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ORIGINAL ARTICLE

Role of Serum Amyloid a Levels in Preeclampsia

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Abstract

Background: **Preeclampsia (PE) is a frequent pregnancy complication and a leading factor in mother and fetal death. The maternal plasma level of Serum amyloid A (SAA) may be anticipated to be higher compared with levels seen during a typical pregnancy since PE is linked to extensive endothelial malfunction, which is thought to be triggered by an enhanced maternal systemic inflammatory response. The maternal plasma level of SAA during a healthy pregnancy may vary from that during a non-pregnancy owing to changes in the inflammatory response, elevated hormone balance, and/or increased adipose tissue.**

Patients and methods: **At the Department of Obstetrics and Gynecology, Al-Hussein and Sayed Galal Hospitals, Al-Azhar University, and El Dalangat general hospital, 100 women were separated into two groups for this prospective case-control research: (Group I): (Cases group): included 50 pregnant preeclamptic women, (Group II): (Control group): included 50 pregnant nonpreeclamptic women who matched in age, and gestational age with the case group between December 2019 to December 2020.**

Results: **Regarding SAA, there were statistically substantial variations between groups where *P* less than 0.001.**

Conclusion: **SAA is a promising biomarker in detecting the ability and predictability of the pathological development of PE. Future research studies should be conducted in a multicentric fashion.**

Keywords: Amyloid A, Biomarker, Preeclampsia

1. Introduction

One of the most prevalent medical conditions during gestation is hypertension, which affects 5%−6% of pregnancies across the board. The majority of maternal deaths and morbidity during gestation are brought on by hypertension, bleeding, and infection. Furthermore, 16% of maternal deaths in affluent nations are related to hypertension.[1]

Preeclampsia's (PE's) etiopathogenesis has not yet been fully understood. PE is recognized to be marked by an increased maternal inflammatory response, nevertheless. Inflammation is linked to PE and cardiovascular illness, and both share risk factors including obesity.[2] C-reactive protein (CRP), which is recognized to be an inflammatory indicator and acute phase reactant, has been measured in preeclamptic women in various investigations with varying degrees of success.[3]

Serum amyloid A (SAA), another inflammatory signal, is a precursor protein for the production of AA fibrils in systemic AA amyloidosis and is crucial for the progression of systemic AA amyloidosis.[4]

The acute-phase response involves the immunoregulatory protein SAA, whose further recognized roles include immunomodulation, cell proliferation, cell differentiation, cell migration, and invasion.[5] The expression of each of the four human SAA isoforms comes from a different gene (SAA1, SAA2, SAA3, and SAA4). Acute-phase proteins are encoded by SAA1 and SAA2, SAA4 is constitutively produced, while SAA3 is a pseudogene.[6]

In response to bacterial and viral infections, inflammation, tumor development, and physical stress, serum concentrations of SAA significantly rise. Acute phase SAA values in serum may rise by up to 1000 times and can be as high as 500−1000 pg/ml.[7]

Hepatocytes produce SAA in response to inflammatory cytokines. According to some reports,

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fibroblasts, synovial cells, macrophages, and adipocytes may also make SAA. Only a few research, to the author's knowledge, tested the SAA values in pregnant people with PE, and inconsistent findings were found.[8]

Blood amyloid an inflammatory marker generated in the liver is CRP. Cytokines like TNF alpha and IL-6 stimulate the creation of these substances in the liver. Through inflammation, SAA may influence the beginning and development of endothelial dysfunction. There is growing evidence that there is a direct connection between inflammation, endothelial malfunction, and preeclampsia. A causal connection between these events has not yet been shown, however. The hunt for indicators of inflammation has been sparked by the connection between inflammation and preeclampsia notwithstanding these ambiguities. This suggests that preprevalence eclampsia's and severity may be related to elevated levels of SAA.[9]

This study's objective was to detect the role of SAA levels in PE.

2. Patients and methods

This was prospective case-control research carried out at the Department of Obstetrics and Gynecology, Al-Hussein and Sayed Galal Hospitals, Al-Azhar University December 2019 to December 2020 including 100 pregnant women with gestational age greater than 20 weeks and PE or eclampsia divided into two groups: Group I: (Cases group): included 50 pregnant preeclamptic women. Group II: (Control group): included 50 pregnant nonpreeclamptic women who matched in age, and gestational age with the case group.

The research excluded all women who had multiple pregnancies, fetal malformations, diabetes mellitus, chronic hypertension, autoimmune illness, premature membrane rupture, infection, systemic illness, such as renal or hepatic problems identified before pregnancy, and women who were in active labor.

All patients underwent thorough history taking including full personal, obstetric, menstrual, and medical history collected in a special form for each patient. Detailed clinical examination was performed in all women including general examinations and local abdominal and pelvic examinations. Laboratory investigations were performed in all cases including complete blood count (CBC), serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) concentrations, serum creatinine, and coagulation profile (prothrombin time [PT], activated partial thromboplastin time [aPTT], and serum albumin) and serum Albumin was assessed by dipstick.

Evaluation of SAA was done after obtaining serum samples which were collected under aseptic condition and centrifuged for 20 min at 2000 rpm. The resulting plasma samples was stored at −70 °C until assayed with a commercially available ELISA kit.

Primary outcome was the evaluation of the role of SAA levels in preeclamptic pregnant women. Secondary outcomes were Fetal and Maternal morbidity and mortality.

Utilizing SPSS version 20 (Statistical Package for the Social Sciences), data input, processing, and statistical analysis were completed.

Table 1. Comparison of two groups based on patient demographics.

	Study group (number = 50) Number (%)	Control group (number = 50) Number (%)	Test of Significance	*P* Value
Age				
Min.–Max.	21–42	23–42	$U = 1170.50$	0.582
Mean ± S.D	29.64 ± 5.074	29.14 ± 4.468		
Parity				
Nulliparous	23 (46.0)	26 (52.0)	–	0.689
Multiparous	27 (54.0)	24 (48.0)		
Height				
Min.–Max.	156–180	155–180	$t = 0.067$	0.946
Mean ± S.D	79.32 ± 8.740	79.20 ± 9.094		
Weight				
Min.–Max.	65–95	66–95	$U = 1129.50$	0.406
Mean ± S.D	167.56 ± 7.214	168.78 ± 8.054		
BMI				
Min.–Max.	20.52–37.73	20.99–36.92	$U = 1156.00$	0.517
Mean ± S.D	28.37 ± 3.704	28.01 ± 4.331		
Gestational Age				
Min.–Max.	35–40	35–40	$U = 1229.50$	0.886
Mean ± S.D	37.30 ± 1.799	37.24 ± 1.779		

Table 2. Comparison between two groups as regard to patient's blood pressure and grades of hypertension.

	Study group (number = 50)	Control group (number = 50)	*U*	*P* Value
Systolic	158.50 ± 9.649	112.30 ± 5.908	0.000	<0.001*
Diastolic	101.50 ± 6.409	71.20 ± 5.852	0.000	<0.001*
Grades of hypertension				
	Study Group (number = 50) No. (%)	Control Group (number = 50) No. (%)	χ^2	*P* Value
Optimal	0	47 (94.0)	100.00	<0.001*
Normal	0	3 (6.0)		
Grade 1 Hypertension (Mild)	26 (52.0)	0		
Grade 2 Hypertension (Moderate)	24 (48.0)	0		
Grade 3 Hypertension (Severe)	0	0		

* *P*-value <0.05.

Table 3. Comparison between two groups as regard to patient's laboratory investigations.

	Study group (number = 50)	Control group (number = 50)	Test of significance	*P* Value
Hb (g/dl)	13.17 ± 0.982	12.67 ± 0.597	$t = 3.114$	0.002*
Platelets (103/μl)	219.08 ± 30.659	237.10 ± 31.505	$U = 862.50$	0.008*
ALT (U/l)	43.38 ± 15.079	41.82 ± 12.262	$U = 1159.00$	0.530
AST (U/l)	50.58 ± 15.604	47.84 ± 14.210	$U = 1145.50$	0.471
Creatinine (mg/dl)	0.70 ± 0.349	0.54 ± 0.090	$U = 807.50$	0.002*
PT (s)	17.48 ± 0.667	12.62 ± 0.314	$U = 0.000$	<0.001*
aPTT (s)	28.96 ± 3.374	28.88 ± 4.139	$U = 1244.50$	0.970
S-Albumin (g/dl)	03.8 ± 6.724	03.50 ± 5.799	$U = 938.00$	0.031*

* *P*-value <0.05.

3. Results

Regarding demographic statistics, there was no substantial variation between the two study groups (Table 1).

When it came to the patient's blood pressure and hypertension grades, there were very statistically substantial variations between the two groups (Table 2).

There was highly statistically substantial variations between the two groups regarding Hb, platelets, creatinine, PT, and albumin (Table 3).

SAA in the Study group ranged between 7.90 and 142.00 with mean ± S.D. 53.16 ± 42.626 and more than half of patients had high SAA while in the Control group was ranged between 4.80 and 24.40 with mean ± S.D. 14.43 ± 5.982 and the most of patients had normal SAA. Between groups, there were statistically substantial variations where *P* less than 0.001 (Table 4).

The receiver operating characteristic (ROC) curve analysis of Serum Amyloid showed that cut-off value to detect PE was greater than 24.4 with 56.0% sensitivity and 100% specificity and accuracy of 78% (Table 5 and Fig. 1).

4. Discussion

This study was conducted on two groups study group (PE) and control group. Each group contained 50 participants.

Both groups were comparable as regard to age, gestational age, parity, and patient's measurements (weight, height, BMI). Systolic and diastolic blood pressure were statistically substantially different between the two groups.

Table 4. Comparison between two groups as regard to patient's serum amyloid A.

Serum amyloid A (SAA)	Study group (number = 50) Number (%)	Control group (number = 50) Number (%)	*U*	*P* Value
Min.-Max.	7.90–142.00	4.80–24.40	423.00	<0.001*
Mean ± S.D	53.16 ± 42.626	14.43 ± 5.982		
Low	2 (4.0)	14 (28.0)	$\chi^{22} = 41.571$	<0.001*
Normal	20 (40.0)	36 (72.0)		
High	28 (56.0)	0		

* *P*-value <0.05.

Table 5. ROC curve analysis of serum amyloid in the studied group.

	Cut-off value	Sensitivity	Specificity	PPV	NPV	AUC	*P* value	Accuracy
Serum Amyloid A (SAA)	>24.4	56.00	100	100	69.40	0.831	<0.001*	78.0

* *P*-value <0.05.

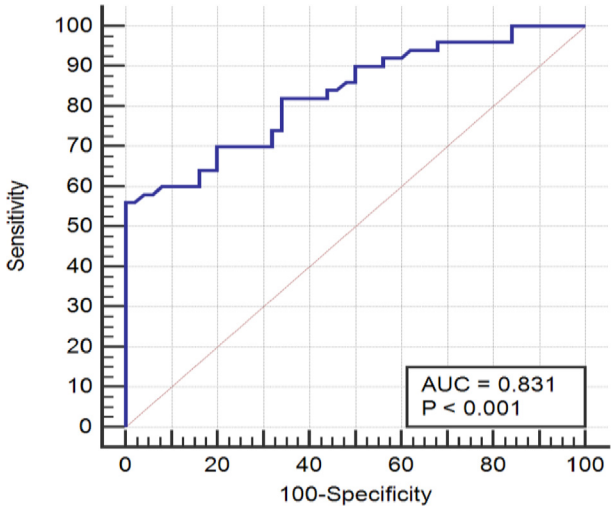

Fig. 1. ROC curve analysis of Serum Amyloid in the studied group.

Our results were in line with study of Reyes and colleagues,[10] Singla and colleagues,[11] Kaduma and colleagues,[12] Mayrink and colleagues,[13] as they reported that Regarding systolic and diastolic blood pressure, there were very statistically substantial variations between the two groups (normal gestation and preeclampsia).

The recent research revealed that between the two groups, there was a very statistically substantial variation in Hb, platelets, creatinine, PT, and albumin.

In accordance with our results study of Yadav and colleagues,[14] as they reported that When compared with the control group, the median blood creatinine and uric acid values in preeclampsia patients indicate a considerably higher value ($P < 0.0001$).

In the study of Ali and colleagues,[15] Women with extreme anemia were substantially more likely to have PE and eclampsia (8.2% and 3.3%, respectively).

During pregnancy, measuring SAA values has shown significant relationships. SAA levels increased in mice with premature birth. In people, SAA levels are correlated with mortality and the degree of newborn encephalopathy. Different research discovered that SAA levels served as a reliable predictor of early pregnancy loss. Early onset neonatal sepsis in preterm newborns was linked to elevated values of the APR proteins haptoglobin, CRP, and SAA in the cord blood Sack.[16]

Our findings showed that there were statistically substantial variations between groups as regard SAA. Out of 50 studied cases; 28 (56%) had high SAA, 20 (40%) had normal SAA, and 2 (4%) had low SAA.

Regarding the ROC curve analysis of Serum Amyloid and it shows that cut-off value to detect PE is greater than 24.4 with 56.0% sensitivity and 100% specificity and accuracy of 78%.

Our results were supported by the study of El-Kady and colleagues,[17] as they reported that the mean serum value of amyloid A was statistically substantially greater in women of the PE research group in comparison to women of the control research group (P value < 0.001).

Also, Engin-Uestuen and colleagues,[7] revealed that SAA levels and CRP levels in preeclampsia were substantially greater than those in a normal gestation (7.8 [4.65–24.6] ng/l and 6.05 [0.3–19] mg/l, respectively) ($P < 0.05$). These levels were 28.2 (7.2–135) ng/l and 21 (6.13–91) mg/l, respectively. Additionally, there was a positive correlation between SAA level and CRP ($r = 0.468$, $P < 0.05$).

Also, Swidan and colleagues,[18] revealed that the association between PE and SAA levels may be due to an inflammatory state associated with PE, according to researchers who have found higher plasma levels of SAA in preeclamptic women. Additionally, SAA may be utilized to distinguish between instances of mild PE and controls as well as cases of severe PE and controls.

An acute reaction protein called SAA1 (SAA1) is mostly produced by the liver when an infection is present. However, it is still unknown if SAA1, which may set off circumstances that lead to the onset of labor, might be produced in human fetal membranes Ye and Sun.[19]

Similar to CRP, elevated serum amyloid protein A (SAA) has been proven to be a marker of systemic inflammation. Interleukin-6 (IL-6) and tumor necrosis factor (TNF- α) stimulate hepatocytes to produce the inflammatory indicators CRP and SAA. However, both blood levels of SAA and CRP may be elevated by around 1000 times in response to inflammation Ling and colleagues.[9]

Serum amyloid A levels rise in a significant manner as pathophysiological response to infectious viral and bacterial insults, tumor enlargement and physical strain. SAA may rise to 1000-fold and could reach to 500–1000 μg/ml. Amyloid A is synthesized by hepatic cells as an inflammatory response to cytokines Enkhmaa and colleagues.[20]

It has been revealed that additionally amyloid A in serum is manufactured by various cell types such as fibroblasts, macrophages, and fat cells. Restricted number of research studies have assessed and evaluated amyloid A levels in serum of gestations suffering the development of PET Boeldt and Bird.[21]

PE is a frequent pregnancy complication and the leading cause of death for both mothers and fetuses. Widespread endothelial dysfunction, which is thought to be a component of an increased maternal

inflammatory response to pregnancy, is what causes the clinical signs of PE El-Kady and colleagues.[17]

An acute reaction protein called SAA1 is mostly produced by the liver when an infection is present. However, it is still unknown if SAA1, which may set off circumstances that lead to the onset of labor, might be produced in human fetal membranes Ye and Sun.[19] Blood amyloid an inflammatory marker generated in the liver is CRP. Cytokines like TNF alpha and IL-6 stimulate the creation of these substances in the liver. However, there are no findings on the association between the SAA and PE. SAA may alter the development and progression of endothelial impairment by causing inflammation Ling and colleagues.[9]

It is interesting to note that a previous study found a substantial variation in amyloid A serum levels between the PE and control groups in maternal blood and umbilical cord blood. In contrast to the present investigation, a previous study found that women with PE did not have higher plasma concentrations of the SAA protein compared with those with normal conception Harmon and colleagues.[22]

Engin-Uestuen and colleagues[7] 25 pregnant women with normal blood pressure and 25 preeclamptic women had their SAA values examined. PE was associated with higher SAA, however both groups' SAA values were too low compared with another research.

Kristensen and colleagues[4] comprised 58 healthy nonpregnant women and 57 PE patients in addition to 295 women with straightforward pregnancies. When compared with preeclamptic and nonpregnant women, they discovered greater SAA values in normal pregnancy, although this improvement was not statistically substantial.

In a study of Can and colleagues[23] reported that When compared with individuals with moderate PE and those with normotension, those with severe PE had considerably higher SAA readings. Procalcitonin, hsCRP, and MAP were significantly positively correlated, according to SAA.

4.1. Conclusion

SAA is a promising biomarker in detect ability and predictability of the pathological development of PE. Future research studies should be conducted in a multicentric fashion.

4.2. Study limitation

Small sample size and the study was conducted in a single center.

Authorship

All authors have a substantial contribution to the article.

Disclosure

The authors have no financial interest to declare in relation to the content of this article.

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Conflicts of interest

The authors declared that there were NO conflicts of Interest.

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