RESEARCH ARTICLE

Increased serum amyloid A and C- Reactive Protein in preterm labour women: A case control study

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Abstract

Objective: To assess the possible relation between serum Amyloid A and pregnant women presenting with preterm births.

Method: The retrospective case-control study was conducted at Al-Yarmouk Teaching Hospital, Baghdad, Iraq, and comprised data from December 1, 2019, to December 1, 2020, of patients who presented with preterm labour with gestational age 28-37 weeks. Data of similar women with complication-free pregnancy was taken to raise the control group. Serum samples were taken from the subjects at admission before any intervention for the measurement of serum amyloid A, total white blood cells, C-reactive protein, and neutrophil-leukocytes ratio. Data was analysed using SPSS 25.

Results: Of the 100 subjects, 50(50%) were in each of the two groups that had no significant differences regarding age, gravida, parity, smoking, and neutrophil-leukocytes ratio ($p>0.05$). There were significant inter-group differences regarding serum amyloid A and C-reactive protein levels ($p<0.05$). The cut-off value for serum amyloid A level was 84.61ng/ml. There was a positive correlation between micro-C-reactive protein and serum amyloid A ($p<0.05$).

Conclusion: Maternal serum amyloid A level in the 2nd trimester may be a predictive marker for preterm labour.

Keywords: Serum amyloid A, C-reactive protein, Preterm labour. (JPMA 71: S-47 [Suppl. 9]; 2021)

Introduction

Preterm delivery is still one of the most troublesome obstetrical complications in pregnancy, and is a significant contributor to global neonatal morbidity and mortality, accounting for around 70% of neonatal deaths.[1] It is considered an obstetrical challenge, and several aspects make it an exciting subject for scientific research.[2,3] The World Health Organisation (WHO) defines preterm birth as a delivery between 24 weeks and 36 weeks + 6 days, and it complicates 7.7% pregnancies.[4] Several risk factors have been related to preterm birth, such as genitourinary tract infections, preterm premature rupture of membranes, previous preterm labour and multiple pregnancies.[5] The newborns delivered preterm can have several complications involving gastrointestinal tract (GIT) and the central nervous system (CNS), as well as acute respiratory and immunological problems, and long-term complications, like cognitive, motor, hearing, growth and health problems.[6]

Generally, there is an agreement that preterm labour is mediated by the pathological activation of a typical terminal pathway in term pregnancy at delivery.[7] There are four mechanisms involved in preterm delivery; amniochorionic-decidual tissue inflammation, activation of the hypothalamic-pituitary-adrenal axis with the maternal-foetal placental interaction, pathological distension of the myometrium, and decidual bleeding.[8,9] The pregnancy is considered an inflammatory state; the balance should be present concerning the anti-inflammatory factors for remodelling intrauterine tissue. There are sterile inflammation or infectious factors for preterm labour and preterm premature rupture of membrane, as the inflammation originates from the maternal or foetal tissue, depending on the exposure risk.[10] It accounts for 40% of cases, and the inflammatory mediators include proinflammatory cytokines, like interleukin 1A (IL1A), IL1B and IL6, and prostaglandin F 2 alpha ($PGF_{2\alpha}$).[11]

It is globally accepted that acute inflammation is responsible for a substantial fraction of preterm births, and serum amyloid A (SAA) is a powerful representative protein in the acute inflammatory phase as its plasma level rises to 500-1000-fold in this phase.[12] It has a family of proteins, and usually the liver is the organ responsible for its production, but SAA is a protein of a family produced by the macrophages in the inflammatory tissue extrahepatically.[13] Unfortunately, one of the main problems in preventing preterm labour is the difficulty in accurately identifying the pregnancy at risk of developing it.[14] The current study was planned to verify the role of

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SAA in predicting at-risk population for preterm labour in order to reduce associated morbidities and mortalities.

Materials and Methods

The retrospective case-control study was conducted at Al-Yarmouk Teaching Hospital, Baghdad, Iraq, and comprised data from December 1, 2019, to December 1, 2020. The study group consisted of patients presenting with preterm labour, while the control group comprised patients at term pregnancy without any complaint. The study was approved by the institutional ethics review committee.

Those included had singleton pregnancy with a gestational age of 28-37 completed weeks, with no co-morbidities or history of smoking.

Preterm labour was diagnosed, according to the guidelines of the American College of Obstetricians and Gynaecologists[15] as uterine contractions at least 4 per 10 minutes, >4cm cervical dilatation, 80% cervical effacement at gestational age 28-37 weeks.

Those excluded were pregnant women with one of these risk factors; antepartum haemorrhage; over-distended uterus (polyhydramnios, multiple pregnancies); uterine anomalies; foetal malformation; previous cervical surgery; confirmed intrauterine infection, like maternal fever, significant maternal tachycardia, uterine tenderness, cervical motion tenderness or purulent vaginal discharge.

After taking informed written consent, all pregnant women with preterm labour diagnosis were enrolled. Detailed history was taken, including gravida, parity, gestational age of the present pregnancy calculated from the last menstrual period or early ultrasound, contractions every 10 minutes or less, vaginal discharge (leaking liquor), vaginal bleeding, backache, abdominal cramps without diarrhoea, associated symptoms, like decreased foetal movement, regular contractions etc., co-morbidities, like diabetes mellitus, hypertension, thyroid disorders, surgical history, like previous caesarean section (CS) or cervical surgery, and smoking status.

Examination of all patients included blood pressure, pulse rate and temperature, followed by abdominal inspection for uterine contractions, foetal heart rate (FHR) assessment by cardiotocography (CTG), foetal presentation, and estimated foetal weight. Pelvic examination under complete aseptic conditions assessed cervical dilatation, effacement and membrane rupture to diagnose preterm labour. SAA was measured using enzyme-linked immunesorbent assay (ELISA) (Casabio). Total white blood cell (WBCs) count and C-reactive protein (CRP) were measured, followed by the assessment of neutrophil-leukocytes ratio (NLR).

Data was analysed using SPSS 25. Mean and standard deviations were assessed for continuous variables using Kolmogorov-Smirnov and Shapiro Wilk tests. The relation between continuous and categorical variables was estimated using chi-square and Mann Whitney U tests. The correlation of CRP, SAA and NLR was evaluated using Pearson correlation. $P<0.05$ was considered statistically significant.

Results

Of the 100 subjects, 50(50%) were in each of the two groups that had no significant differences regarding age, gravida, parity, smoking, and NLR ($p>0.05$). There were

Table-1: Demographic and clinical features of the study and control groups.

	Study group (n=50)	Control group (n=50)	P value
Age (years)	28.64	28.48	0.881
Gravida ≤ 2	30 (60%)	32 (64%)	0.947
> 2	20 (40%)	18 (36%)	
Parity ≤ 1	30 (60%)	32 (64%)	0.929
> 1	20 (40%)	18 (36%)	
Smokers (%)	6 (12%)	7 (14%)	0.942
SAA	87.517	27.0518	0.0001*
CRP	6.92	1.2534	0.0001*
NLR	5.215	4.6506	0.224

* Significant difference.
SAA: Serum amyloid A), CRP: C-reactive protein, NLR: Neutrophil-leukocyte ratio.

Table-2: Clinical features of the newborns in the groups.

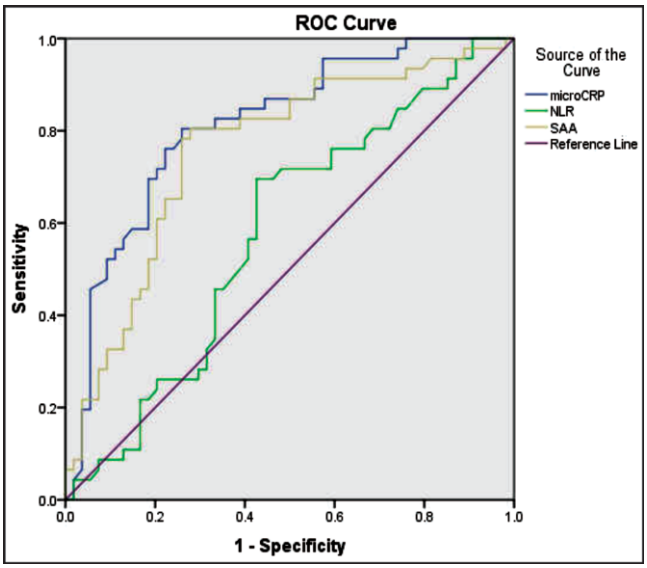
Factors		Study group	Control group	P-value
Birth weights (grams)		2.0827±0.041	3.531±0.053	0.0001*
Gestational age at delivery (weeks)		30.944±0.35	38.868±0.21	0.0001*
≤ 28		2 (4%)	-	
28-32		34 (68%)	1 (2%)	
>32		14(28%)	49 (98%)	
Delivery type				0.934
Vaginal (%)		28 (56%)	27 (54%)	
Caesarean section(%)		22 (44%)	23 (46%)	
Gender				1
Female (%)		27 (54%)	27 (54%)	
Male (%)		23 (46%)	23 (46%)	
APGAR 1	4 (%)	2 (4%)	-	0.086
	5 (%)	3 (6%)	-	
	6 (%)	9 (18%)	-	
	7 (%)	30 (60%)	19 (38%)	
	8 (%)	6 (12%)	31 (62%)	
APGAR 5	7 (%)	3 (6%)	4 (8%)	0.973
	8 (%)	7 (14%)	4 (8%)	
	9 (%)	40 (80%)	42 (84%)	

APGAR: Appearance-Pulse-Grimace-Activity-Respiration score.

Table-3: Pearson correlation analysis.

	MicroCRP		NLR	
	R	P	R	P
Serum amyloid A	0.891	0.000	0.307	0.002

R: Correlation coefficient, P: P-value, CRP: C-reactive protein, SAA: Serum amyloid A, NLR: Neutrophil-leukocyte ratio.



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CRP: C-reactive protein, SAA: Serum amyloid A, NLR: Meutrophil-leukocyte ratio.

Figure: Receiver operating characteristics (ROC) analysis and area under the curve (AUC) value of plasma MicroCRP, NLR and SAA levels in spontaneous preterm labour.

significant inter-group differences regarding SAA and CRP levels (p<0.05) (Table-1).

The difference regarding birth-weight and gestational age at the time of delivery between the groups was significant (p=0.0001) (Table-2).

There was a positive correlation between micro-CRP and SAA (p<0.05) (Table-3).

The cut-off value for SAA was 84.61ng/ml (Figure).

Discussion

To date, there is no safe treatment that can stop preterm labour effectively. It is vital to understand the mechanisms controlling the human labour process to create a new prevention technique.[15] Preterm birth is regarded as a continuous obstetric challenge, and several pathways are thought to be initiated many weeks and months before the clinical symptoms surface.[16] It is advantageous to identify the risk factors to predict preterm labour. Several biochemical markers are present in different body fluids, like vaginal secretions, cervical mucous, plasma, serum, saliva and amniotic fluids.[16] Others, like foetal fibronectin, CRP, interleukin-6 (IL-6), beta human chorionic gonadotropin (hCG), and alpha fetoprotein (AFP), are used to detect preterm labour.[16,17]

SAA is contemplated as an acute-response protein produced by the liver. It can induce events pertinent to labour initiation, and is expressed in the epithelium of the amnion, fibroblasts and trophoblasts of the chorion.[17] Understanding preterm birth is challenging as a result of pathophysiological heterogeneity and multifactorial aetiologies.[18] CRP is regarded as a nonspecific biomarker as its levels could be different in the presence of infection and various pathogenic abnormalities.[19]

The current study summarised SAA markers' beneficial effects to predict women at risk of having a preterm birth.

There is a growing interest in creating assessment tools by using multiple markers as these could increase the sensitivity of prediction through the combination of risk predictors.[20,21] Köseoglu SB et al.[22] showed the possible association between maternal and foetal parameters in pregnancies complicated with preterm pre-labour rupture of membranes (PPROM) and maternal SAA. Tthere was a significant difference between the two groups with regard to micro-CRP, NLR and SAA, and the SAA levels were higher in the PPROM group (p<0.005), which is similar to the current study, while the rported SAA cut-off value was 95.63ng/ml compared to 84.61ng/ml in te current study.

The current findings supported those of Villiers W. et al.[23] who reported a parallel rise of SAA to CRP during peri-partum period in women with premature rupture of membranes (PROM). Serial CRP in such women was not significantly different from the level detected in the normal post-partum period.[23]

Çetinkaya M. et al.[24] showed used SAA as a reliable and accurate marker in the diagnosis of neonatal sepsis in women who delivered prematurely, particularly at the onset of the inflammation. They reported the association between SAA levels and maternal pro-adrenomedullin (pro-ADM) in PPROM patients regarding foeto-maternal infections.

Çekmez Y. et al recommended using SAA and pro-ADM biomarkers in women with PPROM in the absence of clinical signs of infection.[25]

The current study has limitations as it did not involve power of analysis and sample size calculation. There is a need for further studies with a larger sample size to explore this critical subject.

Conclusion

Serum amyloid A could be an effective biomarker for predicting spontaneous preterm delivery.

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