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Research Article

EVALUATION OF PREDICTIVE VALUE OF HS-CRP IN PREECLAMPSIA

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A B S T R A C T

Background: The pregnancy is the state of carrying a developing embryo or fetus within female body[1]. Preeclampsia affects 3-5% of pregnancies. Ten million women develop preeclampsia each year around the world. Placental ischemia and inflammation occur due to impaired trophoblastic invasion in uterine spiral artery. Hs-CRP is the marker of inflammation

Aim: To evaluate the predidctive value of Hs-CRP in Preeclampsia.

Materials And Methods: A case control study of 60 subjects (30 preeclamptic primigravida and 30 age matched healthy pregnancies). Hs-CRP by immunoturbidimetric method.

Results: 30 women in preeclamptic compared with 30 normal pregnant with similar age and period of gestation . The mean SBP of the cases and controls are 157.7 mm of Hg and 113.6 mm of Hg with significant p value < 0.0001. The mean DBPin cases and controls is 101.4 mm of Hg and 77.47 mm og Hg with significant p< 0.0001. The hs-CRP levels in cases is 1.08 ± 0.79 mg/L, when compared to controls 0.23 ± 0.19 mg/L with p <0. Hs-CRP has significant cut off point of >0.26 with sensitivity of 90 and specificity of 73.33 that is if value of Hs-CRP >0.26 then, there is significantly high risk of disease.

INTRODUCTION

Pregnancy is a physiological state associated with many alterations in metabolic, biochemical, physiological, hematological and immunological processes. Usually these changes are reversible[1]. Ten million women develop preeclampsia each year around the world. Worldwide about 76,000 pregnant women die each year from preeclampsia and related hypertensive disorders. Approximately 500,000 babies die from these disorders every year[2]. Preeclampsia develops in 4-5% of human pregnancies[3].

Hypertensive disorders of pregnancy and their complications rank as one of the major cause of maternal mortality and morbidity in the world after obstetric heamorrhage, preexisting medical disorders, sepsis and abortions.[4] In addition, as it is strongly associated with fetal growth retardation and prematurity and also it contributes largely to perinatal mortality and morbidity. Incidence of hypertension in pregnancy is 11.9% in nulliparous women and 4.7% in multigravidae. Multiparous women who become pregnant by a new partner (primipaternity) behave like primigravidae with high incidence of PIH of 24%.

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Family history of preeclampsia in mother or sister is associated with 3 fold increased risk of preeclampsia and 4 fold risk of gestational hypertension.[5] Hypertension complicates 30% of multifetal gestations.[6]

Recurrence risk is of 19% for gestational hypertension, 32% for preeclampsia and 46% for preeclampsia superimposed on pre-existing chronic hypertension[7].

Preeclampsia is defined as presence of elevation of BP ≥140/90 mm of Hg after 20 weeks of gestation and proteinuria ≥ 300mg/24 hours or ≥1+ by dipstick method in a random urine sample.

Increased certainty of preeclampsia

BP ≥ 160/110 mm of Hg, Proteinuria ≥ 2.0 g/24 hours or ≥2+ by dipstick method in a random urine sample. Serum Creatinine > 1.2mg/dl unless known to be previously elevated. Platelet count < 1,00,000 cells/µl. Microangiopathic hemolysis- increased serum LDH levels. Elevated serum transaminases levels. (ALT and AST)

Several aetiologies have been implicated in the development of preeclampsia, including abnormal trophoblast invasion of uterine blood vessels and immunological tolerance between feto-placental and maternal tissues. Endothelial cell

dysfunction and inflammation are considered to have a role in the pathophysiology of PE.

The etiology of endothelial dysfunction in preeclampsia is not known, but it has been postulated to be part of an exaggerated maternal inflammatory response to pregnancy[8]. Activated circulating leukocytes[9,10] increased production of reactive oxygen species[11], and increased release of inflammatory cytokines, such as Tumor necrosis factor α (TNF α) and Interleukin-6(IL-6) , 10, 11 as well as abnormal activation of the clotting system in women with preeclampsia compared with normotensive women, supports this hypothesis.

In hypertensive pregnancy however, there is incomplete trophoblastic invasion upto decidual vessels, but not upto myometrial vessels. Because of this, myometrial spiral arteriolar lumen remains narrow which impairs blood flow to produce placental hypoxia. It leads to release of placental debris that incites a systemic inflammatory response.[12]

C – Reactive Protein (CRP) is one of the acute phase reactants in humans. It is an important first-line host defense molecule as it activates the compliment system and mediates the phogocytic clearance of pathogens and damaged cells[13,14].

The term high sensitivity CRP (hs CRP) refers to the lower detection limit of assay procedures being used and otherwise similar to routine CRP in its structure and function. It has been suggested that hs-CRP has provided better sensitivity than CRP in establishing inflammation. Hs – CRP gives better idea about ongoing inflammation and tissue damage very accurately when compared to other laboratory parameters of acute-phase response[15]. It is useful in differentiating acute inflammation as well as assessment of severity of inflammation[16].

Human CRP is calcium-dependent ligand binding protein, which binds with highest affinity to phosphocholine (PC) residues, as well as a variety of other autologous and extrinsic ligands, and aggregates or precipitates the cellular, particulate or molecular structures bearing these ligands.

CRP synthesis*:* Plasma CRP is produced by hepatocytes on stimulation by cytokine IL-6 and also IL -1 or TNF- α. CRP can also be locally produced at peripheral tissue level Control of CRP expression is principally at the level of transcription. Liver failure impairs CRP production.

In physiological conditions CRP is known to raise with advancing age, increase in Body Mass Index (BMI).CRP is also elevated with cigarette smoking, oral contraceptive pills, systemic hormone replacement therapy, myocardial infarction and coronary artery disease. CRP values reduced in liver disorders and patients on HMG CoA- reductase.

Recently, CRP has shown to possess proatherogenic properties. Hence it is used as systemic inflammatory marker. CRP activates endothelial cells to express adhesion molecules, Intracellular adhesion molecule-(ICAM-1), Vascular cell adhesion molecule 1(VCAM-1), selectins and the chemokine, monocyte chemotactic protein-1.[17]

In healthy individuals, the median concentration of CRP is 0.8mg/L (800µg/dl). The sequence interval in adults being 6.8-820µg/dl. Following an acute phase stimulus, value may increase by as much as 10,000 fold with de novo hepatic synthesis starting very rapidly, serum concentration beginning to rise by about 6hr and peaking around 48hr after a single stimulus.

Plasma half-life of CRP is 19 hours, the sole determinant of the plasma concentration is therefore the synthesis rate, which in turn reflects the intensity of the pathological processes stimulating CRP production.

CRP, if not the most but is sensitive of the acute phase reactants. Among other acute phase proteins, CRP is the first to rise in serum within 4-6 hours. Thus CRP value is a very useful non-specific biochemical marker of inflammation, which can be used in:

1. Screening for organic disease
2. Monitoring response to treatment of inflammation and infection
3. Detecting intercurrent infection in specific disease like SLE, leukemia, after surgery.

CRP is one of most sensitive acute phase proteins and has been traditionally used for diagnosing and monitoring infections and various auto immune disorders. However the lower limit of detection of CRP assays of about 2mg/litre has severely limited the clinical usefulness of such assays.

Recent improvements in assay development has resulted in a new generation of highly sensitive assay that can detect CRP at levels 100 folds lower than earlier assays.

High sensitive CRP (hs-CRP) assay plays a pivotal role in the exploration of its involvement in endothelial dysfunction and subclinical infammatoin.[18] These methods allows the reliable measurement of low concentrations of serum CRP and are often easily automated, which permit the investigation of serum CRP in healthy population

Liver failure impairs CRP production, but no other intercurrent pathologies. Very few reduce CRP values unless they also affect the underlying acute phase stimulus.

METHODOLOGY

It is a case control study which comprise of preeclamptic primigravida patients of gestational age above 20 weeks in Department of Obstetrics and Gynecology, Vani Vilas Hospital and Bowring & Lady Curzon Hospital attached to Bangalore Medical College and Research Institute.

Selection of study subjects

Based on inclusion and exclusion criteria a total number of 60 subjects (30 cases and 30 controls) were selected for the present study.

Inclusion Criteria used to select the study subjects

1. Preeclamptic primigravida of gestational age above 20 weeks.
2. The diagnosis of preeclampsia was made according to the criteria by

American College of Obstetrics and Gynecology

1. Blood pressure higher than 140/90 mmHg.
2. Edema.
3. Proteinuria >300mg/24 hours or 1+ dipstick method after 20th weeks of gestation.

Controls – It includes 30 normal pregnant women of same gestational age group without any complications.

Exclusion criteria

1. Patients with history of Gestational Diabetes Mellitus.
2. Patients with history of Essential Hypertension, Diabetes Mellitus and other Cardio-Vascular Diseases.

Based on the inclusion and exclusion criteria, age matched cases and controls were included in the present study after obtaining informed consent. A proforma was used to record relevant information and patient's data.

Collection of blood samples

Following selection of subjects and after obtaining informed consent about the proposed study, clinical history was taken from subjects and examination findings were noted down. About 5ml of fasting venous blood sample was collected from median cubital vein by venepuncture.

The results were obtained on on COBAS INTEGRA 400 analyzer after proper calibration of the method. Results were determined via calibration curve which is instrument-specifically generated by 2-point calibration and a master curve provided via the reagent barcode.

Estimation of Hs- CRP

Hs-CRP estimation was done by a solid phase, chemiluminescent immunometric assay. First, the alkaline phosphatase conjugate (reagent) is bound to the bead (within the test unit) during the immunological reaction. The amount of alkaline phosphatase captured is directly proportional to the concentration of hs-CRP in the patient sample.

Once the test unit is washed, a luminogenic substrate is added to the test unit and is moved onto the luminometer chain. In the luminogenic reaction, the substrate (an adamantyl dioxetane phosphate) is dephosphorylated into an unstable anion intermediate by the alkaline phosphatase conjugate captured on the bead. The unstable intermediate emits a photon upon decomposition. The amount of light emitted is directly proportional to the amount of bound alkaline phosphatase and in turn to the amount of hs-CRP in the sample.

hs-CRP test was done in COBAS INTEGRA 400 chemiluminescence analyzer (Siemens make) after proper calibration of the method.

RESULTS

The mean gestational age of cases and controls in weeks is 36.06 ± 0.82 and 36.3 ± 0.46 and was statistically not significant. So, the study is gestational age matched.

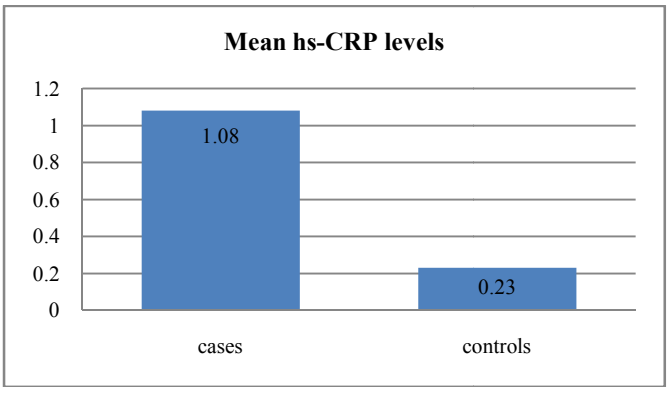

Figure I Showing mean hs-CRP levels in cases and controls

The mean blood pressure distribution in mm of Hg in cases and controls for SBP is 157.73 ± 15.4 and 113.6 ± 5.66 respectively with p value 0.0001*** which is statistically significant.

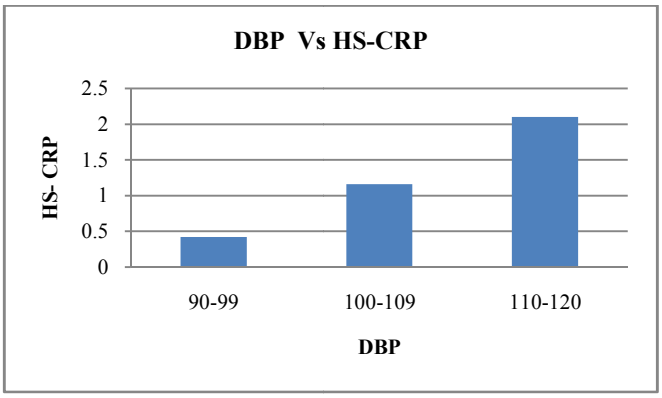

Figure II Comparison of DBP and hs - CRP

The mean DBP in cases and controls 101.4 ± 9.2 and 77.46 ± 4.51 respectively with p value 0.0001*** which is significant. The preeclamptic women had an equal distribution (33.3%) of urine protein as 1+, 2+ and 3+ on dipstix whereas control group had 80% nil and 20% in 1+ category.

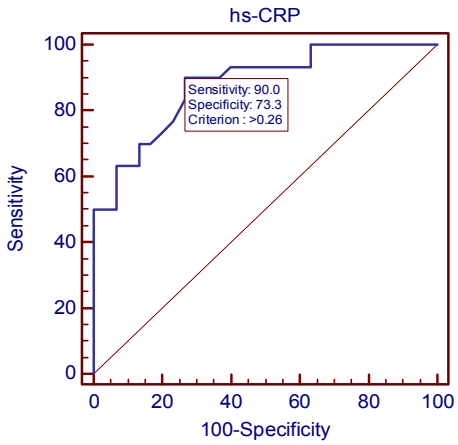

Figure III Sensitivity and Specificity of Hs-CRP.

HS-CRP has significant cut off point of >0.26 with sensitivty of 90 and specificity of 73. 3 that is if the value of Hs-CRP is >0.26 then there is significantly high risk of disease

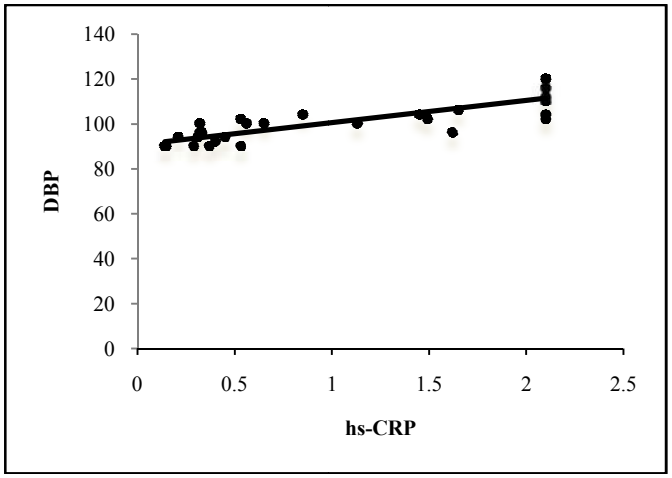

Figure III Correlation between Hs-CRP and DBP

The Mean ± SD hs-CRP levels in cases is 1.08 ± 0.79 mg/L, when compared to controls 0.23 ± 0.19 mg/L, with p value significant

The mean serum uric acid in cases and controls are 6.41 mg/dl and 4.33 mg/dl respectively with p valvue of < 0.0001.

Hs – CRP has significant cut off point of > 0.26 with sensitivity of 90 and specificity of 73.3 that is if the value of Hs-CRP is >0.26, then there is high risk of the diasease.

Table I Correlation between different parameters of the study

		SBP	DBP	PROTEIN	SBP	DBP	Protein
AGE	Correlation Coefficient	-.314	-.233	-.021	-.141	-.329	.092
	P value	.091	.214	.910	.456	.076	.628
POG	Correlation Coefficient	.475**	.342	.393*	.116	-.055	.036
	P value	.008	.064	.031	.540	.772	.849
SBP	Correlation Coefficient	1.000	.804**	.557**	1.000	.272	.306
	P value		<.0001	.001		.145	.100
DBP	Correlation Coefficient	.804**	1.000	.571**	.272	1.000	.024
	P value	<.0001		.001	.145		.899
Hs-CRP	Correlation Coefficient	.851**	.872**	.543**	.066	.308	.477**
	P value	<.0001	<.0001	.002	.730	.098	.008

Table II Correlation between Hs-CRP and different parameters of the study

		CASES	CONTROLS
		hs-CRP	hs-CRP
AGE	Correlation Coefficient	-.169	.041
	P value	.371	.832
SBP	Correlation Coefficient	.851**	.066
	P value	<.0001	.730
DBP	Correlation Coefficient	.872**	.308
	P value	<.0001	.098
	P value	.0001	.368
hs-CRP	Correlation Coefficient	1.000	1.000
	P value		
UA	Correlation Coefficient	.898**	.289
	P value	<.0001	.122

Table III Table showing Mean Hs-CRP and Different groups of DBP

DBP	No of patients	%	hs-RP(mg/L) Mean ± SD
90 -99	12	40	0.42 ± 0.39
100-109	11	36.66	1.16 ± 0.63
110-120	7	23.33	2.1 ± 0.0
TOTAL	30	100	1.08 ± 0.79

Table IV Univariate regression table

In univariate logistic regression for the diasease as dependent variable, with the increase in Hs-CRP by 0.01 unit risk of disease signifivantly increase by 88.19% with p value 0.05.

	P value	Odds ratio	95% C.I.for odds ratio	
			Lower	Upper
HsCRP	.005	89.191	3.899	2040.281

From table, 40% of the patients with DBP between 90-99 have hs- CRP 0.42 ± 0.39 mg/L, 36.66% of the patients with DBP between 100-109 have hs-CRP 1.16 ± 0.63 mg/L, and 23.3% of the patients with DBP between 110-120 have hs-CRP 2.1 mg/L which is increasing with increase in DBP.

In univariate logistic regression for the diasease as dependent variable, with the increase in Hs-CRP by 0.01 unit risk of disease signifivantly increase by 88.19% with p value 0.05.

DISCUSSION

C- reactive Protein (CRP) has been associated with several diseases, involving metabolic syndrome and cardio vascular diseases.[20,21] Endothelial dysfunction and inflammation are involved in the in the pathogenesis of preeclampsia and other important complications of pregnancy, including gestational diabetes and fetal over growth.[22] Hence serum CRP concentrations at different stages of pregnancy can be measured to know the association with various pregnancy complications.

CRP and Endothelial Dysfunction

Endothelial dysfunction is associated with atherosclerosis, an inflammatory disease that has several other features in common with preeclampsia.[23] Epidemiologic risk factors for preeclamsia such as obesity, diabetes and hypertension are also important risk factors for atherosclerosis.[24] Metabolically, both preeclampsia atherosclerosis are associated with insulin resistance, dyslipidemia and hypercoagulability.[25]

Nitric oxide (NO) is the key endotheliam-derived relaxing factor that plays a pivotal role in the maintenance of vascular tone and reactivity. Apart from being a main determinant of basal vascular smooth muscle tone, NO acts to negate the actions of potent endothelium – derived contracting factors such as angiotensin II and is a central orchestrator of atherosclerotic lesion formation, progression and eventually rupture.[26]

Inflammation results in endothelial dysfunction and facilitates the interaction among modified lipoproteins, monocyte-derived macrophages, T-cells and normal cellular elements of the arterial wall, thus high sensitive CRP has merged as most important marker for evaluating inflammation. Hence CRP is a powerful independent predictor of Mycocardial infarction, stroke and vascular events than LDL cholesteron.[27]

CRP and Inflammation

C – reactive protein is an acute phase reactant produced by liver in response to the proinflammatory cytokines Interleukin 6 (IL-6) and Tumor necrosis factor α (TNF-α). Because it has relatively short half life, the serum C- reactive protein level is dependent almost entirely on the rate of hepatic synthesis; therefore it is a sensitive index of systemic inflammation.

C-reactive protein is a sensitive index of systemic inflammation that predicts adverse atherosclerotic events, including myocardial infarction, stroke, peripheral vascular disease, and death.[28] Elevated CRP level are correlated with obesity, an association that might explain part of the excess cardiovascular risk linked to obesity.[29]

The mechanisms of the proinflammatory effects of CRP on endothelial cell are not completely clear. Further studies are needed to elucidate the basic mechanism of the proinflammatory effects of CRP on endothelial cell. This suggests that CRP is not merely a marker of inflammation but has complex modulatory functions that may contribute to the development and evolution of inflammation.[30]

CRP and Preeclampsia

In nulliparous women there is a significant association between elevated first-trimester C-reactive protein levels and subsequent development of preeclampsia. But after adjusting for BMI, the association between C-reactive protein and preeclampsia is mitigated.

In pregnancy, C-reactive protein has been studies primarily as a potential early marker for chorioamnionitis in women with premature rupture of membranes and as a predictor of

outcomes in preterm labour, including the likelihood of successful tocolysis. The normal reference ranges for C-reactive protein at various stages of normal gestation, delivery and the puerperuim was studied and found that the qualitative assays for C-reactive protein was useful. In quantitative assay, the lower thresholds for C-reactive protein detection were significantly higher than in currently available high resolution assays.[31]

Systemic maternal inflammatory response to pregnancy is responsible for the endothelial dysfunction which gives the clinical and pathological picture of preeclampsia. The association between first trimester C-reactive protein levels and subsequent preeclampsia supports the hypothesis that systemic inflammation is involved in the pathogenesis of preeclampsia.

Body Mass index is a validated, independent risk factor for preeclampsia.[24] It is suggested that BMI and C-reactive protein might share a common pathway linking obesity to preeclampsia. It has been seen that increase in BMI causes increase in the levels of C- reactive protein.[29] Physiologically, preeclampsia is characterized by elevated circulating levels of TNF-α and IL-6, where IL-6 are the major source from adipose cells. Thus they are the principle determinants of hepatic C-reactive protein production. Therefore C- reactive protein might be an intermediary in the pathway between BMI and preeclampsia.

Obesity is also a validated risk factor for preeclampsia.[24] Obesity has an association with insulin resistance, a syndrome of metabolic derangement characterized by hyperinsulinemia, hyperlipidemia, hypertension and endothelial dysfunction[25] causing activation of inflammatory mechanism. Thus elevated C-reactive protein is another distinct feature of the insulin resistance syndrome.

REVIEW OF LITERATURE

In the year 2006, study done by Selahattin Kumru *et al* showed that Serum hs-CRP levels increase significantly in women with preeclampsia. Elevated serum levels of hs-CRP in preeclamptic women are correlated with clinical and biochemical parameters of preeclampsia. Determination of serum hs-CRP levels may be used as a marker for the severity of preeclampsia[19]

Study done by Delia M. Paternoster *et al* in 2006, showed that in Transient Hypertension, Preeclampsia and HEELP syndrome, CRP levels were higher than in the controls, suggesting that inflammation may be the common pathogenic cause of TH and PE. Finally CRP levels in preeclampsia are believed to correlate with preeclamptic process severity.[32]

In the year 2007, Hwang HS *et al*, showed that hs-CRP levels were positively correlated to pregnancy duration in healthy women and could be used as a severity marker in women with severe PE. The median values of hs-CRP in each group were 0.76 mg/L (0.16-13.61 mg/L), 1.53 mg/L (0.39-20.31 mg/L), 2.08 mg/L (0.50-9.45 mg/L), and 2.28 mg/L (0.44-8.11 mg/L) and showed a trend toward increase. Serum levels of hs-CRP were positively correlated with each severity.[33]

Study done by Samira Behboudi-Gandevani *et al* in 2012, showed that Mean±SD hs-CRP levels in mild (7.2±2.2 mg/L) and severe (9.4±3.9 mg/L) PE were significantly higher than the normal group (2.5±2.7 mg/L). Mean±SD birth weights in severe (3100±590 g) and mild (3150±742 g) PE were significantly lower than uncomplicated pregnancies (3340±590 g). He showed that hs-CRP can be useful in identifying pregnant women at risk for preeclampsia and low-birth weight infants.[34]

Study by Mehdi Farzadnia in 2013, showed that hs-CRP levels elevated in severe PE compared with mild PE and normal pregnant group ($p<0.001$) and is useful in predicting the severity of PE.[35]

LIMITATIONS OF OUR STUDY

Sample size was too small. We did not correlate the parameters with different gestational age groups. We did not estimate for severity of preeclampsia and its complications The prognosis and mortality of the subjects was not considered. We did not consider the BMI of the patient. Detection of these parameters in early pregnancy could help in development of preeclampsia in these patients, so that the prognosis is guarded.

CONCLUSION AND SCOPE OF FUTURE STUDY

Increased hs-CRP considered as a supportive useful tool in prediction of preeclampsia. Hypertensive disorders of pregnancy are the complex multisystem disorders characterized by widespread endothelium dysfunction involving almost all vital organ systems. These disorders are associated with marked mortality and morbidity in both mother and fetus.

The main cause behind endothelial dysfunction is release of inflammatory mediators from ischemic placenta. These mediators on one side cause decreased synthesis and release of vasodilator agents (e.g. PlGF, VEGF, NO, PGI_2, etc) and increased release of vasoconstrictor agents (e.g. endothelin-1, TxA_2, etc) leading to hypertension.

The increased hs- CRP levels in the patients can also identify the persons with future risk of developing cardiovascular disease. So that certain preventive measures can be taken to prevent it.

Further studies on a larger sample are needed to substantiate our findings before firm conclusion can be drawn on the utility of these parameters for the diagnostic assessment of Preeclampsia.

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