

CA-125 and Severity of Preeclampsia

Thesis

*Submitted for the Partial Fulfillment of Master Degree
in Obstetrics and Gynecology*

Presented By

Marwa Mohamed Ibrahim

*M.B., B.Ch. Ain Shams University (2011)
Resident in Al-salam Specialized Hospital*

Under Supervision of

Prof. Dr. Hassan Tawfek Khairy

*Professor of Obstetrics and Gynecology
Faculty of Medicine – Ain Shams University*

Dr. Sherif Hanafi Hussain

*Assistant Professor of Obstetrics and Gynecology
Faculty of Medicine – Ain Shams University*

Dr. Ahmed Mohamed Bahaa Eldin

*Assistant Professor of Obstetrics and Gynecology
Faculty of Medicine – Ain Shams University*

Faculty of Medicine

Ain Shams University

2017

Acknowledgment

*First thanks to **ALLAH** to whom I relate any success in achieving any work in my life.*

*I wish to express my deepest thanks, gratitude and appreciation to **Prof. Dr. Hassan Jawfek Khairy**, Professor of Obstetrics and Gynecology Faculty of Medicine – Ain Shams University for his meticulous supervision, kind guidance, valuable instructions and generous help.*

*Special thanks are due to **Dr. Sherif Hanafi Hussain**, Assistant Professor of Obstetrics and Gynecology Faculty of Medicine – Ain Shams University Care for his sincere efforts, fruitful encouragement.*

*I am deeply thankful to **Dr. Ahmed Mohamed Bahaa Eldin**, Assistant Professor of Obstetrics and Gynecology Faculty of Medicine – Ain Shams University for her great help, outstanding support, active participation and guidance.*

Marwa Mohamed Ibrahim



This work is dedicated to . . .

My beloved father, to whom I owe everything I ever did in my life and will achieve.

My mother for always being there for me and all the nights she stayed with me.

My husband for being support me and God's gift to me, my backbone

Finally *my son* light of my life



بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ

قالوا

سبحانك لا علم لنا
إلا ما علمتنا إنك أنت
العليم العظيم

صدق الله العظيم

سورة البقرة الآية: ٣٢

List of Contents

Title	Page No.
List of Tables	i
List of Figures.....	iii
List of Abbreviations	v
Protocol	
Introduction	1
Aim of the Work	10
Review of literature	11
Patients and Methods.....	48
Results	55
Discussion.....	72
Summary	79
Conclusion	82
References	83
Arabic Summary	

List of Tables

Table No.	Title	Page No.
Table (1):	Criteria for diagnosis of preeclampsia, (diastolic blood pressure is determined based upon the fifth Korotkoff sound (disappearance) with patient sitting).....	14
Table (2):	The presence of one or more of the following criteria are features of severe preeclamptic disease.....	15
Table (3):	Criteria for diagnosis of gestational hypertension	16
Table (4):	Conditions associated with high levels of CA-125	45
Table (5):	Comparison between the three studied groups (control, mild and severe preeclampsia) according to age, parity, number of abortions and gestational age.	56
Table (6):	Comparison between the three studied groups (controls, mild and severe preeclampsia) according to systolic and diastolic B.P.	57
Table (7):	Comparison between the three studied groups (controls, mild and severe preeclampsia) according to platelet count and albumin in urine.....	58
Table (8):	Comparison between the three studied groups (controls, mild and severe preeclampsia) according to AST and ALT.....	60
Table (9):	Comparison between the three studied groups (controls, mild and severe preeclampsia) according to serum creatinine and uric acid.....	62

List of Tables cont...

Table No.	Title	Page No.
Table (10):	Comparison between the three studied groups (controls, mild and severe preeclampsia) according to estimated fetal weight and birth weight.....	64
Table (11):	Comparison between the three studied groups (controls, mild and severe preeclampsia) according to mode of delivery.....	65
Table (12):	Frequency of complications in patients with severe preeclampsia.....	66
Table (13):	Comparison between the three studied groups (controls, mild and severe preeclampsia) according to CA125.	67
Table (14):	Correlation between CA125 and other variables in controls, patients with mild and severe preeclampsia.....	68
Table (15):	Diagnostic accuracy of CA125 to differentiate between controls and patients with severe preeclampsia.....	69
Table (16):	Diagnostic accuracy of CA125 to differentiate between patients with mild and severe preeclampsia.....	70
Table (17):	Best cut off point to differentiate between controls and patients with preeclampsia.	71

List of Figures

Fig. No.	Title	Page No.
Figure (1):	Showing the four major hypertensive disorders related to pregnancy.....	11
Figure (2):	Shows the difference in trophoblastic invasion and arteriolar remodeling between normal and preeclamptic pregnancies whereas placenta in preeclamptic pregnancy shows defective implantation which is characterized by incomplete invasion of the spiral arteriolar wall by extravillous trophoblasts and results in a small-caliber vessel with high resistance.....	21
Figure (3):	PlGF and sVEGFR-1 concentrations trends during pregnancy.....	22
Figure (4):	Showing endothelial dysfunction in preeclampsia.....	25
Figure (5):	Pathways by which reduced uterine perfusion pressure (RUPP) and placental ischemia may lead to endothelial and cardiovascular dysfunction during pregnancy.....	26
Figure (6):	Two-stage disorder of preeclampsia. Stage 1 is poor placentation at early stage of pregnancy and stage 2 is placental oxidative stress at late stage of pregnancy	29
Figure (7):	Shows high resistance uterine artery Doppler at 23 weeks with increased S/D ratio and diastolic notching.	37
Figure (8):	MUC16 structure. Model shows the three domains of MUC16 and potential location of the CA125 epitope in a tandem repeat.	43
Figure (9):	Flow chart of the patients included in this study.	55

List of Figures cont...

Fig. No.	Title	Page No.
Figure (10):	Comparison between the three studied groups (controls, mild and severe preeclampsia) according to platelet count.....	59
Figure (11):	Comparison between the three studied groups (controls, mild and severe preeclampsia) according to albumin in urine.....	59
Figure (12):	Comparison between the three studied groups (controls, mild and severe preeclampsia) according to AST and ALT.	61
Figure (13):	Comparison between the three studied groups (controls, mild and severe preeclampsia) according to serum creatinine.....	63
Figure (14):	Comparison between the three studied groups (controls, mild and severe preeclampsia) according to uric acid.	63
Figure (15):	Comparison between the three studied groups (controls, mild and severe preeclampsia) according to mode of delivery.....	65
Figure (16):	Frequency of complications in patients with severe Preeclampsia.	66
Figure (17):	Comparison between the three studied groups (controls, mild and severe preeclampsia) according to CA125.	67
Figure (18):	Diagnostic accuracy of CA125 to differentiate between controls and patients with severe preeclampsia.	69
Figure (19):	Diagnostic accuracy of CA125 to differentiate between patients with mild and severe preeclampsia.	70

List of Abbreviations

Abb.	Full term
<i>ACOG</i>	<i>American College of Obstetricians and Gynecologists</i>
<i>ALT</i>	<i>Alanine aminotransferase</i>
<i>Ang-1</i>	<i>Angiopoietin-1</i>
<i>Ang-2</i>	<i>Angiopoietin-2</i>
<i>Ang-II</i>	<i>Angiotensin II</i>
<i>AST</i>	<i>Aspartate aminotransferase</i>
<i>ATI-AA</i>	<i>Angiotensin II type 1 receptor autoantibody</i>
<i>ATI-AB</i>	<i>Angiotensin II type 1 receptor antibody</i>
<i>BKCa⁺⁺</i>	<i>Large conductance calcium-activated potassium channels</i>
<i>BMI</i>	<i>Body mass index</i>
<i>BP</i>	<i>Blood pressure</i>
<i>CA-125</i>	<i>Cancer Antigen-125</i>
<i>CNS</i>	<i>Central nervous system</i>
<i>CRP</i>	<i>C-reactive protein</i>
<i>CT</i>	<i>Computed Tomography</i>
<i>DIC</i>	<i>Disseminated intravascular coagulation</i>
<i>DM</i>	<i>Diabetes mellites</i>
<i>DNA</i>	<i>Deoxyribonucleic acid</i>
<i>ET-1</i>	<i>Endothelin-1</i>
<i>ffDNA</i>	<i>Free fetal DNA</i>
<i>GWLS</i>	<i>Genome-wide linkage analyses</i>
<i>hCG</i>	<i>Human chorionic gonadotropin</i>
<i>hCG-h</i>	<i>Hyperglycosylated human chorionic gonadotropin</i>
<i>HELLP</i>	<i>Hemolysis, elevated liver enzymes, low platelet count</i>
<i>HTN</i>	<i>Hypertension</i>
<i>IBI</i>	<i>Inter-birth interval</i>
<i>IL</i>	<i>Interleukin</i>
<i>IQR</i>	<i>Inter quartile range</i>
<i>IUFD</i>	<i>Intrauterine fetal demise</i>
<i>IUGR</i>	<i>Intrauterine growth restriction</i>
<i>IV</i>	<i>Intravenous</i>
<i>LMP</i>	<i>Last menstrual period</i>

List of Abbreviations **cont...**

Abb.	Full term
<i>MRI</i>	<i>Magnetic resonance image</i>
<i>NICU</i>	<i>Neonatal intensive care unite</i>
<i>NK</i>	<i>Natural killer</i>
<i>NO</i>	<i>Nitric oxide</i>
<i>OC125</i>	<i>Ovarian cancer 125</i>
<i>OR</i>	<i>Odds Ratio</i>
<i>PAI-1</i>	<i>Plasminogen activator inhibitor-type 1</i>
<i>PAPP-A</i>	<i>Pregnancy-associated plasma protein-A</i>
<i>PCR</i>	<i>Polymerase chain reaction</i>
<i>PET</i>	<i>Preeclampsia</i>
<i>PI</i>	<i>Pulsatility index</i>
<i>PIGF</i>	<i>Placental growth factor</i>
<i>RI</i>	<i>Resistive index</i>
<i>RNA</i>	<i>Ribonucleic acid</i>
<i>ROC</i>	<i>Receiver Operating Characteristic</i>
<i>ROS</i>	<i>Reactive Oxygen Species</i>
<i>RUPP</i>	<i>Reduced uterine perfusion pressure</i>
<i>SD</i>	<i>Standard deviation</i>
<i>sFlt-1</i>	<i>Soluble fms-like tyrosine kinase-1</i>
<i>Siglec-9</i>	<i>Sialic acid-binding Ig-like lectin-9</i>
<i>SRD</i>	<i>Serous retinal detachment</i>
<i>sTie-2</i>	<i>Soluble endothelial cell-specific tyrosine kinase receptor-2</i>
<i>STOX-1</i>	<i>Storkhead box-1</i>
<i>sVEGFR-1</i>	<i>Soluble vascular endothelial growth factor receptor-1</i>
<i>TNF</i>	<i>Tumor necrosis factor</i>
<i>TPR</i>	<i>Total peripheral resistance</i>
<i>TX</i>	<i>Thromboxane</i>
<i>US</i>	<i>Ultra sonography</i>
<i>UVPI</i>	<i>Utero-Placental Vascular Insufficiency</i>
<i>VEGF</i>	<i>Vascular endothelial growth factor</i>
<i>WHO</i>	<i>World Health Organization</i>

Abstract

By statistically analyzing data, a positive correlation between preeclampsia and systolic blood pressure, diastolic blood pressure, platelets count and serum uric acid. A negative correlation between preeclampsia and gestational age at time of delivery. We found no significant correlation between preeclampsia and maternal age.

There is statistically significance between CA-125 and preeclampsia for normal and mild group to severe group ($P < 0.01$), but weak sensitivity (67.5%) and specificity (52.5%).

In pregnancy, serum CA-125 levels are increased in early pregnancy and immediately after birth implicating the disintegration of the maternal decidua (i.e., blastocyst implantation and placental separation) as a possible source of the tumor marker elevation.

This study was conducted at Ain Shams University Maternity Hospital to assess free serum CA-125 in pregnant women with preeclampsia in the third trimester to find out possible relation between the level of CA-125 and severity of preeclampsia.

Keywords: *Serous retinal detachment - Tumor necrosis factor- Vascular endothelial growth factor- World Health Organization*

INTRODUCTION

Pre-eclampsia, defined as hypertension and proteinuria after 20 weeks of gestation, affects approximately 2-8% of pregnant women and may lead to severe maternal and neonatal complications (*Duley, 2009*).

Preeclampsia with its complications such as prematurity, IUGR, perinatal asphyxia and abruptio placentae is one of major causes of maternal and fetal morbidity and mortality due to its morbid course so it is necessary to identify those at risk for the illness and take precautions (*Gerulewicz-Vannini et al., 2006*).

The etiology of preeclampsia is unknown, although several risk factors have been identified as primiparity, advanced maternal age ethnicity and multiple pregnancies. Recent studies show that treatment with low-dose aspirin may reduce the risk of early-onset preeclampsia, i.e., preeclampsia diagnosed before 34 weeks of pregnancy, which usually is a severe form of the disease (*Roberge et al., 2012*).

The pathophysiologic abnormalities of preeclampsia are numerous. Some of the reported abnormalities include abnormal implantation, generalized vasospasm, vascular endothelial dysfunction, angiogenic factors imbalance, immune and inflammatory mechanisms (*Redman et al., 2012*).

Several methods have been reported for the prediction of preeclampsia including maternal characteristics, doppler

ultrasound, calcium/creatinine ratio and serum uric acid. Other methods have been investigated recently as placental growth factor, soluble vascular endothelial growth factor receptor-1, soluble fms-like tyrosine kinase-1, soluble endoglin, free fetal nucleic acids, angiopoietins and pregnancy-associated plasma protein-A (*D'Anna et al., 2011*).

CA-125 is one of the tumor markers in hybridoma family, the most widely used serum marker in the detection of ovarian tumor from surface epithelium (*Radka et al., 2013*).

Threshold concentrations of CA-125 in healthy person are below 35 IU/mL, CA-125 levels are increased in 80%-85% of women in the advanced stages of ovarian cancer and in 50% of women with stage I disease. Elevated serum levels of CA-125 are found in physiological conditions as menstruation and pregnancy and levels also increased in pathological conditions as endometriosis, fibroid, pelvic inflammatory disease, ovarian hyperstimulation syndrome, end-stage liver disease and a variety of gynecological and non-gynecological neoplasms (*Alper et al., 2007*).

In pregnancy, serum CA-125 levels are increased in early pregnancy and immediately after birth implicating the disintegration of the maternal decidua (i.e., blastocyst implantation and placental separation) as a possible source of the tumor marker elevation (*Ayaty et al., 2007*).

AIM OF THE WORK

Research hypothesis:

CA -125 may be elevated in pregnant women with preeclampsia.

Research question:

- In pregnant women with preeclampsia, dose serum CA-125 level elevate?
- The aim of this work is to study the changes in serum CA-125 level in pregnant women with preeclampsia.