CLINICAL SIGNIFICANCE OF PLASMA LEVEL OF NEOPTERIN AND HIGHLY SENSITIVE CRP IN PRE-ECLAMPSIA

Thesis

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Shams Eldoha Galal Eldean Mansour

Dedication

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

My lovely sister (Marwa) for for being the light of my life.

My best friends (Safia Ahmed & Mena Zakria) for their love and support.

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G6PDH	:	Glucose-6-phosphate dahydrogenase
GFR	:	Glomerular filtration rate
GLDH	:	Glutamate dehydrogenase
GTP	:	Guanosine triphosphate
GVH	:	Graft versus host
Hb	:	Hemoglobin
HDL	:	High-density lipoprotein
HELLP	:	Haemolysis elevated liver function tests, and low platelets
HIF	:	Hypoxia-inducible factor
HIV	:	Human immunodeficiency virus
HK	:	Hexokinase
HPLC	:	High performance liquid chromatography
Hs-CRP	:	Highly sensitive C - reactive protein
ICSI	:	Intra-cytoplasmic sperm injection
IFN-γ	:	Interferon gamma
IL-2	:	Interleukin-2
IUGR	:	Intrauterine growth retardation
IVF	:	In vitro fertilization
KDR	:	Kinase domain region
KIR	:	Killer Ig-like receptor
LCN-2	:	Lipocalin-2
LDH	:	Lactate dehydrogenase
LDL	:	Low density lipoprotein
LIA	:	Latex immunoassay
MAb	:	Monoclonal antibody
MDH	:	Malate dehydrogenase
mRNA	:	Massenger riboneucleic acid

List of Abbreviations

Abb.		
NAFLD	:	Non-alcoholic fatty liver disease
NASH	:	Non alcoholic steatohepatits
NEO	:	Neopterin
NK	:	Natural killer
NPV	:	Negative predictive value
OMT	:	Oral mucosal transudates
PACIA	:	Particle counting immunoassay
PAPP-A	:	Pregnancy associated plasma protein- A
PlGF	:	Placental growth factor
PP-13	:	Placental protein-13
PPV	:	Positive predictive value
PTPS	:	Pyrovoyl- tetrahydropterin synthase
PTX-3	:	Pentraxin-3
RA	:	Rheumatoid arthritis
RIA	:	Radioimmunoassay
RNS	:	Reactive nitrogen species
ROC	:	Receiver operating characteristic
ROS	:	Reactive oxygen species
RNS	:	Reactive nitrogen species
RT-PCR	:	Reverse transcriptase polymerase chain reaction
SAP	:	Serum amyloid P
SBP	:	Systolic blood pressure
SD	:	Standard deviation.
s-Eng	:	Soluble endoglin
sFlt-1	:	Soluble fms-like tyrosine kinase-1
SIRS	:	Systemic inflammatory response syndrome
SLE	:	Systemic lupus erythematosus

List of Abbreviations

Abb.		
SOGC	:	Society of Obstetricians and Gynaecologists of Canada
TGF-β1	:	Transforming growth factor-β1
TH	:	T helper
TN	:	True negative
TNF-α	:	Tumer necrotic factor-α
VEGF	:	Vascular endothelial growth factors

INTRODUCTION

Pre-eclampsia complicates 3–7% of all pregnancies and continues to be a major contributor to maternal and neonatal morbidity and mortality. It is characterized by a new onset of maternal hypertension, proteinuria, and edema *(Naghavi et al., 2010).* It also, accounts for 12-18% of pregnancy-related maternal deaths especially in developing countries *(Sharon et al., 2008).*

In spite of its relevant epidemiologic impact, the complete pathogenesis of this disease still remains unclear, underlining a multifactorial aetiology. Deficient remodelling of the spiral arteries during the interaction between maternal and fetal sides at the time of trophoblast invasion has been postulated as a cause of placental insufficiency leading to the release of the inflammatory factors in the systemic maternal circulation *(Carty et al., 2010).* Endothelial dysfunction has been hypothesized to be part of an excessive maternal inflammatory response to pregnancy *(Fisher et al., 2011).*

Several biological markers were investigated to diagnose pre-eclampsia in pregnant women, although these markers were altered in pre-eclampsia, they have a major disadvantage lacking both specificity and sensitivity *(Baumann et al., 2007).*

Neopterin (NEO) is a protein derivative present in body fluids which is synthesized and released solely by activated macrophages and monocytes in response to inflammation and

immune system activation *(Ashok et al., 2011).* It exhibit distinct biochemical effects as it acts as a mediator and modulator in the course of inflammatory and infectious processes most likely via interactions with reactive oxygen or nitrogen intermediates affecting the cellular redox state *(Hoffmann et al., 2011).*

Measurements of plasma NEO concentrations have been used to evaluate progression of viral infections, renal transplant rejection, severe systemic inflammatory diseases, nephritic syndrome and several autoimmune diseases *(Plata-Nazar and Jankowska, 2011).*

C-reactive protein (CRP) is low molecular weight protein produced by the liver as an acute phase reactant in response to inflammatory stimuli, as it exhibits important role in the inflammatory process such as complement activation, T-cell binding, inhibition of clot retraction, suppression of platelet and lymphocyte function and enhancement of phagocytosis by polymorphonuclear leukocytes *(Nakamura et al., 2013).*

A high-sensitivity CRP (hs.CRP) is a sensitive assay that measures very low levels of CRP. So, it is considered as an important marker of subclinical inflammation and thus improves the clinical assessment and prognosis *(Clyne and Olshker, 2013).*

AIM OF THE STUDY

The aim of the present study is to assess serum neopterin and highly sensitive CRP in a group of pregnant females with pre-eclampsia to evaluate their clinical utility in diagnosis and assessment of severity of the disease.

I- PRE-ECLAMPSIA

A- Definition:

Pre-eclampsia is a multi-system disorder peculiar to human pregnancy and considered the major leading cause of maternal and perinatal mortality and adverse pregnancy outcomes worldwide. It is defined as de novo hypertension (blood pressure ≥140/90 mmHg measured at least 2 or more occasion 4 hours apart) appearing after 20 weeks of gestation accompanied by proteinuria (≥0.3 g/24 h or ≥2+ by dip stick on 2 or more occasions 4 hours apart) *(Rangeen, 2010)*.

B- Epidemiology:

Pre-eclampsia complicates about 2-8% of all pregnancies worldwide and results in more than 63,000 maternal deaths every year. The maternal mortality rate is highest in low- and middle- income countries but pre-eclampsia is also potentially life threatening in high income countries, as it affects 3% of pregnant women in the western world *(Hutcheon et al., 2011)*.

In developing countries, pre-eclampsia is responsible for 12-18 % of pregnancy-related maternal deaths. It affects 4.4% of all deliveries because of illiteracy, lack of health awareness and education, poverty, and false beliefs that prevent women from seeking medical advice during pregnancy *(Sablah, 2011)*.