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Gamma Glutamyl Transferase and Lactate Dehydrogenase as Biochemical Markers of Severity of Preeclampsia

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Abstract**—**This study was conducted to examine the possible role of serum Gamma-glutamyltransferase (GGT) and Lactate dehydrogenase (LDH) in the prediction of severity of preeclampsia. The study group comprised of 40 preeclamptic cases (22 with mild and 18 with severe) and 40 healthy normotensive pregnant controls. Serum samples of all the cases were assayed for GGT and LDH. Demographic, hemodynamic and laboratory data as well as serum GGT and LDH levels were compared among the three groups.

The results indicated that severe preeclamptic cases had significantly increased levels of serum GGT and LDH. The symptoms in severe preeclamptic women were significantly increased in patients with GGT > 70 IU/L and LDH >800 IU/L. Elevated levels of serum GGT and LDH can be used as biochemical markers which reflects the severity of preeclampsia and useful for the management of preeclampsia to decrease maternal and fetal morbidity and mortality.

Keywords**—**Severe Preeclampsia, GGT, LDH.

I. Introduction

PREECLAMPSIA is one of the most common medical complications of pregnancy and it is characterized by hypertension, proteinuria and/or edema, usually occurring after 20 weeks of gestation [1]. It is an important cause of maternal and perinatal morbidity and mortality worldwide, especially in developing countries. In India, the incidence of preeclampsia amongst the hospital patients is about 7-10% of all antenatal admissions [2]-[3]. Although the precise etiology of preeclampsia is not clear, defective placentation and endothelial dysfunction are considered the core features of preeclampsia [4].

It is a multisystem disorder that affects the maternal kidneys, liver, brain, clotting system and primarily the placenta [1]. Hepatic dysfunction with preeclampsia has long been recognized. Several studies have suggested that liver involvement in preeclampsia is serious and frequently accompanied by evidence of other organs involvement, especially the kidney and brain along with hemolysis and thrombocytopenia. This is commonly referred to as HELLP syndrome (hemolysis, elevated liver enzymes and low platelets) [5]-[6].

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The enzyme γ-glutamyltransferase (GGT) is widely distributed throughout the body in many tissues, particularly the liver. At the cellular level, significant activity occurs in both endothelium and epithelium [7]. Association between serum GGT concentration and blood pressure in non pregnant hypertensive patients have been reported in some population surveys. Also raised levels of serum GGT have been reported in stroke patients, which were assumed to be due to vascular endothelial damage [8]-[9]. Lactate dehydrogenase (LDH) is an intracellular enzyme which converts lactic acid to pyruvic acid and its elevated levels indicates cellular death and leakage of enzyme from the cell [10]. Increased levels of LDH were found in association with preeclampsia in a limited numbers of studies [11]-[13]. This is the first study that examines the frequency symptoms occurring in severe preeclamptic patients according to the levels of GGT and LDH, indicating multiorgan involvement and severity of the disease. As severe preeclampsia causes numerous multisystem complications, we hypothesize that elevated levels of serum GGT and LDH may reflect the severity of preeclampsia and the occurrence of complications.

II. Material and Methods

This prospective study was conducted in the department of Biochemistry, S.R.T.R. Medical College and Hospital, Ambajogai during the period of 2006 -2007. A total of 40 preeclampsia women (22 with mild and 18 with severe Preeclampsia) and 40 healthy normotensive pregnant women (controls) were enrolled in the study. All the cases were selected in the third trimester and belongs to the age group 19-35 years cases with any medical history of hypertension, diabetes, renal disease, thyroid disease or liver disease, were excluded from the study. Controls were selected from the patients regularly attending the Antenatal clinic (ANC) and preeclampsia cases were selected from the patients admitted in the ANC ward.

Mild preeclampsia was defined as onset of hypertension after 20 weeks of gestation with diastolic blood pressure (DBP) >90 and ≤ 110 mmHg with or without proteinuria. When diastolic blood pressure (DBP) > 110 mmHg was measured on two occasions 6 hours apart with significant proteinuria (>500mg / 24hrs or ≥2+ on dipstick), Preeclampsia was considered as severe.

Detailed clinical and anthropometric data was recorded using proforma. 5ml of fasting venous blood was collected aseptically from all cases by venipuncture. The blood was

allowed to clot and serum separated was used for the estimations. Serum GGT was estimated using commercial kit from Teco Diagnostics by Rosalkis gamma glutamyl P-nitroaniline (GGPNA) colorimetric end point method [14]. LDH was estimated using commercial kit from AGAPEE diagnostics by kinetic method [15]. The estimations were carried out on semiautoanalyzer (ERBACHEM- 5 plus). The results were expressed as means ± SD and compared by applying unpaired student 't' test to find out the statistical significance according to the severity of preeclampsia

III. Result

Demographic data of women with preeclampsia and healthy normotensive controls are shown in Table I. A statistically significant decrease ($p<0.05$) in terms of age, gravidity and parity was found among women with severe preeclampsia than normotensive controls. Systolic and diastolic blood pressure were significantly increased in mild ($p<0.05$) and severe ($p<0.001$) preeclamptic women, when compared with normotensive controls. Maternal weight was increased and newborn birth weight (from records) was found to be significantly low in severe preeclamptic women than normotensive controls ($p<0.05$).Table II shows the laboratory and hemodynamic data of the study groups. The levels of urea, creatinine, uric acid and bilirubin were found to be significantly increased in severe preeclamptic women as compared with normotensive ones ($p<0.05$). A statistically significant decrease ($p<0.05$) was found in total protein, albumin concentration and platelet count among severe preeclamptic women when compared with those in normotensive controls. The activities of enzymes AST and ALT were significantly increased in mild ($p<0.05$) and severe ($p<0.001$) preeclamptic women when compared with those in normotensive controls. The degree of proteinuria was persistant 1+ on dipstick in mild and 2+ or 3+ in severe preeclamptic cases. Table III shows the levels of serum GGT and LDH in the study groups. Serum GGT and LDH levels were found to be significantly increased among mild ($p<0.05$) and severe ($p<0.001$) preeclamptic women when compared with normotensive controls. Highly significant increase in LDH level was found in women with severe preeclampsia ($P<0.001$) as compared with mild preeclampsia.

Table IV shows the frequency of symptoms according to the levels of GGT and LDH in severe preeclampsia cases. Among the severe preeclamptic women, headache was the most frequent symptom observed in 66.66% cases and epigastric pain, vomitting and blurred vision were each observed in 55.5 % cases. The frequency of epigastric pain was found to be higher in severe preeclamptic women with GGT >70 IU/L (33.33%) and LDH> 800 IU/L (44%). Vomitting was observed in 38.8% of severe preeclamptic cases with each GGT >70 IU/L and LDH >800 IU /L. Headache and blurred vision were observed in 27.7 % and 16.6 % of cases having GGT >70 IU/L respectively .These symptoms were observed in 33.33 % of women with LDH >800 IU/L. Some women had multiple symptoms.

TABLE I
Demographic Data of the Study Groups

Parameters	Normal pregnancy (n = 40)	Mild Preeclampsia (n = 22)	Severe Preeclampsia (n = 18)
Age(Yrs.)	25.13 ± 2.34	24.18 ± 3.71	22.16 ± 2.25 *
Gravidity	3.2 ± 2.4	3.1 ± 2.5	2.2 ± 1.4 *
Parity	2.6 ± 0.5	1.7 ± 0.6	1.2 ± 0.4 *
Systolic BP (mmHg)	110.0 ± 10.4	143.0 ± 12.5 *	170.5 ± 10.6**
Diastolic BP (mmHg)	67.4 ± 4.8	92.0 ± 7.5 *	112.0 ± 5.8 **
Maternal weight (Kg)	65.6 ± 7.5	68.2 ± 5.2	72.4 ± 4.6 *
Birth weight (Kg)	3.2 ± 0.17	2.9 ± 0.22	2.2 ± 0.18*

Values are given as mean ± SD * P <0.05; ** P < 0.001

TABLE II
Hemodynamic and Laboratory Data of the Study Group

Parameters	Normal Pregnancy (n = 40)	Mild Preeclampsia (n = 22)	Severe Preeclampsia (n = 18)
Urea (mg/dl)	18.65 ± 4.31	19.22 ± 2.04	24.85 ± 4.30 *
Creatinine (mg/dl)	0.62 ± 0.14	0.75 ± 0.23	1.3 ± 0.19 *
Uric acid (mg/dl)	3.5 ± 0.76	5.0 ± 1.2	7.20 ± 1.4 *
Bilirubin (mg/dl)	0.79 ± 0.17	0.82 ± 0.24	1.4 ± 0.29 *
Total protein (gm/dl)	5.91 ± 0.30	5.6 ± 0.71	5.1 ± 0.42 *
Albumin (gm/dl)	3.67 ± 0.82	3.40 ± 1.2	2.63 ±0.61 *
Platelets (×109/l)	220 ± 30.2	205 ± 22.0	185.5 ±28.33 *
AST (IU/L)	22.26 ± 2.55	30.00 ± 3.08 *	46.27 ± 3.03 **
ALT (IU/L)	16.74 ± 2.90	29.23 ± 2.93 *	44.16 ± 4.28 **
Proteinuria (dipstick)	nil	1 +	2+ or 3+

Values are given as mean ± SD * P<0.05; ** P <0.001

TABLE III
SERUM GGT AND LDH LEVELS IN THE STUDY GROUPS

Parameters	Normal Pregnancy (n = 40)	Mild Preeclampsia (n = 22)	Severe Preeclampsia (n = 18)
GGT (IU/L)	10.25± 2.01	39.48± 4.11 *	61.66± 12.04 **
LDH (IU/L)	305.20± 42.24	535.22± 44.82 *	819.88± 90.7 **

Values are given as mean ± SD * P<0.05; ** P <0.001

TABLE IV
SYMPTOMS ACCORDING TO THE LEVELS OF GGT AND LDH IN SEVERE PREECLAMPSIA

Symptoms	nn	GGT =35-70 IU/L	GGT >70 IU/L	LDH =600-800 IU/L	LDH >800 IU/L
Epigastric pain (55.5%)	110	04 (22.22%)	06 (33.33 %)	02 (11.11%)	08 (44.00%)
Vomitting (55.5%)	110	03 (16.6 %)	07 (38.8 %)	03 (16.6%)	07 (38.8%)
Headache (66.66 %)	112	07 (38.8 %)	05 (27.7 %)	06 (33.33%)	06 (33.33%)
Blurred vision (55.5 %)	110	07 (38.8 %)	03 (16.6 %)	04 (22.22%)	06 (33.33%)

IV. DISCUSSION

Preeclampsia is a pregnancy-specific disease with multisystem complications. A complex of endocrinological mechanisms is believed to be responsible for the multiorgan dysfunction [2]. Several potential markers have been proposed to predict the severity of preeclampsia [10], [11]. Most useful among these are GGT and LDH. There are very limited studies with conflicting data on GGT and LDH in preeclampsia [7], [11], [12]. This study was undertaken to investigate the possible role of GGT and LDH in the prediction of severity of preeclampsia to prevent further complications. Young age and primigravidity are the well known risk factors for the development of preeclampsia [16]. In the present study, women with severe preeclampsia were significantly younger and with low gravidity and parity compared with normotensive controls and mild preeclamptic women. Preeclampsia is associated with reduced placental perfusion and fetal growth retardation [17]. In our study, the mean birth weight of babies born to severe preeclamptic mothers was found significantly low as compared to normotensive controls. These findings are in agreement with the previously reported studies [10]-[18]. Vascular endothelial dysfunction has been recently suggested as central pathogenic cause of preeclampsia [4]. This dysfunction increases the sensitivity of the vasculature to vasoactive substances, with a subsequent reduction of perfusion and loss of fluid from intravascular compartment. These hemodynamic changes along with the activation of a coagulation cascade with micro thrombi formation as a result of endothelial damage leads to various clinical complications associated with preeclampsia [10]. Eclampsia, abruptio placenta, HELLP syndrome, acute renal failure, intracranial hemorrhage is well recognized complications of preeclampsia [19]. In the present study the symptoms indicating multiorgan dysfunction correlated with the levels of GGT and LDH in severe preeclamptic women .We found that 87.5% of preeclamptic cases had abnormal levels of GGT.

It is possible that endothelial cell destruction within the uteroplacental circulation leads to systemic release of GGT [7]. Our data support this hypothesis suggesting an association between serum GGT levels and preeclampsia. It was found that 90% of preeclamptic women had abnormal levels of LDH. In agreement with previous findings [11]-[13] we propose that the multiorgan dysfunction in severe preeclampsia caused by vascular endothelial damage, including maternal liver, kidney, lungs and coagulation system; will lead to excessive LDH leakage and elevated levels in serum due to cellular dysfunction. Epigastric pain or right upper quadrant pain is often a symptom of severe preeclampsia and may be caused by subcapsular hematoma, abnormal liver function in HELLP syndrome due to periportal hemorrhagic necrosis or it may be indicative of imminent eclampsia. In most of the cases this symptom is associated with headache, blurred vision or vomitting [19]. In our study, epigastric pain and vomitting were observed in 55.5% of women with severe preeclampsia. Headache and blurred vision were observed in 66.66% and 55.5% of severe preeclamptic women respectively. Interestingly these symptoms were significantly higher in severe preeclamptic women with levels of GGT >70 IU/L and LDH >800 IU/L; indicative of hepatic cellular damage. Thus elevated levels of GGT and LDH, indicative of endothelial dysfunction and cellular damage, can be used as biochemical markers which reflect the severity of the disease and occurrence of complications.

V. CONCLUSION

High levels of GGT and LDH may be useful for the monitoring and correct management of preeclampsia to decrease maternal and fetal morbidity and mortality.

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