Serum Amyloid A in Preeclampsia

Thesis

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By

Manar Khammas Jewi

M.B.B.Ch, Faculty of Medicine, Baghdad University

Under Supervisors

Prof. Dr. Khaled Hassan Swidan

Professor of Obstetrics and Gynecology

Faculty of Medicine – Ain Shams University

Prof. Dr. Mohamed Samer Sweed

Assistant Professor of Obstetrics & Gynecology

Faculty of Medicine – Ain Shams University

Dr. Ahmed Mohammed Abbas

Lecturer of Obstetrics & Gynecology

Faculty of Medicine – Ain Shams University

Faculty of Medicine
Ain Shams University
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List of Abbreviations

ACC/AHA : American College of Cardiology/American Heart Association
ACE : Angiotensin converting enzyme
ACOG : American College of Obstetricians and Gynecologists
AFLP : Acute fatty liver of pregnancy
ALT : Alanine aminotransferase
ARBs : Angiotensin II receptor blockers
A-SAAs : Acute-phase serum amyloid A proteins
AST : Aspartate aminotransferase
AT : Angiotensin receptor
B2 : Bradykinin
CD94 : Cluster of differentiation 94
CRP : C reactive protein
DHA : Docosahexaenoic acid
DIC : Disseminated intravascular coagulation
DI water : De inoized water
EEG : Electroencephalography
EPA : Eicosapentaenoic acid
ESRD : End-stage renal disease
EVT : Extravillous trophoblast
GFR : Glomerular filtration rate
HDL : High-density lipoprotein
HELLP : Hemolysis, elevated liver enzyme levels, and low platelet levels
HLA-G : Human leukocyte antigen G
hsCRP : High sensitivity C reactive protein
HUS : Hemolytic uremic syndrome

IL-6	: Interluking
KIR	: killer cell immunoglobulin like receptor
LDH	: Lactate dehydrogenase
LPS	: Lipopolysaccharide
MRAs	: Mineralocorticoid receptor antagonists
NK	: Natural killer
NMDA	: n-methyl d-aspartate
PlGF	: Placental growth factor
PRES	: Posterior reversible encephalopathy syndrome
PUFA	: Polyunsaturated fatty acids
RDA	: Recommended daily allowance
RPLS	: Posterior leukoencephalopathy syndrome
SAA	: Serum amyloid A
sEng	: Soluble endoglin
sFlt-1	: Soluble fms-like tyrosine kinase-1
SGA	: Small for gestational age
SLE	: Systemic lupus erythematosus
STOX1	: Storkhead box 1
TNF	: tumor necrosis factor
TTP	: Thrombotic thrombocytopenic purpura
USPSTF	: The US Preventive Services Task Force

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Abstract

This study was one of the first studies that correlated between amyloid A and different demographic data in preeclamptic women. In currant study among cases group, we found non-significant correlation between Amyloid A and age (r = 0.05 & p=0.66) and there was non-significant correlation between Amyloid A and BMI (r= -0.001 & p=0. 66), hemoglobin concentration (r= - 0.08 & p=0. 47) or platelet count (r= -0.17 & p=0. 12). Overall, statistically significant positive correlation was found between serum amyloid A level and most of the indices of severity of preeclampsia. A statistically significant correlation was found between serum amyloid A and systolic blood pressure measurements (r = 0.82 & p < 0.001) and diastolic blood pressure measurements (r = 0.82 & p < 0.001), ALT (r = 0.64 & p < 0.001), AST (r = 0.45 & p < 0.001) serum creatinine (r = 0.26 & p =0.02) and albuminuria (r = 0.73 & p < 0.001) and we think that this is a matter of association rather than causation

Our data sustain the limited number of studies investigating the SAA levels in both preeclamptic and healthy pregnant women, in which it was hard to reach a consensus regarding the association between SAA levels and preeclampsia. Taken in consideration that an elevated plasma level of SAA in preeclamptic women should be considered pathologic, we believe that the response of relationship between the preeclampsia and SAA levels could be caused by an inflammatory condition associated with preeclampsia.

Keywords: Serum Amyloid A - Preeclampsia - Tumor Necrosis Factor

Introduction

Preeclampsia is a common complication of pregnancy and remains a common cause of maternal and fetal mortality. The clinical symptoms of preeclampsia are caused by widespread endothelial dysfunction suggested to be a part of an exaggerated maternal inflammatory response to pregnancy ***(Jeyabalan, 2013).***

The syndrome of preeclampsia is a condition with many manifestation, and suspected organ impairment is monitored by serum marker for hemolysis, coagulopathy, liver and renal function ***(Townsend et al., 2016).***

Serum amyloid A (SAA) is acute phase protein predominantly produced and secreted by hepatocytes. Other cells including lymphocytes, monocytes and macrophage can also produce this protein. The induction of SAA synthesis is trigged by a number of cytokines, chiefly IL-6 and TNF - predominantly released from macrophage and monocyte at the inflammatory site ***(Siegmund et al., 2016).***

The synthesis is influenced by steroid hormones and adipose tissue (due to IL-6 production in the adipocytes ***(Coelho et al., 2013).***

Increased baseline levels of SAA analyzed by high sensitivity assays has been recognized as marker of vascular

wall inflammation and as clinical marker of vascular wall marker for the prediction of cardiovascular events ***(Al Shahi et al., 2015).***

Since preeclampsia is associated with widespread endothelial dysfunction, proposed to be provoked by an increased maternal systemic inflammatory response, the maternal plasma level of SAA might be expected to be increased when compared to normal pregnancy levels. The maternal plasma level of SAA in normal pregnancy could differ from non-pregnant level due to increased hormone levels, increased adipose tissue and\or secondary to modifications of inflammatory response in normal pregnancy ***(Gathiram and Moodley, 2016).***

The level of SAA, which is a major acute phase protein, has previously been found to be unaltered by pregnancy. In a recent pilot study, the SAA level was found to be increased in women with preeclampsia correlating with other pro inflammatory cytokines ***(Lopalco et al., 2015).***

Aim of the Work

The aim of this study is to estimate serum amyloid A in pregnant women with preeclampsia.

Research hypothesis:

In pregnant women with preeclampsia serum amyloid A may be high.

Research question:

In pregnant women with preeclampsia does serum amyloid A increase?

Chapter (1)
Hypertensive Disorders with Pregnancy

Gestational hypertension and preeclampsia/ eclampsia are hypertensive disorders induced by pregnancy; both disorders resolve postpartum. Gestational hypertension is the most common cause of hypertension in pregnant women ***(ACOG, 2013)***.

Gestational hypertension:

Gestational hypertension is the most common cause of hypertension during pregnancy. It occurs in 6 to 17 percent of healthy nulliparous women and 2 to 4 percent of multiparous women. The prevalence is highest in women with preeclampsia in a previous pregnancy, women with multifetal gestation, and overweight/obese women ***(Gaillard et al., 2011).***

Gestational hypertension is a clinical diagnosis defined by the new onset of hypertension (defined as systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg) at ≥20 weeks of gestation in the absence of proteinuria or new signs of end-organ dysfunction. The blood pressure readings should be documented on at least two occasions at least four hours apart. Gestational hypertension is severe when systolic blood pressure is ≥160 mmHg and/or diastolic blood pressure is ≥110 mmHg ***(ACOG, 2013).***

Gestational hypertension is a temporary diagnosis for hypertensive pregnant women who do not meet criteria for preeclampsia or chronic hypertension (hypertension first detected before the 20th week of pregnancy) ***(Whelton et al., 2018)***.

The diagnosis is changed to:

1. Preeclampsia, if proteinuria or new signs of end-organ dysfunction develop ***(Whelton et al., 2018)***.

2. Chronic hypertension, if blood pressure elevation persists ≥12 weeks postpartum. Of note, in 2017, the definition of hypertension in non-pregnant adults was revised by the American College of Cardiology/ American Heart Association (ACC/AHA) ***(Whelton et al., 2018).***

**** Normal blood pressure:** Systolic <120 mmHg and diastolic <80 mmHg ***(Whelton et al., 2018)***.

**** Elevated blood pressure:** Systolic 120 to 129 mmHg and diastolic <80 mmHg ***(Whelton et al., 2018)***.

**** Hypertension:**

- **Stage 1:** Systolic 130 to 139 mmHg or diastolic 80 to 89 mmHg ***(Whelton et al., 2018)***.

- **Stage 2:** Systolic at least 140 mmHg or diastolic at least 90 mmHg ***(Whelton et al., 2018)***.

If there is a disparity in category between the systolic and diastolic pressures, the higher value determines the stage ***(Whelton et al., 2018)***.

**** Isolated systolic hypertension:** Blood pressure ≥130/<80 mmHg ***(Whelton et al., 2018)***.

**** Isolated diastolic hypertension:** Blood pressure <130/≥80 mmHg ***(Whelton et al., 2018)***.

**** Mixed systolic/diastolic hypertension:** Blood pressure ≥130/≥80 mmHg ***(Whelton et al., 2018)***.

3. Transient hypertension of pregnancy, if blood pressure returns to normal by 12 weeks postpartum. Thus, reassessment up to 12 weeks postpartum is necessary to establish a final diagnosis ***(Whelton et al., 2018)***.

PATHOPHYSIOLOGY:

Abnormal development of the placenta: The critical role of the placenta in the pathophysiology of preeclampsia is supported by epidemiologic and experimental data that show: ***(Matsuo et al., 2007)***

- Placental tissue is necessary for development of the disease, but the fetus is not.
- Preeclampsia is always cured within days to weeks after delivery of the placenta; however, in rare cases

postpartum hypertension and preeclampsia can occur up to 6 to 8 weeks post-delivery. The factors involved in the clinical expression of preeclampsia after delivery of the placenta are unclear, but may involve delayed clearance of antiangiogenic factors, activation of the complement system after delivery, and/or response to mobilization of extracellular fluid into the intravascular compartment.

Examination of human placentas at various stages of gestation in women with normal pregnancies, as well as those with preeclampsia, has led to an understanding of normal placental morphology and pathologic changes in the uteroplacental circulation that are likely relevant to preeclampsia. It is clear that defects in spiral artery remodeling and trophoblast invasion, two related but separate processes, are characteristic of hypertensive disorders of pregnancy and fetal growth restriction. These processes result in impaired placentation and placental ischemia, which are thought to be the primary events leading to placental release of soluble factors that cause systemic endothelial dysfunction resulting in the preeclamptic phenotype ***(Pijnenborg et al., 2006).***

Abnormal remodeling of spiral arteries: In normal pregnancies, the cytotrophoblast cells of the developing placenta migrate through the decidua and part of the myometrium to invade both the endothelium and highly muscular tunica media of the maternal spiral arteries, the terminal branches of the uterine artery that supply blood to the