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Original Article **DOI: https://doi.org/10.3329/jninb.v7i1.54752**

Journal of National Institute of Neurosciences Bangladesh, ISSN (Online) 2518-6612
January 2021, Vol. 7, No. 1, pp. 47-51 ISSN (Print) 2410-8030

Role of Maternal Serum Placental Protein 13 at 11-13 weeks of Pregnancy as a Predictor of Pre-eclampsia

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[**Received on:** 22 November 2020; **Accepted on:** 12 December 2020; **Published:** 1 January 2021]

Abstract

Background: Prediction of pre-eclampsia is very important during pregnancy. **Objective:** The purpose of the present study was to find out the role of maternal serum placental protein 13 at 11 to 13 weeks of pregnancy as a predictor of pre-eclampsia. **Methodology:** This prospective cohort study was carried out including 83 pregnant women with early gestation (11-13 weeks) attending the antenatal clinic of BSMMU hospital, Dhaka, during the period of July 2019 to December 2019 for a period of six months. Maternal serum was taken for measurement of Placental Protein 13 by ELISA technique. Then the subjects were regularly followed up to term. At each visit they were clinically evaluated by measuring blood pressure and testing urine for protein by heat coagulation method. Proteinuria was confirmed by measuring 24 hour urinary total protein. **Result:** Out of 83 cases, 5 developed preeclampsia. The mean value of Placental Protein 13 in non-preeclampsia patients was 167.5±8.79 and in pre-eclamptic patients was 131.54±20.06. The cutoff point value of Placental Protein 13 for prediction of preeclampsia was 0.68 MoM. Area under curve (AUC) was 0.93. Sensitivity, specificity, positive predictive value and negative predictive value of this test were 80.00%, 94.94%, 50.00% and 98.68% respectively. The accuracy of this test was 93.98%. **Conclusion:** In conclusion maternal serum Placental Protein 13 can predict risk of development of preeclampsia. *[Journal of National Institute of Neurosciences Bangladesh, January 2021;7(1): 47-51]*

Keywords: : Multiple disabilities; cerebral palsy; intervention

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Conflict of interest: There is no financial conflict of interest relevant to this paper to disclose.

Funding agency: This research project was not funded by any group or any institution.

Contribution to authors: Asma M, Sharmin F, Begum F contributed from the protocol preparation, data collection up to report writing. Manuscript writing was performed by Sharmin F; Begum F, Momin A, Akhter S Begum M, Alam MM have revised the manuscript.

How to cite this article: Asma M, Sharmin F, Begum F, Begum M, Alam MM. Role of Maternal Serum Placental Protein 13 at 11-13 weeks of Pregnancy as a Predictor of Pre-eclampsia. J Natl Inst Neurosci Bangladesh, 2021;7(1): 47-51

Introduction

Pre-eclampsia is a leading cause of maternal and perinatal morbidity and mortality worldwide complicating approximately 10 to 17% of pregnancies[1]. According to the World Health Organization (WHO) the incidence is 7 times greater in developing countries compared to developed countries[2]. Yearly 8.5 million cases are reported, but this is probably an underestimate due to lack of proper diagnosis[3]. Pre-eclampsia is the most common causes of fetal and maternal death. World Health Organization (WHO) systematically reviews maternal mortality worldwide and 16.0% of maternal

deaths were reported to hypertensive disorders[4].

Placental protein 13 (PP13) is a carbohydrate binding protein synthesized in the syncytiotrophoblast, which is involved in early placentation process[5]. It is essential for the normal development and function of placenta. The level of PP13 in serum increases slowly during normal pregnancy. Decreased levels of PP13 and its low concentration in the first trimester maternal sera are associated with elevated risk of preeclampsia[6]. The biological specificity of the PP13 to the glycans of the membrane and extracellular matrix proteins such as annexin II is a primary requisite for the placental implantation to the endometrium[7]. PP13 also binds to b- and g-actin within trophoblasts, which facilitates the migration of trophoblasts toward the placental bed and also increases the release of prostacyclins for vascular remodeling of maternal spiral arteries in early placentation[8]. From the immunological point of view, for an effective placentation, PP13 induces the apoptosis of maternal T cells to progress the deepening of implantation. The expression of PP13 is also important for differentiation and syncytialization of the villous trophoblast which is vital for the release of placental hormones and immune proteins for embryo development and immune tolerance[9].

Currently this protein has been attracted as a potential marker for early diagnosis of PE. Indeed, PP13 turned to be a good early biomarker to assess maternal risk for the subsequent development of preeclampsia. In this study maternal serum placental protein 13 concentration in early weeks of gestation was investigated to evaluate its efficacy as a predictor of pre-eclampsia.

Methodology

This was a cohort study. This study was conducted in the Department of Feto-Maternal Medicine at Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, Bangladesh. This study was conducted from July to December 2019 over a period of six months. Patients attending the OPD with a viable pregnancy between 11 to 13 weeks of gestation were included in the study. Pregnant women at her first trimester (11 to 13 weeks of gestation) attending in antenatal outpatient department of BSMMU who agreed to participate was included in the study. Pregnant women with following characteristics were excluded like Chronic hypertension, Women who already have persistent proteinuria before 20 weeks of gestation, Multifetal gestation, Diabetes Mellitus, Chronic Renal disease, Heart disease, Family history of Hypertensive disorder of pregnancy and history Hypertensive disorder in previous pregnancy. Sample selection was done by purposive and convenient sampling method. After obtaining approval of Institutional Review Board, this cohort study was conducted in Bangabandhu Sheikh Mujib Medical University (BSMMU). Patient attending the antenatal OPD of BSMMU fulfilling the before mentioned criteria were included in the study. During the period the purpose and procedure of the study was discussed with the patient and informed written consent was obtained from those who agreed to participate in the study. Following the exclusion and inclusion criteria purposive and convenient sampling was done. Detailed socio-demographic data, obstetrics history, gestational age was recorded in a predesigned data sheet. Then physical examination was performed and recorded and relevant laboratory investigations was done. Period of gestation was confirmed by recording CRL from early ultrasound. With all aseptic precaution 05 ml venous blood was collected for the measurement of placental protein 13 level which was done in the department of Biochemistry at BSMMU by Bio-Vendor placental Protein 13 ELISA KIT as per schedule. Results of PP13 was given as pg/ml (picogram/ml) and recorded. In normal pregnant women delivering at term, median maternal serum PP13 levels were 166 pg/ml, 202 pg/ml and 382 pg/ml in the first, second and third trimesters, respectively, while pre-eclamptic women was at significantly reduced PP13 levels in the first trimester.

Follow up of the patient and data collection: The participants was followed up monthly up to 24 weeks, then twice weekly up to 36 weeks, then weekly up to delivery. At each visit they were clinically evaluated by measuring blood pressure and routine ANC given. If any patient developed preeclampsia then she was followed up more frequently. For this study purpose patients who developed preeclampsia before 34 weeks were designated as early onset preeclampsia and patients who developed preeclampsia after 34 weeks were designated as late onset preeclampsia.

Statistical Analysis: Measured concentration of Placental Protein 13(pg/ml) was converted to MOM for the specific gestational age of each patient. Data was processed and analyzed by using SPSS version 26. Categorical variable was presented in the form of frequency and percentage and quantitative data was presented in the form of mean and standard deviation. ROC (receiver operator curve) was used to find out the best cut off point of placental protein 13 MoM value. The accuracy of placental protein 13 in predicting the development of Pre-eclampsia was calculated by

statistical analysis. The measures were used to evaluate a screening test like sensitivity, specificity, Positive predicting value of the test (PPV), Negative predicting value of the test (NPV) and diagnostic accuracy.

Results

A total number of 83 patients were recruited for this study. The mean (±SD) age of the non-preeclampsia patients was 27.25±4.78 and the mean (±SD) age of preeclampsia patients was 29.0±5.24 yearsr. The difference was not statistically significant (p=0.582) (Table 1).

Table 1: Age Distribution of the Study Population (n=83)

Age Group	Preeclampsia	Non-Preeclampsia	P value
18 to 25 Years	2(40.0%)	33(42.3%)	
26 to 33 Years	2(40.0%)	35(44.9%)	
34 to 41 Years	1(20.0%)	10(12.8%)	
Total	**5(100.0%)**	**78(100.0%)**	
Mean ±SD	29.0±5.24	27.25±4.78	0.582^{ns}

Unpaired student t-test was done, ns=not significant

Comparison of placental protein 13 in preeclampsia and non-preeclampsia women was done. Placental protein 13 was positive in 9 cases of which 4 cases were each in preeclampsia and non-preeclampsia groups. However, out of 75 negative placental protein 13, majority were in non-eclampsia group which was 74 cases and the rest of 1 case was found in eclampsia group (Table 2).

Table 2: Comparison of Placental Protein 13 in Preeclampsia and Non-Preeclampsia Women (n=83)

Screening Test	Preeclampsia	Non-Preeclampsia	Total
Positive	4	4	8
Negative	1	74	75
Total	**5**	**78**	**83**

Positive= less than 130.3pg/mL; negative= more than 130.3pg/mL

The sensitivity, specificity, positive predictive value and negative predictive value and accuracy of placental protein 13 were 80.0% (95% CI 28.36% to 99.49%), 94.9% (95% CI 87.39% to 98.60%), 50.0% (95% CI 15.70% to 84.30%), 98.7%(95% CI 92.79% to 99.97%) and 94.0%(95% CI 86.50% to 98.02%) respectively (Table 3).

The X-axis (1- specificity) showing false positive fraction. The Y-axis (sensitivity) showing true positive fraction. Considering the number of true positive and false positive case, the best cut of point was considered at 0.68 (Figure I).

Table 3: Diagnostic Validity Test of Placental Protein 13

Validity	Values	95% CI
Sensitivity	80.0%	28.36% to 99.49%
Specificity	94.9%	87.39% to 98.60%
Positive Predictive Value	50.0%	15.70% to 84.30%
Negative Predictive Value	98.7%	92.79% to 99.97%
Accuracy	94.0%	86.50% to 98.02%

95% CI= 95% Confidence Interval

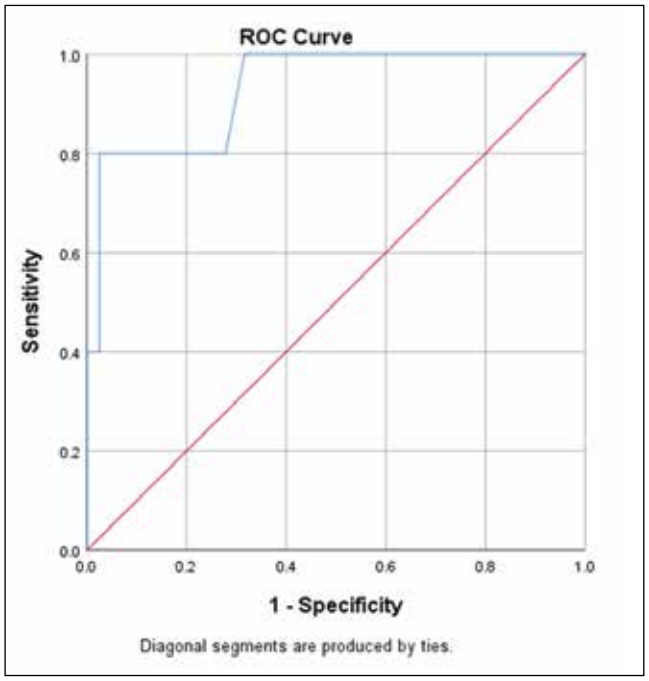

Figure I: ROC curve showing the relationship between clinical sensitivity and specificity for every possible cut-off

The area under the curve was very high which was 0.93 with the 95.0% confidence interval of 0.825 and 1.000. This was statistically significant (p=0.001). The cut-off value of placental protein 13 was found 130.3pg/mL (Table 4).

Table 4: Area under the Curve of Test Result Variables of Placental protein 13 (pg/ml)

AUC	Cut off point	Std. Error	P value	95% CI	
				Lower	Upper
0.930	130.3pg/ml	0.054	0.001	0.825	1.000

95% CI= 95% Confidence Interval

Discussion

Total Eighty three patients were included in this study from obstetric and fetomaternal medicine OPD of BSMMU. Among them 5 patients developed

preeclampsia. The concentration of maternal serum Placental Protein 13 in preeclamptic patient is reduced at 11 to 13 weeks of gestation compared to non preeclamptic women.

Among the 5 patients who developed PE, 4 had low level of Placental Protein 13 at 95% confidence interval p value of this association was less than 0.001 which was significant. Among 5 preeclampsia patients 2 developed severe preeclampsia and 3 developed mild preeclampsia. Moslemi-Zadeh et al[10] showed in his study that 66.0% cases had mild preeclampsia while 34.0% cases had severe preeclampsia and maternal serum PP13 levels were significantly lower in women who developed preeclampsia. Different studies showed, there is increased shedding of PP13 rich syncytiotrophpblast micro vesicles from placental villi when women enter into the clinic-pathological stage of PE. There may be an association with the level of PP13 with the severity of preeclampsia. But more studies are needed to reveal the association.

Out of 5 patients 3 developed early onset (<34 week) and 2 developed late onset (>34 week) preeclampsia. Odibo et al[11] showed in his study that PP13 was best in predicting early onset preeclampsia with a sensitivity of 79.0% at a FPR of 20.0% and considered as individual predictors of women at risk to develop preeclampsia. In another study, Khalil et al[12] sowed that women who developed preeclampsia had significantly lower level of PP13 in first trimester for a FPR of 10.0%, sensitivity was 50.0% for PE at term (more than 37 weeks), 62.0% for preterm preeclampsia (less than 37 weeks) and 71.0% for early onset PE (less than 34 weeks). Based on these results, the first trimester PP13 can predict early-onset better than late-onset disease[13].

Using the analysis of Roc curve, the best cut off points was determined. For this study purpose, MoM values of PP13 were categorized as normal and low with a cut off value 0.68 MoM. The value above 0.68 was categorized as normal and at or below 0.68 MoM was categorized as low. Among 5 pre-eclamptic patients, 4 were at the level of low MoM, which was very much significant (p-value <0.001). Khalil et al[12] showed in their study that cut off value of MoM for controls and preeclampsia cases were 1.0 and 0.4. In both study the MoM values of preeclampsia groups were low.

The specificity, sensitivity, positive and negative predictive values were estimated to assess the efficacy of PP13 to predict preeclampsia. In this study, at 95.0% confidence interval Sensitivity, Specificity, Positive Predictive Value and Negative Predictive Value were 80.0%, 94.94%, 50.0% and 98.68% respectively. So, low level of maternal serum PP13 in early pregnancy (11 to 13 weeks) can predict the development of preeclampsia very effectively. Beljan et al[14] showed in their study that decreased level of PP13 can predict preeclampsia with a sensitivity of 66.7% and a specificity of 97.3% which is very similar to this study. Whereas, in another study by Moslemi-Zadeh et al[15] the sensitivity, specificity, positive and negative predictive value of this marker in the first trimester were 77.8%, 82.0%, 81.1% and 78.1% respectively.

The median, interquartile range and range of PP13 in normal pregnancy and in PE, which shows clearly that the median value of PP13 among normal subjects was very close to 1 but in PE patients it is on 0.68 MoM. In this study, the risk of development of PE in low level of PP13 (<0.68) was found 15.6 times higher than normal level of PP13 which was very much significant (p-value < 0.001). In one study by Gadde et al16 PP13 were significantly lower among the PE group and odd ratio was 16.0 (95% CI 18.2-169.2). The low level of PP13 is associated with development of PE which is also reflected in other studies.

PP13 produced in placenta, is bounded to carbohydrate particles in extracellular matrix which have role in placental implantation. Moreover, PP13 increases releasing of prostaglandins which improve vascular remodeling and placental development. Thus, it is possible that its decreased level interferes with functions which are necessary for placental development, and so reduced level of PP13 in the first trimester can be a predictive marker of PE[17]. If PP13 can be used as predictor of PE, interventional therapy like low dose aspirin can be started early to reduce feto-maternal complications related to PE. Early identification of women who are at high risk for development of preeclampsia could potentially improve pregnancy outcomes because intensive maternal and fetal monitoring in such patients would lead to an earlier diagnosis of the signs of the diseases and the complication related to preeclampsia. Development of serious complications can be avoided for these patients through interventions like administration of antihypertensive medication and early delivery.

Therefore, maternal serum PP13 is a good early biomarker which can predict the development of preeclampsia. Future studies may reveal the potential role of this biomarker for early detection of preeclampsia and effective interventions to improve placentation and reduce the prevalence of the disease.

Conclusion

In conclusion maternal serum Placental Protein 13 can predict risk of development of preeclampsia. So, Placental Protein 13 is an important biomarker that can help obstetrician by raising awareness about development of preeclampsia and subsequent adverse conditions. The identification of first trimester marker will contribute to a better understanding of the pathophysiology of PE and will give us a clinically validated screening procedure for a better management of this disorder. In addition, the early identification of high-risk cases will offer the opportunity for prophylactic therapy, thus improving the perinatal outcome.

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