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Association of antepartum blood pressure levels and angiogenic profile among women with chronic hypertension

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A B S T R A C T

Background: Angiogenic factors have been implicated in the pathogenesis of preeclampsia. This pilot study explored the association between antenatal blood pressure levels and angiogenic biomarkers (sFlt1 and PlGF) among women with chronic hypertension (cHTN).

Methods: Blood samples were collected from women with cHTN (with/without superimposed preeclampsia) within 96 h prior to delivery. Subjects were stratified by mean outpatient BP as controlled (cBP < 140/90) or uncontrolled (uBP ≥ 140/90). Descriptive statistics were generated and assessed as appropriate. Logistic regression was employed to assess for adverse pregnancy outcomes between groups.

Results: Data from seventy-eight women were analyzed, of which 58 (74.4%) were African American. Fifty-six (71.8%) had cBP and 22 (28.2%) had uBP. Use of antepartum outpatient antihypertensive medications was more frequent in patients with uBP (46.4% vs. 13.6%, p = 0.01). Compared to women with cBP, women with uBP had higher levels of pre-delivery sFlt1 and sFlt1/PlGF ratio (sFlt: 4218.5 vs. 3056.0 pg/ml, p = 0.046; sFlt/PlGF: 62.5 vs. 25.0, p = 0.04). Additionally, more uBP patients had superimposed preeclampsia with severe features (54.6% vs. 25.0%; p = 0.01) and preterm delivery (defined as a gestational age < 35 weeks (40.9% vs. 10.7%; p = 0.002)) than cBP patients. In the multivariable model, women with uBP had greater odds of preterm delivery (OR 6.78; p = 0.01), superimposed preeclampsia (OR 3.20; p = 0.03) and preeclampsia with severe features (OR 3.27; p = 0.04) than women with cBP.

Conclusion: In women with cHTN, elevated antepartum BP is associated with worsened outcomes and may be associated with abnormal angiogenic profile at delivery. Larger studies are needed to confirm these findings.

1. Introduction

During pregnancy, chronic hypertension (cHTN) is defined as having been present and observable prior to pregnancy or diagnosed before the twentieth week of gestation [1]. The prevalence of cHTN is 5% in all pregnant women with a higher prevalence among high risk groups such as obese and African American women [2]. cHTN is associated with higher maternal and fetal morbidity and mortality, including superimposed preeclampsia, abruption placentae, and intrauterine growth restriction [3]. The management of hypertension during pregnancy remains controversial. The 2015 CHIPs trial found no effect of tight control of blood pressure on the risk of pregnancy loss, high-level neonatal care, or overall maternal complications, although less-tight control was associated with a higher frequency of severe maternal hypertension [4]. In addition, the American College of Obstetrics and Gynecology (ACOG) recommends antihypertensive therapy only for women with severe, persistent chronic hypertension (systolic blood pressure [BP] ≥160 mmHg or diastolic BP > 105 mmHg) [5]. However, a large 2017 retrospective study observed that blood pressures ≥140/90 mm Hg were associated with a greater risk of maternal complications and adverse fetal outcomes regardless of the number of medications used to control the blood pressures. This study concluded that blood pressure control, rather than the number of agents used to achieve that control, was most associated with pregnancy outcomes [6]. A randomized trial evaluating the benefits and harms of pharmacologic treatment of mild cHTN in pregnancy is currently underway in the United States (NCT02299414).

Angiogenic factors have been implicated in the pathogenesis of preeclampsia and its associated outcomes [7–11]. Existing data find abnormalities in angiogenic factors among women with cHTN that develop preeclampsia [12–14]. However, few studies have evaluated the association of blood pressure control during pregnancy on levels of angiogenic factors at the time of delivery.

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We hypothesized that women with uncontrolled blood pressures would have elevated anti-angiogenic factor levels and be more likely to have poor maternal and fetal outcomes. To test our hypothesis, we measured the relationship between antepartum blood pressures during prenancy and angiogenic factor levels at the time of delivery in pregnant women with cHTN. We also wanted to confirm the relationship between blood pressure control and adverse outcome that has been previously reported.

2. Methods

2.1. Patient population

We performed a retrospective cohort analysis among subjects who consented to participate in a prospective ongoing observational study, Angiogenic Dysfunction Of Pregnancy and Transthoracic echocardiogram (ADOPTe). Institutional Review Board approval was obtained from the University of Chicago Biological Sciences Division (IRB# 14-0977). Subjects in ADOPTe are enrolled upon admission for delivery to the University of Chicago Family Birth Center. This study involved a subset of patients with chronic hypertension (cHTN) who received prenatal care and delivered at the University of Chicago between January 2015 and March 2017.

The primary exposure was blood pressure during pregnancy. The criterion for outpatient treatment was per individual physicians based on their practice and American College of Obstetricians and Gynecologists (ACOG) recommendations [5] and varied by provider preference and experience. All blood pressures documented in a patient's chart for each prenatal visit were abstracted from the medical record for analysis. The average of all of these outpatient blood pressure values was then calculated. The diagnosis of cHTN was abstracted by the research staff and confirmed by two authors (JLP and SR). All measurements of BP's were part of routine clinical care.

Members of the study team abstracted maternal data from the medical record from electronic medical records and entered into a database for further analysis. Baseline data collection included demographic data (age, pre-pregnancy height and weight, race/ethnicity, parity, history of preterm birth or pre-eclampsia and maternal comorbidities). All systolic and diastolic blood pressure readings during pregnancy were obtained at each outpatient prenatal visit. Outcome data included mode of delivery, gestational age at delivery, indication for delivery, highest blood pressures during admission, diagnosis of a hypertensive disorder and maternal complications. Neonatal outcome data included birth weight and neonatal intensive care unit (NICU) admission and was abstracted from both the maternal and fetal chart to ensure concordance.

2.2. Diagnosis of preeclampsia

Chronic hypertension was defined using the ACOG definition of elevated blood pressures (≥ 140 SBP or 90 DBP) prior to 20 weeks gestation. Superimposed preeclampsia was defined by the new onset of proteinuria (urine protein creatinine ratio of ≥0.3 or a 24 h urine protein of ≥ 300 mg) or significant end-organ dysfunction including, 1) rise in liver enzyme activity to twice the upper limit of normal, aspartate aminotransferase (AST) ≥74 U/L or alanine transaminase (ALT) ≥70 U/L), 2) acute renal insufficiency (creatinine ≥ 1.1 mg/dL), 3) right upper quadrant pain, severe headaches, pulmonary congestion or edema, 4) a decrease in platelet levels (< 100,000 /mm^3) after 20 weeks of gestation in a woman with chronic/preexisting hypertension. Preeclampsia with severe features was defined as ACOG [1] All diagnoses were assigned by the study coordinator based on the above standard definition and confirmed by two authors (JP and SR).

2.3. Automated assays

All consenting patients had a blood sample collected within 96 h prior to delivery. Blood samples were centrifuged at 3000 RPM for 10 min at 4 degrees Celsius, and then plasma was aliquoted and frozen at -80^0 degrees until the time of analysis. All de-identified samples were thawed once for analysis. Assays for sFlt1 and PlGF were performed on BRAHMS KRYPTOR Compact Plus (ThermoFisher Scientific) automated immunoassay platform using automated kits as previously described, at the clinical chemistry laboratory at the University of Chicago. The detectable ranges for sFlt1 and PlGF are 90 to 69,080 and 11 to 7000 pg/mL, respectively [15]. The coefficient of variation for both assays were < 5%. All measurements were performed once in batches after delivery on all patients so none of the treating physicians were aware of the assay results. The technician performing the analysis was blinded to the final patient diagnosis.

2.4. Statistical analysis

Based on prior studies stratifying antepartum blood pressures [6] we did *a priori* stratified analyses by the average antepartum blood pressure of < 140/90 mmHg (controlled) or ≥140/90 mm Hg (uncontrolled). Uncontrolled BPs occurred either in patients not taking blood pressure medications or those with BP's exceeding the 140/90 threshold despite treatment with oral antihypertensive medications. All blood pressures from all of the prenatal visits were abstracted from the medical record. The average of all recorded blood pressures was used in the analysis. The primary maternal outcome was difference in levels of angiogenic factors at delivery. Other outcomes included superimposed preeclampsia, preeclampsia with severe features, preterm delivery (< 35 weeks), cesarean delivery, antepartum hospitalizations to rule out superimposed preeclampsia and small for gestational age.

Trained members of the study team abstracted maternal data from the medical record. All data is first collected on a standardized data form before being entered into an electronic database (REDCap) for further analysis. Descriptive statistics were generated and reported as mean ± standard deviation, median (interquartile range) or frequencies and proportions, depending on type and distribution. Normality was assessed with the Shapiro-Wilk test. Differences between groups were assessed with a *t*-test, Wilcoxon rank sum, chi-square, or Fisher's Exact test, as appropriate. Logistic regression was used to assess differences in outcome after controlling for pre-pregnancy body mass index, age and race. Odds ratios (OR) and 95% confidence intervals (CI) are presented. All two-sided p-values < 0.05 were considered significant. SAS 9.4 (SAS Institute Inc., Cary, NC) was used for all analyses.

3. Results

3.1. Clinical demographics

Data from 78 patients with chronic hypertension was included in this analysis. The majority of our study population identified as African American (74.4%). A total of 719 outpatient blood pressures were recorded for all patients, of which only 3.2% were documented within seven days of delivery and exceeded a blood pressure of 140/90. Averaging these values resulted in fifty-six (71.8%) patients having an average prenatal blood pressures < 140/90 (cBP) and 22 (28.2%) had average prenatal blood pressures ≥140/90 (uBP). Hypertensive agent use was more frequent in patients with uBP (46.4% vs. 13.6%, p = 0.01) and more patients in the uBP were using multiple agents (uBP 31.8% vs. cBP 12.5%; p = 0.01). Race, ethnicity, mean age, median pre-pregnancy body mass index, smoking status, substance abuse history, obstetric history, and aspirin use was not statistically different between groups (Table 1). As expected, when compared to women with cHTN alone, women with superimposed preeclampsia had higher sFlt1