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Biomarkers

B-Type Natriuretic Peptide in Pregnant Women With Heart Disease

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Objectives The objectives of this study were to examine: 1) B-type natriuretic peptide (BNP) response to pregnancy in women with heart disease; and 2) the relationship between BNP levels and adverse maternal cardiac events during pregnancy.

Background Pregnancy imposes a hemodynamic stress on the heart. BNP might be a useful biomarker to assess the ability of the heart to adapt to the hemodynamic load of pregnancy.

Methods This was a prospective study of women with structural heart disease seen at our center. Serial clinical data and plasma BNP measurements were obtained during the first trimester, third trimester, and after delivery (>6 weeks).

Results Seventy-eight pregnant women were studied; 66 women with heart disease (age 31 ± 5 years), and 12 healthy women (age 33 ± 5 years). During pregnancy, the median peak BNP level was higher in women with heart disease compared with control subjects (median 79, interquartile range 51 to 152 pg/ml vs. median 35, interquartile range 21 to 43 pg/ml, $p < 0.001$). In women with heart disease, those with subaortic ventricular dysfunction had higher BNP levels ($p = 0.03$). A BNP >100 pg/ml was measured in all women with events during pregnancy ($n = 8$). Sixteen women had increased BNP levels during pregnancy but did not have clinical events. None of the women with BNP ≤100 pg/ml had events. BNP ≤100 pg/ml had a negative predictive value of 100% for identifying events during pregnancy.

Conclusions Many pregnant women with heart disease have increased BNP levels during pregnancy. Incorporating serial BNP levels in into clinical practice can be helpful, specifically in adjudicating suspected adverse cardiac events during pregnancy. (J Am Coll Cardiol 2010;56:1247–53) © 2010 by the American College of Cardiology Foundation

Pregnancy is characterized by a number of adaptive hemodynamic changes, including increases in plasma volume, heart rate, and cardiac output. The increased volume loading is thought to be a central mechanism underlying the pathogenesis of adverse maternal cardiac events during pregnancy. In the nonpregnant state, B-type natriuretic peptide (BNP) increases in response to these types of volume loading conditions and predicts the risk of adverse outcomes in a variety of cardiac conditions (1–6). Although clinical and echocardiographic predictors of adverse cardiac events during pregnancy have been identified (7,8), risk stratification is incomplete, and current risk stratification does not include evaluation of the adequacy of maternal cardiac adaptation during pregnancy. Furthermore, because the signs and symptoms of pregnancy can mimic those of cardiac decompensation, clinical recognition of heart disease is more difficult during pregnancy and, therefore, there might be a role for additional markers such as serum BNP levels to detect decompensation. The objectives of this study were: 1) to prospectively study BNP levels in pregnant women with structural heart diseases compared with those without heart disease; and 2) to determine the relationship between BNP levels and adverse cardiac events during pregnancy.

Methods

Study design. The study prospectively enrolled pregnant women with heart disease and healthy pregnant women (control subjects) receiving obstetric and cardiac care at our center. All women with structural congenital or acquired heart disease followed during pregnancy in our clinic between November 2006 and June 2008 were asked to

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Abbreviations and Acronyms

BNP = B-type natriuretic peptide

IQR = interquartile range

LV = left ventricular

LVEF = left ventricular ejection fraction

NYHA = New York Heart Association

participate in the study. Women with cardiac arrhythmias and structurally normal hearts were excluded. Women who presented late in pregnancy or at the time of labor and delivery were not included. Three women with heart disease declined participation. All women were followed throughout pregnancy and until 6 months after delivery in our clinic. The study received approval from the institutional ethics review board, and all participating subjects gave written informed consent.

Baseline and serial assessments. Clinical assessments and venous blood samples were obtained at the time of clinical visits. Baseline data were recorded at the time of the first antenatal visit (mean weeks gestation at the time of enrollment: 14 ± 5; 5 women were included that were first seen after the first trimester) and included: age; gestational age; gravity and parity status; details pertaining to cardiac lesions and comorbid conditions such as hypertension, renal disease, or other conditions that might affect natriuretic peptide levels; prior surgery/interventions; prior cardiac events; use of cigarettes; and presence of cyanosis (oxygen saturation <90%). When possible, the following serial measures were obtained in the first and third trimester and after delivery (>6 weeks after delivery): details pertaining to clinical status and adverse events, New York Heart Association (NYHA) functional class, medication use, 12-lead electrocardiograms, and BNP plasma levels.

Baseline echocardiographic measures were obtained at the time of the initial clinic visit. Left ventricular (LV) volumes at end diastole and end systole were measured by Simpson's biplane method according to American Society of Echocardiography guidelines, and ejection fraction was calculated (9). Left ventricular dilation was defined as a LV end-diastolic volume >104 ml (9). Systemic (subaortic) ventricular dysfunction was defined as a left ventricular ejection fraction (LVEF) <55% (9). In patients with transposition complexes, the presence of subaortic right ventricular dysfunction and dilation was determined qualitatively by an experienced echocardiographer blinded to the natriuretic peptide level. Subpulmonary ventricular size and function were assessed visually by an experienced echocardiographer and graded as normal, mild, moderate, or severe dilation or hypokinesis, respectively. Left atrial volume was determined by the area-length method (9). Quantitation of inflow or outflow obstruction, quantitation of valvular regurgitation, and estimates of systolic pulmonary artery pressure were performed by standard methods (10). Pulmonary artery hypertension was defined as a right ventricular systolic pressure >40 mm Hg in the absence of right ventricular outflow tract obstruction.

Risk assessment of adverse maternal cardiac events during pregnancy. A validated maternal cardiac risk score (Cardiac Disease in Pregnancy risk score) (7) was calculated for each woman by assigning 1 point to each of the following variables: cardiac events before pregnancy (arrhythmia, heart failure, or stroke/transient ischemic attack), baseline NYHA functional class >II or cyanosis (saturation <90%), systemic ventricular dysfunction, and left heart obstruction. Systemic ventricular systolic dysfunction was defined as an ejection fraction <40%. Left heart obstruction was defined as a mitral valve area <2 cm^2, an aortic valve area <1.5 cm^2, or a peak LV outflow tract gradient >30 mm Hg.

BNP measurements. Peripheral venous samples were obtained in the seated position. Blood was collected into a tube containing ethylenediaminetetraacetic acid and immediately placed on ice. The sample was centrifuged at 1,800 *g* for 10 min at 4°C, and isolated plasma was stored at −80°C. Analyses for BNP concentrations were performed within 2 months of sample acquisition. BNP was measured with a chemiluminescence immunoassay kit on the i2000 Architect platform (Fujirebio Diagnostics, Inc., Malvern, Pennsylvania). Our laboratory and others use BNP levels >100 pg/ml to define a value suggestive of heart failure (11). In all cases where BNP was elevated (>100 pg/ml), serum creatinine was measured to exclude renal dysfunction.

Outcomes. As previously reported, adverse maternal cardiac events were defined as any of the following: sustained symptomatic tachyarrhythmia or bradyarrhythmia requiring treatment, stroke, cardiac arrest or cardiac death, pulmonary edema (documented on chest radiograph or by crackles heard over more than one-third of posterior lung fields), a decline in NYHA functional class (≥2 classes) compared with baseline, or need for urgent invasive cardiac procedures during pregnancy or within 6 months after delivery (7).

Statistical analyses. All data analyses were performed with SPSS (version 17.0, SPSS Inc., Chicago, Illinois). Continuous variables are expressed as mean ± SD where indicated. Non-normal distributed variables, including BNP, were expressed as a median and interquartile range (IQR). The peak BNP was defined as the maximal level measured during the study period. Differences in clinical and echocardiographic variables between patients with and without BNP levels >100 pg/ml or adverse maternal cardiac events were determined with chi-square, Fisher exact, or Student *t* tests as appropriate. Because BNP values were non-normally distributed, Mann-Whitney *U* tests were used to compare levels in patients with and without adverse cardiac events. Similarly, a Friedman nonparametric test was used to compare BNP levels at different time-points during pregnancy. A p value <0.05 (2-tailed) was considered significant.

Results

In total, 78 pregnant women were included in the study: 66 with heart disease, and 12 healthy control subjects without heart disease. Apart from heart disease, baseline characteristics in women with and without heart disease were similar (mean age: 31 ± 5 years vs. 33 ± 5 years, p = 0.31; nulliparity: 42% vs. 42%, p = 0.96; smoking during preg-

nancy: 8% vs. 8%, p = 0.58). Baseline characteristics and echocardiographic characteristics in women with heart disease are outlined in Table 1. Of the 66 women with heart disease, 74% (n = 49) had congenital heart disease. None of the women had more than mild systemic ventricular dysfunction (ejection fraction >40% in all) at baseline, and none had cyanotic heart disease (oxygen saturation >90% in all).

Three women with heart disease and baseline measurements had spontaneous abortions (aortic regurgitation after repair of a sinus of Valsalva rupture [n = 1], stenotic bicuspid aortic valve [n = 1], Marfan syndrome with mitral regurgitation [n = 1]) and were not included in the outcome analyses. One woman without heart disease was recruited but developed preeclampsia and was also not included in any analyses, due to the reported association between preeclampsia and elevations in natriuretic peptides (12,13).

Table 1 Baseline Maternal Characteristics in Women With Heart Disease

Clinical characteristics	
Maternal age at study (mean ± SD) (yrs)	31 ± 5
Median gestational age at enrollment (weeks)	13
Nulliparity	28 (42%)
Smoking in pregnancy	5 (8%)
Prior cardiac events (heart failure, arrhythmia, TIA, stroke)	11 (17%)
New York Heart Association functional class	
I	54 (82%)
II	10 (15%)
>II	2 (3%)
Cardiac diagnosis	
Repaired tetralogy of Fallot or pulmonary valve disease	16 (24%)
Cardiomyopathy*	13 (20%)
Bicuspid aortic valve disease and/or aortic stenosis and/or aortic regurgitation and/or LV outflow tract obstruction	10 (15%)
Intracardiac shunt lesions	7 (11%)
Repaired coarctation of aorta	5 (8%)
Mitral valve prolapse and/or mitral regurgitation	4 (6%)
Ebstein's anomaly	3 (4%)
Rheumatic mitral stenosis	3 (4%)
Marfan syndrome	1 (2%)
Other	4 (6%)
Medications	
Cardiac medications at first visit	10 (15%)
Receiving anticoagulants	6 (9%)
Echocardiographic parameters	
Mean LVEF (%)	61 ± 7
Mean left atrial volume (ml)	64 ± 42
Left heart obstruction†	11 (17%)
Subaortic ventricular dilation (n = 57)‡	14 (25%)
Subaortic ventricular dysfunction§	15 (23%)
Subpulmonic ventricular dilation‖	16 (24%)
Subpulmonic ventricular dysfunction¶	8 (12%)
Pulmonary hypertension#	10 (15%)
Aortic or subaortic atrioventricular valve regurgitation ≥moderate	9 (14%)
Pulmonic or subpulmonic atrioventricular valve regurgitation ≥moderate	12 (18%)

n = 66, unless otherwise indicated. Values given are n (%), unless otherwise indicated. *Cardiomyopathy = dilated cardiomyopathy (n = 3), hypertrophic cardiomyopathy (n = 4), systolic dysfunction post-anthracycline therapy (n = 2), congenitally corrected transposition of the great arteries (n = 3), or previous peripartum cardiomyopathy with residual mild systolic dysfunction (n = 1). †Left heart obstruction = mitral valve area <2 cm^2 or aortic valve area <1.5 cm^2 or peak left ventricular (LV) outflow tract gradient >30 mm Hg. ‡Subaortic ventricular dilation = LV volume >104 ml, assessable in n = 57 patients. §Subaortic ventricular dysfunction = left ventricular ejection fraction (LVEF) <55% (in 3 patients with systemic [subaortic] right ventricle, size and function assessed visually). ‖Subpulmonic ventricular dilation = mild or greater dilation. ¶Subpulmonic ventricular dysfunction = mild or more hypokinesis. #Pulmonary hypertension = pulmonary artery systolic pressure >40 mm Hg.

TIA = transient ischemic attack.

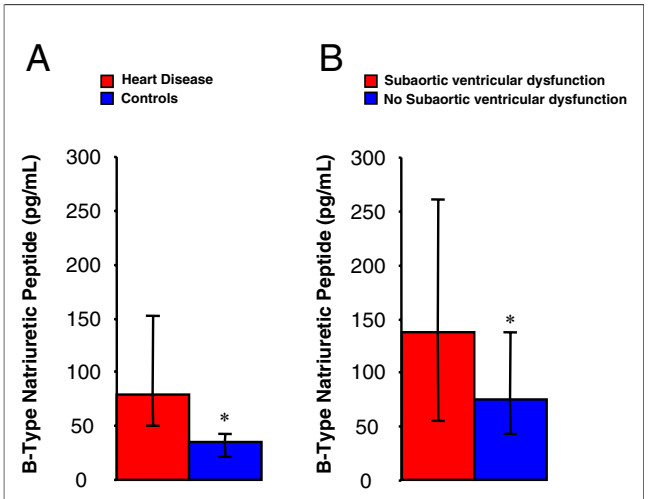

Figure 1 BNP Levels During Pregnancy

(A) Median peak plasma B-type natriuretic peptide (BNP) levels were increased in pregnant women with heart disease compared with healthy pregnant control subjects. **(B)** Median plasma BNP levels were significantly greater in women with heart disease who had subaortic ventricular dysfunction compared with women with heart disease without subaortic ventricular dysfunction. **Error bars** denote interquartile range. *p < 0.05.

BNP during pregnancy in women with and without heart disease. In all healthy control subjects, BNP levels were low and did not increase throughout pregnancy (peak median BNP: 35 pg/ml, IQR: 21 to 43 pg/ml). In women with heart disease, BNP levels (peak median BNP: 79 pg/ml, IQR: 51 to 152, p < 0.001) were higher than healthy control subjects (Fig. 1A). At all times during pregnancy and after delivery, BNP levels were significantly higher in women with heart disease compared with women without heart disease (p < 0.001). The range of BNP levels in women with heart disease was variable (range 15 to 1,425 pg/ml) but was highest in women with subaortic ventricular dysfunction (peak median BNP: 137 pg/ml, IQR: 55 to 261 pg/ml, p = 0.03) (Fig. 1B). Although subgroups were small, no differences in BNP levels were identified among women with other specific cardiac diagnostic subgroups.

Over the course of pregnancy and after delivery, BNP levels in a range suggestive of heart failure (BNP >100 pg/ml) were found in 38% (24 of 63) of women with heart disease; 10% (n = 6) of women with heart disease had BNP in this range in the first trimester, and this had increased to 26% (n = 15) by the third trimester during peak hemodynamic stress (Fig. 2). Five percent (3 of 66) of women in this study had a BNP level >500 pg/ml. None of the healthy

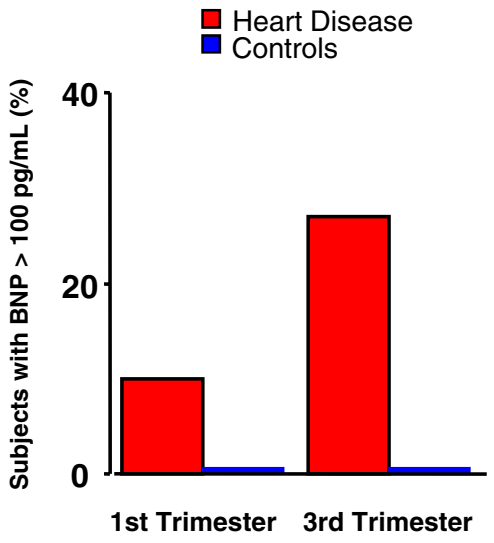

Figure 2 **Significant Elevations of BNP Levels Early and Late in Pregnancy**

Plasma B-type natriuretic peptide (BNP) levels in a range suggestive of heart failure (BNP >100 pg/ml) were found in 10% of women with heart disease by the first trimester and in 26% of women by the third trimester. None of the healthy control subjects had a BNP >100 pg/ml at any time.

control subjects had BNP elevations in the range suggestive of heart failure (BNP >100 pg/ml) at any time during pregnancy (Fig. 2). All women with BNP >100 had normal renal function as measured by the serum creatinine levels (mean creatinine 56 ± 11 μmol/l). Clinical parameters associated with BNP levels >100 pg/ml are shown in Table 2.

Adverse maternal cardiac events and their association with BNP levels. Adverse maternal cardiac events occurred in 13% (8 of 63) of women with heart disease (Table 3). There was 1 maternal death at 17 weeks gestation in a woman with hypertrophic cardiomyopathy. She had a family history of sudden death, and a prophylactic internal cardiac defibrillator was inserted before pregnancy. Early in pregnancy she had recurrent atrial arrhythmias and heart failure. She was clinically stable at the time her BNP level (BNP >1,425 pg/ml) was obtained. At 17 weeks gestation, she had a witnessed cardiac arrest. Three patients developed heart failure, 2 of whom had an associated deterioration in ventricular function after delivery. Three women developed arrhythmias: 2 had supraventricular tachycardias, and 1 had a combination of atrial fibrillation and recurrent nonsustained ventricular tachycardia. One woman with a mechanical systemic atrioventricular valve replacement developed valve thrombosis at 12 weeks gestation after being subtherapeutically anticoagulated. All 8 women with adverse cardiac events had significantly elevated peak BNP levels (median peak BNP 354, IQR 229 to 805 pg/ml). The increased BNP measurements predated or occurred at the time of decompensation in 88% (7 of 8) of women; increased BNP levels predated the adverse cardiac event in 4 women, and levels were drawn at the time of decompensation in 3 women. In 1 woman (a 31-year-old woman with bioprosthetic mitral valve replacement) the elevated BNP measurement was obtained after the first episode of supraventricular tachyarrhythmia.

The univariate predictors of maternal cardiac events in women with heart disease are outlined in Table 3. Compared with women with no maternal cardiac events, women with adverse cardiac events during pregnancy were more likely to have had a history of adverse cardiac events antedating pregnancy ($p = 0.003$) and lower baseline LVEF ($p = 0.006$) and were more likely to be taking cardiac medications ($p = 0.003$) or anticoagulants ($p = 0.002$) at baseline. Peak BNP levels were significantly higher in

Table 2 **Relationship Between Baseline Maternal Characteristics and Elevated BNP Levels in Pregnant Women With Heart Disease**

	BNP >100 pg/ml (n = 24)	BNP ≤100 pg/ml (n = 42)	p Value
Maternal age (mean ± SD) (yrs)	31 ± 6	31 ± 5	0.90
Prior cardiac events (heart failure, TIA, stroke)	7 (29%)	4 (10%)	0.09
Baseline New York Heart Association functional class >II	2 (8%)	0	0.14
Cardiac medications	10 (42%)	1 (3%)	0.001
Left heart obstruction*	5 (21%)	6 (14%)	0.74
Subaortic ventricular dilation (n = 57)†	7 (29%)	5 (12%)	0.10
Subaortic ventricular dysfunction‡	9 (38%)	6 (14%)	0.045
Subpulmonic ventricular dilation§	8 (33%)	8 (19%)	0.26
Subpulmonic ventricular dysfunction‖	5 (21%)	3 (7%)	0.24
Pulmonary hypertension¶	4 (17%)	6 (14%)	1.00
Aortic or subaortic atrioventricular valve regurgitation ≥moderate	5 (21%)	3 (7%)	0.24
Pulmonic or subpulmonic atrioventricular valve regurgitation ≥moderate	4 (17%)	8 (19%)	1.00

*Left heart obstruction = mitral valve area <2 cm^2 or aortic valve area <1.5 cm^2 or peak LV outflow tract gradient >30 mm Hg. †Subaortic ventricular dilation = LV volume >104 ml, assessable in n = 57 patients. ‡Subaortic ventricular dysfunction = LVEF <55% (in 3 patients with systemic [subaortic] right ventricle, size and function assessed visually). §Subpulmonic ventricular dilation = mild or greater dilation. ‖Subpulmonic ventricular dysfunction = mild or more hypokinesis. ¶Pulmonary hypertension = pulmonary artery systolic pressure >40 mm Hg.
BNP = B-type natriuretic peptide; TIA = transient ischemic attack.

Table 3 Predictors of Adverse Maternal Cardiac Events in Women With Heart Disease

	Adverse Maternal Cardiac Events (n = 8)	No Adverse Maternal Cardiac Events (n = 55)	p Value
Maternal age, mean ± SD (yrs)	31 ± 7	31 ± 5	0.86
Cardiac event before pregnancy	5 (63%)	6 (11%)	0.003
New York Heart Association functional class >2	1 (13%)	1 (2%)	0.11
Use of cardiac medications	5 (63%)	6 (11%)	0.003
Use of anticoagulants	4 (63%)	2 (4%)	0.002
Subaortic ventricular dysfunction*	4 (50%)	11 (20%)	0.08
Subaortic ventricular dilation (n = 57)†	3/6 (50%)	9/49 (18%)	0.11
Left heart obstruction‡	2 (25%)	9 (16%)	0.62
Aortic or subaortic atrioventricular valve regurgitation ≥moderate	1 (13%)	7 (13%)	1.0
Pulmonic or subpulmonic atrioventricular valve regurgitation ≥moderate	2 (25%)	10 (18%)	0.64
Pulmonary arterial hypertension§	3/6 (50%)	7/45 (16%)	0.08
LVEF on initial echocardiogram (%)	54 ± 4	62 ± 7	0.005
BNP max (pg/ml), median (IQR)	354, (229–805)	73, (43–131)	<0.001
Maximum BNP >100 pg/ml	8 (100%)	16 (19%)	<0.001
Initial BNP >100 pg/ml	4 (50%)	2 (4%)	0.002

*Subaortic ventricular dysfunction = LVEF <55% (in 3 patients with systemic [subaortic] right ventricle, size and function assessed visually). †Subaortic ventricular dilation = LV volume >104 ml, assessable in 57 patients. ‡Left heart obstruction = mitral valve area <2 cm^2 or aortic valve area <1.5 cm^2 or peak LV outflow tract gradient >30 mm Hg. §Pulmonary hypertension = pulmonary artery systolic pressure >40 mm Hg.

IQR = interquartile range; other abbreviations as in Table 1.

women with cardiac events during pregnancy ($p < 0.001$). A peak BNP >100 pg/ml occurred in 100% (8 of 8) of women with adverse maternal cardiac events, compared with 19% (16 of 55) of women without events ($p < 0.001$). A BNP >100 pg/ml had, on the basis of this cohort, a negative predictive value of 100% and a sensitivity and specificity of identifying women with maternal cardiac event during pregnancy of 100% and 70%, respectively.

Adverse maternal cardiac events during pregnancy according to the maternal cardiac risk score (Cardiac Disease in Pregnancy risk score) were 2%, 30%, and 50% for women with 0 (n = 41), 1 (n = 20), and >1 (n = 2) risk scores, respectively. Because there were only 2 women with risk scores >1, it was not possible to determine the incremental value of high BNP levels for this subgroup. However, estimates of maternal adverse event rates in women with a risk score of 0 or 1 differed when BNP levels were incorporated into risk estimates. In women with risk scores of 0 (low risk for adverse cardiac events), the rates of adverse maternal cardiac events during pregnancy were 0 in women with BNP levels ≤100 pg/ml and 8% in women with BNP levels >100 pg/ml. In women with risk scores of 1 (intermediate risk for adverse cardiac events), rates of adverse cardiac events were 0 in women with BNP levels ≤100 pg/ml and 60% in women with BNP >100 pg/ml ($p = 0.03$). However, elevated BNP level (BNP >100 pg/ml) did not predate the adverse cardiac event in all women, and therefore the role of BNP in predicting adverse events could not be determined.

Adverse fetal/neonatal and obstetric events in women with heart disease. Adverse fetal and/or neonatal events occurred in 9 pregnancies: 2 fetal deaths, 4 premature births (<37 weeks gestation, 2 of which had associated respiratory distress), and 3 low birth-weight (<2,500 g) births. Peak BNP levels were not associated with adverse fetal and/or neonatal events ($p = 0.77$). Pregnancy-induced hypertension (blood pressure increase of systolic ≥30 mm Hg and/or diastolic ≥15 mm Hg) was observed in 6 pregnancies. There were no occurrences of after-delivery hemorrhage. The BNP levels were similar ($p = 0.25$) in women with or without pregnancy-induced hypertension.

Discussion

This is the first study to examine BNP levels in pregnant women with heart disease. During pregnancy, many women with heart disease had increased BNP levels. Normal levels of BNP during pregnancy in women with heart disease were an important finding, predicting a low risk for adverse maternal cardiac events. There is a subset of women with elevated BNP levels in the range typically found in patients with clinical heart failure who did not show clinical decompensation during pregnancy; the significance of this finding is presently unknown.

We found that, similar to findings of previous studies (12,14,15), despite the hemodynamic load of pregnancy, most healthy pregnant women have low and stable concentrations of BNP throughout pregnancy and after delivery. This suggests that healthy women are, in general, able to compensate for the increased volume load that occurs during pregnancy (16). By comparison, women with heart disease have higher natriuretic peptide levels throughout pregnancy compared with nonpregnant women, suggesting perhaps an impaired adaptation to the hemodynamic load of pregnancy.

Elevations in natriuretic peptides have been shown to occur in patients with heart disease in other conditions that resemble pregnancy. For instance, hemodynamic changes of

pregnancy have some similarities to the changes seen with exercise. In nonpregnant patients with heart disease (congenital and acquired), higher BNP levels at rest are correlated with latent ventricular impairment only evident during exercise (17,18). In these patients, increased baseline resting natriuretic peptide levels might reflect subclinical abnormalities that become clinically manifest only with the stress of exercise. In women with preeclampsia, natriuretic BNP levels are increased compared with healthy pregnant women (13,14). This is paralleled by increased LV wall mass and LV chamber dimensions (12). Furthermore, crystalloid infusion in women with preeclampsia leads to further rises in atrial natriuretic peptide levels (19,20), a change not found in healthy pregnant women, suggesting that women with preeclampsia do not adequately compensate in response to volume challenges. A similar phenomenon might be present in women with underlying heart conditions who have less hemodynamic reserve and less ability to accommodate to the hemodynamic changes of pregnancy.

BNP levels in the range suggestive of heart failure were found in 38% of women with heart disease during pregnancy, including many who did not have clinical evidence of cardiac decompensation. Although not known, this abnormal response could be a marker of limited cardiac reserve with prognostic significance late after pregnancy. This group requires further study.

Clinically, women with ventricular dysfunction represent a group at high risk for cardiac complications during pregnancy. Not unexpectedly, BNP was highest during pregnancy in this group of women, in both those with and without clinical events. Elevations in BNP during pregnancy suggest that volume overload and subsequent ventricular dilation might explain, at least in part, the mechanism responsible for clinical deterioration. There are some data to suggest that pregnancy adversely affects the natural course of the disease in women with LV systolic function (21) and might have late effects on the function of the ventricles (22,23). Therefore, this group of women, specifically those with abnormally high BNP levels during pregnancy, should have continued surveillance after pregnancy.

Early identification of deterioration in status, before acute events, is particularly important in pregnant women with heart disease, because acute conditions are often dangerous for both the mother and the fetus, and treatment options might be constrained because of the pregnant state. Because early detection is important, studies have focused on risk stratification with antenatal echocardiographic and clinical variables (7,8); however, no studies have examined the utility of biomarkers or other measures with the ability to assess the adaptation of the heart to the hemodynamic load of pregnancy. We found that serial BNP measurements during pregnancy incorporated into traditional antenatal risk assessment were able to improve risk stratification in some cases. More importantly, BNP levels ≤100 pg/ml had a very high negative predictive value for adverse maternal cardiac events. Therefore, BNP could be potentially useful when confusion exists regarding the clinical cardiac status in pregnant women with cardiac disease.

Study limitations. This study investigated serial changes in BNP levels in women with various structural cardiac diseases. Because of the relatively small number of women in each of the cardiac diagnostic subgroups, difference in natriuretic peptide response to pregnancy between women with differing cardiac lesions could not be determined. We did not assess women with arrhythmias and structurally normal hearts, a group of patients who commonly present in pregnancy. In previous work from our group, poor functional class (NYHA functional class >2), cyanosis, and impaired ventricular function (LVEF <40%) were clinical risk factors for predicting maternal cardiac events (7). However, we were unable to determine the independent role of BNP in predicting adverse maternal cardiac outcomes during pregnancy. Perhaps, with a larger sample size, more frequent BNP measurement during pregnancy, or with the use of a range of BNP thresholds, the positive predictive value of BNP to identify high-risk women could be determined. Furthermore, although our laboratory and others use BNP levels >100 pg/ml to define a value suggestive of heart failure, there is debate regarding the optimal BNP threshold to diagnose heart failure. With a larger sample size, other BNP thresholds might prove to be clinically important in this cohort.

Conclusions

BNP levels are elevated in many women with heart disease during pregnancy. Normal levels of BNP during pregnancy in women with heart disease are an important finding and predict low risk for adverse maternal cardiac events. Conversely, high levels can be associated with adverse maternal cardiac events. There exists a subgroup of pregnant women with heart disease who have elevated levels of natriuretic peptide levels during pregnancy but do not have clinical events. The significance of this finding requires further study.

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