First Trimesteric Doppler Study and Maternal Serum PAPP-A for Prediction of Pre-Eclampsia

Thesis

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قَالُواْ سُبْحَانَكَ لاَ عِلْمَ لَنَا إِلاَّ مَا
عَلَّمْتَنَا إِنَّكَ أَنتَ الْعَلِيمُ الْحَكِيمُ

سورة البقرة
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LIST OF ABBREVIATIONS

AUC	Area Under the Curve
β-HCG	Beta Human Chorionic Gonadotrophs
BMI	Body Mass Index
cDNA	Complementary Deoxyribonucleic Acid
CW	Continuous Wave
DBP	Diastolic Blood Pressure
FGR	Fetal Growth Restriction
FSH	Follicular Stimulating Hormone
GA	Gestational Age
HELLP	Hemolytic anemia, Elevated Liver enzymes and Low Platelet count
HPL	Human Placental Lactogen
ICSI	Intracytoplasmic Sperm Injection
IGF	Insulin Growth Factor
IGFBP	Insulin Growth Factor Binding Protein
IV	Intravenous
IVF	In vitro Fertilization
LH	Luteinizing Hormone
L/S	Lecithin/Sphyngomyelin
Lt	Left
MAP	Mean Arterial Pressure
mRNA	Messenger ribonucleic acid
MMP	Matrix metalloproteinase
Ng	Nanogram
NPV	Net present value
NT	Nuchal translucency thickness
PAPP-A	Pregnancy-associated plasma protein-A
PE	Pre-eclampsia
PI	Pulsatility index
PP-١٣	Placental protein-١٣
PPE	Previous pre-eclampsia
PPV	Peak particle velocity
proMBP	Proform of eosinophil major basic protein

PW	Pulsed wave
RI	Resistance index
ROC	Receiver operator characteristic
RT	Right
SBP	Systolic blood pressure
SD	Standard deviation
TTP	Thrombocytopenic purpura
UARI	Umbilical artery Doppler resistance indices
US	Ultrasound
UtA	Uterine artery

INTRODUCTION

Pre-eclampsia is a complication of pregnancy constituting a major cause of maternal morbidity and mortality worldwide. The cardinal clinical features of the condition are hypertension and proteinuria occurring after ٢٠ weeks gestation in women who were not previously known to be hypertensive. Other signs and symptoms include edema and headache and in severe cases the condition is associated with seizures (eclampsia), liver and kidney dysfunction as well as clotting abnormalities, adult respiratory distress syndrome (ARDS) and fetal growth restriction (FGR) ***(Davison et al.,***).

Although the cause of pre-eclampsia remains elusive, the origin of the condition is recognized as lying in the placenta. This is because preeclampsia occurs only in the presence of pregnancy, it resolves after delivery of the placenta and it can occur in absence of a viable fetus, for example in molar pregnancies ***(David et al.,*** . ***and Cunningham et al.,***).

Pregnancy-associated plasma protein A (PAPP-A) is a large highly glycosylated protein complex produced by the developing trophoblast ***(Bersinger et al.,***), which is used in many centers as a marker for Down's syndrome. It has been shown to be responsible for the cleavage of insulin-like growth factor (IGF) binding proteins, which are inhibitors of IGF action in several biological fluids ***(Laursen et al.,***).

There is recent evidence that low first-trimester maternal serum PAPP-A in chromosomally normal pregnancies is associated with an increased risk for subsequent development of PE ***(Poon et***

al.,).). Since insulin –like growth factor is believed to play a significant role in trophoblast invasion, it is not surprising that low–serum PAPP-A is associated with a higher incidence of PE ***(Irwin et al.,).***

Doppler ultrasound provides a non-invasive method for the study of the uteroplacental circulation. In normal pregnancy, impedance to flow in the uterine arteries decreases with gestation, as a result of trophoblastic invasion of the spiral arteries and their conversion into low-resistance vessels. Pre-eclampsia is associated with failure of trophoblastic invasion of spiral arteries and studies have shown that impedance of flow in the uterine arteries is increased ***(Schuchter et al., & Dugoff et al.,).***

Doppler screening studies performed at ١٨-٢٠ weeks of gestation can demonstrate an association between increased impedance to flow in the uterine arteries with subsequent development of pregnancy related hypertensive disorders and their complications. In addition, several studies showed that elevated first trimester uterine artery mean resistivity index (RI) is significantly associated with fetal IUGR ***(Schuchter et al., & Dugoff et al.,).***

First trimester uterine artery Doppler can identify over half of women who will develop pre-eclampsia and fetal IUGR. Recent studies have documented that detection rates may be increased by a combination of uterine artery Doppler with first trimester maternal serum markers ***(Campbell and Papageorghiou, ٢٠٠٦).***

AIM OF THE WORK

The aim of this study is to determine the value of first trimesteric uterine artery Doppler and serum PAPP-A in prediction of pre-eclampsia.

PRE-ECLAMPSIA

Terminology and classification

The term gestational hypertension is used now to describe any form of new-onset pregnancy-related hypertension. It was adopted by the Working Group of the National High Blood Pressure Education Program ***(NHNPEP, ٢٠٠٠)***. The classification of hypertensive disorders complicating pregnancy by the Working Group of the ***NHNPEP, (٢٠٠٠)*** is shown in table (١). There are five types of hypertensive diseases

Table (١): Classification of hypertension in pregnancy

١. Gestational hypertension (formerly pregnancy-induced hypertension that included transient hypertension).
٢. Pre-eclampsia.
٣. Eclampsia.
٤. Pre-eclampsia superimposed on chronic hypertension.
٥. Chronic hypertension.

Diagnosis:

Hypertension is diagnosed when a systolic blood pressure (SBP) of ١٤٠mmHg or higher or a diastolic blood pressure (DBP) of ٩٠mmHg or higher is recorded in a woman whose blood pressure has previously been normal ***(Schroeder, ٢٠٠٢)***. It has been shown that a rise in SBP of ٣٠mmHg or greater and/or a rise in DBP of ١٥mmHg or greater does not indicate an adverse

outcome by itself, as long as the woman remains normotensive (i.e., with blood pressure "BP" that remains below ١٤٠/٩٠mmHg) ***(Reif, ٢٠٠٣)***. Edema is no longer included because of the lack of specificity ***(James and Piercy, ٢٠٠٤)***.

Gestational hypertension is diagnosed when elevated blood pressure without proteinuria develops after ٢٠ weeks of gestation and blood pressure returns to normal within ١٢ weeks after delivery. One fourth of women with gestational hypertension develop proteinuria and thus progress to pre-eclampsia ***(Wagner, ٢٠٠٤).***

Pre-eclampsia is best described as a pregnancy-specific syndrome of reduced organ perfusion secondary to vasospasm and endothelial activation. Proteinuria is an important sign of pre-eclampsia, and the diagnosis is questionable in its absence. Significant proteinuria is defined by ٢٤hrs urinary protein exceeding ٣٠٠mg per ٢٤hrs, or persistent ٣٠mg/dL (١ + dipstick) in random urine samples. The degree of proteinuria may fluctuate widely over any ٢٤hrs period, even in severe cases. Therefore, a single random sample may fail to demonstrate significant proteinuria ***(Chesley, ١٩٨٥).*** To avoid contamination, urine specimens are collected by catheter after rupture of the membranes or in the presence of vaginitis ***(Levine et al., ٢٠٠٣).***

Importantly, both proteinuria and alterations of glomerular histology develop late in the course. It is apparent that pre-eclampsia becomes evident clinically only near the end of a covert pathophysiological process that may begin as early as implantation ***(Ferrazzani et al., ١٩٩٠)***.