



STUDY ON CORRELATION BETWEEN MATERNAL SERUM LDH LEVELS AND SEVERITY OF PRE-ECLAMPSIA – MATERNAL AND PERINATAL OUT COME

DR. T.G. REVATHY

M.d., D.g.o. (ob&g), Professor, Iso – Kasturba Gandhi Hospital, Madras Medical College, Chennai, Tamilnadu.

Dr. C. Dhivya

M.d. (ob&g), Iso – Kasturba Gandhi Hospital, Madras Medical College, Chennai, Tamilnadu. - CO. AUTHOR

ABSTRACT

AIM:-

- 1) To Compare Serum LDH Levels in normal pregnant women and in women with pre-eclampsia.
- 2) To find the relationship between severe LDH levels and of pre eclampsia maternal and perinatal outcome.
- 3) To find prognostic value of LDH in maternal morbidity in pre eclampsia.

MATERIALS & METHODS:

Study design	: Prospective Comparative Study
Study Period	: August 2015 to August 2016
Place of study	: Department of obstetrics and gynaecology Government Kasturba Gandhi Hospital Triplicane Chennai.

Sample Size	: 200
Methods	: Estimation of Maternal serum LDH

Results:

In this Study There was no statistical significance with respect to age, BMI, Socio economic status., LDH levels were found higher among pre eclampsia group compared to healthy normal pregnant women. Among the pre eclampsia group high level of LDH were seen in severe pre eclampsia when compared to mild pre eclampsia.

Conclusion:

Elevated levels of maternal serum Lactate dehydrogenase (LDH) is indicative of cellular damage and dysfunction can be used as biochemical marker because it reflects the severity of disease, because of complications and perinatal outcome. Increased LDH methods close monitoring and management to decrease both maternal and fetal morbidity and mortality.

KEYWORDS :

INTRODUCTION

Worldwide about 10 million women develop preeclampsia every year. Out of them about 76,000 pregnant women die each year from preeclampsia and related hypertensive disorders. The number of babies who die from these disorders is around 500,000 per annum. The World Health Organization (WHO) systematically reviews maternal mortality worldwide, and in developed countries, 16 % of maternal deaths were attributed to hypertensive disorders (Khan, 2006). In developing countries, a woman is seven times as likely to develop preeclampsia than a woman in a developed country. Hypertensive disorders of pregnancy complicate around 5-10% of all pregnancies. The mechanism behind elevation of blood pressure or aggravation of hypertension still remains an enigma despite the research for many decades, thus remaining one among the most significant and unsolved problems in obstetrics. Placental hypoperfusion and diffuse endothelial injury are considered to be the main pathologic events. Several markers have been investigated as the predictors of pre-eclampsia and to assess severity of preeclampsia. Early detection of women at higher risk helps in making decision, regarding the management strategies to improve the maternal and fetal outcome.

REVIEW OF LITERATURE

Hypertensive disorders complicate 5 to 10% of all pregnancies, and together they are one member of the deadly triad—along with hemorrhage and infection—major contributors to maternal morbidity and mortality. Out of these disorders, the *preeclampsia syndrome*, either alone or superimposed on chronic hypertension, is the most dangerous.

These are the following:-

Couple related risk factors:

- Primipaternity
- Limited sperm exposure

- Pregnancy after donor insemination

Maternal/ pregnancy related risk factors:

- Extremes of age
- Obesity and insulin resistance / gestational diabetes
- Smoking
- Multifetal pregnancies
- Preeclampsia in previous pregnancy
- Maternal low birth weight
- Family history of preeclampsia

Pre existing medical disease:

- Pre-gestational diabetes
- Chronic hypertensive or renal disease
- Maternal immunological disease
- Preexisting thrombophilia, antiphospholipid antibody syndrome

LACTATE DEHYDROGENASE:

Lactate dehydrogenase (LDH) is mainly an intracellular enzyme. It is responsible for interconversion of lactate and pyruvate inside the cells playing a role in glycolytic metabolism. It permits cells to generate a temporary oxygen debt in the form of accumulated lactate to be later discharged by reoxidation of lactate to pyruvate when oxygen becomes available. It is present in many body tissues, especially heart, liver, kidney, skeletal muscles, brain, blood cells and lungs.

LDH levels inside the cells are several times greater than in the plasma. Thus serum LDH levels are elevated in scenario of increased cell leakiness, hemolysis and cell death. Since preeclampsia is a multisystem disorder, serum LDH levels can be used to assess the extent of cellular damage and thus the severity of disease. LDH activity when measured using spectrophotometry at 340nm follows either the oxidation of NADH by pyruvate (decrease in

absorption) or reduction in NAD+ with lactate (increase in absorbance) at rates producing a change in absorbance of 0.05 to 0.1 per minute. Under standard conditions one unit of enzyme catalyses the oxidation

	SERUM LDH LEVELS (U/L)
Nonpregnant adult	115 – 221
First trimester	78 – 433
Second trimester	80 – 447
Third trimester	82 – 524

MATERIALS AND METHODS

INCLUSION CRITERIA

All Pregnant women with 20weeks of gestation or more will be enrolled in this study and grouped as healthy normotensives and those with preeclampsia.The latter are subdivided as mild preclampsia and severe preeclampsia.

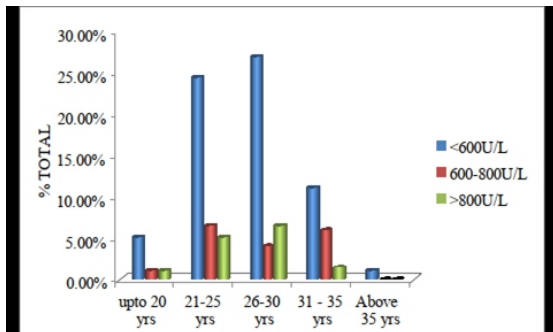
EXCLUSION CRITERIA

Pregnant women with essential hypertension or hypertension <20 weeks gestation; Preexisting diabetes mellitus, renal disease, liver disorder, thyroid disorder, epilepsy & with urinary tract infection, anemia,heartdisease,and those in labour.

METHODOLOGY

A total of 200 antenatal patients who attended the antenatal clinic of the Department of Obstetrics & Gynecology, Government Kasturba Gandhi Hospital, were selected based on the inclusion & exclusion criteria after obtaining their informed consent.All selected women were subjected to a detailed historytaking,clinical examinationand routine laboratory investigationsalong with LDH .patients were followed in terms of maternal outcome (complications, mode of delivery)and fetal outcome (birth weight, preterm birth,NICU admission) till early neonatal period.

RESULTS :-



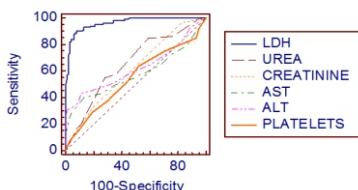
There was no significant relation between the study groups categorised according to LDH levels, with respect to age.

Statistical analysis showed no significant relationship between the study groups categorised according to LDH with respect to socio economic status.

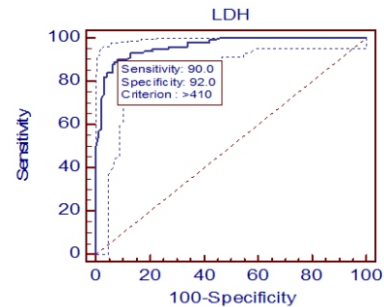
LDH * STUDY GROUP

	N	Mean	Std. Deviation	Std. Error
Normal	100	254.74	110.616	11.062
Mild Preeclampsia	49	584.76	155.615	22.231
Severe Preeclampsia	51	870.41	462.305	64.736
Total	200	480.34	361.839	25.586

COMPARISON OF ROC CURVES (NORMAL VS PREECLAMPSIA)

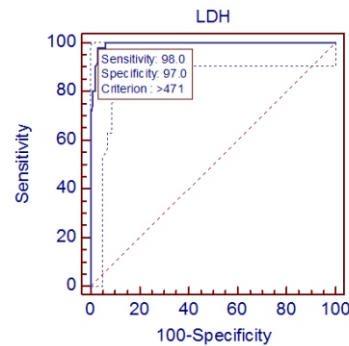
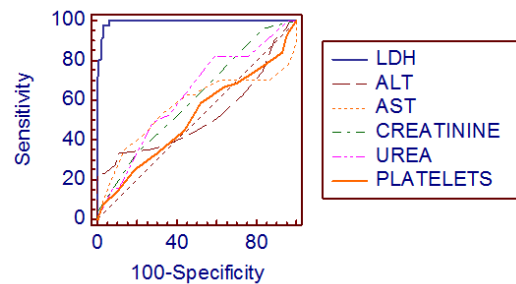


The objective of the study was to find the biomarker value of LDH between the normal healthy pregnant women and women with preeclampsia (both mild and severe). So a ROC curve was plotted. The area under the curve was found to be 0.963 for LDH. Since the values of Urea, Creatinine,ALT,AST,Platelets were available,ROC curves were plotted for these variables also. On comparing the area under the curve of all the variables it was clearly evident that AUC was more for LDH.Thus indicating that LDH is better biochemical marker to assess severity of preeclampsia.



ROC graph of LDH clearly shows that for criterion > 410 U/L, sensitivity is 90 and specificity is 92 and AUC 0.963, in assessing the severity of preeclampsia.

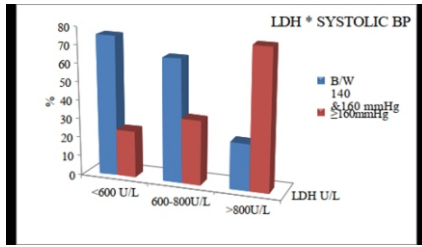
COMPARISON OF ROC CURVES AMONG SEVERE PREECLAMPSIA & NORMAL



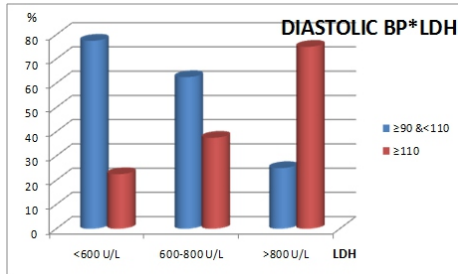
ROC graph of LDH shows that for the criterion >471, sensitivity is 98, specificity is 97 and area under curve 983 in predicting severe preeclampsia.

Out of the patients with LDH > 800 U/L 74% were severe preeclampsia and 26% were mild preeclampsia with none belonging to the normotensive group.Out of the patients with LDH between 600 and 800U/L 48.6% were mild preeclampsia and 42.9% were severe preeclampsia.About 70% of the patients in LDH<600U/L group were normal

With the mean value obtained from above table, patients with preeclampsia were grouped as those with LDH< 600 U/L LDH between 600 and 800, LDH> 800 u/l to assess the severity of preeclampsia and its relationship with maternal and perinatal outcome

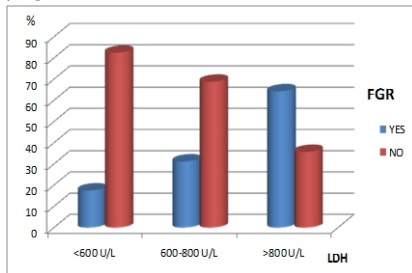


Pearson Chi-Square=19.027* p<0.001 – STATISTICALLY SIGNIFICANT

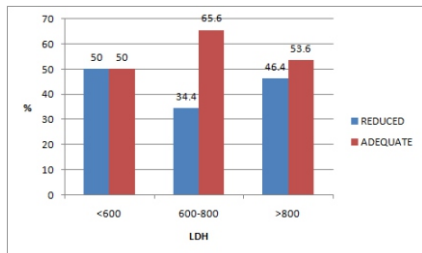


Among the preeclampsia women, 75% of those with LDH >800 U/L had diastolic BP more than 110 mmHg; 62.5% of those with LDH 600 – 800 U/L had diastolic BP 90 mmHg and above but less than 110 mmHg, while it was 77.5% for those with less than 600 U/L.

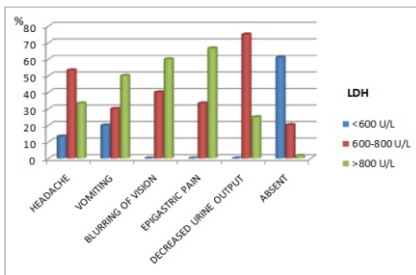
Pearson Chi-Square=16.138* p<0.001. Occurrence of fetal growth restriction in preeclampsia women with respect to LDH values is statistically significant



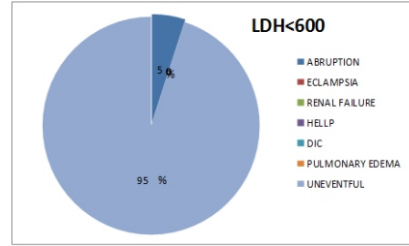
Incidence of fetal growth restriction was high in the group of preeclamptic women whose LDH was greater than 600 than those with LDH less than 600 U/L. 64.3% of preeclamptic women with LDH >800 U/L were complicated with fetal growth restriction whereas it was 31.2% for those with LDH between 600 – 800 U/L.



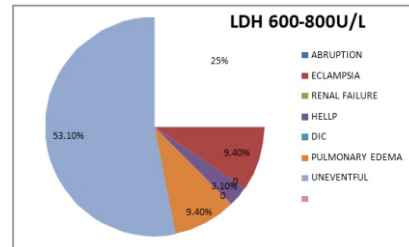
Though statistical significance was established with respect to reduced AFI among women with preeclampsia, correlation was not seen with respect to LDH among the preeclamptic women with reduced AFI



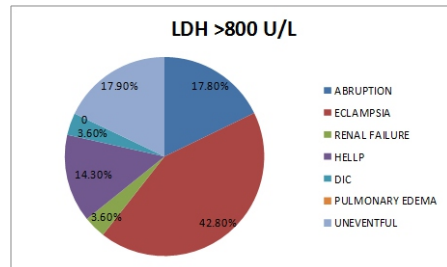
Headache was the most frequent premonitory symptom of severe preeclampsia followed by vomiting, blurring of vision, decreased urine output and epigastric pain. Those with epigastric pain had marginal elevation of AST and ALT in addition to LDH.



Maternal outcome of 95 % of the preeclampsia women with LDH <600 U/L was uneventful.

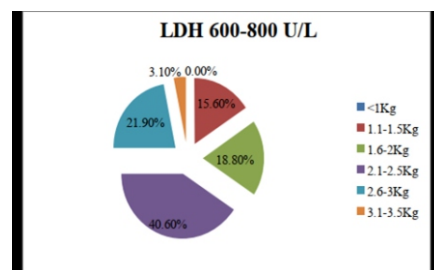


Out of the preeclamptic women with LDH 600-800 U/L, 46.9% developed complications with the most common among them being abruption followed by eclampsia, pulmonary edema and HELLP.

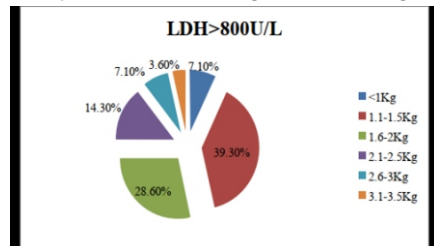


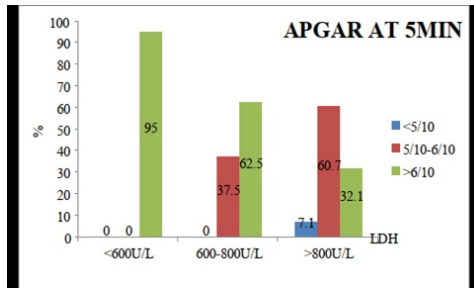
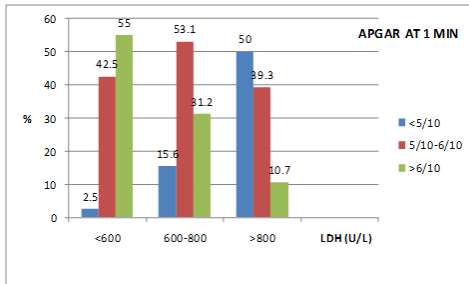
Out of the preeclampsia women with LDH >800 U/L 82.1% developed complications with eclampsia contributing most of it (42.8%) followed by abruption (17.8%), HELLP (14.3%), DIC (3.6%) and renal failure (3.6%).

In the subgroup of preeclampsia patients with LDH < 600 U/L 60% had babies weighing 2.6 to 3 kg, 40% were 2.5 kg and lesser.



This figure shows distribution of birth weight of the babies among the preeclamptic women with LDH between 600 and 800 U/L. 37.5% of those patients had birth weight less than 2.6 kg.





This chart shows lower apgar scores corresponding to higher LDH levels especially with LDH levels greater than 800 U/L

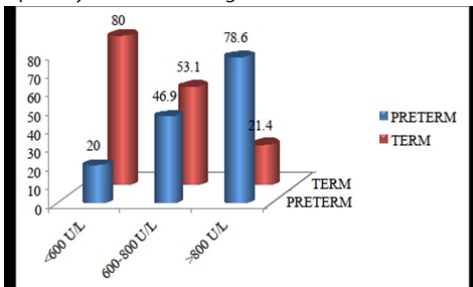


Chart shows that incidence of preterm births are significantly high with serum LDH levels above 800 U/L.

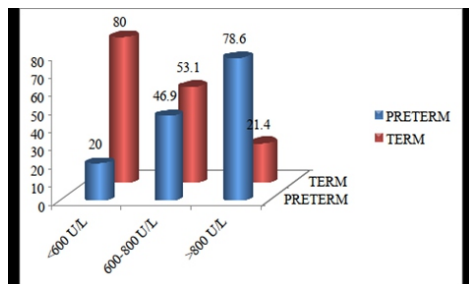
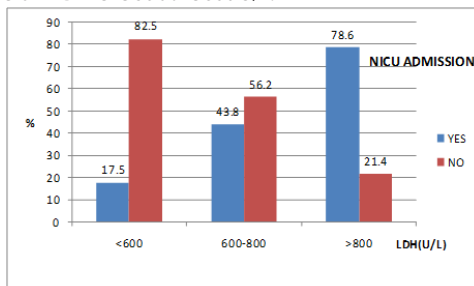


Chart shows that incidence of preterm births are significantly high with serum LDH levels above 800 U/L.



DISCUSSION

Out of the total 200 patients included in the study, 100 were normal healthy pregnant women, 51 were severe preeclampsia and 49 were mild preeclampsia constituting 50%, 25.5% & 24.5% of the total respectively.

Among the study group 7% were <20yrs of age, 36% between 21 – 25years, 37.5% between 26 – 30 years, 18.5% between 31 – 35 years of age and 1% above 35 years of age. In my study there was no statistical significance among the study groups with respect to age. 16.5% of the study group had BMI 18.5 – 25 kg/sq.m, 51.5% between 25 – 30 Kg/sq.m, 32% had BMI more than 30kg/sq.m. There was no statistical significance with respect to BMI among the study group. 43.5% were primigravida, 40% were second gravida, 12% were third gravida. Gravida 4 and above constituted 4.5% of the patients. There was no statistical significance between the study groups with respect to gravidity and parity.

In my study none of the patients were in class I and class II. Those of Class III, Class IV and Class V constituted 33.3%, 27.7% and 21% respectively. Statistical analysis did not show any significance with respect to socioeconomic status between the study groups.

On analysing the antenatal visits of the study group it was seen that the antenatal visits of severe preeclampsia patients were highly irregular.

The values of blood urea, serum creatinine, AST and ALT and platelets which were taken as a part of routine laboratory investigations and these values were compared with serum LDH. The values of blood urea, serum creatinine, AST and ALT were found to be higher among women with severe preeclampsia compared to normotensives and those with mild preeclampsia as concluded in many previous studies (N. R. Hazari 2014; Andrews L, 2014) (6, 7, 10). ROC curves were plotted for these variables between the normal and preeclampsia. Though the values of LDH, urea, creatinine, AST and ALT were increased among the preeclampsia women when compared to the normotensives, the area under the curve for LDH was highest. ROC curves were also plotted for the above variables between the normal women and those with severe preeclampsia. It was inferred that LDH was a better marker of severity of preeclampsia.

The mean LDH levels that were obtained for normal group was 254.7 U/L, mild preeclampsia was 584.76 U/L and severe preeclampsia was 870.41 U/L

In Qublan et al study 2005, LDH levels >600U/L were seen in 54.8% with severe preeclampsia compared with 8.3% and 12.2% of normotensives and mildly preeclamptic women.

Statistical significance was found to exist in my study with respect to fetal growth restriction among the preeclampsia women grouped according to serum LDH levels. Incidence of fetal growth restriction was high in the group of preeclamptic women whose LDH was greater than 600 than those with LDH less than 600U/L. 64.3% of preeclamptic women with LDH >800 U/L were complicated with fetal growth restriction whereas it was 31.2% for those with LDH between 600 – 800 U/L. This was consistent with a previous study (12) in which the mean gestational age at delivery was less in patients with increasing LDH levels (>500 U/L) indicating increase in preterm and IUGR deliveries in patients with higher LDH levels. Though amniotic fluid index was found to be reduced among the preeclampsia group when compared to the normal group, statistical significance didn't exist among the preeclampsia group categorised according to LDH with respect to AFI.

Headache was the most frequent premonitory symptom (40.5%) of severe preeclampsia followed by vomiting (27%), blurring of vision (13.5%), decreased urine output (10.8%) and epigastric pain (8.2%). Those with epigastric pain had marginal elevation of AST and ALT in addition to LDH. Ophthalmic fundus examinations of all the patients were normal. There existed statistical significance preeclampsia patients with premonitory symptoms and the LDH levels. Those with LDH >800U/L had a significant raise in the frequency of epigastric pain and vomiting compared to the other groups.

Pregnancy was terminated at an earlier gestational age in women

with preeclampsia when compared to the normal healthy pregnant women. All the preeclampsia patients whose pregnancy was terminated before 32 weeks had LDH levels > 800 U/L. (12)

Out of the preeclamptic women with LDH 600-800U/L, 46.9% developed complications with the most common among them being abruption followed by eclampsia, pulmonary edema and HELLP

Out of the preeclampsia women with LDH >800 U/L 82.1% developed complications with eclampsia contributing most of it (42.8%) followed by abruption (17.8%), HELLP (14.3%), DIC (3.6%) and renal failure (3.6%).

Richard. B. Schwartz et al in his study in the year 2000 found that the women with preeclampsia – eclampsia had raised LDH levels even before the development of neurological abnormalities and concluded that cerebral edema at Magnetic Resonance Imaging in these patients was associated with abnormal endothelial damage markers rather than the blood pressure.

Analysis of my study showed existence of statistical significance between the LDH subgroups with respect to birth weight. In the preeclampsia patients with LDH < 600 U/L 60% had babies weighing 2.6 to 3kg. 40% were 2.5kg and lesser. 37.5% of women with LDH between 600 and 800 U/L patients had birth weight less than 2.6kg. Among the preeclamptic women with LDH between 600 and 800 U/L, 89.3% patients had birth weight of their babies less than 2.6kg. Those less than 2kg constituted 75%. The low birth weight in my study could be partially due to higher incidence of premature births. The association of low birth weight of infants with increase in serum LDH levels was also suggested by He et al (8) in their study. But this was in contrary to Qublan et al who did not find any significant association

My analysis showed lower apgar scores corresponding to higher LDH levels especially with LDH levels greater than 800 U/L. (12) 78% of the preeclamptic women with LDH >800 U/L had their babies admitted in NICU. Out of the 43 babies admitted in NICU, 21 needed admission in NICU for more than 7 days. Out of the other 20 babies admitted in NICU, 14 expired. My study showed that perinatal mortality is increased significantly in patients with LDH >800 U/L which could be due to significant low birth weight associated with this level. 2 of the severe preeclampsia women had intrauterine fetal demise and their LDH levels were 760 U/L and 694 U/L. These results were similar to a study conducted by Sreelatha et al in 2015 (12)

A reliable correlation between the level of maternal serum LDH and severity of preeclamptic complications makes it valuable for clinical decision-making.

CONCLUSION

Preeclampsia is a pregnancy specific multisystem disorder. Elevated levels of maternal serum lactate dehydrogenase, indicative of cellular damage and dysfunction can be used as a biochemical marker because it reflects severity of the disease, occurrence of complications, perinatal outcome. These complications may be preventable. Detection of pregnancies with higher risk with increased levels of LDH mandates closer monitoring and management to decrease both maternal and fetal morbidity and mortality

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