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ORIGINAL ARTICLE

Maternal Serum Concentration of IL-22 in Pregnancy Complicated by Preterm Premature Rupture of Membrane

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ABSTRACT

Intra-amniotic inflammation is a major contributor to preterm labor and premature birth. While few studies have explored the role of maternal serum interleukin-22 (IL-22) in preterm premature rupture of membranes (PPROM), its precise value in diagnosis and prediction remains unclear. This study aimed to evaluate maternal serum IL-22 levels in women with PPROM compared to those with intact membranes and to assess their association with pregnancy outcomes. This case-control study was conducted at Al-Diwaniyah Maternity and Pediatric Teaching Hospital, Iraq, from February to December 2024. It included 60 pregnant women (24–34 weeks of gestation): 30 with PPROM and 30 healthy pregnant controls with intact membranes. Positive C-reactive protein (CRP) was more frequent in the PPROM group (30.0% vs 16.7%), but the difference was not statistically significant (p=0.222). Maternal serum IL-22 levels were significantly higher in the PPROM group (p<0.001). At a cutoff value >200 pg/ml, IL-22 demonstrated excellent diagnostic performance with 96.7% sensitivity, 96.7% specificity, 96.7% positive predictive value, 96.7% negative predictive value, and 96.7% accuracy. The rate of clinical chorioamnionitis was significantly higher in the PPROM group (p=0.002). APGAR scores at 1 and 5 minutes were significantly lower in the PPROM group (p<0.001). The study concluded that Maternal serum IL-22 is a highly accurate biomarker for confirming PPROM. While CRP showed limited predictive value, PPROM remains a significant risk factor for chorioamnionitis and adverse neonatal outcomes. WBC and platelet counts may serve as additional supportive markers.

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1- INTRODUCTION

Preterm premature rupture of membranes (PPROM) is a major cause of preterm delivery. Approximately 50% of women with PPROM deliver within one week, 75% within two weeks, and 85% within one month [1]. Preterm birth is defined as delivery before 37 completed weeks of gestation [2, 3]. While the mortality rate of infants born after 32 weeks is similar to that of term infants [4], the risk of neonatal death or survival with major disability rises substantially in very preterm infants (28–32 weeks) and is highest in extremely preterm infants (<28 weeks) [5]. Preterm labor is not a single disease but a complex syndrome resulting from multiple underlying etiologies [1].

Despite its clinical importance, data on maternal morbidity associated with early preterm delivery remain limited, and this area has been highlighted as a priority for further research [6]. There is a strong association between preterm birth and a wide range of adverse neurodevelopmental sequelae, including cognitive and motor impairments, cerebral palsy (CP), visual impairment and hearing impairments, and long-term behavioral and psychiatric disorders such as anxiety and depression, autism spectrum disorder (ASD), and attention deficit hyperactivity disorder (ADHD) [7]. Infection and inflammation are critical elements in the development of preterm labor and preterm premature rupture of membranes (PPROM) due to microbial invasion of the amniotic cavity and an associated inflammatory response (increased expression of TLR4, TNF-α, IL-1, IL-6) in the amniotic fluid. This sequence of events results in leukocyte influx, cell death, weakening of the membranes, cervical ripening, and ultimately preterm labor. Because cytokine production is genetically determined, maternal genetic polymorphisms have previously been studied in detail to identify risk factors for preterm delivery [8]. Interleukin-22 (IL-22) is a multitalented cytokine with functional roles in mediating inflammation, and whether IL-22 acts as pro-inflammatory or anti-inflammatory is contingent on the specific situation in which it is acting [9,10].

In pregnancy, IL-22 appears to have a bifunctional role in maternal–fetal immune interactions. On one hand, excessive IL-22 may directly damage fetal tissues and contribute to neonatal morbidity or mortality. On the other hand, it may contribute to host defense against microbial invasion of the amniotic cavity [10]. Although a few studies have examined the relationship between maternal serum IL-22 levels and PPROM [11], the exact role of IL-22 in predicting, progressing, and managing PPROM remains unclear and controversial. The study aimed to evaluate maternal serum IL-22 levels in women with PPROM compared to women with intact membranes and to assess the association of these levels with pregnancy outcomes.

2- MATERIALS AND METHODS

This case-control study was conducted at the Department of Obstetrics and Gynecology and the Emergency Department of Al-Diwaniyah Maternity and Pediatric Teaching Hospital in Iraq over the time period of 10 months (February - December 2024). Sixty women aged 18 - 40 years old with a gestational age of 24 - 34 weeks were included. The subjects were divided into two equal groups of 30 women for the preterm premature rupture of membranes (PPROM group) and 30 healthy women who had intact membranes (control group). The study protocol was reviewed and approved by the Iraqi Board for Medical Specialization and the Ethical Committee of the Teaching Hospital. Written informed consent was obtained from all participants prior to enrollment in this study.

2.1 Inclusion criteria

The study will enroll a specific, homogeneous population of pregnant individuals so that comparisons remain reliable and valid. Participants must be 18 to 40 years old and have a singleton pregnancy with a confirmed gestational age of 24 to 34 weeks. Those in the study group must have a diagnosis of preterm prelabor rupture of membranes (PPROM). The control group will include women matched by age and gestational age who do not have PPROM, allowing the effects of the condition to be examined directly.

2.2 Exclusion criteria

Exclusion criteria were chronic medical disorders, including hypertension, diabetes mellitus, or epilepsy; acute infectious or inflammatory conditions; autoimmune or other immune-mediated disorders, such as inflammatory bowel disease or rheumatoid arthritis, that could affect the inflammatory markers measured (CRP or IL-22); a body mass index (BMI) above 25 kg/m²; and refusal to participate.

2.3 Data collection

Data were collected on maternal age, parity, height, weight, and gestational age. PPROM was confirmed in the labor room through a sterile Cusco speculum examination showing amniotic fluid pooling in the posterior vaginal fornix. The examination also assessed cervical dilatation and possible cord prolapse. Clinical signs of chorioamnionitis were documented as well: maternal fever, uterine fundal tenderness, maternal tachycardia (>100 beats/min), fetal tachycardia (>160 beats/min), and foul-smelling or purulent amniotic fluid.

2.4 Laboratory investigations

All participants received laboratory testing that included a complete blood count (CBC), with white blood cell (WBC) count and hemoglobin level; random blood sugar (RBS); serum interleukin-22 (IL-22), measured by enzyme-linked immunosorbent assay (ELISA) with a commercial kit (Invitrogen/Thermo Fisher Scientific, UK; detection range 15.6–1000 pg/mL); and C-reactive protein (CRP), also measured by ELISA and reported as positive or negative.

2.5 Outcome measures

This study examined outcomes for both mothers and their fetuses or neonates. Maternal assessment included gestational age at delivery, preterm delivery, and the development of clinical chorioamnionitis; neonatal assessment was based on Apgar scores at 1 and 5 minutes after birth.

Statistical analysis

Data were processed in Microsoft Excel 2010 and analyzed in IBM SPSS (Version 26). The quantitative variables have been displayed using mean ± SD, or as a range, and the qualitative variables have been shown in terms of number and percentage. The independent samples t-test was used to compare group differences between the two samples for means. The chi-square test was used to check for associations between categorical variables. Receiver operating characteristic (ROC) curve analysis was used to determine the optimal cutoff value of serum IL-22. A p-value ≤ 0.05 was considered statistically significant.

3- RESULTS AND DISCUSSION

The mean age of women in the PPROM group was 26.80 ± 5.76 years (range 18–37), which was significantly lower than that of the control group (30.03 ± 6.08 years, range 19–40; p = 0.039). There was no significant difference in body mass index (BMI) between the two groups (22.07 ± 2.05 kg/m² vs 22.40 ± 1.75 kg/m²; p = 0.501). Parity was also comparable between groups (median 3 in both groups; p = 0.684). Gestational age at enrollment did not differ significantly between the PPROM and control groups (29.0 ± 3.16 weeks vs 28.7 ± 2.84 weeks; p = 0.701) (Table 1).

Table (1): Demographic characteristics of the study participants

Characteristic	PPROM group (n=30)	Control group (n=30)	P-value
Age (years)			
Mean ± SD	26.80 ± 5.76	30.03 ± 6.08	0.039*
Range	18–37	19–40	
BMI (kg/m²)			
Mean ± SD	22.07 ± 2.05	22.40 ± 1.75	0.501
Range	19–25	20–25	
Parity			
Median (IQR)	3 (3)	3 (2)	0.684
Range	0–5	1–5	
GA at enrollment (weeks)			
Mean ± SD	29.0 ± 3.16	28.7 ± 2.84	0.701
Range	24–34	24–34	

BMI: body mass index; GA: gestational age; SD: standard deviation; IQR: interquartile range; *p ≤ 0.05 (significant)

Laboratory findings are presented in Table 2. The mean white blood cell (WBC) count was significantly higher in the PPROM group compared with the control group (14.15 ± 3.09 × 10³/µL vs 12.32 ± 2.19 × 10³/µL; p = 0.011). Platelet count was also significantly elevated in the PPROM group (253.07 ± 36.26 × 10³/µL vs 178.00 ± 11.11 × 10³/µL; p < 0.001). There was no significant difference in hemoglobin level between the groups (p = 0.813).

Table (2): Comparison of hematological parameters between the PPROM and control groups

Characteristic	PPROM group (n=30)	Control group (n=30)	P-value
WBC (×10³/µL)	14.15 ± 3.09	12.32 ± 2.19	0.011*
Range	10–19.4	10.1–19	
Hemoglobin (g/dL)	11.45 ± 0.41	11.42 ± 0.35	0.813
Range	10.8–12.2	10.9–12	
Platelet (×10³/µL)	253.07 ± 36.26	178.00 ± 11.11	<0.001***
Range	195–300	163–200	

WBC: white blood cell; SD: standard deviation; *p ≤ 0.05; ***p ≤ 0.001

Inflammatory markers are shown in Table 3. Positive C-reactive protein (CRP) was detected in 9 (30.0%) women in the PPROM group and 5 (16.7%) in the control group, but the difference was not statistically significant (p = 0.222). Serum IL-22 levels were markedly higher in the PPROM group than in the control group (449.00 ± 156.96 pg/mL vs 151.33 ± 33.09 pg/mL; p < 0.001).

Table (3): Comparison of inflammatory markers between the PPROM and control groups

Characteristic	PPROM group (n=30)	Control group (n=30)	P-value
CRP			0.222
Positive, n (%)	9 (30.0)	5 (16.7)	
Negative, n (%)	21 (70.0)	25 (83.3)	
IL-22 (pg/mL)	449.00 ± 156.96	151.33 ± 33.09	<0.001***
Range	200–710	100–250	

CRP: C-reactive protein; IL-22: interleukin-22; SD: standard deviation; ***p ≤ 0.001

Receiver operating characteristic (ROC) curve analysis demonstrated excellent diagnostic performance of serum IL-22 for identifying PPROM (Figure 1). At a cutoff value of >200 pg/mL, the area under the curve (AUC) was 0.997 (p < 0.001), with sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and overall accuracy all reaching 96.7% (Youden index = 0.933) (Table 4).

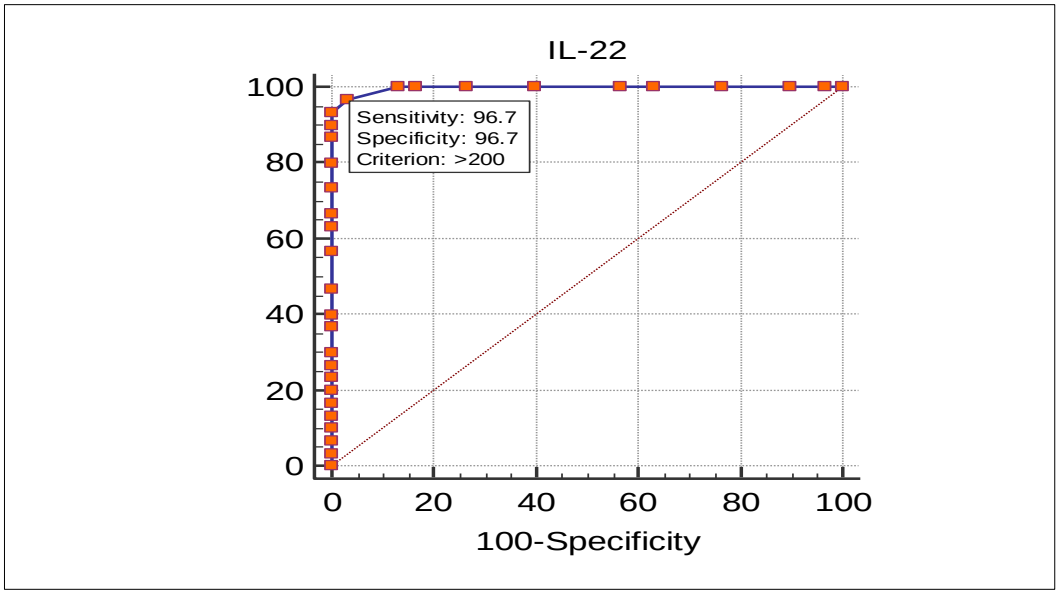

Fig (1): Receiver operating characteristic (ROC) curve analysis describing the sensitivity and specificity of the IL-22 cutoff value predicting a diagnosis of PPROM

Table (4): ROC curve analysis for serum IL-22 in predicting PPROM

Characteristic	IL-22
Cutoff value	> 200 pg/mL
AUC	0.997
95% CI	0.934–1.000
p-value	<0.001***
Sensitivity (%)	96.7
Specificity (%)	96.7
PPV (%)	96.7
NPV (%)	96.7
Accuracy (%)	96.7
Youden index (J)	0.933

Maternal outcomes are summarized in Table 5. All women in the PPROM group delivered preterm (100%), compared with only 2 (6.7%) in the control group ($p < 0.001$). Mean gestational age at delivery was significantly lower in the PPROM group (29.29 ± 3.12 weeks vs 38.07 ± 1.74 weeks; $p < 0.001$). Clinical chorioamnionitis occurred in 8 (26.7%) women in the PPROM group and in none of the controls ($p = 0.002$). The mean latency period in the PPROM group was 2 ± 1.8 days (range 0–7 days).

Table (5): Comparison of maternal outcomes between the PPROM and control groups

Characteristic	PPROM group (n=30)	Control group (n=30)	P-value
Latency period (days)	2.0 ± 1.8	—	—
Range	0–7	—	
GA at delivery (weeks)	29.29 ± 3.12	38.07 ± 1.74	<0.001***
Range	24–34.29	33–40	
Preterm delivery			<0.001***
Yes, n (%)	30 (100.0)	2 (6.7)	
No, n (%)	0 (0.0)	28 (93.3)	
Chorioamnionitis			0.002**
Yes, n (%)	8 (26.7)	0 (0.0)	
No, n (%)	22 (73.3)	30 (100.0)	

Fetal outcomes are shown in Table 6. Apgar scores at both 1 minute and 5 minutes were significantly lower in the PPROM group compared with the control group ($p < 0.001$ for both).

Table (6): Comparison of neonatal outcomes between the PPROM and control groups

Characteristic	PPROM group (n=30)	Control group (n=30)	P-value
Apgar score at 1 min	2.83 ± 0.79	7.13 ± 1.28	<0.001***
Range	1–4	4–9	
Apgar score at 5 min	5.27 ± 1.17	8.23 ± 1.07	<0.001***
Range	3–7	5–9	

In the present study, women in the PPROM group were significantly younger than those in the control group (mean age 26.80 ± 5.76 years vs 30.03 ± 6.08 years; $p = 0.039$). This finding contrasts with several reports suggesting that advanced maternal age (≥30 or ≥40 years) increases the risk of PPROM and preterm birth, even after adjusting for confounders [12, 14]. In a study of mid-trimester PPROM, the mean maternal age for women has been reported to be 32±5.98 years [13], which is older than that of women in our cohort. However, other studies suggest that there may be a non-linear relationship between maternal age and PPROM, with higher rates of PPROM seen in younger women (20-29 years) in certain populations. These discrepancies may be explained by differences in study design, population characteristics, and confounding variables such as socioeconomic status and parity. There were no statistically significant differences in either mean BMI or parity between the two groups. While large cohort studies have shown an association of pre-pregnancy overweight/obesity with an increased probability of developing PPROM [15, 16], other studies report contradictory results or a protective association of increased BMI [17, 18].

Similarly, Parity has produced conflicting results regarding PPROM risk; there is some evidence that multiparous women experience higher rates of PPROM due to possible changes to uterine vascularization [19]; however, many studies, including the current study, did not find a relationship. In our study, both groups of women were enrolled in our study at similar gestational ages, which is relevant considering that later gestational age at PPROM is associated with better neonatal outcomes and fewer complications, with no proportional increase in risk of neonatal sepsis [20].

Hematology results demonstrated that the PPROM group had higher WBC and platelet counts when compared to their counterparts, while hemoglobin concentrations between groups did not differ significantly. The elevated platelet count in our PPROM group is similar to previous studies that have documented increased platelet counts in PPROM and spontaneous preterm labor [21]. During periods of inflammatory processes, the number of circulating platelets increases, and these activated platelets migrate to sites of active infection/inflammation and release pro-inflammatory mediators. While WBC are reported routinely as a part of the management of women with PPROM, the diagnostic utility of WBC in diagnosing intra-amniotic infection or chorioamnionitis is limited due to the extremely wide physiological variability of WBC throughout normal gestation [23] and also due to their poor

predictive ability for diagnosing chorioamnionitis via histology or clinically [22]. Anemia in pregnant women is more common and occurs much more frequently in mothers with multiple pregnancies; the anemia itself may lead to a weakened immune response and increased risk for developing infections [24].

Regarding inflammatory markers, the proportion of positive CRP results was higher in the PPROM group (30.0% vs 16.7%), but the difference did not reach statistical significance. In contrast, serum IL-22 levels were markedly elevated in the PPROM group (449.00 ± 156.96 pg/mL vs 151.33 ± 33.09 pg/mL; $p < 0.001$). ROC curve analysis demonstrated excellent discriminatory ability for serum IL-22, with a cutoff value >200 pg/mL yielding an AUC of 0.997 ($p < 0.001$), sensitivity, specificity, PPV, NPV, and accuracy all at 96.7%. The findings of this study are similar to those of Behram et al. (2021), who also found that maternal serum IL-22 levels were significantly higher in mothers with PPROM, but their optimal cutoff was much lower (23.86 pg/mL) and had a modest sensitivity (72%) and specificity (61.5%) [25]. The differences between the cutoff points could be attributed to assay kit differences, variations in study population characteristics, or differences in gestational age at the time of sampling. The pathogenesis of PPROM is largely attributed to inflammation/oxidative stress; specifically, these factors weaken fetal membranes via collagen breakdown and extracellular matrix remodeling [26]. In addition, inflammatory cytokines such as IL-1, IL-6, IL-22, and TNF-α contribute to this process by being produced locally (within the feto-maternal unit) and systemically [27]. Although analysis of cytokines within the amniotic fluid provides direct information, performing amniocentesis can be technically difficult due to oligohydramnios and is an invasive procedure [31]. Instead, measuring these cytokines in maternal serum represents a simpler, non-invasive method; therefore, this type of analysis has significant advantages, particularly in developing countries with limited access to advanced diagnostic procedures. Maternal outcomes for the PPROM group demonstrated significantly worse results. One-hundred percent of women delivered preterm compared to 6.7% of subjects in the control group ($p < 0.001$). The mean gestational age at delivery was significantly lower for the PPROM group (29.29 ± 3.12 weeks vs. 38.07 ± 1.74 weeks) ($p < 0.001$). Clinical chorioamnionitis occurred in 26.7% of the cases in the PPROM group compared to 0% in the control group ($p = 0.002$). The mean latency period was short (2.0 ± 1.8 days). Consistent with our findings, previous studies have demonstrated that median latency after PPROM remains relatively constant between 24–28 weeks but decreases markedly at and beyond 29 weeks [32]. PPROM continues to be one of the leading causes of morbidity and mortality related to preterm birth due to ascending infections and chorioamnionitis, which may trigger fetal inflammatory response syndrome and increase the risk of cerebral palsy, sepsis, and other complications in neonates [33, 34]. Additionally, neonatal outcomes in the PPROM group were poor, with lower mean Apgar scores ($p < 0.001$) at both one and 5 minutes. This supports previous studies associating PPROM with poor neonatal conditions at birth and an increase in severe adverse outcomes when 5-minute Apgar scores are low [35, 36].

Overall, the current study supports the possibility of using maternal serum IL-22 as an alternative means of testing for PPROM. Larger, multicenter studies should be conducted to validate these findings across diverse populations and to elucidate the exact mechanisms that link IL-22 with membrane rupture and preterm labor. The study has several limitations. First, it was conducted at a single center with a relatively small sample size (n=60), which may limit the generalizability of the findings to broader populations. Second, the case-control design of the study does not allow for the establishment of causality or temporal relationships between IL-22 levels and the development of PPROM. Finally, long-term neonatal neurodevelopmental outcomes were not evaluated due to the short follow-up period.

4- CONCLUSION

This case-control study showed that maternal serum IL-22 levels were significantly higher in women with PPROM than in those with intact membranes. The sensitivity, specificity, positive predictive value, negative predictive value, and overall accuracy of IL-22 to identify women with PPROM were all equal to 96.7% (cutoff >200 pg/mL; AUC 0.997). Women with PPROM had higher white blood cell counts and platelet counts, shorter durations of latency, an earlier time to delivery, greater frequencies of clinical chorioamnionitis, and significantly lower Apgar scores at 1 and 5 minutes. These findings support the hypothesis that maternal serum IL-22 is a useful non-invasive biomarker for PPROM. The study demonstrates further that systemic inflammation may play a role in the pathophysiology of PPROM and suggest that serum-based testing can be beneficial in clinical practice, particularly in resource-limited areas where amniotic fluid sampling is not possible.

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