Utility of brain natriuretic peptide as a biomarker for early detection of preeclampsia among women attending antenatal clinic in a secondary health facility in Edo State, Nigeria

ABSTRACT

Aims: The aim was to determine the suitability of brain natriuretic peptide as a biomarker for early detection of preeclampsia
Study design: This was aprospective case-control research.
Place and Duration of Study: The study was conducted at the Department of Obstetrics and Gynecology, Central Hospital Benin, from November 2014 – December 2017.
Methodology: The study involved 248 women who were organized into two groups; a preeclampsia group and a normotensive, normal pregnant group. Patients with a history of cardiovascular illness, renal disease, diabetes, thyroid disease, hepatic disease, or any other connected conditions, including urinary tract infections, were not eligible. Participants in the study underwent a single antecubital venipuncture, during which 5ml of venous blood was taken using a sterile disposable syringe. The enzyme linked immunosorbent assay was used to determine the levels of plasma brain natriuretic peptides.
Results: The area under the curve (AUC) of BNP fluctuated across trimesters, reaching 87.1% in the second and 70.5% in the third (p 0.05). Sensitivity ranged from 80.0% in the second trimester to 79.1% in the third, but was 100% in the postpartum period for sensitivity, specificity, PPV, and negative predictive value. Reference values for BNP as a yardstick for questioning preeclampsia were determined to be 395.56 pg/ml at the start of the second trimester and 438.81 pg/ml at the end of the third trimester, with sensitivities and specificities all above 75%.
Conclusion:BNP can be relied upon as a diagnostic biomarker for predicting preeclampsia.

Keywords: Hypertension, risk assessment, pregnancy induced hypertension, preeclampsia

1. INTRODUCTION

Pregnancy-induced hypertension ranks as one of the main factors of maternal and perinatal death globally [1]. Pre-eclampsia refers to a pregnancy-specific condition characterized by high blood pressure, severe proteinuria, and edema [2]. It is a complex component of the progression of pregnancy hypertensive problems. Pre-eclampsia impairs around 2%-8% of pregnancies worldwide. [3]. The World Health Organisation (WHO) reports that it is 7 fold more common in underdeveloped nations (2.8% of those born alive) than in industrialized nations (0.4%) [4]. Pregnancy has been associated with a significant increase in BNP levels compared to non-pregnant women. Elevations in BNP has also been associated with heart failure, premature birth [5].
BNP primarily is secreted by the ventricles in the heart as a response to left ventricular stretching or wall tension. The adverse effects associated with preeclampsia include left ventricle wall thickening, left-sided cardiac dysfunction, cardiovascular disease, stroke, sudden renal malfunction, sudden lung edema, hepatic collapse, and fetal developmental delays, premature infants, and fetal death [6]. The moment myocardium strain or ischaemia is present, myocytes within the heart produce B-type natriuretic peptides (BNP) and its inert N-terminus segment cleavage product, the N-terminus pro B-type natriuretic peptides (NT-proBNP) released into the circulation. BNP is a reliable prognostic marker of deaths and coronary incidents across a variety of individuals [7].
Preventing an illness is typically preferable to trying to find a treatment. However, there are situations when avoiding the illness is overlooked. However, early detection would provide adequate opportunity to manage the medical condition, potentially sparing the surverer's life. Perhaps early detection could also aid in disease prevention. After previously linking BNP levels to the severity of preeclampsia, the researchers decided to look into the possibility of using BNP levels as a yardstick for early identification of preeclampsia in this investigation. Given that it has been established that natriuretic peptides play a

significant part in the management of body fluid, electrolyte balance, and heart health via their effects on diuresis, natriuresis, and vascular tone [8], the present research aims at looking into the usefulness of brain natriuretic peptides as a diagnostic tool for earlier identification of preeclampsia.

2. METHODOLOGY

2.1 Participants and Methods

This study was conducted at the Department of Obstetrics and Gynecology, Central Hospital Benin. It was a prospective case-control research involving 248 women. The study participants were organized into two groups; a preeclampsia group (n = 138) and a normotensive, normal pregnant group (n = 110). For the present investigation, maternal illnesses with a history of cardiovascular disease, renal disease, diabetes mellitus, thyroid disease, hepatic disease, or any related disorders including urinary tract infections were excluded. Blood pressure measurements were performed on patients, while they were seated, on at least two separate occasions with a mercury sphygmomanometer. The research was carried out between November 2014 and December 2017.

The study participants had a single antecubital venipuncture, during which 5ml of venous blood was drawn using a sterile disposable syringe. The obtained whole blood was drawn into a heparin vaccutainer tube that had been heparinized, instantly separated, and the plasma was collected into a 5 ml plain vial by a Pasteur pipette.. The sample was stored at minus 4 degree until ready for analysis. Plasma Brain Natriuretic peptides concentration estimation was by enzyme linked immunosorbent assay (ELISA).

2.2 Method of data management and statistical analysis

In the present study, statistical analyses of data were carried out using SPSS, version 23 (the Statistical Package for Social Science SPSS Version 23 USA). Data obtained were presented as mean ± standard deviation. A Receiver operator characteristic curve was performed to determine reference values of BNP at 2nd and 3rd trimester as well as at postpartum respectively.

3. RESULTS AND DISCUSSION

Preeclampsia has been linked to an increase in brain natriuretic peptide levels [9]. This study attempted to answer the question of linking its increasing patterns as a feasible biomarking approach. BNP levels in preeclamptic and normotensive pregnant women were compared in this study. Many socio-demographic characteristics, such as gestational age and age at previous confinement, have been identified as risk factors. Remarriage is also a risk factor for preeclampsia, as indicated by the current study, which found that the likelihood of the condition occurring in a population was higher in the remarried group than in those in their first marriage. Young age and remarriage have been identified as major risk factors for preeclampsia [10]. This was also supported by the findings of this investigation. The NHLBI [11] also found a greater prevalence of preeclampsia among mothers aged 30 to 44 years.

In this study, the socio-demographic information of study participants is shown in Table 1. In terms of marital status, 71.1% of preeclamptic respondents claimed being in their first marriage as compared to 91.1% of the control particicants who were also in their first marriage. Whereas 26.7% of the preeclamptic participants were remarried, only 2.2% of the control subjects were remarried. At least 80% of those polled had completed high school, while 20.0% were unemployed.

Table 1 Socio-demographic information of study participants

Parameters	Preeclampsia n (%)	Control n (%)	Incidence factor (%)	P-value
Marital status				
Single	1 (2.2)	3 (6.7)	25.00	
First Marriage	32 (71.1)	41 (91.1)	43.83	0.003
Remarried	12 (26.7)	1 (2.2)	92.31	
Educational status				
None	1 (2.2)	0 (0.0)	100.00	

Primary	8 (17.8)	4 (8.9)	66.67	0.433
Secondary	17 (37.8)	18 (40.0)	48.57	
Post-secondary	19 (42.2)	23 (51.1)	45.24	
Job status				
Employed	36 (80.0)	35 (77.8)	50.70	0.796
Unemployed	9 (20.0)	10 (22.2)	47.39	
Religion				
Christians	44 (97.8)	45 (100.0)	49.44	1.000
Islam	1 (2.2)	0 (0.0)	100.00	
Obstetric characteristics	**Mean ± SD**	**Mean ± SD**		P value
Age at menarche	14.64 ± 1.97	14.09 ± 1.74	NA	0.215
Parity	2.13 ± 1.67	1.18 ± 1.53	64.35	0.006
Age at last confinement	29.2 ± 4.12	30.5 ± 4.14	NA	0.255
Gestational age	26.95 ± 6.54	25.37 ± 6.57	NA	0.266

BNP levels were determined in both the preclapsia and control groups, with results suggesting a significant rise in due to preeclampsia (795.89.) whereas the control group had lower levels of BNP (Figure 1). The determination of mean BNP levels among subjects in each trimester is shown in Table 2. Mean BNP during second trimester was 829.80pg/mL in women with preeclampsia, compared to 225.46 in the control group ($p<0.01$). Similarly, preeclampsia increased BNP levels throughout both the third trimester (p0.01) and postpartum ($p<0.01$).

The significance test of separated means of BNP in preeclamptic patients was originally provided on the basis of trimesters. BNP level during second trimester significantly differered from those at both their third trimester ($p=0.004$) and postpartum.

This study found that preeclamptic women had significantly higher mean Brain natriuretic peptide (BNP) levels than control participants. This reflects preeclampsia-related ventricular stress and/or subclinical heart impairment. BNP concentrations were found to be higher than usual in women with preeclampsia in one investigation [12]. Similar to this work, Resnik et al. [13] found elevated BNP levels in severe preeclampsia. This study also demonstrated that BNP can be used to predict the early start of preeclampsia, as previously confirmed by Resnik et al [13]. However, non-parametric and diagnostic statistics revealed that BNP might be used as a biomarker for preeclampsia.

With a view to determining suitability of BNP as a marking tool, Receiver operator characters curve determining reference values of BNP at (a) 2nd trimester, (b) 3rd trimester and (c) postpartum were determined respectively

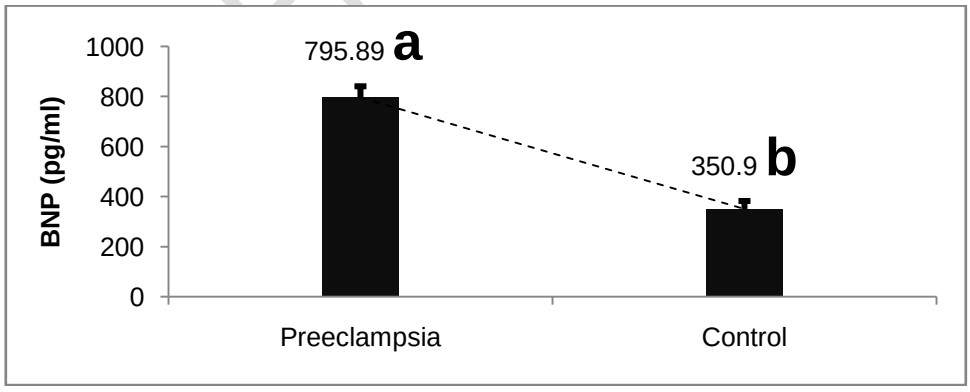

Figure 1:Mean BNP of study vs control

Table 2:Mean BNP levels of subjects in each trimesters

Trimester	**Pregnant women with preeclampsia**	**Normal pregnant women (pg/mL)**	**P value**

		(pg/mL)			
	n(%)	Mean ± SD	n(%)	Mean ± SD	
Second	20 (44.4)	829.80 ± 40.52	20 (44.4)	225.46 ± 18.34	0.001
Third	20 (44.4)	746.30 ± 39.74	20 (44.4)	543.75 ± 19.38	0.035
Postpartum	5 (11.2)	497.98 ± 7.50	5 (11.2)	102.07 ± 5.00	0.000
Total	45	-	45	-	-

Table 3: Test of significance of separated means of BNP in preeclamptic subjects originally presented on the basis of trimesters

Group 1	Group 2	P value
Second	Third	0.042
	Postpartum	0.004
Third	Second	0.042
	Postpartum	0.006
Postpartum	Second	0.004
	Third	0.006

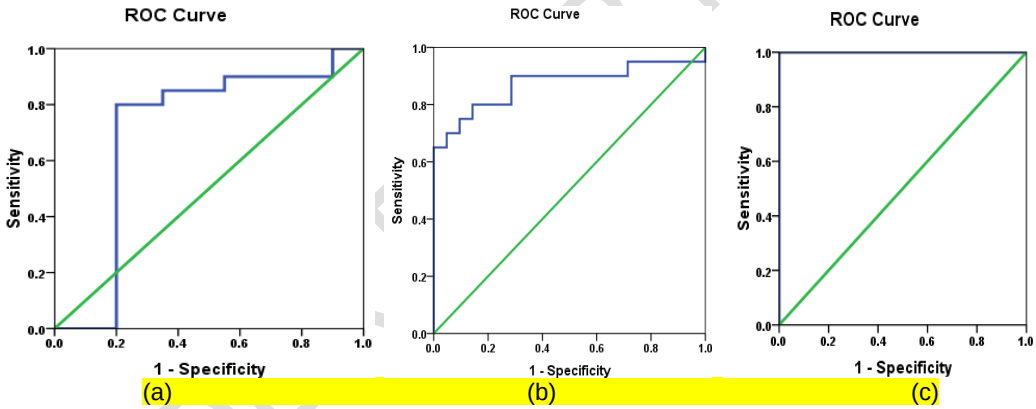

Figure 2: Receiver operator characters curve determining reference values of BNP at (a) 2nd trimester, (b) 3rd trimester and (c) postpartum respectively

Table 4: Sensitives, specificities and predictive values of test BNP levels

Parameters	2nd trimester	3rd trimester	Postpartum
Reference value (pg/ml)	395.56	438.81	300.45
AUC	0.871	0.705	1
p-value	<0.001	0.027	0.009
Sensitivity	80.00	76.19	100.00
Specificity	85.71	78.95	100.00
PPV	84.21	80.00	100.00
NPV	81.81	75.00	100.00

Odds Ratio	24.00	12.00	NA
Relative risk	5.18	3.75	NA
Likelihood Ratio	19.38	12.84	13.86
Fisher's Exact Test			
Linear-by-Linear Association	17.36	11.83	9.00

The sensitivity, specificity, and predictive values of the test BNP levels are shown in Table 4 and Figure 2. The BNP area under the curve (AUC) varied between the trimesters; it was 87.1% in the second trimester and 70.5% in the third ($p < 0.05$). Sensitivity varied from 80.0% in the second trimester to 79.1% in the third, but it was 100% in the postpartum period for sensitivity, specificity, positive predictive value (PPV), and negative predictive value. With sensitivities and specificities all above 75%, reference values for BNP as a yardstick for querying preeclampsia was determined to be 395.56 pg/Ml at the onset of second trimester, and 438.81 pg/ml at third trimester.
BNP levels increased in mild instances (873.79 pg/mL), compared to severe preeclampsia cases (756.93 pg/mL), when BNP levels were attempted to be distributed by the severity of preeclampsia (Figures 3 and 4) and body mass index (Figure 4). BNP levels showed a similar positive correlation with BMI.

The prevalence of preeclampsia according to BMI, on the other hand, revealed a proportion of cases among those who were overweight (24%), obese (60%) and normotensive (16%). this increase in the proportion of individuals with both preeclampsia and increasing BMI further highlights BMI as a risk factor for preeclampsia (Figure 4). apart from BMI, a possible association between BNP levels and booking blood pressure was determined. the closest association came with BNP and systolic booking blood pressure, which showed a partial positive relationship ($y=6.7x +102.6$, $r^2=0.2$) (figure 5).

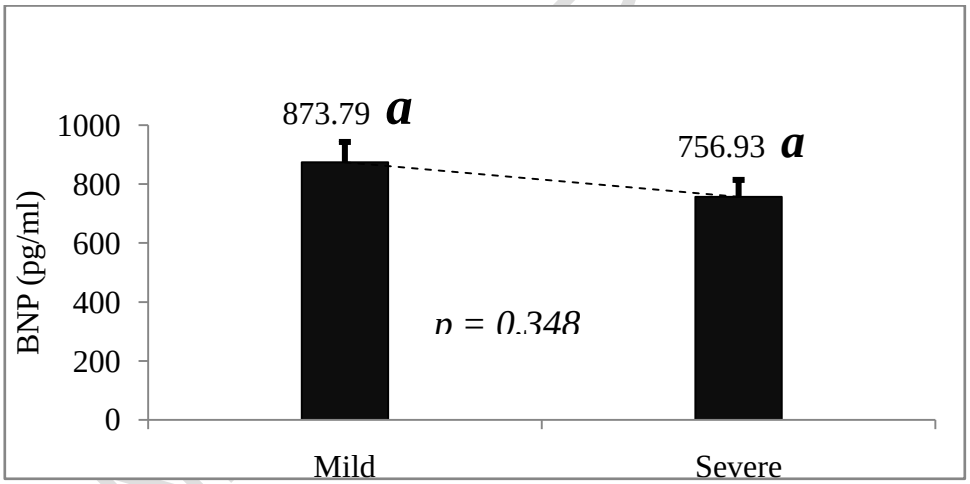

Figure 3: Mean BNPlevels of preeclamptic subjects separated on the basis of severity of disease

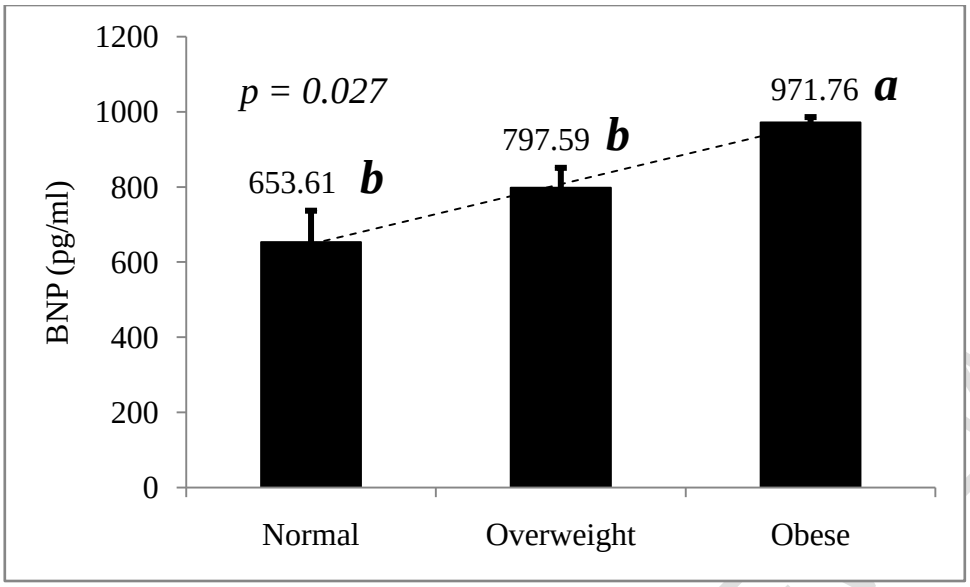

Figure 4: Distribution of BNP levels on the basis of BMI

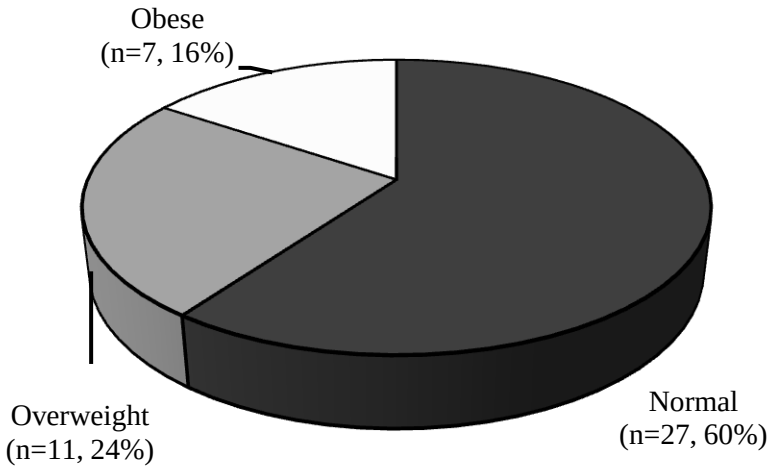

Figure 5: Prevalence of preeclampsia on the basis of body mass index

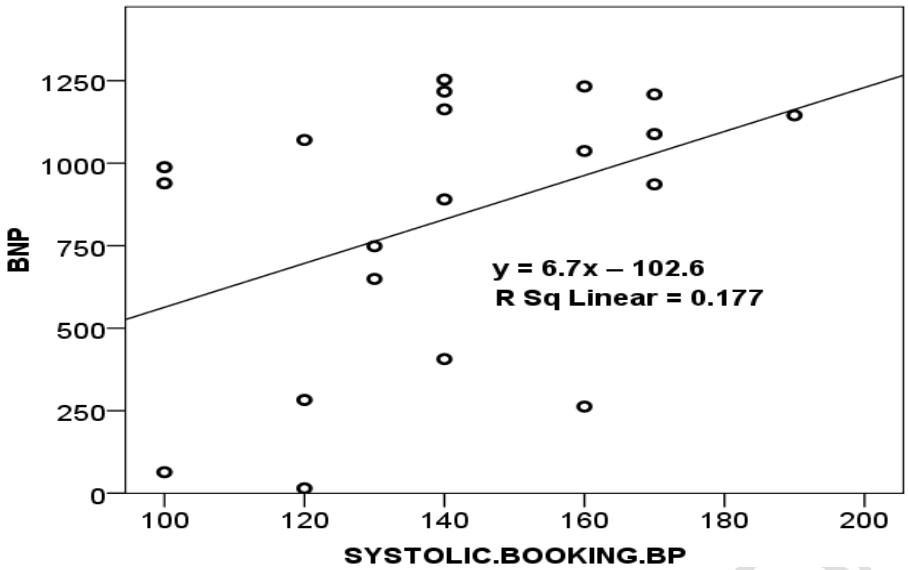

Figure 6: Partial regression plot for selected parameters at second trimester

The association between elevated BMI and increasing BNP levels was established also in this study. The outcome of BMI as a possible risk factor in preeclampsia was observed. Pakniat et al. [14] reported that pre-pregnancy obesity is strongly associated with certain pregnancy complications and perinatal conditions. Maternal obesity predisposes a woman to developing preeclampsia and a dose-dependent relationship between increasing Body Mass Index (BMI) and the risk of developing preeclampsia is well established. As previously established [15, 16], BMI is an important risk factor for preeclampsia.

4. CONCLUSION

Significant changes in serum levels of BNP were observed in preeclampsia. The role of BMI as a possible risk factor in preeclampsia was demonstrated in this study. Remarriage as well as age of the preeclamptic pregnant women were significantly linked as possible risk factors for preeclampsia. The study also suggested that BNP could be relied upon as an early biomarker for predicting preeclampsia.

Consent

Informed consent was obtained from all the study participants. The nature and aim of this work was fully discussed with the study participants and they had the right to withdraw from the study without being adversely affected regarding the medical service they received.

ETHICAL APPROVAL

Ethical approval of Ethical Committee (ref. no. a.723/56) was obtained from the Hospitals Management Board, Edo State, Nigeria.

STUDY LIMITATION

Major limitation of the study was getting participants for recruitment.

REFERENCES

[1.] Lo JO, Mission JF, Caughey AB. Hypertensive disease of pregnancy and maternal mortality. Curr Opin Obstet Gynecol, 2013.; 25(2):124-132.

[2.] Better Health Channel - "Pregnancy - Preeclampsia". https://www.betterhealth.vic.gov.au/health/healthyliving/pregnancy-preeclampsia [Accessed: 24 July, 2023].

[3.] Jeyabalan A. Epidemiology of preeclampsia: impact of obesity. Nutrition reviews, 2013; 71 Suppl 1(0 1), S18–S25. https://doi.org/10.1111/nure.12055

[4.] Osungbade KO, Ige OK. Public health perspectives of preeclampsia in developing countries: implication for health system strengthening. Journal of pregnancy, 2011; 481095. https://doi.org/10.1155/2011/481095

[5.] Afshani N, Moustaqim-Barrette A, Biccard BM, Rodseth RN, Dyer RA. Utility of B-type natriuretic peptides in preeclampsia: a systematic review. International Journal of Obstetric Anesthesia, 2013; 22(2), 96–103. https://doi.org/10.1016/j.ijoa.2012.11.001

[6.] Phyllis A. Baha MS. Preeclampsia: Clinical features and diagnosis. UpToDate. www.uptodate.com. [Accessed: 24 July, 2023].

[7.] Weber M. Hamm C. Role of B-type natriuretic peptide (BNP) and NT-proBNP in clinical routine. Heart (British Cardiac Society), 2006; 92(6), 843–849. https://doi.org/10.1136/hrt.2005.071233

[8.] Lumsden NG, Khambata RS, Hobbs AJ. C-type natriuretic peptide (CNP): cardiovascular roles and potential as a therapeutic target. Curr Pharm Des., 2010; 16(37):4080-8. doi: 10.2174/138161210794519237.

[9.] Okwor CJ, Adedapo KS, Bello OO, Meka IA, Okwor CV, Uche CZ, Nwajiobi C, Nto-Ezimah UA, Uchechukwu CE, Arum EJ. Assessment of brain natriuretic peptide and copeptin as correlates of blood pressure in chronic hypertensive pregnant women.Clin Hypertens 28, 37 (2022). https://doi.org/10.1186/s40885-022-00221-6

[10.] Korzun WJ. Sodium and potassium. Methods of analysis by Lawrence A. Kaplan and Amadeo J. pesee. 5th ed. 2010, pp.111-114.

[11.] NHLBI High blood pressure in pregnancy. National Heart, Lung, and Blood Institute. Working Group Report (NIH Publication No. 00-3029). Accessed on 15-07-2017.

[12.] Melchiorre K, Sutherland G, Sharma R, Nanni M, Thilagamatan B. Mid-gestational maternal cardiovascular profile in preterm and term pre-eclampsia: a prospective study. BJOG, 2013; 120:496–504. DOI: 10.1111/1471-0528.12068

[13.] Resnik JL, Hong C, Resnik R, Kazanegra R, Beede J, Bhalla V. Evaluation of B-type natriuretic peptide (BNP) levels in normal and preeclamptic women. American Journal of Obst. And Gynecol., 2005; 193(2): 450–454

[14.] Pakniat H, Mohammadi F, Ranjkesh F. The Impact of Body Mass Index on Pregnancy Outcome. Journal of Midwifery and Reproductive Health, 2015; 3(2):361-367

[15.] Mbah AK, Kornosky JL, Kristensen S, August EM, Alio AP, Marty PJ. Super-obesity and risk for early and late pre-eclampsia. BJOG, 2010; 117:997–1004.

[16.] Bartsch E, Medcalf KE, Park AL, Ray JG. Clinical risk factors for pre-eclampsia determined in early pregnancy: systematic review and meta-analysis of large cohort studies. BMJ, 2016; 353:i1753.