Evaluation of B-type natriuretic peptide (BNP) levels in normal and preeclamptic women

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Objective: B-type natriuretic peptide (BNP) is synthesized in cardiac ventricles in response to volume expansion. This study evaluated BNP levels to determine trends during pregnancy, and to assess BNP as a diagnostic tool in preeclampsia.

Study design: We studied 163 BNP levels in 118 pregnant women, ranging from first trimester to term. An additional 34 patients with preeclampsia were studied and compared to 25 normal control patients at term. Plasma BNP values were determined using a standard assay.

Results: The median BNP levels during the 1st, 2nd, 3rd trimester, and at term were equivalent (18.4, 17.9, 15.5, and 17.8 pg/mL, respectively, $P = .796$). The median BNP levels in normal patients, mild preeclamptics, and severe preeclamptics were 17.8, 21.1, and 101 pg/mL, respectively, with the severe group being significantly higher than the mild group ($P = .003$) and any phase of normal pregnancy ($P < .001$ in each case). A BNP cut-off of <40.6 pg/mL had a negative predictive value of 92% in excluding preeclampsia.

Conclusion: In normal pregnancies, median BNP values are <20 pg/mL, and stable throughout gestation. In severe preeclampsia BNP levels are elevated. This may reflect ventricular stress and/or subclinical cardiac dysfunction associated with preeclampsia.

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Preeclampsia is one of the most common disorders of pregnancy, affecting about 5% of pregnancies, and resulting in substantial maternal and neonatal morbidity and mortality.[1,2] Untreated preeclampsia is characterized by a marked increase in peripheral vascular resistance, which, in turn, causes an increase in blood pressure.[3,4] This increase in afterload is superimposed upon the existing volume overloaded hemodynamic state of pregnancy.

B-type natriuretic peptide (BNP) is synthesized in cardiac ventricular tissue in response to volume expansion and pressure overload. It is an approved marker for the diagnosis of congestive heart failure (CHF) in patients with dyspnea in an acute care setting.[5,6] BNP levels

correlate to wedge pressure,[7] as well as to the severity and medical prognosis in patients with CHF.[8-10] BNP levels have also been used to screen for ventricular dysfunction in the community setting,[11,12] and in patients who are considered high risk for heart disease, such as diabetics.[13] BNP values have also been known to increase in conjunction with renal disease and hypertension.[14] The objective of this study was to determine whether BNP levels fluctuate during pregnancy, and if BNP could be a useful diagnostic tool in preeclamptic women.

Material and methods

Study population

Approval of this study was obtained from the Human Research Protection Program Subjects Committee at University of California, San Diego (UCSD). All women with singleton pregnancies who presented to the UCSD Ambulatory Care Centers were given the opportunity to participate in the prospective arm of the study. After informed consent was obtained, blood samples were collected. Specimens were obtained at the time of the initial visit, at subsequent scheduled blood draws, and at presentation to labor and delivery. All medical charts were reviewed to evaluate for the presence of medical conditions complicating pregnancies, with particular attention to chronic hypertension, diabetes, systemic lupus erythematosus, renal disease, and a personal history of preeclampsia.

Additionally, patients presenting to labor and delivery with preeclampsia were enrolled into the study. This population of patients had BNP levels drawn at the time of their initial assessment for preeclampsia on labor and delivery, before magnesium sulfate was administered. The BNP values of these preeclamptic patients were compared with the median BNP levels found in normal control patients at term gestation. The normal control patients consisted of those patients who had participated in the longitudinal arm of the study, and who ultimately presented to labor and delivery at term with no evidence of preeclampsia.

Diagnosis of preeclampsia

The diagnosis and classification of preeclampsia was based on standard criteria as outlined in the Technical Bulletin from the American College of Obstetrics and Gynecology on Hypertension in Pregnancy.[15] Mild preeclampsia was diagnosed in patients with 2 or more elevated blood pressures taken 6 hours apart along with proteinuria. Blood pressures were considered elevated if systolic blood pressure (SBP) was greater than 140 mm Hg, or if diastolic blood pressure (DBP) was greater than 90 mm Hg. Proteinuria associated with mild preeclampsia was defined as ≥300 mg per 24 hours.

Table I Characteristics of healthy pregnant patients at enrollment: mean ± STDEV

Variable	Subjects n = 118
Maternal age (y)	32.3 ± 4.7
Gestational age (wk)	14.5 ± 8.5

Severe preeclampsia was diagnosed in patients with markedly elevated blood pressures, defined as SBPs ≥160 mm Hg or DBPs ≥110 mm Hg. Additionally, patients were classified as severe preeclamptics if they had elevated blood pressures combined with evidence of involvement of other organ systems. Criteria included symptoms of headache, blurry vision, and epigastric pain; laboratory findings of thrombocytopenia, elevated liver enzymes, elevated creatinine, severe proteinuria >5 g/24 hours; and signs of oliguria, intrauterine growth restriction, and pulmonary edema.

Measurement of levels of B-type natriuretic peptide

Blood was drawn by standard venipuncture technique at the time of otherwise scheduled blood draws, or upon presentation to labor and delivery. Blood samples were collected into tubes containing potassium EDTA. BNP values were obtained before the use of magnesium sulfate therapy. B-type natriuretic peptide levels were then determined using a standard point of care assay. After centrifugation of the whole-blood samples, plasma was isolated and frozen at −20 degrees until determination of BNP levels. Plasma specimens were then measured with a fluorescence immunoassay kit (Triage, Biosite Inc, San Diego, Calif) for the quantitative determination of BNP. The precision, analytic sensitivity, and stability of this system have been previously described.[5,16]

Statistical analysis

Comparisons of B-type natriuretic peptide values among groups were performed using Kruskal-Wallis nonparametric analysis of the variance, followed by Mann-Whitney U tests for pairwise comparisons. In the longitudinal arm of the study, this analysis assumes independence of observations. Subject characteristics were compared across diagnostic groups using analysis of variance (ANOVA) with post-hoc Tukey tests, and with chi-square tests as appropriate. This was performed using SPSS, Release 12 (SPSS Corporation, Chicago, Ill).

Results

In the study, we analyzed 163 BNP levels in 118 women from the first trimester to term (n = 74, 49, 15, 25 for

Table II Characteristics of preeclampsia patients and term control

Variable	Normal (n = 25)	Mild preeclampsia (n = 9)	Severe preeclampsia (n = 24)
Maternal age (y, mean $\pm$ SD)	31.2 $\pm$ 4.7	29.9 $\pm$ 8.3	27.4 $\pm$ 7.3
Gestational age (wk, mean $\pm$ SD)*	37.9 $\pm$ 2.7	36.0 $\pm$ 3.2	32.2 $\pm$ 4.8
Maternal height (in, mean $\pm$ SD)	64.9 $\pm$ 2.4	64.1 $\pm$ 2.4	63.5 $\pm$ 3.0
Maternal weight (lb, mean $\pm$ SD)[†]	166 $\pm$ 33	225 $\pm$ 97	175 $\pm$ 31
Hemoconcentration	10%	0%	28%
Gravity >1	52%	78%	60%
Parity >0	38%	67%	44%
Ethnicity			
Caucasian	57%	14%	29%
Hispanic	14%	44%	33%
Other	29%	44%	36%

There were no statistical differences across groups with respect to maternal age, hemoconcentration, gravity, parity, or ethnicity.

  * $P < .05$ when compared between normal and severe and mild and severe preeclamptics.

  † $P < .05$ when comparison between mild and severe and mild and normal preeclamptics.

first, second, third trimester, and term, respectively). An additional 34 patients admitted with preeclampsia (9 mild, 25 severe) were evaluated at term, and were compared with normal control patients.

Table I shows the characteristics of the healthy pregnant patients enrolled in the prospective arm of the study, and Table II describes the characteristics of those with mild or severe preeclampsia, and their term control patients. There were no statistical differences among term control patients, mild, or severe preeclamptics with respect to maternal age, height, gravity, parity, hemoconcentration, or ethnicity (Table II). Earlier gestational age is seen in the patients with severe preeclampsia ($P < .001$ vs normal patients), as these patients are delivered upon presentation at any gestational age. While patients with mild preeclampsia were significantly heavier than those with severe preeclampsia ($P = .026$) and normal patients ($P = .008$), there was no significant difference in weight between normal and severe preeclamptics. The weight difference among groups became nonsignificant if a single mild preeclampsia case (which was an outlier at 450 pounds) is eliminated.

The median BNP levels during the first, second, third trimesters, and term pregnancy were 18.4, 17.9, 15.5, and 17.8 pg/mL, respectively (Figure 1). There was no significant difference between these values ($P = .796$). The median BNP levels in normal patients, patients with mild preeclampsia, and those with severe preeclampsia were 17.8, 21.1, and 101 pg/mL, respectively (Figure 1). Pairwise comparisons were significant between the severe group and the other groups ($P < .001$ for normal and $P = .004$ for mild), but not between normal and mild preeclamptics.

The receiver operating characteristic curve of BNP predicting preeclampsia (Figure 2) gave the area under the curve to be AUC 0.86 (95% CI 0.76−0.95, $P < .001$). The best cutoff was determined to be 40 pg/mL based on the closest point to the 100% sensitivity and 100% specificity, yielding a sensitivity of 73%, specificity of 85%, positive predictive value 57%, negative predictive value of 92%, and accuracy of 82%.

Comment

BNP levels have gained wide acceptance both for the diagnosis and screening of left ventricular dysfunction. While 100 pg/mL has been the established cut-off for the acutely dyspneic patient, lower levels may also be diagnostic for less symptomatic degrees of left ventricular dysfunction.[13,17] The fact that elevated BNP levels are perhaps the most important prognostic marker for heart failure is now well accepted among cardiologists and emergency room physicians.[18] Wang et al has demonstrated in the Framingham Offspring cohort that levels as low as 20 pg/mL may be prognostic for future cardiac events in previously asymptomatic patients.[19]

The present study demonstrates several important findings. First, we found that median BNP levels in normal pregnancy remain less than 20 pg/mL throughout gestation, suggesting that the increased intravascular volume in late pregnancy is likely handled without an increase in left ventricular end-diastolic pressure.[20] Of note, Yoshimura et al found a doubling of BNP levels from 25 $\pm$ 2 in the first trimester to 49 $\pm$ 9 pg/mL at term pregnancy ($P < .01$).[21] The results could be explained by the difference in study population as well as precision of the assay. The study by Yoshimura was published over 10 years ago, and the BNP assays used at that time were not as accurate as those which are currently available.

The second major finding of this study was that patients with severe preeclampsia had BNP values that were significantly elevated compared with both the normal study population and the group with mild preeclampsia.
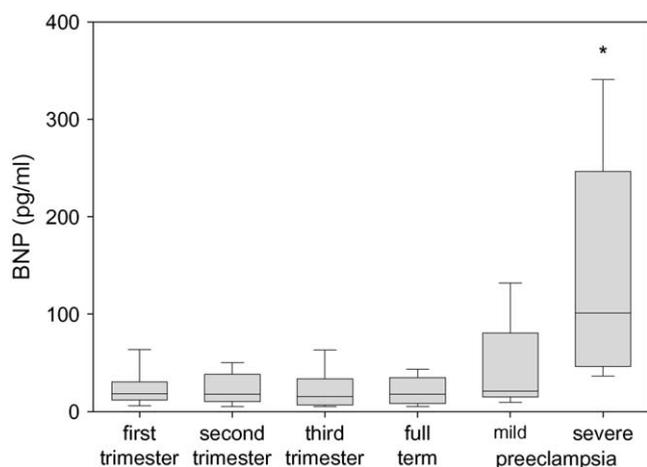
Figure 1 Box whisker representation of median BNP levels throughout pregnancy in healthy subjects, and in both mild and severe preeclampsics. Error bars represent values in the 10th and 90th percentiles in each category. BNP levels are stable and normal throughout normal pregnancies. *P value < .05 when compared between severe preeclampsics vs all groups.

Figure 2 The receiver operating characteristic curve analysis showing AUC of BNP predicting preeclampsia (mild and severe combined).

Our results are similar to those published in several previous studies that confirmed an increase in BNP levels in the presence of preeclampsia. A retrospective observational study conducted by Itoh et al[22] detected significantly higher BNP levels in pregnant women with mild pregnancy-induced hypertension (PIH) (n = 17) compared with those in gestational age-matched normal pregnant patients (n = 30) or in nonpregnant women (n = 10). In their study, the pregnant women with severe PIH (n = 11) had BNP levels that were higher than those found in pregnant women with mild PIH. Before these findings, a similar study,[23] also conducted by Itoh et al, indicated an 8-fold increase in BNP levels in patients with severe PIH compared with those in normal pregnant women. In a study by Furuhashi et al[24] of 19 normotensive pregnant women and 35 preeclamptic patients, the maternal plasma BNP levels were significantly higher in the preeclamptics than in normal pregnancy. Similarly, Okuno et al[25] found a 7-fold increase in BNP levels in preeclamptic women when compared with the plasma BNP levels drawn from the same women during the subsequent puerperal period.

Left ventricular dysfunction is more likely to be present when BNP levels are greater than 20 pg/mL. Therefore, BNP levels have been proposed to be used as a cost-effective prescreening tool for left-ventricular dysfunction. Borghi et al[26] showed significant increases in left ventricular mass and left ventricular end-systolic and end-diastolic volumes in echocardiograms in preeclamptic patients (BNP 37.1 ± 10.0.) compared with normotensive pregnant (BNP 21.5 ± 8) and nonpregnant women (BNP 15.2 ± 5). This study also showed significant reductions in left ventricular ejection fraction and percentage of fractional shortening. These changes
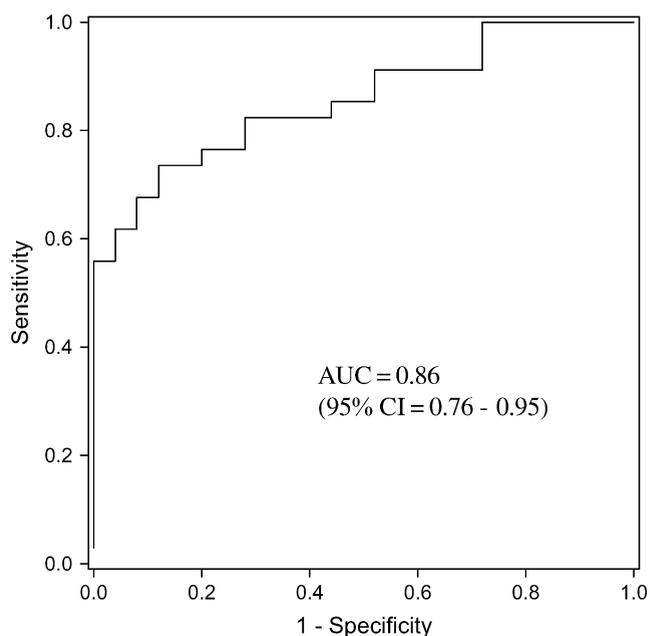
coincided with increases in plasma levels of brain natriuretic peptide that were linearly related to the left ventricular structural and functional changes observed in patients with preeclampsia. The increase in BNP levels was significant when compared between three groups, respectively. Thus, based on this data and from the known association of BNP with ventricular dysfunction in heart failure patients, we believe that the elevation of BNP levels in the severe preeclamptics may reflect ventricular stress and/or subclinical cardiac dysfunction associated with the disease process.

In normal pregnancies, we found the median BNP values to be <20 pg/mL, and they remained stable throughout gestation. Patients with severe preeclampsia have significantly elevated BNP values compared with both normal patients and mild preeclamptics. The elevation of BNP levels in these patients may reflect left ventricular stress associated with the pathophysiology of preeclampsia. In fact, elevated BNP levels have been suggested to correlate with both ventricular stress and with subclinical cardiac dysfunction,[5] and may help in the evaluation of the disease. Furthermore, a low BNP level (<20 pg/mL) in the setting of a patient who presents in the later stages of pregnancy with shortness of breath might serve to effectively rule out heart failure as a cause of her symptoms. The fact that BNP levels can now be measured rapidly, accurately, and inexpensively, and that a rapid point-of-care assay could be made available on the labor and delivery suite, suggests that further studies should be undertaken. These studies should explore the utility of BNP assessment in screening and diagnosis of preeclampsia, as well as in its management.

Limitations

We did not have sequential samples of all the trimesters for the normal control participants, and had to evaluate the data as independent observations. However, analysis of truly independent samples (excluding repeated BNP observations) yielded similar results.

References

1. Walker JJ. Pre-eclampsia. Lancet 2000;356:1260-5.
2. Roberts JM, Cooper DW. Pathogenesis and genetics of pre-eclampsia. Lancet 2001;357:53-6.
3. Cunningham FG, Lindheimer MD. Hypertension in pregnancy. N Engl J Med 1992;326:927-32.
4. Visser W, Wallenburg HCS. Central hemodynamic observations in untreated preeclamptic patients. Hypertension 1991;17:1072-7.
5. Maisel A, Krishnaswamy P, Nowak RM, McCord J, Hollander JE, Duc P, et al. Rapid measurement of B-type natriuretic peptide in the emergency diagnosis of heart failure. N Engl J Med 2002;347:161-7.
6. Bhalla V, Willis S, Maisel AS. B-type natriuretic peptide: the level and the drug–partners in the diagnosis and management of congestive heart failure. Congest Heart Fail 2004;10(Suppl 1):1-27.
7. Kazanegra R, Cheng V, Garcia A, Krishnaswamy P, Gardetto N, Clopton P, et al. A rapid assay for B-type natriuretic peptide correlates with falling wedge pressures in patients treated for decompensated heart failure: a pilot study. J Card Fail 2001;7:21-9.
8. Harrison A, Morrison LK, Krishnaswamy P, Kazanegra R, Clopton P, Dao Q, et al. B-type natriuretic peptide predicts future cardiac events in patients presenting to the emergency department with dyspnea. Ann Emerg Med 2002;39:131-8.
9. Cheng V, Kazanagra R, Garcia A, Lenert L, Krishnaswamy P, Gardetto N, et al. A rapid bedside test for B-type peptide predicts treatment outcomes in patients admitted for decompensated heart failure: a pilot study. J Am Coll Cardiol 2001;37:386-91.
10. Bettencourt P, Ferreira S, Azevedo A, Ferreira A. Preliminary data on the potential usefulness of B-type natriuretic peptide levels in predicting outcome after hospital discharge in patients with heart failure. Am J Med 2002;113:215-9.
11. Vasan RS, Benjamin EJ, Larson MG, Leip EP, Wang TJ, Wilson PW, et al. Plasma natriuretic peptides for community screening for left ventricular hypertrophy and systolic dysfunction: the Framingham heart study. JAMA 2002;288:1252-9.
12. Cowie MR, Struthers AD, Wood DA, Coats AJ, Thompson SG, Poole-Wilson PA, et al. Value of natriuretic peptides in assessment of patients with possible new heart failure in primary care. Lancet 1997;350:1349-53.
13. Epshteyn V, Morrison K, Krishnaswamy P, Kazanegra R, Clopton P, Mudaliar S, et al. Utility of B-type natriuretic peptide (BNP) as a screen for left ventricular dysfunction in patients with diabetes. Diabetes Care 2003;26:2081-7.
14. Cheung BM, Brown MJ. Plasma brain natriuretic peptide and C-type natriuretic peptide in essential hypertension. J Hypertens 1994;12:449-54.
15. American College of Obstetrics and Gynecology. Hypertension in pregnancy. Washington, DC: The College; ACOG Technical Bulletin No. 219; 1996.
16. Mair J, Hammerer-Lercher A, Puschendorf B. The impact of cardiac natriuretic peptide determination on the diagnosis and management of heart failure. Clin Chem Lab Med 2001;39:571-88.
17. Atisha D, Bhalla MA, Morrison LK, Felicio L, Clopton P, Gardetto N, et al. A prospective study in search of an optimal BNP level to screen patients for cardiac dysfunction. Am Heart J 2004;148:518-23.
18. Mark DB, Felker GM. B-type natriuretic peptide —a biomarker for all seasons? N Engl J Med 2004;350:718-20.
19. Wang TJ, Larson MG, Levy D, Benjamin EJ, Leip EP, Omland T, et al. Plasma natriuretic peptide levels and the risk of cardiovascular events and death. N Engl J Med 2004;350:655-63.
20. Clark SL, Cotton DB, Lee W, Bishop C, Hill T, Southwick J, et al. Central hemodynamic assessment of normal term pregnancy. Am J Obstet Gynecol 1989;161:1439-42.
21. Yoshimura T, Yoshimura M, Yasue H, Ito M, Okamura H, Mukoyama M, et al. Plasma concentration of atrial natriuretic peptide and brain natriuretic peptide during normal human pregnancy and the postpartum period. J Endocrinol 1994;140:393-7.
22. Itoh H, Sagawa N, Nanno H, Mori T, Mukoyama M, Itoh H, et al. Impaired guanosine 3′, 5′-cyclic phosphate production in severe pregnancy-induced hypertension with high plasma levels of atrial and brain natriuretic peptides. Endocr J 1997;44:389-93.
23. Itoh H, Sagawa N, Mori T, Mukoyama M, Nakao K, Imura H. Plasma brain natriuretic peptide level in pregnant women with pregnancy-induced hypertension. Obstet Gynecol 1993;82:71-7.
24. Furuhashi N, Kimura H, Nagae H, Yajima A, Kimura C, Saito T. Brain natriuretic peptide and atrial natriuretic peptide levels in normal pregnancy and preeclampsia. Gynecol Obstet Invest 1994;38:73-7.
25. Okuno S, Hamada H, Yasuoka M, Watanabe H, Fujiki Y, Yamada N, et al. Brain natriuretic peptide (BNP) and cyclic guanosine monophosphate (cGMP) levels in normal pregnancy and preeclampsia. J Obstet Gynaecol Res 1999;25:407-10.
26. Borghi C, Esposti DD, Immordino V, Cassani A, Boschi S, Bovicelli L, et al. Relationship of systemic hemodynamics, left ventricular structure and function, and plasma natriuretic peptide concentrations during pregnancy complicated by preeclampsia. Am J Obstet Gynecol 2000;183:140-7.