INTRODUCTION

Preeclampsia (PE) is a serious complication of pregnancy with increased perinatal morbidity which can be potentially life-threatening.It is characterized by maternal hypertension, proteinuria, edema and endothelial dysfunction ***(Khan et al., 2006)***. It is not uncommon and its incidence has been found to range between2% and 8% of all pregnancies***(Duley, 2009)***.

The complete pathogenesis of this disease remains unclear, underlining a multifactorial etiology. Deficient remodeling of the spiral arteries during the interaction between maternal and fetal sides at the time of trophoblast invasion has been postulated as a cause of placental insufficiency. This would lead to the release of inflammatory factors in the systemic maternal circulation ***(Young et al., 2010)***.Some studies suggested that adipokines may play an important role in the pathogenesis of pre-eclampsia through their role in low-grade systemic inflammation, atherosclerosis, and insulin resistance. Therefore, it is reasonable to suppose that adipokines may directly or indirectly influence the function of placental endothelial cells ***(Arikan et al., 2010)***.

Visfatin, also known as pre-β- cell colony-enhancing factor, is a novel adipokine secreted by fat tissue and macrophages. It is involved in the regulation of glucose homeostasis ***(Fukuhara et al., 2005)***. Visfatin shows insulin-

mimicking effects through the activation of an insulin receptor. During pregnancy visfatin transcript and protein are present both in human fetal membranes and the placenta ***(Morgan et al., 2008)***.

Peripheral visfatin concentrations were found to be elevated in obese subjects, althoughdifferent findings exist ***(Haider et al., 2006)***. In patients with type-2 diabetes mellitus, an increase ***(Dogru et al., 2007)***, a decrease ***(Li et al., 2006)***and no change ***(Jian et al., 2006)*** in blood visfatin have been reported, similar findings are available with gestationaldiabetes mellitus ***(Chan et al., 2006)***.

Based on the changesin visfatin in insulin resistance-associated diseases, aswell as the physiological activity of visfatin, it washypothesized that serum visfatin levels are altered in women with pre-eclampsia***(Hu et al., 2008).***

There is compelling evidence that insulin resistance may alsoplay a pivotal role in the development of pregnancy complicationsincludingintrauterine growth restriction (IUGR). Since dysregulation of visfatin is found in insulin resistance, therefore itmight contribute to IUGR**(*Fasshauer et al., 2007).***

AIM OF THE WORK

The aim of the present study is to assess the clinical utility of Visfatin in pre-eclampsia and its relation to disease severity.Moreover, the role of visfatin in detection of intra-uterine growth restriction in pre- eclamptic females will be investigated.

I- PRE-ECLAMPSIA

A) Definition:

Pre-eclampsia(PE) is a multi-system disorder of unknown cause that is unique to human pregnancy. It is characterized by sudden onset of hypertension; with blood pressure ≥ 140/90 mmHg; presenting after the 20^{th} week of gestation accompanied by edema and/or proteinuria. It is considered severe if blood pressure and proteinuria are increased substantially or symptoms of end-organ damage, including fetal growth restriction occured ***(Sharon et al., 2008).***

Pre-eclampsia may also occur in the immediate post-partum period or up to 6-8 weeks post-partum. This is referred to as "post-partum pre-eclampsia". The most dangerous time for the mother is the 24-48 hours post-partum and careful attention should be paid to pre-eclampsia signs and symptoms ***(Reynolds et al., 2006).***

B) Epidemiology:

Pre-eclampsia affects 5%–7% of all pregnancies worldwide and approximately 3% of pregnant women in the western world ***(Roberts et al., 2010).*** While, in developing countries, pre-eclampsia affects 4.4% of all deliveries because illiteracy, lack of health awareness and education, poverty, and superstitious beliefs prevent women from seeking medical advice during pregnancy. 50, 000 cases of women experiencing life threatening eclamptic convulsions can be expected each year ***(Muhmed et al., 2009).***

C) Risk Factors:

There aremany risk factors of pre-eclampsiaincluding pregnancy-associated factors and maternal-specific factors as seen in table(1)***(Dekker and Sibai, 2009).***

1. Pregnancy-Associated Factors:

Evidence points to the placenta as a key source of factors that lead to the maternal endothelial cell dysfunction in pre-eclampsia. This is evident in that the clinical signs and lesions of pre-eclampsia remit within days after termination of pregnancy. The disease can occur in non-embryonic pregnancy (hydatidiform mole), suggesting that the presence of a fetus is not strictly necessary ***(Page, 2010).*** Moreover, pre-eclampsia is more common in the presence of a greater trophoblastic mass for instance in multiple pregnancy and hydrops fetalis,either due to immunologic or non immunologic causes. The frequency and severity of the disease are substantially higher in women with multiple birth as reported by ***Wen et al. (2009).***

2- Maternal-Specific Factors:

a- Chromosomal abnormalities:

Genome-wide linkage studies have identified at least three pre-eclampsia loci showing substantial linkage: 2p12, 2p25 and 9p13 ***(Caulfield et al., 2010).*** In addition, ***Paula and Fiona (2011)*** added the susceptibility locus on chromosome 10q22 to be involved in pre-eclampsia.

b- Age:

Pre-eclampsia occurs more frequently at the extremes of the reproductive period. These include women who are younger than 20 years and those who are older than 40 years ***(Wen et al., 2009).***

c- Race:

Some studies indicate that pre-eclampsia occurs three times more often in black women than in white women. Although the precise reasons for the racial differences remain elusive, the differences may be indicative of disparities in health status, as well as the quality of prenatal care***(Mackay et al., 2009).***

d- Familial predisposition:

A familial predisposition to pre-eclampsia has been confirmed in numerous studies from the different parts of the world. These studies record a 2–5 folds increase in risk to first-degree relatives of women with pre-eclampsia ***(Fausett et al., 2007).***

e-Nulliparity:

Frequency of pre-eclampsia ranges between 2% - 7% in healthy nulliparous women. The risk ratio of pre-eclampsia in nulliparous women in comparison to multiparous women is about 3:1 ***(Vatten and Skjaerven, 2010)***

f- Pre-eclampsia in a previous pregnancy:

The repeated occurrence of pre-eclampsia inseveral pregnancies of the same woman is not a rare event since the

incidence of recurrence ofpre-eclampsia in subsequent pregnancies has been as high as 50% ***(Troendle et al., 2008).***

g- Specific medical conditions:

i) Diabetes mellitus:

Insulin resistance has been observed before, during, and afterpre-eclampsia suggesting a strong association between diabetes and the disease. Moreover, reports have suggested that insulin signaling and angiogenesis are intimately related, and that insulin regulates the expression of genes involved in angiogenesis, including the expression of vascular endothelial growth factor (VEGF) mRNA. These data suggest that alterations in angiogenesis and insulin resistance may have an additive effect that leads to alterations in critical cellular functions, endothelial cell injury and subsequently, increased risk of developing pre-eclampsia ***(Vicent et al., 2008).***

ii) Hypertension and renal diseases:

There is much higher risk to develop pre-eclampsia in women with chronic hypertension and renal diseases**.** The incidence reaching 10:1 and 20:1 respectively, than those who are healthy. During normal pregnancy, there is significant elevationin renal plasma flow and glomerular filtration rate. Renin concentration, Renin activity and Angiotensin II (ANG II) levels are elevated; however, the vascular responsiveness to ANG II appears to be reduced ***(Say et al., 2007).***

iii) Obesity:

Obesity is a definite risk factor for pre-eclampsia. The exact mechanism by which obesity or insulin resistance is associated with the disorder is not completely understood. Possible explanations are increased stress associated with a hyperdynamic circulation, dyslipidaemia or enhanced cytokine-mediated oxidative stress, amplified sympathetic activity, increased tubular sodium resorption and insulin resistance ***(Cedergren, 2010).***

iv) Inflammatory diseases:

Pre-eclampsia is simply the extreme end of a range of maternal systemic inflammatory responses induced by the pregnancy itself. As such, any factor that increases the maternal inflammatory response such as infections and rheumatic diseases will also predispose women to pre-eclampsia. Many studies indicate that maternal infections as urinary tract infection and some viruses as (chlamydia and cytomegalovirus) are associated with pre-eclampsia ***(VonDadelszen and Magee, 2010).***

h- Nutritional factors:

Malnutrition has been considered, for a long time, as a predisposing factor to pre-eclampsia since the use of multi-vitamins in the peri-conceptional period help to decrease risk of development of the disease as stated by***John et al. (2008).***This is further supported by ***Roberts et al. (2010)***who found that fruits and vegetables rich in vitamin C and other anti-oxidants may decrease incidence of pre-eclampsia.Calcium supplementation plays an important role in lowering the risk of the disease to almost the half as reported by ***Hofmeyr et al. (2010).***

Table (1): Risk Factors of Pre-eclampsia.

• **Pregnancy-Associated Factors:**
- Hydatidiform mole. - Hydrops fetalis. - Multi-fetal pregnancy.
• **Maternal-Specific Factors:**
- Chromosomal abnormalities. - Age greater than 40 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 1 diabetes mellitus, obesity, chronic hypertension, renal disease and thrombophilias. - Nutritional factors as decreased calcium and vitamin C in diet.

(Dekker and Sibai, 2009)

D) Pathophysiology of Pre-eclampsia:

The basic pathophysiology of pre-eclampsia is the intense vasospasm; increasing peripheral resistance of arteries leading to marked increase in blood pressure; intravascular coagulation and decreased organ blood flow ***(Michelle et al., 2007).***

Defective remodelling of the placental spiral arterioles with subsequent placental hypoperfusion is the main cause of triggering lipid peroxides, reactive oxygen species, and many proinflammatory cytokines in the maternal circulation. These events lead to the main hallmark of the disease, the diffuse endothelial cell dysfunction, which results in imbalance between vasopressor (endothelin-1) and platelet derived growth factor (PDGF) and vasodilator substances as prostacyclins and nitric

oxide (NO) and the generalized systemic vasoconstriction with decreased organs perfusion ***(Harskamp and Zeeman, 2007).***

Similarily, placental hypoxia causes platelet activation and aggregation with the release of thromboxane A2, serotonin and PDGF. Thus, intravascular coagulation with intense vasospasm occurs and represents the basic pathophysiology of pre-eclampsia as seen in figure (1) ***(Michelle et al., 2007).***

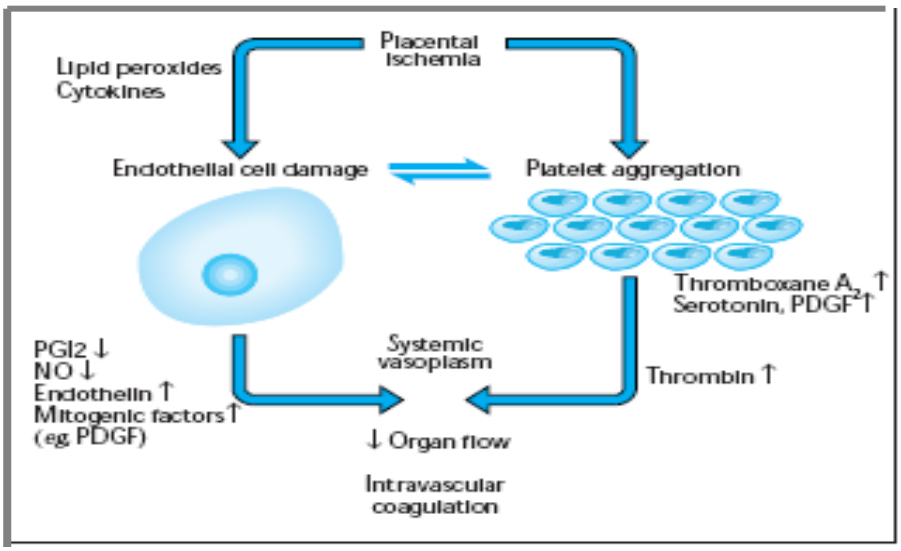

Figure (1): Pathophysiological events in pre-eclampsia ***(Michelle et al., 2007).***

E) Causes of Pre-eclampsia:

The most approved theories of pre-eclampsia include the genetic, abnormal placentation, immunological, aberrant cytokineproduction and oxidative theories ***(Redman and Sargent, 2010).***

1. Genetic Hypothesis of Pre-eclampsia:

The familial predisposition to pre-eclampsia suggests the tendency of the disease to be inherited genetically ***(Salonen et al., 2007).*** Attention has focused on the role of genetic factors such as gene polymorphisms of the renin-angiotensin system (RAS), genetic thrombophilias, the nitric oxide synthase (NOS) gene and epoxide hydrolase gene polymorphism which play an important role in the regulation of blood pressure in pre-eclampsia as well as its vascular complications ***(Xia et al., 2007).***

a- Genetic polymorphisms of the renin–angiotensin system (RAS) in pre-eclampsia:

Pre-eclamptic females carrying variants of angiotensinogen gene, such as M235T**,** could lead to increased production of angiotensin II, the final effector vasopressor hormone of the renin angiotensin system (RAS). This over-stimulation could result in increased vascular tone and vascular hypertrophy ***(Sheiner, 2005).*** It also inhibits human trophoblast invasion and stimulates plasminogen activator inhibitor-1 (PAI-1) synthesis and secretion in human trophoblasts inducing thrombosis of the vessels of the placenta***(Xia et al., 2002).***

In addition, it has been found that the angiotensin II receptor type-1 (AT1) gene was 5-fold upregulated in decidua of pre-eclamptic females. This receptor through its agonistic autoantibodies, increases activity of NADPH oxidases, leading to impaired nitric oxide(NO) mediated endothelial function through the generation of reactive oxygen species (ROS) ***(Xia et al., 2007).***

Mello et al. (2003)found thatangiotensin-converting enzyme (ACE)gene polymorphism has a significant impact on

the development of pre-eclampsia. The ACE (I/D) polymorphism is characterized by the presence of insertion or deletion of a fragment in intron 16 of the ACE gene. The frequency of the DD genotype in patients with pre-eclampsia was about 2.5 times higher compared to general population and normotensive women during pregnancy. The D allele is associated with higher levels of ACE, increased production of Ang II and increased PAI-1 expression.

b- Genetic thrombophilias in pre-eclampsia:

Factor V Leiden point mutation (FVR 506 Q) occurs in the factor V gene at the site where protein C acts. Therefore, protein C cannot be activated and as a consequence factor V cannot be broken down, leading to the hypercoagulable effect ***(Spina et al., 2007).***Factor V Leiden point mutation was demonstrated in up to 26% of patients with pre-eclampsia as seen in **f**igure (2) ***(De Stefano et al., 2008).***

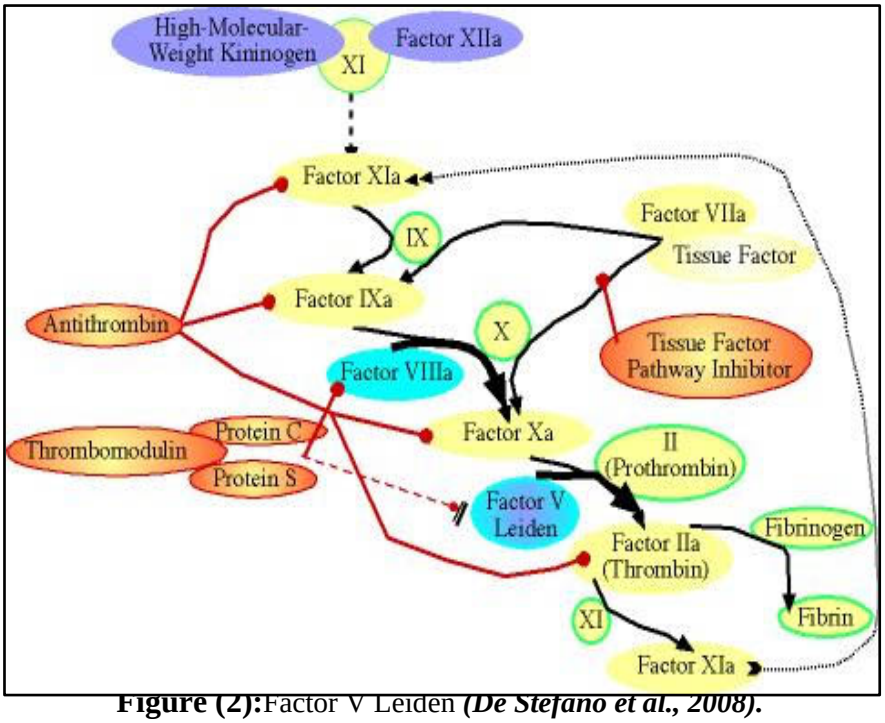

Figure (2): Factor V Leiden ***(De Stefano et al., 2008).***

The prothrombin (factor II) mutation, the second most important congenital thrombophilic factor, is associated with elevated plasma prothrombin concentration and a three-fold risk of venous thrombosis. The onset of severe pre-eclampsia was proved to be significantly earlier in women with the prothrombin gene mutation **(*Gerhardt et al., 2010).***

c- Endothelial nitric oxide synthase (eNOS) gene:

Savvidou and colleagues (2006) showed strong association between pre-eclampsia and a mutation within intron 13 of the endothelial nitric oxide synthase gene (eNOS).A similar association with pre-eclampsia was noted in a study performed by ***Bashford et al. (2008),*** a repeat polymorphisms in intron 4 of the

NOS gene. These common polymorphisms of the NOS gene render the enzyme liable to enhanced proteolytic cleavage and potentially lower concentration leading to vasospasm reported in pre-eclampsia.

d- Epoxide hydrolase gene:

Epoxide hydrolase is a liver microsomal enzyme, involved in metabolism of endogenous and exogenous toxins, such as lipid peroxides and oxygen-free radicals. Genetic polymorphisms in the gene coding for this enzyme have been associated with decrease in its activity ***(Pinarbasi et al., 2007).***In a case-control study of more than 300 pregnant women in the Netherlands, ***Pinarbasi and associates (2007)*** found that those women with pre-eclampsia were nearly twice as likely as the healthy women to have the low-activity variant of the enzyme.

2. Abnormal Placentation Theory:

The placenta is central to the pathophysiology of PE being a potential source of circulating inflammatory cytokines***(Wang et al., 2009).*** There are two broad stages of PE; placental and maternal, although many cases are a mix of the two ***(Redman and Sargent, 2010).***

In normal placental development, cytotrophoblasts of fetal origin invade the maternal spiral arteries, transforming them from small-caliber resistance vessels to high-caliber capacitance vessels capable of providing placental perfusion adequate to sustain the growing fetus. During the process of vascular invasion, the cytotrophoblasts differentiate from an epithelial phenotype to an endothelial phenotype, a process

referred to as “pseudovasculogenesis” or “vascular mimicry”. The first stage (placental stage) is usually an asymptomatic stage in which invasion of the spiral arteries is shallow, and they remain small caliber, resistance vessels as seen infigure (3)***(Silasi et al., 2010).***The second stage (maternal stage) is mediated by the imbalance between pro-angiogenic cytokines as vascular endothelial growth factor (VEGF) and placental growth factor (PlGF) and antiangiogenic cytokines as soluble fms-like tyrosine kinase-1 (sFlt-1) ***(Varughese et al., 2010).***

The elevation of serum concentration of anti-angiogenic factors binds to the pro-angiogenic factors preventing their interaction with endothelial receptors ***(Woolcock et al., 2008)***. This result in disrupting the maternal endothelium and result in hypertension, proteinuria, and the other systemic manifestations of PE***(Wang et al., 2009).***