≥ 80mmHg, on two measurements. Blood pressure measurements were taken by trained study staff using a standard research protocol. Briefly, patients were seated comfortably, with legs uncrossed after at least five minutes at rest. Aneroid sphygmomanometer instruments were used and multiple cuff sizes were available based on the size of the patient's arm, which was measured at the midpoint of the upper arm. Two sitting blood pressures were obtained and if the first and second blood pressure differed by 10 or more mmHg, a third measurement was obtained. We excluded women who had a postpartum visit >12 months after delivery (n=50) as we sought to explore risk factors for hypertension in the first year postpartum. All women provided written informed consent and this study was approved by the University of Pittsburgh's Institutional Review Board.

At enrollment (mean gestational age 8.9 weeks $\pm$ 2.6), participants completed a questionnaire which included demographic information as well as self-reported pre-pregnancy height and weight. Participants' first study weight measure and self-reported pre-pregnancy weight were highly correlated (>0.97). Pre-pregnancy BMI (kg/m^2) was calculated with self-reported weight and height and categorized based on World Health Organization (WHO) guidelines as normal weight (BMI 18.5 to 24.9 kg/m2), overweight (BMI 25 to 29.9 kg/m^2), obese class I (BMI 30–34.9 kg/m^2), class II (BMI 35 to 39.9 kg/m^2) and class III (BMI 40 kg/m^2). Postpartum BMI was based on height and weight measurement at the postpartum study visit and was categorized based on WHO guidelines. Delivery data abstracted from the electronic medical records of participants included gestational age at delivery, mode of delivery, and pregnancy complications including gestational diabetes, spontaneous or iatrogenic preterm delivery and pregnancy-associated hypertensive disorders. Gestational hypertension (two or more BP measurements 140/90 mmHg) and preeclampsia (gestational hypertension plus proteinuria) were defined based on American College of Obstetricians and Gynecologists (ACOG) guidelines in 2002 and adjudicated by the PEPP3 research team based on chart reviews.[28]

At the postpartum visit, demographic and clinical data were collected and participants completed a questionnaire. Fasting blood samples were collected from the participants at their postpartum visit. HsCRP was measured using 100μl of serum with reagents obtained from Beckman Coulter and analyzed on an Olympus AU400 Chemistry Analyzer from Olympus America, Inc at the Heinz Nutrition Lab at the University of Pittsburgh. The intra- and inter-assay coefficients of variation are 1.5% and 3.4%, respectively. Cystatin C was also measured turbidimetrically on an Olympus AU 400 in the same lab using 100μl of sample and reagents obtained from DakoCytomation N. America, Inc. The intra- and inter-assay coefficients of variation are 1.7% and 2.2%, respectively.

Statistical analyses were completed using Stata IC 15 software package (StataCorp LP, College Station, TX). Baseline characteristics were compared between women with hypertension and women who were normotensive at the postpartum study visit. Continuous variables were compared using Student's t-tests and Wilcoxon-Mann Whitney tests as appropriate. Categorical variables were analyzed using Chi-square or Fisher's exact, where appropriate. P-values <0.05 were considered statistically significant.

We examined the relationship between development of hypertension for women with (a) normotensive pregnancies, (b) preeclamptic pregnancies, or (c) gestational hypertensive pregnancies. We further explored the relationship of hypertensive disorders of pregnancy and abnormal biomarkers. We defined the most adverse cardiovascular profile as hypertension accompanied by both elevated hsCRP (hsCRP 3 mg/L)[29] and elevated cystatin C (in the highest quartile, 0.83 mg/L). Moderate risk cardiovascular profiles were defined as hypertension with either elevated hsCRP or cystatin C. Multinomial logistic regression was used to adjust for potential confounding variables including maternal age, time since delivery, BMI at the postpartum visit and any breastfeeding as these varied by hypertension status or are known to be related to hsCRP or cystatin C. We performed sensitivity analyses restricting the sample to obese women only (BMI 30 kg/m^2) and in women followed up to

25 months postpartum to confirm that the observed relationships were consistent across these subgroups.

RESULTS

The PEPP3 cohort was comprised of 656 predominantly overweight or obese women. Of these, 439 attended the postpartum visit and 315 were included in this study (mean postpartum visit at 7.0 months, standard deviation (SD) 1.8 months postpartum). Women were excluded from this analysis if they had a pre-pregnancy BMI <25 kg/m^2 (n=68), had a study visit >12 months postpartum (n=50) or did not have blood drawn or had missing data on pregnancy outcome (n=6) (Figure 1). Women who attended the postpartum visit were more likely to be of black race, lower income bracket, and to have Medicaid insurance compared with those who did not (Supplemental Table 1). Of the 315 women included in the study, 22 women had preeclampsia (7.0%) and 39 women had gestational hypertension (12.4%).

A total of 91 women had elevated blood pressure at the postpartum study visit (28.9%, 95%CI 24.3–34.4%). Of the women with elevated blood pressure, 81 women had stage 1 hypertension (89.0%) and 10 women had stage 2 hypertension (11.0%). Women with hypertension postpartum were older, had a higher pre-pregnancy and postpartum BMI, and underwent their study visits at a later time postpartum compared to normotensive women (Tables 1 and 2). There were no differences according to hypertensive status in race, education, insurance status, tobacco use or parity. Aside from hypertensive disorders of pregnancy, other pregnancy characteristics of the two groups were similar, with comparable rates of preterm birth and gestational diabetes and similar breastfeeding rates and duration. One patient reported taking anti-hypertensives at the postpartum study visit.

Women with pregnancy-associated hypertension were more likely to have hypertension at their postpartum study visit compared to women with a normotensive pregnancy (59.1%, 43.6%, and 24.0%, respectively; p<0.001). Among overweight and obese women with preterm preeclampsia, 80% (8/10) developed hypertension. After adjustment for maternal age, BMI, lactation and number of months postpartum, hypertensive disorders of pregnancy were associated with an aOR 1.86 (95%CI 1.37–2.52) of development of hypertension at one year in our cohort. Women with preeclampsia had an aOR 2.35 (95%CI 1.63–3.41) and women with gestational hypertension had an aOR 1.61 (95%CI 1.09–2.39) of development of hypertension at one year (Table 3).

We then categorized women by the presence of abnormal biomarkers in the first year postpartum. A total of 190 women in our cohort (60.3%) had an abnormal hsCRP and 92 women (29.2%) had an abnormal cystatin C level. Preeclampsia was associated with an aOR 3.23 (95%CI 1.56–6.68) of the most adverse profile (hypertension, elevated hsCRP (3 mg/L) and cystatin C in the highest quartile) compared to women with normotensive pregnancies, adjusted for age, BMI and months postpartum. Similar findings were seen for the more moderate risk profiles (hypertension, elevated hsCRP (3 mg/L) or cystatin C in the highest quartile) in the first year postpartum. Gestational hypertension was associated

with an aOR 2.03 (95%CI 1.07–3.85) of a moderate-risk profile at one year postpartum compared to women with normotensive pregnancies at one-year postpartum (Table 4).

In sensitivity analyses, we performed the same analysis only in obese women (n=223, mean BMI 33.9 ± 6.6) and in all women with a postpartum study visit up to 25 months postpartum (n=365, mean 8.5±4.4 months) and found similar results (Supplemental Tables 2–5).

DISCUSSION

In this prospective cohort study of over 300 overweight and obese women, we report a high prevalence of hypertension as defined by the new ACC/AHA guidelines in the first year postpartum. While rates of hypertension within one year of delivery among overweight and obese women with normotensive pregnancies were quite high in our cohort (24.0%), this is consistent with recently published data, describing the prevalence of stage 1 hypertension among reproductive age women.[30] Further, rates of hypertension among overweight and obese women with preeclampsia were twice as high. Further, preeclampsia was also associated with an increased risk of abnormal biomarkers at one year postpartum compared to normotensive pregnancies. In our cohort, the number of overweight and obese women with preterm preeclampsia was small and yet 80% of them progressed to hypertension within a year, aligned with the seven-fold increased risk of later-life CVD that has been reported for this group.[31]

Tools for individualized risk estimates after a hypertensive disorder of pregnancy are currently lacking. Traditional risk prediction models for cardiovascular disease, such as the Framingham risk score, the ACC/AHA Pooled Cohort Equations, the Systematic Coronary Risk Evaluation (SCORE) and the QRISK score underestimate risk in young women.[32] The adverse cardiovascular profile variables we used in this analysis (chronic hypertension with elevated hsCRP and/or cystatin C) have not been previously studied in this population, however both hsCRP and cystatin C are associated with CVD risk and are currently being investigated for first-trimester prediction and late pregnancy diagnosis of preeclampsia. Given that preeclampsia is a multi-system disease with systemic inflammation and endothelial dysfunction in addition to hypertension, we sought to define adverse profiles that included not only sustained hypertension but also other subclinical biomarkers that may be disrupted by the disease process.

A strength of this study is the use of the new definitions of hypertension recently published by the ACC/AHA guidelines, including women with stage I hypertension, making it particularly relevant to current practice.[26] While the majority of women in this study with elevated blood pressure had stage 1 hypertension (89%), in addition to the long-term cardiovascular risk of stage 1 hypertension emphasized by the recently updated ACC/AHA guidelines,[26] our recent work suggests that among high-risk women, stage 1 hypertension is also associated with an increased risk of preeclampsia recurrence.[33] While we measured blood pressure using a standardized research protocol, we were limited by a single day of measurements, without additional time points or ambulatory blood pressure monitoring. A recent study by Benschop et al utilized ambulatory and in-office BP monitoring and found that 41.5% of women with severe preeclampsia had hypertension at one-year postpartum,

with 17.5% of these cases only detected by APBM.[24] The rates of hypertension in the first year postpartum were slightly lower than the rates in our cohort, however, this study included mainly normal weight and overweight women with median BMI in their cohort of 25.5 (90% range 19.3–36.6) and did not use the new AHA/ACC definitions of hypertension, which may explain differences in findings. Additional strengths of our study include the prospective design, formal research adjudication of hypertensive disorders of pregnancy to ensure accurate distinction of preeclampsia and gestational hypertension, and the inclusion of biomarkers to characterize a high-risk profile.

This study had several limitations including the small number of participants with pregnancy-associated hypertension. As we are particularly interested in risk that can be identified in the first year postpartum, our follow up was limited to 12 months and thus we are unable to evaluate longer-term associations. In sensitivity analyses, we included participants followed up to 25 months postpartum (n=365) and demonstrated similar findings (Supplemental Tables 2, 3). We focused on hypertension developing in the first year postpartum as this is a time when women are more engaged with the healthcare system and may be a feasible time for transition of care and multidisciplinary follow up.[34] Our participants are from one study site, are all overweight and obese and are predominiantly African American. While this may limit the generalizability of these findings, this is a population who is at higher risk of hypertension, preeclampsia and cardiovascular disease. [35] We used the ACOG definitions of gestational hypertension and preeclampsia that were in place at the time of our study, however these definitions have since been updated.[28] The newer definition of preeclampsia now includes women without proteinuria who have other systemic findings consistent with preeclampsia.[36] This newer definition would likely include some women in our study who were classified as gestational hypertension. This study is also limited by our lack of information on traditional cardiovascular risk factors, such as family history and hyperlipidemia. Smoking status was not different between groups, and our results were unchanged when smoking status was incorporated into our model. Finally, there were significant differences in the severity of obesity between women who developed hypertension compared to those who were normotensive at one year postpartum, which we attempted to account for in our analysis. However, these groups are of particular importance given their excess burden of hypertension risk and the high prevalence of obesity in the United States.[37]

Cardiovascular disease (CVD) is the leading cause of death in women worldwide and despite declines in all other age groups, mortality rates from CVD are increasing in women aged 35 to 54 years.[3] The AHA and ACOG have identified hypertensive disorders of pregnancy as risk factors for later-life CVD with a magnitude of risk on par with smoking and diabetes. However, the mechanisms by which preeclampsia heralds an increased risk of CVD are still unclear. Whether pregnancy unmasks underlying subclinical CVD or whether preeclampsia causes vascular and metabolic damage that leads to future CVD is unknown. While ongoing efforts to understand mechanisms linking the two processes is imperative, attention also needs to be turned towards management of women with hypertensive disorders of pregnancy, as effective evidence-based interventions have not yet been adequately studied or implemented.[32,38] In addition, postpartum care after a hypertensive disorder of pregnancy is often fragmented, with no cohesive transition from the obstetrician to internist

or cardiologist with few heath care providers carrying out postpartum CVD risk counseling or screening.[32] Nor is it clear when women should be screened for risk. Our results indicate that one-year postpartum might be too late to prevent development of hypertension for many overweight and obese women with hypertensive disorders of pregnancy. However, prior studies have shown that as many as 40% of women do not attend the traditional 6-week postpartum visit after delivery, underscoring the need for development of innovative models to care for these high-risk women.[39–41] Recognizing the underutilization of postpartum care, the American College of Obstetricians and Gynecologists recently updated its guidelines to reflect the importance of appropriate postpartum care and to propose a new paradigm for management in this period.[42] With the recommended changes in the scope of postpartum care and redefining this period as the "fourth trimester", incorporation of innovative interventions for risk reduction in this population should be considered.

Because pregnancy occurs early in a woman's life, often before the onset of clinically evident CVD, it serves as a unique opportunity for sex-specific screening to initiate primary prevention. If applied to this high-risk population early enough to avert cumulative damage of chronic disease, primary prevention may reduce cardiovascular disease incidence. Risk reduction in this group should focus on lifestyle interventions to reduce blood pressure and increase weight loss, which have been shown to impact future pregnancy outcomes as well as future CVD.[36,43]

CONCLUSIONS

In summary, our study demonstrates high rates of sustained hypertension as well as an adverse cardiometabolic profile associated with hypertensive disorders of pregnancy among overweight and obese women in the first year postpartum. To meaningfully impact rates of CVD in women, we may need to shift our focus towards structured postpartum follow up for these women and begin identifying interventions to reduce this risk.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Highlights:

- We demonstrate a high prevalence of development of sustained hypertension and abnormal biomarkers associated with hypertensive disorders of pregnancy among overweight and obese women as early as one year postpartum.

- In line with the updated Committee Opinion from ACOG recommending changes in the scope of postpartum care and redefining this period as the "fourth trimester", our findings suggest that incorporation of innovative interventions for risk reduction in this population should be considered.
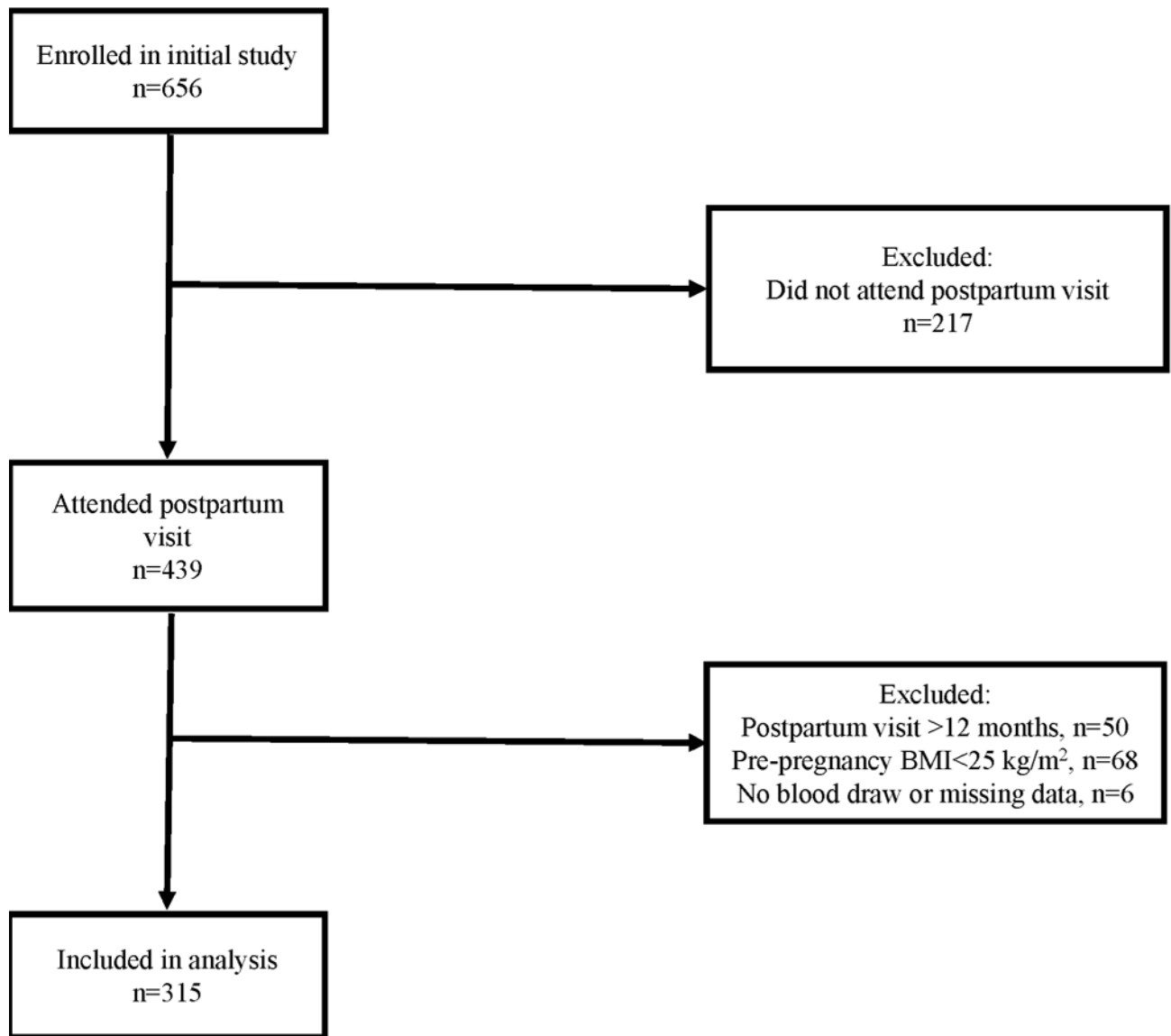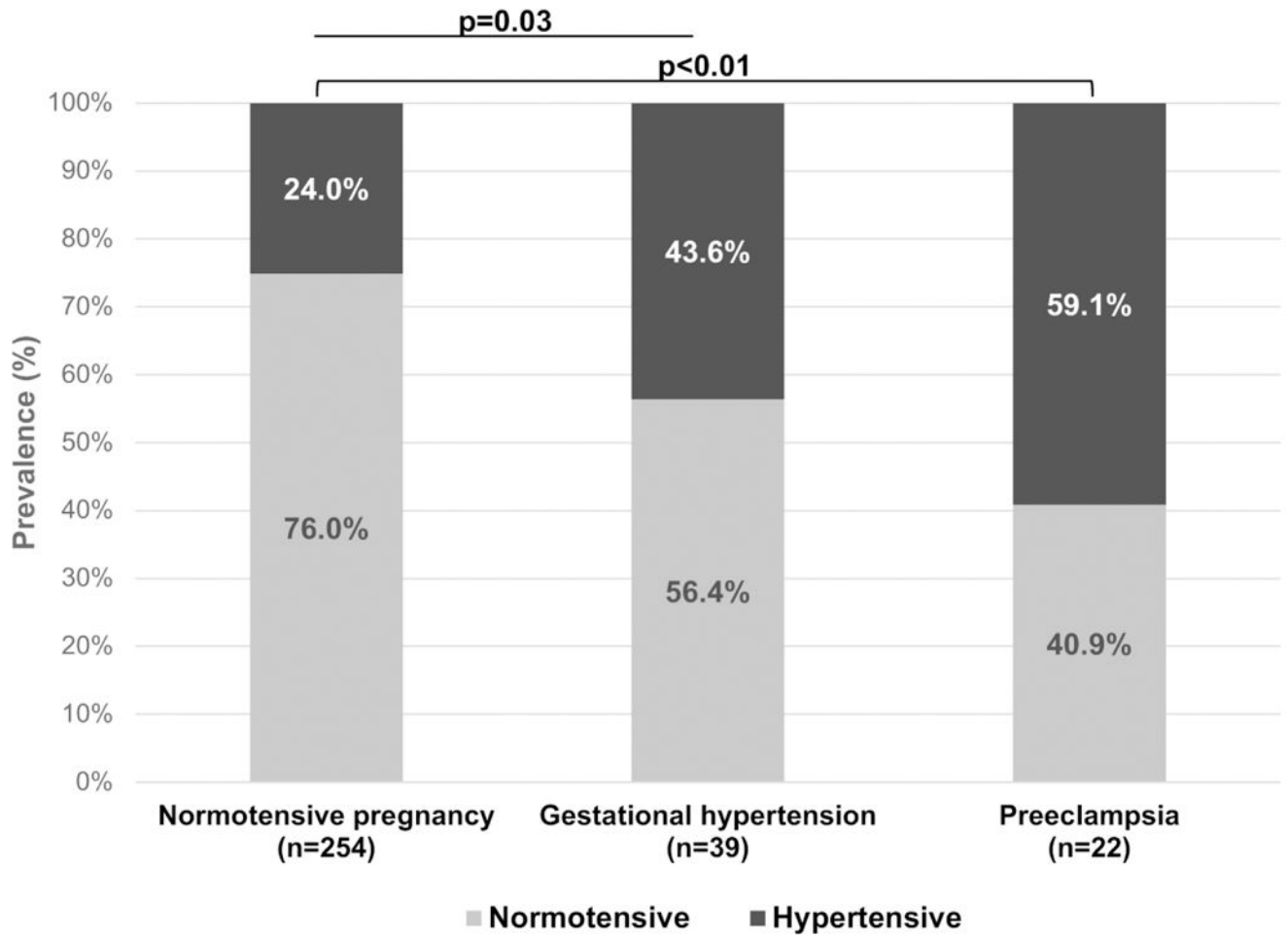
Figure 1.
Description of included cohort.

Figure 2.
Proportion of women with hypertension at postpartum study visit by pregnancy outcome.

Table 1.

Cohort characteristics by presence of hypertension at postpartum study visit (n=315)

	Normotensive n=224	Hypertensive n=91	p-value
Age (years) *	23.5 ± 3.8	24.8 ± 4.7	0.03
Race			
Black	157 (70.1)	59 (64.5)	
White	62 (27.7)	29 (31.9)	0.62
Other	5 (2.2)	3 (3.3)	
Education			
Less than High School	15 (6.7)	11 (12.1)	
High School or equivalent	113 (50.7)	46 (50.6)	0.41
College and above	95 (42.4)	34 (37.4)	
Insurance			
Private	24 (10.8)	6 (6.6)	
Medicaid	138 (62.2)	58 (63.7)	0.67
None at enroll	58 (26.1)	27 (30.0)	
Smoking (in past 2 years)	94 (42.2)	39 (42.9)	0.95
Nulliparous	170 (75.9)	63 (69.2)	0.22
Pre-pregnancy BMI *	32.3 ±5.4	38.0 ± 7.4	<0.01
Preterm Birth (<37wks)	19 (8.5)	13 (14.3)	0.11
Pregnancy-associated hypertension	31 (13.8)	30 (33.0)	<0.01
Preeclampsia	9 (4.0)	13 (14.3)	<0.01
Gestational hypertension	22 (9.8)	17 (18.9)	0.03
Gestational diabetes	7 (3.1)	4 (4.4)	0.58

*
Mean ± standard deviation; BMI=body mass index

Table 2.

Postpartum visit characteristics by presence of hypertension at postpartum study visit (n=315)

	Normotensive	Hypertensive	p-value
	n=224	n=91	
Postpartum BMI [*]	34.3 ± 7.1	41.3 ± 9.2	<0.01
Months Postpartum at Study Visit [*]	6.9 ± 1.9	7.3 ±1.8	0.05
Any breastfeeding	141 (63.2)	57 (63.3)	1.0
Months of breastfeeding [*]	3.0 ± 1.8	3.2 ± 1.5	0.55
hsCRP (mg/L) [†]	3.7 (1.5–7.8)	5.1 (2.9–11.6)	<0.01
Cystatin C (mg/L) [†]	0.77 (0.70–0.82)	0.81 (0.74–0.87)	<0.01

[*] Mean ± standard deviation

[†] Median (interquartile range)

Table 3.

Relative risk of progression to hypertension by 1 year postpartum in overweight and obese women (n=315).

	Unadjusted Model	Multivariable model [*]
	OR (95% CI)	aOR (95% CI)
Normotensive pregnancy (n=254)	Referent	Referent
Any hypertensive disorder of pregnancy (n=61)	2.05 (1.46–2.86)	1.86 (1.37–2.52)
Gestational hypertension (n=39)	1.82 (1.19–2.76)	1.61 (1.09–2.39)
Preeclampsia (n=22)	2.46 (1.63–3.71)	2.35 (1.63–3.41)

[*] adjusted for maternal age, BMI, lactation, months postpartum

Table 4.

Prevalence and multivariable model for prediction of various high-risk profiles at postpartum study visit in obese and overweight women (adjusted for maternal age, BMI, lactation, months postpartum).

Cardiovascular Profile	Normotensive Pregnancy	Gestational hypertension		Gestational hypertension	
	N=254	N=39		N=22	
	n (%)	n(%)	aOR‡ (95%CI)	n(%)	aOR‡ (95%CI)
Elevated hsCRP*	146 (57.5%)	27 (69.2%)	1.11 (0.87–1.43)	17 (77.3%)	1.32 (1.03–1.69)
Elevated cystatin C†	72 (28.4%)	12 (30.8%)	0.94 (0.58–1.52)	8 (36.4%)	1.20 (0.72–2.02)
Hypertensive with elevated hsCRP* and cystatin C†	24 (9.4)	3 (7.7)	1.07 (0.40–2.85)	6 (27.3)	3.23 (1.56–6.68)
Hypertensive with either elevated hsCRP* or cystatin C†	24 (9.4)	10 (25.6)	2.03 (1.07–3.85)	5 (22.7)	3.13 (1.44–6.78)

*Elevated hsCRP defined as hsCRP 3mg/L

†Elevated cystatin C defined as cystatin C in highest quartile

‡Referent group is normotensive pregnancy