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ROLE OF N-TERMINAL PRO-B-TYPE NATRIURETIC PEPTIDE AS A PREDICTOR OF CARDIOVASCULAR COMPLICATIONS IN PREGNANT WOMEN WITH RHEUMATIC HEART DISEASE

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Abbreviations: ANC- antenatal case, MS-mitral stenosis, MR-mitral regurgitation, AS-aortic stenosis, AR- aortic regurgitation.

ABSTRACT

Background and objective: Rheumatic heart disease (RHD) is a common valvular heart disease in our country. RHD in pregnant women is very important as it can lead to many complications during pregnancy and labour. Early diagnosis of complications and appropriate management is essential in reducing maternal mortality. Hence, we intended to find out whether NT-pro BNP at early weeks of gestation will help in predicting the complications during antenatal and postnatal period in pregnant women with RHD. **Methods:** A prospective study was conducted in a tertiary care hospital in Madurai between January 2021 to December 2022. A total of 30 cases (ANC with RHD) and 30 controls (ANC without RHD) of comparable age were chosen and NT-pro BNP was tested around 20 weeks of gestation. All the cases were followed up throughout their pregnancy and 12 weeks postpartum to identify complications if any. Appropriate management (medical/ advanced treatment) was given as required. At the end of the study the NT-pro BNP values of cases and controls were analysed. **Results:** The value of NT-pro BNP among the ANC with RHD was significantly higher than the ANC without RHD, 53.33% of ANCs were diagnosed as RHD in their antenatal visit only. NT-pro BNP levels compared between advanced treatment and non-advanced treatment group did not show any significant difference. Among the moderate to severe cases of RHD, 16% went for advanced treatment. **Interpretation and Conclusions:** Rheumatic heart disease is sub-clinical in the population and manifests only during pregnancy and labour. Hence, screening all the ANCs for RHD with ECHO and NT-pro BNP will help in risk stratification of patients and choosing appropriate treatment to reduce the maternal mortality rate.

INTRODUCTION

Rheumatic Heart Disease is a prevalent valvular heart disease in eastern countries like India, Pakistan, China and Indonesia, accounting for 73%[1] of global cases. It is endemic in almost 20 countries. Though the age of affection is between 5 and 15 years, the manifestations of valvular heart disease may be at a later age. The disease affects females more than males. Hemodynamic changes occurring during pregnancy compromise their cardiac status and increase their morbidity and mortality in antenatal and postnatal period.

Pregnancy being a physiologically stressful state, heart disease becomes a health hazard for mother and foetus. Heart disease complicating pregnancy is one of the important cause of maternal mortality. Rheumatic heart disease tops the list in India. Stenotic or regurgitant lesions in heart valves are observed in RHD complicating pregnancy. Mitral stenosis being most common valvular involvement, is observed in 74% of ANCs with RHD. Among those ANCs with RHD 47% were diagnosed only during antenatal screening by Echocardiography.

The hemodynamic changes occurring in antenatal and postnatal period will compromise the mother and baby in many ways. Increased heart rate and cardiac output has an impact on trans mitral gradient hence worsens the disease leading to heart failure and arrhythmias like atrial fibrillation. Auto transfusion and increased sympathetic activity during labour will rapidly shift the fluid into the intravascular compartment leading to heart failure during and after delivery. Hence meticulous monitoring of the patient during pregnancy, labour and puerperium is very mandatory to reduce maternal mortality. Heart disease complicating pregnancy also leads to fetal complications

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like abortions, IUGR and preterm deliveries. Efforts must be taken to detect rheumatic heart disease antenatally, so that close monitoring and follow-up help in reducing the risk imposed upon pregnant women.

NT-proBNP is an excellent biomarker for heart failure. Being a product of BNP, it promotes diuresis, natriuresis and vasodilatation. NT-pro BNP is more stable in vivo and in vitro (t½ - 120 minutes) compared to BNP (t½ - 20 minutes). These biomarkers are used as diagnostic and prognostic indicators in heart failure. Increase in NT-proBNP levels will indicate heart failure even before the ECHO findings of heart failure. Current literature search showed very scarce reports on the role of NT-pro BNP in pregnancy, particularly RHD. Therefore, we intended to find whether NT pro-BNP levels in early weeks of pregnancy can predict cardiovascular outcome in ANCs with RHD.

MATERIALS AND METHODS

This prospective case control study was conducted from January 2021 to December 2022, at antenatal clinic and Department of Cardiology in the tertiary care hospital (Government Rajaji Hospital, Madurai, Tamilnadu, India). Prior to enrollment, all patients provided written informed consent outlining the procedure's risks and benefits, which was approved by the institution's ethics committee. All pregnant women with Rheumatic heart disease in their mid-trimester approximately 20 weeks, who were asymptomatic, were included in the study. ANCs with RHD who were symptomatic, having heart failure, atrial fibrillation, PIH, renal failure and on drugs like ACE inhibitors, beta blockers and diuretics were excluded from the study. Complete medical and obstetric history was obtained. Routine blood investigations [Blood sugar, RFT, Hemoglobin] , ECG, 2D ECHO was done. Thirty healthy normotensive pregnant women were taken as controls. All controls had normal echo examination at the time of recruitment.

Analysis of NT-pro BNP: After enrollment of the patient, 2 ml of blood samples were taken between the hours of 8 and 10 in the morning. Samples were drawn into prechilled tubes containing EDTA, put on ice right away, and then quickly centrifuged at 4°C. Serum was separated and kept at a temperature of - 80 °C. ELISA, a two-step sandwich assay with antibody-coated microtitre plates, was used to quantify NT-pro BNP as per manufacturer protocol (R&D Systems, Inc.). The kit do not exhibit any detectable cross reactivity with this assay ANP CNP NPR-1 NPR-2, which does not call for sample extraction.

The recruited patients were reviewed every month and assessed clinically for their cardiac status throughout pregnancy up to 12 weeks postpartum. Patients having symptoms pertaining to cardiac illness were admitted by cardiologist and opinion was sought regarding medical management or advanced treatment (Balloon Mitral Valvotomy / Mitral valve replacement). Once the patient delivers, they are followed up for the next twelve weeks to monitor the possible complications.

Statistical analysis was performed using Graph pad prism 8 and data analysed. In categorical variables, the data are displayed as n (% of cases). Whereas non-parametric data are shown as median, the parametric data for continuous variables are presented as mean and standard deviation (SD). A two-tailed P-value of <0.05, was considered significant.

RESULTS

A total of 30 participants with pregnancy and rheumatic heart disease were tested for NT-Pro BNP from Jan-2021 to Dec-2022. The study was coordinated by a team of doctors in General Medicine, Cardiology and Obstetrics departments. A total of 30 participants with pregnancy who did not have rheumatic heart disease were taken as controls. The controls were selected in the same obstetrics OPD from where cases were enrolled, taking maximum effort to have two groups to be similar in demography. The mean + SD age of the cases was 24.77 ± 4.1 and the mean age of the control group was 24.83 ± 4.1.

All the patients had valvular heart disease with varying involvement of mitral, aortic and tricuspid valves. Out of the 30 ANCs 16 patients [53.33%] are diagnosed as RHD in their antenatal visit only.

They are categorized as pure mitral and multivalvular involvement group (Table 1) Those who have pure mitral valve involvement was 23 (76.66%) and those with multivalvular involvement was 7(23.34%). Out of the pure mitral valve disease, 7 patients had MS (2 patients had mild MS, 4 patients had moderate MS and 1patient had severe MS), 12 patients had MR (9 patients had mild MR, 2 patients had moderate MR and 1 patient had severe MR), 4 patients had MS & MR (1patient had mild MS & MR and 1patient had moderate MS & MR, 2 patients had severe MS & MR). Multivalvular heart disease included varying degrees of MS/MR along with aortic valve involvement (4 patients had mild AR, 2 patients had moderate AR,1 patient had mild AS).

Table 1. NT-pro BNP levels in ANCs with Rheumatic Heart Disease patients.

S.No	Pure Mitral valve disease in ANCs	NT-pro BNP pg/ml	Multi-valve disease in ANCs	NT-pro BNP pg/ml
1	RHD 002	628.66	RHD 001	238.53
2	RHD 003	404.77	RHD 009	1124.02
3	RHD 004	94.56	RHD 010	416.06
4	RHD 005	86.02	RHD 011	321.80
5	RHD 006	1094.74	RHD 015	125.06
6	RHD 007	324.85	RHD021	1648.67
7	RHD 008	159.83	RHD023	317.23
8	RHD 012	187.59		
9	RHD 013	111.33		
10	RHD 014	567.96		
11	RHD 016	50.33		
12	RHD 017	315.09		
13	RHD 018	695.77		
14	RHD019	208.03		
15	RHD020	269.34		
16	RHD022	20.74		
17	RHD024	459.06		
18	RHD025	392.26		
19	RHD026	1616.95		
20	RHD027	807.41		
21	RHD028	149.46		
22	RHD029	242.80		

23	RHD030	169.59		

All mild MS and MR did not have any complications. Some of the moderate and severe valvular involvement patients had complications, admissions and few needed advanced treatment like Balloon Mitral valvotomy [BMV] or Mitral valve replacement (MVR). Out of our 30 patients, 5 patients required advanced treatment. Out of 5, BMV was done for 3 patients in the antenatal period. MVR was done for 1 patient in the post partum period. Another 1 patient became symptomatic at 2 weeks postpartum, BMV was planned but expired before the procedure due to resistant heart failure.

The value of NT-pro BNP among the pregnant women who had RHD (cases) was higher than the women who did not have RHD (controls) and the difference was statistically significant. The mean NT-pro BNP level among cases was 441.62 ± 427.46 pg/ml and the mean NT-pro BNP levels among controls was 147.67 ± 101.06 pg/ml. P = 0.001 (Table 2). We compared NT-pro BNP levels between the mild, moderate and severe RHD cases. Though the mean values were different among the groups, comparison was not statistically significant.

Table 2 Comparison of NT-pro BNP levels among cases and controls

	Cases (mean+SD)	Controls (mean+SD)	P value
NT-pro BNP	441.62 ± 427	147.67 ± 101.06	0.001

Out of the 30cases, 5 patients (16%) went for advanced treatment [BMV/MVR]. Pure Mitral valve disease was observed in 4 patients (80%) out of the 4 patients 3 had severe MS, 1 patient had moderate MS. Multivalvular disease with severe MS, mild MR, mild AR was observed in 1 patient (20%). Rest of the 25 (84%) cases had safe confinement without advanced treatment.

When we compare NT-pro BNP levels in pure mitral valve and

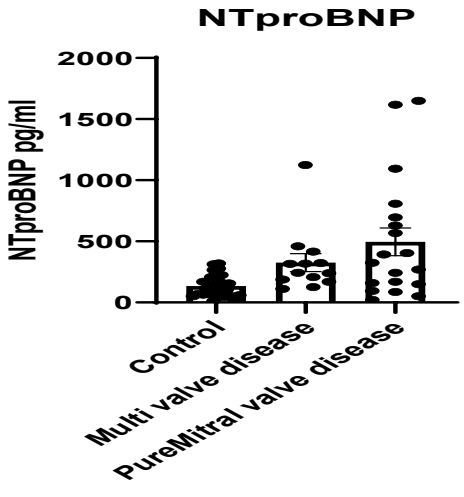

Figure 1 N-terminal pro-B-type natriuretic peptide (pg/mL) at 20 weeks of gestation in women with Rheumatic heart disease

Tukey's multiple comparisons test	Significant	P Value
Control vs Multi valve disease	No	0.142
Control vs. Pure Mitral valve disease	Yes	<.001
Multi valve disease vs. Pure Mitral valve disease	No	0.426

Multivalvular diseases, there is a significant increase in NT-pro BNP in pure mitral valve disease (Figure 1) .The difference in NT-pro BNP levels in advanced treatment and no advanced treatment group, is not statistically significant (Figure 2).

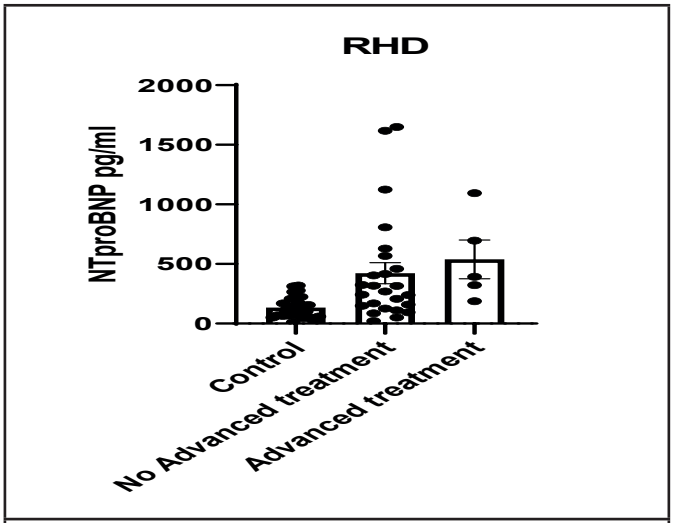

Figure 2 NT pro BNP values among Advanced treatment and No Advanced treatment groups.

Tukey's multiple comparisons test	Significant	P Value
Control Vs Non Advanced Treatment	Yes	0.0045
Control Vs Advanced Treatment	Yes	0.0283
Non advanced treatment Vs Advanced treatment	No	0.7331

DISCUSSION

RHD is a well known valvular heart disease in the eastern world. Maternal mortality rate is influenced by many parameters. Nearly 50% of maternal mortality may be due to heart disease and its complications. Out of them, half of the deaths occur in postpartum period. The high risk period in ANC with heart disease starts with early second trimester till the end of six weeks postpartum. In one statistics it was found that 60% of deaths due to heart disease complicating pregnancy can be avoided by early identification of high risk cardiac patients and referring them to higher centers for treatment and delivery. Our study showed that, NT-pro BNP values were higher among pregnant women with RHD than among those without RHD. An article published by Karan veer singh et.al. in 2019 based on a study done in pregnant women with heart disease, he concludes that BNP levels are higher in women with heart disease at all periods of gestation as well as 6 weeks postpartum compared to controls. The same observation was made in our study as well. This is a significant finding which would pave way for early diagnosis of cardiac disease in pregnant women using NT-pro BNP levels in resource poor setting.

According to REMEDY study (Global Heart Disease Registry) the complications observed in ANC with RHD were, antenatal atrial fibrillation (9%), Peripartum atrial fibrillation (10%), Peripartum heart Failure (34%) and Pulmonary hypertension (48%). Our study was done mainly to risk stratify ANCs with RHD using the bio-marker NT-pro BNP, so that intervention can be planned accordingly to get best pregnancy outcome. Two large meta analysis showed that NT-pro BNP levels increased with severity of valvular involvement in RHD.

Patients with mild MS or MR did not have any complications and

had safe confinement. Five (16.66%) patients required advanced treatment for their heart disease before or after delivery. Three patients underwent BMV around 7 months of gestation, (a) Severe MS with mild MR

NT-pro BNP -392.264. (b) Moderate MS NT-pro BNP- 1094.741. (c) Severe MS mild MR

NT-pro BNP – 695.766) one patient underwent MVR (Moderate MS mild TR NT-pro BNP – 187.591) 1 month after delivery, one patient had heart failure 2 weeks after delivery, got admitted and planned for BMV, (Severe MS mild MR mild TR mild AR NT-pro BNP – 321.803) but she expired before the procedure.

In ZAHARA study conducted in pregnant women with congenital heart disease it is clearly evident that woman with NT-Pro BNP less than 128 picogram per ml at 20 weeks of gestation had no adverse cardiovascular events (96.9% negative predictive value). In our study on pregnant women with RHD it's evident that NT-Pro BNP levels less than 187 pg/ml did not have any cardiac adverse events requiring advanced treatment.

Our study is aimed at identification of high risk patients in ANCs with RHD using NT-pro BNP. From the result we can clearly say that NT-pro BNP is not an independent marker for expected complications. The severity of valve involvement along with NT-pro BNP may guide us regarding active intervention in a particular patient. Since we see a significant increase in NT-pro BNP in RHD patients compared to controls, NT-pro BNP levels along with ECHO were provide valuable information about the complications in antenatal period for Rheumatic heart disease patients

LIMITATIONS

As the study population is small, the relation between NT-pro BNP and complications in RHD were not clearly established. We need more studies with larger population to prove NT-pro BNP as a predictor of RHD and its complications.

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Conflict of interest: None

Ethical approval

The study was approved by the Institutional Ethics Committee of Madurai Medical College, Madurai and performed as per the standards laid down by the Declaration of Helsinki for medical research involving human subjects.

Authors Contribution:

1. P.S. Vallidevi: Idea and conceptualization, original draft preparation.
2. R. Ramesh: Methodology and Interpretation
3. Ramajayam Govindan: NT-pro BNP analysis of samples and statistical work
4. Maheshkumar Poomarimuthu: NT-pro BNP analysis of samples and statistical work

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