INTRODUCTION

Preeclampsia refers to the new onset of hypertension and either proteinuria or end-organ dysfunction or both after 20 weeks of gestation in a previously normotensive woman ***(Sibai et al., 2003)***. Pre-eclampsia affects about 2–8% of pregnancies worldwide and has a negative impact on maternal and neonatal morbidity and mortality ***(Walker et al., 2000)***. In developing countries, 20% to 80% of maternal mortality is attributable to preeclampsia ***(Roberts et al., 1998).*** In developed countries, the perinatal mortality rate among preeclamptic pregnancies is five times as great as non-preeclamptic pregnancies ***(Roberts et al., 1998).*** Severe pre-eclampsia is pre-eclampsia with severe hypertension and/or with symptoms, and/or biochemical and/or haematological impairment ***(NICE Clinical Guideline, 2011).***

Little is still known about the pathogenesis of preeclampsia, making its prevention an ongoing challenge ***(Dekker et al., 2001).*** Maternal obesity and insulin resistance are believed to be important risk factors for the development of placental endothelial dysfunction and preeclampsia ***(Hayman et al., 1999).***

Obesity now affects more than one-third of reproductive-aged women, and escalating rates of obesity may contribute to an increased prevalence of hypertensive disorders in pregnancy ***(Bodnar et al., 2007)***.

Several studies have identified maternal pre-pregnancy body mass index (BMI) as an important risk factor for pre-eclampsia ***(Valensise et al., 2008)***. However, not all studies have examined the relationship between BMI and the incidence of early and late pre-eclampsia independently ***(Bodnar et al., 2007).***

As preeclampsia presents at varied gestational ages and varies in severity, two distinct subtypes have been recognized. Early onset preeclampsia occurs prior to 34 weeks gestation, and late onset preeclampsia occurs at or beyond 34 weeks gestation ***(Lisonkova et al., 2013).***

Perinatal death and severe neonatal morbidity are higher in women with early onset disease than late onset one, and rates of severe maternal morbidity and mortality are higher in women with early onset disease ***(Lisonkova et al., 2014)***.

Early onset preeclampsia has been explained as a result of poor placental implantation leading to chronic placental insufficiency and subsequent inflammatory cascade with resultant hypertensive disease ***(Ness et al., 1996).*** Late onset preeclampsia has been described as both a placental disease and a result of maternal metabolic and cardiovascular risk factors ***(Vatten et al., 2004).***

In a previous study, increasing maternal weight was not associated with preeclampsia with severe features. However,

overweight, obese, and morbidly obese women are at increased risk of developing late onset preeclampsia with severe features ***(Durst et al., 2015).***

There is a great need to study the relation between BMI and the rate of developing preeclampsia, time of onset and severity, as few studies have addressed this item.

AIM OF THE WORK

The aim of the present work is to identify the relation between increasing BMI and development of pre-eclampsia.

Research question:

In pregnant women, does the risk of pre-eclampsia increase with increasing BMI?

Research hypothesis:

In pregnant, women increasing maternal BMI may increase the rate of developing pre-eclampsia.

Secondarily, this effect would be more pronounced with late onset preeclampsia than early onset disease.

PREECLAMPSIA

Preeclampsia is a common complication of pregnancy associated with high maternal morbidity and mortality and intrauterine fetal growth restriction. There is extensive evidence that the reduction of utero placental blood flow in this syndrome results from the toxic combination of hypoxia, imbalance of angiogenic and anti-angiogenic factors, inflammation, and deranged immunity ***(Eiland et al., 2012).***

Hypertensive disorders associated with pregnancy

Hypertensive disorders represent the most common medical complication of pregnancy, affecting 6 to 8 percent of gestations in the United States. In 2000, the National High Blood Pressure Education Program Working Group on High Blood Pressure in Pregnancy defined four categories of hypertension in pregnancy: chronic hypertension, gestational hypertension, preeclampsia, and preeclampsia superimposed on chronic hypertension ***(Walker et al., 2000).***

Chronic Hypertension

Chronic hypertension is defined as a blood pressure measurement of 140/90 mm Hg or more on two occasions 4 hours apart before 20 weeks gestation or persisting beyond 12 weeks postpartum ***(Walker et al., 2000).***

Gestational Hypertension

Gestational hypertension replaced the term of pregnancy-induced hypertension to describe women who develop hypertension without proteinuria after 20 weeks of gestation ***(Barton et al., 2001)***.

Preeclampsia superimposed on chronic hypertension

A sudden increase in blood pressure, new proteinuria, or signs and symptoms of severe preeclampsia on top of chronic hypertension ***(Barton et al., 2001)***.

Preeclampsia

Preeclampsia is defined as the presence of a systolic blood pressure ≥ 140 mm Hg or a diastolic blood pressure ≥ 90 mm Hg, on 2 occasions at least 4 hours apart in a previously normotensive patient. In addition to the blood pressure criteria, proteinuria of ≥ 0.3 grams in a 24-hour urine collection, a protein (mg/dl)/ creatinine (mg/dl) ratio of 0.3 or higher, or a urine dipstick protein of 1+ is required to diagnose preeclampsia ***(Jeyabalan et al., 2013).***

Two types are recognized: mild and severe preeclampsia. The severity of preeclampsia is measured by the frequency and intensity of abnormalities ***(Freeman, 2008).***

Severe features of preeclampsia:

- Severe hypertension (SBP ≥160 mm Hg or DBP ≥110 mm Hg)
- Thrombocytopenia (platelets <100,000/mL).
- Elevated liver enzymes (ALT, AST).
- Severe right upper quadrant or epigastric pain not responding to treatment.
- Severe cerebral or visual symptoms.
- Renal insufficiency (creatinine >1.1 mg/dl).
- Pulmonary edema.

(Uzan et al., 2011)

As preeclampsia presents at varied gestational ages, two distinct subtypes have been recognized. Early onset preeclampsia occurs prior to 34 weeks gestation, and late onset preeclampsia occurs at or beyond 34 weeks gestation. Perinatal death and severe neonatal morbidity are higher in women with early onset disease than late onset one, and rates of severe maternal morbidity and mortality are higher in women with early onset disease ***(Lisonkova et al., 2013).***

Epidemiology of Preeclampsia

The incidence of preeclampsia in the United States is estimated to range from 2% to 6% in healthy, nulliparous women. Among all cases of the preeclampsia, 10% occur in pregnancies of less than 34 weeks' gestation (early onset preeclampsia). The global incidence of preeclampsia has been estimated at 5-14% of all pregnancies ***(Sibai, 2003)***.

In developing nations, the incidence of the disease is reported to be 4-18%, with hypertensive disorders being the second most common obstetric cause of stillbirths and early neonatal deaths ***(Ngoc et al., 2006)***.

Risk factors of Preeclampsia

- Null parity (3:1)
- Age more than 35 or less than 20 years old (3:1)
- Black race (1.5:1)
- Family history (5:1)
- Chronic renal disease (20:1)
- Chronic hypertension (10:1)
- Antiphospholipid syndrome (10:1)
- Diabetes mellitus (2:1)

- Twin gestation (4:1), triplet gestation carries a greater risk than twin, suggesting that increasing placental mass plays some role.
- Obesity (3:1).
- Genetic factors: Association have been described between risk for preeclampsia and polymorphisms of the genes or factor V Leiden, angiotensinogen (homozygosity for angiotensinogen gene T235 (20:1) heterozygosity for angiotensinogen gene T235 (4:1)) and endothelial nitric oxide synthase, although these associations have not been confirmed consistently.
- History of preeclampsia in the previous pregnancies (7:1).
- Molar pregnancy.
- High altitude has also been shown to increase the incidence of preeclampsia, and is attributed to greater placental hypoxia.
- Collagen vascular disease ***(Yogev et al., 2010).***

Pathophysiology of Preeclampsia

The mechanisms by which preeclampsia occurs are not certain, and numerous maternal, paternal, and fetal factors have been implicated in its development. The factors currently

considered to be the most important include the following: Maternal immunologic intolerance, abnormal placental implantation, genetic, nutritional, environmental factors, cardiovascular and inflammatory changes ***(Cunningham et al., 2010).***

Immunologic Factors in Preeclampsia

Immunological factors have been considered to be key players in preeclampsia. One important component is a poorly understood dysregulation of maternal tolerance to paternally derived placental and fetal antigens. This maternal-fetal immune maladaptation is characterized by defective cooperation between uterine natural killer cells and fetal human leukocyte antigen C, and results in histologic changes similar to those seen in acute graft rejection. The endothelial cell dysfunction that is characteristic of preeclampsia may be partially due to an extreme activation of leukocytes in the maternal circulation, as evidenced by an up regulation of type1 helper T cells ***(Kee-Hak Lim et al., 2016).***

Placentation in Preeclampsia

Placental implantation with abnormal trophoblastic invasion of uterine vessels is a major cause of hypertension associated with preeclampsia syndrome. In fact: studies have shown that the degree of incomplete trophoblastic invasion of the spiral arteries is directly correlated with the severity of

subsequent maternal hypertension. This is because of the placental hypoperfusion resulting from incomplete invasion leads to an unclear pathway of the release of systemic vasoactive compounds that cause an exaggerated inflammatory response, vasoconstriction, endothelial damage, capillary leak, hypercoagulability, and platelet dysfunction, all of which contribute to organ dysfunction and the various clinical features of the disease ***(Redman et al., 2005).***

Normal placentation and pseudo vascularization in normal pregnancies, a subset of cytotrophoblasts called invasive cytotrophoblasts migrate through the implantation site and invade decidua tunica media of maternal spiral arteries and replace its endothelium in a process called pseudo vascularization. The trophoblastic differentiation along the invasive pathway involves alteration in the expression of a number of different classes of molecules, including cytokines, adhesion molecules, extracellular matrix, metalloproteinase, and the class Ib major histocompatibility complex molecule, HLA-G. For example, during normal differentiation, invading trophoblasts alter their adhesion molecule expression from those that are characteristic of epithelial cells (integrin alpha 6/beta 1, alpha V/beta 5, and E-cadherin) to those of endothelial cells (integrin alpha 1/beta 1, alpha V/beta 3, and VE-cadherin). As a result of these changes, the maternal spiral arteries undergo transformation from small, muscular arterioles to large capacitance, low-resistance vessels. This allows increased

blood flow to the maternal-fetal interface. Remodeling of these arterioles probably begins in the first trimester and ends by 18-20 weeks gestation ***(Kee-Hak Lim et al., 2016).***

In preeclampsia, cytotrophoblast cells infiltrate the decidual portion of the spiral arteries, but fail to penetrate the myometrial segment. The spiral arteries fail to develop into large, tortuous vascular channels created by replacement of the musculoelastic wall with fibrinoid material; instead, the vessels remain narrow, resulting in placental hypoperfusion, defective differentiation of trophoblast is one possible mechanism responsible for defective trophoblast invasion of the spiral arteries. Trophoblast differentiation during endothelial invasion involves alteration in expression of a number of different classes of molecules, including cytokines, adhesion molecules, extracellular matrix molecules, metalloproteinases, and the class Ib major histocompatibility complex molecule ***(Huppertz, 2008).***

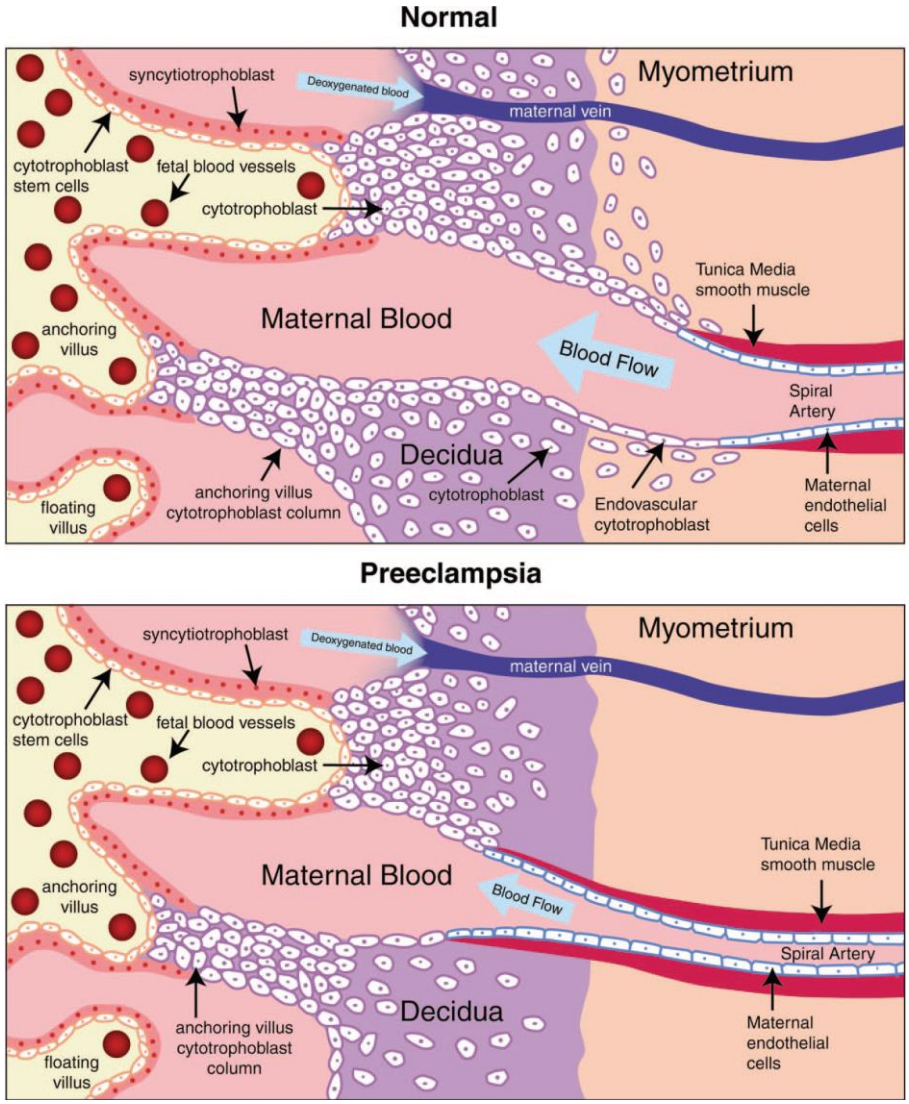

Figure (1): Abnormal placentation in pre-eclampsia in normal placental development, invasive cytotrophoblasts of fetal origin invade the maternal spiral arteries, transforming them from small-caliber resistance vessels to high-caliber capacitance vessels capable of providing placental perfusion adequate 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 pseudo-vasculogenesis, or vascular mimicry (top). In preeclampsia, cytotrophoblasts fail to adopt an invasive endothelial phenotype. Instead, invasion of the spiral arteries is shallow, and they remain small-caliber resistance vessels (bottom) ***(Lam et al., 2005).***

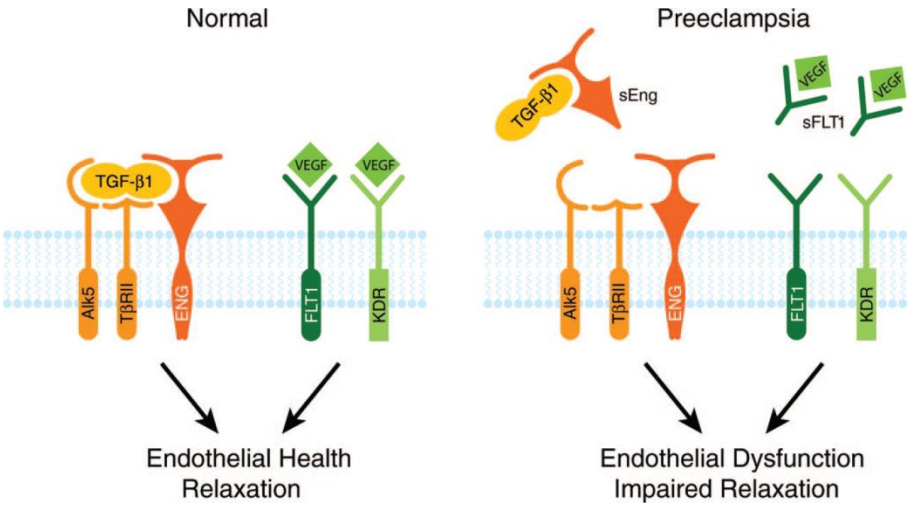

Figure (2): sFlt1 and soluble endoglin (sEng) cause endothelial dysfunction by antagonizing vascular endothelial growth factor (VEGF) and transforming growth factor-1 (TGF-1) signaling. There is mounting evidence that VEGF and TGF-1 are required to maintain endothelial health in several tissues including the kidney and perhaps the placenta. During normal pregnancy, vascular homeostasis is maintained by physiological levels of VEGF and TGF-1 signaling in the vasculature. In preeclampsia, excess placental secretion of sFlt1 and sEng (2 endogenous circulating antiangiogenic proteins) inhibits VEGF and TGF-1 signaling, respectively, in the vasculature. This results in endothelial cell dysfunction, including decreased prostacyclin, nitric oxide production, and release of procoagulant proteins. TRII indicates transforming growth factor-type II receptor ***(Camille et al., 2016)***.

Endothelial Dysfunction

Data show that an imbalance of proangiogenic and antiangiogenic factors produced by the placenta may play a major role in mediating endothelial dysfunction. Angiogenesis is critical for successful placentation and the normal interaction between trophoblasts and endothelium. Several circulating markers of endothelial cell injury have been shown to be elevated in women who develop preeclampsia before they

became symptomatic. These include endothelin, cellular fibronectin, and plasminogen activator inhibitor-1,with altered prostacyclin/thromboxane profile. Evidence also suggests that oxidative stress, circulatory maladaptation, inflammation, humoral, mineral and metabolic abnormalities contribute to the endothelial dysfunction and pathogenesis of preeclampsia ***(Taylor et al., 1998).***

Angiogenic Factors in Preeclampsia

The circulating pro angiogenic factors secreted by the placenta include vascular endothelial growth factor and placental growth factor. The anti angiogenic factors include soluble fms-like tyrosine kinase I receptor (sFlt-1) (otherwise known as soluble VEGF receptor type I) and soluble endoglin (sEng). VEGF and PlGF promote angiogenesis by interacting with the VEGF receptor family. Although both growth factors are produced by placenta, the serum level of PlGF rises much more significantly in pregnancy. In a study, it is demonstrated that the serum level of PlGF decreased in women who later on develop preeclampsia ***(Taylor et al., 2003).***

The fall in serum level of PIGF was noted as early as the second trimester in women who developed preeclampsia and intrauterine growth restriction. In another investigation, ***Maynard et al. (2003)*** observed that the serum levels of VEGF and PlGF were decreased in women with pre-eclampsia. However, the magnitude of decrease was less pronounced for