INTRODUCTION

Pre-eclampsia is also known as pregnancy induced hypertension; it has a triad of hypertension, proteinuria and edema. In certain circumstances may progress to fits and coma "eclampsia". It is more likely to occur in primigravida patient and especially the older women. It is more common on obese patient of low socioeconomic groups; it occurs only after 20 weeks of pregnancy **(Lain and Roberts, 2002).**

It complicates 3- 8% of all pregnancies and 5-10% of pregnancies is primigravida women **(Oken et al., 2007)**

The most plausible theory of development of preeclampsia is that of some alteration in the metabolism of trophoblast, a vasoconstrictor substance is formed which act directly on the alpha receptors in the arterial wall of the uterine vessels result in vasospasm with a reduction of placental blood supply. The placenta responds to the relative hypoxia by trophoblastic proliferation of the villi. So, large area of syncytium is presented to the less-well oxygenated maternal blood **(Roberts and Redman, 1993).**

These syncytial sprouts are likely to become detached to embolize into general circulation and be carried to lungs where they are destroyed with release of thrombplastin. The

generalized vasospasm causes a reduced renal plasma flow and relative hypoxia in the glomeruli, the epithelial cells of which swell, further reducing the glomerular filtration rate (GFR). The generalized vasospasm accounts for the symptoms of hypertension, the renal glomerular lesion for the sign of proteinuria and reduced glomerular filtration and sodium retention for the edema. The reduced uteroplacental blood flow may cause fetal malnutrition or death **(Innes and Wimsatt, 1999).**

AIM OF THE WORK

To evaluate the possible role that could be played by nutritional pattern as a risk factor in etiology and prognosis of preeclampsia.

HYPERTENSIVE DISORDERS OF PREGNANCY

Hypertensive disorders represent the most common medical complication of pregnancy, affecting 6 to 8 percent of gestations in the United States.1 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 **(Abalos et al., 2007).**

I- Chronic Hypertension:

Chronic hypertension is defined as a blood pressure measurement of 140/90 mm Hg or more on two occasions before 20 weeks of gestation or persisting beyond 12 weeks postpartum**.** Treatment of mild to moderate chronic hypertension neither benefits the fetus nor prevents preeclampsia **(Sibai, 2003).**

Excessively lowering blood pressure may result in decreased placental perfusion and adverse prenatal outcomes; when a patient's blood pressure is persistently greater than 150 to 180/100 to 110 mm Hg, pharmacologic treatment is needed to prevent maternal end-organ damage. Methyldopa (Aldomet; brand no longer available in the United States), labetalol, and nifedipine (Procardia) are oral agents commonly used to treat

chronic hypertension in pregnancy. Angiotensin-converting enzyme inhibitors and angiotensin-II receptor antagonists are not used because of teratogenicity, intrauterine growth restriction (IUGR), and neonatal renal failure **(Abalos et al., 2007).**

The beta blocker atenolol (Tenormin) has been associated with IUGR,3 and thiazide diuretics can exacerbate intravascular fluid depletion if superimposed preeclampsia develops. Women in active labor with uncontrolled severe chronic hypertension require treatment with intravenous labetalol or hydralazine **(Sibai, 2003).**

Morbidity occurs primarily from superimposed preeclampsia or IUGR. A sudden increase in blood pressure, new proteinuria, or signs and symptoms of severe preeclampsia indicate superimposed preeclampsia. Fetal growth may be assessed by serial fundal height measurements supplemented by ultrasonography every four weeks starting at 28 weeks of gestation **(ACOG, 2001).**

II- Gestational Hypertension:

Gestational hypertension has replaced the term pregnancy-induced hypertension to describe women who develop hypertension without proteinuria after 20 weeks of gestation **(Am, 2000).**

Gestational hypertension is a provisional diagnosis that includes women eventually diagnosed with preeclampsia or chronic hypertension, as well as women retrospectively diagnosed with transient hypertension of pregnancy. Fifty percent of women diagnosed with gestational hypertension between 24 and 35 weeks develop preeclampsia (**Barton et al., 2001).**

Expectant management of mild gestational hypertension can reduce the increased rate of cesarean delivery associated with the induction of nulliparous women who have an unripe cervix (**Gofton et al., 2001).**

Women who progress to severe gestational hypertension based on the degree of blood pressure elevation have worse perinatal outcomes than do women with mild preeclampsia, and require management similar to those with severe preeclampsia **(Buchbinder et al., 2002).**

PREECLAMPSIA

Preeclampsia is a multiorgan disease process of unknown etiology characterized by the development of hypertension and proteinuria after 20 weeks of gestation **(Davison et al., 2004).**

▪ Epidemiology and risk factors:

Preeclampsia affects 3–14% of all pregnancies worldwide and about 5–8% in the United States and can have a significant impact on health for both mother and fetus. For the fetus, preeclampsia can result in growth restriction. For the mother complications of preeclampsia include renal failure, HELLP syndrome (hemolysis, elevated liver enzymes, and thrombocytopenia), seizures, stroke or death. New onset of hypertension and proteinuria after 20 weeks of gestation in a previously normotensive woman are key diagnostic criteria, but the clinical features and associated prognostic implications are somewhat heterogeneous and may reflect different mechanisms of disease. Risk factors include past obstetrical history of preeclampsia, advanced maternal age, maternal co-morbidities, such as obesity, diabetes, and chronic hypertension, multiple gestation, primigravid state, genetic factors and paternal factors **(Duckitt and Harrington, 2005).**

The clinical manifestations of preeclampsia generally appear anytime between the second trimester and the first few days postpartum; however, the initial pathogenetic findings of the disease arise much earlier in pregnancy. The exact etiology of preeclampsia is not known. It is quite certain that the pathology is caused by the placenta **(Naicker et al., 2003).**

It is further hypothesized that the physiopathological mechanisms involve an aberrant invasion of trophoblasts in the spiral uterine arteries **(Kadyrov et al., 2003).**

Trophoblast invasion is tightly restricted to the 12th week of pregnancy and is linked to a peak in human chorionic gonadotropin (hCG) expression. However, how this deficiency of trophoblast invasion translates into endothelial dysfunction, hypertension, and the multi-organ deficiency of the mother is not understood. Unfortunately, the only reliable marker for preeclampsia is a hypertension exceeding 140/90, which develops in the 2nd trimester. There are currently no early detection screening methods available **(Bischof and Irminger-Finger, 2005).**

▪ Pathogenesis:

Preeclampsia is a disease of abnormal placentation. Even more so, the placenta, but not the fetus is required for development of the syndrome, since preeclampsia can also

develop in molar pregnancies. While in normal placentation cytotrophoblastic cells invade the maternal spiral arteries and affect their striking transformation, such as a four-fold increase in diameter and loss of smooth muscle of the vessel wall. This results in flaccid tubes with low resistance circuit to the intervillous space. The endometrial arteries from women with preeclampsia characteristically do not show these physiological changes. The result of these defective vascular changes is impaired blood flow to the intervillous space. Pathologic studies show abnormal development of an ischemic placenta with a high-resistance vasculature, which cannot deliver an adequate blood supply to the fetoplacental unit. Endothelial dysfunction plays a central role in the pathogenesis of the maternal syndrome **(Roberts, 1998).**

Dysfunctional endothelial cells produce altered quantities of vasoactive mediators, which lead to an imbalance towards vasoconstriction. This imbalance in circulating angiogenic factors is emerging as a prominent mechanism that mediates the endothelial dysfunction and the clinical signs and symptoms of preeclampsia. Since the endothelium also regulates vessel permeability and platelet adhesion, endothelial alterations could explain edema and intravascular coagulation and thrombocytopenia **(Hiby et al., 2008).**

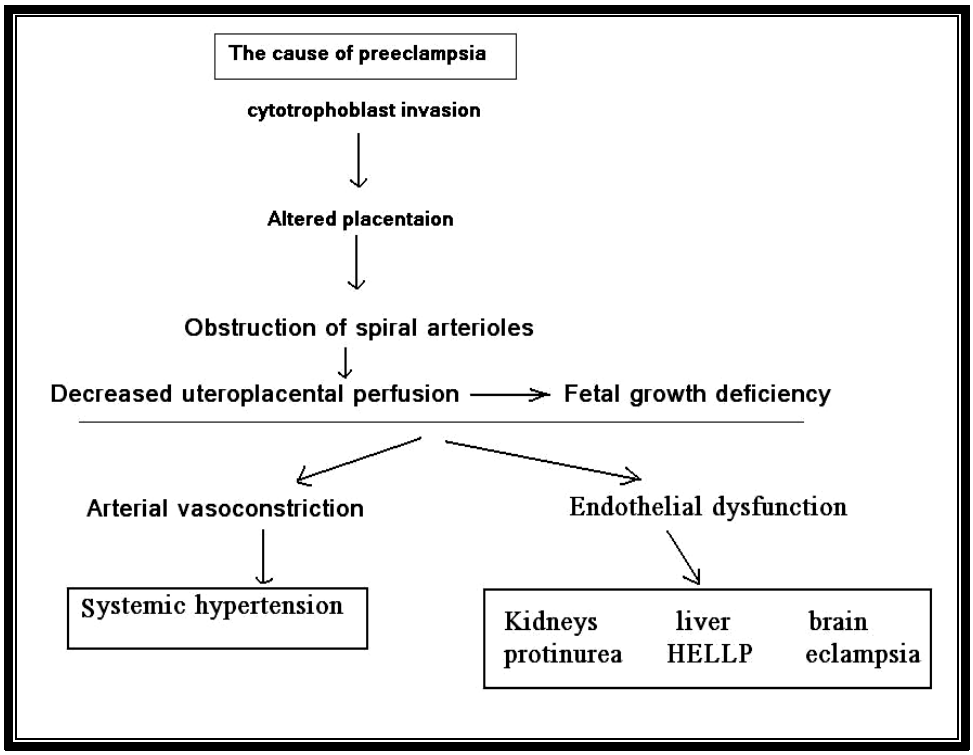

Fig. (1): Pathogenesis of pre-eclampsia. A simplified diagram that summarizes the most pertinent mechanisms leading to the pathophysiology of preeclampsia, as discussed in the test, is presented **(Hiby et al., 2008).**

The origin of preeclampsia is poorly understood. It might be genetic and immunologic. The decidua harbors special immune cells the uterine natural killer cells (uNK). Cytotrophoblast invasion is regulated by the interaction of killer immunoglobulin receptors (KIR) on the maternal uNK with markers of trophoblastic cells. Most important is the human leukocyte antigen C (HLA-C), a major histocompatibility complex class I molecule. Apparently, normal placentation requires a balance between inhibition and activation of

uNKcells, which might be mediated by maternal and fetal factors. In preeclampsia HLA-C molecules and KIR interaction leads to reduced cytotrophoblastic invasion. Indeed, specific genotypic combinations of HLA-C and KIR result in an increased risk of preeclampsia and might be a cause of recurrent miscarriage **(Hiby et al., 2008).**

The hypothesis was also presented that syncytiotrophoblast debris as well as soluble factors, originating from the placenta, could be the source of inflammation and the imbalance of angiogenic and anti-angiogenic factors circulating in the maternal organism. Thus, genetic and immunological factors could cause altered placentation associated with mechanical or functional obstruction of the spiral arterioles, thus leading to decreased uteroplacental perfusion. This affects vasoconstrictors and vasodilators resulting in arterial vasoconstriction, which leads to systemic hypertension, and disseminated intravascular coagulation (DIC), responsible for the proteinuria, seizures, abnormal liver function tests, and ischemia **(Germain et al., 2007).**

▪ Pathophysiology of Preeclampsia:

The woman with overt preeclampsia is vasoconstricted, has multiple organ dysfunctions secondary to reduced perfusion, has evidence of activation of the coagulation

cascade, and has a loss of endothelial integrity. These profound derangements make it difficult to discriminate pathophysiologic causes and effects in women with preeclampsia. Studies of pathophysiologic changes before manifest disease are thus especially pertinent to understanding the disorder. Increased sensitivity to pressors, platelet activation and increased turnover, reduced plasma volume, increased atrial natriuretic factor (ANF), and several indicators of endothelial activation are all evident weeks to months prior to manifestation of preeclampsia **(Adam et al., 1998).**

The glomerular and pathophysiologic changes of preeclampsia, especially those before clinically evident disease, suggest that altered endothelial function is responsible for many of the changes in the syndrome **(Roberts, 1998).**

This hypothesis is supported by abundant evidence of endothelial dysfunction in women with preeclampsia. Women with preeclampsia show increased circulating markers of endothelial activation von Willebrand factor, cellular fibronectin (cFN), thrombomodulin, endothelin, and VCAM and increased growth factor activity. The endothelial prostanoid, prostacyclin (prostaglandin I), is reduced in women with preeclampsia whereas thromboxane, released from activated platelets, is increased **(Mills et al., 1999).**

Vessels removed from women with preeclampsia manifest reduced endothelial-mediated vasodilator function. Several in vitro assays indicate that serum or plasma from women with preeclampsia can alter endothelial function. These alterations include increased release of cFN, prostanoid, and VCAM; increase generation of nitric oxide; increase uptake of fatty acids; and increase expression of platelet derived growth factor by endothelial cells incubated with serum or plasma from women with preeclampsia **(Endresen et al., 1998).**

Many of these activities are not only greater in the blood of women with preeclampsia compared with healthy women, but, as with the syndrome, disappear shortly after delivery. Epidemiologic data support the possibility that immunologic interaction between mother and fetus accounts for the abnormal placental implantation in preeclampsia. These data suggest that exposure to paternal antigen is protective against preeclampsia. Preeclampsia is largely a disease of the first full-term pregnancy, two thirds of cases occurring in first pregnancies **(Roberts, 1998).**

It is proposed that the normal fetal-maternal transfusion associated with delivery exposes the mother to products of the fetal (and hence paternal) genome, protecting her in subsequent pregnancies. In keeping with this concept, the protective effect of first pregnancy is partially lost if a woman has a child with a new partner **(Jacques et al., 2002).**

Similarly, the risk of preeclampsia is less as the duration of time the woman has had sexual contact with the father of the baby increases. In keeping with the protective effect of exposure to the paternal genome through semen, barrier contraception prior to first pregnancy increases the risk of preeclampsia. As would be predicted, women inseminated with sperm that is not from their husband have an increased risk of preeclampsia **(Jacques et al., 2002).**

Since all pregnant women have placentas and only about 5% develop preeclampsia, there must be something different about the placenta of women with the disorder. Sixty years ago, Page concluded that reduced perfusion was the placental feature that led to the development of preeclampsia. The abnormal implantation and reduced vascular invasion characteristic of preeclampsia support this hypothesis. Additionally, medical conditions associated with microvascular disease such as diabetes, hypertension, and collagen vascular diseases all increase the risk of preeclampsia. In addition to the increased trophoblastic tissue present with hydatidiform mole, other conditions with large placentas including multiple gestations increase the risk of preeclampsia. The contribution of the large placenta to the genesis of preeclampsia is posited to be secondary to a relative reduction in placental perfusion. Normal uterine blood flow is inadequate to perfuse the large placenta.

Direct measurements of intervillous blood flow in preeclamptic women indicate that blood flow to the placenta is reduced in preeclampsia **(Livingston and Sibai, 2001).**

Finally, although animal models of preeclampsia have been difficult and not reproducible, there are several animal models in which reducing uterine or placental blood flow produces a preeclampsia like syndrome .Thus, it is generally believed that the first stage in the development of preeclampsia is the reduction in placental blood flow, frequently because of abnormal implantation. The second stage of preeclampsia would be the transduction of reduced placental perfusion to systemic maternal pathophysiology. Reduced placental perfusion results in the production of mediators that can act systemically to alter endothelial function and reduce organ perfusion **(Jacques et al., 2002).**

The search for this factor led to the identification of numerous cytokines and growth factors that are increased in the circulation of women with preeclampsia. Additionally, factors associated with the ability of serum or plasma to alter endothelial function in vitro has been partially characterized **(Budak et al., 1998).**

The panoply of differences demonstrable in preeclamptic women has prompted a more directed approach based on

clinical features of the disorder and the phenotype of the preeclamptic woman. One of the first conclusions reached with this approach is that reduced placental perfusion is not sufficient to explain preeclampsia. Fetal growth restriction, indicating reduced perfusion and delivery of nutrients, occurs in many pregnancies without the systemic manifestations of preeclampsia. Abnormal implantation is also not uniquely associated with preeclampsia. Infants with intrauterine growth restriction and one third of infants with preterm birth manifest abnormal features of implantation identical to those seen in preeclampsia. Interestingly, only one third of infants of preeclamptic women are growth restricted. Furthermore, conditions associated with large infants such as obesity and gestational diabetes increase the risk of preeclampsia. Thus, it appears that although reduced placental perfusion may be necessary for preeclampsia, it is certainly not sufficient. It is proposed that the abnormal implantation must interact with maternal factors to result in the preeclampsia syndrome. Thus, genetic, behavioral, and environmental factors would predispose woman to preeclampsia. These "constitutional" factors, likely influenced by the unique physiologic changes of pregnancy, interact with fetal placental factors induced by reduced placental perfusion to bring about the pathophysiologic changes of preeclampsia **(Jacques et al., 2002).**