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Research Article

Serum Lactate Dehydrogenase as a Predictor of Severity of Preeclampsia and its Association with Fetomaternal Outcomes

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ABSTRACT
Background: Preeclampsia is a rapidly progressing pregnancy-specific disorder which is the leading cause of maternal and neonatal morbidity and mortality. Serum lactate dehydrogenase (LDH) is a valuable and potential biomarker for predicting the severity of preeclampsia. The present study was undertaken to find out the association between serum LDH levels with feto-maternal outcomes in preeclamptic women with and without severity.
Materials and Methods: This institution-based observational prospective cohort study included 100 pregnant women beyond 28 weeks of gestation diagnosed with preeclampsia; among them 50 were non-severe preeclamptic mothers(Group1) and another 50 were severe preeclamptic mothers(Group2). The serum LDH were measured and subsequently categorized based on the serum LDH levels into the followings: (<600IU/L, 600-800IU/L and >800IU/L). Severity of preeclampsia and feto-maternal outcomes were evaluated according to the serum LDH levels.
Results: The serum LDH levels were significantly higher($p<0.0001$) in severe preeclamptic mothers. Both mean systolic blood pressure and mean diastolic blood pressure were seen statistically high with serum LDH level≥600IU/L($p<0.0001$). Cesarean delivery was less likely when serum LDH level was ≥600IU/L compared to <600IU/L($p=0.0031$). Apgar scores at 5 minutes were statistically lower($p<0.0001$) with serum LDH levels ≥600IU/L. Maternal complications, neonatal intensive care unit (NICU) admission and stillbirth rate were higher in severe preeclamptic mothers with high serum LDH levels(≥600IU/L).
Conclusions: The serum LDH levels were high in the mothers with severe preeclampsia and associated with the disease severity as well as poor feto-maternal outcomes. So, serum LDH may be a valuable biomarker for predicting the severity of preeclampsia.

Keywords: Preeclampsia, Serum Lactate Dehydrogenase (LDH), Predictor of Disease Severity, Fetomaternal Outcomes.

INTRODUCTION

Hypertensive disorders of pregnancy (HDP) represent a significant public health concern, being one of the leading causes of maternal, fetal and perinatal morbidity and mortality. Approximately 5–8% of pregnancies are affected by this multisystem disorder and among them 15% of pregnancies are complicated by non-severe preeclampsia, while severe preeclampsia occurs in 1–2% of pregnancies (1). It is estimated that HDP account for approximately 14% of maternal deaths worldwide needing additional immediate intervention for quick detection and effective management of the problem in order to reduce poor maternal and perinatal outcomes (2-3).

Although the precise etiology of preeclampsia is not clear, increasing evidence suggests that placental hypoxia plays a crucial role in its pathogenesis, leading to endothelial dysfunction and cellular death. Defective placentation and endothelial injury are considered the core features of the condition

(4). Endothelial cell dysfunction promotes vasoconstriction, platelet aggregation and coagulation system activation; resulting in decreased blood flow to the vital feto-maternal organs and ultimately causing multi organ failure (1).

Lactate dehydrogenase (LDH) is a cytoplasmic enzyme that is present in all tissues but at higher concentrations in muscles, liver, heart, red blood cell and kidney (5). It plays a vital role in the interconversion of pyruvate and lactate during cellular metabolism (6). Hypoxia increases LDH activity in trophoblasts, resulting in increased lactate generation in preeclampsia (7). Elevated level of serum LDH; as a sign of oxidative stress, cellular damage, dysfunction and haemolysis; can be utilized as a biomarker in HDP as it is indicative of the severity of the disease, multi organ involvement, the prevalence of complications and also been demonstrated to co relate with feto-maternal outcomes (8). It is therefore necessary to evaluate this association with high quality evidence.

Its ease of testing, combined with its diagnostic and prognostic utility, makes serum LDH a prognostic biomarker for guiding clinical management of preeclampsia and improving feto-maternal outcomes (9).

The present study was carried out at an institution where abundant numbers of preeclampsia cases are being dealt with. In Eastern India such types of institution-based studies are rare. Therefore the study was undertaken with the aim to find out the association between serum LDH levels with feto-maternal outcomes in preeclamptic women with and without severity.

MATERIALS AND METHODS

This institution-based observational prospective cohort study was carried out in the Department of Obstetrics and Gynaecology at Chittaranjan Seva Sadan College of Obstetrics, Gynaecology and Child Health, Kolkata, West Bengal, India from 1st December 2022 to 30th November 2023. The study was approved by the Institutional Ethics Committee through the certificate with memo number (CSS/Estt/3096/IEC11/2022dated:28.11.2022)

Inclusion Criteria:

Pregnant women beyond 28 weeks of gestation diagnosed with preeclampsia attended or admitted at Gynae outdoor/triage or indoor were enrolled in this study and divided into two groups.

- **Group 1-** Non-severe Preeclamptic mothers.
- **Group 2-** Severe Preeclamptic mothers.

- **Non-Severe Preeclampsia**: defined as a pregnant woman beyond 20 weeks of gestation presenting with blood pressure ≥140/90 mm of Hg but <160/110 mm of Hg noted first time during pregnancy on 2 occasions, measured at least 4-6 hours apart with proteinuria of ≥1+ (≥30mg/dl) detected by dipstick method in a random urine sample, after excluding urinary tract infection (1).
- **Severe Preeclampsia**: defined as the presence of any of the following symptoms or signs:
  Systolic blood pressure (SBP) of 160 mm Hg or higher or diastolic blood pressure (DBP) of 110 mm Hg or higher on 2 occasions at least 4-6 hours apart while at rest; proteinuria of 5g or higher in a 24-hour urine specimen or 3+ or greater on two random urine samples collected at least four hours apart; oliguria of less than 500ml in 24 hours; Cerebral or visual disturbances; pulmonary oedema or cyanosis; epigastric or right upper quadrant pain; impaired liver function; thrombocytopenia(platelets<100000/mm^3) or intrauterine growth restriction (1).

Exclusion Criteria:

Pregnancy with diabetes, renal failure, liver disease, stroke, coronary artery disease, chronic lung disease, connective tissue disorder, chronic hypertension, previous h/o haemolytic anemia, smoking and alcoholism, hepatotoxic drug intake, multifetal gestation were excluded.

Sample Size Calculation:

The sample size was calculated using the formula by Kotrlik JW at a confidence of 95% (10)

$n/group = 2\times (Z_\alpha + Z_\beta)^2 \times S^2 / \delta^2$

Where:

Z_α = value for alpha of 0.025 in each tail (1.96), Z_β = 0.84 (equivalent to 80% statistical power), S= difference in the standard deviation in serum LDH level in severe preeclamptic women and non-severe preeclamptic women (136.92-24.47) = 112.45 according to a previous study done by Andrews L (11), δ=is the difference likely to be detected/acceptable margins of error=18.0. So a sample size of 50 was taken for each group in this study.

This study included 100 pregnant women beyond 28 weeks of gestation diagnosed with preeclampsia; among them 50 were non-

severe preeclamptic mothers (Group1) and another 50 were severe preeclamptic mothers (Group2).

It was determined that data collections were to be done twice in a week. The days for data collection were selected via simple random sampling using lottery method at the start of each week. Group allocation was done using computer-generated random number tables.

After proper counseling and informed consent from each pregnant mother, they were matched according to their age, gravida and body weight. Detailed history taking, clinical examination and necessary investigations were done. In this study serum LDH were measured for all pregnant women from both groups during selection. Whenever a non-severe preeclamptic mother had developed signs of severe preeclampsia, another sample was taken and she was transferred to the severe group. The serum LDH level of 135–214 IU/L was considered normal and higher than that amount was deemed elevated (12). Because serum LDH levels <400IU/L are common in normal pregnancy and only levels >600IU/L were reported to be associated with complications (13), therefore the study population was further categorized on the basis of the serum LDH levels into the followings:<600 IU/L, 600-800 IU/L and > 800 IU/L.

All mothers were followed until delivery and early postpartum period and babies till early neonatal period. Subsequently severity of preeclampsia and feto-maternal outcomes were evaluated according to the serum LDH levels.

The data were collected in predesigned and pretested proforma and then entered into a Microsoft excel spreadsheet; summarized as mean and standard deviation for numerical variables; count and percentage for categorical variables. The data were analyzed by SPSS software (version 27.0; SPSS Inc., Chicago, IL, USA) and Graph Pad Prism version 5 with the use of Student's t -test, Chi-square test, Independent sample t-test, ANOVA test.

P-value ≤ 0.05 was considered for statistically significant.

RESULTS & ANALYSIS

[Table-1]: Distribution of the Study Population According to Sociodemographic Characteristics, Gestational Age at Delivery & Mode of Delivery.

Characteristics	Group1(N=50) Number (%)	Group2(N=50) Number (%)	Total (N=100) Number (%)	P-Value
Age(years)- ≤20 21-30 ≥31	 4(8) 41(82) 5(10)	 3(6) 46(92) 1(2)	 7(7) 87(87) 6(6)	0.2126 (Chi-square)
Gravida- Primi Second Multi	 28(56) 17(34) 5(10)	 31(62) 15(30) 4(8)	 59(59) 32(32) 4(4)	0.8234 (Chi-square)
Body Weight(kg)	Mean±SD 61.3±6.2311	Mean±SD 63.600±6.1710		0.0667(t-Test)
Gestational age at delivery (weeks)- 28-36 37-40	Mean±SD 37.12±1.78 19(38) 31(62)	Mean±SD 36.04±3.4 45(90) 5(10)	 64(64) 36(36)	<0.0001 (Chi-square)
Mode of delivery LSCS VD	 8(16) 42(84)	 14(28) 36(72)	 22(22) 78(78)	0.1475 (Chi-square)

Table-1 shows that majority of the mothers in both groups were between 21 and 30 years old, accounting for 82% of non-severe and 92% of severe preeclamptic cases. The youngest group (≤ 20years) comprised 8% of non-severe and 6% of severe preeclamptic cases. There was no significant difference in the age between the groups (p= 0.2126).

In this study the primigravida mothers made up 56% of the non-severe preeclampsia group

and 62% of the severe preeclampsia group. Second gravida mothers comprised 34% and 30%, while multi gravida mothers represented 10% and 8% of the non-severe and severe preeclampsia groups, respectively. There was no significant difference in gravida between the groups (p= 0.8234).

No significant difference was seen in the mean body weight among non-severe and severe preeclampsia groups (61.3±6.2311 Vs 63.600±6.1710, p= 0.0667).

A statistically significant difference was observed in terms of gestational age at delivery (p<0.0001) with a mean of (37.12±1.78weeks Vs 36.04±3.4weeks) for the non-severe and severe preeclampsia group respectively. Majority of preterm deliveries (90%) were seen in severe preeclampsia group whereas most of mothers (62%) from non-severe group delivered at term.

In term of mode of delivery; majority of the mothers from both groups, had vaginal delivery (VD) (84% in non-severe Vs 72% in severe preeclampsia group). Lower segment Cesarean section (LSCS) rate was quite high in severe preeclampsia group (28%) in respect with non-severe group (16%) although the findings were statistically non-significant (p=0.1475)[Table-1].

[Table-2]: Distribution of the Serum LDH Levels among the Non-Severe and Severe Preeclamptic Women

Groups (N=50 Each Group)	Serum LDH Levels (IU/L) In The Study Population(N=100)			
	<600 Number (%)	600-800 Number (%)	>800 Number (%)	P-value
Non-severe preeclampsia(Group1)	50(100)	0	0	<0.0001 (Chi-square)
Severe preeclampsia(Group2)	28(56)	18(36)	4(8)	
Total(n=100)	78(78)	18(18)	4(4)	

The study population was finally categorized on the basis of the serum LDH levels into followings: (<600IU/L, 600-800IU/L and >800IU/L). Out of 50 non-severe preeclamptic mothers in Group-1, all of them had serum LDH levels <600IU/L. In severe preeclamptic group, 28(56%) mothers had serum LDH levels < 600 IU/L, 18(36%) mothers had serum LDH levels between 600-800 IU/L and 4(8%) mothers had serum LDH levels > 800IU/L [Table-2]. This distribution was statistically significant (p value <0.0001).

[Table-3]: Association of Serum LDH Levels with Mean Systolic Blood Pressure and Mean Diastolic Blood Pressure in the Study Population.

Pregnancy BP Status(mmHg)	Serum LDH Levels (IU/L) In The Study Population(N=100)			
	<600(N=78) Mean±SD	600-800(N=18) Mean±SD	>800(N=4) Mean±SD	P-Value (ANOVA-Test)
systolic blood pressure(SBP)	126.82±17.66	154.11±10.48	161.00±10.39	<0.0001
Diastolic blood pressure(DBP)	85.77±8.07	101.50±9.15	103.00±8.92	<0.0001

It was found that mean systolic blood pressure (SBP) as well as mean diastolic blood pressure (DBP) were significantly high (p value <0.0001) with high levels of serum LDH [Table-3]. Higher values of mean SBP (154.11±10.48mmHg Vs 161.00±10.39mmHg) were found when serum LDH levels between 600-800IU/L and over 800IU/L respectively. Similarly higher values of mean DBP (101.50±9.15mmHg Vs 103.00±8.92mmHg) were observed when serum LDH levels between 600-800IU/L and over 800IU/L respectively.

A statistically significant observation (p=0.0031) was seen in mode of delivery according to the serum LDH levels. 12(54.5%) women underwent LSCS when serum LDH levels were less than 600 IU/L. Among women with serum LDH levels between 600-800 IU/L, 7(31.8%) women underwent LSCS whereas 3(13.6%) women with serum LDH levels over 800 IU/L underwent LSCS. Cesarean deliveries

were significantly less (10 Vs 12 out of 22 LSCS) when serum LDH levels were ≥600IU/L compared to <600IU/L [Table-4].

Regarding mean neonatal birth weights, the differences were not significant in the study population with different serum LDH levels (p=0.7718).

[Table-4]: Association of Serum LDH Levels with Labour Events in the Study Population.

Labour Events	Serum LDH Levels (IU/L) In The Study Population(N=100)			
	<600(N=78)	600-800(N=18)	>800(N=4)	P-Value
Mode of delivery VD LSCS	66(84.6%) 12(54.5%)	11(14.1%) 7(31.8%)	1(1.3%) 3(13.6%)	0.0031(Chi-square)
Neonatal birth weight(kg)	Mean±SD 2.8250±0.3096	Mean±SD 2.7389±0.3550	Mean±SD 2.7321±0.3193	0.7718(ANOVA-Test)
APGAR score at 1 minute	8.00±0.6838	7.11±1.23	5.25±3.59	<0.0001(ANOVA-Test)
APGAR score at 5 minutes	8.27±0.68	7.33±1.08	5.75±3.95	<0.0001(ANOVA-Test)

In this study it was noticed that the mean APGAR scores were significantly lower both at 1 minute and at 5minutes in babies of mothers with higher serum LDH levels(p value <0.0001). Among babies of women with LDH level less than 600IU/L, the mean APGAR score at 5 minutes was 8.27±0.68 whereas (7.33±1.08 Vs 5.75±3.95) when serum LDH levels between 600-800IU/L and over 800IU/L respectively[Table-4].

[Table-5]: Association of Serum LDH Levels and Maternal Complications in Between Group.

Maternal Complication	LDH Levels (IU/L) in Group1(N=50)				LDH Levels (IU/L) in Group2(N=50)				Total (N=100)
	<600	600-800	>800	Total	<600	600-800	>800	Total	
ARF	0	0	0	0	0	0	1	1(2%)	1(1%)
HELLP	0	0	0	0	0	1	1	2(4%)	2(2%)
Pulmonary oedema	0	0	0	0	0	1	1	2(4%)	2(2%)
Postpartum convulsion	0	0	0	0	0	1	0	1(2%)	1(1%)
PPH	1	0	0	1(2%)	1	2	0	3(6%)	4(4%)
Nil	49	0	0	49(98%)	27	13	1	41(82%)	90(90%)
Total	50	0	0	50(100%)	28	18	4	50(100%)	100(100%)

(ARF- Acute renal failure; HELLP- Haemolysis, elevated liver enzymes, low platelet; PPH-Postpartum haemorrhage)

According to this study, there was only one case of post-partum hemorrhage in non-severe preeclampsia group when serum LDH level was <600 IU/L. Among severe preeclampsia group, there were one case of acute renal failure, two cases of HELLP syndrome, two cases of pulmonary oedema, one case of post-partum convulsion and two cases of post-partum hemorrhage when serum LDH levels were ≥600 IU/L [Table-5]. So higher cases of maternal complications were found in severe preeclamptic mothers with higher serum LDH levels ≥600IU/L compared to <600IU/L (5 cases of maternal complications out of 10 when serum LDH levels were 600-800 IU/L whereas 3 cases when serum LDH levels were >800IU/L).

Among non-severe preeclampsia group, there were 6 cases of respiratory distress syndrome (RDS) and 1 case of meconium aspiration syndrome (MAS) when serum LDH levels were <600 IU/L. In severe preeclampsia group, there were 2 cases of fetal growth restriction (FGR), 4 cases of MAS, 8 cases of RDS, 1 case of sepsis and also one incidence of still birth when serum LDH levels were ≥600 IU/L [Table-6]. So neonatal complications and NICU admissions were higher in the babies of mothers associated with severe preeclampsia

with higher serum LDH levels ≥600IU/L compared to <600IU/L (10 cases of neonatal complications out of 23 when serum LDH levels were 600-800 IU/L whereas 3 cases including one stillbirth when serum LDH levels were>800IU/L).

[Table-6]: Association of Serum LDH Levels and Neonatal Complications in Between Group.

Neonatal Complication	LDH Levels (IU/L) in Group1(N=50)				LDH Levels (IU/L) in Group2(N=50)				Total (N=100)
	<600	600-800	>800	Total	<600	600-800	>800	Total	
FGR,RDS	0	0	0	0	0	2	0	2(4%)	2(2%)
MAS	1	0	0	1(2%)	1	2	1	4(8%)	5(5%)
MAS,RDS	0	0	0	0	0	1	0	1(2%)	1(1%)
RDS	6	0	0	6(12%)	2	4	1	7(14%)	13(13%)
Sepsis	0	0	0	0	0	1	0	1(2%)	1(1%)
Stillbirth	0	0	0	0	0	0	1	1(2%)	1(1%)
Nil	43	0	0	43(86%)	25	8	1	34(68%)	77(77%)
Total	50	0	0	50(100%)	28	18	4	50(100%)	100(100%)

(FGR – Fetal growth restriction; MAS – Meconium aspiration syndrome; RDS- Respiratory distress syndrome)

DISCUSSION

This observational study was conducted to find out the association between serum LDH levels with feto-maternal outcomes in non-severe and severe preeclamptic mothers. The participants were matched according to age, gravida and body weight. No significant difference in these characteristics between both groups was found and therefore, both groups were comparable and the difference in serum LDH levels found is not likely attributable to other extraneous variables.

In this study, a significant portion of mothers with severe preeclampsia (90%) delivered preterm. It indicates that severe preeclampsia is directly related to preterm delivery and immature neonate, which might lead to NICU admission and neonatal death. Similar finding was seen by Nasir SK (12).

Serum LDH levels were significantly ($p<0.0001$) elevated in severe preeclampsia compared to non-severe preeclampsia. This is consistent with the study by Yadav U (1).

The study established a significant association ($p<0.0001$) of higher levels of serum LDH with severity of preeclampsia reflected as high values of mean systolic blood pressure and mean diastolic blood pressure.

Yadav U, Nasir SK, Awoyesuku PA et al and Eleti MR reported a significant rise in serum LDH levels with increasing severity of preeclampsia (1, 12-14).

The study observed a significant association ($p=0.0031$) between serum LDH levels and the mode of delivery in the study population, with cesarean delivery (LSCS) less likely to occur with serum LDH levels ≥600 IU/L. Similar finding was noticed by Awoyesuku PA et al (13). This observation was contrary to a previous study by Deshmukh VL (15) that reported significantly higher LSCS rate with higher levels of serum LDH, as it was expected that, with increase in severity of the disease, the maternal morbidity including LSCS will increase. Severity of the blood pressure and adequacy of control measures, as well as many other factors influenced the decision to deliver these women by cesarean section.

It was noticed that the mean Apgar scores were significantly lower at 1 minute and 5 minutes in babies of mothers with higher serum LDH levels (p value <0.0001). This was in accordance with the study done by Eleti MR (14).

Higher cases of maternal complications, neonatal complications and NICU admissions were found in association with severe preeclampsia having high serum LDH levels. Similar references were derived in Yadav U and Nasir SK studies where maternal complications were in direct proportion to serum LDH and BP values (1,12). Poor perinatal outcomes have been reported by Deshmukh VL(15), Bhati BS(16) and Moharana JJ(17).

These findings of the study underscored the importance of serum LDH as an early predictor of preeclampsia, offering a window for early intervention and improved clinical management. By incorporating serum LDH measurement into routine antenatal care, healthcare providers could better identify at-risk pregnancies and tailor their management strategies to mitigate adverse outcomes.

CONCLUSIONS

The serum LDH levels are high among the women with severe preeclampsia and it associates with the severity of the disease as well as poor feto-maternal outcomes. Therefore serum LDH can be a valuable biomarker for predicting the severity of preeclampsia. Preeclamptic women with elevated serum LDH levels need to be closely monitored and managed accordingly to reduce adverse feto-maternal outcomes.

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