سورة البقرة الاية ٣٢

Comparative study between early second trimester maternal serum homocysteine and leptin as predictors of preeclampsia

A thesis study Submitted in Partial Fulfillment of MS Degree in Ob/Gyn

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دراسة مقارنة لقياس مستوى الهموسيستيين والليبتن فى مصل الامهات للتنبؤ المبكر لحدوث حالات ارتفاع ضغط الدم المصاحبة للحمل

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Abstract

50 women were included into the statistical analysis and 26 (52%) of them developed pre-eclampsia during follow-up.

This study revealed a cutoff level of homocysteine and leptin which are 8.44 and 96.4 ng/ml respectively above which pregnants are more prone to develop preeclampsia.

The present study qualitatively showed a more positive association between homocysteine and preeclampsia (PE) (sensitivity: 95.8%, specificity: 100%) than between leptin and PE (sensitivity: 58.33%, specificity: 66.67%). Thus our study reveals that homocysteine is a more useful predictor marker than leptin in predicting preeclampsia

Keywords:

Homocysteine; pre-eclampsia; leptin; gestational age; pregnancy; Hypertension .

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ACOG	American College of Obstetrics and Gynecology
ADAMTS13	A disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13.
ADPase	Adenosine diphosphatase
ADP	Adenosine diphosphate
AFI	Amniotic fluid index
Ag II	Angiotensin II
AgRP	Agouti-related peptide
ALT	Alanine transaminase
ANOVA	Analysis of variance
APCR-V	Activated protein C resistance – V
AST	Aspartate transaminase
AT III	Anti-thrombin III
ATP	Adenosine triphosphate
BAECs	Bovine aortic endothelial cells
BeWo	Choriocarcinoma cell
CAD	Coronary artery disease
CAM	Chorioallantoic membrane
CBS	Cystathionine beta-synthase
CD	Cluster of differentiation
CI	Confidence interval
COX-1	Cyclooxygenase -1
CVA	Cerebrovascular accident
DNA	Deoxyribonucleic acid
EDTA	Ethylenediaminetetraacetic acid
ET	Essential thrombocytopenia
fl	falcon
FMV	Flow-mediated vasodilatation
FPIA	Fluorescence polarization immunoassay
G	Group
GA	Gestational age
GLM	General linear models
GP	Glycoprotein
H.S	High significance
hCG	Human chorionic gonadotropin
H2O2	Hydrogen peroxide
HELLP	Hemolytic anemia, elevated liver enzymes, low platelet count
HIT	Heparin-induced thrombocytopenia
HLA-G	Histocompatibility leucocyte antigen-G
HMEC-1	Human microvessel endothelial cell-1
HOPE-2	Heart Outcomes Prevention Evaluation-2
hsCRP	High sensitive C-reactive protein
IGF-1	Insulin-like growth factor-1
ILβ	Interleukin β

IL6	Interleukin 6
ITP	Immune thrombocytopenic purpura
IUGR	Intra-uterine growth restriction
LDH	Lactate dehydrogenase
LDL	Low density lipoprotein
LEP	Leptin gene
LEPOB	Lifelong Educational Project on Brownfields
LEPRA	Leptin receptor-A
LEPRB	Leptin receptor-B
LEPRC	Leptin receptor-C
LEPRD	Leptin receptor-D
LIBS1	Ligand-induced binding site 1
LIGHT	Lymphotoxin-like Inducible protein that competes with Glycoprotein D for Herpesvirus entry mediator on T lymphocytes.
mcg	Microgram
MI	Myocardial infarction
ml	milliliter
mmHg	Millimiter of mercury
MS	Methionine synthetase
MTHFR	Methylenetetrahydrofolate reductase
ng	nanogram
NHBPEP	National High Blood Pressure Education Program
NO	Nitric oxyde
NPV	Negative predictive value
NPY	Neuropeptide Y
NSAID	Non steroidal anti-inflammatory drugs
O2	Oxygene
Ob/Gyn.	Obstetrics and Gynecology
ob/ob	Obese
Ob-R	Leptin receptor
P	Probability
PAC1	Postsynaptic density and cytoskeleton enriched -1
PAF	Platelet activating factor
PAOD	Peripheral artery occlusive disease
PAR-1	Protease activated receptor type 1
P2Y-1	Purinergic receptor, G-protein coupled,1
PDGF	Platelet derived growth factor
PDW	Platelet volume distribution
PE	Preeclampsia
PECAM	Platelet endothelial cell adhesion molecule
PGD2	Prostaglandin D2
PGI2	Prostacyclin
PlGF	Placental growth factor
PLT	Platelets
PPV	Positive predictive value
PRP	Platelet-rich plasma
PTG	Beta-thromboglobulin
PTHrP	Parathyroid hormone related peptide

PV	Prevalence
r	Correlation coefficient
RANTES	Regulated upon activation, normal T-cell expressed and secreted.
RIBS	Receptor-induced binding site
RNA	Ribonucleic acid
ROC	Receiver operating characteristic curve
ROS	Reactive oxygen species
RR	Relative risk
sCD40L	Serum soluble CD40 ligand
SAM	S-adenosyl methionine
SD	Standard deviation
sFlt-1	Soluble form tyrosine kinase like receptor type-I
T-test	Test for significance
Tct	Thrombocrit
TFG	Transforming growth factor
Th1	Helper T-cell type 1
Th2	Helper T-cell type 2
THF	Tetrahydrofolate
TNF-α	Tissue necrotic factor-alpha
Trc	Platelet count
TTP	Thrombotic thrombocytopenia
TXA2	Thromboxane A2
VEGF	Vascular endothelial growth factor
VLCD	Very low calory diet
vWF	Von willebrand factor
αδSPD	Alpha-delta platelet storage pool deficiency
α-MSH	Alpha-melanocyte stimulating hormone
μmol/L	Micromole per liter
-CH2-	Methylene group
12-HETE	12-hydroxyeicosatetrenoate

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INTRODUCTION

Introduction

Preeclampsia (PE) is a pregnancy-specific multisystem disorder that is characterized by development of hypertension and proteinuria after 20 weeks of gestation, resolving by 6-12 weeks postpartum in a previous normotensive women (**Sibai et al., 2003).** It occurs in about 5% to 10% of all pregnancies and results in substantial maternal and neonatal morbidity and mortality (**Cunningham et al., 2001).**

Although the etiology of preeclampsia is still unclear, recent studies and successive hypothesis have been proposed, each being challenged by subsequent publications, the current most plausible hypothesis involves abnormal placentation leading to placenta ischaemia **(Chun Lam et al., 2005)**

Preeclampsia has been reported to be associated with an increase in maternal plasma leptin concentrations. Leptin, a protein product of the obesity ;Lifelong Educational Project on Brownfields (Lepob) gene, is synthesized and secreted by adipocytes . It is also synthesized by the placenta and could contribute to circulating leptin during pregnancy . The significant increase in maternal circulating leptin during the first and second trimesters of normal pregnancy is suggested to be in response to the marked changes in maternal weight, energy expenditure, and hormonal status. Also, increased maternal Leptin will increase circulating free fatty acids and glucose, providing nutritional support for the fetus (**Masuzaki et al., 2004)**

Homocysteine is a demethylated metabolite of the essential amino acid methionine and is associated with increased oxidative stress and lipid peroxidation, smooth muscle proliferation, abnormalities of coagulation, and endothelial dysfunction.(**Granger et al., 2002)**

Homocysteine has been reported to inhibit endothelial cell proliferation, which is closely related to angiogenesis. However, the relationship between homocysteine and angiogenesis has been unknown. To clarify whether homocysteine would inhibit angiogenesis in vitro and in vivo, **Nagai** examined the effect of homocysteine on tube formation by bovine aortic endothelial cells (BAECs) and by human microvessel endothelial cell-1 (HMEC-1) in vitro, and on angiogenesis in vivo using the chorioallantoic membrane (CAM) assay, as well as on BAEC proliferation and migration. Homocysteine, but not cysteine, inhibited BAEC proliferation, migration, and tube formation in a dose-dependent

manner. It was suggested that homocysteine inhibited angiogenesis by preventing proliferation and migration of endothelial cells. (**Murakami S. et al., 2001)**

Most studies qualitatively showed a positive association between hyperhomocysteinemia and preeclampsia. Homocysteine concentrations were slightly increased in normotensive pregnancies that later developed preeclampsia and were considerably increased once preeclampsia is established.**(Zeeman GG. Et al., 2003).**

However, another study was unable to exhibit any difference in serum homocysteine levels at 16 weeks gestation between the 2 groups. They concluded that there were not major differences in homocysteine levels before the manifestation of preeclampsia.**(Vollset et al., 2000).**

Leptin stimulates angiogenesis resulting in maintaining energy homeostasis and its serum concentrations correlate highly with the amount of body fat (**Considine et al. 1996, Mantzoros & Moschos 1998**). Leptin may facilitate lipid release from the fat stores to maintain energy homeostasis (**Sierra-Honigmann et al. 1998**).

During pregnancy the maternal serum leptins levels are elevated about two to three times compared to the non pregnant state and the concentrations are highest during the second trimester of pregnancy (**Sattar et al. 1998, Sivan et al. 1998**). This extra production of leptin could be derived from adipocytes but placental trophoblasts must also be taken into account as a source of leptin production (**Masuzaki et al. 1997, Mise et al 1998).**

In PE the serum leptin levels of the mother are higher and the leptin gene (LEP) is upregulated in the placenta **(Iwagaki et al. 2004**).

Preeclampsia has been reported to be associated with an increase in maternal plasma leptin concentrations . In cross-sectional and longitudinal study, plasma leptin concentrations were significantly greater in women with preeclampsia than in normal control subjects. However some studies report the mild elevation of Leptin before 20 weeks of gestational age in patients who developed later on preeclampsia.

In this current thesis, we will emphasize, through an observational study, the role of homocysteine and leptin in preeclampsia and if they can be used as predictors of preeclampsia before 20 weeks of gestation.