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Role of Serum Lactate Dehydrogenase as a Biochemical Prognostic Marker for Pre-eclampsia: A Case Control Study in a Tertiary Care Hospital in South India

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Abstract

Introduction: Pre-eclampsia is a multisystem disorder specific to pregnancy and puerperium. Lactate Dehydrogenase (LDH), an intracellular cytoplasmic enzyme is ubiquitous to all major organ systems and cells. The central feature of pre-eclampsia is endothelial cell dysfunction and cellular death. With this cellular death, LDH leaks out with consequent raised serum LDH levels. Assessment of serum levels of LDH which is highly sensitive for any abnormality in the organ systems of the human body predicting maternal and fetal prognosis has always been debatable.

Objectives: To compare serum LDH levels in normal pregnant women and in women with pre-eclampsia in late antepartum period and to study the correlation of maternal and perinatal outcomes with serum LDH levels.

Materials and methods: Total of 223 pre-eclamptic women (142 with mild pre-eclampsia and 81 with severe pre-eclampsia) and 223 controls were taken who satisfied the inclusion and exclusion criteria of the study. Demographic, hemodynamic and laboratory data were compared among the three groups. The symptoms and complications of severe pre-eclampsia along with the fetal outcome were analysed according to serum LDH levels.

Result: Age, gravidity and parity in women with severe pre-eclampsia shows statistically significant lower values ($p<0.05$). Increased systolic and diastolic blood pressure, urine albumin, serum uric acid, LDH, AST and ALT levels were seen in severe pre-eclampsia group, which was statistically significant ($p<0.05$). In severe pre-eclampsia group, symptoms, complications, maternal morbidity and perinatal mortality were significantly increased with increasing serum LDH levels ($p<0.05$). The correlation analysis with Spearman's Rank correlation coefficient (rho ρ) was 0.701 which show highly positive correlation between maternal and perinatal outcomes with serum LDH levels.

Conclusion: Serum LDH is a reliable biochemical prognostic marker for severity of pre-eclampsia and its influence on the maternal and fetal outcome.

Keywords: Serum lactate dehydrogenase; Pre-eclampsia; Maternal morbidity; Perinatal mortality

Introduction

Hypertension is one of the most common medical complications occurring during pregnancy, with an incidence varying between 5-10% [1]. It accounts for a quarter of all antenatal admissions and is a leading cause of maternal and perinatal morbidity and mortality [1-4]. Pre-eclampsia is a hypertensive disorder, of unknown etiology, specific to pregnancy and puerperium. It affects 3% of pregnancies [1]. A number of social, genetic, medical and obstetric conditions predispose to its increased risk [5]. One of the most accepted hypotheses for its etiology is that of abnormal placentation with incomplete secondary wave of trophoblastic invasion leading to reduced uteroplacental blood flow, placental ischemia and hypoxia, aberrant expression of proinflammatory cytokines and vasoactive molecules finally eliciting endothelial cell dysfunction, the central feature in pre-eclampsia [6,7]. It affects multiple systems in the body such as renal, hepatic, hematological and nervous system, leading to cellular death and consequent leakage from cells and raised serum lactate dehydrogenase (LDH) levels.

Previously, various proposed serum markers for the established disease are urea, creatinine, uric acid, transaminases, vascular function (prostacyclin, thromboxane, fibronectin, homocysteine, nitric acid, cytokines), coagulation and fibrinolytic systems (tissue plasminogen activators, platelets, fibrinogen, antithrombin III, Von Willebrand factor), oxidative stress and lipids (lipid peroxides, antioxidants, lipoproteins) and placental function (human chorionic gonadotropin, corticotrophin releasing hormone, placental growth factor, a-fetoprotein, inhibin, activin and uteroplacental flow (velocity wave form) [8-10].

Lactate Dehydrogenase (LDH) is a multifaceted tetrameric intracellular cytoplasmic enzyme, ubiquitous to all major organ systems. It belongs to 2-hydroxy acid oxidoreductase family which catalyses the simultaneous interconversion of pyruvate to lactate and Nicotinamide Adenine Dinucleotide (NAD)H to NAD^+ and thereby being involved in anaerobic glycolysis. The major stimulants are pH and hypoxia. Normal levels of LDH vary from 200-400 IU/L. It has five isoenzymes (LDH_{1-5}) all of which could occur in the placenta. Pregnancy itself does not affect serum LDH levels. Its effects in pregnancy related complications like pre-eclampsia is now gaining attention [11,12].

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In pre-eclampsia, LDH_4 and LDH_5 are majorly seen in placenta and LDH_1 and LDH_2 in the serum with LDH-A4 isoenzyme activity and gene expression in placental endothelial cells being the marker for endothelial dysfunction [11,13]. Hypoxia and placental ischemia, as encountered in pre-eclampsia increases the glycolytic rate and thereby the activity of LDH which forms increasing amounts of lactate. As severity of disease increases, end-organ damage ensues and leakage of LDH outside the cell occurs. LDH is rightly termed as the cell death marker. Thus, LDH production could be triggered and its serum levels can contribute to the outcomes and prognosis of pre-eclampsia, hence the importance of undertaking this study.

Objectives

- To compare serum LDH levels in normal pregnant women and in women with pre-eclampsia in antepartum period.
- To study the correlation of maternal and perinatal outcomes with serum LDH levels.

Materials and Methods

- Health care setup-Tertiary care hospital.
- Setting-JJM Medical College, Davangere, Karnataka.
- Duration of the study-January 2018 to December 2018 (1 year).
- Type of the study-Case-control study.
- Sample size-446.
- Level of evidence-Level IV.
- Selection of cases-Total of 446 patients with 223 cases and 223 controls were taken who satisfied the inclusion and exclusion criteria of the study.
- For the purpose of the study, Pre-Eclampsia (PE) was defined based on new American college of obstetricians and gynaecologists' criteria as onset of hypertension (BP ≥ 140/90 on two occasions at least 6 h apart) after 20 weeks of gestation and resolution by 12 weeks postpartum with or without proteinuria as long as there is evidence of other end organ damage [4].

Inclusion criteria

a) Singleton pregnancy

b) **Cases:** Subjects diagnosed with pre-eclampsia (both mild and severe) in third trimester (≥ 28 weeks)

c) **Controls:** Normotensive pregnant women in third trimester (≥ 28 weeks)

Exclusion criteria

a) Patients with history of diabetes, renal disease, chronic hypertension, thyroid dysfunction, liver disease, chronic lung diseases, connective tissue disorders, seizures, disseminated intravascular coagulation, stroke, smoking, alcoholism, hepatotoxic drugs and urinary tract infections.

b) Patients with multiple pregnancy, molar pregnancy, gestational diabetes

c) Patients refused participation as per our protocol

After getting informed written consent from the patients enrolled in our study, they were subjected for thorough examination and clinical information was obtained. They were divided into three groups namely:

- **Group 1:** Controls comprised of normal healthy women (n=223),
- **Group 2a:** Mild pre-eclamptic women (BP ≥ 140/90 <160/110 mmHg) (n=142) and
- **Group 2b:** Severe pre-eclamptic women (BP ≥ 160/110 mmHg) (n=81)

- The three groups were matched for age, gravidity, parity, maternal weight, laboratory and hemodynamic results.
- Values of serum LDH >600 IU/l were reported in cases of complicated pre-eclampsia cases. Thus, after analysis of results group 2b i.e. women with severe pre-eclampsia were divided further into three categories according to the level of serum lactate dehydrogenase (LDH<600, 600-800 and >800 IU/l) in order to identify the group with maximum risk of complications.
- Complete blood parameters: 6 ml of blood was drawn from antecubital vein and dispensed into EDTA (2 ml) and clot activator (4 ml) tubes. Sysmex 1000 haematological auto analyser was used to quantify complete blood count while RANDOX auto analyser and ERBA semi-auto analyser was used for determination of creatinine, urea, uric acid, ALT, AST and LDH in our institution [14,15].
- LDH activity determination: it measured the oxidation of L-lactate to pyruvate with simultaneous reduction of Nicotinamide Adenine Dinucleotide (NAD). The change in absorbance at 340 nm due to appearance of reduced NAD (NADH) was directly proportional to the LDH activity, since other reactants were present in non-rate limiting quantities and was measured using modified Wacker's method with biochromatic (340, 383 nm) rate technique [16].
- Urinalysis: On a random spot sample of urine, urine albumin levels were examined by quantitatively using ERBA semi quantitative analyser by principle of turbid metric immunoassay.
- Blood pressure measurement: Conventional mercury sphygmomanometer is the gold standard. Sitting position with arm at the level of the heart, cuff length 1.5 times that of circumference of arm and wide enough to cover at least to-thirds of upper arm Korotkoff phase 5 or disappearance of Korotkoff sounds measures diastolic pressure [17].

Results

A total of 446 patients were recruited for the study with 223 normotensive healthy pregnant women and 223 pregnant women with pre-eclampsia. The descriptive analytical statistics were evaluated statistically with IBM SPSS Statistics for Windows, Version 20.0, IBM Corp, Chicago, IL. Unpaired student 't' test was used to compare serum LDH levels in normal pregnant women and in women with pre-eclampsia in antepartum period. Spearman's Rank correlation coefficient (rho ρ) was performed to correlation of maternal and perinatal outcomes with serum LDH levels.

Age, gravidity and parity in women with severe pre-eclampsia shows statistically significant lower values as compared with normotensive controls and cases with mild pre-eclampsia (Table 1).

Variables	Group 1 (n=223)	Group 2a (n=142)	Group 2b (n=81)
Age (years)	29.01 ± 4.32	26.73 ± 2.43	24.12 ± 3.57*
Gravidity	2.91 ± 2.20	2.43 ± 1.47	2.13 ± 1.03*
Parity	2.39 ± 1.07	1.73 ± 0.93	1.21 ± 0.15*
Maternal weight (kg)	63.47 ± 8.29	66.54 ± 6.25	74.76 ± 6.93
*p<0.05, Values are described as mean ± SD			

Table 1: Demographic analysis.

In comparison to normotensive and mild pre-eclamptic women, women with severe pre-eclampsia had statistically significant increased systolic and diastolic blood pressure, urine albumin, serum uric acid, serum LDH, AST and ALT levels. LDH values more than 600 were seen in 59 patients (72.83%) with severe pre-eclamptic women (Table 2).

The most frequent symptom complained by a patient with severe pre-eclampsia was headache seen in 84.4% cases when LDH levels were found to be more than 800. It was followed by epigastric pain seen in 71.9%, vomiting seen in 59.4% and blurred vision seen in 37.5% cases of severe preeclampsia, all in the category of elevated LDH levels of more than 800. The difference between other groups with lesser LDH levels as compared to LDH of more than 800 was statistically significant (Table 3).

Women with severe pre-eclampsia in the category of LDH levels >800 (87.5%) was found to have significantly increased incidence of complications such as eclampsia (40.6%), abruptio placentae (21.9%), intracranial haemorrhage (3.1%), HELLP syndrome (9.4%), pulmonary edema (6.5%) and DIC (6.2%) as compared to women in categories with lesser LDH levels, LDH<600 (0%) and LDH 600-800 IU/l (25.9%), p<0.05. Eclampsia was the most common complication accounting for 40.6%, followed by abruptio placentae (Table 4).

Among birth weight and mode of delivery in different categories of severe pre-eclamptic women no statistically significant differences were found. But the perinatal mortality was significantly higher in the category which had LDH levels more than 800 IU/l (37.5%) as compared to 14.8% with LDH 600-800 IU/l and 4.5% in LDH <600 IU/l. The correlation analysis with Spearman's Rank correlation coefficient (rho ρ) was 0.701 which show highly positive correlation between maternal and perinatal outcomes with serum LDH levels (Table 5).

Variables	Group 1 (n=223)	Group 2a (n=142)	Group 2b (n=81)
Systolic BP (mm Hg)	119.03 ± 14.54	146.47 ± 15.03	167.56 ± 19.70*
Diastolic BP (mm Hg)	89.01 ± 3.04	96.16 ± 5.33	114.83 ± 12.51*
Urine albumin (mg/dl)	0.20 ± 0.32	0.72 ± 0.40	2.13 ± 0.71*
Haematocrit (%)	31.15 ± 4.23	34.77 ± 3.41	36.16 ± 4.63
Platelets (x 10^9/L)	292.01 ± 41.33	196.36 ± 21.31	170.31 ± 22.50
Creatinine (mg/dl)	0.32 ± 0.10	0.81 ± 0.14	1.93 ± 0.11
Urea (mg/dl)	9.42 ± 3.41	18.93 ± 4.67	25.16 ± 7.31
Uric acid (mg/dl)	2.91 ± 0.39	5.36 ± 0.93	7.84 ± 1.07**
LDH (IU/L)	329.75 ± 49.90	497.35 ± 58.99	778.82 ± 75.74***
AST (IU/L)	19.34 ± 4.02	37.63 ± 6.73	95.42 ± 4.89***
ALT (IU/L)	26.17 ± 7.43	36.03 ± 9.25	94.27 ± 11.75***
** p<0.01, *** p<0.001, ALT-Alanine Transaminase, AST-Aspartate Transaminase, Values are described as mean ± SD			

Table 2: Hemodynamic and laboratory data.

Variables	LDH<600 IU/L (n=22)	LDH 600-800 IU/L (n=27)	LDH>800 IU/L (n=32)
Epigastric pain	3	9	23***
Blurred vision	2	7	12***
Vomiting	11	12	19**
Headache	15	17	27*
** p<0.05, ** p<0.01, *** p<0.001			

Table 3: In severe pre-eclampsia, symptoms according to LDH levels.

Variables	LDH<600 IU/L (n=22)	LDH 600-800 IU/L (n=27)	LDH>800 IU/L (n=32)
Eclampsia	0	3 (11.1%)	13 (40.6%)
Abruptio placentae	0	1 (3.7%)	7 (21.9%)
Intracranial haemorrhage	0	0	1 (3.1%)
HELLP syndrome	0	0	3 (9.4%)
Acute renal failure	0	0	0
Pulmonary edema	0	0	2 (6.2%)
DIC	0	3	2 (6.2%)
Total	0	7 (25.9%)	28* (87.5%)
*p<0.05, DIC: Disseminated intravascular coagulation			

Table 4: In severe pre-eclampsia, complications according to LDH.

Variables	LDH<600 IU/L (n=22)	LDH 600-800 IU/L (n=27)	LDH>800 IU/L (n=32)
Perinatal death	1	4	12***
Birth weight (g)	1925.12 ± 723.49	1657.01 ± 471.64	1523.26 ± 512.93
Normal vaginal delivery	23	19	9
Caesarean section	26	25	23
*** p<0.001			

Table 5: In severe pre-eclampsia, pregnancy outcome according to LDH levels.

Discussion

In our study, younger age and nulliparity was more often seen in women with severe pre-eclampsia group than in mild pre-eclampsia and normotensive controls. This finding was consistent with other studies done by Vinitha et al. and Qublan et al. [18,19]. High maternal weight, being primigravidae are some of the significant risk factors as has been documented previously [5].

With increasing serum LDH levels, disease severity significantly increased. In the present study, high systolic and diastolic BP was associated with higher levels of serum LDH. Significant proteinuria, raised serum creatinine and serum liver enzymes are seen in the high serum LDH group. Thus, features of end organ damage are more likely to be seen in pre-eclampsia as serum LDH levels increase. Mean LDH levels of 329.75 ± 49.90 IU/l was found in normotensive women, as compared to higher levels of 497.35 ± 58.99 IU/l and 778.82 ± 75.74 IU/l were seen in women with mild pre-eclampsia and severe pre-eclampsia respectively. Similar results were seen in other studies as well done by Vinitha et al., Qublan et al., Hak et al., Jaiswar et al., Umasatyasri et al. and Munagavalasa [18-23]. Another study done by Sarkar et al. concluded that the main cause of pre-eclampsia is due to elevated levels of serum LDH, which indicates the tissue damage is related to endothelial vascular damage [24].

Higher levels of LDH in pre-eclampsia were associated with increased symptoms of impending eclampsia and adverse complications during pregnancy. It was found that in the group with LDH>800 IU/l, complaints of the symptoms of headache, blurred vision, vomiting and epigastric pain were significantly higher, most of the times with multiple symptoms at once. In patients with pre-eclampsia, as LDH increased so did the number of pregnancies with complications. In severe pre-eclampsia group with LDH in the range 600-800 IU/l, 25.9%

had complications such as eclampsia, abruptio placentae and DIC as compared to 87.5% complications when LDH was found to be more than 800 IU/l with Eclampsia (40.6%), Abruptio placentae (21.9%), Intracranial haemorrhage (3.1%), HELLP syndrome (9.4%), Pulmonary edema (6.2%) and DIC (6.2%) which is statistically significant. Vinitha et al. found a very significant increased rate of occurrence of complications in pregnancies as the level of LDH increased from less than 600 (none) to 600-800 (13.6%) and to more than 800 IU/l (94.3%) [18]. Also, in severe pre-eclampsia group with LDH> 800, 77.7% had epigastric pain, 66.6% had blurred vision, 83.3% had vomiting and 89.5% had headache. Increase in maternal morbidity was observed with increasing serum LDH levels as evidenced by previous studies [19-23].

Adverse pregnancy outcome in terms of increased perinatal mortality was seen in pre-eclamptic women with LDH> 800. Perinatal death was seen in 37.5% of women with LDH>800 as compared to 14.8% in women with LDH 600-800 and 4.5% with LDH<600IU/l which was found to be statistically very significant. Average birth weight of babies was found to be lesser in group with higher LDH levels, but this was statistically insignificant. This finding points out the increased prevalence of IUGR and preterm babies with severity of disease which is indicated objectively by increased value of serum LDH. This was in accordance with studies done elsewhere [18,20-23]. Contrary to this, Qublan et al. did not find any significant association [19]. Jaiswar et al. and Umasatyasri et al. demonstrated significantly reduced mean Apgar scores at 1 min and 5 min, showing mild to severe depression of the newborn babies with increasing serum LDH levels [21,22].

Thus, serum LDH is an effective biochemical marker which can be useful in early diagnosis of pre-eclampsia and can reflect the disease severity such that appropriate measures can be taken to reduce the morbidity and mortality associated with the disease. The limitations of the study are smaller sample size with a limited follow up of one year.

Conclusion

Serum Lactate Dehydrogenase (LDH) is a reliable biochemical marker for pre-eclampsia and is a significant prognosticator of the disease severity and its influence on the maternal and fetal outcome. Strict monitoring of serum LDH levels in a high-risk pregnant woman may help in early diagnosis and early intervention thus, preventing maternal and fetal complications.

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