Original Research Article

Correlation between inflammatory markers, LFT in Preeclampsia

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Abstract

The pregnancy is the state of carrying a developing embryo or fetus within female body1. Preeclampsia affects 3-5% of pregnancies. Placental ischemia and inflammation occur due to impaired trophoblastic invasion in uterine spiral artery. Preeclampsia is an idiopathic multisystem disorder that typically starts after the 20th week of pregnancy; high blood pressure is a main contributing factor. Ten million women develop preeclampsia each year around the world. 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. In the last trimester liver disease associated with abnormal liver disease associated with abnormal liver function tests, nausea and/or vomiting and abdominal pain is due to severe preeclampsia, HELLP syndrome or acute fatty liver of pregnancy with or without sub-capsular hepatic haematomas, amongst which there is an overlap. Lactic dehydrogenase (LDH) is an intracellular enzyme that converts lactic acid to pyruvic acid , and elevated levels indicate cellular death and leakage of the enzyme from the cell. As severe preeclampsia may lead to numerous multisystem complications, elevated level of LDH may reflect the severity of preeclampsia and the occurance of complications. **Aims and Objective:** To evaluate the Liver Function Tests and inflammatory markers like hs-CRP, in preeclampsia patients and compare with normal pregnancy. **Results:** The liver function tests like Direct Bilirubin, AST, ALP, Total proten and Albumin showed significant p value $p < 0.001$ between cases and controls. The mean LDH levels in cases and controls 451mg/dl and 185 mg/dl respectively with significant p value of $p < 0.0001$. The hs-CRP levels in cases is 1.08 ± 0.79 mg/L, when compared to controls 0.23 ± 0.19 mg/L with $p < 0.0001$.

Key Word:

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INTRODUCTION

The pregnancy is the state of carrying a developing embryo or fetus within female body[1]. Pregnancy is a physiological state associated with many alterations in metabolic, biochemical, physiological, hematological and immunological processes. If there are no complications, all these changes are reversible following a few days to a few months after delivery [2]. Pregnancy induced hypertension syndrome, is an idiopathic disease prone to occur in late pregnancy. PIH is the one of the top 3 leading causes of death in pregnant women seriously affecting maternal and infant health and safety [3].

Preeclampsia develops in 4-5% of human pregnancies and is charecterised by hypertension, dyslipidemia and increased systemic inflammatory response[4]. PIH is a serious complication of the second half of pregnancy with urinary loss of proteins, odema and activation of hemostatic mechanisms[5]. Preeclampsia is characterized by an increased BP equal to or above 140/90 mmHg in presence of proteinuria that develops after 20 weeks of gestational age. PE results in eclampsia if develops or manifests as hemolysis, elevated liver enzymes and low platelet count syndrome (HELLP). Severe complication like cerebral hemorrhage, renal failure, lung edema and

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liver hemorrhage are associated with eclampsia and HELLP syndrome[6]. 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[7]. Activated circulating leukocytes[8,9] increased production of reactive oxygen species[10] , 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. C – Reactive Protein (CRP) is one of the acute phase reactants in humas. 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[11,12]. 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 hsCRP 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[13]. It is useful in differentiating acute inflammation as well as assessment of severity of inflammation[14]. Uric acid is a marker of oxidative stress, tissue injury and renal dysfunction, and therefore might be helpful in the prediction of complications of preeclampsia [15]. Hypoxia and Ischemia of the placenta and cytokines such as interferon induce the expression of xanthine oxidase and therefore increase the production of uric acid and also reactive oxygen species[16]. Uric acid contribute to failed placental bed vascular remodeling by impending trophoblast invasion with resultant with reduced placental perfusion, setting the stage for ischemia reperfusion injury to the placenta and oxidative stress. Maternal tissue may experience ischemic injury due to vasospasm secondary to endothelial dysfunction . Ischemic injury and oxidative stress promotes a feed-forward cycle of uric acid production. With tissue injury , purines are liberated and with hypoxia, ATP is degraded to both adenine and xanthine (substrate). Hypoxia is the potent inducer of the xanthine oxidase/dehydrogenase enzyme. With the parallel increase in both substrate and enzyme concentrations, uric acid production will increase[17]. As the result of endothelial dysfunction, ischemia , oxidative stress which cause a systemic inflammation , and as the uric acid is a marker of inflammation, its levels are increased in preeclampsia. Liver Function Tests (LFT) abnormalities occur in 3% of the pregnancies and preeclampsia is the most frequent cause[18]. The liver diseases peculiar to pregnancy have a characteristic time of onset. In liver diseases peculiar to pregnancy have a characteristic time of onset. In the last trimester liver disease associated with abnormal liver disease associated with abnormal liver function tests, nausea and/or vomiting and abdominal pain is due to severe preeclampsia, HELLP syndrome or acute fatty liver of pregnancy with or without sub-capsular hepatic haematomas, amongst which there is an overlap[19]. Lactic dehydrogenase (LDH) is an intracellular enzyme that converts lactic acid to pyruvic acid , and elevated levels indicate cellular death and leakage of the enzyme from the cell. As severe preeclampsia may lead to numerous multisystem complications, we hypothesise that elevated level of LDH may reflect the severity of preeclampsia and the occurance of complications[20].

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 and Lady Curzon Hospital attached to Bangalore Medical College and Research Institute.

A) 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:

a. Preeclamptic primigravida of gestational age above 20 weeks.

b. The diagnosis of preeclampsia was made according to the criteria by

American College of Obstetrics and Gynecology

i.Blood pressure higher than 140/90 mmHg.

ii.Edema.

iii.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

a. Patients with history of Gestational Diabetes Mellitus.

b. 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.

B) 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.

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. Of the 30 cases and 30 controls included in the study, the Systolic and Diastolic Blood Pressure was significantly higher in pre-eclamptic pregnancies as compared with healthy pregnant women. (P<0.001)

Table 1: Showing the percentage of urine protein in patients with controls

		Case	Control	Total
PROT	1+	33.33%	20%	26.67%
	2+	33.33%	0%	16.67%
	3+	33.33%	0%	16.67%
	Absent	0%	80%	40.00%
Total		**100.00%**	**100.00%**	**100.00%**

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.

Table 2: Pearson correlation between the parameters

		Case			Control		
		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
UA	Correlation Coefficient	.780**	.888**	.484**	-.164	.503**	.164
	P value	<.0001	<.0001	.007	.386	.005	.387
TB	Correlation Coefficient	.102	.072	-.083	.098	-.034	.064
	P value	.590	.704	.663	.607	.857	.738
DB	Correlation Coefficient	.144	.225	.029	.119	.069	.370*
	P value	.447	.233	.880	.531	.715	.044
TP	Correlation Coefficient	-.125	-.318	.104	-.152	-.233	-.034
	P value	.511	.087	.583	.424	.216	.859
ALB	Correlation Coefficient	-.325	-.409*	-.182	-.113	-.135	-.116
	P value	.080	.025	.335	.553	.476	.542
ALP	Correlation Coefficient	.453*	.258	.415*	-.193	.155	-.116
	P value	.012	.169	.023	.307	.413	.543
AST	Correlation Coefficient	.348	.431*	.158	-.089	-.404*	-.371*
	P value	.060	.018	.404	.639	.027	.043
ALT	Correlation Coefficient	.376*	.369*	.118	.161	-.306	-.125
	P value	.041	.045	.534	.395	.100	.509
LDH	Correlation Coefficient	-.021	-.085	-.309	.214	.085	.169
	P value	.912	.657	.097	.257	.655	.373
PROTEIN	Correlation Coefficient	.557**	.571**	1.000	.306	.024	1.000
	P value	.001	.001		.100	.899	

Table 3: Diagnostic value of hs – CRP

HS – CRP (mg/L) CUT OFF VALUE > 0.5mg/ L			
Hs - CRP	Cases	Controls	Total
>0.5	19	2	21
<0.5	11	28	39
TOTAL	30	30	60
P VALUE – 0.0001***SENSITIVITY = 63 %SPECIFICITY = 93.33%POSITIVE PREDICTIVE VALUE = 90. 47%NEGATIVE PREDICTIVE VALUE = 71.79 %			

Table 4: Comparison of hs – CRP and DBP

DBP	No of patients	%	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 5: Pearson correlation between DBP with other parameters

Pair	p- Value	r – value
DBP Vs hs- CRP	0.0001	0.85

The current study is a case-control study in which the SHBG and hs-CRP levels in 30 preeclamptic patients were compared with 30 healthy normal pregnant women. The results were tabulated and statistically analysed. The Mean ± SD age of cases and controls were 36.06 ± 0.82.years and 36.3 ± 0.46 years respectively and was statisticslly not significant. So the study is age matched. 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. 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. 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. In the current study, hs-CRP levels in cases is 1.08 ± 0.79 mg/L, when compared to controls 0.23 ± 0.19 mg/L. In the present study the mean levels of hs-CRP is increased in preeclampsia subjects when compared with healthy normal pregnant women with p value of < 0.0001 which is significant. Thirty women in preeclamptic group compared with 30 normal pregnant women with similar age and period of gestation . The mean systolic blood pressure 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 diastolic blood pressure in cases and controls is 101.4 mm of Hg and 77.47 mm of Hg with significant p value of < 0.0001. The preeclamptic women had an equal distribution (33.3%) of urine protein as 1+, 2+ and 3+ on dipstick whereas control group had 80% nil and 20% in 1+ category. The mean serum uric acid in cases and controls are 6.41 mg/dl and 4.33 mg/dl respectively with p value of < 0.0001. The mean LDH levels in cases and controls 451mg/dl and 185 mg/dl respectively with significant p value of p <0.0001 The liver function tests like Direct Bilirubin, AST, ALP, Total proten and Albumin showed significant p value p < 0.001 between cases and controls.

On the other hand , Hs- CRP is correlated significantly positively with SBP, DBP , Uric Acid. Statistical analysis by multiple correlation coefficient showed that , there is significant positive correlation between UA and LDH with SBP and DBP. And significant positive correlation between inflammatory markers such as UA and Hs- CRP with SBP and DBP.

DISCUSSION

A similar study by Amir Taefl *et al* showed that the mean uric acid level in preeclampsia and normal healthy pregnancy is 5.8 mg/dl and 4.9 mg /dl , which is in accordance with our study.[21] In a study by Triveni *et al*, the showed that uric acid was very significantly higher in severe preeclampsia (<0.01) and in eclampsia (p<0.01) than in normal healthy pregnant controls . [22] In a study by Shirish T *et al* , which is is in accordance with our study, where the serum uric acid in cases was 7.52 mg/dl which

is much higher than in controls was 4.55 mg/dl with p value of $p < 0.0001$. [23] Inflammation is being increasingly recognized as the key contributer and component of serious and major health issues / diseases including CAD, DM and PIH. Systemic maternal inflammatory response to pregnancy is the cause of endothelial dysfunction which gives the clinical and pathological picture of pre-eclampsia[24]. This study is in accordance with study done by Anil Bargale *et al*, who studied 30 preeclamptic in which 17 mild and 13 severe preeclamptic and 30 normal pregnant women of between age 19-30 years with gestational age 28-40 weeks. He showed that hs-CRP levels increased in preeclampsia (3.733 ± 1.096mg/l) when compared to normal pregnant women (1.216 ± 0.552 mg/l). And also observed that gradual increase in hs-CRP level as disease progresses from mild (2.941 ± 0.390) to severe preeclampsia (4.769 ± 0.807)[14]. Hwang HS *et al*, showed that hsCRP 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 hsCRP 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 hsCRP were positively correlated with each severity[25]. The study by Ramadan D *et al* showed that, there is statistically significant difference in serum AST, ALT,and Total cholesterol in serum of pregnant women and newborns with IUGR and healthy pregnant women. ($p<0.001$)[26] A study by Vinita P *et al* showed that in women with preeclampsia, showed statistically significant increase in terms of systolic blood pressure ($p <0.05$), urine albumin ($p<0.05$), uric acid ($p<0.5$), LDH ($p<0.0001$) and liver enzymes ($p<0.05$)[20].

CONCLUSION

Preeclampsia is considered an idiopathic multisystem disorder that is specific to pregnancy. A complex of endocrinological mechanisms is believed to be responsible for the multiorgan dysfunction. In order to prevent it, we must diagnose the disease at the earliest. Thus it can be concluded that hyperuricemia and increased serum CRP level can be used as biomarkers for identifying women at risk of preeclampsia and complications along with adverse effects. Raised levels of serum bilirubin and liver enzymes showed the poor prognostic markers in preeclampsia. Detection of high risk patients with increased levels of LDH mandate close monitoring and management to prevent maternal and fetal morbidity and mortality.

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