

C-Reactive Protein and Albumin Ratio as a Predictor of Premature Uterine Contractions in Pregnancy

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Abstract

Objective: The objective of this study was to investigate the association between the CRP/Albumin ratio and premature uterine contractions, and to evaluate the potential of CRP as a biomarker for predicting preterm delivery.

Methodology: A prospective case-control study was conducted at the Biochemistry Section of the Diagnostic and Research Laboratory, in collaboration with the Gynecology and Obstetrics Department of Liaquat University of Medical and Health Sciences Hospital, Jamshoro, Pakistan. Peripheral venous blood samples totaling 10 ml were collected in anticoagulant-free test tubes and allowed to clot. Serum was then separated from the samples. The concentration of C-reactive protein (CRP) was measured using a highly sensitive immunoassay test with the Modular Roche Cobas C311. Additionally, serum albumin concentrations were analyzed via photospectrometry using the same instrument.

Results: A total of 178 pregnant women were studied comparatively. The average age in the case group was 26.87 years, while in the control pregnancy group, it was 27.35 years. The mean CRP level in the case group was significantly higher than in the control group ($p < 0.001$). Although the case group had slightly lower albumin levels (mean=3.30 g/dl) compared to the control group (mean=3.43 g/dl), this difference was statistically insignificant ($p = 0.089$). Notably, the CRP/albumin ratio was substantially higher in the case group (mean=1.52) compared to the control group (mean=0.60), with a significant difference ($p < 0.001$). The CRP level showed a stronger association with premature contractions, as indicated by the ROC curve area of 0.789.

Conclusion: CRP/albumin ratio was higher among cases with premature uterine contractions compared to those without, indicating that an elevated CRP/albumin ratio could potentially serve as a predictor of premature birth, especially in cases of premature contractions. The observed association between elevated CRP levels and premature contractions suggests a possible connection between inflammation and the onset of premature labor.

Keywords: C-Reactive Protein, Albumin, Premature birth.

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Introduction

Premature uterine contractions (PUC) present a significant concern during pregnancy, potentially leading to preterm birth and associated complications. Identifying reliable predictors of PUC is crucial for early intervention and improving maternal and fetal outcomes. The C-reactive protein (CRP) to albumin ratio has garnered attention as a potential prognostic marker in various medical contexts, including pregnancy-related complications.

Preterm birth poses a substantial public health challenge, occurring in more than 10 percent of global births. It significantly contributes to neonatal mortality and various health issues during childhood and later stages of life. Pakistan ranks fourth globally in terms of the highest number of premature births, with statistics showing 748,100 preterm births (PTB) annually.¹

The incidence of preterm birth was observed to be 18.89% under the fixed-effect model, 16.81% under the

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random-effect model, and 18.89% under the fixed-effect heterogeneity model.² Preterm birth in humans is defined as the delivery of a baby before 37 weeks or 259 days of gestation.^{3,4} Infants born prior to 32 weeks of gestation are classified as very preterm, while those born before 28 weeks of gestation are classified as extremely preterm.⁵

Seventy-two percent of fetal deaths occur between 26 and 36 weeks of gestation, with only 28% occurring at term pregnancy.⁶ In Pakistan, 16 out of 100 babies are born preterm.⁷ The CRP to albumin ratio can serve as a powerful indicator of premature uterine contractions. C-reactive protein is an acute-phase protein generated in response to various cytokine stimulations following infection, ischemia, trauma, and other inflammatory circumstances.⁸ It has been proposed as a biomarker for premature uterine contractions.⁹ Women experiencing threatened preterm labor often exhibit elevated levels of cervicovaginal interleukin-8 (IL-8). To predict delivery within a 2–7-day timeframe, clinicians commonly assess cervicovaginal hCG levels, cervical length, absence of fetal breathing movements, IL-6 concentration in amniotic fluid, and C-reactive protein (CRP) levels in serum.¹⁰ Human Serum Albumin (HSA) stands out as the predominant protein in plasma, functioning as a monomeric, multi-domain macromolecule pivotal for maintaining plasma oncotic pressure and regulating fluid distribution within the body. It demonstrates a robust capacity for ligand binding, acting as a reservoir and transporter for various endogenous and exogenous substances. HSA plays a crucial role as a carrier for fatty acids, influencing the pharmacokinetics of many medications, aiding in metabolic transformations of specific ligands, neutralizing potential toxins, significantly contributing to plasma antioxidant capacity, and exhibiting pseudo-enzymatic characteristics. Moreover, HSA serves as a significant biomarker for various conditions, including rheumatoid arthritis, cancer, obesity related to menopause, ischemia, severe acute graft-versus-host disease, and medical conditions requiring glycemic control monitoring.¹¹ Studies have investigated the CRP/Albumin ratio in polycystic ovarian syndrome, demonstrating a specificity of 85% compared to CRP alone.¹² This ratio has proven effective as an inflammation-based prognostic indicator in osteosarcoma and predicting mortality in critically ill patients.^{13,14} However, its potential application in premature uterine contractions warrants further exploration. Combining CRP and Albumin measurements may provide more accurate prognostic

information and assist in managing preterm labor cases effectively. Preterm birth due to premature uterine contractions remains a significant concern in Pakistan. This study proposes utilizing the CRP/Albumin ratio as an economical biomarker for predicting premature uterine contractions, potentially enabling obstetricians to manage these cases promptly through dietary modifications or other interventions.

Methodology

A prospective case-control study was conducted at the Biochemistry Section of the Diagnostic and Research Laboratory, in collaboration with the Gynecology and Obstetrics Department of Liaquat University of Medical and Health Sciences Hospital, Jamshoro, Pakistan. The study duration was six months, from January 2021 to June 2021. Ethical guidelines were strictly followed, and approval was obtained from the Ethical Review Board (ERB) of LUMHS. The study enrolled women aged between 20-40 years, with gestational periods ranging from 24 to 36 weeks and singleton pregnancies. Women meeting the inclusion criteria were approached for participation during routine prenatal care visits at antenatal clinics or obstetric units. Demographic information, medical history, and lifestyle factors were collected through structured interviews and review of medical records. Detailed informed consent was obtained from each study participant, outlining the study's purpose, procedures, risks, and benefits. A 10 ml of peripheral venous blood sample was collected from each case in anticoagulant-free test tubes and allowed to clot, followed by separation of the serum from the sample. The concentration of C-reactive protein (CRP) was measured using a highly sensitive immunoassay test with the Modular Roche Cobas C311. Additionally, serum albumin concentrations were analyzed by photospectrometry using the same device. Patients were categorized into two groups: cases and controls. The Case Group comprised pregnant patients diagnosed with premature uterine contractions based on clinical examination and/or ultrasound findings. The Control Group consisted of pregnant patients without any history or current evidence of premature uterine contractions, matched for gestational age and other pertinent demographics. All collected data, including demographic information, medical history, and laboratory results, were recorded via a study proforma. Strict measures were implemented to ensure the privacy and confidentiality of participant information.

Following data collection, the analysis was conducted using SPSS Version 26. Quantitative data for continuous variables were summarized using statistics such as mean, median, and standard deviation, while simple frequency and percentage were computed for categorical variables. A t-test was applied, with a p-value of ≤ 0.05 was considered as significant.

Results

A total of 178 pregnant were comparatively studied. The average age of the women of the case group was 26.87 ± 4.76 years and average age of the control pregnancy group was 27.35 ± 4.81 years. In this study mean gestational age was 33.01 ± 2.52 weeks was in case group, which was statistically insignificant in contrast to the control pregnancy group as 32.59 ± 2.09 weeks. (Table I)

Table I: Average age comparison in both study groups. (n=178)

Variables	Study group	Mean	SD	P value
Age (years)	Case group	26.87	4.769	0.502
	Control group	27.35	4.812	
Gestational age(weeks)	Case group	33.01	2.52	0.253
	Control group	32.59	2.30	

Case group (n=89)= Premature cases with contractions
Control group (n=89)= Premature cases without contractions

Table II: Parity comparison in women of the both study groups. (n=178)

Variables	Case group (n = 89)	Control group (n = 89)	Total	P value	
Parity	1-3	54 (60.7%)	49 (55.1%)	103 (57.9%)	0.721
	4-6	19 (21.3%)	23 (25.8%)	42 (23.6%)	
	> 6	16 (18.0%)	17 (19.1%)	33 (18.5%)	

Most of the women had parity 1-3 in both groups, 60.7% and 55.1% in each case and control groups respectively, followed by parity 4-6 was 21.3% in premature contractions group and 25.8% in control group, parity >6 was 18.0% in case group and 19.1% was in control group, these findings were statistically insignificant (p=0.721). (Table II)

Table III: Average CRP/Albumin ratio in both study groups. (n=178)

Variables	Study group	Mean	SD	P value
CRP level	Case group	4.94	3.96	0.001
	Control group	2.10	2.61	
Albumin Level	Case group	3.30	0.43	0.089
	Control group	3.42	0.54	
CRP/albumin ration	Case group	1.52	1.284	0.001
	Control group	0.60	0.68	

In the case group, the mean CRP level was significantly higher than the control group's ($p < 0.001$). Regarding albumin levels, the case group had a mean of 3.30 g/dl (SD=0.43), slightly lower than the control group's ($p = 0.089$). Notably, the CRP/albumin ratio was markedly higher in the case group (mean=1.52, SD=1.284) compared to the control group (mean=0.60, SD=0.68), with a significant difference observed ($p < 0.001$). Table III

Furthermore CRP/albumin ration was also higher among cases compared to controls ($p=0.001$). (Table III) CRP level showed more assumption if the cases with contractions with ROC curve area 789 and serum albumin level showed ROC curve area 456. Figure 1

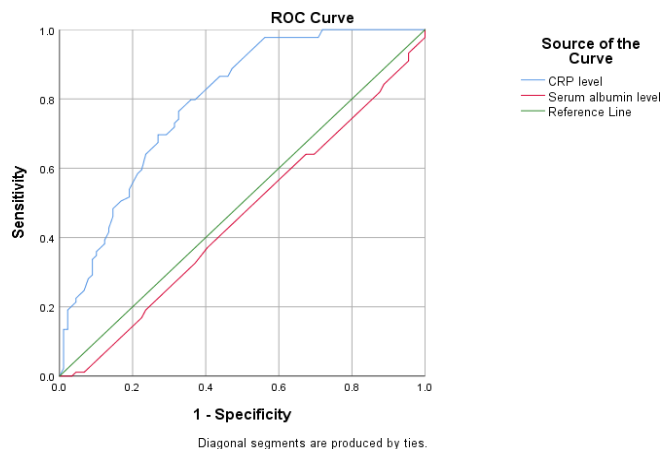


Figure 1. Assumption of the premature contractions according to CRP and albumin. (n=178)

Discussion

Premature uterine contractions (PUC) are a common obstetric complication that can lead to preterm labor and delivery. Identifying reliable biomarkers that can predict the likelihood of PUC and preterm delivery is critical for early intervention and improving the pregnancy outcomes. In this study a total of 178 pregnant were comparatively studied to evaluate the association between CRP/ Albumin ratio and premature uterine contractions, whether CRP can be used as a bio-marker to predict pre mature delivery; their mean age was 26.87 ± 4.76 years in contraction group while mean age was 27.35 ± 4.81 years in without contraction group. These finding were supported by previous research that has shown that age is not a major factor in premature birth.¹⁵ Other factors such as maternal health, lifestyle, and genetics may have a stronger impact on the likelihood of premature birth.¹⁶ It is important to note that while the average age of the women in both groups was similar, there may be individual differences within each

group that could impact the likelihood of premature birth. Further research is needed to identify other potential risk factors for premature birth. Despite the slight difference in average age, there was no significant difference between the two groups ($p = 0.502$).

In this study most of the women had parity 1-3 in both groups, 60.7% and 55.1% in each premature contractions and control groups respectively, followed by parity 4-6 was 21.3% in premature group and 25.8% was in control group, parity >6 was 18.0% in premature group and 19.1% was in control group, while findings were statistically insignificant ($p = 0.721$). Comparative findings on parity in premature contractions and control groups of women show that most of the women had parity 1-3 in both groups. The findings showed that 60.7% of women in the premature contractions group had parity 1-3, while 55.1% of women in the control group had parity 1-3. However, the findings were statistically insignificant. It is widely accepted that parity is an important predictor of pregnancy outcomes. Women with higher parity are more likely to experience premature delivery, low birth weight, and other complications during pregnancy.¹⁷ However, in the present study, the results did not show a significant difference in parity between the two groups of women. This suggests that other factors, such as maternal age, socioeconomic status, and prenatal care, may play a more important role in determining pregnancy outcomes.

In recent years, there has been an increasing trend towards having fewer children, which is reflected in the findings of the study of Cao, J et al.¹⁸ The majority of women in both groups had 1-3 children, which is consistent with the trend of declining parity rates in many countries. The reasons for this trend are multi-factorial and include factors such as the increasing cost of living, the increasing cost of education, and the increasing availability of effective contraception.^{13,6} The comparative findings of this study indicate that parity is not a significant predictor of pregnancy outcomes in premature contractions and control groups of women. While most of the women had parity 1-3 in both groups, the findings were statistically insignificant. This highlights the importance of considering other factors, such as maternal age, socioeconomic status, and prenatal care, when evaluating pregnancy outcomes. Further research is needed to fully understand the impact of parity on pregnancy outcomes.

In this study average serum albumin level was decreased in contraction group 3.30 ± 0.43 g/dl

compared to the control group 3.42 ± 0.54 g/dl, without significant difference ($p = 0.089$). Serum albumin is an important protein that acts as a major contributor to maintaining the overall fluid balance and colloid osmotic pressure in the human body. A decreased serum albumin level can have serious implications for the overall health of an individual, especially for premature contractions. In the present study, the average serum albumin level was found to be decreased in the premature contractions group (3.30 ± 0.43 g/dl) compared to the control group (3.42 ± 0.54 g/dl) with a p -value of 0.089.

This finding has several implications for the health of premature contractions and requires further investigation. Albumin is a protein produced by the liver that serves as a marker of nutritional status. It is an important protein in maintaining the balance of fluids in the body, as it helps to regulate the distribution of fluids between the blood and tissues. However, it is thought that low albumin levels may be indicative of poor maternal nutrition, which could lead to a weakened cervical structure and increased uterine contractions. It is suggested that there is a potential link between albumin levels and PUC/preterm delivery, more research is needed to establish the clinical utility of albumin as a biomarker for predicting PUC and preterm delivery. Other factors, such as gestational age, maternal age, and medical history, can also impact the risk of PUC/preterm delivery, and it is important to consider these factors when interpreting albumin data. Furthermore, the use of albumin as a standalone biomarker for predicting preterm delivery may be limited, as low albumin levels can also be caused by a wide range of factors, such as liver disease, kidney disease, and malnutrition. Therefore, a comprehensive approach that incorporates multiple biomarkers and clinical factors may be necessary for accurate prediction of preterm delivery. On suspected mechanism like low serum albumin levels can lead to fluid accumulation in the body, which can increase the risk of infections and other health problems. Additionally, low serum albumin levels can also lead to decreased oxygen delivery to the body's tissues, which can further compromise the premature contractions. The present study found that the average serum albumin level was decreased in the premature contractions group compared to the control group. This finding has several implications for the health of premature contractions and requires further investigation. By understanding the causes of decreased serum albumin levels in premature contractions, it will be

possible to develop effective interventions to improve their overall health and wellbeing.

In this study average CRP level was significantly increased in contraction group 4.94 ± 3.96 g/dl compared to the control group 2.10 ± 2.61 g/dl, with significant difference ($p < 0.001$). Consistently, few other studies have found that premature contractions have significantly higher CRP levels compared to term pregnancy.^{19,20} A meta-analysis of 10 studies conducted by Kim et al.²¹ found that the average CRP level in premature contraction group was 2.2 times higher than that in term pregnancy, with a significant difference ($p < 0.001$). The results of this study suggest that premature birth is associated with increased CRP levels, which may reflect an exaggerated acute phase response. This finding is in line with previous studies, which have reported elevated CRP levels in women with premature contractions and a possible association with long-term health outcomes. The elevated CRP levels may reflect an increased risk of inflammation and oxidative stress, which may contribute to the development of long-term complications, such as respiratory distress, infections, and developmental delay. Some studies have also suggested that CRP levels may be influenced by gestational age, birth weight, and type of delivery.^{22,23} It is important to monitor CRP levels in premature contraction as it may indicate the presence of an underlying infection and may help in early diagnosis and treatment. Therefore, it is crucial for health professionals to understand the significance of elevated CRP levels in premature contraction and to monitor their CRP levels closely to prevent adverse health outcomes. The recent study showed that CRP level was significantly higher in premature contractions group (4.94 ± 3.96 g/dl) compared to the control group (2.10 ± 2.61 g/dl), with a significant difference ($p < 0.001$).

This finding is supported by several studies conducted in 2020.^{19,24} The exact cause of elevated CRP levels in premature contraction is not yet known, but it is thought to be related to the immaturity of their immune system and the increased risk of infection.^{13,7} Further research is needed to understand the underlying mechanisms of the exaggerated acute phase response in premature contractions and to develop effective strategies for preventing and treating the associated complications.

Conclusion

Based on the study's conclusion, the CRP/albumin ratio was found to be higher among cases of premature uterine contractions compared to those without such

contractions. This suggests that an elevated CRP/albumin ratio could potentially serve as a predictor of premature birth, particularly in cases of premature contractions. The association between elevated CRP levels and premature contractions suggests that inflammation might contribute to the onset of premature labor.

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