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Serum levels of LDH and protein/creatinine index in pregnant women with preeclampsia: A single-center retrospective study

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ABSTRACT

Introduction: Preeclampsia is the major cause of maternal death in Latin America, which presents with hypertension and proteinuria after 20 weeks of gestation, increasing the levels of inflammatory markers. We aimed to determine the ratio of LDH and protein/creatinine index (PCI) in Peruvian pregnant women with preeclampsia at the Hospital Nacional Docente Madre Niño San Bartolomé in 2017.

Materials and methods: we conducted a cross-sectional study in 3415 pregnant preeclamptic women without eclampsia or HELLP syndrome. The kinetic method was used to determine urine creatinine (mg/dl), the turbidimetric method for protein quantification (mg/dl), and the kinetic method for LDH (U/L). Kendall's Tau-b correlation and non-paired t-test were used.

Results: Of the total, 168 (4.9%) had a clinical diagnosis of preeclampsia with a higher frequency in the 25-35 age group (41.7%). We observed 9-fold frequency of multiparous pregnant women ($p<0.001$). In 121 (72%) pregnant women, LDH was elevated (>414 U/L). The mean LDH was 536±206.7 U/L (range: 264 to 1715 U/L). Seventy-two (42.9%) pregnant women had LDH values between 416-599 U/L, 37 (22%) had LDH values between 600-800 U/L, and 12 (7.1%) had >800 U/L of LDH. Sixty-one percent of pregnant women (n=113) had CPI alterations. We found a correlation between LDH and CPI ($p<0.001$) and hypertension levels ($p<0.05$).

Conclusions: Our results suggest a significant correlation between LDH and CPI in Peruvian pregnant women with preeclampsia allowing the diagnosis of >60% of cases. In addition, all corresponded to the third trimester of gestation, were ≤35 years-old and mostly multiparous.

Keywords: pre-eclampsia, pregnant women, lactate dehydrogenases, hypertension, proteinuria, Peru

INTRODUCTION

Ninety-nine percent of all annual deaths of pregnant women from birth-related complications (estimated at 800 per year in the USA) occur in low- and middle-income countries (LMICs) and are the consequence of inequities in health services. The main complications are caused by infections, severe bleeding (usually after delivery), high blood pressure during pregnancy (preeclampsia and eclampsia), and unsafe abortion [1,2]. In LMICs, the percentage of pregnancies is higher than in high-income countries, and, therefore, the risk of mortality is higher during this period. This is most significant in adolescents under 15 years old, where approximately 1 in 150 complications occur during pregnancy [3,4].

Preeclampsia is the main cause of maternal death in Latin America, which is a hypertensive disorder occurring after 20 weeks of gestation, characterized by hypertension and proteinuria [5]. In some cases, this kind of disorder may manifest in the absence of proteinuria [6].

In the USA, the incidence of preeclampsia increased from 2.4% in 1980 to 3.8% of pregnancies in 2010 [7]. In the case of LMICs, women are seven times more likely to develop pre-eclampsia than women in high-income countries, resulting in 10-25% of maternal deaths overall [8]. In turn, with an incidence ranging from 4% to 18%, various forms of preeclampsia and eclampsia are more common in LMICs [9].

Several biochemical markers have been proposed to establish a rapid diagnosis of preeclampsia. In these patients, 24-hour proteinuria (300 mg/24 hours), protein/creatinine ratio (0.3 mg/dl), serum uric acid (6.0 mg/dl), alkaline phosphatase (44 to 147 IU/L), lactate dehydrogenase-LDH-(420 U/l), and other assays are usable clinical tools of great use and prognosis [10-12].

LDH (EC.1.1.1.27) is an intracellular enzyme that converts lactic acid to pyruvic acid, and is frequently used as a biochemical marker of cell damage and death in the management of cardiac or pulmonary infarction, muscular dystrophies, connective tissue diseases, among other diseases. There are five LDH isoenzymes determined by their subunits (LDH1 to LDH5). Previous reports have related elevated serum LDH levels to the severity of preeclampsia [11-15], so it is important to relate this serological marker to this specific pregnancy condition in different population groups. Likewise, estimating its possible association with other markers will allow us to optimise the clinical management of pregnant patients with preeclampsia.

This study aimed to determine the relationship between LDH and protein/creatinine index in Peruvian pregnant women with preeclampsia during 2017. Likewise, risk factors were evaluated and their relationship with preeclampsia and LDH levels was established.

MATERIALS AND METHODS

Design, Study Site, and Inclusion Criteria

We designed a retrospective cross-sectional study in the Gynecology Department of the Hospital Nacional Docente Madre Niño San Bartolomé (HONADOMANI SB) in Lima, Peru [15]. From April to September 2017, all pregnant women with a suspected diagnosis of preeclampsia were included from whom biochemical tests were requested, respecting the following inclusion criteria: pregnant women ≥18 years old, with available and complete medical records, with a diagnosis of pre-eclampsia, with or without a history of pre-eclampsia, and raised proteinuria. Pregnant women with eclampsia or HELLP syndrome (haemolysis, elevated liver enzymes, and thrombocytopenia) were not included.

Biochemical Analysis

All biochemical assays were performed on the BTS-350 biochemistry analyser and the BA 400 biochemistry analyser (Biosystems S.A, Barcelona, Spain). The methods for urine creatinine determination were the kinetic method (mg/dl), the turbidimetric method for protein quantification (mg/dl), and the kinetic method for LDH (U/L) (all from Biosystem S.A., Barcelona, Spain). Normal values for urine creatinine (11-250 mg/dl), urine protein (<15 mg/dl), creatinine protein index (≥0.3 mg/dl), and LDH (207-414 U/L) were established according to the manufacturer's guidelines, which were consistent with previous reports [16,17]. For hypertensive classification in pregnant women, the recommendations of the World Health Organization have been considered, which classifies mild or grade I hypertension as 140-159/90-99 mmHg, moderate or grade II hypertension as 160-179/100-109 mmHg, and severe or grade III hypertension as 180-110 mmHg or higher [18].

Data Collection and Sample Processing

Data gathering was performed from the SIGHOS (Hospital Management Information System) computer system and observation of medical records using a validated collection form (internal reliability, α-Cronbach=0.675). For patient inclusion, the following international code for diseases (ICD) concerning pre-eclampsia was used: ICD=014-Gestational hypertension with significant proteinuria [19]. In this system, data recorded was validated at each stage, all analyses followed the Standard Operating Procedures (SOP) established by the institution. In addition, epidemiological data such as age, gestational status, the number of pregnancies, and clinical data such as blood pressure and origin were considered. All this data was coded into a data analysis matrix.

Table 1. Baseline characteristics of pregnant women diagnosed with preeclampsia

	Pregnant women with preeclampsia	LDH(U/L)[¶] Mean±SD	p-value**
Age			
16-25	62(36.3)	483.9±123	0.001
26-35	71(41.7)	560±243.5	
36-46	36(21.4)	566±223.5	
>46*	1(0.6)	916	
Pregnancy trimester			
I-II	0(0)	-	0.842
III	168(100)	536±206.7	
Previous stage of pregnancy			
Primigravida	17(10.1)	449±136.7	0.001
Multigravida	153(89.9)	545.8±211.2	
1-2	100(58.3)	555.6±228.8	
3-5	51(30.4)	536.4±172.1	
>6	2(1.2)	303±55.2	
Blood pressure[§]			
Normal	136(81)	503±170.8	0.002
Grade 1	20(11.9)	538.7±244.4	
Grade 2	11(6.5)	606.8±262.1	
Grade 3	1(0.6)	1715	
Type of childbirth			
Caesarean	142(84.5)	540.3±204.7	0.003
Natural birth	26(15.5)	512.5±219.8	

*One patient was over 45 years old (ID:148), and 60-year-old patient reported IVF. **Data indicate significant differences between assessed components of the pregnant women. [§]Classification according to World Health Organisation recommendations (see [18]). LDH: Lactate dehydrogenase & SD: Standard deviation

Data Analysis and Ethics Statement

The statistical analyser used was IBM SPSS v21.0 (Armonk, USA). Descriptive statistics and univariate analysis were used for the included pregnant variables. Kendall's Tau-b and Spearman's non-parametric correlation and non-paired T-test for independent samples were used. A p-value <0.05 and a 95% confidence interval (CI) was considered statistically significant. The ethical principles for human-based medical research established in the Declaration of Helsinki have been adhered to in all phases of the study phases [20]. The study has approbation of Hospital's IRB (N° 16913-16-HONADOMANI SB).

RESULTS

Of 3,415 pregnant women 168 (4.9%) had a clinical diagnosis of preeclampsia. The most frequent age group of pregnant women with preeclampsia was 25-35 years (41.7%), followed by 16-25 years (36.3%); one patient with assisted fertilisation (IVF) was 60 years old (0.6%). In this study, nine times more multigestational pregnant women (≥1 previous pregnancy) were observed than primigravid or nulliparous women (p<0.001). Most of these pregnant women had between 1 and 2 previous pregnancies (58.3%). All the pregnant women were in their third trimester of gestation, and only 15.5% (26 pregnant women) had spontaneous deliveries. **Table 1** displays the study's clinical-epidemiological data.

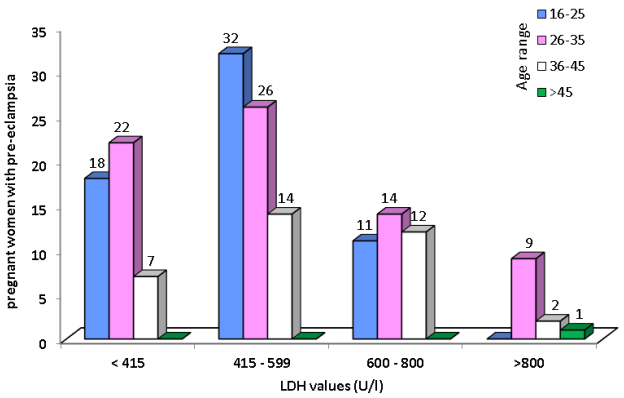

Figure 1. Distribution of pregnant women with a clinical diagnosis of pre-eclampsia discriminated according to age group and LDH levels (n=168). Note the significant proportion of pregnant women ≤35 years and the difference between LDH values close to the pathological cut-off point

In 121 (72%) pregnant women, the LDH enzyme was elevated (>414 U/L). The mean LDH was 536±206.7 U/l (range: 264 to 1715 U/l). Of this population, 72 (42.9%) pregnant women had LDH values between 416-599 U/l, 37 (22%) pregnant women had LDH values between 600-800 U/l, and 12 (7.1%) pregnant women had LDH values >800 U/l (**Figure 1**). Of the group of pregnant women with LDH values between 416-599 U/l, 51 (30.4%) pregnant women had an elevated protein/creatinine index (≥0.3 mg/dl). In the group of pregnant women with LDH values between 600-800 U/l, 28 (16.7%) had increased protein/creatinine index, and in pregnant women, with >800 U/l LDH, 8 (4.8%) had an abnormal protein/creatinine index. However, 27 (16.1%) pregnant women with normal LDH values had elevated protein/creatinine index.

In total, 113 (61.3%) pregnant women had an altered protein/creatinine index. We found a positive linear correlation between LDH and protein/creatinine index (p<0.001) and hypertension levels (p=0.025). No relationship was found between LDH and type of delivery (p=0.530) or the number of gestations (p=0.283).

Regarding the characteristics of the previous number of pregnancies, primigravid or nulliparous pregnant women with altered protein/creatinine index presented decreasing values with increasing serum LDH [five (3%) pregnant women ≤24 years presented LDH values between 416-599 U/l; three (1.8%) pregnant women ≤35 years presented LDH values between 600-800 U/l, and no primigravid pregnant women presented >800 U/l of serum LDH]. The group of patients with normal LDH values consisted of 8 (4.8%) pregnant women ≤35 years old. No significant difference was seen between the evaluation of pregnant women with LDH and protein/creatinine index and the assessment with LDH alone (p=0.872).

Although in the multi-gestation group (≥3 previous pregnancies) a similar LDH-related decrease was seen (13 (7.7%) pregnant women with LDH values between 416-599 U/l, seven (4.3%) pregnant women with LDH values between 600-800 U/l, and four pregnant women with >800 U/l serum LDH) no significant association was found between LDH and multiple pregnancies (p=0.126).

Finally, 21 (12.5%) pregnant women had mild or grade I hypertension, 11 (6.5%) pregnant women had moderate or grade II hypertension, and only one (0.6%) pregnant woman had severe or grade III hypertension. The mean age of the pregnant women in group I was 32.4±7.3 years, 16 (9.5%) had elevated protein/creatinine index, and 14 (8.3%) had LDH values ≥415 U/l (four (2.4%) between 600-800 U/l, and 3 (1.8%) >800 U/l), so, 11 (6.5%) pregnant women had both markers elevated. In addition, only one (0.6%) pregnant woman was primigravida, and 3 (1.8%) delivered spontaneously.

In group II, the mean age was 32.2±7.8 years. In this group, 6 (3.6%) pregnant women had elevated protein/creatinine index, and 8 (4.8%) had LDH values ≥415 U/l (three (1.8%) pregnant women had >800 U/l), and 5 (3%) had both markers elevated. All pregnant women in this group had caesarean deliveries. The only pregnant woman (ID: 140) belonging to group III was 32 years old and had a caesarean delivery, in addition to an elevated protein/creatinine index (0.4 mg/dl) and LDH (1715 U/l). In each stage, a significant association was found between LDH values and protein/creatinine index (p<0.001).

DISCUSSION

In the present study, we evaluated the relationship between LDH and protein/creatinine index in Peruvian pregnant women with preeclampsia, showing a correlation between these biochemical markers and the condition. We also found that a large proportion of young pregnant women (≤35 years old) were in the third trimester of their pregnancy and had a history of previous pregnancies.

Preeclampsia is strongly linked to maternal mortality worldwide, with the incidence in Canada, the United States, and Western Europe alone fluctuating in the range of 2-5% [21]. In this study, we determined a prevalence of preeclampsia of 4.9%, in agreement with a previous report on Latin American pregnant women with pregnant women (4.8%) [1]. Furthermore, our data agree with studies on risk factors in France [22] and Ethiopia [23] and the world average (4.6%) [24]. In Latin America, approximately 25% of maternal deaths are due to preeclampsia. In Africa and Asia, this rate is close to 10%. Thus, these results infer that 16% of maternal deaths due to pre-eclampsia occur in LMIC.

The impact of preeclampsia is reflected in the coupled relationship between maternal and neonatal health, as more than 3 million newborns die each year and another 2.6 million are born prematurely [7]. Our results showed that >35% of pregnant women with preeclampsia, aged ≤25 years, as in previous reports in African [25], Indian [26], American [27], and Latin American [1] populations. This depicts the high risk of morbidity and mortality in adolescents and young pregnant women with preeclampsia, as many of these women also receive little health, educational, and social assistance due to unwanted pregnancies.

A high correlation has been found between maternal age and adverse processes during pregnancy, with preeclampsia playing a particularly significant role [28]. In this study, we found that >60% of patients with preeclampsia had an elevated protein/creatinine index (≥0.3mg/dl), mainly young pregnant women. Our results are consistent with previous reports [10, 29, 30]. However, the diagnostic performance of this test is subject to various factors, such as the degree of analysis, cut-off points, and reporting systems which must be considered [31]. Both biochemical markers allowed the diagnosis of preeclampsia in 106 (62.7%) cases, enabling the management

and prevention of complications for both mother and newborn.

Furthermore, more than 70% of pregnant women had elevated LDH enzyme levels, with 42.9% having values of 600 U/l, similar to the reports in India, where 50% of pregnant women evaluated had LDH levels of 600 U/l [26]. Additionally, LDH levels were significantly higher as the severity of the condition increased (p=0.002), which is consistent with previous reports [32]. This severity is attributable to maternal morbidity and mortality, as reflected in the increased incidence of maternal complications such as HELLP syndrome [26]. In this study, we observed that 7.1% of pregnant women had elevated serum LDH values (**Table 1**), which concerning since previous studies have reported that during prenatal or maternal complications, serum LDH values are higher than 800 U/l, showing severe preclampsia [26,32]. Other researchers have demonstrated the relationship between maternal complications and serum LDH levels [11].

Approximately 10 million women develop preeclampsia each year worldwide. Annually, 76,000 pregnant women die from this condition and other hypertensive disorders, and the number of neonatal deaths due to preeclampsia alone is 500,000 per year [33]. The correlation between LDH and pregnant women with a history of multiple pregnancies determined in this study coincides with previous reports [1]. Thus, multiparity is an important risk factor in pregnant women with this disorder. Several studies [34,35] support the high frequency and risk of preeclampsia in multiparous pregnant women. Since in this research we observed a higher frequency of multiparous pregnant women, nine times more than primigravid women (p=0.001). We differ from other studies in groups of primigravid pregnant adolescents that indicate a higher frequency of the latter [26,29,36]. However, we infer that due to complications related to preeclampsia, only 3 (1.8%) of the 17 (10.1%) primigravid patients had a spontaneous delivery. If this assumption is true and if during the first gestation, they developed preeclampsia, this would be a poor predictor for subsequent gestations, as it increases the risk of developing eclampsia [35]. In multiparous pregnant women with the development of preeclampsia, no previous history of hypertension during pregnancy was evaluated, which could explain the observed frequency.

Preeclampsia can occur at any time after the 20th gestational week and is marked by elevated blood pressure and, usually, but not always, urine proteinuria. Regarding the trimester of gestation, our results show that all preeclampsia women were in the third trimester of pregnancy, which is consistent with previous studies [37-39]. Assessment and management of blood pressure, as well as other signs, during the first trimester of gestation, serves as a good predictor of preeclampsia [40,41]. The relatively high frequency and devastating impacts of preeclampsia, which are hypertensive disorders of pregnancy (eclampsia, haemolysis, etc.), elevated liver enzymes, high rate of cell destruction, low platelet count (HELLP), among others, can be unified.

Although labour can “cure” preeclampsia, in preterm labour it is often required to save the lives of the mother and newborn with high health care costs (2.18 billion dollars per year in the US), corresponding to up to 20% of intensive newborn care. However, if delivery is not the immediate solution to the effects of preeclampsia, many of which persist for up to six months after delivery [7]. This may explain the low rates of spontaneous delivery in pregnant women with preeclampsia reported in this study (15.5%).

Finally, our results should be interpreted under the following limitations:

1. Although ICD=014 was used for patient selection, other studies have used other ICD codes, allowing more pregnant women with other risk factors to be chosen, potentially increasing the number of patients [35] and
2. LDH test and protein/creatinine index have been included as markers of preeclampsia, but other serum markers should be considered as possible candidates for the prevention, management, and control of this condition. Although these limitations were not considered, we developed the first national report on LDH in pregnant patients diagnosed with preeclampsia.

This study suggests a high correlation between LDH and protein/creatinine index with preeclampsia, enabling diagnosis in more than 60% of cases. Furthermore, all pregnant women were in the third trimester of gestation, were mostly multiparous, and had >80% of deliveries by caesarean section.

Author contributions: JMS: provided the study concept and design, statistical analysis, data management, and wrote the manuscript; **NCV:** provided the design, data acquisition, formal analysis, and performed data management. **VRZ:** provided the design, data acquisition, and wrote the manuscript; **MZ:** provided the design and data acquisition; **KCF:** provided the design, formal analysis, and wrote the manuscript; **GC:** provided the data management and wrote the manuscript; and **HCP:** provided the statistical analysis, data analysis and interpretation, and wrote the article. All authors have agreed with the results and conclusions.

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Declaration of interest: No conflict of interest is declared by authors.

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