ORIGINAL ARTICLE

Severity of preeclampsia and maternal serum lactate dehydrogenase: Is there a link?

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Abstract

Background: Preeclampsia (PET) is one of the most common medical conditions complicating pregnancy and an important cause of maternal and neonatal morbidity and mortality. Predicting the severity of this disease is crucial for good management outcome. Serum lactate dehydrogenase is a marker of tissue damage and preeclampsia is associated with significant tissue damage.

Methods: This was a comparative cross-sectional study involving 55 preeclamptic women aged 18-40 years with gestational age >20 weeks and 55 normotensive pregnant women matched for age, gestational age and parity recruited from the Antenatal clinic of Jos University Teaching Hospital. Socio-demographic, biophysical and obstetric data were obtained. Serum lactate dehydrogenase levels were assayed and both groups were followed up till delivery and their pregnancy outcome noted. Data was analyzed using IBM SPSS version 22.0, P<0.05 was considered significant.

Results: The mean serum LDH level of the study group (355±364IU/L) was significantly higher than the control group (136±50IU/L), P <0.001. The mean serum LDH level among preeclamptics with complications was significantly higher (880±12.6IU/L) compared to preeclamptics without complication (266.2±151.2IU/L), P <0.001.

Conclusion: Serum Lactate Dehydrogenase is a good marker of preeclampsia and higher levels of Lactate Dehydrogenase among preeclamptic patients could be a predictor of possible complications.

Keywords: Preeclampsia, eclampsia, serum lactate dehydrogenase, maternal complications

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Introduction

Pregnancy is a physiological state that is associated with many alterations in metabolic, biochemical, physiological, hematological and immunological processes.[1] All these changes are reversible within a few weeks to few months after delivery if there are no complications. However, pregnancy may sometimes be complicated by certain disorders and one of these common disorders affecting pregnancy is preeclampsia.

Preeclampsia is a pregnancy specific condition that is characterized by hypertension and proteinuria occurring after 20 weeks of gestation.[2] It is associated with substantial risks to both mother and fetus with subsequent increase in maternal and perinatal morbidity and mortality.[2, 3] Preeclampsia affects about 2-10% of all pregnancies and accounts for about one quarter of all antenatal admissions.[4 - 8] It is also associated with fetal growth restriction, prematurity and contributes largely to perinatal mortality and morbidity.[9, 10]

Although the precise aetiology of preeclampsia is not known, defective placentation and endothelial dysfunction are considered the core features of preeclampsia.[7, 11] Many other theories such as immunological intolerance between maternal and fetal tissues, genetic predisposition, nutritional imbalance and oxidative stresses had also been postulated.[12 - 14]

Several biochemical markers have been proposed as the markers of preeclampsia, including markers for renal and liver function (creatinine, uric acid, aspartate and alanine transaminases), vascular function (prostacyclin, thromboxane, fibronectin, homocystine, nitric acid and 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, alpha foeto-protein, inhibin, activin and uteroplacental flow velocity wave form).

There is increasing evidence that altered endothelial cell function plays a role in the pathogenesis of preeclampsia and this altered endothelial cell function leads to multiorgan dysfunction which then results in excessive leakage of lactate dehydrogenase and its elevated levels in the serum.[7, 15, 16]

Lactate dehydrogenase (LDH) is mainly an intracellular enzyme; it is responsible for the interconversion of pyruvate and lactate in the cells. Its levels are several times higher inside the cells than in the plasma and so it increased levels are seen in the scenario of increased cell leakiness, hemolysis and cell death.[17]

Acute critical symptoms of preeclampsia that may threaten the life of the fetus have been found to correlate

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with distinct activity of lactate dehydrogenase in the serum and thus has been found to be a useful biochemical marker of severe preeclampsia in a number of limited studies.[7, 8, 18, 19 - 21]

We therefore sought to examine the relationship between serum levels of lactate dehydrogenase and severity of preeclampsia and pregnancy outcome.

Materials and Methods

Study Area

This study was carried out at the Jos University Teaching Hospital, a tertiary Institution located in Jos, the capital of Plateau State in North Central Nigeria. It offers services to patients from Plateau state and receive referrals from neighbouring states including Benue, Nasarawa, Kogi, Adamawa, Taraba, Bauchi, Gombe, and parts of Kaduna and Niger states.

Study design

This was a comparative cross-sectional study

Study population

The study population consisted of 55 women with preeclampsia that were either primigravidae or multigravidae and the control group consisted of 55 normotensive pregnant women who were matched for age, parity and gestational age as the study group. Systolic blood pressure (BP) of 140-159mmHg and diastolic blood pressure of 90-109mmHg with proteinuria of 2+ was taken as mild preeclampsia, while systolic BP of 160mmHg and above and diastolic BP of 110mmHg and above with proteinuria of 3+ and above with or without the presence of symptoms like severe headaches, blurring of vision, epigastric pain, vomiting and convulsion was taken as severe preeclampsia.[13, 24] Proteinuria was determined using urinalysis on dipstick method. Proteinuria was graded as negative, trace, 1+ (30mg/dl), 2+ (100mg/dl), 3+ (300-1999mg/dl) and 4+ (at least 2000mg/dl).

Women with multiple gestation, diabetes mellitus, renal disease, chronic hypertension, and haemoglobinopathies were excluded from the study.

Sample size estimation

The sample size was arrived at using the formula for calculating minimum sample size involving comparison between 2 means, using a significance level of 5% and a power of 80%. Using also the difference between the standard deviations for serum LDH of the two groups; (348 ± 76 vs 299 ± 99 cases and controls respectively, mean difference of 49) from a similar study.[7]

Therefore a total of 110 subjects (comprising 55 preeclamptic and 55 normotensives) were used for this study.

Data collection

Fifty-five (55) preeclamptics and normotensives each were recruited for the study from September 2016 to October 2017. Informed consent was obtained from the study participants before data collection. Five milliliters of venous blood under aseptic condition from both study groups were obtained. Participants were matched for age (±1), parity (±1), and gestational age. The sera obtained were stored at -20 degree centigrade until the required sample size was reached and then samples analyzed at the same time for the levels of serum LDH. Results of serum LDH levels were grouped into two categories: <600IU/L and ≥ 600U/L (obtained from a similar study).[7, 21] All the participants were then followed up till the time of delivery to determine their pregnancy outcome.

Data analysis

All statistical analyses were performed using IBM SPSS version 22. Socio-demographic characteristics of the cases and controls were computed using frequencies and percentages.

Student's t-test, median using Whit-mann U test and Fisher's exact test were used to test the difference between groups where appropriate. Statistical significance was set at $p < 0.05$.

Ethical Consideration

This study was conducted after due approval from the ethics committee of the Jos University Teaching Hospital. Informed consent was obtained from all participants.

Results

A total of 110 pregnant women participated in this study; 55 preeclamptics and 55 normotensive pregnant women. Table1shows the socio-demographic and clinical profiles of all the participants in the study. The mean age, gestational age and body mass index were comparable in both groups. The median parity was 0 for study group and 1 for the controls. Mean systolic blood pressures were 171±16mmHg and 107±10mmHg in the study and the control groups respectively, while the mean diastolic blood pressures in the two groups were 110±13mmHg and 66±8mmHg respectively.

The mean serum LDH among preeclamptic patients was 355±364IU/L while the mean serum LDH among the control was 136±50IU/L, thus Serum LDH levels was significantly higher among preeclamptic patients when compared to the normotensives women, P<0.001. The mean serum lactate dehydrogenase among women with mild preeclampsia was 352.91±352.20IU/L and that women severe preeclampsia was 362.32.±425.38 IU/L with P-value of 0.993. This was however, not statistically significant. The mean serum level of LDH

among preeclamptic women that developed eclampsia and other complications was at least three times that of preeclamptic women who did not have any complication, (880.01±712.61IU/L vs 266.19±151.17 IU/L, P-value <0.001)

Table 2 shows that >50% of preeclamptic women with maternal complications had a serum LDH level that was >600IU/L. Breaking the complications down into

Table 1: Socio-demographic and clinical characteristics of all the study participants

Characteristics	Study group		Total n=110 (%)	p-value
	Preeclamptics n=55(%)	Normotensives n=55(%)		
Age (years)Mean±SD	28.36 ±5.05	27.69±4.66	28.03±4.85	0.469
Parity				
0	29(52.7)	24(43.6)	53(48.2)	
1-4	24(43.6)	31(56.4)	55(50.0)	
≥5	2(3.6)	0(0.0)	2(1.8)	0.229
Gravidity				
Primigravida	26(47.3)	27(49.1)	53(48.2)	
2-4	18(32.7)	23(41.8)	41(37.3)	
≥5	11(20.0)	5(9.1)	16(14.5)	0.262
Gestational age, Mean±SD	34.47±3.88	34.91±3.01	34.69±3.45	0.510
BMI (Kg/m2)	29.27±5.06	27.85±4.39	28.56±4.77	0.119
Systolic BP (mmHg)	171.89±16.06	107.70±9.91	139.50±34.86	<0.001
Diastolic BP(mmHg)	110.15±12.57	66.72±8.03	88.23±24.21	<0.001

Table 2: Pregnancy outcome according to serum LDH levels among Preeclamptic patients

Outcome	<600 n=48	≥600 n=7	n=55	p-value
Maternal complication*	4(8.3)	4(57.1)	8(14.5)	0.006
Mode of delivery				
SVD	21(43.8)	3(48.9)	24(43.6	
EMLSCS	24(50.0)	4(57.1)	28(50.9)	0.999
ELLSCS	3(6.2)	0(0.0)	3(5.5)	
Convulsion	10(20.8)	5(71.4)	15(27.3)	0.013
IUFD/stillbirth	6(12.5)	1(14.3)	7(12.7)	0.161
Prematurity	38(79.2)	6(85.7)	44(80.0)	0.571
Birth asphyxia	6(12.5)	2(28.5)	8(14.5)	0.561
IUGR	2(4.2)	1(14.3)	3(5.5)	0.341
SCBU Admission	1(2.1)	1(14.3)	2(3.6)	0.240

*Maternal Complications: Abruptio, Postpartum haemorrhage, ICU admission

types (Abruptio placentae, IUGR, postpartum haemorrhage, ICU admission and death) there were no statistically significant difference between serum LDH levels and occurrence of any of these single complications, even though women with these complications had a higher serum LDH levels when compared to those without these complications. Having any complication at all was however significantly associated with a higher serum LDH levels. Still on table 4 about 57% of preeclamptics with LDH >600IU/L had emergency caesarean section as against 50% in preeclamptics with LDH <600IU/L, this was not statistically significant. Of the 7 preeclamptics with LDH >600IU/L, 5 (71.4%) became eclamptic as opposed to only 2 (20.8%) of women with LDH <600IU/L. Approximately 85.7% of babies born to preeclamptics

with LDH >600IU/L were preterm as against 79.2% in women with serum LDH lower than 600IU/L, this also was statistically significant.

Discussion

The analysis of biochemical markers in preeclampsia and in particular markers related to vascular dysfunction such as lactate dehydrogenase may be a good predictor of severity of this disease.[21, 22] In this present research, the role of serum lactate dehydrogenase as a marker of severe preeclampsia and pregnancy outcome was studied.

The results showed that there was no statistically significant difference in the mean age, parity, and other socio-demographic parameters of both study and control groups, with the mean age of the study population being 28±5 years and that of the control as 27±4 years. This finding is in keeping with results from similar studies by Qublan et al, Rubina et al, Rizwana et al, and Umasatyasri et al.[7,8,22,24]

The mean body mass index (BMI) among the preeclamptic patients in this study was 29.3±5kg/m^2, while that of the normotensive women was 27.9±4.4kg/m^2. This finding was not statistically significant and is not in keeping with studies by Rubina et al. and Rizwana et al. who reported a statistically significant difference in BMI of Preeclamptic patients and normotensive pregnant women.[8, 23] The patients in our study were matched for weight and height and that could be the reason we did not find any significant difference in the biophysical parameters of our subjects.

The mean systolic and mean diastolic blood pressures among the preeclamptic women were 171±16mmHg and 110±13mmHg respectively while that of the control group were 107±10mmHg and 66±8mmHg respectively. This finding was statistically significant because the study was on pregnant women with hypertension being compared with normotensive pregnant women. Rizwana et al. had a similar result.[23] The mean serum LDH level among preeclamptics was significantly higher than in the controls; however our study was not able to find any statistically significant difference in serum levels of LDH in patients with mild and severe preeclampsia with respect to systolic and diastolic blood pressure. The serum levels of LDH among preeclamptics was at least three times higher in preeclamptics with complications than preeclamptics without complications. This may have been due to the extent of tissues and organ damage, hence higher serum levels and different complication among this subgroup. This finding was statistically significant and was in keeping with a similar study by Umasatyasri et al and Anupama et al who also found that severe preeclamptic patients with serum LDH levels of ≥ 800IU/L had significant complications like abruptio placentae, acute renal failure, disseminated intravascular coagulopathy (DIC), cerebrovascular accident and postpartum hemorrhage when compared to preeclamptic patients with lower serum LDH levels.[24,25] Qublan et al., Catanzerite et al. and Demir et al. concluded from related studies that there was a statistically significant relationship between the occurrence of maternal complications and high serum LDH levels.[7, 25,26] Also Feriha et al who also concluded in their study that maternal serum LDH is a good prognostic marker in predicting the severity of preeclampsia.[27,28]

Eighty percent (80%) of preeclamptic women from this study delivered before 37 weeks of gestation (preterm) and 20% delivered at ≥37 weeks of gestation (term), while all (100%) of the normotensive pregnant women delivered at term (≥37 weeks of gestation), and this finding was statistically significant, ($p<0.001$). This study however, did not find any significant association between serum LDH levels and gestational age at delivery among preeclamptic patients ($P = 0.571$) and it is not in keeping with a similar work by Jaiswar et al who found that the mean gestational age at delivery among the preeclamptic patients was 36.9±3.4 weeks at serum LDH levels of <600IU/L, while at serum LDH levels of between 600-800IU/L, the gestational age at delivery had decreased to 34.8±3.1 weeks and at LDH levels of >800IU/L, the gestational age at delivery was 35.3±3.2 weeks.[21]

Twenty eight out of the preeclamptic women (58.3%) from this study delivered babies with low birth weight at serum LDH levels of <600IU/L while 4 (57.1%) with serum LDH levels of >600IU/L delivered babies with low birth weight. This finding was not statistically significant ($P>0.999$) and was in keeping with finding from Qublan et al. and Umasatyasri et al. who also did not find a significant association between fetal birth weight and levels of serum LDH among preeclamptic patients.[7,24] However, the above finding was not in keeping with similar work by Jaiswar et al. who found a statistically significant association between low birth weight and serum LDH levels.[21]

Perinatal complications from this study such as IUFD/stillbirth, prematurity and IUGR among preeclamptic patients were not found to be significantly associated with levels of serum LDH ($p>0.05$). Again, this not in keeping with studies by Qublan et al and Jaiswar et al. who found a significant association between perinatal deaths and neonatal complications with increasing serum levels of LDH.[7,21]

A limitation of our study is that it was a hospital based study with a small sample size; therefore a larger multicenter study could bring out a clearer picture of the association between serum LDH and preeclampsia in our environment as LDH is non-specific marker of many events, which may then be used to improve patient

management.

In view of the significant association between preeclampsia, occurrence of maternal complications among preeclamptic women and serum lactate dehydrogenase levels from this study, we recommend that serum LDH assay should become part of the parameters used for evaluating and monitoring of women with preeclampsia in our hospitals.

Conclusion

We therefore conclude that high serum LDH level is significantly associated with preeclampsia and higher levels among preeclamptic patients may be a predictor of maternal complications.

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