Original Article

Can hsCRP be the sole investigation for predicting the severity and outcome in women with pre-eclampsia presenting late in pregnancy?

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ABSTRACT

Context: Healthcare facilities in developing countries are over burdened and proper triage of patients requiring attention more than others is needed in every sub speciality of medical sciences in them. Patients with pre-eclampsia require attention to prevent any associated complication.

Aims: The aim of this study was to evaluate whether hsCRP alone or in combination could be used as an indicator of severity and predictor of outcome in women with PE presenting to a healthcare facility late in the third trimester.

Settings and Design: Prospective observational study conducted at a teaching medical college and referral hospital catering primarily to rural, semi urban and tribal population.

Methods and Material: 85 women with PE who reported to the hospital after completed 36 weeks of gestation were included. Patients were divided in three groups. hsCRP, biochemical and hematological investigations were performed for each patient. Results were expressed as median. Independent samples Kruskall Wallis one way ANOVA and Mann Whitney U tests were performed and correlation of hsCRP with other parameters and fetal outcome was examined.

Statistical Analysis Used: Kruskall Wallis one way ANOVA and Mann Whitney U tests.

Results: hsCRP was significantly elevated in severe PE as compared to PE without severe features and normal patients. Higher requirement of labour induction and caesarean section was seen in severe PE patients along with higher still births and low baby weight babies. hsCRP had positive correlation with other markers of severity of PE and negative correlation with still births and fetal weight in severe PE patients. However, although raised in every case of severe PE, a wide variation was noted in hsCRP values.

Conclusions: hsCRP alone cannot be recommended as a marker of severity or a predictor of outcome in women presenting late in the third trimester of pregnancy. However, in combination with serum uric acid it can be used for that purpose.

Key words: Diastolic blood pressure; hsCRP; Pre-eclampsia; serum uric acid; still births.

Introduction

Pre-eclampsia (PE) is an important complication of pregnancy affecting about 2-8% of all pregnancies.[1,2] PE is believed to be a leading cause of maternal, peri-natal morbidity, and

Access this article online	
Website: www.tjogonline.com	Quick Response Code
DOI: 10.4103/TJOG.TJOG_66_18	

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How to cite this article: Mishra N, Pradhan K, Sahoo GD, Rohilla M, Meena M. Can hsCRP be the sole investigation for predicting the severity and outcome in women with pre-eclampsia presenting late in pregnancy? Trop J Obstet Gynaecol 2019;36:54-60.

mortality.[3] Around 10–15% of maternal deaths are associated with PE and eclampsia.[2] PE affects women in both developed and developing countries, but the maternal mortality is much lower in the developed countries.[3] PE may lead to eclampsia, HELLP syndrome, central nervous system, renal, and pulmonary complications.[2]

PE is diagnosed based on clinical presentation, detailed examination, and blood pressure measurements. Hematological and biochemical investigations have been historically used for prognostication of severity of PE. While clinical examination, blood counts, liver function test, renal function test, ultrasonography along with uterine artery Doppler[4] help in diagnosis of HELLP syndrome and other complications of PE,[2] serum uric acid levels,[5,6] circulating angiogenic factors like soluble Fms-like tyrosine kinase -1 (sFlt-1) and placental growth factor (PlGF)[7] contribute in predicting adverse fetal-maternal outcome. These have been proposed to be used as indicators of the severity of PE and adverse maternal-fetal outcomes.[7] The greatest utility of these markers is to predict the progression of gestational hypertension to PE. However, negative predictive values of these markers are low and recommendations for their use can't be made based on the available evidence.

PE is believed to progress in two stages.[3] Placental stage[3,8] includes atypical maternal immune response to trophoblasts with either impaired decidualization or failure of proper uterine preconditioning.[3] Vascular endothelial growth factor (VEGF), placental growth factor (PlGF), Soluble Fms-like tyrosine kinase -1(sFlt-1), Soluble endoglin (sEng), Pregnancy-associated plasma protein-A (PAPP-A) and Neutrophil gelatinase-associated lipocalin (NGAL) are few biomarkers with utero-placental origin which are under investigation in PE.[9] These investigations are useful till 34 weeks of pregnancy. They are expensive and are not widely available.

The second stage has been found to be associated with an inflammatory state.[3,8] Markers of inflammation like C-reactive protein (CRP) is postulated to be raised in PE and may be used as indicator of severity of PE.[10,11] Highly sensitive CRP assay (hsCRP) has become popular due to its ability to detect very low concentrations of CRP[12,13] and its acceptance as a predictor of cardiovascular disease.[14] Measurement of hsCRP can be done using the blood sample which is routinely drawn for the hematological investigations.

In developing countries, symptoms of PE are often neglected or missed, and it is not uncommon for pregnant women to present to a hospital for the first time late in the third trimester or in early labor with PE. These are the patients who have never visited any hospital during their entire pregnancy. The tertiary hospitals in developing countries are invariably overburdened. Simple, reliable and easy to interpret investigation which could help in identification of patients requiring greater attention over others is often desired.

The study aimed to evaluate whether hsCRP could be used alone on its own as an effective indicator of severity and predictor of outcome of PE in pregnant women presenting for the very first time to a healthcare facility in the late third trimester. Additionally, correlation of hsCRP with the currently available investigations was also done.

Subjects and Methods

This was a prospective observational study which was conducted at a Medical college hospital in India over two years after obtaining institutional ethical committee clearance. All pregnant women presenting to the hospital for the first time after completed 36 weeks of pregnancy were included. Patients with singleton pregnancy with no obvious foci of infection, non-smokers, those with a body mass index (BMI) of less than 30, those who didn't have any history of cardiac disease or prior hypertension and who consented for participation were included. While those who were in active labor, those who had history of prior hypertension, BMI <15 or >30, smokers, those with any focus of infection, Pre-Mature Rupture of Membranes (PROM), any other chronic disease and those who were on steroids.

After physical and obstetric examination presence of urinary protein was detected by dipstick. Patients with systolic blood pressure (SBP) ≥ 140 mmHg and diastolic blood pressure (DBP) ≥ 90 mmHg, measured on two occasions 6 hours apart with presence of proteinuria on dipstick (minimum 1+) were considered to have PE. Patients with PE were further sub-divided into PE without severe features (SBP <160 mmHg and/or DBP >90 mmHg but <110 mmHg) and severe PE (SBP ≥ 160 mmHg and/or DBP ≥ 110 mmHg). Height and weight of all the patients were measured. Totally, 10 ml blood was drawn from the ante-cubital vein at the time of admission and sent for estimation of hemoglobin, total leukocyte count, total platelet count, serum bilirubin, serum glutamic oxaloacetic transaminase (SGOT), serum glutamic pyruvic transaminase (SGPT), blood urea, serum creatinine, serum uric acid and hsCRP. hsCRP was estimated using the immuno-nephelometric method. hsCRP value between 0 and 5 mg/dl was considered to be within normal limits. Values more than or equal to 5 mg/dl

were taken as elevated. All patients underwent obstetric ultrasonography. Fetal parameters and uterine artery doppler were done.

Patients were managed as per departmental protocol and regular monitoring was done aimed at ensuring maternal and fetal well-being. Anti-hypertensive agents were started based on existing guidelines and the protocol followed in the department. In all patients with PE presenting at or after completed 37 weeks, labor was either induced or augmented depending on the clinical assessment. Caesarean section was performed for either maternal or fetal indications. Post-delivery status of the child (live-born or stillborn), placental weight, and baby weight were recorded.

The data was analyzed using SPSS version 20 (IBM analytics, USA). Shapiro-Wilk test was used to check whether the data was normally distributed. The results were expressed as median. Comparison of nominal data with respect to hsCRP was done using cross tabs and Chi-square test. Independent samples Kruskall Wallis one-way ANOVA was used to compare the results across the three groups for non-parametric data. In case a statistically significant difference was found in any of the parameters, further comparison between the groups was done by Mann Whitney test. Spearman's correlation was calculated between hsCRP and the rest of the other parameters under investigation. For all the tests, a "*P*" value of < 0.05 was considered statistically significant.

Results

Eighty-five patients were included in the study. Forty patients had uneventful pregnancy, 33 patients had severe PE and 12 patients had PE without severe features. The median values of various parameters as well as the *P* values of the non-parametric tests used are summarized in Table 1.

Serum uric acid levels were significantly different between normal and severe PE, normal, and PE without severe feature groups as well as PE without severe feature and severe PE groups (*P* values 0.00, 0.00, and 0.029, respectively). hsCRP levels were found to be statistically significantly different between normal and severe PE and normal and PE without severe feature groups (*P* values 0.00 and 0.00). However, hsCRP levels were not significantly different between PE without severe feature and severe PE groups (*P* value 0.275). hsCRP was more than or equal to 5 mg/L in 23 out 33 patients with severe PE; thus, the sensitivity of hsCRP in detecting severe PE patients was 69.7%. Its specificity was 87.5% (35 out of 40 normal patients had hsCRP <5 mg/L).

Uterine artery doppler study details have been summarized in Table 1. No significant difference was found between normal and PE without severe features (*P* value 0.488), normal and severe PE (*P* value 0.573) and PE without severe features and severe PE (*P* value 0.261) groups in the Doppler studies.

Table 1: Table showing the median values of clinical, hematological, and biochemical parameters for the three study groups

Parameter	Normal pregnancy group ($n=40$)	Severe pre-eclampsia group ($n=33$)	Pre eclampsia without severe feature group ($n=12$)	*P* (independent sample Kruskall Wallis test)
Age in years	21 (20-30)	23 (18-35)	21.5 (20-30)	0.056
Gestational age in weeks	39.8 (37-41)	38.5 (37-40.5)	38.7 (38-40)	0.069
Weight in kg	64 (55-70)	62 (48-68)	59 (50-65)	0.011
Height in meters	1.54 (1.47-1.65)	1.54 (1.44-1.62)	1.52 (1.44-1.54)	0.037
Body mass index	26.84 (23.4-29.4)	26.37 (22.5-28.6)	25.20 (22.5-28.1)	0.038
SBP (mm Hg)	117 (100-130)	170 (150-220)	150 (150-160)	0.00
DBP (mm Hg)	76 (60-90)	120 (110-190)	100 (96-108)	0.00
MAP (mm Hg)	90 (73.3-98.7)	136.6 (123.3-200)	116.6 (116.6-120)	0.00
Haemoglobin (g/dl)	10.7 (9.2-14.0)	12 (6.4-14)	11 (10-12)	0.03
Total Leukocyte count (/ml)	10,100 (7,600-12,600)	12,100 (9,800-15,000)	10,800 (10,000-11,800)	0.00
Total platelet count ($\times 10^5$/ml)	2.5 (1.8-3.2)	2.2 (1.8-4.10)	2.15 (1.8-3.10)	0.015
SGOT (U/L)	34 (23-55)	70 (29-90)	42 (30-88)	0.00
SGPT (U/L)	33 (11-50)	56 (18-88)	41 (30-90)	0.00
Serum bilirubin (mg/dl)	0.8 (0.2-1.6)	1.2 (0.6-2)	1.05 (0.6-1.6)	0.00
Blood urea (mg/dl)	30 (18-50)	47 (18-90)	38 (24-88)	0.00
Serum creatinine (mg/dl)	0.8 (0.3-2.2)	1.3 (0.7-9.0)	1 (0.8-2)	0.00
Serum uric acid (mg/dl)	3.95 (2.4-8.0)	8.6 (5-15)	5.9 (4.2-12)	0.00
hsCRP (mg/L)	2.25 (1.1-7.6)	6.2 (2.5-26.2)	5.3 (2.8-12.4)	0.00
Uterine artery doppler S/D ratio	N 31, R 6, A 3	N 23, R 5, A 5	N 11, R1, A 0	

SBP, DBP, and MAP stand for systolic blood pressure, diastolic blood pressure, and mean arterial pressure, respectively. S/D ratio stands for systolic flow to diastolic flow ratio. N, R, and A stand for Normal, Reversed, and Absent, respectively

The need for induction of labor, mode of delivery, fetal outcome, baby weight, and placental weight during pregnancy has been summarized in Table 2. Chi-square test showed a significant difference (*P* value 0.009) in the number of women requiring labor induction in severe PE group as compared to normal and between women with severe PE and PE without severe features groups (*P* value 0.035). There was no significant difference in the number of women undergoing caesarean section and vaginal delivery between any of the three groups. A significant difference was noted in the number of women delivering still born fetuses in severe PE group as compared to normal (*P* value 0.011) but no significant difference was found in still births between normal and PE without severe features as well as severe and PE without severe features groups (*P* values 0.065 and 0.552, respectively).

Weight of the babies and the placentas were not found to be statistically different across the three study groups by the Kruskall Wallis test [Table 2] with the *P* values being 0.948 and 0.078, respectively.

Patients with PE without severe features had a positive correlation of hsCRP with DBP, serum bilirubin and serum uric acid level (*P* values 0.016, 0.034, and 0.029, respectively). In patients with severe PE however, significantly positive correlation between hsCRP and SBP, DBP, MAP, TLC, SGOT, SGPT, serum bilirubin, blood urea, serum creatinine, serum uric acid, and S/D ratio was noted. A negative correlation between hsCRP and baby weight was found. Figures 1 and 2 show the positive and negative correlation of hsCRP with the DBP and baby weight. There was no maternal mortality in any of the groups.

Table 2: Table summarizing the events around delivery in the women of the three groups

Parameters		Normal pregnancy group	Severe pre-eclampsia group	Pre-eclampsia without severe features group
Induction of labor	Not required	28	13	9
	Required	12	20	3
Mode of delivery	Vaginal delivery	24	16	6
	Caesarean section	16	17	6
Fetal outcome	Live birth	40	28	11
	Still birth	0	5	1
Baby weight (kg)		2.5 (1.9-3.5)	2.39 (1.0-3.5)	2.45 (1.5-4.0)
Placental weight (kg)		0.5 (0.3-0.6)	0.5 (0.2-1.2)	0.5 (0.2-0.7)

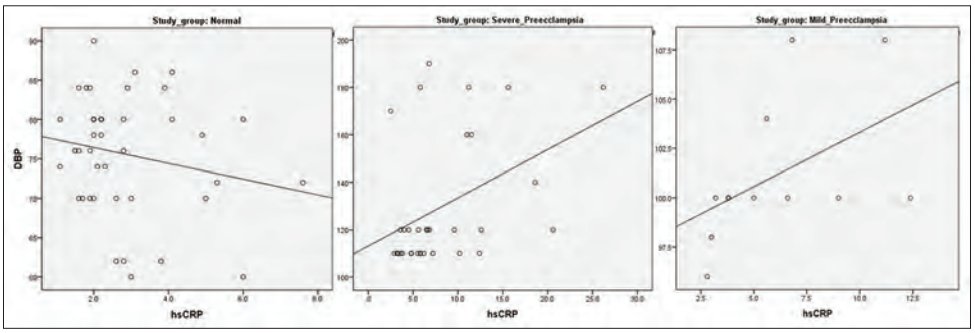

Figure 1: Scatter plot showing the positive correlation of hsCRP with the diastolic blood pressure (DBP). The strong positive correlation between sever PE and DBP is demonstrated in middle plot

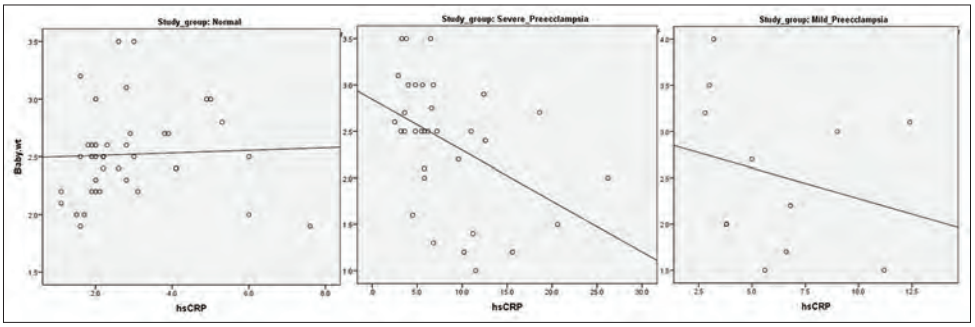

Figure 2: Scatter plot showing the negative correlation of hsCRP with the newborn baby's birth weight in severe PE

Discussion

Pre-eclampsia is characterized by new-onset hypertension detected after 20 weeks of gestation which adversely affects both the mother and fetus. New onset proteinuria, symptoms of headache, visual disturbances, epigastric pain, vomiting are the symptoms which should heighten suspicion of PE. Pregnant women often do not seek timely medical care in many developing countries due to numerous factors. Quite often these patients turn up late in the third trimester with multiple issues to a healthcare facility, which themselves are often overburdened with patients. Late presentation often precludes proper management and can contribute to increased maternal and perinatal complications. Explanation of prognosis of complications to the patient and her relatives is crucial in management of these late presenting cases. Simple markers which can help in prognostication are constantly under investigation of researchers. Prognostic markers which can quickly and accurately predict the severity and possibility of adverse outcomes could be useful as a guide for management. As it is believed that a systemic inflammatory response is associated with pregnancy, CRP could play a role in defining the severity of PE and has been investigated as a marker previously. This study was conceptualized and conducted to evaluate whether hsCRP alone can be used as an indicator replacing the battery of other tests in patients who have presented to a healthcare facility for the very first time in her entire pregnancy in the late third trimester.

In the present study, patients were of comparable age and had similar gestational age at presentation. BMI of patients was comparable. Women in the normal group had the different parameters under study within acceptable limits and there were no still births in these patients. Patients with PE without severe features had similar values of hematological parameters but had raised values of bilirubin, serum creatinine, and blood urea when compared to the normal group. The hsCRP levels were significantly raised in these patients when compared to women with normal pregnancy. Caesarean section was performed in 50% of such cases and there was one still birth. The median baby weight was similar to the normal group.

Women with severe PE had significant differences in SBP, DBP, and MAP compared to both the normal and those with PE without severe features patients. The biochemical parameters including hsCRP and uric acid were also significantly different between severe PE, normal and PE without severe features groups. Requirement of induction of labor and rate of caesarean section was higher in the women with severe PE. The number of still births in women with severe PE was more as compared to those with normal pregnancy and PE without severe features groups. However, the difference among the baby weight and the weight of placenta between these groups was not statistically significant.

Correlation analysis showed positive correlation of hsCRP with SBP, DBP, MAP, TLC, SGOT, SGPT, serum bilirubin, blood urea, serum creatinine, serum uric, and a significant negative correlation between hsCRP and baby birth in women with severe PE. Additionally, in women with severe PE there was a negative correlation between hsCRP and placental weight, but it was not statistically significant. Moreover, blood pressure measurements, and biochemical parameters like SGOT, SGPT, TLC, serum bilirubin, and serum uric acid had significant negative correlation with baby weight in severe PE but not in any other group.

Many previous studies have examined the role of CRP/hsCRP as a marker of severity of PE. Table 3 summarizes these studies which were obtained through a literature search. Teran *et al*.[15] Belo *et al*.[17] Utsun *et al*.[11] Batashki *et al*.[19] and Deveci *et al*.[21] have found that CRP levels were elevated in PE. Savvidou *et al*.[16] however reported that PE may not be preceded by a maternal inflammatory response when the CRP levels were used as an indicator. Kumru *et al*.[18], Gandevani *et al*.[22] and Farzadnia *el al*.[23] used hsCRP as a marker and found it to be raised in PE. Gandevani *et al*.[22] had the largest number of patients and found that hsCRP could be useful in identifying pregnant women at risk for PE. Notably though, they studied pregnant women between 14 and 20 weeks of gestation and did not actually study patients with diagnosed PE. Their study was focused on evaluating the predictive capability hsCRP in the mid trimesters of pregnancy. A wide variation in the CRP levels has been pointed out by Belo *et al*.[17] We too noted that while hsCRP levels were raised in patients with PE, with the hsCR*P* values being significantly more in patients with severe PE as compared to normal patients, the actual values have wide variations (range of 2.5–26.2 mg/dl), which means that absolute numerical value of hsCRP is not proportionate to the severity of PE. Thus, a patient may have severe PE but her hsCRP level might not be elevated. In the present study the sensitivity and specificity of hsCRP was 69.7% and 87.5% respectively for detecting patients with severe PE. This in our view makes it difficult to recommend hsCRP as the sole investigation for prognostication in women presenting late in third trimester. In other words, although hsCRP level might be increased in a patient of PE but that value alone might not predict the severity. However, we believe that when combined with blood pressure records and serum uric acid measurements, hsCRP can be used with reasonable confidence for predicting severity and for prognostication. While the role of uric acid as a predictor was earlier questioned,[5] the Task Force on

Table 3: Table summarizing the studies on CRP/hsCRP as an indicator of severity of Pre-eclampsia and a comparison with the current study

Study	Country	Study type	Population included	Parameters evaluated	Conclusion
Teran *et al*. (2001)[15]	United Kingdom	Cross sectional	26 normal pregnancy 25 PE pregnancy 21 non-pregnant	CRP TNF-alpha IL-6	CRP and pro-inflammatory cytokines are present in higher concentrations in women with pre-eclampsia
Savvidou *et al*.(2002)[16]	United Kingdom	Cross sectional	45 patients each with Normal and abnormal uterine doppler	CRP	PE may not be preceded by a maternal inflammatory response, as assessed by measurement of CRP
Belo *et al*. (2005)[17]	Portugal	Longitudinal	23 pregnant women 24 nulliparous women	CRP, total and differential leukocyte count, GM-CSF, Lactoferrin, Elastase	Changes in CRP levels vary in a wide manner between subjects along pregnancy, median CRP value is raised.
Utsun *et al*. (2006)[11]	Turkey	Cross sectional	26 healthy pregnant women, 26 mild PE and 26 severe PE women	CRP, Plasma fibrinogen	Elevated level of CRP and fibrinogen in PE. Good correlation between CRP and mean arterial pressure
Kumru *et al*. (2006)[18]	Turkey	Cross sectional	20 healthy pregnant women and 20 PE women	hsCRP, Biochemical investigations and hematological investigations	Serum hsCRP levels increase in women with PE which correlate with other clinical and biochemical parameters
Batashki *et al*. (2006)[19]	Bulgaria	Cross sectional	30 women with PE and 30 women with normal pregnancy	CRP	Significantly higher values of CRP in women with pre-eclampsia
Hwang *et al*. (2007)[20]	South Korea	Longitudinal	25 PE women, 202 healthy pregnant women in 4 groups	hsCRP, biochemical investigations, MAP, uterine artery S/D ratio	hsCRP levels positively correlate to pregnancy duration in healthy women and could be used as a severity marker in women with severe PE
Deveci *et al*. (2009)[21]	Turkey	Cross sectional	67 women with PE and 56 women with normal pregnancy	CRP and plasma pregnancy-associated plasma protein-A (PAPP-A)	higher levels of PAPP-A and CRP and the presence of a good correlation between CRP and MAP in PE
Gandevani *et al*. (2012)[22]	Iran	Longitudinal	778 pregnant women between 14-20 weeks of gestation	hsCRP	hsCRP can be useful in identifying pregnant women at risk for PE and low birth weight infants.
Farzadnia *et al*. (2013)[23]	Iran	Cross sectional	40 normal pregnant women, 37 mild PE and 38 severe PE women	hsCRP and sVCAM-1	hsCRP is elevated in severe PE compared with mild PE and normal pregnancy. sVCAM-1 is elevated in severe PE
Udenze *et al*. (2015)[24]	Nigeria	Cross sectional	50 normal pregnant women and 50 women with severe PE	IL-6, TNF-alpha and CRP	IL6, TNF α and CRP are elevated in severe preeclampsia and may mediate some of the clinical manifestations of the disorder
Ali *et al*. (2015)[25]	Pakistan	Cross sectional	60 women with PE 60 women with normal pregnancy	hsCRP	Elevated CRP levels in the preeclamptic pregnant women correlates with low fetal birth weight
Maged *et al*. (2017)[26]	Egypt	Retrospective	90 patients each with normal pregnancy, mild PE and severe PE	Biochemical investigations, cardiotocography and ultrasound	Blood urea nitrogen, serum uric acid, CRP alanine transaminase, and the platelet count were linked with the presence and severity PE
Present study	India	Cross sectional	40 women with normal pregnancy, 12 mild PE and 33 severe PE. All presenting for first time in late 3rd trimester	hsCRP, biochemical, hematological investigations, ultrasound for evaluating uterine artery S/D ratio	hsCRP is significantly elevated in pre-eclampsia. hsCRP along with blood pressure measurement and uric acid level can be used as an indicator of severity of pre-eclampsia and predictor of the outcomes in late presenting pregnant women. However, hsCRP alone can't be used for this purpose

Hypertension in Pregnancy[7] have recently suggested uric acid to be a useful parameter. We also found that uric acid levels correlate well with a decreased baby weight. Once the severity of PE has been predicted, additional attention can be given to the patient and due precautions taken to ensure optimal maternal and fetal outcomes.

This is the first study which evaluates the role of hsCRP as the sole investigation for predicting the severity and the outcome in women presenting very late in the third trimester. There were a few notable limitations. The small sample size especially of PE without severe features patients is a major factor. We believe that a study with a larger number of patients would be appropriate for clarifying the role of hsCRP as a predictor of severity and outcome of PE especially in patients presenting late in the third trimester.

Conclusion

hsCRP is significantly elevated in patients of pre-eclampsia (both with and without severe features) presenting very late in the

third trimester. However, it solely can't be used as an indicator of severity and predictor of outcome of PE. That being said, hsCRP along with serum uric acid can be used to predict the severity and outcome of pre-eclampsia presenting late in third trimester and the available resources can then be utilized better to provide optimum care to such patients.

Financial support and sponsorship

The funding of the study was borne by the researchers.

Conflicts of interest

There are no conflicts of interest.

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