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# The Role of Serum Amyloid A in Predicting Short Term Preterm Labor

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Preterm labor
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**ABSTRACT**

Background: preterm labour ( PL) is a major contributor to prenatal morbidity and mortality, defined by birth before completed 37 weeks of pregnancy. Not all cases with threatened PL end with labor; the reason is unclear. Many accredited infections as a cause for PL. We hypothesized that serum amyloid A (SAA), an acute-phase inflammatory reactant, may be used in predicting cases that proceed rapid PL. Material and methods: A prospective case-control study recruited 70 participants from the gynecology department of our University Hospital. All presented with threatened PL with intact membrane; in gestational age of 28-36 weeks of a singleton viable cephalic pregnancy. Detailed history and physical examination were made, and venous blood samples were aspirated and divided into two parts for CRP assessment and SAA estimation by ELIZA Kit. Patients were followed 31/70 delivered in 1 week times assigned as the study group, and the rest 39/70 were discharged home and continued pregnancy assigned as healthy controls. Results: Maternal serum SAA, CRP, and Gestational age were strongly significant as P<0.001. Significantly High serum SAA in the cases versus healthy controls. The ROC defines the SAA cutoff value by 27.2, AUC 0.92, P<0.001. Conclusion: SAA strongly correlated with gestational age r =0.52, with 90% sensitivity and specificity implying a reliable predictor for short-term PL. It outstands CRP in performance. An accurate test for the prediction of preterm labor is an urgent necessity. It allows vigorous monitoring and implementation of preventive measures aimed to improve neonatal outcomes.

## دورمصل أميلويد أ في التنبؤ بالمخاض المبكرعلى المدى القصير

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**الكلمات المفتاحية:**
المخاض المبكر
التنبؤ
أميلويد المصل A
البروتين التفاعلي C

**الملخص**

الخلفية: المخاض المبكر (PL) هو مساهم رئيسي في المراضة والوفيات السابقة للولادة ، والتي يتم تعريفها بالولادة قبل إكمال 37 أسبوعا من الحمل. ليست كل الحالات التي تتعرض للتهديد PL تنتهي بالعمل. السبب غير واضح. العديد من الإصابات المعتمدة كسبب ل PL. افترضنا أن مصل أميلويد A (SAA) ، وهو متفاعل التهابي حاد الطور ، يمكن استخدامه في التنبؤ بالحالات التي تستمر بسرعة PL. المواد والأساليب: قامت دراسة مستقبلية لمراقبة الحالة بتوظيف 70 مشاركا من قسم أمراض النساء في مستشفى Univesity الخاص بنا. جميع المقدمة مع PL مهددة مع غشاء سليم ؛ في عمر الحمل من 28-36 أسبوعا من الحمل الرأسي القابل للحياة المفردة. تم إجراء التاريخ المشوه والفحص البدني ، وتم شفط عينات الدم الوريدية مقسمة إلى قسمين لتقييم CRP وتقدير SAA بواسطة ELIZA Kit. تمت متابعة المرضى 70/31 الذين تم تسليمهم في أوقات أسبوع واحدة تم تعيينها كمجموعة دراسة ، وتم إخراج الباقين 70/39 إلى المنزل ومواصلة الحمل المعين كضوابط صحية. النتائج: كان مصل الأم SAA و CRP وعمر الحمل معنويا بقوة حيث P<0.001. ارتفاع كبير في المصل SAA في الحالات مقابل الضوابط الصحية. تحدد ROC قيمة القطع SAA بنسبة 27.2 ، AUC 0.92 ، P<0.001. الاستنتاج: ارتبطت SAA ارتباطا وثيقا بعمر الحمل r = 0.52 ، مع حساسية وخصوصية 90٪ مما

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يعني وجود مؤشر موثوق به على المدى القصير PL. إنه يتفوق على CRP في الأداء. يعد الاختبار الدقيق للتنبؤ بالمخاض المبكر ضرورة ملحة. وهو يسمح بالرصد القوي وتنفيذ التدابير الوقائية الرامية إلى تحسين نتائج المواليد الجدد.

**Introduction**

Preterm labor (PL) is a significant cause of prenatal morbidity and mortality, with an estimated global incidence of 10%, defined as delivery before completed 37 weeks of pregnancy [1]. Prediction of PL based on the clinical background was poor since 50 % of women who suffer from premature uterine contractions, and other preterm labor symptoms will proceed till the term [2]. Therefore, an urgent need was raised for a reliable prediction module for women most likely to proceed to PL [3]. Such modules will improve obstetrical service outcomes by arranging for in utero fetal transfer, administering corticosteroids, and developing appropriate preventive and possibly therapeutic measures [4]. Nonetheless, no consensus was reached on one approach; the prediction of threatened PL women remains challenging. The quest to enhance our understanding of PL's pathophysiological cause was stratified into three main categories: The prediction based on risk factors, Ultrasonic parameters, and various biochemical indicators. They were used to assess the primary inflammatory response expected to be rising among the high group [5,6].

Intrauterine infection accompanied PL and early membrane rupture with substantial evidence indicating a causal relationship; many pieces of the literature confirmed elevations of many cytokines and inflammatory markers in those patients' serum and amniotic fluid. Such as C-reactive protein, neutrophil to lymphocyte ratio, interleukins -6, and inflammatory cytokines [7-9]. Serum Amyloid A is a member of serum lipoprotein secreted by the liver, some tumor cells, and placental cytotrophoblast. Its serum level increases as a part of the primary inflammatory response once monocytes and macrophages are triggered. SAA's primary action is immunomodulation; it suppresses lymphocyte proliferation and inhibits neutrophils and monocyte aggregation [10].

This study aimed to verify if SAA may predict short onset PL in patients with threatened PL by evaluating serum SAA levels along with other inflammatory markers.

**Patient and methods**

This prospective case study enrolled 70 pregnant women at the University Teaching Hospital from June 2020 for one year in the gestational age of 26–36 +6 weeks confirmed by early dating scan and LMP dating presented at the Department of Obstetrics and Gynecology of our University Hospital with threatened preterm labor. The scientific committee in the gynecology/Obstetrics department of the University Hospital approved the study (MOG 182). Participants gave their informed consent. Detailed medical, obstetrical history, and examination were taken; we included a case with threatened PL confirmed by uterine contraction in 10 minutes. Cases should not have been associated with cervical changes nor water breaks. All fetuses were singleton, viable, cephalic in presentation, and free of congenital malformation. An exclusion was made for participants with a history of previous PL, evidence of overt infection, and associated medical co-morbidity DM, preeclampsia, thyroid diseases. Twin pregnancy, fetal growth restriction, and congenitally abnormal fetuses were excluded too. All participants have five ccs of venous blood aspirated before any intervention take place, and the blood was divided into two parts; the first for CRP estimation and the second for SAA estimation via ELIZA kit

The study participants receive the standard care for PL cases, including IV fluids, bed rest, screening for infection and corticosteroid administration, and tocolytics.

Upon following the participants, 31/70 preceded into PL in 1 week time ( assigned as the study cases ); the pediatrician examined the neonates, and birth weight was checked.

The rest of the participants, 39/70, continued pregnancy till term ( assigned as a control group) and were discharged home.

Patient information was recorded regarding demographic, reproductive, laboratory, and ultrasonographic data and were stored on an excel sheet for later analysis.

**Statistics**

The data normality was checked by the Shapiro Wilkinson test. Continuous data were expressed as means and standard deviations. We compared the study versus the control group, basic demographic criteria by the Unpaired T-test. Correlation strength was assessed by the regression equation between SAA versus CRP. The ROC curve calculated the SAA cutoff value associated with the best sensitivity and specificity. Finally, we compared both ROC curves for both markers through AUC, SE a, and 95% CI b. The level of significance was set at $P < 0.05$ for all tests.

**Results**

This prospective study enrolled 70 pregnant women threatened PL diagnosis. 31/70 cases preceded into PL taken as the study group, and 39/70 cases continue till term taken as controls. The demographic criteria of the two groups were summarized in Table 1. Neither maternal age, gravidae, and parity scored significantly as $P > 0.05$.

SAA, CRP, and gestational age showed statistical significant as P value <0.05.

The strength of association between SAA versus gestational age was tested by linear correlation, highlighting a significant positive association as ( r)= 0.5, P-value <0.001 illustrated in Figure 1.

The ROC calculated the SAA cutoff value as > 27.7 micrograms/ml with 90%,90 % sensitivity, and specificity.AUC 0.92, P-value <0.001 demonstrated in Figure 2. and Table 3.

Finally, we compared the cutoff values for the SAA and CRP as a predictor for short term PL. Though SAA scored higher by AUC, the difference was statistically non-significant; shown in Table 3.

**Discussion**

The principal objective of this prospective research was to see if maternal serum SAA levels are beneficial in the detection and management of threatened PL.

The analysis showed that pregnant with high SAA, CRP, and Gestational age of more than 31 weeks are more liable to proceed into PL. Furthermore, the association between SAA versus gestational age proved to be statistically meaningful as $p<0.001$ with a strong correlation coefficient (0.52). None of the maternal demographic criteria showed statistical value regarding maternal age, parity, and gestational age in line with earlier studies [11].

Although the precise causes and characteristics of preterm labour's onset pregnancies remain a mystery, mounting evidence suggests that inflammatory reactions and ascending genital infections are critical factors in PL pathogenesis [12].

Once invading pathogen gets access to the intrauterine cavity, the decidual macrophages produce a wide variety of cytokines to combat microbial attack. When cytokines get access to maternal circulation, they cause leukocytosis and/or CRP production [13]. Past evidence confirmed that CRP has higher sensitivity than fever, leukocytosis, or fetal tachycardia in setting subclinical infection [14]. Based on that evidence, many inflammatory markers and cytokines were investigated as a possible predictors of preterm delivery and subclinical infection[15].

Cekmez et al. investigated the role of serum SAA and pro adrenomedullin in PPROM and fetomaternal morbidities. They recruited 43 pregnant women with PPROM at a gestational age of 24 - 34 weeks subdivided into two subgroups PPROM and PPROM-histological chorioamnionitis. Cekmez et al. compared them to 20 pregnant women taken as matched healthy controls. The authors discussed that both markers under study showed

better sensitivity and specificity than CRP and white blood cell count. Furthermore, their SAA cutoff value was 69 µg/mL; discriminated cases with histological chorioamnionitis showed no clinical signs. The author recommended its usage as a reliable marker [16].

Kayabaş h et al. discussed the value of SAA in predicting preterm premature rupture of

membrane and chorioamnionitis in high-risk groups. They enrolled 20 pregnant at 26-37 weeks of gestation with confirmed preterm premature rupture of membrane versus 20 pregnant women with intact membranes. SAA values in cord blood and blood of pregnant women with PPROM were significantly higher than in the healthy controls ($p<0,05$). Moreover, the values in confirmed clinical chorioamnionitis cases were meaningfully higher than both preterm premature rupture of membrane patients without chorioamnionitis and healthy controls [17]. Therefore, the author recommended SAA in women with PPROM as a precursor parameter for chorioamnionitis that preceded the onset of clinical signs in high suspicious patients treated conservatively.

CRP is used to diagnose chorioamnionitis in the literature. The rise in CRP and SAA concentrations were synchronous in the current research. Although the analysis showed that SAA performance as a predictor marker was higher, still it fails to have statistical values over CRP.

The simple, affordable readily available CRP have some drawback since it levels stay normal in viral infections, while SAA levels rise in both viral and bacterial infections[18].

Thus we recommend SAA as a better marker in identifying and following up on cases with threatened PL. Further studies are recommended to verify the possible therapeutic application of SAA.

**Conclusion**

This study revealed that elevated SAA levels in the blood of pregnant women as an acute phase reactant might be a valuable tool to obstetricians in defining women at a higher rate of giving birth prematurely. A point of utmost importance in management and follow up. Earlier diagnosis allows intervention and preventive strategies to decrease neonatal morbidity and mortality.

**Abbreviations and Acronyms**

PL= preterm labour
SAA= serum amyloid A (SAA)
CRP=C-reactive protein

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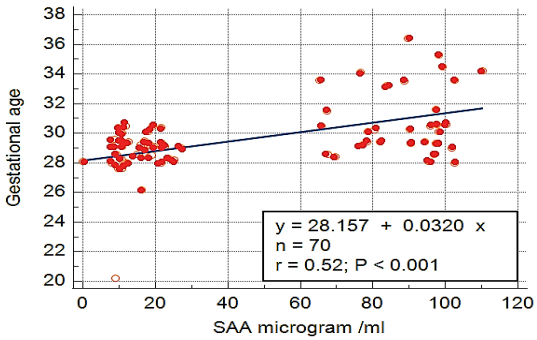


**Fig. 1:** Highlighting the correlation between serum amyloid A as an independent variable versus gestational age as a dependent variable

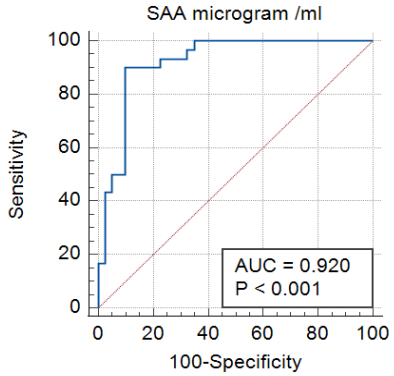


**Fig. 2:** Illustrating the SAA cutoff values associated with the highest sensitivity and specificity.

**Table 1: Titel Showing the essential demographic criteria of the study participants.**

| Parameters | Study group, N=31 Mean ±SD | Control group, N=39 Mean ±SD | P-value |
|---|---|---|---|
| Maternal age ( years) | 28.0±4.9 | 28.6±5.7 | P = 0.38 |
| Gravida | 2.3±0.8 | 2.0±0.9 | P = 0.69 |
| Parity | 1.3 ± 0.89 | 1.06 ± 0.85 | P = 0.8 |
| SAA microgram /ml | 88.36± 12.68 | 15.24± 5.78 | P < 0.001* |
| CRP mg/L | 7.56 ± 0.68 | 1.17 ± 1.1 | P = 0.003* |
| Gestational_age (weeks) | 31.0 ± 2.3 | 28.6 ±1.66 | P = 0.048* |

**Table 2: Criterion values and coordinates of the ROC curve for maternal SAA.**

| Criterion | Sensitivity | 95% CI | Specificity | 95% CI | +LR | -LR |
|---|---|---|---|---|---|---|
| >18.1 | 100.00 | 88.4 - 100.0 | 65.00 | 48.3 - 79.4 | 2.86 | 0.00 |
| >18.3 | 96.67 | 82.8 - 99.9 | 65.00 | 48.3 - 79.4 | 2.76 | 0.051 |
| >18.6 | 96.67 | 82.8 - 99.9 | 67.50 | 50.9 - 81.4 | 2.97 | 0.049 |
| >19.1 | 93.33 | 77.9 - 99.2 | 67.50 | 50.9 - 81.4 | 2.87 | 0.099 |
| >21.68 | 93.33 | 77.9 - 99.2 | 77.50 | 61.5 - 89.2 | 4.15 | 0.086 |
| >21.7 | 90.00 | 73.5 - 97.9 | 77.50 | 61.5 - 89.2 | 4.00 | 0.13 |
| >27.2 | 90.00 | 73.5 - 97.9 | 90.00 | 76.3 - 97.2 | 9.00 | 0.11 |
| >83.82 | 50.00 | 31.3 - 68.7 | 90.00 | 76.3 - 97.2 | 5.00 | 0.56 |