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NT-proBNP: When is it useful in Obstetric Medicine?

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Abstract

Pregnancy, viewed as a stress test of the haemodynamic system, may unmask underlying cardiac disease. Pregnancy may also induce de novo cardiac disease. N-terminal *pro* brain-type natriuretic peptide (NT-proBNP) is a useful biomarker in all clinical conditions in which the ventricle is stressed and especially stretched in the general population. In hypertensive diseases of pregnancy, increased levels of NT-proBNP in preeclampsia are associated with increased cardiac filling pressures and diastolic dysfunction. Increased levels of NT-proBNP in pregnant women with known cardiac disease may lead to earlier diagnosis of impending heart failure. Similarly, elevated levels of NT-proBNP assist with the diagnosis of peripartum cardiomyopathy and are increasingly used in follow-up. Women with known congenital heart disease who are pregnant can be screened for risk of cardiac events such as heart failure by the use of NT-proBNP levels. There is a paucity of data in pregnancy with the use of NT-proBNP and more research is needed.

Keywords

Cardiac, general medicine, maternal–fetal medicine

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Introduction

Hemodynamic changes occurring during pregnancy may increase the stress on the maternal cardiovascular system in women with underlying disease or unmask cardiovascular pathology in previously healthy women. Additionally, several symptoms that may occur in normal pregnancy mimic those of early cardiac disease and this may pose a diagnostic challenge to the treating physician. Cardiac biomarkers have been investigated extensively in the non-pregnant population and are used to aid in the diagnosis of heart failure and monitor disease progression.[1] The diagnostic value of biomarkers in pregnancy-associated conditions associated with cardiac stress, such as preeclampsia, gestational hypertension and gestational diabetes, are not well established.

The natriuretic peptides (NPs), atrial NP (ANP), brain fraction (BNP) and endothelial NP (CNP) are released from the heart and vasculature into the systemic circulation in response to volume or pressure overload. Intracellular processing produces the pro-peptide proBNP which is subsequently cleaved into the active peptide BNP and the biologically inert N-terminal *pro* brain-type natriuretic peptide (NT-proBNP) and both are released into plasma. NPs are secreted in response to cardiac ventricular stretch and stress, implying pressure and volume overload of the ventricles.[2] Neprilysin (NEP) is the main enzyme that degrades the biologically active cardiac NPs ANP and BNP but it does not inactivate NT-proBNP.[3] The clinical performance of BNP and NT-proBNP as biomarkers is similar.[2]

NPs can be considered from two viewpoints: as a compensatory mechanism in heart failure (or a ventricle in stress) and as a biomarker with specific clinical uses. As a compensatory mechanism, it is seen as a ''good guy'' because it is associated with natriuresis, diuresis, vasodilatation, inhibition of the renin-angiotensin-aldosterone system (RAAS) and as an inhibitor of ventricular remodeling. These ''good'' actions are in opposition to the RAAS which are seen as the ''bad guys'' in heart failure. The clinical use of measuring NPs, including NT-proBNP includes diagnosing heart failure, as a prognostic marker, as a marker for the response to therapy in heart failure or as a screening biomarker in high-risk patients.

In a systematic review of BNP and NT-proBNP in the management of heart failure, both biomarkers had a good diagnostic performance in ruling out heart failure but a lesser performance in ruling in heart failure compared to the reference standard of global assessment using patients' medical records.[4] Furthermore, there was no evidence to suggest that BNP should be favoured over NT-proBNP or vice versa. Comorbidities including age, renal function and body mass index ((BMI) for BNP only) were found to have important effects on the performance of the tests.

NT-proBNP levels

NT-proBNP values must be viewed as a continuous variable with ''normal'' values below 70 pg/ml to rule out the diagnosis of heart failure as a cause in acute dyspnoea in patients presenting to the emergency room. A value above 450 pg/ml, when measured in the acutely dyspnoeic patient with uncertain diagnosis, may aid in the diagnosis of heart failure in the age-group below 50 years.[5] In the age range 50–75 years, the value of 900 pg/ml, and in people older than 75 years, a value of 1800 pg/ml is used. For BNP, there is only one cut-off value of 100 pg/ml.[5] In the ''grey zone'' of NT-proBNP values between 70 and 450 pg/ml, there are a number of possible causes for elevated levels: heart failure, acute coronary syndrome, atrial fibrillation, right heart failure due to acute pulmonary embolism, cor pulmonale secondary to chronic lung disease such as COPD and other non-cardiac causes such as acute pneumonia, pulmonary hypertension and renal disease.[4] It is advisable to use these biomarkers in conjunction with the clinical picture as a support tool to aid in the diagnosis of heart failure.

NT-proBNP levels in non-pregnant females

Sex is an important determinant of circulating levels of many different biomarkers suggesting that sex-based cut points should be considered

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for these biomarkers. The Dallas Heart Study is one of the largest and most comprehensive comparisons of biomarkers from a population free of cardiovascular disease. In the Dallas Heart Study of 3439 healthy people, 56% were women; the NT-proBNP levels in women were 39 pg/ml (95% CI: 20–75) which was higher than in normal in men (17 pg/ml).[6]

NT-proBNP levels in pregnancy

The clinical use of NT-proBNP has not been studied extensively in pregnancy. Pregnancy is a physiological stress test for the cardiovascular system because of the 45–50% increase in intravascular volume, an increase of about 43% in cardiac output associated with an increase in left ventricular end diastolic dimension.[7] The levels of NT-proBNP are therefore usually higher in pregnancy than in the non-pregnant state. An elevated NT-proBNP level in pregnancy may indicate subclinical, compromised cardiac function. In a small study of 88 pregnant women (mean age: 30.5 years and mean gestational age: 39.5 (95% CI: 35–42) weeks), NT-proBNP levels were 81 ng/ml before delivery and 165 ng/ml after delivery. Levels of up to 700 ng/ml have been reported in other studies.[8]

There is no association between levels of NT-proBNP and parity, duration of labour or birth weight of offspring, but a study by Lev-Sagie et al.[9] reported an increase in levels in women receiving epidural, pethidine or inhaled nitrous oxide. Diagnostic roles of NT-proBNP measurement in pregnancy may include: evaluation of hypertensive disorders in pregnancy, evaluating women with symptoms and signs of heart failure (symptoms and signs which are common in a normal pregnancy), monitoring of pregnant women with known and established cardiac disease and screening for left ventricular dysfunction.[10]

NT-proBNP levels in hypertensive disease of pregnancy

The role of cardiac biomarkers has been most widely investigated in preeclampsia. NT-proBNP has been tested as a predictor for the development of preeclampsia in high-risk pregnant women but NT-proBNP is not currently recommended as a screening tool for preeclampsia as it has not been shown to accurately predict the development of preeclampsia.[11–13] Preeclampsia, once established, as opposed to gestational hypertension and normotensive pregnancy, is associated with elevated levels of NT-proBNP which increases further with increasing severity of preeclampsia. The elevated levels are considered to reflect ventricular stress rather than actual damage or dysfunction of the myocardium.[13] There are limitations to these studies as most are cross-sectional, and there is very limited data on an association between longitudinal NT-proBNP levels and progression to severe preeclampsia.

In one small study, 35 preeclamptic women and 30 gestational- and age-matched normotensive, pregnant women were evaluated by echocardiography and NT-proBNP levels.[14] There were significant differences between the two groups with regard to echo findings and levels of NT-proBNP which persisted at three to six months postpartum. Significant differences in left ventricular and left atrial dimensions and function between the groups were found. A higher septal and lateral E/E′ ratio (E = early transmitral diastolic flow velocity and E′ = early diastolic myocardial velocity) ($P < 0.0001$, 0.0008) and higher levels of NT-pro-BNP ($P < 0.0001$) were seen in the preeclamptic group both during pregnancy and at follow-up.[14] Women with early onset preeclampsia (n = 8, 23%) requiring delivery before 34 weeks had higher NT-proBNP levels than women who developed late onset preeclampsia. Left ventricular mass index was independently associated with elevated levels of NT-proBNP in both the preeclamptic and normotensive groups of women. A systematic review of B-type NPs in preeclamptic women found that elevated systemic vascular resistance and cardiac filling pressures, echocardiographic features of left ventricular diastolic dysfunction and depression of cardiac output in pre-eclamptic patients were associated with elevated NT-proBNP levels.[15] No specific NT-pro-BNP level was mentioned in the systematic review as the different studies had different laboratory cut-off limits. Testing of NT-proBNP levels in pregnant women may therefore aid in the early diagnosis and management of potential underlying cardiovascular compromise. This may become more relevant, as in the past few decades there have been more pregnant women with advanced maternal age, concomitant comorbidities, lower cardiac reserve and congenital cardiac disease survivors.[10]

Cardiac disease in pregnancy

The utility of NP testing (including NT-proBNP) in pregnant women with known cardiac disease is of great potential.[16] Cardiac failure in pregnant women may develop in two different contexts: heart failure developing in pregnancy in women with documented cardiac disease, while the second is the development of heart failure without pre-existing cardiac disease such as peripartum cardiomyopathy (PPCM).[17] The risk of developing heart failure in pregnancy in women with known cardiac disease varies considerably depending on the nature of the cardiac disease but the prevalence can be between 13% and 16% and it is in this group that NT-proBNP testing may aid in earlier diagnosis of impending heart failure.

A prospective study of BNP levels during pregnancy included 66 women with heart disease and 12 healthy controls. During pregnancy, the mean peak level of BNP was higher in women with heart disease as compared to controls (median: 79 vs. 35 pg/ml). None of the women with a BNP level below 100 pg/ml had an adverse cardiovascular event.[18]

NT-proBNP has been studied as a predictive marker for developing cardiovascular events during pregnancy in women with pre-existing heart disease. In the ZAHARA study, NT-proBNP values of <128 pg/ml at 20 weeks' gestation had a 96.9% negative predictive value, while levels > 128 pg/ml were independently predictive of adverse cardiovascular events.[19] Therefore, the value of NT-proBNP levels in women with congenital heart disease is its high negative predictive value. The positive predictive value of 50% of elevated NP levels in this study was poor.

NT-proBNP has an important prognostic role in women diagnosed with PPCM. NT-proBNP is significantly higher in women with acute PPCM compared to matched healthy postpartum women.[20] Forster et al.[20] found that women who experience some degree of LVEF improvement at six months postpartum had significantly lower NT-proBNP levels at incident presentation than women who did not experience left ventricular ejection fraction (LVEF) improvement. High levels of NT-proBNP at incident presentation are a better predictor of future prognosis than incident LVEF.[21] A BNP value exceeding 1860 pg/ml was found to independently predict persistent left ventricular dysfunction.

NT-proBNP and other gestational conditions

There are limited data on levels of NT-proBNP in women with gestational diabetes. In a study of 81 women with gestational diabetes and 35 control subjects, there was no significant difference in serum levels of NT-proBNP between the two groups, and NT-proBNP is therefore is not used for disease prediction or progression.[22]

Several biomarkers, mainly placenta and fetal hormones, have been studied to assist in the diagnosis of placenta accreta spectrum. In a study of 54 women with placenta praevia, troponin I and proBNP levels were higher than in controls and proBNP could predict placenta accreta.[23]

Conclusions

1. The clinical utility of NP testing (including NT-proBNP) has been tested in various clinical conditions, but their use in pregnancy and pregnancy-related cardiac conditions has not been studied extensively.
2. Heart failure in pregnancy is especially difficult to diagnose and manage. Making a secure and prompt diagnosis is critical and NT-proBNP aids in this process.
3. The use of NT-proBNP testing as a diagnostic biomarker and a predictor of adverse cardiac events as well as its role as a marker of therapeutic response requires further research.
4. This is rapidly evolving field and may prove very valuable in the diagnosis and management of cardiovascular disease in pregnancy and postpartum.

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