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Elevated maternal serum ferritin and C-reactive protein: Potential biomarkers for predicting preterm labor

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Abstract
Preterm labor remains one of the leading challenges in obstetrics, contributing significantly to perinatal morbidity and mortality worldwide. Although several factors have been associated with its onset, growing evidence suggests that inflammation and subclinical intrauterine infections play a major role in the pathogenesis of preterm labor. Among the various biochemical markers under investigation, serum ferritin and C-reactive protein (CRP) have emerged as promising indicators due to their established roles in inflammatory pathways. This prospective case-control study, conducted in the Department of Obstetrics and Gynaecology at SCB Medical College and Hospital, Cuttack, from June 2020 to May 2021, aimed to evaluate the predictive value of maternal serum ferritin and CRP levels in preterm labor.

A total of 200 pregnant women were recruited and categorized into two groups: Group A (cases) comprised 100 women experiencing spontaneous preterm labor between 30 and 34 weeks of gestation, and Group B (controls) included 100 women with uncomplicated term pregnancies. Serum ferritin and CRP levels were measured using chemiluminescence immunoassay. Statistical analyses revealed significantly higher serum ferritin (38.04±4.04 ng/mL vs. 14.49±4.55 ng/mL) and CRP levels (5.31±1.33 mg/L vs. 1.50±0.29 mg/L) in the preterm group compared to the term group (P=0.001 for both). A strong positive correlation between ferritin and CRP was observed only in the preterm group (r=0.735, P=0.001), indicating a distinct inflammatory profile. Furthermore, ROC analysis demonstrated high diagnostic accuracy for serum ferritin in predicting preterm labor.

These findings underscore the potential role of serum ferritin and CRP as valuable biomarkers for early identification of women at risk of preterm labor. Incorporating these markers into routine antenatal screening may enable timely interventions, thereby improving maternal and neonatal outcomes. However, larger multicenter studies are needed to validate these findings and clarify the combined predictive value of these biomarkers.

Keywords: C-reactive protein, preterm labor, serum ferritin, inflammation, biomarker, pregnancy outcomes, prediction model, maternal health

Introduction

Preterm labor presents a major problem for obstetricians, as it affects around 10% of all new-borns and significantly increases both perinatal mortality and long-term morbidity. Even with medical research improvements, the precise processes causing preterm labor remain unknown. However, growing research suggests that chronic inflammation and subclinical intrauterine infections are primarily responsible for their onset and early membrane rupture [1].

Researchers have identified many risk factors for preterm labor, including a history of preterm labor, prior abortions, pregnancies produced using assisted reproductive technologies, multiple gestations, and vaginal haemorrhage during pregnancy [2]. Bacteria can either directly or indirectly cause prostaglandin synthesis via phospholipase A2, resulting in cervical ripening and uterine contraction in an infection setting [3].

The ability of serum ferritin and C-reactive protein (CRP) to predict preterm labor has drawn a lot of interest in these biochemical markers. Serum ferritin, an intracellular protein that stores and releases iron, also functions as an acute-phase reactant that rises in response to infection and inflammation [4]. Elevated levels of ferritin in the blood during pregnancy may indicate an inflammatory response, potentially leading to its use as a preterm labor predictor. Women with high ferritin levels have a higher chance of giving birth prematurely because of an underlying

illness or inflammatory condition [5]. We use C-reactive protein (CRP), a recognized measure of inflammation, to identify and track inflammatory diseases. During pregnancy, elevated CRP levels may indicate systemic inflammation or subclinical infections, both of which are associated with the onset of premature labor. Numerous studies have linked elevated CRP levels to preterm birth risk. For instance, studies have linked higher CRP levels during the second trimester to an increased risk of preterm birth, suggesting that CRP could serve as a biomarker to identify pregnancies at risk of premature labor due to inflammatory disorders [6, 7].

Their study is important because these indicators have the potential to improve preterm labor prediction and treatment. Our study emphasizes the functions of serum ferritin and CRP separately. We still need comprehensive research to confirm the combined predictive value and usefulness of the biomarkers in clinical settings. Research that simultaneously accounts for the two indicators is currently lacking, which might lead to a more reliable preterm labor prediction model. This discrepancy emphasizes the necessity of research that combines serum ferritin and CRP levels to better comprehend how they work together to predict premature labor.

This study aims to improve preterm labor prediction models by comparing the serum ferritin and CRP levels of women going through premature labor to those of normal pregnancies. The results may help create more precise prediction models that use these indicators to more consistently and early detect at-risk pregnancies. Early detection of women in danger of preterm labor might result in prompt interventions, which may reduce the number of preterm deliveries and the problems that accompany them. Furthermore, even if previous studies have supported the functions of these biomarkers, this study seeks to collect further data to comprehend the interactions and combined predictive value of these biomarkers.

The objectives of this study were to compare serum ferritin and CRP levels in women admitted to the labor ward for preterm labor with those in uncomplicated pregnancies going to term in order to assess the levels in these individuals. Through a concentration on these goals, the research intends to further knowledge and treatment of preterm labor, therefore enhancing the health outcomes for both the mother and the new-born.

Materials and Methods

The department of obstetrics and gynaecology at SCB medical college and hospital, Cuttack, conducted this prospective case-control research over a year, from June 2020 to May 2021. The main goal was to assess the value of maternal serum ferritin and CRP levels as a preterm labour indicator.

We formed two groups out of the 200 gravid women who made up the research population. Group A (cases) consisted of one hundred gravid women who experienced spontaneous preterm labour between thirty and thirty-four weeks into their pregnancy. Group B (controls) consisted of 100 gravid women with low risk pregnancies. Defined inclusion criteria guarantee the proper choice of members for every group. Women experiencing spontaneous preterm labour that is, regular uterine contractions along with cervical changes before 37 weeks of gestation was the inclusion criteria for Group A. The inclusion criteria for Group B was women who were term that is, who were 37 weeks along in their pregnancy without any problems. For both groups, the exclusion criteria were used consistently in order to remove confusing elements. To prevent the effect of multiple gestations on premature labour, women having multiple pregnancies were not included. To avoid their influencing serum ferritin levels, women with known haematological illnesses, chronic infections, or inflammatory diseases were not included. Women who had received blood transfusions recently were also not included in order to prevent any changes in serum ferritin levels brought on by transfusions.

The Institutional Ethics Committee (IEC) of SCB Medical College and Hospital, Cuttack, examined and approved the study protocol (Review Date: 08.02.2021). Every process followed the 1964 Helsinki Statement and its subsequent revisions, as well as the ethical guidelines of the institutional and national research committees. Throughout the study, participants' ethical rights and confidentiality were upheld.

On the fully automated Beckman Coulter Access TWO analyzer, serum ferritin and CRP levels were determined by chemiluminescence immunoassay (CLIA). The test was carried out precisely and accurately by following the manufacturer's instructions, guaranteeing serum ferritin levels were measured. The reliability of the laboratory results was guaranteed, and the possibility of variability was reduced by the application of an automated and standardized method.

All patients received routine antepartum and intrapartum treatment as per departmental guidelines. Labour outcomes, including birth weight, gestational age at delivery, and neonatal results were documented. This guaranteed that every participant received the right care and made it possible to gather outcome data as a whole for additional study.

Statistical Analysis

SPSS version 17.0 was used for analysis after the data were input into Microsoft Excel. With means (SD) or medians (range) computed for continuous variables and percentages for categorical variables, descriptive statistics were used to summarize the data. Categorical variables were compared using the chi-square test; continuous variables, like birth weight, haemoglobin, and serum ferritin levels, were compared using independent t-tests for two groups and ANOVA for three. The area under the curve (AUC) was computed to evaluate diagnostic performance after receiver operating characteristic (ROC) curve analysis was used to establish the cut-off values for blood ferritin levels. At the best cut-off value, sensitivity and specificity were ascertained, a statistically significant p-value was defined as < 0.05.

Results

Table 1 compares characteristics of the term and preterm labor groups. Though this difference was not statistically significant (P=0.22), the mean age of women in the preterm labor group was 26.11 years (± 4.01), which was higher than the mean age of 24.84 years (± 3.76) in the term labor group. Preterm group had a far higher percentage of vaginal deliveries (86%) than term group (64%), and term labor group had a higher incidence of lower segment caesarean section (LSCS), (36%) than preterm group (14%) (P=0.001).With 65% males and 35% females in the preterm group and 54% males and 46% females in the term group (P=0.113), there was no statistically significant variation in the sex distribution of the new-borns between the two groups. In the control group the mean birth weight of new-borns was 2.91 kg (± 0.29), but in the preterm labor group it was much lower at 1.85 kg (± 0.33) (P=0.001).These results highlight the greater susceptibility and various clinical treatment requirements of preterm deliveries by revealing notable variations in the mode of delivery and birth weight between preterm and term labor.

Table 1: Comparison of various characteristics of preterm & term Labour

Variables	Preterm labour (N=100)	Term labour (N=100)	P-Value
Age of mother (mean ± SD)	26.11(4.01)	24.84(3.76)	0.22
Mode of delivery (%)			0.001
Vaginal	86(86%)	64(64%)	
LSCS	14(14%)	36(36%)	
Sex of baby (%)			0.113
Male	65(65%)	54(54%)	
Female	35(35%)	46(46%)	
Birth wt of baby (mean ± SD)	1.85(0.33)	2.91(0.29)	0.001

Table 2 compares the biochemical aspects of women in the term and preterm labor groups. In the preterm labor group, the mean hemoglobin (Hb) level was 11.50 g/dL (± 0.79) and in the term labor group, 11.74 g/dL (± 1.03); there was no statistically significant difference between the groups (P=0.67). The two groups did, however, have quite different serum ferritin and C reactive protein (CRP) levels. In the term labor group, the mean serum ferritin level was 14.49 ng/mL (± 4.55), but in the preterm labor group, it was much higher at 38.04 ng/mL (± 4.04) (P=0.001). In the same vein, the preterm group had a higher mean CRP level 5.31 mg/L than term group which was 1.50 mg/L with p value of 0.001. These results indicate the possible use of these biomarkers in predicting preterm labor by highlighting notable variations in inflammatory and infection markers between preterm and term labor.

Table 2: Biochemical Parameters

Variables	Preterm labour (N=100)	Term labour (N=100)	P-Value
Hb (mean ± SD)	11.50(0.79)	11.74(1.03)	0.67
Sr. ferritin (mean ± SD)	38.04(4.04)	14.49(4.55)	0.001
CRP (mean ± SD)	5.31(1.33)	1.50(0.29)	0.001

Serum ferritin and CRP correlation in preterm and term labor

Preterm and term labor showed quite different correlations between blood ferritin and C-reactive protein (CRP) levels (Table 3). A strong positive connection (r=0.735, P=0.001) was seen between serum ferritin and CRP levels in the preterm labor group. This suggests a strong relationship and implies that in preterm labor, higher ferritin levels are intimately associated with higher CRP levels. In contrast, there was a modest and non-statistically significant connection (r=0.085, P=0.398) between serum ferritin and CRP levels in the work group. These results demonstrate the clear distinction in the inflammatory profile between term and preterm labor; only in preterm labor do serum ferritin and CRP exhibit a significant correlation. This can highlight role of inflammation in the pathogenesis of preterm labor and have implications for clinical evaluation and treatment plans.

Table 3: Correlation between sr. ferritin & CRP in preterm & term labour

Labour		CRP	P-Value
Pre-term labour	Sr. Ferritin	.735	.001
Term labour		.085	0.398

Serum ferritin levels and C-reactive protein (CRP) in both preterm and term labor groups are shown by scatter plots in Figure 1. As seen by a linear regression line with the equation y=26.24 + 2.22x and a coefficient of determination (R_2) of 0.541, serum ferritin and CRP are positively correlated in the preterm population. Accordingly, the linear correlation between serum ferritin and CRP in the preterm labor group accounts for around 54.1% of the variability in the blood. Conversely, the term group has a far lower association; a regression line with a R2 of 0.007 and a regression line formed by the equation y=12.47±1.32x indicate that CRP accounts for just 0.7% of the variability in serum ferritin in the labor group. These results imply that, in preterm labor, the relationship between serum ferritin and CRP is stronger than in term labor.

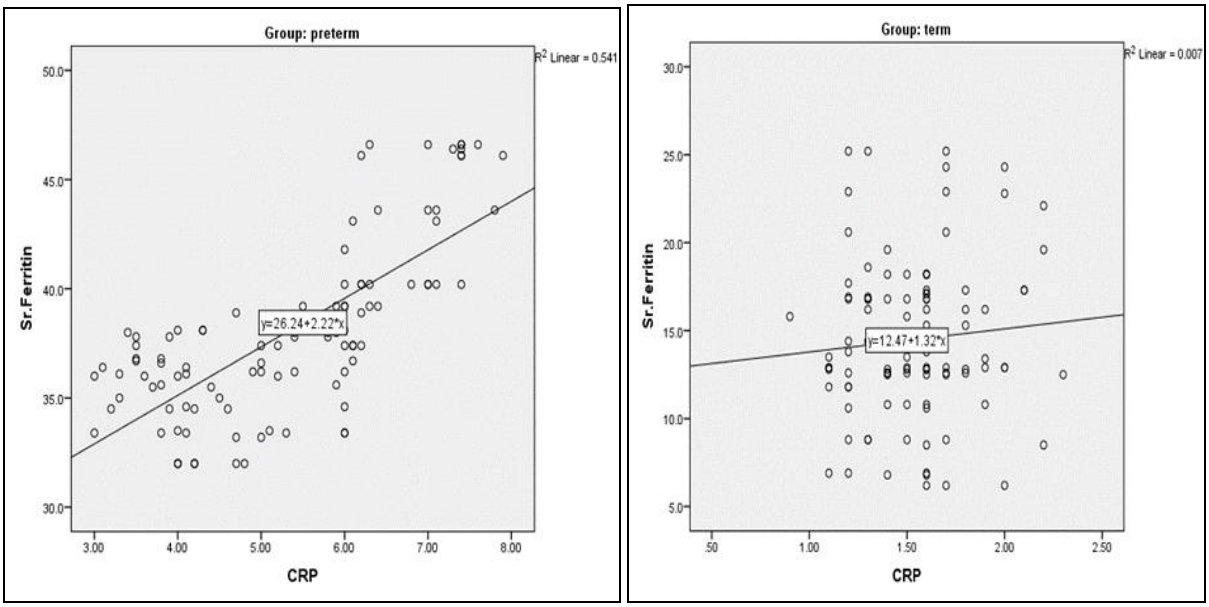

Fig 1: Scatter plot showing Correlation between sr. ferritin & CRP in preterm & term labour

Discussion

Using 200 pregnant women divided into Group A (preterm birth) and Group B (full-term delivery), this large research thoroughly examined blood ferritin levels as possible indicators of preterm labor. The preterm group had increased serum ferritin, which is often associated with inflammatory disorders; Group A had far higher levels than Group B. This result supports earlier research that highlights the role inflammation plays in preterm birth [8, 9].

One of the primary benefits of the study is its stringent exclusion criteria, which ensure consistency in factors like maternal age and haemoglobin levels and thus lower confounding variables that may skew the results. Similar demographics among the groups indicate that serum ferritin is a reliable indicator of early labor [10].

The study used a strong statistical method to create a receiver operating characteristic (ROC) curve that helped find the serum ferritin cut off value that is most accurate at predicting early labor. As in other studies the findings for serum ferritin demonstrated remarkable sensitivity (96.0%) and specificity (98.0%) [11, 12]. Such tests underline the clinical significance of serum ferritin as a biochemical marker in prenatal care.

Apart from serum ferritin, the study examined serum C-reactive protein (CRP) as biomarker. This revealed significant variation between the preterm and term groups of women. As in earlier research examining the inflammatory environment in preterm birth, the high levels of these markers in the group of women who went into labor before their due date imply that they might be involved in the inflammatory pathways leading to early delivery [13, 14].

The study also found a significant correlation between serum ferritin and CRP levels in preterm birth pathophysiology, specifically in the preterm labor group. The fact that this connection was noticeably absent from the term labor group emphasizes the particular inflammatory profiles associated with early labor [15].

The study also considered the clinical outcomes of term and preterm deliveries. While vaginal deliveries were far more prevalent in the preterm group (86%), lower segment caesarean section (LSCS) births were more common in the term group (36%) than in the preterm group (14%). Preterm labor often requires a higher degree of therapeutic treatment, which aligns with this modification of delivery technique [16].

Moreover, the mean birth weight of the infants in the preterm labor group was 1.85 kg (P=0.001), lower than that of the term labor group (2.91 kg). This outcome is in line with the widely recognized risks associated with preterm delivery, like low birth weight and the need for specialized infant care that follows [17].

Despite the numerous benefits of this study, it is important to acknowledge a few drawbacks. Firstly, conducting the study in a single medical facility limits the applicability of the results to different demographics and environments. Second, even with strict exclusion standards, there could be unmeasured confounding factors that affect the outcomes. Third, despite being adequate for preliminary results, the sample size could not be large enough to identify lower effect sizes or apply the findings to a larger population. Lastly, the study failed to consider any long-term variations in biomarker levels during pregnancy, which could shed light on the exact moment and course of preterm labor.

To improve the applicability of the results future research should try to overcome these constraints by incorporating larger, more varied populations across several sites. Longitudinal studies monitoring biomarker levels during pregnancy may provide valuable insights into the dynamics of these indicators and their relationship with preterm labor. Investigating the underlying biological processes that link inflammation to preterm labor may also provide novel treatment options. We should include these biomarkers in standard prenatal screening methods to enhance prenatal care, lower the rate of preterm delivery, and evaluate their cost-effectiveness and influence on clinical outcomes.

Conclusion

This study supports the use of serum ferritin and C-reactive protein (CRP) as reliable biomarkers for predicting preterm labor. Inflammation-triggered processes that lead to early delivery strongly correlate with elevated levels of these biomarkers. The findings emphasize the need to incorporate these indicators into clinical practice in order to improve prenatal care and outcomes for both the mother and the newborn. It will require additional research in more diverse and sizable groups to confirm these results and fully explain the underlying processes.

Conflict of Interest

Not available

Financial Support

Not available

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