e-ISSN: 0975-1556, p-ISSN:2820-2643

Available online on www.ijpcr.com

International Journal of Pharmaceutical and Clinical Research 2022; 14(7); 463-470

Original Research Article

A Study to Assess the Role of NT-PROBNP as a Prognostic Marker in Pregnant Women with Heart Disease

Hemant Narayan Ray[1], Prattay Guha Sarkar[2], Nishu Kumar[3], Dhananjay Kumar[4]

[1]Head of Department, Department of Cardiology, Rajendra Institute of Medical Sciences, Ranchi

[2]Assistant Professor, Department of Cardiology, Rajendra Institute of Medical Sciences, Ranchi

[3]DM Resident, Department of Cardiology, Rajendra Institute of Medical Sciences, Ranchi

[4]Assistant Professor, Department of Cardiology, Narayan Medical College, Sasaram, Bihar

Received: 15-04-2022 / Revised: 20-05-2022 / Accepted: 05-06-2022
Corresponding author: Dr Nishu Kumar
Conflict of interest: Nil

Abstract

Background: The signs and symptoms of pregnancy can be very similar to the signs and symptoms of cardiac decompensation, the clinical diagnosis of cardiac disease in pregnant patients is complicated even more; as a result, additional tests, such as serum NT prob-BNP levels, may be useful diagnostic markers to detect adverse events during pregnancy. When ventricular volume and pressure rise, the neurohormone NT pro-BNP is released. It has a high sensitivity and specificity for detecting heart disease that is unaffected by subjective variables.

Aim and Objectives: To assess the performance of NT-proBNP as diagnostic tools for cardiac complications, including heart failure and pre-eclampsia, in pregnant women and recently delivered women.

Material and Methods: This study prospectively enrolled 50 pregnant women with heart disease and 50 pregnant women without heart disease receiving care at RIMS. All pregnant women with congenital or acquired cardiac lesions admitted from Jan 2020 to June 2021 were eligible for enrolment. All women were followed throughout pregnancy and until 3 days after delivery.

Results: Median age of both cases and control was 26 years. 44 % of cases (n=22) and 42% of control (n=21) were of gravida 2, with median gravida of 2 in both cases and control. There was significant association between level of NT-proBNP in all the three trimester and requirement for increased dose of diuretics, hospitalization for heart failure, pulmonary arterysystolic pressure, severity of tricuspid regurgitation, NYHA class, DCMP and requirement for LSCS.

Conclusions: There was significant association between level of NT-proBNP in all the three trimester and requirement for increased dose of diuretics, hospitalization for heart failure, pulmonary arterysystolic pressure, severity of tricuspid regurgitation, and all NYHA class.

Keywords: NT-proBNP, Heart disease, DCMP, LSCS

Background

The physiological adaptations of pregnancy make a cardiac patient more prone to decompensation. Pregnancy is associated with a variety of hemodynamic changes, including increases in cardiac output, plasma volume (by 50%), and heart rate. Excessive volume loading is frequently cited as a key pathogenic mechanism that predisposes pregnant women to adverse outcomes.

Heart disease causes complications in around 1% of all pregnancies [1-6], and it is currently the main cause of indirect maternal fatalities, accounting for 20.5 percent of all cases [5,6]. The most common cardiac disorders diagnosed in women of reproductive age are rheumatic and congenital heart diseases [7]. The most common cause of maternal death is heart disease, which is second only to suicide [4]. Although the frequency of pregnancy complications due to rheumatic heart disease (RHD) has reduced in affluent nations [1,8], rheumatic heart disease remains a major source of maternal morbidity and death in poor countries [1,9].

The majority of women with heart problems may successfully carry a child without severe difficulties [1,3,7,10]. Pregnancy, on the other hand, might produce specific therapeutic issues in some patients, potentially jeopardising the mother and foetal well-being and life. Maternal and neonatal mortality and morbidity in pregnancies complicated by cardiac diseases vary depending on the kind of condition, the patient's functional level, and the pregnancy's difficulties [9,10]. Cardiac failure, pulmonary oedema, shock (cardiogenic), arrhythmia, hospitalisation, and even maternal death are all possible outcomes of maternal morbidity.

Many women in impoverished nations become pregnant without seeking therapeutic intervention for cardiac abnormalities, and many are first identified with heart disease during pregnancy [1].

The circulatory alterations of pregnancy may have negative effects in the presence of maternal heart disease, including death of the mother or foetus [11]. Despite the discovery of clinical predictors of cardiac problems during pregnancy and the use of diagnostic techniques like echocardiography [12,13], current risk stratification is inadequate because it does not include maternal heart adequacy and adaptability throughout pregnancy. Furthermore, because the signs and symptoms of pregnancy can be very similar to the signs and symptoms of cardiac decompensation, the clinical diagnosis of cardiac disease in pregnant patients is complicated even more; as a result, additional tests, such as serum NT prob-BNP levels, may be useful diagnostic markers to detect adverse events during pregnancy. When ventricular volume and pressure rise, the neurohormone NT pro-BNP is released [14]. It has a high sensitivity and specificity for detecting heart disease that is unaffected by subjective variables. Studies on the appearance and function of NT pro-BNP in heart disease have consistently shown that it is significantly featured in heart failure assessments in recent years [15]. NTpro - BNP levels have been shown to be useful as a biomarker in the early detection of clinical worsening in pregnant women undergoing heart disease intervention in emergency situations.

The main purpose of this study was to assess the performance of NT-proBNP as diagnostic tools for cardiac complications, including heart failure and pre-eclampsia, in pregnant women

Material and Methods

This study prospectively enrolled 50 pregnant women with heart disease and 50 pregnant women without heart disease receiving care at RIMS. All pregnant women with congenital or acquired cardiac lesions admitted from Jan 2020 to June 2021 were eligible for enrolment. All

women were followed throughout pregnancy and until 3 days after delivery.

Sample size was calculated on the basis of monthly visit of pregnant cardiac patients in Department of Cardiology and OBG. On an average 4-5 pregnant woman with cardiac disease visited per month in our hospital.

Inclusion criteria

All pregnant females with congenital or acquired heart disease presenting on or before 12 weeks of pregnancy, and structurally normal heart in control group.

Exclusion criteria

1. Patients presenting for the first time after first trimester.
2. Patients referred for termination of pregnancy
3. Renal failure.
4. Patients with COPD or other significant pulmonary problems
5. Cardiac arrhythmias.

The study received approval from the institutional ethical committee, and all participating subjects gave written informed consent.

Baseline data recorded at the first prenatal visit included age, gravida status, New York Heart Association (NYHA) functional class, comorbid conditions, cardiac lesions, types of medication used, base line NT pro-BNP and 12-lead ECG.

Baseline echocardiographic measures were obtained at the time of the initial clinic visit. Transthoracic echocardiography, including two-dimensional, colordoppler and tissue Doppler imaging was performed using GE Vivid E9 echocardiographic machine. Parasternal and apical views with pulsed and continuous wave Doppler evaluation, was performed with subjects in the left lateral decubitus position. Mitral valve area calculated in short axis view by using planimetry method in appropriate cases.

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 [16] Quantitation of inflow or outflow obstruction, quantitation of valvular regurgitation, and estimates of systolic pulmonary artery pressure were performed by standard methods [16]. Pulmonary artery hypertension was defined as a right ventricular systolic pressure 34 mm Hg in the absence of right ventricular outflow tract obstruction.

Women found to have a TSH level greater than 10 mIU/L in the first trimester of pregnancy were defined as hypothyroid anemia was defined as women with haemoglobin≤10 gm/dl IUD was defined as dead fetus of 1000 g or more at birth, or after 28 completed weeks of gestation.

Adverse cardiac events were defined as any of the following: pulmonary edema (by crackles heard over more than one-third of posterior lung fields) cardiac arrest, or cardiac death, decline in NYHA class (≥1 classes) compared with baseline, requirement of increased dose of diuretics, hospitalisation for heart failure, maternal death, IUD, neonatal ICU admission, low birth weight.

Data Analysis

Data analysis was done by using SPSS 20.0 software. For quantitative variables, mean, median, mode was calculated. Frequency distribution was calculated for qualitative variable. Chi square was used to test statistical significance for qualitative variables, whereas t-test for quantitative variables. Level of significance was 0.05.

Result

Age range was from 18 to 37 years. Median age of both cases and control was 26 years. 44 % of cases (n=22) and 42% of control (n=21) were of gravida 2, with median gravida of 2 in both cases and control.

Table 1: Distribution of study subjects according to NT-proBNP levels in different trimester of pregnancy and post-partum

NT-pro BNP	Frequency							
	12-14 weeks		24-26 weeks		34-36 weeks		3rd Day Post-Partum	
	Case (n=50)	Control (n=50)	Case (n=50)	Control (n=50)	Case (n=50)	Control (n=50)	Case (n=50)	Control (n=50)
≤ 125pg/ml	16 (32%)	43 (86%)	6 (12%)	48 (96%)	5 (10%)	44 (88%)	6 (12%)	46 (92%)
> 125pg/ml	34 (68%)	7 (14%)	44 (88%)	2 (4%)	45 (90%)	6 (12%)	44 (88%)	4 (8%)
Total	50	50	50	50	50	50	50	50

In cases, 34 (68%), had NT-proBNP level more than 125pg/ml at 12-14 weeks, 44 (88%) had NT-proBNP levels more than 125pg/ml at 24-28 weeks of gestation, 45(90%) had NT-proBNP levels more than 125 pg/ml at 34-36 weeks of gestation and 44 (88%) had NT-proBNP levels more than 125 pg/ml 3rd day PP. In control 7 (14%), had NT-proBNP level more than 125pg/ml at 12-14 weeks, 2 (4%) had NT-proBNP levels more than 125pg/ml at 24-28 weeks of gestation, 6(12%) had NT-proBNP levels more than 125 pg/ml at 34-36 weeks of gestation and 4 (8%) had NT-proBNP levels more than 125 pg/ml 3rd day PP.

Table 2: NT-proBNP levels in cases according to trimester

NT-pro BNP	Frequency			
	12-14 weeks	24-26 weeks	34-36 weeks	3rd Day Post-Partum
	Cases (n=50)	Cases (n=50)	Cases (n=50)	Cases (n=50)
≤ 125	16 (32%)	6 (12%)	5 (10%)	6 (12%)
126 – 500	16 (32%)	6 (12%)	5 (10%)	6 (12%)
501 – 1500	15 (30%)	25 (50%)	3 (6%)	7 (14%)
≥ 1501	3 (6%)	13 (26%)	37 (74%)	31 (62%)
	50	50	50	50

Among the cases, 6% (n=3), 26% (n=13), 74% (n=37) and 62% (n=31) of cases had NT-proBNP level ≥ 1501 at 12-14 weeks, 24-26 weeks, 34-36 weeks, 3rd Day Post-Partum. Among the case, more than two thirds (74%, n=37) of the newborn weighed ≥ 2.5 kg while only 20%% (n=10) were below 2.5 kg or low birth weight, while among control (96%, n=48) had weight more than 2.5 kg.

Table 3: Association between NT-pro BNP at 12-14 weeks with pregnancy outcome and other independent variables

(A) Pregnancy Outcomes	NT-pro BNP (12-14 weeks)		Chi Square (X^2)	p value
	≤ 125pg/ml	>125pg/ml		
IUD				
NO	17	30	1.108	.293
YES	00	02	Df= 1	
Maternal Death				
NO	17	32	1.073	.449
YES	00	01	Df= 1	
Increased Dose of Diuretics				

NO	13	10	9.628	.002
YES	04	23	Df= 1	
LSCS				
NO	13	12	6.273	.012
YES	04	20	Df= 1	
Hospitalization for Heart Failure				
NO	14	14	7.260	.007
YES	03	19	Df= 1	
Neonatal ICU Admission				
NO	13	25	.330	.566
YES	04	05	Df= 1	
PASP				
≤ 34	09	04	9.927	.019
35 - 50	02	05	Df= 3	
51 - 70	03	13		
≥ 71	03	11		

There was significant association between level of NT-proBNP at 12-14 week and requirement for increased dose of diuretics, hospitalization for heart failure, pulmonary arterysystolic pressure, severity of tricuspid regurgitation, NYHA class, DCMP and requirement for LSCS.

Table 4: Association between NT-pro BNP at 24-26 weeks with pregnancy outcome and other independent variables

(A) Pregnancy Outcomes	NT-pro BNP (24-26 weeks)		Chi Square (X^2)	p value
	≤125pg/ml	>125pg/ml		
IUD				
NO	6	42	0.291	0.590
YES	0	2	Df=1	
Maternal Death				
NO	6	43	0.284	0.594
YES	0	1	Df=1	
Increased Dose of Diuretics				
NO	6	17	8.004	0.005
YES	0	27	Df=1	
LSCS				
NO	5	21	2.683	0.101
YES	1	22	Df=1	
Hospitalization for Heart Failure				
NO	5	23	2.067	0.150
YES	1	21	Df=1	

There was significant association between level of NT-pro BNP at 24-26 week and requirement for increased dose of diuretics, hospitalization for heart failure, pulmonary arterysystolic pressure, and severity of tricuspid regurgitation, NYHA class and VSD.

Table 5: Association between NT-pro BNP at 34-36 weeks with pregnancy outcome and other independent variables

(A) Pregnancy Outcomes	NT-pro BNP (34-36 weeks)		Chi Square (X^2)	p value
	≤125pg/ml	>125pg/ml		
IUD				
No	5	42	0.237	0.626
Yes	0	2	Df=1	
Maternal Death				
No	5	43	0.231	0.630
Yes	0	1	Df=1	
Increased Dose of Diuretics				
No	5	18	6.522	0.011
Yes	0	27	Df=1	
LSCS				
No	4	22	1.743	0.187
Yes	1	22	Df=1	
Hospitalization for Heart Failure				
No	4	24	1.299	0.254
Yes	1	21	Df=1	
Neonatal ICU Admission				
No	5	33	1.325	0.250
Yes	0	9	Df=1	

There was significant association between level of NT-proBNP at 34-36 week and requirement for increased dose of diuretics, pulmonary artery systolic pressure, severity of tricuspid regurgitation, NYHA class in 2nd and 3rd trimester and VSD

Discussion

This is a prospective case control study conducted for "role of NT-proBNP as a prognostic marker in pregnant women with heart disease" at RIMS. In this study 50 pregnant women with heart disease and 50 pregnant women without heart disease were selected from the OBG and cardiology department. Very few studies are carried for establishing role of NT-proBNP in pregnant women with heart disease, for pregnancy outcome. In this study, among the cases majority had NT-proBNP level more than 125pg/ml in first trimester (68%), second trimester (88%), and third trimester (90%) and at 3rd day PP (88%). In our study 90% of the cases had NT-proBNP more than 125 pg./ml in 3rd trimester. Majority of the patients (74%) with NT-proBNP level ≥ 1501 were present in 3rd trimester and at 3rd day PP. Among the controls NT-proBNP level more than 125 pg/ml in first, second, third trimester and 3rd day PP were 14%, 4%, 12% and 8% respectively. During post-partum period less number (62%) of patients were with NT-proBNP level ≥ 1501 pg./ml. This finding was supported by the study carried by Tanous *i* [16] where 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% of women with heart disease had BNP in this range in the first trimester, and this had increased to 26% by the third trimester. Results were also similar to findings of previous studies [17,18], where despite the hemodynamic load of pregnancy, most healthy pregnant women have low and stable concentrations of NT-proBNP 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 [19]. By comparison, women with heart disease have higher NT-proBNP levels throughout pregnancy compared with nonpregnant women,

suggesting an impaired adaptation to the hemodynamic load of pregnancy.

In our study 44 patients had NT-proBNP level > 125mg/dl in second trimester and among them, 44 had requirement for increased dose of diuretics (*P* = 0.005) and 37 had pulmonary artery systolic pressure more than or equal to 35 mm Hg(*P* =0.001). Similarly, 44 patients had NT-proBNP level > 125mg/dl in third trimester and among them 27 had requirement for increased dose of diuretics (*P* = 0.011), 37 had pulmonary artery systolic pressuremore than or equal to 35 mm Hg (*P* = 0.001). There was no significant association between NT-proBNP level and IUD and maternal mortality, this may be due to small sample size. Findings in our study was supported by study carried by Linsen *et al* [20] in university of Groningen which concluded NT-proBNP at baseline was significantly related to NYHA class. Findings in our study was also supported by study carried by Siu *et al* [21] which concluded first-trimester NT-proBNP levels were associated with adverse CV complications

Our study showed significant association between effect of heart diseases and pregnancy outcome like, NT-proBNP level in first trimester(*P* = 0.001), NT-proBNP level in second trimester (*P* <0.001), NT-proBNP level in third trimester (*P* <0.001), NT-proBNP level in post-partum period (*P* <0.001), hospitalization for heart failure (*P*<0.001), pulmonary artery systolic pressure (*P* <0.001), increased dose of diuretics (*P* = 0.000), and neonatal ICU admission (*P* =0.019).

Women with NT-proBNP concentration <128pg/mL had no cardiovascular complications. Among cases there was significant association between level of NT-proBNP at 12-14 weeks, (*P* value < 0.019) 24-26 weeks, (*P* value < 0.018) 34-36 weeks (*P* value < 0.002) and PP day 3(*P* value < 0.022) with NYHA class worsening.

In both cases and control Predictors of adverse pregnancy outcomes were pulmonary artery systolic pressure, mitral regurgitation (*P* = 0.042), atrial septal defect (*P* = 0.023), worsening of NYHA class (*P* = 0.010), change in NT-proBNP levels (*P* = 0.012), hospitalization for heart failure (*P* = 0.000) and increased dose of diuretics (*P* = 0.003).

Patients with cardiovascular events had significantly higher NT-proBNP levels than without cardiovascular events. This may suggest that women with heart disease who develop cardiovascular complications do not have the required cardiac reserve to adapt to the haemodynamic changes of pregnancy.

Base line NT proBNP was comparable between both the group (adverse pregnancy outcome, verses normal pregnancy outcome, *P* =0.11) however the mean change in NT pro BNP was significant higher in adverse outcome groups (*P* =0.11).

Conclusions

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. 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. There was significant association between level of NT-proBNP at each of the trimester.

References

1. Sawhney H, Aggarwal N, Suri V, Vasishta K, Sharma Y, Grover A. Maternal and perinatal outcome in rheumatic heart disease. Int. J. Gynaecol Obstet 2003; 80: 9-14.
2. Wasim T., Amer W., Majrroh A., Siddiq S. Foetomaternal outcome of pregnancy with cardiac disease. J Pak Med Assoc. 2008; 58: 175-8.
3. Davies GA, Herbert WN. Assessment and management of cardiac disease in

pregnancy. J. Obstet Gynaecol Can; 2007; 331-6.
4. Philip Steer. Heart disease in Pregnancy. Women's Health Medicine. Volume 2, Issue 2, March-April 2005; Pages 18-21. Medical problems in pregnancy.
5. Carovascular disease. In F. Gary Cunningham *et al* editors. Williams Obstetrics, 22nd edition. McGraw Hill publications. 2005;1017-1041.
6. Mark W. Tomilson. In D. K. James *et al* editors. In High risk preg- nancy management options. 3rd edition. Elsevier Publications, 2006; 799.
7. Gonzalez Maqueda I. *et al*. Practice Guideline of Spanish society of cardiology for the management of cardiac disease in pregnancy. Rev Esp Cardiol. 2000; 53: 1474-95.
8. Laura L. Klein, MD, Henry L. Galan, MD. In Cardiac disease in preg- nancy. In Management of the high-risk pregnancy. In Obstetrics and Gynecology Clinics of North America. June-2004; Volume 31, No.2. p 429-459.
9. Nqayana T, Moodley J., Naidoo DP. Cardiac disease in pregnancy. Cardiovasc J Afr. 2008; 19: 145-51.
10. Scirica BM, O'Gara PT. Valvular heart disease in pregnancy. Curr Cardiol Rep.2006; 8:83-9.
11. Samuel c. Siu MD, SM *et al*. Adverse Neonatal and cardiac outcomes are more common in Pregnant women with cardiac disease. Circulation. 2002; 105: 2179.
12. Siu SC, Sermer M, Colman JM, et al. Prospective multicenter study of pregnancy outcomes in women with heart disease. Circulation 2001; 104:515–21.
13. Khairy P, Ouyang DW, Fernandes SM, Lee-Parritz A, Economy KE, Landzberg MJ. Pregnancy outcomes in women with congenital heart disease. Circulation 2006; 113:517–24.
14. Adams KF Jr, Giblin EM, Pearce N, Patterson JH. Integrating new pharmacologic agents into heart failure care: Role of heart failure practice guidelines in meeting this challenge. Pharmacotherapy. 2017; 37:645–56.
15. McMurray JJ, Adamopoulos S, Anker SD, *et al*. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. Eur J Heart Fail 2012;14: 803–69
16. Tanous D, Siu SC, Mason J, Greutmann M, Wald RM, Parker JD, Sermer M, Colman JM, Silversides CK. B-type natriuretic peptide in pregnant women with heart disease. J Am Coll Cardiol, 2010;56:1247–1253.
17. Borghi C, Esposti DD, Immordino V, *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.
18. 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.
19. Katz R, Karliner J, Resnik R. Effects of a natural volume overload state (pregnancy) on left ventricular performance in normal human subjects. Circulation 1978; 58:434 – 41.
20. Linssen, Gerardus Christiaan Maria. BNP and NT-proBNP in cardiovascular disease. University of Groningen. 2011
21. Siu SC, Sermer M, Colman JM, Alvarez AN, Mercier LA, Morton BC, *et al*. Prospective multicenter study of pregnancy outcomes in women with heart disease. Circulation. 2001;104(5):515-21.1987;137(8):728-32