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Serum Lactate Dehydrogenase as an Indicator of Maternal and Neonatal Outcomes in Hypertensive Disorders of Pregnancy

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ABSTRACT

Objective: To ascertain the sensitivity and specificity of serum lactate dehydrogenase as an indicator for maternal and neonatal outcomes in hypertensive disorders of pregnancy.

Study Design: Cross-sectional, analytical study.

***Place and Duration of Study*:** Departments of Anesthesia and Gynecology & Obstetrics, Combined Military Hospital, Okara Cantt Pakistan, from Apr to Sep 2018.

Methodology: Eighty-six pregnant women with pregnancy-induced hypertension were included in our study. Group-A included pregnant women with raised serum LDH, and Group-B included pregnant women with normal LDH levels. The patients were followed up until delivery and hospital discharge. Maternal and neonatal outcomes were studied.

Results: The progression to hemolysis elevated liver enzyme low platelet (HELLP) syndrome was 4(4.8%) in Group-A versus zero in Group-B, p=0.022. The two groups did not vary in mode of delivery (cesarean section in 28 vs. 33); preterm delivery (22 versus 15); intrauterine growth retardation (8 vs. 6); intrauterine demise (9 vs 5); low APGAR at birth (13 vs. 7); eclampsia (3 vs. 3) which were comparable between the two groups, p-value>0.05. For overall maternal outcomes, the sensitivity for raised LDH was 57.1% and specificity 53.3%. The sensitivity was 51.2%, and the specificity was 54.7% for overall neonatal outcomes.

***Conclusion*:** Elevated serum LDH alone in pregnancy-induced hypertension cannot considered as a prognostic indicator for maternal and neonatal adverse outcomes, except HELLP syndrome.

Keywords: Eclampsia, HELLP syndrome, Lactate dehydrogenase, Pre-eclampsia, Preterm birth

How to Cite This Article: *Zainab S, Akbar A, Ehsan A, Mushtaq S, Tabbasum H, Ikram M. Serum Lactate Dehydrogenase as an Indicator of Maternal and Neonatal Outcomes in Hypertensive Disorders of Pregnancy. Pak Armed Forces Med J 2024; 74(2): 451-454. DOI: https://doi.org/10.51253/pafmj.v74i2.10077*

INTRODUCTION

Hypertensive disorders of pregnancy are one of the leading causes of maternal morbidity and mortality. The incidence of hypertensive disorders of pregnancy is 180.79 per 10000 live births, with maternal mortality reported to be 27.83 in 1000 live births globally, with 4.6% of pregnancies being complicated by pre-eclampsia and 1.4% by eclampsia.[1,2] The incidence of pre-eclampsia is higher in developing countries (14.4%) than 2.3 % to 2.9% in developed countries.[3,4] Maternal complications like HELLP (hemolysis, elevated liver enzymes and low platelet) syndrome, eclampsia, acute renal failure can result in maternal deaths. Neonatal complications like intra-uterine growth retardation, preterm labour, and low birth weight can worsen neonatal survival.[5]

Various tests are used for screening and prognosis of hypertensive disorders in pregnancy. Raised serum lactate dehydrogenase (LDH) level is a non-specific test for hemolytic anaemia; hypotension; intestinal ischemia; liver, lung, muscle disease or injury; pancreatitis and various cancers.[6] It has been extensively studied as a biomarker of cardiovascular disease including myocardial ischemia and infarct, stroke.[7] Pre-eclampsia, eclampsia and HELLP syndrome have multi-system, complex pathophysiology due to abnormal placentation.[8] Serum LDH level can be used as an indicator of cellular injury in such patients. Uncertain results have been reported regarding its reliability in the context of screening and prognostic tests for hypertensive disorders of pregnancy.[9] Limited data shows the validity and reliability of serum LDH as a prognostic test in hypertensive disorders in pregnancy (HDP) in the absence of hemolysis. Our study aims to ascertain the sensitivity and specificity of serum LDH as a prognostic tool and its correlation with maternal and neonatal outcomes in hypertensive disorders in pregnancy.

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Received: 13 Mar 2022, revision received: 02 Jul 2023; accepted: 05 Jul 2023

METHODOLOGY

The cross-sectional analytical study was conducted at the Departments of Anesthesia and Gynecology & Obstetrics, CMH, Okara Cantt Pakistan, from April 2018 to September 2019, after the approval of the Hospital Ethical Review Committee (IERC/obs/2018/03; dated 02 March 2018). The sample size was calculated using the WHO sample size calculator, taking a reported incidence of 41.7% in the Control Group versus 15.2% adverse maternal outcome in Cases.[9]

Inclusion Criteria: Pregnant women aged 18-35 years with singleton pregnancy, gestational age greater than 28 weeks, presenting to Obstetrics Outdoor with hypertension were included.

Exclusion criteria: Pregnant women who were diagnosed with chronic hypertension or HELLP syndrome at presentation were excluded.

Baseline laboratory tests and serum LDH levels were taken during their presentation. The obstetrician provided the obstetrical care per institute protocol, and patients were prospectively followed up till delivery. The patients were divided into two groups by convenient sampling. Patients with elevated LDH (≥250IU/L) were included in Group-A, while patients with normal LDH (< 250IU/L) levels were included in Group-B. The maternal outcomes included sensitivity and specificity of LDH for maternal outcomes. The neonatal outcomes include preterm labour, mode of delivery, progression of the disease, intrauterine growth retardation, intrauterine death and low APGAR scores at birth.

Statistical Package Social Sciences version 23.00 was used for statistical analysis. Qualitative variables were presented as frequency and percentage. Chi-square was used to calculate significance. The quantitative variables were presented as Mean±SD. Independent sample t-test was used to calculate signi-ficance. The *p*-value of ≤ 0.05 was taken as significant. The sensitivity calculated true positive divided by the sum of true positive and false negative. The specificity was calculated by dividing the true negative by the sum of the true negative and false positive.

RESULTS

Our study included 86 patients. Three women were excluded due to incomplete data. The final analysis had 43 pregnant women in group A and 40 pregnant women in group B. Table-I compares the demographic profiles of the study groups. 46(55.4%) of the study population had pregnancy-induced hypertension, 17(20.5%) had pre-eclampsia, and 4(4.8%) developed eclampsia. The association of elevated LDH levels on maternal and neonatal outcomes is given in Table-II.

Table No. I: Comparison of demographic profile of groups.

Variable		Group A (n=43)	Group B (n=40)	*p*-value
Age (years)		28.2±4.94	29.07±4.10	0.331
Gestational age (weeks)		35.15±3.72	36.2±3.07	0.132
Gravidity	Primagravida	19(47.5%)	18(41.8%)	0.519
	2-4	14(32.5%)	20(46.5%)	
	≥ 5	7(17.5%)	5(11.6%)	

Table No. II: Association of elevated LDH with mode of delivery and Neonatal Outcomes

Variable		Group A (n=40)	Group B (n=43)	*p*-value
Mode of delivery	Cesarean section	28(70%)	33(76.7%)	0.620
	Vaginal Delivery	12(30%)	10(23.3%)	
Preterm delivery		22(55%)	15(34.8%)	0.080
Intrauterine growth retardation		8(20%%)	6(13.9%)	0.562
Intrauterine death		9(22.5%)	5(11.6%)	0.245
Low APGAR at birth		13(32.5%)	7(16.2%)	0.123
Pre-Eclampsia	Yes	10(25%)	7(16.2%)	0.417
Eclampsia	Yes	7(17.5%)	4(9.3%)	0.340
HELLP Syndrome	Yes	4(10%)	-	0.022

For maternal outcomes, the sensitivity for raised LDH was 57.1% and specificity 53.3%. 41(49.4%) neonates had adverse neonatal outcomes in our study population. The sensitivity is 51.2%, and the specificity is 54.7% for overall neonatal outcomes. Raised serum LDH was found to be raised in all patients who developed HELLP syndrome, whereas it was normal in all patients who did not develop HELLP syndrome. Table-III compares the sensitivity and specificity of raised serum LDH as a prognostic test.

Table No. III: Sensitivity, Specificity of Raised LDH as Prognosis for Maternal Outcome (n=83)

Outcome	Odds Ratio (95% Confidence Interval)	Sensitivity	Specificity
Pre-eclampsia	0.583(0.198-1.719)	58.8%	45.5%
Eclampsia	0.925(0.176-4.87)	61.5%	48.0%
HELLP syndrome	0.456(0.358–0.580)	100%	54.4%

DISCUSSION

Various laboratory tests are being performed to identify hypertensive pregnant women at risk of deve-

loping complications during childbirth. These include serum uric acid; D-dimers, HDL, IL-6, eosinophil counts, and plasma N-terminal pro-atrial natriuretic peptide level.[10-12] However, their feasibility has not been proved beyond a shadow of doubt. In a resource-limited country, the chosen screening test should be readily available, affordable and reliable in its efficacy. Though serum uric acid, albumin, and creatinine levels are economical tests, their prognostic value is equivocal.[13,14]

LDH is an intracellular enzyme used in the metabolism of lactic acid into pyruvic acid. Cellular death and the leakage of enzymes from cells raise its extracellular quantity. Raised serum LDH may reflect the severity of cellular injury and death, making it a sensitive but non-specific screening test. Its value as a prognostic test for patient outcomes is still under investigation.

Serum LDH is used as a biomarker for hemolysis for various conditions, including thrombosis in the left ventricular assist device, hemolytic anaemia, and sickle cell disease.15,16 Studies have also reported raised LDH in severe pre-eclampsia.[17,18] It is also an indicator of hemolysis in HELLP syndrome. However, its utility as a prognostic tool in severe pre-eclampsia and eclampsia is not fully understood. Our study has shown comparable maternal and neonatal outcomes in pregnant women with HDP, whether their serum LDH was normal or raised. Hence, we report that single raised serum LDH at 28-32 weeks of pregnancy is not a sensitive or specific test for maternal outcomes, except HELLP syndrome. According to the authors' knowledge, limited data on the sensitivity and specificity of LDH as a prognostic tool in maternal and neonatal outcomes is available.

Afroz *et al.* have reported raised serum LDH levels in 82.9% of mild pre-eclampsia and 91.4% of severe pre-eclampsia, $p<0.001$.[19] They used LDH> 200U/L as raised versus 275U/L taken as raised at our laboratory. In addition, we did not classify pre-eclampsia as mild or severe but grouped our outcomes as pre-eclampsia and eclampsia. However, they have not commented on the neonatal outcomes in their study, whereas we found no difference in neonatal outcomes, whether they were normal or raised maternal LDH levels. A study by Vinitha *et al.* reported 94.3% maternal complications and 77.7% perinatal deaths were in severe pre-eclampsia patients with LDH greater than 800IU/L.[20] The main differences in these studies are: their cut-off for raised LDH was 800IU/L which is almost three times the cut-off value selected by us. In addition, they included patients with LDH >600U/L as well as normotensive pregnant ladies. We cannot comment on perinatal deaths as we only studied IUDs.

Another study reported lower birth weight (16.08g±1132) in severe pre-eclampsia compared to 2687g±845 in normotensive patients; $p=0.002$. They did not mention birthweight in neonates born to mothers with pre-eclampsia and LDH>600IU/L. However, they reported an Odds ratio=4.76(95% CI 1.26-18.72) for raised LDH in pre-eclampsia.[21] Similar results have been reported by other authors.[22] All the studies have used a single value of serum LDH at 24-36 weeks. The results may differ if serial values are studied with a larger sample size.

LIMITATION OF STUDY

Our study had certain limitations. We took serum LDH levels greater than 275IU/L as high. Therefore, we cannot comment on the effect of 4-5 times raised LDH on maternal/ neonatal outcomes. Further studies with larger sample sizes are required to confirm the validity and reliability of LDH as a prognostic test for complications of hypertensive disorders of pregnancy.

CONCLUSION

Elevated serum LDH alone in pregnancy-induced hypertension cannot be considered an indicator for maternal and neonatal adverse outcomes, except for HELLP syndrome.

Conflict of Interest: None.

Authors' Contribution

Following authors have made substantial contributions to the manuscript as under:

SZ & AA: Conception, study design, drafting the manuscript, approval of the final version to be published.

AE & SM: Data acquisition, data analysis, data interpretation, critical review, approval of the final version to be published.

HT & MI: Data acquisition, drafting the manuscript, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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