ORIGINAL RESEARCH PAPER

Gynaecology

SEVERITY OF PRE-ECLAMPSIA WITH MATERNAL SERUM LDH LEVELS

KEY WORDS: Pre eclampsia, LDH, Fetal growth restriction, Hypertension

Dr A. Prabha MD.,OG., Assistant Professor,Thiruvarur Medical College.

Dr . P. Suganthi* MS.,OG, Assistant Surgeon,Thiruvarur Medical College. *Corresponding Author

ABSTRACT

AIM : Perinatal outcome between maternal serum LDH and severity of pre-eclampsia
SUBJECT & METHODS: Prospective study which included 200 antenatal patients . All pregnant women > 20 weeks , normotensives compared with pre-eclampsia. Pregnant women with other medical diseases are excluded in this study.
CONCLUSION : Increased levels of LDH in high risk pregnancies mandates monitoring . It decreases both maternal and fetal morbidity and mortality.

INTRODUCTION

Hypertensive disorders of pregnancy complicates 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. Lactate Dehydrogenase (LDH) is mainly an intracellular enzyme. serum LDH levels can be used to assess the extent of cellular injury and thereby the severity of disease . 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

PREECLAMPSIA:

It is a multiorgan disease process of unknown etiology characterized by denovo development of hypertension and proteinuria after 20 weeks of gestation. It is a pregnancy specific syndrome.

Clinical manifestations of preeclampsia may be either maternal syndrome alone (Hypertension and proteinuria >0.3g/24 hour-urine with or without other multisystem dysfunction) or in association with fetal syndrome (fetal growth restriction, oligohydramnios) Incidence of preeclampsia varies between 2-7% in healthy nulliparous women. Incidence and severity of the disease is higher in women with multifetal gestation, chronic hypertension, previous preeclampsia, pre-gestational diabetes or pre-existing thrombophilia.

ETIOLOGY

The exact etiology of preeclampsia is not known. But there are risk factors predisposing to development of pre-eclampsia.
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

PATHOGENESIS:

- **Vascular endothelial activation:**

The endothelial cell dysfunction is attributed to the extremely activated state of leucocytes in maternal circulation.Cytokines thus released contribute to oxidative stress by forming free radicals and self propagating lipid peroxides

- **Angiogenic imbalance:**

Trophoblastic tissue was described to produce excessive amount of antiangiogenic factors like Soluble Fms-like tyrosin kinase1 which inturn decreases circulating free PLGF (Placental like growth factor) and VEGF (Vascular Endothelial Growth Factor)

- Genetic factors
- Increased pressor response
- Decreased endothelial nitric oxide synthase expression
- Prostaglandins:
- The prostacyclin : thromboxane A2 ratio decreases leading to increased vasopressor response

COMPLICATIONS

Complications can be expected in many organ in this multi-system disorder.Maternal complications include

- Eclampsia
- Cerebral hemorrhage
- Cortical blindness
- Pulmonary edema
- ARDS(Adult Respiratory Distress syndrome)
- HELLP syndrome
- DIC
- Renal failure
- Hepatic rupture,
- Abruptio placenta
- Sudden postpartum collapse.

Fetal complications

- Prematurity
- IUGR
- Intra uterine death.

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 with

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

Hussein S. Qublan et al (2005) made a study on Lactate dehydrogenase as a biochemical marker of adverse pregnancy outcome in severe preeclampsia. 171 women were included in the study.Out of them 111 were pre eclamptic (49 with mild and 62 with severe pre eclampsia) and 60 were healthy normotensives.It was a prospective study.The incidence of severe preeclampsia was 1.3%.

Sreelatha S, ShwethaSharau et al (2014)studied the correlation between serum LDH levels and its correlation with maternal and perinatal outcome. It was a prospective study. Their study included 80 preclamptic women. Patients were followed up with respect to maternal outcome (Eclampsia, HELLP syndrome, mode of delivery etc.) and fetal outcome (birth weight, preterm delivery,NICU admission etc.)In their study the mild preeclampsia group had LDH less than 500 U/L. The mean gestational age at delivery at the time of delivery in the study was lesser in patients with increasing LDH levels and thus the increase in preterm and IUGR deliveries in patients with higher LDH levels.

AIM

1. To find the relationship between maternal serum LDH levels and severity of preeclampsia,maternal and perinatal outcome
2. To find prognostic value of LDH in maternal morbidity in preeclampsia.

Materials And Methods

Study Design

Prospective comparative study

Study Period

August 2017 to August 2018

Place Of Study

Department of Obstetrics and gynaecology, Government Thiruvarur medical college, Thiruvarur.

Sample Size

200

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 pre eclampsia 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 & Gynaecology, Govt Thiruvarur medical college , Thiruvarur , were selected based on the inclusion & exclusion criteria after obtaining their informed consent. All selected women were subjected to a detailed history taking ,clinical examination and routine laboratory investigation along 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

Out of the 200 pregnant women included in the study,100 were healthy normotensive and 100 were those with preeclampsia .Among the women with preeclampsia 51 were with severe pre eclampsia and 49 with mild preeclampsia. Demographic and hemodynamic factors like age, Body Mass Index, birthorder, socioeconomicstatus, other laboratory parameters were compared. Because levels of LDH <600 U/L were common in normal pregnancy and levels more than 600 U/L were associated with complications,after the analysis of results women in the preeclampsia group were subdivided into three groups according to the level of LDH as <600 U/L , 600 – 800 U/L,>800 U/L. Statistical analysis done using IBM SPSS 20.Results expressed as percentages were compared using the chi-square test.Differences were considered significant when p <0.01.

Results

Laboratory Parameters In Studygroup

		N	Mean	Std. Deviation	Std. Error	Sig.
Urea (mg/dl)	Normal	100	14.14	1.912	.191	.000
	Mild Preeclampsia	49	15.45	1.838	.263	
	Severe Preeclampsia	51	14.98	1.923	.269	
	Total	200	14.68	1.969	.139	.
Creatinine (mg/dl)	Normal	100	.636	.1177	.0118	
	Mild Preeclampsia	49	.690	.0984	.0141	
	Severe Preeclampsia	51	.688	.1107	.0155	.004
	Total	200	.663	.1141	.0081	
AST (IU/L)	Normal	100	22.92	3.858	.386	
	Mild Preeclampsia	49	26.73	4.804	.686	.000
	Severe Preeclampsia	51	22.33	5.659	.792	
	Total	200	23.71	4.906	.347	
ALT (IU/L)	Normal	100	23.28	2.948	.295	.001
	Mild Preeclampsia	49	26.80	4.463	.638	
	Severe Preeclampsia	51	24.82	5.645	.790	
	Total	200	24.54	4.382	.310	
Platelets (lakhs/cu. mm)	Normal	100	1.742	.3032	.0303	.307
	Mild Preeclampsia	49	1.657	.3416	.0488	
	Severe Preeclampsia	51	1.733	.3491	.0489	
	Total	200	1.719	.3252	.0230	

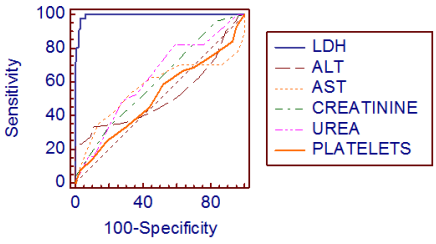
Analysis showed existence of statistical significance with respect to serum LDH levels among the study groups

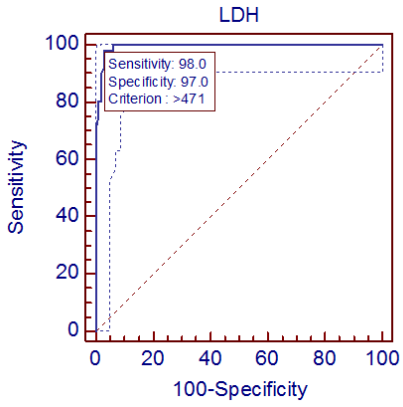
LDH levels were found higher among the preeclampsia group when compared to healthy normotensive pregnant women. Among the preeclampsia group higher levels of LDH were seen in severe preeclampsia when compared to mild preeclampsia.

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

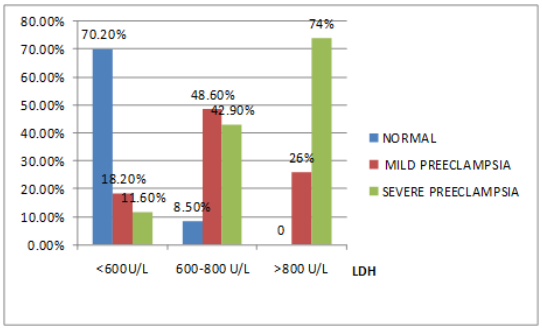
biochemical marker to assess severity of preeclampsia

Comparison Of Roc Curves Among Severe Preeclampsia & Normal





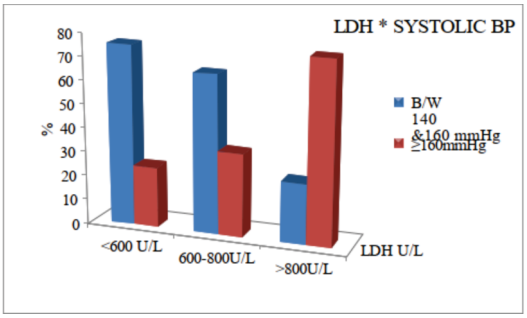
Pearson chi square = 87.1* p<0.001



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

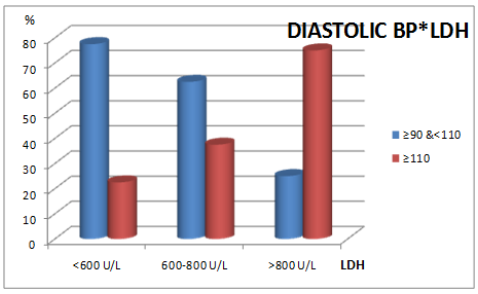
With the mean value obtained from above table, patients with preeclampsia were grouped as those with LDH< 600 U/L LDH between 600 and 800, LDH> 800 u/l to assess the severity of preeclampsia and its relationship with maternal and perinatal outcome

SYSTOLIC BP Vs LDH :



Among the preeclampsia women ,75% of those with LDH >800U/L had systolic BP more than 160mmHg , 65.6% of those with LDH 600 – 800 U/L had systolic BP 140 mmHg and above but less than 160mm Hg ,while it was 75% for those with less than 600 U/L.

DIASTOLIC BP *LDH



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

Fetal Growth Restriction In Study Group

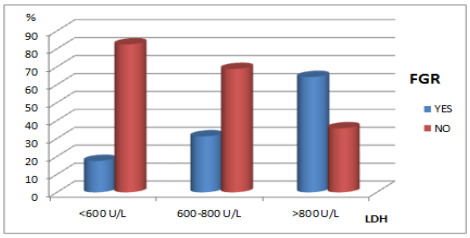
FGR		Normal	Mild preeclampsia	Severe preeclampsia	Total
Present	Number	9	1	34	44
	% within FGR	20.5%	2.3%	77.3%	100.0%
	% within study group	9.0%	2.0%	66.7%	22.0%
	% of Total	4.5%	.5%	17.0%	22.0%
Absent	Number	91	48	17	156
	% within FGR	58.3%	30.8%	10.9%	100.0%
	% within study group	91.0%	98.0%	33.3%	78.0%
	% of Total	45.5%	24.0%	8.5%	78.0%
Total	Number	100	49	51	200
	% within FGR	50.0%	24.5%	25.5%	100.0%
	% within study group	100.0%	100.0%	100.0%	100.0%
	% of Total	50.0%	24.5%	25.5%	100.0%

P <0.001 shows statistical significance. Occurance of fetal growth restriction was more among preeclamptic women than the normotensives

Ldh * Fetal Growth Restriction(fgr)

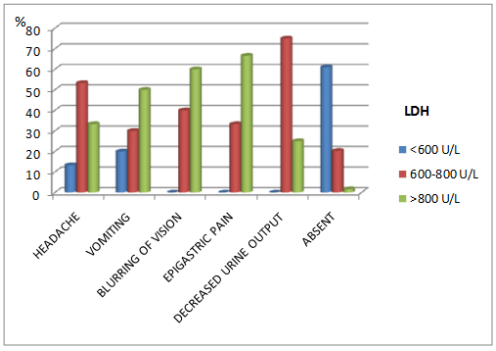
FGR IN PREECLAMPSIA		LDH(U/L)			Total
		<600	600-800	>800	
YES	Number	7	10	18	35
	% within LDH	17.5%	31.2%	64.3%	35.0%
NO	Number	33	22	10	65
	% within LDH	82.5%	68.8%	35.7%	65.0%
Total	Number	40	32	28	100
	% within LDH	100.0%	100.0%	100.0%	100.0%

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

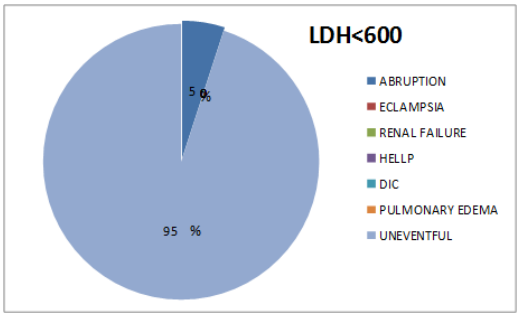


Incidence of fetal growth restriction was high in the group of preeclampticWomen whose LDH was greater than 600 than those with LDH less than 600U/L.64.3% of preeclamptic women with LDH >800 U/L were complicated with fetal growth restriction whereas it was 31.2% for those with LDH between 600 – 800 U/L.

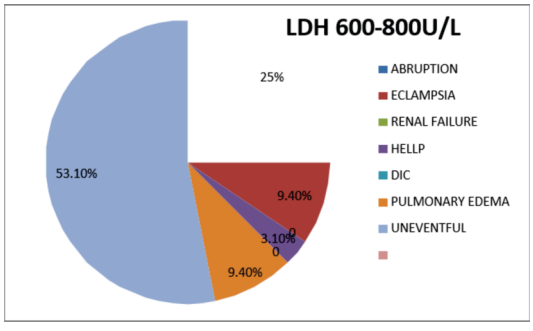
LDH * Symptoms Of Severe Preeclampsia



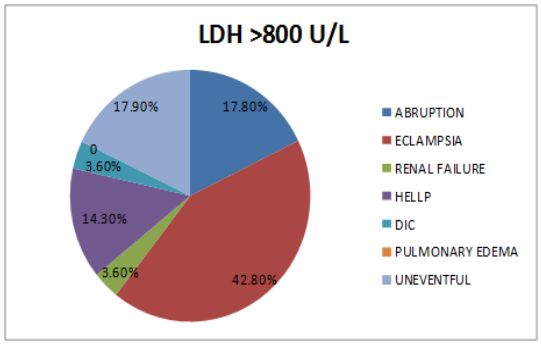
Headache was the most frequent premonitory symptom of severe preeclampsia followed by vomiting, blurring of vision, decreased urine output and epigastricpain. Those with epigastric pain had marginal elevation of AST and ALT in addition to LDH.



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



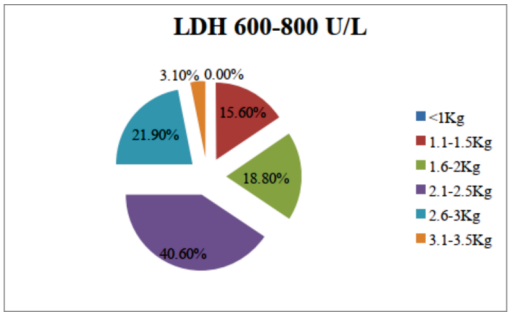
Out of the preeclamptic women with LDH 600-800U/L,46.9% developed complications with the most common among them being abruption followed by eclampsia, pulmonaryedema and HELLP.



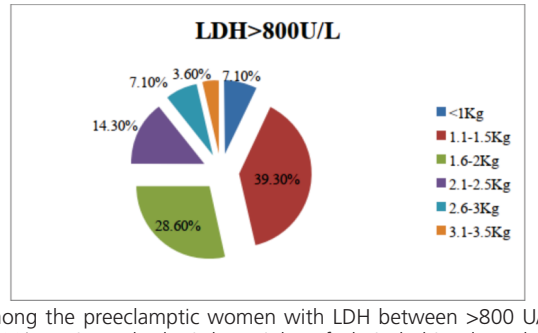
Out of the preeclampsia women with LDH >800 U/L 82.1% developed complications with eclampsia contributing most of it (42.8%) followed by abruption (17.8%),HELLP(14.3%),DIC (3.6%) and renal failure(3.6%).

PERINATAL OUTCOME :.

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



Among the preeclamptic women with LDH between >800 U/L, 89.3% patients had Birth weight of their babies less than 2.6kg.Those less than 2kg constituted 75%.

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.

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.To assess relation between the severity of preeclampsia and maternal serum LDH levels,the preeclampsia patients were grouped as those with LDH <600U/L , LDH 600 – 800 U/L and LDH >800U/L ,and the maternal and perinatal outcomes were compared.Out of the total number of patients included in the study 69% had LDH less than 600 U/L,17.5 % had LDH 600 – 800 U/L, 13.5 % had LDH > 800 U/L.

None of the normotensives women (Group A) had LDH more than

800 U/L.97% of them had LDH less than 600 U/L,3% had LDH between 600 and 800 U/L.

Among the patients with severe preeclampsia 51% had LDH <600 U/L,34.6% had LDH 600 – 800 U/L,14.4% had LDH >800 U/L

Among the mild preeclampsia patients 31.4% patients had LDH <600 U/L,29.4% had LDH 600-800 U/L,39.2% had LDH >800 U/L.

Among those with LDH < 600U/L, 70.2% belonged to the normal group,18.2% were mild preeclampsia,11.6% were severe preeclampsia.

Among those with LDH 600 - 800U/L, 18.2% belonged to the normal group,48.6% were mild preeclampsia,26% were severe preeclampsia

Among those with LDH > 800U/L, 11.6% belonged to the normal group,42.9% were mild preeclampsia,74% were severe preeclampsia.

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 LDHwith 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.Among the patients who had decreased urine output,one progressed to renal failure (LDH – 916 U/L) contributing to maternal mortality.This is similar to a previous study (1),in which headache was the most frequent symptom but the next common symptoms were vomiting, blurred vision and epigastric pain. Those with LDH >800U/L had a significant raise in the frequency of epigatric pain and vomiting compared to the other groups.But in that study no significant difference in the frequency of other symptoms were noted according to LDH levels.
Pregnancy was terminated at an earlier gestational age in women with preeclampsia when compared to the normal healthy pregnant women. Analysis of the relation with respect to gestational age at termination between preeclamptic women who were grouped according to the serum LDH levels showed existence of statistical significance. All the preeclampsia patients whose pregnancy was terminated before 32 weeks had LDH levels > 800 U/L. (12)

Analysis showed existence of statistical significance with respect to complications of preeclampsia between the study groups

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

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 pulmonaryedema 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%).

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, occurance 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

REFERENCES

1. Andrews L, Mehta L, Sharma A, Haridas N, Vaishnav S, Jadav P Iosr Journal of Dental And Medical Sciences. Volume 13, Issue 2 Ver. Ii. (Feb. 2014), Maternal Outcome in Relation to Biochemical Parameters In Hypertensive Disorders In Pregnancy
2. Increased Concentrations of Lactate Dehydrogenase in Pregnancy with Preeclampsia: A Predictor for the Birth of Small-For-Gestational-Age Infants.HeS1, BremmeK, KallnerA, BlombäckM1Department of Laboratory Medicine/Blood Coagulation Research, Karolinska Hospital, Karolinska Institute, Stockholm, Sweden.
3. Serum Lactate Dehydrogenase In Detecting Liver Damage Associated with Pre-Eclampsiap. K. Shukla Reader In Pathology1, D. Sharma Professor1and R. K. Mandal Registar2article First Published Online: 23 Aug 2005 Doi: 10.1111/J.1471-0528.1978.Tb15823. Bjog: An International Journal of Obstetrics &Gynaecology.
4. Dr. Y. Ruth Lavanya1 Dr.Shobharani. B2. Study Of Liver Enzymes And Proteinuria In Pregnancy Induced Hypertension.Iosr Journal Of Dental And Medical Sciences (Iosr-Jdms) Feb 2015volume 14.
5. PurnimaDeySarkar, SonalSogani*SarkarPd Et Al. Evaluation of Serum Lactate Dehydrogenase and Gamma GlutamylTransferase in Preeclamptic Pregnancy and its Comparison with Normal Pregnancy in Third Trimester International Journal of Research in Medical Sciences. Int J Res Med Sci. 2013 Nov;
6. Sreelatha S Et Al. International Journal Of Advances in Case Reports, 2015;Estimation of Serum LDHand Uric Acid in Pre Eclampsiaand its Correlation with Maternal and Perinatal Outcome
7. Rubina Aziz, TabassumMahboob.Relation BetweenPreeclmapsiaand Cardiac Enzymes.Arya Atherosclerosis Journal 2008,4(1):29-32
8. Jaiswar S.P.,Gupta Amrit,SachanRekha,Natu S.N,Shaili Mohan. Lactic Dehydrogenase:A Biochemical Amrkerfor Preeclampsia-Eclampsia. Jogi, Nov-Dec 2011, 61(6):645-648
9. Amit D. Sonagra, Dattatreya. K, Jayaprakash Murthy D.S. Serum LDH,ALPand Uric Acid in Hypertensive Disorders of Pregnancy.Ijpbs,Volume 2, Issue 3, July-Sept,2012:201-209
10. Evaluation of Serum Lactate Dehydrogenase and Gamma GlutamylTransferasein Preeclamptic Pregnancy and its Comparison with Normal Pregnancy in Third Trimester.International Journal of Research in Medical Sciences. IntJ Res Med Sci. 2013; 1(4): 365-368doi: 10.5455/2320-6012.Ijrms20131110
11. Hypoxia and Lactate Production in TrophoblastCellsxh.H. Kay Department of Obstetrics and Gynecology, College of Medicine, University of Arkansas for Medical Sciences, USA. Accepted: November 15, 2006; Published Online: February 05, 2007
12. Ian Donald.RenuMisraMs,Editor.Ian Donald's Practical Obstetric Problem.6th Edition.New Delhi.Bi Publications Pvt. Ltd;2012.Chapter: Hypertensive Disorders in Pregnancy:281-309
13. Duley L.Pre-Eclampsiaand the Hypertensive Disorders of Pregnancy.Br Med J 2003;67:161
14. Jai Prakash, RubinaVohra, LkPandey, Shashidhar Shree Niwas, SKBehura, Usha Singh. Spectrum of Kidney Diseases in Patients With Preeclampsia-EclampsiaJapi Sep 2010; 58:543-546.
15. Richard B. Schwartz, Md, Phd Steven K. Feske, Md Joseph F. Polak, Md, Mph Umberto Degirolami, Md. Preeclampsia-Eclampsia:Clinical and Neuroradiographic Correlates and Insights into the Pathogenesis of Hypertensive Encephalopathy1.Radiology 2000.