

Estimation of Level of Serum Lactate Dehydrogenase in Pre-eclampsia Patients and its Association with Maternal and Fetal Outcome

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Abstract

Introduction: Pre-eclampsia is a pregnancy-specific syndrome recognised as a leading cause of maternal and perinatal mortality. Etiopathogenesis of preeclampsia is defective placentation and endothelial dysfunction leading to oxidative stress and cellular lysis. Lactate Dehydrogenase (LDH) is an intracellular enzyme of glycolysis. Hypoxia and cellular lysis results in elevated levels of LDH. Early detection and management are important in prevention of Preeclampsia complications and deaths. Hence, the present study was conducted to estimate levels of Sr. LDH in Pre-eclampsia patients to find its association with maternal and fetal outcome was undertaken. **Materials and Methods:** Present prospective study was conducted in Department of Obstetrics and Gynaecology from August 2016 to December 2018 consisting of 84 cases of preeclampsia of ≥ 28 weeks gestation divided in 2 groups; Mild and Severe Preeclampsia. Sr. LDH was estimated in all study participants and its association with parameters of maternal and fetal outcome was observed. **Results:** In the present study, 46 patients had Mild Preeclampsia and 38 had Severe Preeclampsia. Most cases of Mild preeclampsia i.e., 78.3% had LDH < 600 IU/L whereas 71.1% of Severe Preeclampsia had LDH > 600 IU/L. Complications like eclampsia in 66.7%, HELLP in 33.3%, Abruptio placenta in 55.6%, ARF and DIC in 33.3% cases were noted more in patients with LDH > 800 IU/L. Fetal still birth in 55.6%, Lower APGAR score and more NICU admission and Early neonatal death was present in babies of preeclampsia mother with LDH > 800 IU/L. There was found statistically significant association ($p < 0.001$) of raised Sr. LDH levels with poor maternal and fetal outcome in preeclampsia patients. **Conclusion:** Elevated levels of Sr. LDH during hypoxia, indicate the cellular damage and dysfunction occurring in preeclampsia. Detection of patients with increased levels of LDH is of crucial importance to detect and promptly manage the complicated cases and decrease the morbidity and mortality in mother and fetus.

Key words: Fetal Outcome, Lactate Dehydrogenase, Maternal Outcome, Pre-eclampsia

1. Introduction

Pre-eclampsia (PE) is a pregnancy-specific syndrome that has been recognized as a leading cause of maternal and perinatal mortality¹ According to ACOG 2013² diagnostic criteria for preeclampsia.

1.1 Mild Pre-eclampsia

Blood pressure $\geq 140/90$ mm Hg and $< 160/110$ mm Hg on 2 occasions at least 4 hours apart after 20 weeks of gestation in a previously normotensive and nonproteinuric women without features of severe preeclampsia.

1.2 Severe Pre-eclampsia

- Blood pressure of 160/110mmHg or higher on at least 2 occasions at least 4 hours apart while the patient is on

bed rest (unless antihypertensive therapy is initiated before this time).

- Thrombocytopenia, impaired liver function, progressive renal insufficiency, pulmonary edema, new-onset cerebral or visual disturbances².

The Etiopathogenesis of preeclampsia has been given as the “two-stage disorder” theory³ stage 1 is caused by faulty endovascular trophoblastic remodeling that subsequently causes the stage 2 clinical syndrome⁴.

The inflammatory changes caused by defective placentation in response to placental factors (anti-angiogenic and metabolic) released by ischemic changes or by other inciting cause provoking endothelial injury and cellular lysis⁵.

LDH is an intracellular enzyme that converts pyruvic acid to lactic acid during the process of glycolysis. In PE

hypoxia enhances glycolysis and increases LDH activity⁶ hypoxia induces LDH activity in trophoblasts resulting in higher lactate production. Cellular dysfunction is indicated by elevated levels of LDH⁷.

WHO estimated that approx 60000 women die each year from preeclampsia world wide. Preeclampsia and Eclampsia account for 24% of all maternal deaths in India, attributing mainly to complications like HELLP syndrome, Disseminated Intravascular Coagulation (DIC), pulmonary edema, renal failure and cerebral hemorrhage. Fetal morbidities include preterm delivery, Intrauterine Growth Restriction (IUGR), still births and Low Birth Weight (LBW) babies⁸.

Access to perinatal care, early detection of the disorder, careful monitoring and appropriate management are crucial elements in prevention of Preeclampsia related deaths. There is currently no single cost effective and reliable screening test for preeclampsia and there are no established measures for primary prevention.

Hence this study was conducted to estimate levels of Serum Lactate Dehydrogenase in Pre-eclampsia patients with an aim to find out the association of Sr. LDH levels in mild and severe preeclampsia with maternal and fetal outcome.

2. Materials and Methods

This was a Prospective study conducted in Department of Obstetrics and Gynecology of Medical College and Tertiary Health Care Centre from August 2016 to December 2018. The study population was 84 antenatal preeclampsia cases with gestational age ≥ 28 weeks after fulfilling inclusion and exclusion criteria and taking written informed consent and were divided into two groups: Mild Pre-eclampsia and Severe Pre-eclampsia, according to ACOG 2013 defining criteria².

2.1 Inclusion Criteria

Pregnant females of ≥ 28 weeks of gestation between 18-35 years age with blood pressure $\geq 140/90$ mm of Hg with proteinuria taken on 2 occasions at least 4 hours apart while the patient is on bed rest.

2.2 Exclusion Criteria

- Pregnant women with documented evidence of hypertension < 20 weeks gestation with proteinuria.
- Patient with history of diabetes mellitus, chronic hypertension, medical renal disease, chronic liver disorder, epilepsy, Rheumatic Heart Disease.

2.3 Serum Lactate Dehydrogenase Estimation

Sr. LDH levels were estimated in all study participants and association of Sr. LDH levels with parameters of maternal and fetal outcome in preeclampsia patients was observed. Blood samples for Sr. LDH levels were collected and repeated as and when required and later value was considered for analysis.

2.4 Method for LDH estimation

UV Modification of optimized standard NADH/Pyruvate method based on the reduction of pyruvate to lactate in the presence of NADH by the action of lactate dehydrogenase enzyme was used. The pyruvate that remains unchanged reacts with 2,4-dinitrophenylhydrazine, which is determined calorimetrically in an alkaline medium⁹.

Maternal outcome in the form of any complications in mother, mode of delivery and maternal death was noted. Fetal and perinatal outcome was noted in form of fetal still birth, birth weight, APGAR score 1 min and 5 min, NICU admission and early neonatal death.

All the results were analysed by using SPSS version 20-Chi Square test.

3. Observation and Results

In the present study out of 84 cases, 46 (54.8%) had Mild Preeclampsia while 38 (45.2%) had severe preeclampsia.

Table 1. Mean blood investigations and LDH in preeclampsia.

	Pre eclampsia	Mean \pm Std. Deviation	P value
Blood Platelet (lakhs/cumm)	Mild	2.19 \pm 0.21	<0.001
	Severe	1.8 \pm 0.13	
Sr. Creatinine (mg/dl)	Mild	0.86 \pm 0.19	0.196
	Severe	0.93 \pm 0.25	
Blood Urea	Mild	22.54 \pm 5.54	0.244
	Severe	24.53 \pm 9.71	
Sr. Aspartate Transaminase (IU/L)	Mild	26.87 \pm 4.72	0.002
	Severe	41.50 \pm 30.90	
Sr. Alanine Transaminase (IU/L)	Mild	25.11 \pm 3.13	0.031
	Severe	36.10 \pm 33.80	
Sr. LDH (IU/L)	Mild	457.39 \pm 176.36	<0.001
	Severe	661.05 \pm 207.65	

In the present study, in mild preeclampsia patients mean value of platelet was 2.19 \pm 0.21 lakhs/cumm, Sr. creatinine was 0.86 \pm 0.19 mg/dl, Blood Urea was 22.54 \pm 5.54, INR was

1.05 ± 0.05, Sr. Aspartate Transaminase (AST) was 26.87 ± 4.72 IU/L, Sr. Alanine Transaminase (ALT) was 25.11 ± 3.13 IU/L and Sr. LDH was 457.39 ± 176.36.

In Severe preeclampsia patients mean value of Platelet was 1.8 ± 0.13 lakhs/cumm, Sr. Creatinine was 0.92 ± 0.25 mg/dl, Blood Urea was 24.53 ± 9.71, INR was 1.05 ± 0.09, Sr. AST was 41.5 ± 30.9 IU/L, Sr. ALT was 36.1 ± 33.8 IU/L and Sr. LDH was 661.05 ± 207.65.

There was statistically significant difference between following parameters of mild and severe pre-eclampsia patients- Platelet count (p < 0.001), Sr. AST levels (P = 0.002), Sr. ALT levels (P = 0.031) and Sr. LDH levels (p < 0.001) with increasing severity of preeclampsia. (Table 1).

Table 2. LDH levels among mild and severe pre-eclampsia patients

LDH (IU/L)	Preeclampsia	
	Mild	Severe
<600	36(78.3%)	11(28.9%)
600 to 800	10(21.7%)	18(47.4%)
>800	0(0%)	9(23.7%)
Total	46(100.0%)	38(100.0%)

In the present study, most of the cases i.e., 36 (78.3%) of Mild Preeclampsia had Sr. LDH levels <600 U/L. and maximum cases i.e. 18 (47.4%) of severe preeclampsia had LDH 600 – 800 U/L, 11 (28.9%) had LDH < 600 U/L and LDH was > 800 U/L in 9 (23.7%) cases of Severe Preeclampsia. There was statistically significant association between high LDH levels with increasing severity of preeclampsia (p<0.001) (Table 2).

Table 3. Association of serum LDH levels with maternal complications in preeclampsia.

Maternal complications		Serum Lactate dehydrogenase levels (IU/L)			P Value
		<600	600 – 800	>800	
Eclampsia	Present	2.1%	14.3%	66.7%	<0.001
	Absent	97.9%	85.7%	33.3%	
HELLP syndrome	Present	0%	3.6%	33.3%	<0.001
	Absent	100%	96.4%	66.7%	
Abruptio placenta	Present	0%	7.1%	55.6%	<0.001
	Absent	100%	92.9%	44.4%	
DIC	Present	0%	3.6%	33.3%	<0.001
	Absent	100%	96.4%	66.7%	
ARF	Present	0%	3.6%	33.3%	<0.001
	Absent	100%	96.4%	66.7%	
Maternal Death	Present	0%	0%	22.2%	<0.001
	Absent	100%	100%	97.6%	

In the present study, out of 9 cases with LDH >800 IU/L 6 cases (66.7%) had eclampsia, 3(33.3%) had HELLP syndrome and 5 (55.6%) had Abruptio placenta. There were 3 cases (33.3%) which developed ARF and DIC. There were no complications in cases which had LDH < 600 IU/L except one case of Eclampsia. Maternal death was noted in 2 (22.2%) cases with Sr. LDH >800 IU/L. There was statistically significant association of occurrence of maternal complications mentioned above and maternal death in preeclampsia patients with Raised Sr. LDH levels (p<0.001) (Table 3).

Table 4. Association of Sr. LDH levels with perinatal outcome parameters.

Perinatal Outcome		Serum Lactate dehydrogenase levels (IU/L)			P Value
		<600	600 – 800	>800	
Delivery outcome	Fetal still birth	0%	0%	55.6%	<0.001
	Live birth	100%	100%	44.4%	
Birth Weight	Mean weight	2.1 Kg	1.9 Kg	1.8 Kg	<0.001
APGAR score at 1 min	Good (7-10)	91.1%	35.7%	-	<0.001
	Moderate (4-6)	8.5%	64.3%	50%	
	Poor (0-3)	-	-	50%	
APGAR score at 5 min	Good	95.7%	35.7%	-	<0.001
	Moderate	4.3%	64.3%	25%	
	Poor	-	-	75%	
NICU admission	Present	8.5%	67.9%	100%	<0.001
	Absent	91.5%	32.1%	0%	
Early Neonatal Death	Present	0%	7.1%	100%	=0.003
	Absent	100%	92.9%	0%	

In the present study, Fetal still birth was noted in 5 (55.6%) cases with Sr. LDH >800 IU/L, rest all the patients had live birth. Mean birth weight was 2.123±0.229 Kg, 1.962±0.219 Kg and 1.800±0.150 Kg in babies of preeclampsia patients with Sr. LDH <600 IU/L, 600 – 800 IU/L and >800 IU/L respectively. Out of 79 live babies of patients of preeclampsia, APGAR score at 1 min and 5 min was Good (7-10) in maximum i.e. 43 (91.5%) and 45 (95.7%) of babies born to preeclampsia mother with sr. LDH <600 IU/L respectively. APGAR score at 1 min and 5 min was Moderate(4-6) in most i.e. 18 (64.3%) babies

of preeclampsia with sr. LDH 600 – 800 IU/L. APGAR score at 1 min and 5 min was Poor (0-3) in 50% and 75% babies of preeclampsia mother with sr. LDH >800 IU/L respectively. Out of 79 live babies of patients of preeclampsia, 4 (8.5%)(Sr. LDH <600 IU/L), 19 (67.9%) (Sr. LDH- 600 – 800 IU/L) and all 4 (100%) babies of pre-eclampsia patients with Sr. LDH > 800 IU/L, were admitted to NICU. Out of 79 live babies of patients of preeclampsia, early neonatal death was seen in 2 (7.1%) and in all i.e., 4 (100%) of babies born to preeclampsia mother with Sr. LDH 600 – 800 IU/L and >800 IU/L respectively.

There was statistically significant association of more fetal still birth, lower birth weight, Lower APGAR score at 1 min and 5 min, NICU admission and Early neonatal death in babies born to preeclampsia patients with Raised Sr. LDH levels ($p < 0.005$)(Table 4).

4. Discussion

In the present study out of 84 cases, 46 (54.8%) had mild pre-eclampsia while 45.2% had severe preeclampsia. Mean Sr. LDH level in cases with mild preeclampsia was 457.39 ± 176.36 U/L and in those with Severe PE it was 661.05 ± 207.65 U/L. There was statistically significant association between high mean LDH levels with increasing severity of preeclampsia ($p < 0.001$). Mean LDH levels in Qublan et al.¹⁰, Jaiswar SP et al.¹¹ and Vinitha PM et al.¹² was in Mild PE 348, 400.45 and 478 IU/L and in Severe PE it was 774.9, 646.95 and 756 IU/L ($P < 0.001$). There was statistically significant association ($p < 0.001$) between high mean LDH levels with increasing severity of preeclampsia in other similar studies which is comparable to present study.

In the present study, most of the cases i.e., 36 (78.3%) of mild preeclampsia had Sr. LDH levels < 600 U/L. Percentage distribution of LDH based on severity in preeclampsia in studies by Jaiswar SP et al.¹¹, Umasatyashri et al.¹³ and Urvashi Sharma et al.¹⁴ in Mild preeclampsia LDH was <600 IU/L in 94.3%, 100% and 50%, LDH was 600 – 800 IU/L in 5.7%, 0% and 42% and it was > 800 in 0%, 0% and 8% cases respectively.

In the present study, maximum cases i.e. 18 (47.4%) of severe preeclampsia had LDH 600 – 800 U/L, 11 (28.9%) had LDH < 600 U/L and LDH was > 800 U/L in 9 (23.7%) cases of Severe preeclampsia and there was statistically significant association between more number of cases having high LDH levels with increasing severity of preeclampsia ($p < 0.001$). In studies by Jaiswar SP et al.¹¹, Umasatyashri

et al.¹³ and Urvashi Sharma et al.¹⁴ in severe preeclampsia LDH was <600 IU/L in 58.3%, 55% and 59%, LDH was 600 – 800 IU/L in 14%, 35% and 35% and it was > 800 in 27.7%, 10% and 6% cases respectively. Thus in other similar studies there were more number of severe preeclampsia cases having high LDH levels than in mild preeclampsia which is comparable to observations in our study.

4.1 Maternal Complications in Preeclampsia Patients and Association of Sr. LDH Levels with them

A. Eclampsia: Eclampsia in Preeclampsia patients with Sr. LDH levels in present study was seen in 2.1%, 14.3% and 66.67% in those with LDH <600, 600-800 and >800 respectively. In other similar studies by Qublan et al.¹⁰, Vinitha PM et al.¹² and Urvashi Sharma et al.¹⁴ it was seen in 0%, 0% and 1% of those with LDH <600, in 4.7%, 6.8% and 0% of those with LDH 600-800 and in 30.8%, 38.8% and 4% of those with LDH>800 IU/L respectively. There was statistically significant association ($p < 0.001$) of occurrence of complication of Eclampsia in preeclampsia patients with Raised Sr. LDH levels in other similar studies which is comparable to observations in our study.

B. HELLP Syndrome: HELLP syndrome in pre-eclampsia patients with Sr. LDH levels in present study was seen in 0%, 3.6% and 33.3% in those with LDH <600, 600-800 and >800 respectively. In other similar studies by Qublan et al.¹⁰, Vinitha PM et al.¹² and Urvashi Sharma et al.¹⁴ it was seen in 0%, 0% and 1% of those with LDH <600, in 0%, 0% and 2% of those with LDH 600-800 and in 15.4%, 11.1% and 7% of those with LDH>800 IU/L respectively. There was statistically significant association ($p < 0.001$) of occurrence of HELLP syndrome in preeclampsia patients with raised Sr. LDH levels in other similar studies which is comparable to findings in our study.

C. Abruptio Placenta: Abruptio placenta in Preeclampsia patients with Sr. LDH levels in present study was seen in 0%, 7.1% and 55.6% in those with LDH <600, 600-800 and >800 respectively. In other similar studies by Qublan et al.¹⁰, Vinitha PM et al.¹² and Urvashi Sharma et al.¹⁴ it was seen in none of those with LDH <600, in 0%, 3.4% and 0% of those with LDH 600-800 and in 15.4%, 22.2% and 3% of those with LDH>800 IU/L respectively. There was statistically significant association ($p < 0.001$) of occurrence of Abruptio placenta in preeclampsia patients with raised Sr. LDH levels in other similar studies which is comparable to our study findings.

D. Acute Renal Failure: Acute renal failure in Preeclampsia patients with Sr. LDH levels in present study was seen in 0%, 3.6% and 33.3% in those with LDH <600, 600-800 and >800 respectively. In other similar studies by Qublan et al.¹⁰, Vinitha PM et al.¹² and Urvashi Sharma et al.¹⁴ it was seen in 0%, 0% and 1% of those with LDH <600, in none of those with LDH 600-800 and in 7.7%, 5.55% and 10% of those with LDH>800 IU/L respectively. There was statistically significant association ($p<0.001$) of occurrence of ARF in preeclampsia patients with Raised Sr. LDH levels in other similar studies which is comparable to observations in our study.

E. Disseminated Intravascular Coagulation (DIC): DIC in Preeclampsia patients with Sr. LDH levels in present study was seen in 0%, 3.6% and 33.3% in those with LDH <600, 600-800 and >800 respectively. In other similar studies by Qublan et al.¹⁰, Vinitha PM et al.¹² and Urvashi Sharma et al.¹⁴ it was seen in none of those with LDH <600, in 0%, 3.4% and 1% of those with LDH 600-800 and in 7.7%, 5.55% and 1% of those with LDH>800 IU/L respectively. There was statistically significant association ($p<0.001$) of occurrence of DIC in preeclampsia patients with Raised Sr. LDH levels in other similar studies which is comparable to our study.

F. Maternal Mortality: In the present study, out of 84 cases of preeclampsia, maternal death was noted in 2 (22.2%) cases of preeclampsia with Sr. LDH >800 and none of the patient with LDH <800 IU/L died. There was statistically significant association of occurrence of maternal death in preeclampsia patients with Raised Sr. LDH levels ($p<0.001$).

In a similar study done by Jaiswar SP et al.¹¹, maternal mortality was seen in 13.8% preeclampsia patients with Sr. LDH >800 IU/L and it was statistically significant ($p=0.006$)

4.2 Association of Sr. LDH levels with perinatal outcome parameters

A. Delivery Outcome (Live/FSB) in Preeclampsia and its Association with Sr. LDH levels: Delivery outcome (Fetal Still birth) in Preeclampsia patients with Sr. LDH levels in present study was seen in 0%, 0% and 55.6% in those with LDH <600, 600-800 and >800 respectively. In other similar studies by Qublan et al.¹⁰ and Jaiswar SP et al.¹¹ it was seen in 0% and 7.14% of those with LDH <600, in 0% and 30.77% of those with LDH 600-800 and in 23.07% and 41.94% of those with LDH>800 IU/L respectively. There was statistically significant association ($p<0.001$)

of occurrence of Fetal still birth in preeclampsia patients with Raised Sr. LDH levels in other similar studies which is comparable to findings in our study.

B. APGAR Score at 1 min and 5 min in Babies of Mother with Preeclampsia and Association of Sr. LDH Levels with APGAR Score:

In the present study, out of 79 live babies of patients of preeclampsia, APGAR score at 1 min and 5 min was Good in maximum i.e. 43 (91.5%) and 45 (95.7%) of babies born to preeclampsia mother with sr. LDH <600 IU/L respectively. AOGAR score at 1 min and 5 min was Moderate in most i.e. 18 (64.3%) babies of preeclampsia with sr. LDH 600 – 800 IU/L. APGAR score at 1 min and 5 min was Poor in 50% and 75% babies of preeclampsia mother with Sr. LDH >800 IU/L respectively. There was statistically significant association of low APGAR score at 1 min and 5 min in babies born to preeclampsia patients with raised Sr. LDH levels ($p<0.001$). In a comparable study done by Jaiswar SP et al.¹¹, there was statistically significant association of Sr. LDH with Low APGAR score at 1 min and 5 min in babies of preeclampsia ($p<0.001$).

C. NICU Admission in Babies Born to Mother with Preeclampsia and its Association with Sr. LDH Levels:

In the present study, out of 79 live babies of patients of preeclampsia, 4 (8.5%), 19 (67.9%) and all i.e., 4 (100%) of babies born to preeclampsia mother with Sr. LDH <600 IU/L, 600 – 800 IU/L and >800 IU/L respectively were admitted to NICU. There was statistically significant association of NICU admission in babies born to preeclampsia patients with Raised Sr. LDH levels ($p<0.001$).

This was similar to study done by Mahalakshmi et al.¹⁵, NICU admissions were 2.2% in babies of those with LDH <600, 13.2% in those with LDH 600 – 800 U/L and 21.4% in those with LDH >800 U/L.

D. Early Neonatal Death in Mild and Severe PE and Association of Sr. LDH Levels with it: Early neonatal death in Preeclampsia patients with Sr. LDH levels in present study was seen in 0%, 7.1% and 100% in those with LDH <600, 600-800 and >800 respectively. In other similar studies by Qublan et al.¹⁰ and Jaiswar SP et al.¹¹ it was seen in 14.3% and 8.93% of those with LDH <600, in 42.9% and 30.77% of those with LDH 600-800 and in 38.46% and 12.9% of those with LDH>800 IU/L respectively. There was statistically significant association ($p<0.001$) of early neonatal death in babies of preeclampsia patients with raised Sr. LDH levels in other similar studies which is comparable to observations in our study.

5. Conclusion

Pre-eclampsia in its severe form causes serious multisystem complications adversely affecting mother and fetus which are preventable if detected at an early stage. Serum Lactate Dehydrogenase is the earliest marker seen in blood during hypoxia and oxidative stress which is the main pathogenic mechanism leading to cellular damage and dysfunction occurring in preeclampsia. Therefore, it can be concluded from this study that, Serum Lactate Dehydrogenase can be used as an early, reliable and inexpensive biochemical marker reflecting the severity of preeclampsia, the occurrence of its complications and fetal outcome. Patients at secondary care facilities in rural areas should be referred to nearby Tertiary care centre if Serum LDH levels are more than 800 IU/L.

6. References

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