Serum Calcium, Magnesium, Uric Acid and C-reactive protein in Preeclampsia and Normal Pregnant Women

Thesis

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ABSTRACT

OBJECTIVE: To evaluate and to compare serum levels of calcium, magnesium, uric acid and C- reactive protein in mild, severe preeclamptic women and normal pregnant women and to correlate these levels with severity of the disease.

METHODS: This study was a prospective observational case-control study that was conducted at the department of Obstetrics and Gynecology, Cairo University Maternity Hospital on 65 pregnant women in the third trimester of pregnancy (gestational age from 28 to 40 weeks of pregnancy) selected from those who had attended the antenatal clinic and the reception room in the period from January 2014 to June 2015. They were divided into 3 groups: 20 patients with severe preeclampsia, 20 patients with mild preeclampsia and 25 normotensive women free of any medical disorder (control group). Blood samples were drawn on admission before initiation of any medical therapy. Serum calcium, magnesium, uric acid and C- reactive protein (CRP) levels were sent for analysis and results were compared between the three groups.

RESULTS: The mean values of CRP and serum uric acid were significantly higher in the pregnant women with preeclampsia than in the healthy control women ($p<0.05$), while the mean values of serum calcium were significantly lower in the pregnant women with preeclampsia than in the healthy control women ($p<0.05$). The mean serum magnesium didn't show significant differences between preeclampsia and healthy women ($p>0.05$).

CONCLUSION: These findings support the hypothesis that hypocalcaemia, hyperuricaemia and increased C-reactive protein could be possible etiologies of preeclampsia and that they correlate to the severity of the disease. Further studies are needed to determine the extent of their utility in identifying women at high risk for developing preeclampsia as well as to detect their role in the progress and outcome of the disease.

Key Words: Serum calcium, Serum magnesium, Serum uric acid, C-reactive protein, Preeclampsia, Normal pregnancy.

Acknowledgment

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LIST OF ABREVIATIONS

ACOG	:	American College of Obstetrics and Gynecology
ACE	:	Angiotensin-converting enzyme
Ach	:	Acetylcholine
AFP	:	Alpha- fetoprotein
ALT	:	Alanine Transaminase
ANOVA	:	Analysis of Variance
AP	:	Aminophenazone
APRT	:	Adenine Phosphorybosyltransferase
aPTT	:	Activated partial thromboplastic time
AT-3	:	Antithrombin-III
ATP	:	Adenosine Tri- Phosphate
ATPase	:	Adenosine Tri- Phosphatase
AST	:	Aspartate Transaminase
BMI	:	Body Mass Index
BP	:	Blood Pressure
BPP	:	Biophysical Profile
C	:	complement
Ca+	:	Calcium ion
CaR	:	Calcium Receptor
CBC	:	Complete Blood Count
CEC	:	Circulating Endothelial Cell
CRP	:	C-reactive protein
CT	:	Computed Tomography
CVP	:	Central Venous Pressure
DBP	:	Diastolic Blood Pressure
DCPS	:	Dichlorophenol sulfonate
DIC	:	Disseminated intravascular coagulopathy
DNA	:	Deoxynucleic Acid
ECF	:	Extracellular Fluid
GFR	:	Glomerular Filtration Rate
GMP	:	Guanosine Monophosphate
HCG	:	Human Chorionic Gonadotropin
HELLP	:	Hemolysis, Elevated Liver enzymes, Low Platelet count
HLA	:	Human Leukocyte Antigen

H2O2	:	Hydrogen Peroxide
HPRT	:	Hypoxanthine Phosphorybosyltransferase
HUS	:	Hemolytic Uremic Syndrome
HYPITAT	:	Hypertension and Preeclampsia Intervention Trial at Term
IL	:	Interleukin
IM	:	Intra-Muscular
IMP	:	Inosine Monophosphate
IOL	:	Induction of Labour
IUGR	:	Intra Uterine Growth Restriction
IV	:	Intra-Venous
K+	:	Potasium ion
K+-ATPase	:	Potassium ion - Adenosine Tri- Phosphatase
LDH	:	Lactate Dehydrogenase
LMP	:	Last menstrual period
MgSO4	:	Magnesium Sulfate
mg	:	Milli Gram
Min	:	Minute
MRI	:	Magnetic Resonance Imaging
Na+	:	Sodium ion
NHBPEP	:	National High Blood Pressure Education Group
NICU	:	Neonatal Intensive Care Unit
NK	:	Natural Killer
nNOS	:	neural Nitric Oxide Synthase
NO	:	Nitric Oxide
NOS	:	Nitric Oxide Synthase
OAT	:	Organic Ion Transporter
PAI	:	Plasminogen Activator Inhibitor
PAPP	:	Pregnancy Associated Protein A
PE	:	Preeclampsia
PGI2	:	Prostacyclin
PH	:	Potential of Hydrogen
PIH	:	Pregnancy-Induced Hypertension
PLGF	:	Placental Growth Factor
POD	:	Peroxidase
PRPP	:	5'-phosphoribosyl-1-pyrophosphate
PT	:	Prothrombin Time

PTD	:	Preterm Delivery
PTH	:	Parathyroid Hormone
PTHR	:	Parathyroid Hormone Receptor
P-Value	:	Value of Probability
R	:	Reagent
RDAs	:	Recommended Dietary Allowances
RNA	:	Ribonucleic Acid
ROS	:	Reactive Oxygen Species
RR	:	Relative Risk
SAA	:	Serum Amyloid A
SAP	:	Serum Amyloid P
SBP	:	Systolic Blood Pressure
SD	:	Standard Deviation
sEng	:	Soluble Endoglin
sFlT-1	:	Soluble Fms-Like Tyrosine Kinase 1
SOGC	:	Society of Obstetricians and Gynecologists of Canada
SPSS	:	Statistical Package for the Social Science
TGF	:	Transforming Growth Factor
Th	:	T- helper
TIPPS	:	Tests in Prediction of Preeclampsia Severity
TNF	:	Tumor Necrosis Factor
TTP	:	Thrombocytopenic Purpura
UA	:	Uric Acid
URAT 1	:	Urate Transporter 1
US	:	United States
VDR	:	Vitamin D Receptor
VEGF	:	Vascular Endothelial Growth Factor
WHO	:	World Health Organization
Wk	:	week
WR	:	Working Reagent
XO	:	Xanthine Oxidase

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INTRODUCTION

Hypertensive disorders of pregnancy affect about 10% of all pregnant women *(1)* and account for more than 50000 maternal deaths per year *(2)* and together they form one member of the deadly triad, along with hemorrhage and infection, that contribute greatly to maternal morbidity and mortality rates *(٣).*

With hypertension, the preeclampsia syndrome, either alone or superimposed on chronic hypertension, is the most dangerous *(٣).* Preeclampsia is a multisystem disorder that complicates 3%–8% of pregnancies in Western countries and constitutes a major source of morbidity and mortality worldwide *(4)(5).*

Preeclampsia (PE) is a syndrome, universally defined by the onset of hypertension (≥140/≥90 mmHg) and proteinuria (≥0.3 g/24 h) after 20 weeks of gestation in a previously normotensive woman that also may be associated with myriad, other signs and symptoms, and often with subnormal fetal growth *(6)(7).*

Preeclampsia is best described as a pregnancy specific syndrome of reduced organ perfusion secondary to vasospasm and endothelial activation, characterized by hypertension and proteinuria that may lead to multisystem involvement including renal, hematological, hepatic and cerebral impairment *(8).*

The exact cause of preeclampsia is currently unknown; the disorder is associated with endovascular abnormalities in the presence of placental trophoblastic tissue and may even occur in absence of fetus as seen in

patients with hydatidiform mole. Placental factors such as regulators of angiogenesis, growth factors, cytokines and regulators of arterial tone are released into maternal circulation leading to systemic endothelial cell dysfunction resulting in development of multisystem disease *(8)(9).*

Diverse medical conditions predispose women to develop preeclampsia. These include nulliparity, multiple gestations, diabetes mellitus, pre-existing renal disease, chronic hypertension, prior history of preeclampsia, extremes of maternal age(>35 years or <15 years), obesity, connective tissue disorders, factor V Leiden mutation and antiphospholipid antibody syndrome *(8)(10).*

Preeclampsia begins with inadequate trophoblastic invasion early in pregnancy, which produces an increase in oxidative stress contributing to the development of systemic endothelial dysfunction in the later phases of the disease, leading to the characteristic clinical manifestation of preeclampsia *(11).*

Elevated serum uric acid levels due to decreased renal urate excretion are frequently found in women with preeclampsia *(6).* Hyperuricemia due to oxidative stress is known to be associated with deleterious effects on endothelial dysfunction, oxidative metabolism, platelet adhesiveness and aggregation *(12).* Hence elevated serum uric acid is highly predictive of increased risk of adverse maternal and fetal outcome*(13).*

There is increasing evidence that preeclampsia is a systemic inflammatory disease *(14).* Inherent to the inflammatory process is the occurrence of an acute phase response. This response is induced by pro-

inflammatory cytokines (Interleukin 1 and 6) which are released from the inflamed tissue by inflammatory and/or parenchymal cells. These in turn stimulate the liver to synthesize a number of acute phase proteins. C - reactive protein (CRP) is a hepatically derived classical acute phase reactant *(15)*. CRP is an objective and sensitive index of overall inflammatory activity in the body *(16)*. Plasma CRP levels rise in cases of acute infection, malignancy and inflammatory diseases. It has been suggested that CRP, in accordance with its proposed function, may play a role in eliciting the inflammatory response characteristics of preeclampsia*(17)*.

On the physiological basis, calcium plays an important role in muscle contraction and regulation of water balance in cells. Modification of plasma calcium concentration leads to the alteration of blood pressure. The lowering of serum calcium and the increase of intracellular calcium can cause an elevation of blood pressure in preeclamptic mothers *(18)(19)*.

Besides, magnesium has been known as an essential cofactor for many enzyme systems. It also plays an important role in neurochemical transmission and peripheral vasodilatation. Magnesium sulfate appears to be safe and effective for the prevention of seizures and has been used as the drug of choice in severe preeclampsia and eclampsia treatment *(20)*.

The understanding of the underlying factors that explain the pathogenesis of preeclampsia and the early identification of the patients at risk of the disease will help in the development of preventative or early therapeutic interventions, aimed to reduce the associated morbidity and mortality during pregnancy, but also the long-term severe problems that preeclampsia may produce or is associated with *(11)*.

In view of the above facts this study aims at evaluating serum levels of calcium, magnesium, uric acid and C- reactive protein in patients with clinical profiles of preeclampsia and in normotensive pregnant women and correlating these levels with severity of preeclamsia.

AIM OF THE WORK

The aim of this study is:

1. To evaluate and to compare levels of serum calcium, magnesium, uric acid and C-reactive protein in pregnant patients with pre-eclampsia and normal pregnant women.

2. To correlate the levels of serum calcium, magnesium, uric acid and C-reactive protein in pregnant patients with preeclampsia with the severity of the disease.

3. To evaluate and to compare the neonatal outcome regarding neonatal birth weight, Apgar score and neonatal intensive care unit admission in both pregnant patients with preeclampsia and normotensive control group.

CHAPTER I

Hypertensive Disorders in Pregnancy

Hypertension is one of the most common medical complications of pregnancy and affects both fetal and maternal health sometimes with life-threatening consequences *(21)*.

Hypertensive disorders of pregnancy are important cause of severe acute morbidity, long term disability and death among mothers and babies*(5)*.

Worldwide, hypertensive disorders of pregnancy affect about 10% of all pregnant women *(1)* and account for more than 50000 maternal deaths per year *(2)*.

The majority of deaths related to hypertensive disorders can be avoided by providing timely and effective care to pregnant women presenting with such complication *(22)*. Thus, many national working groups have presented consensus documents aiming at achieving consistency in diagnosis and management of these diseases *(23)*.

Classification and Characteristics of Hypertensive Disorders Complicating Pregnancy:

Preeclampsia is part of a spectrum of hypertensive disorders that complicate pregnancy. As specified by the National High Blood Pressure Education Program (NHBPEP) Working Group, the classification is as follows *(24)*:

- Preeclampsia/Eclampsia