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CORRELATION OF C-REACTIVE PROTEIN, SERUM URIC ACID AND SERUM LDH WITH SEVERITY OF PRE-ECLAMPSIA AMONG THE PREGNANT WOMEN.

Obstetrics & Gynaecology

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ABSTRACT

Background: Pregnancy-related hypertension diseases rank among the leading causes of maternal and neonatal mortality worldwide. After 20 weeks of pregnancy, high blood pressure and proteinuria are hallmarks of the pregnancy-specific illness known as preeclampsia. Early detection with serum biomarkers aids in better preventive and management strategies. This study sought to determine the relationship between pre-eclampsia and serum uric acid, serum LDH, and CRP. **Methodology:** A case-control study was conducted with 60 preeclamptic women and 60 normotensive women. Serum CRP, LDH, and uric acid levels were measured, and statistical comparisons were made between the groups. **Results:** The study group had significantly higher mean CRP levels (43.7 ± 22.2 mg/L) compared to the control group (13.7 ± 8.4 mg/L; p = 0.0001). Mean serum uric acid levels were also higher in the study group (5.14 ± 1.2 mg/dL) than in controls (4.55 ± 1.2 mg/dL; p = 0.0001). Similarly, LDH levels were elevated in the study group (679.3 ± 306.5 U/L) compared to controls (411.25 ± 162.2 U/L; p = 0.001). A significant positive correlation was found between these biomarkers and increasing blood pressure. **Conclusion:** Maternal issues can be avoided, and the severity and course of the illness process can be diagnosed with the use of CRP, LDH, and uric acid monitoring. A significant correlation could be established between serum biomarkers and pre-eclampsia.

KEYWORDS

Pre-eclampsia, hypertensive disorders of pregnancy, CRP, lactate dehydrogenase, uric acid.

INTRODUCTION:

The International Society for the Study of Hypertension in Pregnancy (ISSHP) defines hypertensive disorders of pregnancy as new onset hypertension (≥140 mmHg systolic or ≥90 mmHg diastolic) after 20 weeks of gestation, which affects 10% of pregnancies. Preeclampsia, gestational hypertension, and chronic hypertension are all included in this broad definition [1].

Both the immediate and long-term health of the mother and fetus can be profoundly affected by these conditions. For the mother, this includes a 1.5-fold increased risk of stroke, a doubling of the likelihood of cardiovascular death and severe cardiovascular events, and a two- to four-fold heightened risk of developing hypertension later in life. For the fetus, prenatal risks include oligohydramnios, placental abruption, intrauterine growth restriction (IUGR), preterm birth, fetal distress, and in utero death. Additionally, growing evidence suggests that maternal exposure to hypertensive disorders during pregnancy may lead to significant long-term cardiovascular issues in the offspring, such as early-onset hypertension, as well as an increased risk of stroke and ischemic heart disease [2, 3].

Although the exact cause of preeclampsia is yet unknown, it is thought to be complex. The placenta's pivotal involvement in its pathophysiology is evident. Preeclampsia has long been thought to result from immune maladaptation between the mother and the foetus in the first weeks of pregnancy. This leads to a two-step disorder progression, which can be summed up as follows: in the first, asymptomatic step, local aberrant feto-maternal immune interactions within the uterine wall cause the trophoblast cells to invade the arteries and damage the tissue. As a result, placental perfusion deteriorates, and the uterine spiral arteries fail to convert. It is anticipated that prolonged hypoxia or intermittent hypoxia/reoxygenation in the intervillous area may cause tissue oxidative stress and raise placental necrosis and apoptosis [4].

Worldwide, the progression from preeclampsia to eclampsia has substantially decreased, largely due to the expanded use of antenatal care, increased rates of facility-based deliveries, and improved access to magnesium sulfate [5]. However, these advancements in care have not consistently led to better clinical outcomes in low- and middle-income countries (LMICs). In fact, over 99% of maternal deaths related to hypertensive pregnancy disorders occur in LMICs, where the progression to eclampsia remains more common, and nearly half of eclamptic seizures take place outside hospital settings [6].

Despite the absence of effective preventive or therapeutic measures for preeclampsia, the pursuit of non-invasive blood or urinary biomarkers to predict or detect this life-threatening pregnancy complication remains critically important. The identification of such biomarkers could significantly influence the medical management of pregnant women and their babies (e.g., timely referral to a tertiary care center) while also reducing the healthcare costs associated with this condition. For many years, various biophysical and biochemical markers have been studied, guided by pathophysiological observations linked to preeclampsia, including placental dysfunction, systemic inflammation, endothelial dysfunction, and activation of the coagulation system [7].

An essential part of the innate immune system is C-reactive protein (CRP). Elevated serum CRP serves as a sensitive biomarker of chronic systemic inflammation when determined with a high-sensitivity test [8]. The degree of endothelial cell damage is indicated by the CRP value as one of the causes of preeclampsia development or onset is endothelial cell damage [9]. Furthermore, CRP can be measured easily and with minimal invasiveness, as it only requires a simple blood test.

Recent research has shown that some serum indicators, particularly uric acid and lactate dehydrogenase (LDH), an intracellular enzyme, may be crucial for diagnosing and treating preeclampsia. Tissue ischaemia, haemolysis, and pregnancy difficulties including preeclampsia are among the pathological situations that cause high levels of LDH, an enzyme involved in cellular metabolism. In preeclampsia, hypoxia raises LDH activity and glycolysis, which raises lactate generation. Of the five isoforms of LDH, the foetal endothelium cells immunolocalize the LDH-A isoenzyme, whereas syncytiotrophoblasts mostly contain the LDH-B isoenzyme [10, 11].

Similar to this, uric acid, a byproduct of purine synthesis, has gained notice. Uric acid in preeclampsia may have multiple causes, including abnormal renal function, accelerated tissue degradation, acidosis, and elevated xanthine oxidase/dehydrogenase activity [12, 13]. Additionally, it is linked to oxidative stress and endothelial dysfunction, two major characteristics of preeclampsia [14].

The relationship between the mentioned markers and the severity of preeclampsia remains inconsistent across studies. Therefore, the present study was conducted to assess the correlation of serum uric acid, serum LDH, and C-reactive protein with the severity of preeclampsia in pregnant women.

Methodology:

This case-control study was conducted after receiving approval from the Institutional Ethics Committee. The research took place in the Department of Obstetrics and Gynaecology at Ballari institute of

medical sciences and research centre, Ballari, Karnataka.

After fulfilling the eligibility criteria, pregnant women were divided into study group-group A (n=60) and control group- group B (n=60). Pregnant women diagnosed with preeclampsia and admitted to the department were considered for enrollment, provided they gave written informed consent. The control group consisted of primi or multigravida pregnant women with gestational age over 20 weeks, aged between 18 and 40 years. Women with pre-existing cardiac, renal, or hepatic conditions, as well as those with diabetes mellitus, thyroid disorders, or infectious diseases, were excluded from the study.

The study team recorded the clinical and demographic information of the participants. Following aseptic precautions, a 5ml blood sample was collected via venipuncture into a plain vacutainer. The serum was separated through centrifugation and analyzed to measure the levels of CRP, LDH, and uric acid. The semiquantitative CRP test utilized the latex agglutination method. Serum LDH levels were measured using the kit method with a semi-automatic analyzer, while uric acid levels were assessed using the kit method with a fully automated biochemistry analyzer.

Data analysis was done with the help of statistical software Graphpad InStat v3.0. Frequency and percentages were used to portray all categorical data, while mean and standard deviation or median and interquartile range, depending on the distribution, was used to describe any continuous data. After verifying the normalcy assumption, the Independent Sample t-test or Mann Whitney U test was used for continuous measurements. The Chi-square test or Fisher's exact test was used for categorical observations based on the expected frequency. For every comparison, the P-value was deemed significant at the 5% level of significance.

RESULTS:

A total of 60 pregnant women with preeclampsia (Group A) and 60 normotensive pregnant women (Group B) were included in the study, as determined by the sample size calculation. The mean ages of the two groups were statistically similar, with no significant difference ($p > 0.05$) based on an unpaired t-test (23.8 ± 4.7 years in Group A compared to 23.8 ± 3.6 years in Group B). Additional clinical and demographic details are provided in **Table 1.**

Table 1: Clinico-demographic Details Of The Patients.

Clinico-demographic parameter	Variable under observation	Group A (n=60)	Group B (n=60)
Obstetric score: Gravida	Primi	25 (41.7%)	18 (30%)
	G2	18 (30%)	22 (36.7%)
	G3	13 (21.7%)	14 (23.3%)
	G4	4 (6.7%)	5 (8.3%)
	G5	0	1 (1.7%)
Pulse rate in beats/minute	Mean ± SD	98.3 ± 13.9	96.3 ± 11.2
Systolic blood pressure in mmHg	Mean ± SD	156.5 ± 17.7	110.5 ± 6.7
Diastolic blood pressure in mmHg	Mean ± SD	101 ± 14.7	78.5 ± 12.2
Urinary albumin categorization	Nil	3 (5%)	24 (40%)
	Traces	2 (3.3%)	12 (20%)
	1+	3 (5%)	3 (5%)
	2+	16 (26.7%)	12 (20%)
	3+	24 (40%)	9 (15%)
	4+	12 (20%)	0

The main aim of the study was to assess and compare the levels of CRP, serum LDH and serum uric acid among group A and group B. **Table 2 and Figure 1 (A,B,C)** illustrates the comparison of the aforementioned variables. It was seen that the levels of CRP, serum LDH and serum uric acid among group A was statistically higher than group B with $p<0.05$ on unpaired T-test.

Table 2: Comparison of serum markers among patients.

Serum markers	Group A (n=60)	Group B (n=60)	P-value
CRP (in mg/l)	43.7 ± 22.2	13.7 ±8.4	0.0001*
Serum LDH (in U/L)	679.3 ± 306.5	411.25 ± 162.2	0.0001*
Serum uric acid (in mg/dL)	5.14 ± 1.2	4.55 ± 1.2	0.008*

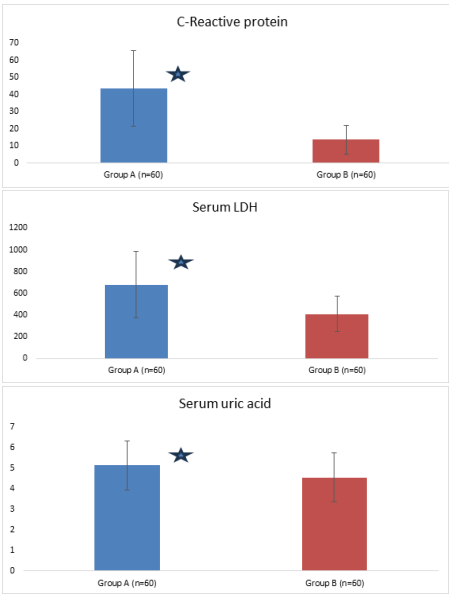

Figure 1: Shows comparison between average values of A-CRP; B-Serum LDH; C- Serum uric acid between the two groups. *Represent $p<0.05$ on unpaired T-test.

Additionally, the patients were categorized based on CRP levels (≤6 mg/L and >6 mg/L), serum LDH levels (<600 U/L, 600–800 U/L, and >800 U/L), and serum uric acid levels (<2.4 mg/dL, 2.4–5.7 mg/dL, and >5.7 mg/dL), as shown in **Table 3**.

Table 3: Distribution of patients based on serum markers categorization.

Serum markers	Categorization	Group A (n=60)	Group B (n=60)	P-value
CRP levels	≤6 mg/L	1 (1.7%)	6 (10%)	0.051
	6-12 mg/L	2 (3.3%)	28 (46.7%)	<0.0001*
	>12mg/L	57 (95%)	26 (43.3%)	<0.0001*
Serum LDH	<600U/L	26 (43.3%)	51 (85%)	<0.0001*
	600-800 U/L	17 (28.3%)	8 (13.3%)	0.04*
	>800 U/L	17 (28.3%)	1 (1.7%)	<0.0001*
Serum uric acid	<2.4 mg/dL	0	1 (1.7%)	1
	2.4-5.7 mg/dL	42 (70%)	52 (86.7%)	0.02*
	>5.7 mg/dL	18 (30%)	7 (11.6%)	0.01*

We also explored the correlation between the increase in blood pressure and the rise in serum markers such as CRP, LDH, and uric acid. A statistically and strong positive correlation was observed between the severity of preeclampsia and CRP levels ($R = 0.6734.$; $p = 0.0001$). Similarly, mild positive and significant correlations were noted for serum LDH ($R = 0.4899$; $p = 0.001$) and uric acid ($R = 0.2335$; $p = 0.73$) with the increasing blood pressure.

The feto-maternal outcomes were evaluated in both groups. It was observed that the majority of women in Group A (35 patients) underwent emergency cesarean sections, compared to 18 women in Group B. This represented a statistically significant increase in emergency cesarean sections among preeclamptic women ($p = 0.03$, Chi-square test). No additional complications were reported in either group. Other perinatal outcomes are illustrated in **Figure 2**.

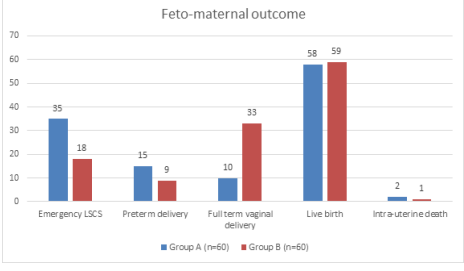

Figure 2: Feto-maternal outcomes between the two groups.

DISCUSSION:

One of the main causes of maternal and perinatal death globally is hypertensive disorders of pregnancy. A pregnancy condition known as preeclampsia, with or without severe symptoms, is characterized by new-onset hypertension, typically accompanied by proteinuria, and normally develops after 20 weeks of gestation and often close to term [15]. Early identification of preeclampsia and the use of simple and reliable markers are imperative due to the condition's significant prevalence and impact during pregnancy. When selecting a biomarker, it is essential to consider its potential as a screening tool, along with its biological properties and role in the disease's pathogenesis. A biomarker that requires advanced technology and lacks a favorable cost-benefit ratio would be impractical. This is especially relevant in low-income countries, where deaths from hypertensive pregnancies are significantly higher compared to developed nations [16]. Serum LDH, serum uric acid, and CRP are routine laboratory tests. The purpose of the case-control study was to evaluate these parameters' usefulness in pre-eclamptic pregnant women.

The sociodemographic details between the two groups were comparable in terms of patient age, obstetric score. On assessing the blood pressure, a statistical increase in the systolic and diastolic blood pressure was seen in pre-eclamptic women (group A) compared to group B. However, other vital parameters were comparable.

The levels of serum CRP was significantly higher in the case group (Group A) compared to the controls. Additionally, a notable upward trend and a significant positive correlation were observed between these serum markers and increasing blood pressure, indicating the severity of preeclampsia. Similar findings were reported by Singh S et al [17], Kaur RB et al [18] where serum CRP levels were higher in preeclamptic patients compared to normotensive pregnant women, aligning with the results of the current study. This study further highlights that CRP is a promising biochemical marker that can not only reflect the severity of preeclampsia but may also help predict its progression in pregnant women.

Our study revealed that an increase in serum uric acid and LDH levels was associated with greater severity of hypertension. Blood pressure demonstrated a positive correlation with both serum LDH and uric acid levels. Additionally, the findings of this case-control study showed that preeclamptic women had significantly higher serum levels of uric acid and LDH compared to normotensive women. Findings from Kaur RB et al [18], Moharana JJ et al [10] showed the consistent findings.

In the current study, we found that 95% of preeclamptic subjects and 43.3% of normotensive subjects had serum CRP levels exceeding 12 mg/L. Similarly, serum LDH levels above 800 U/L were observed in 28.3% of preeclamptic cases and 1.7% of controls. Additionally, uric acid levels above the normal upper limit (>5.7 mg/dL) were noted in 30% of preeclamptic cases and 11.6% of controls. Similar results were seen in studies by Punthumapol C et al [19], Dave A et al [20].

During glycolysis, the intracellular enzyme LDH converts pyruvic acid into lactic acid. Glycolysis serves as the primary energy pathway for the placenta. In preeclampsia, hypoxia leads to increased LDH activity, which further enhances glycolysis. Hypoxia-induced LDH isoenzyme activity in trophoblasts results in greater lactate production. Among the five LDH isoforms, LDHA4 is the most responsive to hypoxia in placentas affected by preeclampsia. Elevated LDH levels are indicative of the disease's severity, the likelihood of complications, and fetal outcomes, making LDH a valuable biochemical marker for identifying cellular damage and dysfunction. Since these complications are preventable, monitoring LDH levels can provide significant clinical benefits [21].

Current study highlighted no complications in either group. However, a statistical increase in the emergency caesarean section was noted in pre-eclampsia. Although preeclampsia is not a direct indication for cesarean delivery and vaginal delivery is often feasible, it has been associated with a higher rate of cesarean births. However, in certain situations, such as placenta previa or uterine rupture, a cesarean section becomes the safest method of delivery [22].

CONCLUSION:

Understanding the pathogenic mechanisms behind preeclampsia, a multisystem pregnancy condition, is essential to creating successful preventative measures. Serum uric acid, LDH, and CRP were all raised in pregnant women with preeclampsia in the current research. In addition to being linked to preeclampsia, elevated serum levels of CRP, LDH, and uric acid also serve as indirect risk factors for placental vasculopathy, which develops before the disease's clinical manifestation. Frequent monitoring of these reasonably priced biomarkers can aid in determining the condition's severity and course. In some situations, an early pregnancy termination can avoid complications for the mother.

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