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Comparison of LDH Levels with Preeclampsia: Clinical study

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Abstract
A clinical predictive test to be useful for PIH it should be simple, innocuous, impose minimal discomfort on the women, technology should be widely available, rapid, inexpensive, noninvasive, easy to perform in early pregnancy. Results of the test must be valid reliable and reproducible, very high likelihood for a positive test result and low likelihood ratio for a negative test result Biological, biochemical and biophysical markers implicated in pathophysiology of preeclampsia have been proposed to predict its development. All the pregnant women with ≥ 20 weeks of gestation who fulfilled the selection criteria registered in the Department of Obstetrics and Gynaecology, enrolled in this study. A total of 151 women registered in the Department of Obstetrics and Gynaecology, during the study period were studied. All the women fulfilling the selection criteria were explained about the nature of the study and a written informed consent was obtained before enrollment. In the present study serum LDH levels ranged between 245 to as high as 5692 IU/L. The mean LDH Levels were 742.4±545.20 IU/L and median levels were 677 IU/L. These findings suggest that, the serum LDH levels were high in the population studied which is likely to be the fact that, there were 101 preeclamptic women as against 50 women with normal pregnancy. Further, more than one third (41.72%) of the women had normal LDH levels (< 600 IU/L), 31.13% of the women had raised LDH levels (between 600 to 800 IU/L) and 27.15% of the women had LDH Levels profoundly raised LDH levels (> 800 IU/L).

Keywords: LDH levels, preeclampsia, clinical Study

Introduction
The factors that initiate pre-eclampsia are unknown. However, it has been postulated that failure of trophoblastic invasion of the spiral arteries is the primary insult.[13,14] Doppler ultrasound has been used to assess the uteroplacental circulation and several studies have reported that high impedance in the uterine arteries during the second trimester of pregnancy, prior to the development of any clinical features of pre-eclampsia, is associated with adverse outcome (subsequent development of pre-eclampsia and/or intrauterine growth restriction).[15,16] Furthermore, the presence of bilateral notching of the uterine arteries, a qualitative assessment of the flow velocity waveform, has been shown to be a highly sensitive predictor of pre-eclampsia and/or intrauterine growth restriction [1, 2].

In the early 1900 before the advent of magnesium sulphate therapy, mortality associated with eclampsia was estimated between 10% to 15% [3].

Perinatal mortality is higher for preeclamptic women. Most of the perinatal deaths are the result of intrauterine death from placental insufficiency and abruptio placentae or the result of prematurity from delivery needed to control the disease and avoid complications [4].

Overall, in spite of improvement in maternal and neonatal care, PIH and its sequelae continue to contribute to maternal and perinatal mortality. It is indeed a constant endeavor of obstetricians to predict the development of preeclampsia and if possible prevent its development. Hence, prediction would identify those women who require more intensive monitoring, result in early recognition of PIH and permit intercession before life threatening complications develop. In addition identification of women at risk might help select the patients most likely to benefit from any therapeutic measure. It could further help clarify pathogenic mechanisms and might ultimately lead to more specific, mechanistically based strategies for prevention and treatment.

A clinical predictive test to be useful for PIH it should be simple, innocuous, impose minimal discomfort on the women, technology should be widely available, rapid, inexpensive, noninvasive, easy to perform in early pregnancy. Results of the test must be valid reliable and

reproducible, very high likelihood for a positive test result and low likelihood ratio for a negative test result Biological, biochemical and biophysical markers implicated in pathophysiology of preeclampsia have been proposed to predict its development [5].

Variety of biological tests like Provocative pressor tests were proposed, but these are cumbersome to perform, expensive, time consuming, invasive and low sensitivities and specificites. Biochemical tests like Alpha FetoProtein, Serum Uric acid, Microalbuminuria, calcium creatinine ratio etc, were proposed but these have less sensitivity and specificity with low positive predictive value. Biophysical markers such as Uterine Artery Doppler Velocimetry, Pulse wave analysis have been proposed and these tests have a better sensitivity and specificity but needs expertise and are not available widely. However, the effects of LDH in pregnancy related complications like preeclampsia is now gaining attention. It is reported that, LDH is an intracellular enzyme and its level is increased in women with eclampsia/preeclampsia due to cellular death [6].

Methodology

Study design

The study design was a prospective comparative study.

Study period

This study was conducted for a period of 18 months.

Source of data

All the pregnant women with ≥ 20 weeks of gestation who fulfilled the selection criteria registered in the Department of Obstetrics and Gynaecology, enrolled in this study.

Sample size

A total of 151 women registered in the Department of Obstetrics and Gynaecology, during the study period were studied.

Sample size calculation

The sample size was calculated considering following formula.

$$n = \frac{2\,(Z_\alpha + Z_\beta)^2\,p\,q}{(P_0 - P_1)^2}$$

Based on the above formula the minimum effect size required in each group was 19. However, during the study period a total of 151 women were eligible and provided written informed consent. Hence a total of 151 women were studied.

Sampling technique

These women were divided into four cohorts as below.

- **Normal pregnancy (NP): N**ormotensive (Normal) pregnant women
- **Mild preeclampsia (MPE):** Women with mild preeclampsia**.**
- **Severe preeclampsia (SPE):** Women with severe preeclampsia**.**
- **Antepartum eclampsia (APE):** Women with anterpartum eclampsia.

Selection Criteria

Inclusion criteria

Pregnant women with gestational age of ≥20 weeks of pregnancy (according to a reliable last menstrual period and ultrasound confirmation) with either mild, severeor antepartum preeclampsia.

Exclusion criteria

Pregnant women with history of;

- Liver disease
- Diabetes mellitus
- Renal failure
- Hemolytic anemias
- Stroke
- Coronary artery disease
- Chronic lung diseases
- Connective tissue disorder
- DIC
- Seizures
- Chronic hypertension
- Gestational diabetes mellitus (GDM)
- Multiple pregnancy
- Hepatotoxic drugs.

Informed Consent

All the women fulfilling the selection criteria were explained about the nature of the study and a written informed consent was obtained before enrollment.

Data collection

After obtaining written informed consent, demographic data such as age, detailed history (including obstetric history, family history and other comorbid conditions) was obtained through an interview. Also presenting complaints were noted. Further these women were subjected to complete examination (general and systemic examination). Blood pressure was recorded by Residents using a mercury sphygmomanometer and stethoscope from the upper arm after the subjects had been sitting for more than 5 minutes according to the guidelines of the American Heart Association. Three readings were recorded after 5 minutes rest interval between the measurements and the average value was recorded. These findings were noted on a predesigned and pretested proforma.

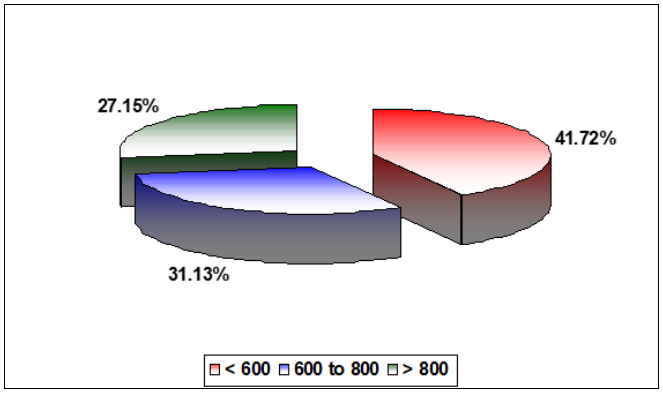
Investigations

All the pregnant women underwent routine hematological test including haemoglobin, blood grouping, human immunodeficiency (HIV)/ surface antigen of the hepatitis B virus (HBsAg), ultrasound examination special investigations were done which included blood urea, serum creatinine, serum uric acid, serum electrolytes, blood sugar level, liver function tests, fundoscopy, bleeding time, clotting time, coagulation profile, urine routine and urine culture. Further all these women were subjected to Serum LDH investigation.

Results

Table 1: Distribution of women according to the LDH levels

LDH levels (IU/L)	Total	
	No.	%
<600	63	41.72
600 to 800	47	31.13
> 800	41	27.15
Total	151	100.00



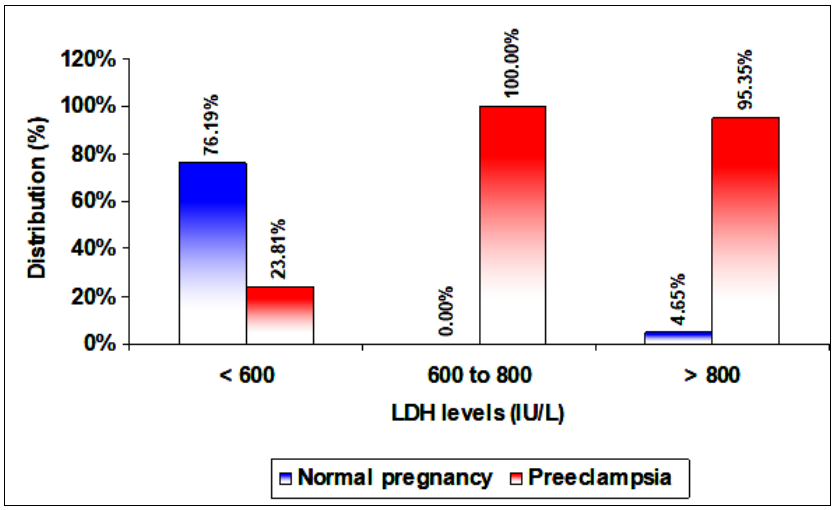
Graph 1: Distribution of women according to the LDH levels

In the present study 41.72% of the patients had LDH levels < 600 IU/L, 31.13% of the women had LDH levels between 600 to 800 IU/L and 27.15% of the women had LDH Levels > 800 IU/L.

Table 2: Association of LDH levels with preeclampsia

LDH Levels (IU/L)	Preeclampsia				Total	
	No		Yes			
	No	%	No	%	No	%
<600	48	76.19	15	23.81	63	63.00
600 to 800	0	0.00	45	100.00	45	45.00
> 800	2	4.65	41	95.35	43	43.00
Total	**50**	**33.11**	**101**	**66.89**	**151**	**100.00**

p<0.001



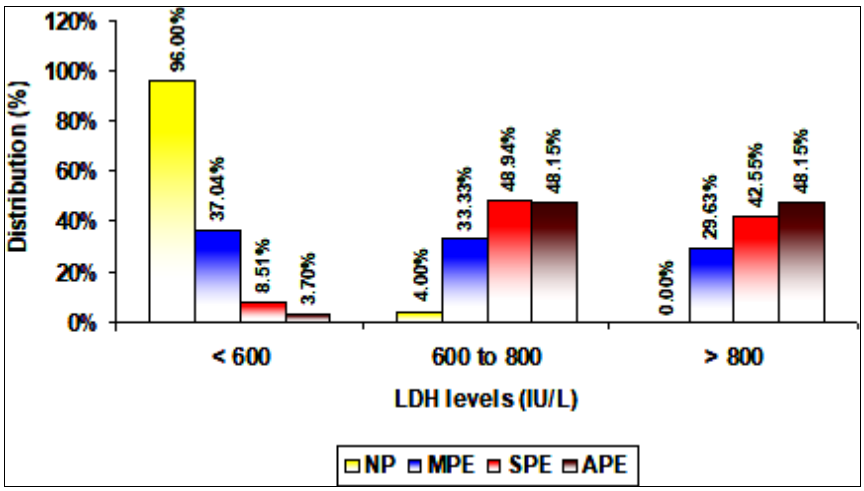
Graph 2: Association of LDH with preeclampsia

In this study 100% of the women with LDH levels between 600 to 800 IU/L had preeclamapsia and 95.35% of the women with LDH levels > 800 IU/L had preeclampsia while 23.81% of the women with LDH levels < 600 IU/L had preeclampsia and this difference was statistically significant (p<0.001)

Table 3: Comparison of LDH levels with preeclampsia

LDH levels (IU/L)	Groups								Total	
	NP		MPE		SPE		APE			
	No.	%	No.	%	No.	%	No.	%	No.	%
<600	48	96.00	10	37.04	4	8.51	1	3.70	63	41.72
600 to 800	2	4.00	9	33.33	23	48.94	13	48.15	47	31.13
> 800	0	0.00	8	29.63	20	42.55	13	48.15	41	27.15
Total	50	100.00	27	100.00	47	100.00	27	100.00	151	100.00

p < 0.001

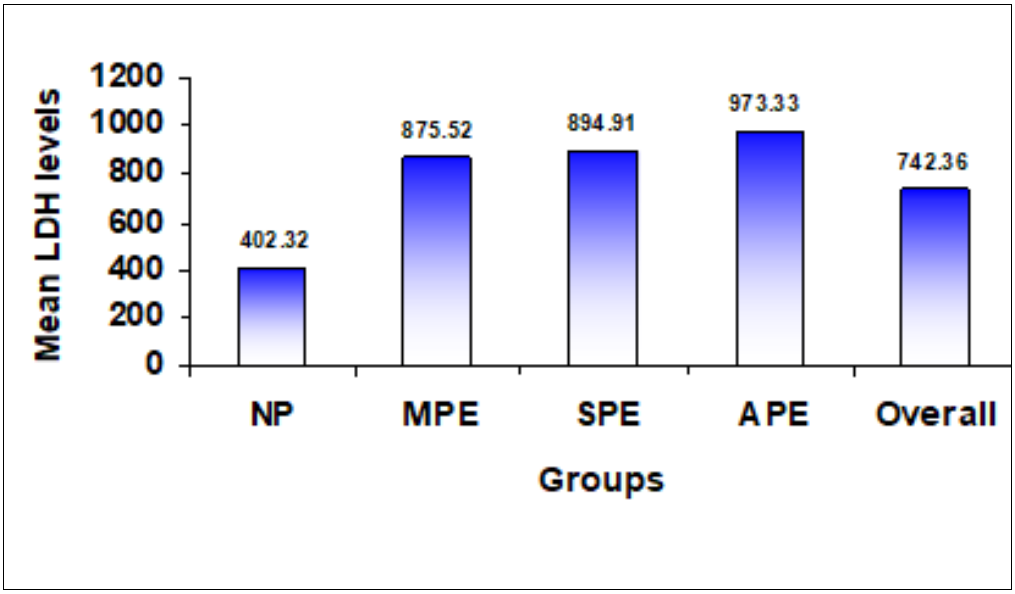


Graph 3: Comparison of LDH Levels with preeclampsia

In the present study 96% of the women with normal pregnancy had LDH levels of < 600 IU/L while, 33.33% of the women with MPE had LDH levels between 600 to 800 IU/L, 48.94% of the women with SPE had LDH levels between 600 to 800 IU/L and 48.15% of the women each with APE had LDH levels of > 800 IU/L and LDH levels between 600 to 800 IU/L. This difference was statistically significant (p<0.001).

Table 4: Comparison of mean LDH levels

Groups	Number of patients (n)	Mean LDH levels (IU/L)	
		Mean	SD
NP	50	402.32	90.28
MPE	27	875.52	986.20
SPE	47	894.91	349.46
APE	27	973.33	415.26
Overall	151	742.36	545.17
F value	12.041		
p value	<0.001		



Graph 4: Comparison of mean LDH levels

In this study the mean LDH levels were 402.32±90.28 IU/L in women with normal pregnancy compared to 875.52±986.20 IU/L in women with MPE, 894.91±349.46 IU in women with SPE and 973.33±415.26 IU/L in women with APE (p<0.001).

Discussion

Lactic dehydrogenase (LDH) is an intracellular enzyme that converts lactic acid to pyruvic acid, and elevated levels indicate cellular death and leakage of the enzyme from the cell. Limited number studies have found high levels of LDH are associated with severe pre-eclampsia. Also it is hypothesized that, the quantitative analysis of LDH reflects the extent of cellular death and thereby severity of complications occurring in preeclampsia and eclampsia. These observations suggest that, LDH can help in making decisions regarding the management strategies to improve the maternal and foetal outcome in pregnant women with preeclampsia. Considering these facts, the present study was undertaken to ascertain the prognostic significance of serum LDH as a marker for preeclampsia-eclampsia and its severity which may be used in making decision, regarding management strategies to improve maternal and fetal outcome.

This prospective comparative study was conducted in the Department of Obstetrics and Gynaecology. A total of 151 women with ≥ 20 weeks of gestation registered in the Department of Obstetrics and Gynaecology, during the study period were investigated for LDH. These women were divided into four cohorts as NP (Normotensive pregnant women) (n=50) MPE (Women with mild preeclampsia) (n=27), SPE (Women with severe preeclampsia) (n=47) and APE **(**Women with anterpartum eclampsia) (n=27).

In the present study serum LDH levels ranged between 245 to as high as 5692 IU/L. The mean LDH Levels were 742.4±545.20 IU/L and median levels were 677 IU/L. These findings suggest that, the serum LDH levels were high in the population studied which is likely to be the fact that, there were 101 preeclamptic women as against 50 women with normal pregnancy. Further, more than one third (41.72%) of the women had normal LDH levels (< 600 IU/L), 31.13% of the women had raised LDH levels (between 600 to 800 IU/L) and 27.15% of the women had LDH Levels profoundly raised LDH levels (> 800 IU/L).

In this study all the women (100%) with LDH levels between 600 to 800 IU/L had preeclamapsia and majority of the women (95.35%) with LDH levels > 800 IU/L had preeclampsia while only 23.81% of the women with LDH levels < 600 IU/L had preeclampsia and this difference was statistically significant (p<0.001). Furthermore, 96% of the women with normal pregnancy had LDH levels of < 600 IU/L while, 33.33% of the women with MPE had LDH levels between 600 to 800 IU/L, 48.94% of the women with severe PE had LDH levels between 600 to 800 IU/L and 48.15% of the women with APE and SPE had LDH levels of > 800 IU/L. This difference was statistically significant (p<0.001). Also, the mean LDH levels were

significantly high in women with MPE (894.91±349.46 IU/L) and APE (973.33±415.26 IU/L) compared to women with normal pregnancy (402.32±90.28 IU) (p<0.001). These findings suggest not only a strong association between raised LDH Levels with preeclampsia but also hypothesize that serum LDH levels increase significantly with severity of preeclampsia. These findings were consistent with a recent study by Dev SV and Hemalatha CR. [7] (2017) who reported that, significantly higher values of serum LDH in mild and severe preeclamptic women when compared to normal pregnant women (p<0.0001). Another recent study by Munagavasala S. *et al.* [8] (2017) also observed a significant rise in the LDH levels with increasing severity of the disease (p<0.001). Qublan HS, *et al.* [9] (2005) in their study also demonstrated a significant association of serum LDH levels with severe preeclampsia. More recently Hemalatha CR and Kittur S. [10] (2018) from our hospital reported that, the mean value of LDH was higher in preeclampsia and eclamosia compared to controls and high LDH levels corresponds to the increasing severity of the disease a findings strongly in agreement with the present study. The comparison of mean LDH levels observed in the present study with other studies is as below.

Conclusion

In the present study 96% of the women with normal pregnancy had LDH levels of < 600 IU/L while, 33.33% of the women with MPE had LDH levels between 600 to 800 IU/L, 48.94% of the women with SPE had LDH levels between 600 to 800 IU/L and 48.15% of the women each with APE had LDH levels of > 800 IU/L and LDH levels between 600 to 800 IU/L. This difference was statistically significant (p<0.001).

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