C reactive protein and uterine artery Doppler ultrasonography in prediction of preeclampsia

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Abstract

Preeclampsia is one of the most common medical complications during pregnancy and a major cause of maternal and neonatal morbidity and mortality. The aim of the study was to predict preeclampsia by means of C reactive protein and uterine artery Doppler ultrasonography. Maternal serum C reactive protein and uterine artery pulsatility index, resistance index, early diastolic notch were assessed in four hundred and thirty eight pregnant women at 16 to 20 weeks of gestation in Central Women's Hospital, Yangon from 1st March 2014 to 31st October 2015. Thirty four cases (7.7%) developed preeclampsia. Pregnant women with preeclampsia had significantly higher level of mean C reactive protein (7.45 mg/L vs 2.9 mg/L, p = < 0.001), mean pulsatility index (1.54 vs 1.15, p = < 0.001) and mean resistance index (0.69 vs 0.58, p = 0.001) than normal pregnant women. In univariable regression analysis, there was a significant association between higher levels of C reactive protein (≥ 5 mg/L), pulsatility index (≥ 1.2), resistance index (≥ 0.58) and presence of early diastolic notch and development of preeclampsia. In multiple logistic regression analysis, only C reactive protein, pulsatility index and early diastolic notch were significantly related to development of preeclampsia. Receiver-operating characteristic curves were constructed for determining the cut off points and the area under curves were calculated for classifying the accuracy of diagnostic test. The best cut off points for predicting preeclampsia of C reactive protein, pulsatility index and resistance index were 4.4 mg/L (sensitivity of 79.41% and accuracy of 71.69%), 1.3 (sensitivity of 76.47% and accuracy of 68.95%) and 0.61 (sensitivity of 82.35% and accuracy of 58.22%) respectively. The area under the curves were 0.755, 0.769 and 0.717 for C reactive protein, mean pulsatility index and resistance index respectively. Combination of all markers had a better area under the curve (0.84). In conclusion, C reactive proteins, uterine artery Doppler ultrasonography are potentially useful as predictors of preeclampsia. In addition, combination of all markers had better predictive value than each marker in prediction of preeclampsia.

Key words: *preeclampsia, c reactive protein, pulsatility index, resistance index*

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Introduction

Preeclampsia (PE) is the medical related obstetric problem and multisystem disorder of pregnancy that contributes maternal and fetal morbidity and mortality worldwide. It complicates 3-8% of pregnancies and 10-15% of maternal deaths[1]. Preeclampsia is characterized by a complex pathophysiology. An early detection might allow the opportunity to improve the outcomes with more focused antenatal surveillance and appropriate therapeutic intervention[2].

There are numerous modalities for prediction of PE. Impaired placental perfusion, one of the hallmarks of PE, can be assessed by measuring flow waveforms or by detecting diastolic notching of the uterine vessels with Doppler ultrasound[3]. In addition, numerous serum markers related to the etiology of PE have been measured. A generalized activation of circulating inflammatory markers have been found in pregnant women with preeclampsia. Among these, C reactive protein (CRP) becomes a potential marker in eliciting the inflammatory response of PE. Nowadays there is improved prediction of PE when inflammatory markers are combined with Doppler indices reported in many studies. Therefore this study intended to investigate the uterine artery Doppler velocimetry and CRP level, which may provide the early detection of PE and allow for planning the appropriate management for prevention of complications. This will in turn to reduce maternal and fetal morbidity and mortality associated with PE.

Materials and methods

This hospital based prospective study was carried out doing uterine artery Doppler ultrasound examination and measuring the serum CRP level of singleton pregnant women at 16-20 weeks in Antenatal Clinic of Central Women's Hospital, Yangon. Pregnant women with fetal structural abnormalities, twin pregnancy, and medical conditions such as chronic hypertension, renal disease, cardiovascular diseases, diabetes mellitus, connective tissue disorders and symptomatic infections were excluded. Ethical approval was obtained from the Research and Ethical Committee of the University of Medicine (1), Yangon in December 2013.

Doppler ultrasound examination of both uterine arteries were performed using colored Doppler ultrasound machine (model iVis 30, Chison machine). Mean pulsatility index (mPI) and mean resistance index (mRI) were measured and presence of early diastolic notches (EDN) were detected. Maternal venous blood (3 ml) for CRP was measured by using a standard reagent by Cobas C 111 assay. Urine protein was measured by using urinary dip stick. All participants were observed throughout pregnancy. When blood pressure (BP) was more than 140/90 mmHg and proteinuria was present >1+, PE was diagnosed. If PE developed before 34

weeks, it was recorded as early onset PE and after 34 weeks as late onset of PE (Tranquilli, 2013)[4]. If systolic blood pressure between 140 and 160 mmHg, diastolic blood pressure between 90 and 100 mmHg, and urine protein 1+ and 2+ , it was recorded as mild PE. If systolic blood pressure ≥ 170 mmHg or diastolic blood pressure ≥110mmHg and urine protein ≥3+ or multiorgan involvement such as acute pulmonary edema, seizure, abnormal liver enzymes, oliguria, it was recorded as severe PE (Dekker, 2011)[5]. Receiver-Operating Characteristic Curve was constructed for determination of cut off points and the area under the curve (AUC) were calculated for screening accuracy. All calculations were performed using the SPSS version 16 and STATA 13 for statistical analysis. Statistically significant difference was taken as $P < 0.05$.

Results

A total of 438 pregnant mothers were recruited in this study. The higher levels of CRP, PI and RI were statistically associated with development of PE. There was also a significant association between presence of EDN and development of PE (Table 1). In this study, 34 cases (7.7%) of the study population developed PE. Among PE cases, 19 cases were early onset PE (15 cases of severe PE and 4 cases of mild PE) and remaining 15 cases were late onset PE (7 cases of severe PE and 8 cases of mild PE).

Table (1). Association between levels of CRP, Doppler indices and development of preeclampsia

Variables		PE (n=34)	Non PE (n=404)	Chi^2 (p value)
		Frequency %	Frequency %	
CRP (mg/L)	<5	9 (2.86)	306 (97.14)	37.69 (0.000)
	≥5	25 (20.33)	98 (79.67)	
mPI	<1.2	6 (2.61)	224 (97.39)	17.97 (0.000)
	≥1.2	28 (13.46)	180 (86.54)	
mRI	<0.58	5 (2.73)	178 (97.27)	11.11 (0.001)
	≥0.58	29 (11.37)	226 (88.63)	
EDN	Yes	13 (24.07)	41 (57.93)	21.89 (0.000)
	No	21 (5.47)	363 (94.53)	

CRP Normal = < 5 mg/L Abnormal = ≥ 5 mg/L

mPI Normal = < 1.2 Abnormal = ≥ 1.2

mRI Normal = < 0.58 Abnormal = ≥ 0.58

For prediction of PE, the best cut off point of CRP level was 4.4 mg/L with sensitivity of 79.41%, specificity of 71.04%, accuracy of 71.69 % and likelihood ratio (LR) of 2.7. AUC of CRP was 0.755 indicating that the test is reasonably accurate. The best cut off point of mPI was 1.3 with sensitivity of 79.41%, specificity of 68.32%, accuracy of 68.95% and LR of 2.5. AUC was 0.769 which shows the appropriate diagnostic accuracy. The best cut off point of mRI was 0.61 with sensitivity of 82.35%, specificity of 56.19%, accuracy of 58.22 %, LR of 2 and AUC 0.717 indicating the fair accuracy of the test (Figure 1a). In addition, combination of AUC of CRP, PI, RI and presence of EDN was 0.84 (Figure 1b), which is more appropriate diagnostic accuracy for prediction of PE. The sensitivity and specificity of combination were 70.59 % and 81.68% with accuracy of 80.82% (Table 2).

Table (2). Values of CRP, PI, RI, EDN and combinations of all markers for Prediction of development of preeclampsia

Marker	Cut off point	Sensitivity %	Specificity %	Accuracy %	PPV %	NPV %	LR	AUC
CRP	4.4 (mg/L)	79.41	71.04	71.69	18.88	70.04	2.7	0.755
PI	1.3	76.47	68.32	68.95	16.88	68.32	2.5	0.769
RI	0.61	82.35	56.19	56.22	13.66	56.19	2.0	0.717
EDN	presence	38.24	89.85	85.84	24.07	94.53	-	-
Combined	-	70.59	81.68	80.82	24.49	97.06	-	0.84

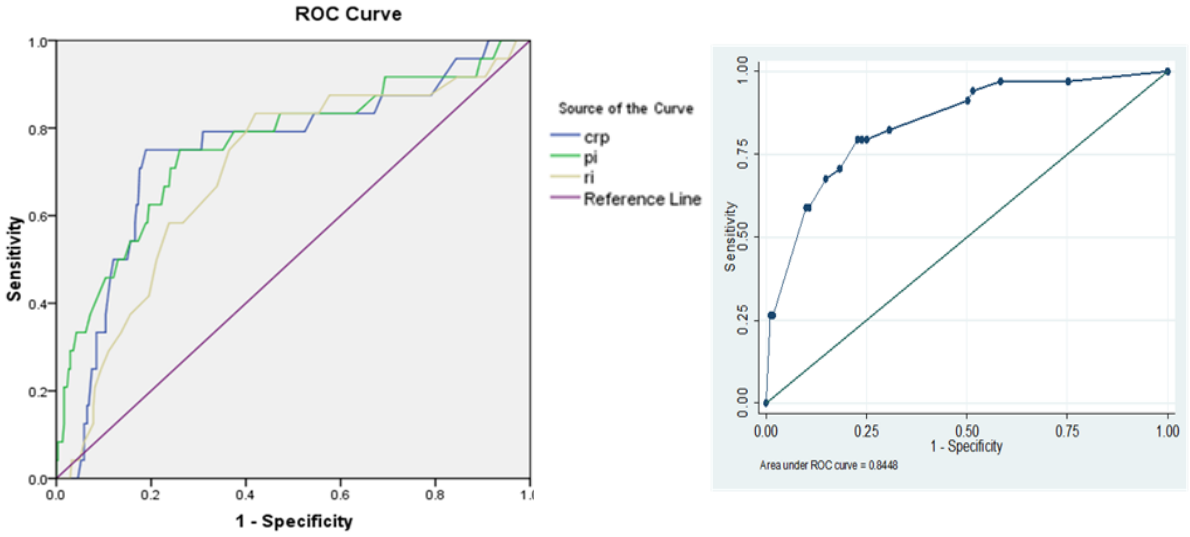

Figure (1a). Area under the Curve of CRP, PI, RI for development of preeclampsia

(1b). Area under the Curve of combination of CRP, PI, RI for development of preeclampsia

In univariable analysis of markers, CRP, mPI, mRI and EDN were significantly correlated with the development of PE with odds ratio (OR) of 8.67 (95 % CI 3.92-19.21, $p < 0.001$), 5.81 (95 % CI 2.35-14.33, $p < 0.001$), 4.57 (95 % CI 1.73-12.04, $p = 0.002$) and 5.48 (95 % CI 2.55-11.76, $p < 0.001$) respectively (Table 3). In multiple logistic regression analysis, CRP, PI and EDN were independent predictors of preeclampsia with OR of 7.98 (95 % CI 3. 44 -18.49, $p < 0.001$), 3.10 (95 % CI 1.16 - 84.30, $p = 0.024$) and 4.39 (95 % CI 1.84-10.46, $p = 0.001$) respectively. RI was not correlated (Table 4).

Table (3). Univariable regression analysis of CRP, PI, RI and EDN for development of preeclampsia

Marker	Odds Ratio	Z	95% Confidence Interval	*P*
CRP	8.67	5.32	3.92 - 19.21	0.000
PI	5.81	3.82	2.35 - 14.33	0.000
RI	4.57	3.07	1.73 - 12.04	0.002
EDN	5.48	4.37	2.55 - 11.76	0.000

Table (4). Multiple logistic regression analysis of CRP, PI, RI and EDN for prediction of preeclampsia

Marker	Odds Ratio	Z	95% Confidence Interval	*P*
CRP	7.98	4.85	3.44 - 18.49	0.000
PI	3.10	2.25	1.16 - 8.30	0.024
RI	2.52	1.71	0.88 - 7.25	0.086
EDN	4.39	3.34	1.84 - 10.46	0.001

For prediction of severe PE, the cut off level of CRP was 5.1 with AUC 0.598 which was not reliable for screening accuracy. The best cut off point of mPI was 1.31 with AUC of 0.843, which shows the appropriate accuracy. The best cut off value of mRI was 0.61. The AUC was 0.766 indicating the reasonable accuracy of the test (Table 5 and Figure 2). For prediction of early onset of PE, the cut off value were 6.8 mg/L with AUC 0.453 for CRP, 1.34 with AUC 0.591for mPI, and 0.63 with AUC 0.6 for mRI (Table 5 and Figure 3).

Table (5). Values of CRP, PI and RI for Prediction of severe and early onset preeclampsi

Markers	Severe PE				Early onset PE			
	Cut off points	Sensitivity %	AUC	LR	Cut off point	Sensitivity %	LR	AUC
CRP(mg/L)	5.1	78.26	0.597	2.1	6.8	65.00	1.86	0.453
PI	1.31	91.30	0.843	12.5	1.34	85.00	4.26	0.591
RI	0.61	91.30	0.766	5.96	0.63	80.00	2.21	0.6

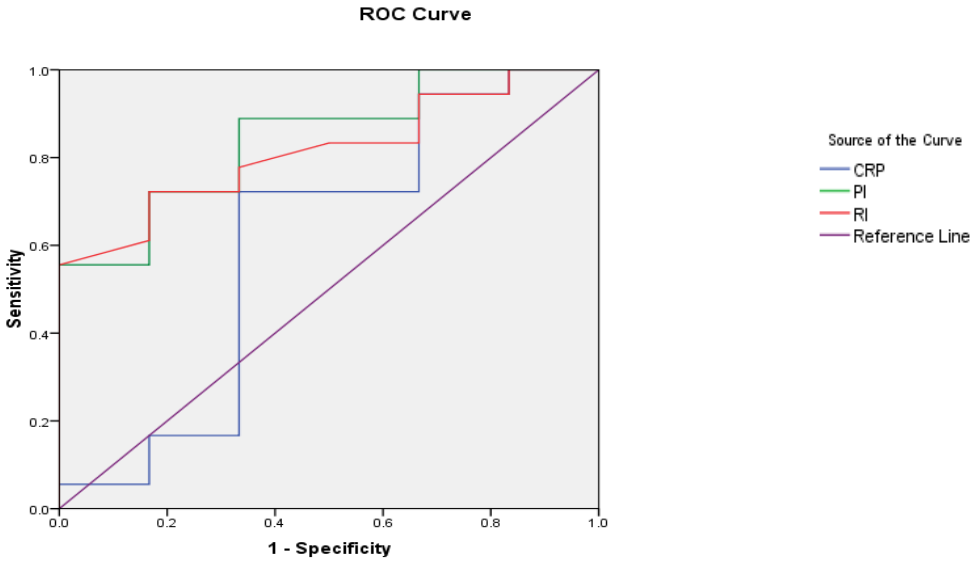

Figure (2). Area under the Curve of CRP, PI, RI for development of severe PE

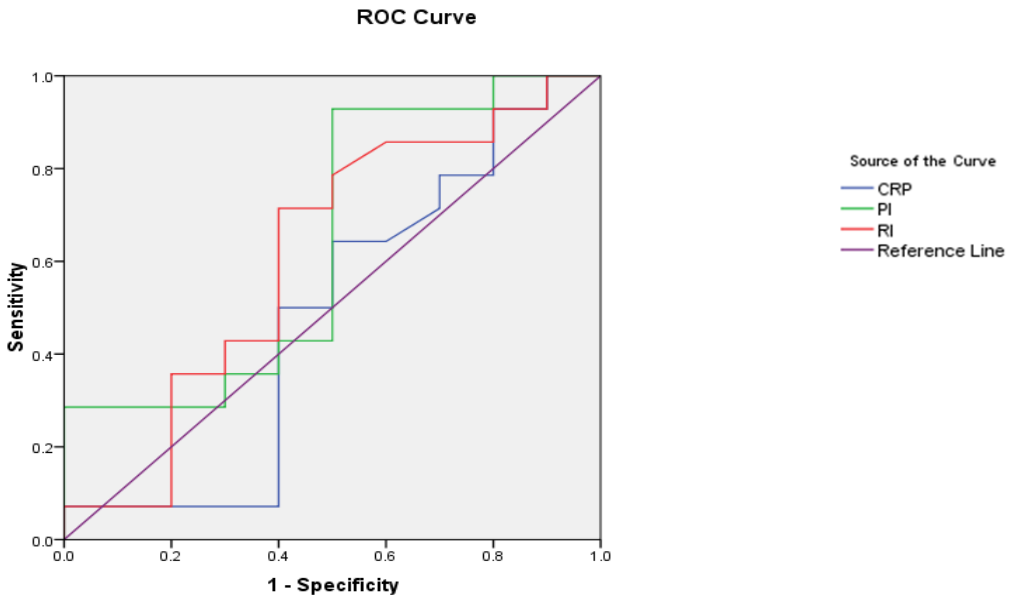

Figure (3). Area under the Curve of CRP, PI, RI for development of early onset PE

Discussion

Preeclampsia is commonly encounter problem in obstetric practice. Although the etiology of PE is not known, CRP which is a sensitive marker arises as a consequence of endothelial cell dysfunction and elevation of its level has been suggested as prediction of PE[6]. A case control study done by Tjoa et al[7] (2003) found that pregnant women with high CRP level subsequently developed PE. Archana et al (2011)[8] also reported that elevated serum CRP concentration could help to predict PE (P<0.01). Similarly in present study, median serum CRP was significantly higher in pregnant women with PE (7.45 mg/L vs 2.9 mg/L) than normotensic pregnant women and high level of CRP (≥ 5 mg/L) was statistically significant association with development of PE (Table 1).

In normal pregnancy, the resistance in uterine artery decreases with advancing gestational age. Pregnancy with abnormal trophoblastic invasion shows increased resistance, manifested as a raised RI, PI, and or the presence of EDN, which were used as predictors for PE. A systematic review and bivariable meta-analysis[9] reported that uterine artery Doppler study provided a more accurate prediction when performed in the second trimester because of complete placental implantation and complete remodeling of trophoblasts at 14-18 weeks[10]. In a prospective study[11], it was found that pregnant women with PE had significant higher mPI (1.27 vs 0.99, p= 0.003) in an unselected population and (1.6 vs 1.0, p= 0.002) in high risk pregnancy at 18-24 weeks. Similarly, studies of Papageorghiou et al (2001)[12] and Fonseca et al (2006)[13] also found higher levels of mPI (1.63 and 1.57 respectively) in pregnant women with preeclampsia. In this study, mPI was significantly higher in pregnant women with PE (1.54 vs 1.15) than normal pregnant women, which was similar to that of other studies and high level of mPI (≥ 1.2) was statistically significant association with development of PE (Table 1).

Regarding the RI, many studies found that RI was significantly higher in PE women. A prospective study[14] done at 14-16 weeks reported that mRI was significantly higher in PE than in normal pregnant women (0.75 vs 0.64). In this study, median level of RI was also higher in PE group than in normotensive group (0.69 vs 0.58) and high level of mRI (≥ 0.58) was significantly associated with development of PE. Regarding the EDN, Carbillona et al (2004)[15] found that presence of EDN was significantly associated with development of PE at 22-24 weeks gestation. The present study found that presence of EDN was also significantly associated with development of PE (p <0.001) (Table 1).

For prediction of PE, different workers have taken different cut off levels and interpreted their findings. Regarding the CRP levels, a study done by Cebesoy et al (2009)[16] reported an optimal cut off point for serum CRP as 5 mg/L. In the study of Qiu et al (2004)[17], CRP level of 4.9 mg/L increased the risk of PE up to 2.5 folds. In this study, at CRP level of 4

mg/L, sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and diagnostic accuracy of CRP were 79.41%, 65.84 %, 16.36%, 65.84% and 66.89 % respectively and positive LR was 2.32. At CRP of 5 mg/L, these values were 73.53 %, 75.74 %, 19.69 %, 74.75 % and 75.57%, respectively, and positive LR was 3. The best cut off point for prediction of PE was found as 4.4 mg/L with sensitivity of 79.41%, specificity of 71.04 % and accuracy of 71.69 % and the likelihood of having PE was 2.7 and AUC was 0.755, indicating that the test is reasonably accurate (Table 2).

For evaluating the cut off level of PI, a systematic review and bivariable meta-analysis[9] reported that sensitivity and specificity of PI were 42 % and 91 % with positive LR 4.5 in low risk patient. In present study, the sensitivity, specificity, PPV, NPV and diagnostic accuracy at the level of mPI 1.2 were 82.35%, 55.69. %, 14.21%, 59.32% and 57.76.0%, respectively and positive LR was 1.8. At level of mPI 1.34, these were found as 73.53 %, 73.27%, 17.54% and 68.93% respectively and positive LR was 2.75. In ROC curve analysis for the screening accuracy, a study conducted by Phuppong and Dejthevaporn (2008)[18] found that AUC of PI was 0.857 with sensitivity 73.1 % and relative risk 3.6 folds. In a study of Ohnmar-Hlaing (2011)[19], the AUC was 0.741 with sensitivity of 70.3% and specificity of 72.7. In present study, the AUC was 0.769 with sensitivity of 76.47%, specificity of 68.32% and accuracy of 68.95 % indicating that the test is reasonably accurate. The cut off point of PI for predicting PE was found as 1.3 with LR 2.4 (Table 2).

For evaluating the cut off level of RI, a systematic review and bivariable meta-analysis[17] stated that sensitivity and specificity at RI 0.58 were found as 83% and 72%. A study of Dehghani-firouzabadiRazieh et al (2013)[14] found sensitivity of 82.4%, specificity of 62.3% at RI 0.7. In the present study, at the level of mRI 0.58, the sensitivity and specificity were 85.29% and 43.81% with LR of 1.5. At mRI 0.67, the values were 61.76% and 74.5%, and LR was 2.4. As the value of screening test depends on high sensitivity, the cut off point was found as 0.61 with high sensitivity of 82.35%, specificity of 56.19 % and AUC of 0.717 in present study, which indicating that the test is reasonably accurate (Table 2). This results was similar to results of Bewley and campbell (1991)[20], Schulman et al (1989)[21] and Fleischer et al (1986)[22] (0.65, 0.63 and 0.62 respectively).

Regarding the EDN, a systematic review and bivariable meta-analysis[9] reported as 42 % and 93 % of sensitivity and specificity respectively when presence of EDN and positive LR was 6.5. A study[23] done at mid trimester found that presence of EDN had a sensitivity of 30% and specificity of 93.8%. In this study, sensitivity and specificity of EDN were 38.24 % and 89.85 % to predict PE (Table 2). Although sensitivity of EDN was low, specificity was high for prediction of PE. It can be concluded that women with absence EDN in second trimester are

likely to have a normal pregnancy outcome whereas those presence with notches tend to develop uteroplacental insufficiency. Therefore EDN can be implicated in prediction of development of preeclampsia and can be used as valuable marker for decreasing the neonatal and maternal mortality and morbidity rate by predicting early development of PE and preventing the complications of preeclampsia.

In the present study, all markers were significantly correlated with development of PE. With univariable regression analysis, high serum CRP had 8.67 times more likely to develop PE. Women with high mPI had 5.8 times and high mRI have 4.5 times more likely to develop PE. Presence of EDN had 5.4 times to develop PE (Table 3). In multiple logistic regression analysis, CRP, PI and EDN were independent predictor of PE (OR of 7.98 and 3.1 respectively) and RI was not correlated (OR 2.52) (Table 4).

Data were additionally analyzed to predict the severity of PE and onset of PE. Severe PE can be predicted at the cut off level of CRP 5.1 mg/L (sensitivity of 78.26%, LR of 2.1, AUC 0.598), mPI 1.31 (sensitivity of 91.30%, LR of 12.5, AUC 0.843) and mRI 0.61 (sensitivity of 91.30%, LR of 5.96, AUC 0.766) (Table 5 and Figure 2). Early onset PE can be predicted at cut off level of CRP 6.8 mg/L (sensitivity of 65%, LR 1.86, AUC 0.453), mPI 1.34 (sensitivity of 85.00%, LR of 4.26, AUC 0.591) and mRI 0.63 (sensitivity of 80.00%, LR of 2.21, AUC 0.6) (Table 5 and Figure 3). Based on these results, mid trimester study may also provide high predictive values for predicting severity and onset of PE.

To improve the predictive value for PE, combination of maternal serum markers and uterine artery Doppler were studied. The study conducted by Thilaganathan et al (2010)[24] reported that a combination of markers had a better AUC (0.825) than when used in isolation (AUC of cystatin C, CRP, RI - 0.725; 0.634; 0.728 respectively) and the combined sensitivity for PE was 69.2%. In this study, the AUC used in combination was 0.84, which was more than each marker (AUC of CRP, PI, RI; 0.755, 0.796, 0.717). The sensitivity of combined markers for prediction of PE was 70.59% (Table 2), which was similar to the previous study. These results revealed that PE has a multifactorial cause. Combining independent markers gives the possibility of establishing a screening test with a high detection rate for the prediction of PE.

In conclusion, CRP and uterine artery Doppler indices (PI, RI and EDN) are independent predictors of PE and prediction of PE is better when these markers are used in combination. In addition, measurements of CRP and uterine artery Doppler ultrasound examination have obvious economic advantage as well as simple, noninvasive and cost effective for prediction of PE. Therefore, CRP and uterine artery Doppler ultrasound examination should be included in basic routine investigation of antenatal care to prevent maternal, fetal and neonatal morbidity and mortality resulting from complications of PE.

However, multicenter studies with larger study population are recommended to achieve better accuracy of CRP and uterine artery Doppler ultrasound examination for prediction of severity and onset of preeclampsia.

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