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. 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 is associated with increased cardiac filling pressures and diastolic dysfunction. Increased levels of NT-proBNP in pregnant women with known cardiac disease often 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.

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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. 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 (NP), atrial NP (ANP), brain fraction (BNP) and endothelial NP (CNP) are released in response to volume or pressure overload in humans. Intracellular processing produces the pro-peptide proBNP which is subsequently cleaved into the active peptide BNP and the biologically inert NT-proBNP. NT-proBNP is used in clinical medicine as it does not breakdown while the other biomarkers metabolise. The clinical performance of BNP and NT-proBNP are similar.(2) Natriuretic peptides 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 biological active cardiac natriuretic peptides ANP and BNP but it does not inactivate NT-proBNP. (3) Natriuretic peptides can be considered from 2 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 NP's, including NT-proBNP can be to diagnose 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.

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 450pg/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. In the age 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 1 cut-off value of 100 pg/ml. 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 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 3 439 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).(5)

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.(6) 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 a 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. (7)

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 reported an increase in levels in women receiving epidural, pethidine or inhaled nitrous oxide. (8) 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. (9)

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 of 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. (10,11,12) 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 more to reflect ventricular stress than actual damage or dysfunction of the myocardium. (12) 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 eclampsia. A study of 35 pre-eclamptic women and 30 gestational-matched and age-matched normotensive pregnant women were evaluated by echocardiography and NT-proBNP levels. (13) There were significant differences between the 2 groups with regard to echo findings and elevated levels of NT-proBNP in the pre-eclamptic group which persisted at 3-6 months postpartum. Women with early onset preeclampsia 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 pre-eclamptic and normotensive groups of women. A systematic review of B-type natriuretic peptides in pre-eclamptic 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. (14) 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.(9)

Cardiac disease in pregnancy

The utility of natriuretic peptide testing (including NT-proBNP) in pregnant women with known cardiac disease is of great potential (15) Cardiac failure in pregnant women may develop in 2 different contexts: heart failure developing in pregnancy in women with documented cardiac disease while the second is the development of heart failure without underlying cardiac disease such as peripartum cardiomyopathy (PPCM). (16) 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 this group that NT-proBNP testing may aid in earlier diagnosis of impending heart failure.

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. (17) Forster et al found that women who experience some degree of LVEF improvement at 6 months postpartum had significantly lower NT-proBNP levels at incident presentation than women who did not experience left ventricular ejection fraction (LVEF) improvement. (17) High levels of NT-proBNP at incident presentation are a better predictor of future prognosis than incident LVEF. (18) A BNP value exceeding 1860pg/mL was found to independently predict persistent left ventricular dysfunction.

A prospective study of 78 pregnant women were studied with BNP levels,66 with heart disease and 12 healthy women. During pregnancy, the mean peak level of BNP was higher in women with heart disease as compared to healthy women(median 79 vs. 35). None of the women with a BNP level of below 100 pg/ml had a cardiovascular event.(19)

Women with congenital heart disease are prone to developing cardiovascular events during pregnancy. In the ZAHARA study, NT-proBNP values of < 128pg/mL at 20 weeks gestation had a 96.9% negative predictive value while levels > 128pg/mL were independently predictive of adverse cardiovascular events.(20) Therefore the value of NT-proBNP levels in women with congenital heart disease is its high negative predictive value. The positive predictive value of elevated NP levels is poor and not necessarily indicative of an adverse cardiovascular event.

Gestational diabetes

There is 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 2 groups and NT-proBNP is therefore is not used for disease prediction or progression.(20)

Placenta accreta spectrum

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. (21)

Conclusions

1. The clinical utility of natriuretic peptide testing (including NT-proBNP) is widely available and 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 as standard medications (Renin-Angiotensin-Aldosterone System blockers) are contra-indicated in pregnancy as they may adversely affect the fetus. Making a secure diagnosis is critical and NT-proBNP aids in this process.
3. The use of NT-proBNP testing as a diagnostic utility, as a predictor of adverse cardiac events and possibly as a marker of therapeutic response still needs much more evidence from trials in pregnancy.
4. This is rapidly evolving field with new literature being published on a regular basis.

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