Lactate Dehydrogenase - A Biochemical Marker for the Prediction of Adverse Outcomes in Pre-Eclampsia

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ABSTRACT

BACKGROUND

Hypertensive disorders are one of the leading causes of maternal mortality. Lactate dehydrogenase (LDH) is one of the markers to study the severity of pre-eclampsia. It is an intracellular enzyme which increases in pre-eclampsia due to cellular lysis. We wanted to assess the LDH levels in normal pregnant women and women with pre-eclampsia in antenatal period and study the role of LDH as a biochemical marker to predict adverse outcomes in pre-eclampsia.

METHODS

This is a prospective observational study conducted between October 2016 and August 2018 at Sri Ramachandra Institute of Higher Education and Research. Antenatal women > 28 weeks were grouped as healthy normotensive women and those with pre-eclampsia and eclampsia. Antenatal women < 28 weeks, with pre-existing diabetes mellitus, renal disease, liver disease and epilepsy were excluded from the study. LDH levels were assessed. Both groups were followed up closely for new or worsening signs and symptoms of pre-eclampsia, till delivery and early postpartum period. LDH levels in both groups were broadly divided into 3 groups (< 600 IU / L, 600 - 800 IU / L, > 800 IU / L). Maternal and perinatal outcomes were studied in these groups.

RESULTS

All normotensive antenatal women and 128 out of 147 (87 %) hypertensive antenatal women had a normal LDH value (< 600 IU / L). While the babies of 58.6 % of hypertensive antenatal women with normal LDH required NICU admission, babies of 68.4 % of those with elevated LDH required NICU admission (p value > 0.05). Hence, levels of LDH do not correlate with the severity of pre-eclampsia and neonatal outcome. Also, 47.4 % of hypertensive antenatal women with elevated LDH had HELLP syndrome; 10.5 % had disseminated intravascular coagulation and 63.2 % required ICU admission. P value was < 0.05. Therefore, increasing LDH level had a positive correlation with maternal complications like HELLP syndrome, disseminated intravascular coagulation and the need for ICU admission.

CONCLUSIONS

Our study showed no correlation between lactate dehydrogenase and the incidence of pre-eclampsia. LDH is a good biochemical marker to predict adverse maternal outcomes of pre-eclampsia but not neonatal outcome.

KEY WORDS

Lactate Dehydrogenase, Maternal and Perinatal Outcome, Pre-Eclampsia, Eclampsia

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BACKGROUND

Preeclampsia is a multi-system progressive disorder characterized by new onset of hypertension and proteinuria. The disorder is caused by placental and maternal vascular dysfunction and always resolves after delivery. A systematic review by the World Health Organization (WHO) indicates that hypertensive disorders account for 16 % of all maternal deaths in developed countries, 9 % of maternal deaths in Africa and Asia, and as high as 26 % in Latin America and the Caribbean.[1] Perinatal morbidity and mortality increase with severity of pre-eclampsia. Approximately 12 to 25 % of fetal growth restriction and small for gestational age infants as well as 15 to 20 % of all preterm births are attributable to preeclampsia.[2]

Pre-eclampsia can be a progressive disease. Although most women develop signs of this disease in late pregnancy, with gradual worsening until delivery, in approximately 25 percent of women, especially those with early-onset pre-eclampsia, hypertension becomes severe and / or signs and symptoms of end-organ damage become apparent over a period of days to weeks. It is important to note that severe sequelae can occur in those without severe hypertension but who have clinical evidence of significant end-organ dysfunction. Chest pain, dyspnoea and low platelet count appear to be particularly predictive of fatal or life-threatening complications.

Delivery of the placenta generally results in complete resolution of maternal signs and symptoms of pre-eclampsia. Typically, mobilization of third space fluid and diuresis begins within 48 hours of delivery. Hypertension may worsen during the first and occasionally, the second postpartum week, but normalizes in most women within four weeks postpartum. Rarely, hypertension persists beyond three months.

Hypertensive disorders is one of the leading causes of maternal mortality worldwide. Pre-eclampsia and eclampsia have its own spectrum of maternal complications like HELLP syndrome, disseminated intravascular coagulation, abruptio placenta, postpartum haemorrhage and the need for intensive care. Fetal complications include intra-uterine growth restrictions, low birth weight, preterm labour, respiratory distress syndrome and ventilatory support at NICU after delivery. There are several markers to study the severity of pre-eclampsia, one of which is lactate dehydrogenase (LDH). Early diagnosis and prompt management is vital to avoid adverse maternal and perinatal outcome.

Lactate dehydrogenase is an intracellular enzyme that converts pyruvic acid to lactic acid during the process of glycolysis. Hypoxia in pre-eclampsia further increases glycolysis and thereby also the activity of LDH. LDH has five isoforms found in different body tissues. They are LDH-1, LDH-2, LDH-3, LDH-4 and LDH-5. LDH 1 and LDH-2 are mainly found in the heart and red blood cells. LDH-3 is seen in the lymphatic tissue, lungs, platelets and pancreas. While LDH-4 and LDH-5 are chiefly found in the liver and skeletal muscles, LDH-4 activity is also found in the placenta of pre-eclamptic patients.[3] An elevated level of LDH is suggestive of the extent of cellular damage and dysfunction. Hence, it can be used as a biochemical marker as it reflects the severity of pre-eclampsia along with its adverse maternal and perinatal complications.
The aim of our study is to assess the serum LDH levels of normal pregnant women and women with pre-eclampsia in antenatal period and to study the role of LDH as a biochemical marker to predict adverse outcomes of pre-eclampsia.

METHODS

This is a prospective observational study conducted at Sri Ramachandra Institute of Higher Education and Research, India, between October 2016 and August 2018. Ethical clearance was obtained from the Institutional Research Ethics Committee at Sri Ramachandra University, Chennai, in compliance with ICMR. The inclusion criteria consist of antenatal women beyond 28 weeks of gestation who were grouped as healthy normotensive antenatal women and those with pre-eclampsia and eclampsia. Exclusion criteria consist of antenatal women less than or equal to 28 weeks, epilepsy, renal disease, liver disease and pre-existing diabetes mellitus. A sample size of 320 antenatal women was decided in order to obtain statistically significant results. Informed consent was obtained from all participants of the study after explaining the purpose of the study. After detailed history taking and physical examination, the antenatal women who meet the inclusion criteria were assessed for their LDH level. Under strict aseptic precautions, 2 ml of venous blood was withdrawn from the patient and collected in a vacutainer that has a clot activator to separate the serum as a supernatant. LDH was assayed from the collected serum using lactate to pyruvate method in the biochemistry laboratory. The antenatal women were followed up till delivery and early postpartum period. They were divided into the 2 groups as mentioned above. While the normotensive group were watched closely for imminent symptoms and signs of pre-eclampsia, those with pre-eclampsia and eclampsia were monitored for worsening signs and symptoms. The LDH values of both these groups were divided into three groups (< 600 IU / L, 600 - 800 IU / L, > 800 IU / L). Symptoms and signs of pre-eclampsia along with maternal and fetal outcome were studied in these three groups. Following delivery, the babies were followed up till early neonatal period to analyse the neonatal outcome.

Statistical Analysis

Statistical analysis was performed using Statistical Package for Social Science (SPSS, version 17) for Microsoft Windows. Data was normally distributed and thereafter, parametric tests were performed. Descriptive statistics were presented as numbers and percentages. Data was expressed as Mean and SD. A one way analysis of variance with a post hoc Tukey HSD was used for normally distributed continuous data. Chi-square test was used for qualitative data. A two sided p value < 0.05 was considered statistically significant.

RESULTS

In our study of 320 patients, 173 were normotensive, 71 had mild pre-eclampsia, 64 had severe pre-eclampsia and 12 had eclampsia. Their LDH levels were compared as given in Table I. All normotensive antenatal women and 128 out of 147 hypertensive antenatal women had a normal LDH value (< 600 IU / L). Hence, the values of LDH did not correlate with the severity of pre-eclampsia. Headache was the most common imminent symptom amongst hypertensive patients with normal as well as elevated LDH levels as mentioned in Table II. Other imminent signs that were studied include blurring of

vision, epigastric pain and decreased urine output. The proportion of hypertensive patients with elevated systolic and diastolic blood pressure was similar in both normal and elevated LDH groups. P values for systolic and diastolic blood pressures in both groups were found to be 0.807 and 0.694 respectively and hence, statistically not significant (Table III). There was no correlation between LDH and neonatal outcome which was assessed based on the need for NICU admission and the duration of intensive care received, as depicted in Table IV. P value being 0.659 for neonatal outcome was not statistically significant. There were totally 6 cases of intrauterine fetal demise and 1 case of neonatal death which did not show statistical significance while there was one case of stillbirth amongst hypertensive patients with elevated LDH which was significant. Table V shows that increasing LDH values in hypertensive patients had a positive correlation with maternal complications like HELLP syndrome, DIC and the need for ICU admission. Others include abruptio placenta and post-partum haemorrhage. There was no maternal mortality in our study.

LDH (IU / L)	Normotensive	Mild Pre-Eclampsia	Severe Pre-Eclampsia	Eclampsia	Total
< 600	173	63	58	7	301
600 - 800		5	5	3	13
> 800		3	1	2	6
Total (n = 320)	**173**	**71**	**64**	**12**	**320**

Table 1. Distribution of LDH between Normotensive Antenatal Women and Those with Pre-Eclampsia and Eclampsia

Imminent Signs	Hypertensive Patients with Normal LDH Level (n = 128)	Hypertensive Patients with Elevated LDH (n = 19)
Headache	53	6
Blurring of Vision	16	0
Epigastric Pain	20	5
Decreased Urine Output	7	4

Table 2. LDH vs. Imminent Signs

Blood Pressure (mm / Hg)	Hypertensive Patients with Normal LDH (n = 128)	%	Hypertensive Patients with Elevated LDH (n = 19)	%	P Value
Systolic < 140	16	12.5	2	10.5	0.807
> 140	112	87.5	17	89.5	
Diastolic < 90	10	7.8	1	5.3	0.694
> 90	118	92.2	18	94.7	

Table 3. LDH vs. Blood Pressure

NICU Admission	Hypertensive Patients with Normal LDH (n = 128)	%	Hypertensive Patients with Elevated LDH (n = 19)	%	P Value
< 24 hours	15	11.7	2	10.5	0.659
> 24 hours	60	46.9	11	57.9	
Did Not Require	53	41.4	6	31.6	

Table 4. LDH vs. Neonatal Outcome

Maternal Complications	Hypertensive Patients with Normal LDH	%	Hypertensive Patients with Elevated LDH	%	p Value
HELLP Syndrome	22	17.2	9	47.4	< 0.05
Abruptio Placenta	4	3.1	0	0	> 0.05
Disseminated Intravascular Coagulation	0	0	2	10.5	< 0.001
Postpartum Haemorrhage	27	21	6	31.6	> 0.05
ICU Admission	29	22.7	12	63.2	< 0.001

Table 5. LDH vs. Maternal Outcome

DISCUSSION

Pre-eclampsia is a well-known obstetric complication faced by obstetricians today. While it can be a life-threatening situation, prompt identification and management with a multidisciplinary team of experts can prove beneficial for both mother and the baby. Pre-eclampsia is usually diagnosed with a blood pressure more than or equal to 140 / 90 mmHg measured on 2 separate occasions at least 6 hours apart along with proteinuria. There are many imminent signs and symptoms associated with this condition. Amongst many biochemical markers used, lactate dehydrogenase is very commonly tested to predict the severity of pre-eclampsia. LDH value more than 600 IU / L is considered significant. Our study aims to correlate the LDH value with the severity of pre-eclampsia as well as to assess the maternal and perinatal outcome of patients with pre-eclampsia and eclampsia.

In our study, antenatal women with elevated blood pressure between the ranges of 140 / 90 mmHg and 160 / 110 mmHg were considered to have mild pre-eclampsia and those with blood pressure above 160 / 110 mmHg were considered to have severe pre-eclampsia. 320 normotensive and hypertensive patients were studied prospectively out of which 173 were normotensive, 71 (22 %) had mild pre-eclampsia, 64 (20 %) had severe pre-eclampsia and 12 (4 %) had eclampsia. All normotensive patients had a normal LDH value less than 600 IU / L. Out of 71 cases of mild pre-eclampsia, 63 cases had LDH less than 600 IU / L and 5 cases were in the range of 600 - 800 IU / L and 3 cases with LDH more than 800 IU / L. The mean LDH value calculated was 351.94 + 204.2 IU / L. Out of 64 cases of severe pre-eclampsia, 58 cases had LDH less than 600 IU / L, 5 cases ranged between 600 - 800 IU / L and only 1 case had LDH more than 800 IU / L. In this group, the mean was 351.3 + 149.4 IU / L. Out of 12 cases of eclampsia, 7 cases had LDH value less than 600 IU / L, 3 ranged between 600 - 800 IU / L and only 2 had LDH more than 800 IU / L. Here, the mean was 860.75 + 1221.6 IU / L. On analysing the above data, it is clear that the levels of LDH did not correlate with the severity of pre-eclampsia.

In contrast to our study, Jaiswar et al[4] demonstrated a significant association of serum LDH levels with severity of pre-eclampsia with a p value < 0.001. Also, Qublan et al[5] had similar findings in their study with a significant association between LDH levels and severe pre-eclampsia. However, Makkonen et al[6] studied that there was no relation between LDH and severity of pre-eclampsia, which was in sync with our study results.

Some of the common symptoms and signs seen in pre-eclampsia include headache, epigastric pain, decreased urine output, blurring of vision. Theories behind the cause of headache in pre-eclampsia include cerebral vasoconstriction and vasogenic oedema. Fluid retention leading to a thickened cornea along with an increase in fluid pressure in the eyeball cause blurring of vision. While stretching of the Glisson's capsule of the liver causes epigastric pain, constriction of the renal arteries leads to reduced urine output. In our study, headache is found to be the most common imminent symptom in both hypertensive groups with normal and elevated LDH, as compared to the others like epigastric pain, blurring of vision and decreased urine output. However, in a study by Qublan et al[5], the incidence of epigastric pain was found to be significantly higher in severe pre-eclamptic patients with LDH more than 800 IU / L.

Pre-eclampsia is defined as hypertension with blood pressure more than or equal to 140 / 90 mmHg on 2 separate occasions at least 6 hours apart along with proteinuria. The proportion of hypertensive patients with an elevated systolic

and diastolic blood pressure values is approximately the same in hypertensive patients with both normal (87.5 %, 92.2 %) and elevated (89.5 %, 94.7 %) LDH values. Hence, our study does not show any significant correlation between LDH and blood pressure, with a P value more than 0.05. However, a study by Hemalatha et al[7] showed that a higher LDH value is associated with elevated systolic and diastolic blood pressures with a P value less than 0.0001. Similar results are also shown by Jaiswar et al[4] and Qublan et al.[5]

Neonatal outcome in our study was analysed by the need for NICU admission for the new-born babies and the duration of intensive care given as to whether they required less than or more than 24 hours. There was no statistical significance between LDH and neonatal outcome as per our study. While He S et al[8] and Jaiswar et al[4] found a significant incidence of low birth weight babies in hypertensive women with elevated LDH, Qublan et al[5] and Umasatyasri et al[9] did not show statistically significant results in this aspect.

Perinatal morbidity and mortality due to pre-eclampsia is a much-feared complication. Fetal growth restriction, stillbirth, intrauterine fetal demise and respiratory distress syndrome requiring ventilatory support following delivery are some of the perinatal risks associated with pre-eclampsia. Our study showed 5 cases of intrauterine fetal demise amongst hypertensive patients with a normal LDH value as compared to only 1 such case in those with elevated LDH value, the reasons being intrauterine growth restriction, Doppler changes and severe oligohydramnios. There was also 1 case of early neonatal death in hypertensive group with a normal LDH value due to respiratory depression. While this did not have any statistical significance, there was 1 case of stillbirth in the hypertensive group with elevated LDH, which was due to eclampsia, with a significant P value less than 0.05. Studies by Qublan et al[5] and Jaiswar et al[4] showed significant increase in perinatal complications and mortality with increasing LDH values, which is not seen in our study.

In pre-eclampsia, apart from lactate dehydrogenase, blood parameters like platelet count, liver enzymes, peripheral smear, fibrinogen level, uric acid, urea and electrolytes are closely monitored to assess the severity of pre-eclampsia. Based on these reports, various maternal complications like haemolysis, elevated liver enzymes and low platelet (HELLP) syndrome, disseminated intravascular coagulation, acute kidney injury, and thrombocytopenia due to platelet consumption are identified. In our study, patients with severe pre-eclampsia and eclampsia with elevated LDH showed a significant increase in maternal complications like HELLP syndrome (p value < 0.05), disseminated intravascular coagulation (p value < 0.001) and the need for ICU admission (p value < 0.001). While other maternal complications like abruptio placenta and post-partum haemorrhage were noted in hypertensive cases with normal and elevated LDH values, they were not statistically significant. There was no maternal mortality seen in our study. Catanzerite Va et al[10] reported that a subgroup of patients who had elevated levels of LDH manifested with haemolysis, elevated liver enzymes, low platelet count (HELLP) syndrome and were at a high risk for developing maternal mortality. Demir SC et al[11] concluded that there was a statistically significant relation between maternal complications and high LDH levels. Many other studies done by Jaiswar et al[4], Qublan et al[5], Hemalatha et al[7] and Umasatyasri et al[9] also show that higher serum LDH values are associated with an increased incidence of maternal complications as well as increased maternal mortality.

CONCLUSIONS

Pre-eclampsia and eclampsia are pregnancy-specific diseases and the complications, morbidity and mortality associated with them increase with the severity of the disease. Although lactate dehydrogenase is theoretically studied to be a good biochemical predictor in assessing the severity of pre-eclampsia and its adverse effects, differences between various studies reflect the diversities between the populations and the analytical methods used.

Our study does not show any significant correlation between lactate dehydrogenase and the incidence of pre-eclampsia as all normotensive and majority of hypertensive women (87 %) included in our study had normal LDH levels. LDH is an acute event marker and hence, it is a good biochemical marker to predict adverse maternal outcomes of pre-eclampsia but not neonatal outcomes. We may need a larger study population to get statistically significant results. Detection of high-risk patients with increased levels of LDH warrants close monitoring and timely multi-disciplinary management to reduce both maternal and fetal morbidity and mortality. Creating awareness among antenatal women at risk of pre-eclampsia, about the imminent signs and symptoms following which it is essential that they report to their practitioners immediately, definitely plays a pivotal role in the early diagnosis of this condition and accurate management at an early stage.

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