The Correlation Between Fetal Hemoglobin in Maternal Blood and The Severity of Pre-eclampsia

Thesis

Submitted for Partial Fulfillment of Master Degree
in **Obstetrics & Gynecology**

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بسم الله الرحمن الرحيم

وقُلِ اعْمَلُوا فَسَيَرَى اللَّهُ عَمَلَكُمْ وَرَسُولُهُ والْمُؤْمِنُونَ

صدق الله العظيم

سورة التوبة آية (١٠٥)

*First, thanks are all due to **Allah** for Blessing this work until it has reached its end, as a part of his generous help throughout our life.*

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Mariam Mohsen Ahmed Nassar

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List of Abbreviations

ACOG	:	American college of obstetrics and gynaecology.
AFLP	:	Acute fatty liver of pregnancy
ALT	:	Alanine aminotransferase
AST	:	Aspartate aminotransferase
AUC	:	Area under the curve
BMI	:	Body mass index
BP	:	Blood pressure
BPP	:	Biophysical profile
CBC	:	Complete blood count
CI	:	Confidence interval
CNS	:	Central nervous system
CO_2	:	Carbon dioxide
DA	:	Diagnostic accuracy
DBP	:	Diastolic blood pressure
DIC	:	Disseminated intravascular coagulopathy
DNA	:	Deoxyribonucleic acid
ELISA	:	Enzyme-linked immunosorbant assay
ET	:	Endothelin
Fe	:	Iron
GA	:	Gestational age
Hb	:	Hemoglobin
Hb F	:	Fetal hemoglobin
HPFH	:	Hereditary persistence of fetal hemoglobin
HRP	:	Horseradish Peroxidase
HUS	:	Hemolytic uremic syndrome
INR	:	International normalised ratio
IQR	:	Inter-quartile range
ISSHP	:	International Society of the Study of Hypertension in Pregnancy
IU	:	International unit
IUGR	:	Intrauterine growth restriction
KIRs	:	Killer immunoglobulin receptors
LDH	:	Lactate dehydrogenase
MAP	:	Mean arterial pressure
NADH	:	Nicotinamide adenine dinucleotide hydrogen
NADPH	:	Nicotinamide adenine dinucleotide phosphate

List of Abbreviations (Cont.)

NHBPEP:		The National High Blood Pressure Education Program
NICE	:	National Institute for Health and Care Excellence
NK	:	Natural killer
NO	:	Nitric oxide
NST	:	Nonstress test
O_2	:	Oxygen
PlGF	:	Placental growth factor
PNV	:	Predictive negative value
PPV	:	Predictive positive value
PT	:	Prothrombin time
RBC	:	Red blood cell
RIA	:	Radioimmunoassay
RO	:	Reactive oxygen species
ROC	:	Receiver operator characteristics
r_s	:	Spearman's rank correlation coefficient
SBP	:	Systolic blood pressure
SD	:	Standard deviation
SE	:	Standard error
SGOT	:	Serum glutamic oxaloacetic transaminase
SGPT	:	Serum glutamic pyruvic transaminase
SLE	:	Systemic lupus erythematosus
SOD	:	Superoxide dismutase
SPSS	:	Statistical package for social sciences
TTP	:	Thrombotic thrombocytopenic purpura
VEGF	:	Vascular endothelial growth factor

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Introduction

Pre-eclampsia has been diagnosed in nearly 3 to 7% of pregnant women annually. It has been estimated that each year it affects 8.5 million pregnant women around the world. Pre-eclampsia is responsible for approximately 40% of severe obstetric morbidity and is considered as one of the leading causes of mortality during pregnancy in both mothers and fetuses. The worldwide annual cost is around 18-22 billion US dollars ***(Hansson et al., 2013)***.

According to the International Society for the Study of Hypertension in Pregnancy (ISSHP), pre-eclampsia can be defined as newly developed hypertension occurring after 20 weeks of pregnancy together with proteinurea. Hypertension involves a systolic blood pressure of more than or equal to 140mmHg and/or a diastolic blood pressure more than or equal to 90 mmHg. There should be two readings with an interval of at least four hours in between. Proteinurea mean total protein in 24 hours equal to or more than 300 mg per day ***(Anderson et al., 2011).***

In order to find a definitive treatment for pre-eclampsia we must first understand its pathology. Many theories have been proposed for its pathogenesis and hence pre-eclampsia has been called the 'disease of theories' ***(Pepple et al., 2006).***

The fact that termination of pregnancy and delivery of the placenta is necessary in the management of pre-eclampsia

leads to the presumption that the placenta is the source of the pathogenesis. A recent theory composed of two stages is now generally accepted.The first stage begins with a defect in placental formation impairing placental perfusion and oxygen transport which results in ischemia and the formation of free oxygen radicals. High levels of free oxygen radicals lead to oxidative stress causing damage to the placental barrier. This damage causes leakage between the maternal and fetal circulation systems and hence placental and fetal factors leak into the maternal circulation ***(Roberts et al., 2009)***.

In the second stage, this leakage leads to maternal systemic inflammation and endothelial damage. The leaking fetal and placental factors are usually foreign to the maternal immune system, contributing to the inflammation that aggravates the endothelial damage. Endothelial damage is responsible for the clinical manifestations of preeclampsia: hypertension, edema and proteinuria. The leaking factors link the two stages and identifying them will significantly help in the management of pre-eclampsia ***(Tjoa et al., 2006)***.

One of these factors is recently thought to be hemoglobin F. Normally it compromises less than 1% of the hemoglobin in adults. Hemoglobin is the major oxygen carrier of blood but it consists of dangerous component. Hemoglobin is a tetramer consisting of four globin subunits each carrying an iron-containing heme group in its active center. Fetal hemoglobin (Hemoglobin F) is made up by two alpha chains and two gamma chains. Most hemoglobin is

found strictly compartmentalized within erythrocytes, but during pathological hemolytic conditions, quantities of hemoglobin leak out into the circulation ***(Sverrisson et al., 2013)***.

Increased serum levels of hemoglobin F in maternal blood of pre-eclamptic patients, suggests that free hemoglobin F leaks through the placental barrier and into the maternal circulation. The heme group contains an iron atom whose redox activity is the basis for the strong oxidative reactivity of free hemoglobin which damages lipids, protein and DNA through direct oxidation and generation of free oxygen radicals such as superoxide anions. Free ferrous hemoglobin is a strong binder of the vasodilator nitric oxide which indirectly leads to a vasoconstrictive effect. As a result hemoglobin and its degradation products are toxic and cause oxidative stress, hemolysis, vasoconstriction, kidney and vascular endothelial damage. ***(Buehler et al., 2010)***

Once elevated gene-expression levels of hemoglobin F in the lumen of the vessels of pre-eclamptic placentas were found, the hypothesis that hemoglobin F is involved in the cause of pre-eclampsia could be formed. By aggravating the oxidative stress, causing damage to the placental barrier and leaking into the maternal bloodstream causing endothelial damage and vasoconstriction hemoglobin F acts as a potential causative factor of pre-eclampsia ***(Hansson et al., 2013).***

Accordingly, hemoglobin F can be used as a prognostic tool for pre-eclampsia. In addition to using it as a diagnostic tool; knowing the factors causing pre-eclampsia will help in its future management. In the case of hemoglobin F, the protein: α1-microglobulin has recently been shown to be involved in the defense against cell-free hemoglobin and heme. It is a radical scavenger that has reductase and antioxidant properties. What gives it more privilege to other antioxidants,is that in addition to its antioxidant properties it has the ability to bind to heme groups and has a higher molar capacity and effective clearance mechanisms ***(Olsson et al., 2009).***

Aim of the Work

Study Hypothesis:

The levels of hemoglobin F in maternal blood are correlated to the severity of pre-eclampsia.

Study Question:

Is the level of hemoglobin F in maternal blood correlated to the severity of pre-eclampsia?

This study aims to find a correlation between fetal hemoglobin in maternal blood and the severity of pre-eclampsia, hence if it is proved to be affected by the severity of pre-eclampsia, factors such as α1-microglobulin can be used as a treatement or prophylaxis for pre-eclampsia. Therefore the study consists of two outcomes:

Primary outcome: fetal hemoglobin in maternal blood is increased with an increase of severity in pre-eclamptic patients.

Secondary outcome: fetal hemoglobin is a factor involved in the pathology of pre-eclampsia and antioxidant substances like α1-microglobulin can be used to counteract fetal hemoglobin and hence treat or prevent pre-eclampsia.