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Research Article

Trends in Peripartum NT-ProBNP levels in Patients with Hypertensive Gestational Syndromes: A Prospective Cohort Study

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Abstract

Hypertensive gestational syndromes (HGS) are increasingly prevalent as more women are delaying pregnancy. The typical high sodium, fat and carbohydrate Western diet has resulted in earlier development of obesity, diabetes, hypertension in premenopausal women. These co-morbidities further increase the number of pregnancies complicated by disorders of hypertension. The importance of screening patients for HGS is well known and treatment guidelines have been established, however there remains a paucity of data on clinical predictive and diagnostic indicators of HGS, particularly in nephrology literature. There is a need to deepen our understanding of the underlying pathophysiology in these patients. Through this understanding we can direct our focus on improving predictive and diagnostic methods of HGS in order to better serve our evolving patient population.

Keywords: hypertensive gestational syndromes; brain natriuretic; nephrology literature

Introduction

Hypertensive gestational syndromes (HGS) are increasingly prevalent as more women are delaying pregnancy. The typical high sodium, fat and carbohydrate Western diet has resulted in earlier development of obesity, diabetes, hypertension in premenopausal women. These co-morbidities further increase the number of pregnancies complicated by disorders of hypertension. The importance of screening patients for HGS is well known and treatment guidelines have been established, however there remains a paucity of data on clinical predictive and diagnostic indicators of HGS, particularly in nephrology literature. There is a need to deepen our understanding of the underlying pathophysiology in these patients. Through this understanding we can direct our focus on improving predictive and diagnostic methods of HGS in order to better serve our evolving patient population.

Serum N-terminal brain natriuretic peptide (NT-proBNP) levels rise in response to cardiac ventricular myocyte stretch. NT-proBNP is used in clinical practice to evaluate cardiac strain of various etiologies. Pregnancy is characterized by complex physiological changes of the cardiovascular system including a 40-50% increase in blood volume which increases left ventricular mass, left ventricular end diastolic pressure and cardiac output.1 Interstitial water and sodium are increasingly retained towards the end of pregnancy and there is a 14% decrease in serum colloid osmotic pressure, further exacerbating extracellular volume overload. During labor up to 500mL of blood from the uterus returns to the systemic circulation with each uterine contraction causing cardiac output to surge.2–5 Postpartum this water and sodium shift back into circulation, further contributing to cardiac load. These peripartum cardiovascular stressors explain findings of higher NT-proBNP levels throughout pregnancy even in normotensive pregnancies versus non-pregnancy. Levels vary by gestational week, with most studies suggesting the highest levels are seen during the immediate peripartum and postpartum periods.6,7 Patients with hypertensive disorders of pregnancy have been shown to have elevated NT-proBNP levels compared to normal pregnancy, and this is especially true in the setting of preeclampsia (PEC).8–12 NT-proBNP has not been shown to predict the future onset of preeclampsia early in pregnancy.13 Studies have shown that levels rise later in the course of a preeclamptic pregnancy suggesting the high levels of NT-

proBNP in this setting are part of a system to counteract ventricular pressure and volume overload by inducing natriuresis, diuresis, vasodilation and inhibition of the renin-angiotensin-aldosterone system.14-15 We were interested in investigating if NT-proBNP levels differed significantly between patients with HGS during their delivery coinciding with the time of maximal cardiovascular strain. During the immediate peripartum period can this information be used to help predict impending PEC, or to help differentiate PEC from other less severe hypertensive disorders of pregnancy?

Hypertensive gestational syndromes include chronic hypertension (cHTN), gestational hypertension (GH) and preeclampsia (PEC). The American College of Obstetrics and Gynecology (ACOG) defines cHTN as BPs >140/90 at <20 weeks gestation, GH the same except occurring > 20 weeks gestation. Approximately half of those with GH will progress to signs or symptoms of PEC.16 PEC is defined blood pressure >140/90mmHg (measured twice within 4hrs) plus at least one of the following; proteinuria, kidney injury, liver injury, thrombocytopenia, pulmonary edema, headache, scotoma. End organ damage (other than proteinuria) and severe range blood pressure SBP>/=160mmHg or DBP >/= 110mmg/Hg characterize PEC as having severe features. HELLP syndrome also falls loosely under this category, defined as hypertension, elevated liver enzymes and low platelets. PEC and HELLP syndrome cause significant maternal and fetal morbidity, mortality and prolonged hospitalization. If undiagnosed, they can evolve into eclampsia with seizure, stroke and maternal and/or fetal death. PEC is well-defined but often difficult to diagnosis when superimposed on cHTN, GH or in those with underlying proteinuria from chronic kidney disease, diabetes or obesity.

Physiologic increases in serum NT-proBNP may be exaggerated in certain patients with hypertensive disorders of pregnancy.18 It is thought that elevated NT-pro BNP levels in HGS represent cardiac strain due to the failure of the maternal cardiovascular system to adapt to the demands of pregnancy.19,20,21 In PEC this failure to adapt is most severe.22 The rate of preeclampsia in the US increased by 25% between 1987 and 2004.23 The incidence of severe PEC increased nearly 7 fold comparing births from 1980 to 2003.24 NT-proBNP has been tested as an early predictor for the later development of PEC in high risk pregnant women but first and second trimester levels do not consistently correlate with those who go on to develop PEC later in pregnancy. Using NT-proBNP in conjunction with other clinical markers as a diagnostic rather than predictive tool for PEC is less clear. We looked at immediate ante and postpartum NT-pro BNP levels in normal pregnancy, cHTN, GH and PEC to investigate trends in peripartum cardiac strain.

Objective:

We assessed the significance of NT-proBNP elevations as related to ascending degrees of cardiac strain induced by cHTN, GH and PEC in the immediate peripartum period. We sampled peripartum serum NT-proBNP levels, drawn once within 24hrs antepartum and again within 24hrs postpartum, of healthy control patients, compared to those of patients with cHTN, GH and PEC. We hypothesized that patients with hypertensive disorders of pregnancy will have higher peripartum NT-proBNP levels as compared to normal controls, due to hemodynamic stressors of labor, particularly in preeclamptics as this vasoconstrictive pro-inflammatory state confers significantly higher degrees of cardiac strain. With this information we can better risk stratify our peripartum patients with HGS, helping differentiate evolving PEC from other more benign conditions such as exacerbation of cHTN, GH or white-coat HTN.

Methods:

This is a prospective observational cohort study conducted from April 2018 to February 2019 at Lenox Hill Hospital Northwell Health, New York, NY. Informed consent was obtained from patients for two separate blood draws of serum NT-pro BNP levels during their hospitalization for delivery. Patient data including age, race, parity, Body Mass Index (BMI), gestational age at delivery, family or personal history of preeclampsia, route of delivery, pre pregnancy weight, serum creatinine, aspartate and alanine transaminases (AST, ALT), hemoglobin, platelet count, uric acid, lactate dehydrogenase, urine analysis, urine protein to creatinine ratio were collected from electronic medical records. All patient data was processed in the HIPPA compliant REDCAP data storage system.

Inclusion criteria were all pregnant individuals between the ages of 18 to 55 admitted at LHH for their delivery at term as defined as gestational week 32 to 42 as normal control and/or with pregnancy related hypertensive disorders PEC, GH and CH. Patients with known heart failure, heart disease or prior cardiac surgery were excluded, as were patients with COPD, history of pulmonary embolism, diabetes mellitus, severe autoimmune disease, anti-phospholipid syndrome and those with cognitive impairment or otherwise unable to provide informed consent. Patients who delivered pre-term, or with intrauterine fetal death not associated with hypertensive disorder of pregnancy were also excluded.

Chronic hypertension was defined as requiring antihypertensive medications prior to conception, or systolic blood pressure (SBP) >140 mmHg or diastolic blood pressure (DBP) >90 mmHg known to predate conception or detected before 20 weeks gestation. Gestational hypertension was defined as SBP >140 mmHg or DBP >90 mmHg on two or more measurements at least four hours apart, occurring after 20 weeks of gestation, without concomitant proteinuria. Preeclampsia was defined as the new onset of hypertension (SBP ≥140mmHg and/or diastolic blood pressure ≥90 mmHg on two measurements at least 4 hours apart) plus proteinuria (24hr urine protein =/> 300mg, urine protein to creatinine ratio =/> 0.3 or 2+ proteinuria on urine dipstick if former measurements unavailable, without a concomitant urinary tract infection or with signs of severe PEC including thrombocytopenia, renal impairment, elevated liver enzymes, pulmonary edema, unexplained headache not relieved by medication or visual disturbances.16

Antepartum blood samples of 5-10 ml were obtained using standard sampling tubes within 24hrs prior to delivery, postpartum blood samples were drawn within 24hrs after delivery. Serum NT-proBNP analyzed by an electro chemiluminescence immunoassay "ECLIA" at our institute's inpatient laboratory. When used with the recommended cut-offs the Elecsys proBNP II STAT assay used yields negative predictive values ranging from 97.8 to 100% depending on age and gender with analytical range of 5–35000pg/dl.

The protocol of the study was approved by the Northwell Health Institutional Review Board (IRB) committee and written informed consent was sought from all study participants.

Statistical methods:

The primary objective of the study was to determine differences in NT-proBNP level associated with hypertensive disorder of pregnancy namely cHTN, GH and PEC, as compared to normal control pregnancy. Predictor and baseline variables includes but not limited to NT-proBNP level, patient's age, race, parity, BMI and gestational age at delivery, family or personal history of preeclampsia, route of delivery, pre-pregnancy weight, serum creatinine, aspartate and alanine transaminases (AST, ALT), hemoglobin, platelet count, uric acid, lactate dehydrogenase, urine analysis, and urine protein to creatinine ratio.

A crude comparison of hypertensive disorders of pregnancy was performed using univariable multinomial logistic regression. Once the confounders are identified ($p < 0.05$), the outcome was analyzed using multivariable multinomial logistic regression with backward elimination. Analysis was conducted using SAS v. 9.4 (SAS Institute, Inc., Cary, NC). Comparisons of the demographic factors of the patients in the different groups were made using analysis of variance (ANOVA), the $\chi 2$ test, and the extended median test, where appropriate. For comparing levels of NT pro-BNP in the different groups, the Mann–Whitney U-test was used. A p-value of < 0.05 was accepted as statistically significant

Assuming that pregnancy induced hypertensive disorders group will have higher NT-pro BNP level, and the log-scale common SD of 0.90, the

Bonferroni adjusted two-sample t-test with 0.01 two-sided significance level will have 80% power to detect the difference between these log-scale means when the sample size is 30 subjects per group. Based on above justification we aimed to enroll 30 patients in each group in various category of hypertensive disorders as well as normal control pregnancy (total 120 subjects).

Results:

A total of ninety-seven patients were enrolled. Thirty-five normotensive controls, fourteen in the cHTN group, twenty-nine in the GH group and nineteen in the PEC group. Four patients in each of the cHTN and GH group, and six in the normotensive group developed peripartum superimposed PEC. These patients were therefore analyzed in the PEC group, resulting in twenty-nine normotensive controls, ten patients with cHTN, twenty-five with GH and thirty-three in the PEC group. The mean gestational age of patients was 38.6 weeks. Serum creatinine (SCr) ranged from 0.37-1.10, mean 0.63 mg/dl. The mean time from ante-partum serum blood draw to delivery was 9.28 hours (SD +/- 6.8), mean time from delivery to postpartum draw was 12.9 hours (SD +/- 6.5). A minority of patients were already receiving at least one antihypertensive prior to admission; 3/10 chronic hypertensives (30%), 1/25 GH patients (4%), 7/33 preeclamptics (21%), this latter group includes eight patients with superimposed PEC on either cHTN or GH, and six normotensives who developed PEC. Oral antihypertensive requirements (labetalol, nifedipine ER, nifedipine IR) during hospitalization included 3/10 (30%) chronic hypertensives, 4/25 (16%) in GH group and 16/33 (48.5%) of preeclamptics. 9/33 (27.3%) preeclamptics required IV antihypertensives (IV labetalol, IV hydralazine) for severe range blood pressures. Vaginal delivery was the most common delivery mode in each group except for the normotensive group in which 18/29 (62%) of patients had caesarian sections. Ten of our thirty-three preeclamptic patients (33%) exhibited severe features (Table 1)

	Normotensive	Chronic hypertension	Gestational Hypertension	Preeclampsia	Total
C-Section	18	2	10	13	43
NSVD	11	8	15	20	54
Total	29	10	25	33	97

Table 1: Mode of Delivery in each Study Group

The mean antepartum NT-proBNP level in the normotensive control group was 65.4pg/dL, 82.1pg/dL in cHTN group, 64.8pg/dL in the GH group and 133.3pg/dL in the PEC group. Although there was a trend towards higher antepartum NT-proBNP levels in patients with cHTN and PEC as compared to control or GH groups, it was not statistically significant. The mean postpartum NT-proBNP level in the control group was 209.2pg/dL, 207.7pg/dL in cHTN group, 259.5pg/dL in the GH group and 198.8pg/dL in the PEC group. We found no significant differences in antepartum (p=0.47) or postpartum (p=0.32) NT-proBNP levels between patients in the normotensive control group, cHTN group, GH group or the PEC group. (Table 2)

Group	N	Antepartum	Postpartum	Difference
Gestational HTN	25	64.76	259.48	194.72
PEC	33	133.27	198.79	65.52
Normal	29	65.34	209.24	143.90
Chronic HTN	10	82.1	207.7	125.60

Table 2: Mean NT-ProBNP (pg/dL)

The mean antepartum NT-proBNP levels for all groups combined was 90pg/dL (5-988pg/dL). The mean postpartum NT-proBNP was significantly more elevated at 218.5pg/dl (11-1151pg/dL). The change in NT-ProBNP level from antepartum to postpartum (i.e. postpartum – antepartum level) did differ significantly across groups (p=0.01). The increase in NT-ProBNP was significantly larger in the gestational HTN group compared to the PEC group (194.7pg/dL vs 65.5pg/dL respectively; p=0.004). A statistically significantly increase in postpartum NT-proBNP was also noted in normotensive controls compared to preeclamptics (mean rise 143.9pg/dL vs. 65.5pg/dL respectively; p=0.0081). There was not enough evidence to conclude that the increase in NT-ProBNP level differed between any other two groups. (Table 3)

Variable	Normal N = 29	Chronic HTN N = 10	Gestational HTN N = 25	PEC N = 33	P-value
Antepartum NT-ProBNP	65.3	82.1	64.8	133.3	0.47
Postpartum NT-ProBNP	209.2	207.7	259.5	198.8	0.32
Difference in NT-ProBNP levels (Postpartum -Antepartum)	143.9	125.6	194.7	65.5	0.01

*A result was considered statistically significant if p-value <0.05

Table 3: Differences in Mean Postpartum vs Antepartum NT-ProBNP (pg/dL)

Discussion:

ProBNP is secreted by cardiac myocytes then cleaved into the active form BNP and the inert N-terminal fragment NT-proBNP which is preferred for measurements as is not enzymatically degraded by neprilysin. Its action is to induce natriuresis in the setting of volume expansion and pressure overload. Serum NT-proBNP is a measurable surrogate for left ventricular cardiac strain in a variety of clinical settings, including hypertensive gestational disorders.

Several studies of NT-proBNP levels in uncomplicated pregnancy and in those with HGS have been previously published mainly in obstetric and cardiology literature. While the data is often conflicting, the consensus is that NT-proBNP levels tend to be mildly higher in pregnancy compared to non-pregnancy even in normotensive pregnant patients.15 This is attributed to increased blood volume, cardiac output and left ventricular end diastolic pressures generating subclinical cardiac strain, with clinical hemodynamic compensation and adequate pressure-natriuresis. In a study of 101 healthy pregnant women, mean NT-proBNP levels at 18-24 weeks gestation were 60pg/ml, the in-labor antepartum mean was 73.5pg/ml. The highest levels

were seen within 48hrs postpartum, 157.98pg/nl, coinciding with an immediate postpartum peak in left ventricular volume.17 The trend of most prior studies is that these elevated NT-proBNP levels stay relatively stable throughout uncomplicated pregnancy up until the immediate peripartum period, where they rise maximally within 24-48hrs postpartum and up to one week postpartum.7

The literature on NT-proBNP levels as they correlate to gestational disorders of pregnancy is more variable. Our goal was to evaluate whether immediate antepartum and postpartum mean NT-proBNP differed significantly between groups of HGS based on the expected cardiac strain conferred by their particular hypertensive disorder. Based on prior studies showing maximal hemodynamic strain in pregnancy occurs in the immediate postpartum period, we measured NT-proBNP levels during labor up to 24hrs prior to delivery, and again within 24hrs of delivery. This allowed us to examine the degree of rise in NT-proBNP levels between each HGS group and controls in response to the cardiovascular demands of delivery, shedding light on potential differences in cardiovascular reserve or adaptability in these patients.

The mean postpartum NT-proBNP levels in all study groups were significantly higher than their antepartum levels. There was a 2-3 fold rise in NT-proBNP within 24hrs of delivery, consistent with literature that delivery confers a measurable degree of maternal cardiac strain even in pregnancies not complicated by hypertension.17 Interestingly, we found a statistically significant rise in peripartum NT-proBNP levels between study groups during the 24 hours pre-delivery to the 24hrs post-delivery as well. This difference was most significant in the patients with gestational hypertension and preeclampsia as compared to normal controls and chronic hypertensives. A study by Giannubilo et al in 201418 found that while NT-proBNP levels were higher in pregnant chronic hypertensives around 16 weeks gestation compared to normotensive pregnancies, their levels plateaued and remained stable throughout the rest of pregnancy. This early elevation and then plateau of NT-proBNP mirrors that seen in studies of uncomplicated pregnancies versus non-pregnancy. The steady NT-proBNP levels even towards term suggests that chronic hypertensives may have an increased ability to adapt to the increased intravascular volume later on in pregnancy without a significant increase in left ventricular end-diastolic pressure or stress, perhaps conferred by the adaptation to chronic pressure overload. It is possible that GH and PEC, both fairly acute processes compared to cHTN, result in a more rapid increase in cardiovascular strain, impairing adaptation. Similarly, Verlohhren et al25 in 2017 noted significantly elevated NT-proBNP levels at 35 weeks gestation in patients with GH and PEC as compared to normotensive pregnancy. We found no significant difference in ante or postpartum NT-proBNP levels between normotensive patients, chronic hypertensives, gestational hypertensives or preeclamptics. The PEC

group had the highest antepartum mean NT-proBNP, trending towards but not reaching statistical significance. Coupled with the fact that the PEC group had the least rise in postpartum NT-proBNP levels, one may consider the higher antepartum levels as a possible signal of impending cardiovascular decompensation in the setting of the vasoconstriction conferred by preeclampsia.

Given that our study was a small population, some of our findings, in particular the trend towards higher mean postpartum NT-proBNP levels in our PEC cohort may not have reached statistical significance due to sampling error and other confounding factors. Another important note is that 62% of our normotensive controls underwent elective cesarean sections, compared to 20% in the cHTN group, 40% in GH and 39.4% in the PEC group. We prioritized minimizing interventions in this sensitive study population and as such, we enrolled more normotensive patients with planned C-sections because per hospital protocol they already required at least one blood draw. Higher peripartum NT-BNP levels in the normotensive groups may have been related to intra-op cardiovascular stress, anesthesia, intravenous fluids and blood products.

While using NT-proBNP is a validated marker for cardiac strain, it can be affected by other factors that need to be considered, particularly in pregnancy. Obesity, infection and intrauterine growth restriction can increase NT-proBNP levels.15,17,18 Lev-Sagie et al26 reported an increase in NT-proBNP in women receiving epidural pain relief versus not. A study from 2007 by Tintonin et al27 published in AJOG found higher levels of NT-proBNP in patients with preeclampsia who were treated with antihypertensives versus not. It is unclear whether these factors cause an independent rise in NT-proBNP regardless of the patient's hemodynamic status or whether the cardiovascular strain conferred by some of these conditions is what drives the rise in NT-proBNP. In those patients with severe PEC and kidney impairment, the reduced clearance of NT-proBNP may lead to exaggerated elevations in peripartum levels.

Conclusion

Gestational hypertensive disorders are increasingly prevalent in the United States due to increases in co-morbidities, maternal age and infertility interventions. Underlying conditions known to confer higher risk of hypertensive complications during pregnancy include obesity, chronic hypertension, diabetes, cardiovascular and kidney disease including proteinuria, and often these patients have several compounding risk factors. As obstetricians, nephrologists and cardiologists treating this high-risk population, we must be aware of the increasing incidence of GHD and work towards a better understanding of the underlying pathophysiology as well as predictors of GHD especially preeclampsia. This is the first study to prospectively assess the NT-proBNP levels of pregnant normotensives, chronic hypertensives, gestational hypertensives and preeclamptics pre- and post-delivery during the period of maximal pregnancy-related cardiovascular strain. Our data show all groups had higher antepartum NT-proBNP levels compared to non-pregnancy. There was a trend towards higher antepartum NT-proBNP in those with chronic hypertension which we think may be secondary to adaptations to longstanding elevated blood volume and pressure. Those with preeclampsia showed an even larger trend towards higher antepartum NT-proBNP which may be an indicator of impending preeclampsia. Mean NT-proBNP rose two-three times antepartum levels immediately postpartum in all groups, however the degree of rise was significantly larger in gestational hypertensives and normotensive controls compared to those with chronic hypertension and even more so in preeclampsia, likely due to the latter two group's already higher antepartum levels. More research is needed to elucidate whether there is a negative predictive value NT-proBNP cut off in immediate antepartum NT-proBNP level or degree of rise in postpartum NT-proBNP that we can use to aid in the often-difficult diagnosis of exacerbation of chronic or gestational hypertension versus developing preeclampsia.

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