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Short Communication

Longitudinal Changes in the B-Type Natriuretic Peptide Levels in Normal Pregnancy and Postpartum

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ABSTRACT

Normal levels of B-type natriuretic peptide (BNP) are not well established in pregnancy. We obtained longitudinal BNP levels in 29 healthy pregnant women in each trimester and postpartum period, and compared these levels to the 25 nonpregnant controls. There were no significant differences among the cases and controls with respect to weight, diastolic blood pressure, and ethnicity. A total of 116 BNP values were obtained during pregnancy. The median (and range) BNP level during pregnancy was 19 (10–143) pg/ml versus 10 (10–37) pg/ml in the nonpregnant controls ($p = 0.003$). However, there were no statistically significant differences in the median BNP levels at various stages of pregnancy: first trimester 20 (10–115) pg/ml versus the second trimester 18 (10–112) pg/ml ($p = 0.8$), second trimester 18 pg/ml versus third trimester 26 (10–143) pg/ml ($p = 0.06$), and third trimester 26 pg/ml versus postpartum 18 (10–62) pg/ml ($p = 0.08$). There were no significant differences between the BNP levels throughout the trimesters and postpartum period. Pregnant BNP levels were approximately twice as high as the nonpregnant BNP levels. Our study is unique in evaluating longitudinal changes in BNP levels in normal pregnancies and the postpartum period in comparison with healthy, nonpregnant controls. It demonstrates that pregnant BNP levels are approximately 2-fold higher than their nonpregnant counterparts, and do not significantly fluctuate during pregnancy. In conclusion, pregnancy is associated with a significant, but small increase in the BNP levels compared with nonpregnant women.

Key words: B-type natriuretic peptide, pregnancy, normal pregnancy

Introduction

The B-type natriuretic peptide (BNP) is a neurohormone secreted by the cardiac ventricles in response to volume or pressure overload. It was first discovered in the brain of pigs and reported by Sudoh and colleagues in 1988.¹ The BNP is a member of the natriuretic peptide family that serves as the body's defense against volume overload by vasodilation, inhibition of the renin-angiotensin-aldosterone system, and natriuresis. The BNP level is elevated in certain conditions and is routinely used today for the diagnosis and follow-up of patients with cardiopulmonary disorders.^{2–6}

Pregnancy is a state of physiologic volume overload. Maternal blood volume rises by 50%, and there is an increase in the left ventricular wall mass and end-diastolic dimensions during normal pregnancy.⁷ Despite the growing role of BNP in the regulation of volume homeostasis in the

nonpregnant state, there are limited data available in normal pregnancies.

We hypothesize that there may be alterations in the BNP levels during normal pregnancy reflecting pressure/volume overload in the cardiac ventricles. To our knowledge, there are no studies available in the literature that report longitudinal data on BNP values in normal pregnancy and the postpartum period. Our objective was to determine serial changes in the BNP levels in the first, second, and third trimesters of pregnancy, as well as, the postpartum period.

Methods

The study protocol was approved by the Institutional Review Board at the Long Beach Memorial Medical Center. Study subjects were recruited from Long Beach Memorial Medical Center between February 2004 and March 2005. Normal, healthy pregnant women in the first trimester of pregnancy were offered participation in the study. Subjects with significant medical history including cardiovascular disease,

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hypertension, pulmonary airway disease, pulmonary hypertension, and symptoms of shortness of breath were excluded from the study. A total of 25 nonpregnant female subjects with comparable age and ethnicity without history of cardiovascular disease, pulmonary or systemic hypertension, pulmonary disease, or shortness of breath were studied as controls. The subjects and controls were not on any medications. In the study subjects, BNP levels were obtained in the first trimester (0–14 wk), second trimester (14–28 wk), third trimester (28–42 wk), and 4–6 wk postpartum. A single BNP value was obtained in the control group. The venous blood samples were obtained in the EDTA tube and BNP levels were determined by the fluorescence immunoassay kit (Triage, Biosite Inc, San Diego, Calif., USA). The test has been validated and used in previous publications.^{3,4,8–11} Systolic and diastolic blood pressures were recorded by an ambulatory sphygmomanometer in standard fashion after a 30 min period of rest in sitting position. Values for pregnant subjects were reported as the average of all measurements in the representative trimesters. For nonpregnant subjects, a single blood pressure measurement was taken.

Sample Size

Based on a presumed 50% difference in BNP values between pregnant and nonpregnant subjects, a sample size of 25 pregnant patients with complete longitudinal follow-up and 25 nonpregnant subjects were calculated as sufficient to satisfy power calculations ($\alpha = 0.05$ and $\beta = 0.20$) to disprove a null hypothesis that BNP levels do not differ in the pregnant and nonpregnant state.

Data Analysis

The baseline characteristics were reported as mean \pm standard deviation and were compared between the 2 groups using the Fisher exact test for categorical variables and the Student *t* test for continuous variables. As BNP levels were left censored due to the lower quantification limit of <10 pg/ml, the data were not normally distributed. Therefore, BNP levels were presented as medians and a Mann-Whitney U test was used to compare the 2 groups. A *p* value of 0.05 was considered statistically significant. SPSS 12 and SAS 9.1 software (SPSS Corporation, Chicago, Ill., USA) were used for statistical analyses.

Results

A total of 29 pregnant subjects with complete longitudinal BNP values during each trimester and postpartum period were studied. One patient was excluded due to the development of severe preeclampsia. A total of 25 nonpregnant women had a single BNP value analyzed for comparison. Baseline demographic characteristics are listed in Table 1. There were no significant differences among the cases and controls with respect to weight, diastolic blood pressure,

TABLE 1: Baseline characteristics

	Case (n = 29)	Control (n = 25)	p value
Age	26 \pm 6	29 \pm 6	0.07
Weight (lb)	161 \pm 44	149 \pm 34	0.30
BP Systolic	106 \pm 8	113 \pm 14	0.03
BP Diastolic	64 \pm 8	66 \pm 9	0.40
Ethnicity			0.77
Hispanic	23 (79%)	19 (76%)	
African American	1 (3%)	3 (12%)	
Caucasian	2 (8%)	2 (8%)	
Asian	3 (10%)	1 (4%)	

Age, weight, and blood pressure displayed as mean \pm standard deviation. Ethnicity listed based on actual frequency with percentages of total in parentheses.

and ethnicity. There was a small, but statistically significant difference in the age among the 2 groups that became nonsignificant when a single outlier in the control group (age 45) was removed. However, the BNP results were similar whether the analysis was done with or without this patient. Subjects remained normotensive throughout the pregnancy and postpartum.

The median (and range) of BNP levels during pregnancy were 19 (10–143) pg/ml versus 10 (10–37) pg/ml in the nonpregnant controls ($p = 0.003$). There, however were no statistically significant differences in the median BNP levels at various stages of pregnancy (Figure 1) first trimester 20 (10–115) pg/ml versus second trimester 18 (10–112) pg/ml ($p = 0.8$), second trimester 18 pg/ml versus third trimester 26 (10–143) pg/ml ($p = 0.06$), third trimester 26 pg/ml versus postpartum 18 (10–62) pg/ml ($p = 0.08$). These values are well below the pathologic levels for heart failure of ≥ 100 pg/ml.¹⁰ There were no significant differences between the BNP levels throughout the trimesters and the postpartum period. Pregnant BNP levels were approximately twice as high as the nonpregnant BNP levels.

Discussion

Our study is unique in evaluating longitudinal changes in BNP levels in normal pregnancies and the postpartum period in comparison to healthy nonpregnant controls. It demonstrates that pregnant BNP levels are approximately 2-fold higher than their nonpregnant counterparts, do not significantly fluctuate during pregnancy, and may serve as a reference range during pregnancy. The rise in BNP level is seen as early as the first trimester and remains

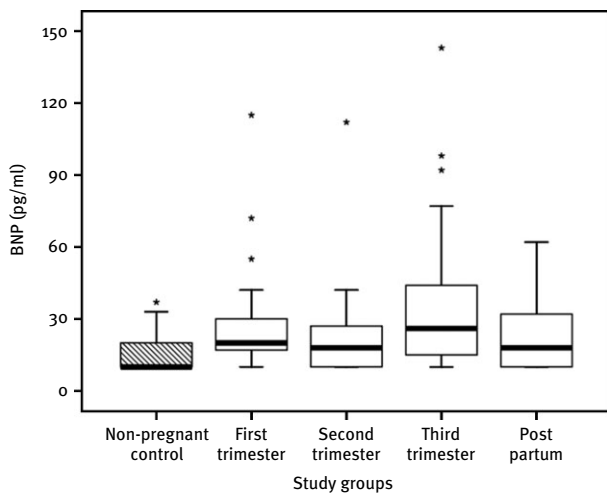


Figure 1:

elevated through the postpartum period. These findings are consistent with investigations that observed significant increases in cardiac output as early as 5 wk of gestation that persist up to 24 wk after delivery.^{12–14}

It is interesting to note that there are 3 outliers as shown in Figure 1. The BNP values were more than 100 pg/ml (1 in each trimester) on 3 separate study subjects. The highest level of BNP was noted to be 143 pg/ml in the third trimester. All 3 of these patients were asymptomatic with normal physical examination findings and their subsequent BNP values were within normal range. Their clinical presentation did not warrant further workup and they had an uncomplicated pregnancy and postpartum course.

The BNP levels have shown to be significantly elevated in patients with preeclampsia.¹⁵ In a cross-sectional study of 36 normal pregnant women and 17 women with preeclampsia, BNP levels were 8 times higher in the preeclampsia group.¹⁶ Resnik et al.¹ demonstrated elevated BNP levels in preeclampsia compared with normal pregnancies. Their findings correlate with our results; however, their data is limited by the small number of subjects in the third trimester (n = 15).

The diagnosis of heart failure during pregnancy may be challenging, as signs and symptoms of pregnancy can mimic heart failure. However, most patients presenting with acute shortness of breath have elevated BNP values.⁶ The results of the present study demonstrate that a normal pregnancy is associated with mild increases in BNP which is significantly lower than the values observed in patients with congestive heart failure.¹⁰ Therefore, determination of BNP levels during pregnancy should be useful in the follow-up of patients with heart disease during pregnancy and the postpartum period.

We acknowledge that our study population was primarily Hispanic due to our representative ethnicity at the

Long Beach Memorial Medical Center. Although the subjects were not evaluated by echocardiography or invasive hemodynamic monitoring, all were carefully evaluated by taking a history and by a physical examination for the presence of signs and symptoms of heart failure.

In conclusion, our study demonstrates a small, but statistically significant elevation of BNP levels during normal pregnancy, and should be taken into consideration when BNP levels are used for the diagnosis of heart failure during pregnancy.

References

- Sudoh T, Kangawa K, Minamino N, Matsuo H: A new natriuretic peptide in porcine brain. *Nature* 1988;332:78–81
- Wieczorek SJ, Wu AH, Christenson R, Krishnaswamy P, Gottlieb S, et al.: A rapid B-type natriuretic peptide assay accurately diagnoses left ventricular dysfunction and heart failure: A multicenter evaluation. *Am Heart J* 2002;144:834–839
- McCullough PA, Nowak RM, McCord J, Hollander JE, Herrmann HC, et al.: B-type natriuretic peptide and clinical judgment in emergency diagnosis of heart failure: Analysis from Breathing Not Properly (BNP) Multinational Study. *Circulation* 2002;106:416–422
- Morrison LK, Harrison A, Krishnaswamy P, Kazanegra R, Clopton P, et al.: Utility of a rapid B-natriuretic peptide assay in differentiating congestive heart failure from lung disease in patients presenting with dyspnea. *J Am Coll Cardiol* 2002;39:202–209
- Altintop L, Yordan T, Cander B, Findik S, Yilmaz O: An increase of BNP levels in massive pulmonary embolism and the reduction in response to the acute treatment. *Resuscitation* 2005;65:225–229
- Folk JJ, Lipari CW, Nosovitch JT, Silverman RK, Carlson RJ, et al.: Evaluating ventricular function with B-type natriuretic peptide in obstetric patients. *J Reprod Med* 2005;50:147–154
- Katz R, Karlner JS, Resnik R: Effects of a natural volume overload state (pregnancy) on left ventricular performance in normal human subjects. *Circulation* 1978;58:434–441
- Cabanes L, Richaud-Thiriez B, Fulla Y, Heloïre F, Vuilleumard C, et al.: Brain natriuretic peptide blood levels in the differential diagnosis of dyspnea. *Chest* 2001;120:2047–2050
- Resnik JL, Hong C, Resnik R, Kazanegra R, Beede J, et al.: Evaluation of B-type natriuretic peptide (BNP) levels in normal and preeclamptic women. *Am J Obstet Gynecol* 2005;193:450–454
- Maisel AS, Krishnaswamy P, Nowak RM, McCord J, Hollander JE, et al.: Rapid measurement of B-type natriuretic peptide in the emergency diagnosis of heart failure. *N Engl J Med* 2002;347:161–167
- Cheng V, Kazanegra R, Garcia A, Lenert L, Krishnaswamy P, 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;37:386–391
- Robson SC, Hunter S, Boys RJ, Dunlop W: Serial study of factors influencing changes in cardiac output during human pregnancy. *Am J Physiol* 1989;256:H1060–H1065
- Robson SC, Dunlop W, Hunter S: Haemodynamic changes during the early puerperium. *BMJ (Clin Res Ed)* 1987;294:1065
- Robson SC, Hunter S, Moore M, Dunlop W: Haemodynamic changes during the puerperium: A Doppler and M-mode echocardiographic study. *Br J Obstet Gynaecol* 1987;94:1028–1039
- Furuhashi N, Kimura H, Nagae H, Yajima A, Kimura C, et al.: Brain natriuretic peptide and atrial natriuretic peptide levels in normal pregnancy and preeclampsia. *Gynecol Obstet Invest* 1994;38:73–77
- Itoh H, Sagawa N, Mori T, Mukoyama M, Nakao K, et al.: Plasma brain natriuretic peptide level in pregnant women with pregnancy-induced hypertension. *Obstet Gynecol* 1993;82:71–77

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000 **Longitudinal Changes in the B-Type Natriuretic Peptide Levels in Normal Pregnancy and Postpartum**

Afshan Batool Hameed, MD, Kenneth Chan, MD, Mark Ghamsary, PhD, Uri Elkayam, MD

Normal levels of B-type natriuretic peptide (BNP) are not well established in pregnancy. Longitudinal BNP levels were obtained in 29 healthy pregnant women in each trimester and the postpartum period. These levels were compared with 25 nonpregnant controls. A total of 116 BNP values were obtained during pregnancy. The median (and range) BNP level during pregnancy was 19 (10–143) pg/ml versus 10 (10–37) pg/ml in the nonpregnant controls ($p = 0.003$). However, there were no statistically significant differences in the median BNP levels at various stages of pregnancy: first trimester 20 (10–115) pg/ml versus second trimester 18 (10–112) pg/ml ($p = 0.8$), second trimester 18 pg/ml versus third trimester 26 (10–143) pg/ml ($p = 0.06$), third trimester 26 pg/ml versus postpartum 18 (10–62) pg/ml ($p = 0.08$). In conclusion, pregnancy is associated with a small, but statistically significant increase in the BNP levels compared with nonpregnant women.

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