INTRODUCTION

Pre-eclampsia which affects 2-5% of pregnancies is a major cause of perinatal and maternal morbidity and mortality *(Granger et al., 2001)*.

During normal pregnancy, invading trophoblast ensures the vascular remodeling of the uterine spiral arteries necessary to cause the physiological increase in blood supply to the intervillous space needed for pregnancy. Defective trophoblastic invasion of the spiral arteries is associated with subsequent development of pre-eclampsia (PE), fetal growth restriction (FGR) and other associated complications. In these pregnancies the uteroplacental circulation remains in a state of high resistance, which causes generalized endothelial cell injury, compromising vascular integrity and an atherosis-like process in the small arteries resulting in vessel occlusion, local ischemia and necrosis *(Pijnenborg et al., 2006)*.

Under these conditions the uteroplacental circulation remains in a state of high resistance and low flow, and this can be measured non-invasively by Doppler ultrasound *(Campbell et al., 1983)*.

Uterine artery Doppler measurements show that impedance to flow in the uterine arteries decreases with gestational age in normal pregnancies *(Campbell et al., 1983)*.

That impedance to flow is increased in established pre-eclampsia and FGR *(Trudinger et al., 1985; Ducey et al., 1987)*; and this increased impedance predates the onset of the clinical syndrome of pre-eclampsia or FGR *(Papageorghiou et al., 2004)*.

There have been a number of studies that have examined the ability of uterine artery Doppler velocimetry to predict complications of impaired placentation *(Papageorghiou et al., 2004)*.

Most have used uterine artery Doppler in the second trimester. Examination of the uterine circulation in the first trimester in order to predict pre-eclampsia and FGR, however, has increasingly been reported *(Papageorghiou et al., 2006)*.

First trimester uterine Doppler ultrasound has also been used to study the process of normal placentation and in screening for complications of early pregnancy, but this has shown limited success *(Detti et al., 2006)*.

There is particular interest in early screening for pre-eclampsia as this may represent the most likely gestation for which pharmacological intervention may confer benefit *(Vainio et al., 2002 and Chiaffarino et al., 2004)*.

AIM OF THE WORK

The aim of the present study is to determine the accuracy of uterine artery Doppler measurement between 11th and 14th week of pregnancy in predicting the development 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, 2000)*. The classification of hypertensive disorders complicating pregnancy by the Working Group of the *NHNPEP, (2000)* is shown in table (1). There are five types of hypertensive disease:

Table (1): Classification of hypertension in pregnancy

1.	Gestational hypertension (formerly pregnancy-induced hypertension that included transient hypertension).
2.	Pre-eclampsia.
3.	Eclampsia.
4.	Pre-eclampsia superimposed on chronic hypertension.
5.	Chronic hypertension.

Diagnosis:

Hypertension is diagnosed when a systolic blood pressure (SBP) of 140mmHg or higher or a diastolic blood pressure (DBP) of 90mmHg or higher is recorded in a woman whose blood pressure has previously been normal *(Schroeder, 2002)*. It has been shown that a rise in SBP of 30mmHg or greater and/or a rise in DBP of 15mmHg 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 140/90mmHg) *(Reif, 2003)*. Edema is no longer included because of the lack of specificity *(James and Piercy, 2004)*.

Gestational hypertension is diagnosed when elevated blood pressure without proteinuria develops after 20 weeks of gestation and blood pressure returns to normal within 12 weeks after delivery. One fourth of women with gestational hypertension develop proteinuria and thus progress to pre-eclampsia *(Wagner, 2004)*.

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 24hrs urinary protein exceeding 300mg per 24hrs, or persistent 30mg/dL (1 + dipstick) in random urine samples. The degree of proteinuria may fluctuate widely over any 24hrs period, even in severe cases. Therefore, a single random sample may fail to demonstrate significant proteinuria *(Chesley, 1985)*. To avoid contamination, urine specimens are collected by catheter after rupture of the membranes or in the presence of vaginitis *(Levine et al., 2003)*.

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., 1990)*.

Thus, the minimum criteria for the diagnosis of pre-eclampsia are hypertension plus minimal protein-uria. The more severe the hypertension or proteinuria, the more certain is the diagnosis of pre-eclampsia. Similarly, abnormal laboratory findings in tests or renal, hepatic, and hematological function increase the certainty of pre-eclampsia. In addition, persistent

premonitory symptoms of eclampsia, such as headache and epigastric pain, also increase the certainty *(Wagner, 2004)*.

Epigastric or right upper quadrant pain is thought to result from hepatocellualr necrosis, ischemia, and edema that stretches the Glisson capsule. This characteristic pain is frequently accompanied by elevated serum hepatic transaminase levels and usually is a sign to terminate the pregnancy. The pain presages hepatic infarction and hemorrhage or catastrophic rupture of a subcapsular hematoma. Fortunately, hepatic rupture is rare *(Cunningham et al., 2005)*.

Thrombocytopenia is characteristic of worsening pre-eclampsia, and it probably is caused by platelet activation and aggregation as well as micro-angiopathic hemolysis induced by severe vasospasm. Evidence of gross hemolysis such as hemoglobinemia, hemoglobinuria, or hyperbilirubinemia is indicative of severe disease *(Wagner, 2004)*.

Other factors indicative of severe hyerptension include cardiac dysfunction with pulmonary edema as well as obvious fetal growth restriction *(Sibai, 2005)*.

Severity of pre-eclampsia:

The severity of pre-eclampsia is assessed by the frequency and intensity of the abnormalities listed in table (2). The more profound these aberrations, the more likely is the need for pregnancy termination. The differentiation between mild and severe pre-eclampsia can be misleading because apparently mild disease may progress rapidly to severe disease.

Table (2): Indications of severity of hypertensive disorders during pregnancy *(Cunningham et al., 2005)*

Abnormality	Mild	Severe
Diastolic blood pressure	<100mmHg	<110mmHg or higher
Proteinuria	Trace to 1+	Persistent 2+ or more
Headache	Absent	Present
Visual disturbances	Absent	Present
Upper abdominal pain	Absent	Present
Oliguria	Absent	Present
Convulsion (eclampsia)	Absent	Present
Serum creatinine	Normal	Elevated
Thrombocytopenia	Absent	Present
Liver enzyme elevation	Minimal	Marked
Fetal growth restriction	Absent	Obvious
Pulmonary edema	Absent	Present

Although hypertension is a requisite to diagnosing pre-eclampsia, absolute blood pressure alone ios not always a dependable indicator of its severity. For example, young adolescent women may have 3+ proteinuria and convulsions with a blood pressure of 135/85mmHg, whereas most women with blood pressures as high as 180/120mmHg do not have seizures. A rapid increase in blood pressure followed by convulsions is usually preceded by an unrelenting severe headache or visual disturbances. For this reason, these symptoms are considered ominous *(Cunningham et al., 2005)*.

Eclampsia is the onset of convulsions in a woman with pre-eclampsia that cannot be attributed to other causes. The seizures are generalized and may appear before, during, or after labor. In older studies, in about 10 percent of eclamptic women, especially nulliparas, seizures did not develop until after 48hrs postpartum *(Lubarsky et al., 1994)*.

Chronic hypertension is defined by elevated blood pressure that predates the pregnancy, is documented before 20 weeks of gestation, or is present 12 weeks after delivery *(NHNPEP, 2000)*.

Pre-eclampsia superimposed on chronic hypertension is characterized by new-onset proteinuria (or by a sudden increase in the protein level if proteinuria already is present), an acute increase in the level of hypertension (assuming proteinuria already exists), or development of hemolysis, elevated liver enzymes, low platelet count (HELLP) syndrome *(Wagner, 2004)*.

Some of the many causes of underlying hypertension that are encountered during pregnancy are essential or familial hypertension, which is the cause of underlying vascular disease in more than 90 percent of pregnancy women, obesity and diabetes are other common causes. In some women, hypertension develops as a consequence of underlying renal parenchymal disease. Although earlier studies of renal biopsies identified abnormalities, especially in multiparas *(Cunningham et al., 2005)*.

Risk factors:

Risk factors for pre-eclampsia include medical conditions with the potential to cause microvascular disease (e.g., diabetes mellitus, chronic hypertension, vascular and connective tissue disorders), anti-phospholipid antibody syndrome, and nephropathy.

Other risk factors are associated with pregnancy itself or may be specific to the mother or father of the fetus (table 3).

Table (3): Risk factors pre-eclampsia ***(Wagner, 2004)***

Pregnancy associated factors:
Chromosomal abnormalities
Hydatidiform mole
Hydrops fetalis
Multifetal pregnancy
Oocyte donation or donor insemination
Structural congenital anomalies.
Urinary tract infection.
Maternal-specific factors:
Age greater than 35 years.
Age less than 20 years.
Black race.
Family history of pre-eclampsia.
Nulliparity.
Pre-eclampsia in a previous pregnancy.
Specific medical conditions: gestational diabetes, type I diabetes, obesity, chronic hypertension, renal disease, thrombophilias.
Paternal-specific factors:
First-time father.
Previously fathered a pre-eclampsia pregnancy in another woman.

Pathogenesis:

The pathogenesis of the disease is generally considered in several stages and currently, there are potential causes of pre-eclampsia including the following:

1. Abnormal trophoblastic invasion of uterine vessels.
2. Maladaptation to cardiovascular or inflammatory changes of normal pregnancy.
3. Immunological intolerance between maternal and fetoplacental tissues.
4. Genetic influences.
5. Dietary deficiencies.

(Sibai, 2003)

A. Abnormal placentation:

The pathogenesis of the disease is generally considered in several stages *(Pijnenborg et al., 2006)*. In the first stage the placental trophoblast cells fail to invade adequately into the deciduas and the spiral arteries to achieve the transformation necessary for the increase in the feto-placental blood flow. The second stage results from the poor placental perfusion through the inadequately transformed arteries. The

placenta fails to grow and develop normally so that an abnormal placental structure with defective branching morphogenesis of the villous tree results. Finally, in the third stage a systemic leukocytic-endothelial inflammatory syndrome is triggered by factors released by the ischemic placenta *(Moffett-King, 2002)*.

B. Vasospasm:

Vascular constriction causes resistance and subsequent hypertension. At the same time, endothelial cell damage causes interstitial leakage through which blood constituents, including platelets and fibrinogen, are deposited subendothelially *(Wang et al., 2002)* have also demonstrated disruption of endothelial junctional proteins *(Suzuki et al. (2003)* demonstrated ultrastructural changes in the subendothelial region of resistance arteries in pre-eclampsia women. With diminished blood flow because mal-distribution, ischemia of the surrounding tissues would lead to necrosis, hemorrhage, and other end-organ disturbances characteristic of the syndrome. Ironically, vasospasm may be worse in women with pre-eclampsia than in those with the HELLP syndrome *(Fischer et al., 2000)*.

C. Endothelial cell activation:

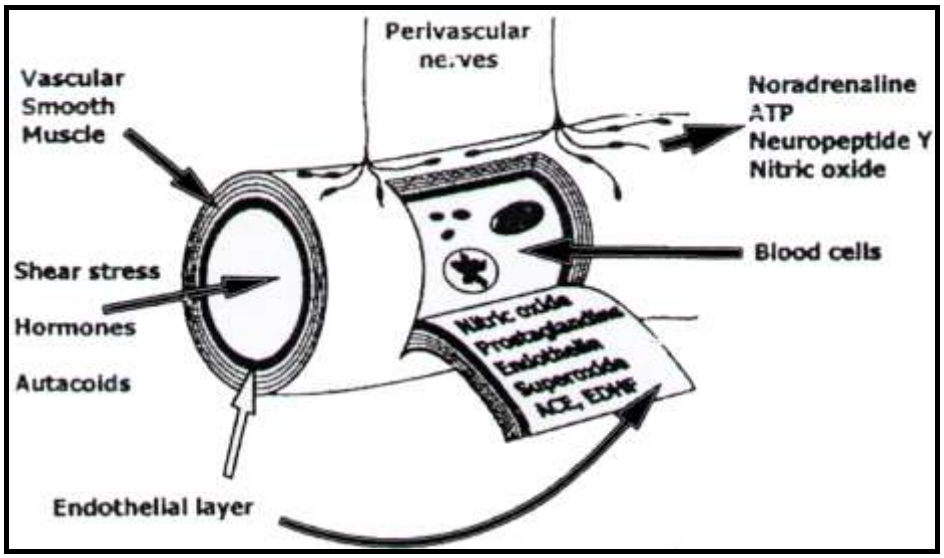

Fig. (1): Vascular tone is influenced by the autonomic nervous system, intrinsic vascular smooth muscle reflexes and the endothelium *(Muna et al., 2007)*.

Over the past two decades, endothelial cell activation has become the centerpiece in the contemporary understanding of the pathogenesis of pre-eclampsia. In this scheme, unknown factor(s), likely from the placenta, are secreted into the maternal circulation and provoke activation and dysfunction of the vascular endothelium. The clinical syndrome of pre-eclampsia is thought to result from these widespread endothelial cell changes *(Roberts, 2000)*.

Intact endothelium has anticoagulant properties, and it also blunts the response of vascular smooth