Comparative Study between the Blood Level of Folate and Vitamin B١٢ in Preeclamptic Versus Normotensive Pregnant Ladies with Correlation to Abnormal Uterine and Umbilical Artery Doppler Findings and Adverse Pregnancy Outcome (Maternal and Fetal)

A Thesis

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بسم الله الرحمن الرحيم

{وَقُلِ اعْمَلُوا فَسَيَرَى اللهُ عَمَلَكُمْ وَرَسُولُهُ وَالْمُؤْمِنُونَ وَسَتُرَدونَ إِلَى عَالِمِ الْغَيْبِ وَالشهَادَةِ فَيُنَبئُكُمْ بِمَا كُنتُمْ تَعْمَلُونَ(١٠٥)}

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Abstract

Preeclampsia is a disease with worldwide significance to mothers and infants. Its greatest impact is in developing countries, where it accounts for 20–80% of the maternal mortality**.** Folate and vitamin B12 play an important in metabolism of homocysteine. Many studies address homocysteine in preeclampsia and prove hyperhomocysteinemia (a factor that causes endothelial injury) in preeclampsia. **Material&Methods:** serum folate and B12 are measured in 79 pregnant patients with preeclampsia 20-35 years old, singleton pregnancy at 34-40 weeks gestation, not obese not chronically hypertensive, not having chronic renal or liver disease nor diabetic and 113 controls matched to case in age , gestational age. Doppler velocimetry of uterine and umbilical arteries is done. **Results:** Serum folate is significantly lower in preeclamptic patients versus normal pregnants (9.4 ±8.8 versus 20.288 ±13.9 nmol/L in controls, $p<0.001$), Serum B12 level is not significantly different in preeclamptic patients from control group (350.7±283 versus 424±364 pg/ml, P-value=0.14). Serum folate is significantly correlated to uterine RI (Pearson correlation=-0.432, $p<0.001$) and PI (Pearson correlation =-0.458, $p<0.001$). Serum folate is also significantly negatively correlated to umbilical RI (Pearson correlation = -0.225, p -Value = 0.002), PI (Pearson correlation =-0.224, p=0.002). Low serum folate is significantly correlated to poor maternal outcome (higher maternal serum creatinine, r== -0.354 $P<0.001$, higher serum ALT (Pearson correlation of Folate and ALT = -0.213, P-Value = 0.004), higher serum AST (Pearson correlation of Folate and AST = -0.244, P-Value = 0.001) and lower platelet count (Pearson correlation of Folate and PLT = -0.235, P-Value = 0.047). Low serum folate is significantly correlated to poor perinatal outcome (preterm labour, low birth weight, low Apgar score –less than 7 at 5minutes- and neonatal ICU admission).**conclusion:** serum folate is significantly lower in preeclamptic pregnants with significant correlation to increased uterine and umbilical RI, PI and bad maternal and neonatal outcome.

Key words: preeclampsia, folate, B12, umbilical, uterine Doppler.

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LIST OF ABBREVIATIONS

AFP	: alpha feto protein
ALT	: alanine aminotransferase
AST	: aspartate aminotransferase
BP	: blood pressure
c	: speed of ultrasound wave in tissue
C3	: complement 3
CI	: confidence interval
CLASP	: Collaborative Group trial of low-dose aspirin for the prevention and treatment of preeclampsia
Co	: cobalt
CW	: continuous wave
DFEs	: dietary folate equivalents
DNA	: deoxy-ribo-nucleic acid
DOC	: deoxycorticosterone
ECE	: endothelin converting enzyme
ET-1	: endothelin 1
f0	: frequency of the emitted ultrasound
fd	: Doppler shift in the frequency
FGR	: fetal growth restriction
FRs	: folate receptors
FVW	: flow velocity waveform
gw	: gestation week
H2folate	: dihydro-folate
H4folate	: tetra-hydro-folate
hCG	: human chorionic gonadotropin
HDL	: high density lipoprotein
HELLP	: hemolysis (H), elevated liver enzymes (EL), and low platelets (LP)
IgA	: immunoglobulin A
IgM	: immunoglobulin M
IUGR	: Intra uterine growth restriction
KHz.	: Kilo-Hertz
LDH	: lactate dehydrogenase
LDL	: low density lipoprotein
MHz	: Mega-Hertz
MMA	: methylmalonic acid
MTHFR	: methylenetetrahydrofolate reductase
ND	: not determined
NHBPEP	: National High Blood Pressure Education Program
NI	: notch index

NICHD	: National Institute of Child Health and Development
NO	: nitric oxide
NTDs	: neural tube defects
OFCs	: orofacial clefts
PAI	: plasminogen activator inhibitor
PGI2	: prostacyclin (prostaglandin I2)
PI	: pulsatility index
PlGF	: placental growth factor
PW	: pulsed wave
RDA	: recommended dietary allowance
RI	: resistance index
SD	: standard deviation
sFlt1	: soluble fms-like tyrosine kinase 1
TBBC	: total vitamin B_{12}-binding capacity
Th1	: T helper 1
Th2	: T helper 2
tHcy	: total homocysteine
TNF	: tumor necrosis factor
UADV	: uterine artery Doppler velocimetry
UA-FVW	: umbilical artery flow velocity waveform
UBBC	: unsaturated vitamin B_{12}-binding capacity
v	: velocity of the moving target
VEGF	: vascular endothelial growth factor
Vmax	: Velocity maximum
θ	: angle between the ultrasound beam and the direction of movement of the target

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INTRODUCTION & AIM OF WORK

Preeclampsia is a disease with worldwide significance to mothers and infants. Its greatest impact is in developing countries, where it accounts for 20–80% of the maternal mortality **(*Williams 2005)***.

Application of appropriate prenatal care and management (consisting largely of the delivery of women with preeclampsia before the disease progresses to become life threatening) has largely eliminated maternal mortality, frequently at the cost of preterm delivery.

Ten percent of cases occur at a stage of gestation where delivery exchanges a sick fetus in utero for a sick premature infant in the nursery.

Perinatal mortality of infants of preeclamptic mothers is five-fold greater than for nonpreeclamptic women, and indicated preterm deliveries for preeclampsia account for 15% of preterm births **(*Williams 2005)***.

In the past 15 years thinking about the disorder has changed and all aspects of the syndrome are considered, with an attendant increase in understanding. For many years nutrition has been suggested to play a role in preeclampsia.

Current concepts of the genesis of preeclampsia that include endothelial dysfunction, inflammatory activation, oxidative stress and predisposing maternal factors provide targets for well-designed nutritional investigation. ***(Tamura et al 2006).***

Folate coenzymes act as acceptors and donors of one-carbon units in a variety of reactions critical to the metabolism of nucleic acids and amino acids.

Another role of methyl donation is the conversion of homocysteine to methionine. Homocysteine is an essential amino acid required for the growth of cells and tissues in the human body.

The amount of homocysteine in the blood is regulated by three vitamins: folic acid, vitamin B_{12}, and vitamin B_6. Reduced folate intake or genetic abnormalities of folate metabolism are associated with increased serum homocysteine concentration (***Powers et al 1998).***

In the past few years many studies address homocysteine in preeclampsia and prove hyperhomocysteinemia (a factor that causes endothelial injury) in preeclampsia and pregnancy induced hypertension ***(Rajkovic 1997, Powers 1998, Laivuori 1999, Hogg 2000, Wang 2000, Vollset 2000, van der Molen***

2000, Hietala 2001, Cotter 2001, Sanchez 2001, Murakami 2001, Cotter 2003, Zeeman 2003, López-Quesada 2003, El-Khairy 2003, Powers 2003, D'Aniello 2003, Patrick 2004, Vanderjagt 2004, Vadachkoria 2004, ***Nurk 2004, Steegers-Theunissen 2004, Powers 2004 and all their colleagues)***.

Homocysteine can be remethylated to methionine by a pathway requiring folic acid as a methyl donor. In addition to adequate folic acid, the pathway requires vitamin B12 as an important cofactor.

Alternatively, homocysteine can be removed by transsulfuration, a pathway dependant on the cofactor vitamin B6. Enzymatic defects in either of these pathways results in increased homocysteine hence increasing the risk of preeclampsia.

Also since last decade, interest has continued in uterine artery Doppler velocimetry (UADV) as a screening technique to predict adverse pregnancy outcome such as preeclampsia, for pregnancy risk scoring, and as an entry criterion in randomized trials on medical therapies for the prevention of preeclampsia and intrauterine growth restriction.

As a result of the trophoblast invasion of the spiral arteries and increase in uterine perfusion, end-diastolic flow in the uterine artery increases as the pregnancy advances.

However, in abnormal pregnancy there is poor trophoblast invasion of the spiral arteries. Subsequently, the end-diastolic flow does not increase or the diastolic notch does not disappear.

As regards the umbilical Doppler, several studies associated abnormal umbilical artery Doppler velocity waveforms (reduced, absent and reversed end diastolic flow) with poor perinatal outcome ***(Karsdorp et al 1998, Oettle et al 2000, Soregalori et al 2001).***

In a more recent study, ***Neilson et al (2003)*** examined eleven good quality trials in nearly 7,000 women. Use of Doppler ultrasound as a guide in management of growth restricted fetuses results in reduction of perinatal deaths, fewer induction of labour and fewer admissions to hospital.