INTRODUCTION

Elevated serum homocysteine level is a risk factor for vascular disorders. Hyperhomocyteinemia could result from a genetic defect on enzyme participating in homocysteine synthesis and metabolism or it could be because of deficiency of folic acid, vitamin B6, B12.The vascular changes induced by homocysteine are similar to those associated with preeclampsia and include endothelial dysfunction ***(Cotter et al., 2003).***

Homocysteine, a sulfur containing amino acid, is an immediate product of methionine metabolism. Methionine cannot be stored in liver and is demethylated to homocysteine for storage until needed. The concentration of plasma homocytseine is regulated by several factors, including genetically determined enzymes and environmental factors. When proteins are metabolized, they are broken down into individual amino acids, including sulfur containing amino acid, methionine. Methionine is in turn broken down further in several steps to produce homocysteine, which once formed can be removed from the body in only two ways. Firstly, it can be remade into methionine through process known as remethylation. This requires folic acid and vitamin B 12 ***(Miller et al., 1994).***

Preeclampsia is a leading cause of maternal and perinatal mortality and morbidity. Incidence of preeclampsia in 8 to

10%, though exact cause of preeclampsia is not known, the basic pathology is endothelial dysfunction and intense vasospasm. Homocysteine is critically important during pregnancy. High maternal homocysteine level (hyperhomocystienemia) causes endothelial damage and dysfunction, platelet dysfunction, thrombus formation and smooth muscle proliferation. Probably, this causes increased incidence of preeclampsia, miscarriage, intra uterine growth retardation, placenta abruption, low birth weight. Also hyperhomocysteinemia causes increased oxidative stress, thereby causing endothelial dysfunction and preeclampsia ***(Georgios et al., 2007).***

Aim of the Work

To estimate maternal serum homocysteine levels in patients with preeclampsia compared to normotensive pregnant women.

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 (2000),*** which proposed a classification system based on clinical simplicity to guide management. The classification is shown in table (1). There are five types of hypertensive disease:

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

Table (1): Diagnosis of hypertensive disorders complicating pregnancy

Gestational hypertension:
BP >140/90mmHg for first time during pregnancy No proteinuria.
BP returns to normal <12 weeks' postpartum.
Final diagnosis made only postpartum.
May have other signs or symptoms of preeclampsia, for example, epigastric discomfort, or thrombocytopenia.
Preeclampsia:
Minimum criteria
BP >140/90mmHg after 20 weeks' gestation.
Proteinuria >300mg/24hrs of >1+ dipstick
Increased certainty of preeclampsia:
BP> 160/110 mmHg.
Proteinuria 2.0g/24hrs or >2+ dipstick.
Serum creatinine >1.2mg/dL unless known to be previously elevated.
Platelet <100.000/mm3.
Microangiopathic hemolysis (increased LDH).
Elevated ALT or AST.
Persistent headache or other cerebral or visual disturbance.
Persistent epigastric pain.
Eclampsia:
Seizure that cannot be attributed to other causes in a women with preeclampsia.
Superimposed preeclampsia (on chronic hypertension):
New-onset proteinuria >300mg/24hrs in hypertensive women but no proteinuria before 20 weeks' gestation.
A sudden increase in proteinuria or blood pressure, platelet count <100.000/mm^3 in women with hypertension and proteinuria before 20 weeks' gestation.
Chronic hypertension:
BP >140/90mmHg before pregnancy or diagnosed before 20 weeks' gestation not attributed to gestational trophoblastic disease.
Or
Hypertension first diagnosed after 20 weeks' gestation and persistent after 12 weeks' postpartum.

Definitions:

Preeclampsia is defined as a syndrome consisting of hypertension and proteinuria that may also be associated with myriad other signs and symptoms, such as edema, visual disturbances, headache and epigastric pain ***(National High Blood Pressure Education Program, 2000).***

Hypertension is defined as a systolic blood pressure level of 140mmHg or higher and a diastolic blood pressure level of 90mmHg or higher that occurs after 20 weeks of gestation in a women with previously normal blood pressure on at least two occasions six hours apart ***(National High Blood Pressure Education Program, 2000).***

Proteinuria is defined as the presence of 0.3gm or more protein in 24-hour urine specimen. This finding usually correlates with a finding of 1^{+} or greater but should be confirmed using a random urine dipstick evaluation and a 24-hour or timed collection ***(National High Blood Pressure Education Program, 2000).***

Eclampsia is defined as the occurrence of seizures in a woman with preeclampsia that cannot be attributed to other causes ***(National High Blood Pressure Education Program, 2000).***

Risk factors for preeclampsia:

Until relatively recently, preeclampsia was estimated to occur in 5-7% of all deliveries, but this figure was based on study samples that were not representative of the national population ***(Tanjung et al., 2005).***

1- Parity and Age:

Young maternal age, nulli-parity, and twin pregnancy are associated with a threefold relative risk. Eighty-five percent of all cases of preeclampsia occur in primigravidas. Other risk factors associated with a relative risk include multiparous women conceiving by a new partner ***(Duckitt and Harrington, 2005).***

Preeclampsia is more common below age 17 and above 35 years. This may be due to poor immune capacity at that age ***(Khalia et al., 2005).***

2- Gestational age:

A peak of gestational age incidence is seen after 20 week of gestation. Rarely, preeclampsia develops earlier than this except in cases of hydatiform mole ***(Cunningham et al., 2001).***

3- Familial factors:

A family history of preeclampsia is associated with 2 to 5 fold increase in risk, suggesting a heritable mechanism in some cases ***(Nilsson et al., 2004).*** The father of the baby also may contribute to the increased risk, as the paternal contribution to fetal genes may have a role in defective placentation and subsequent preeclampsia. The risk of preeclampsia was found to be higher among the mothers, sisters, daughters and granddaughters of women with preeclampsia. There is increased incidence of HLA-DR4 in preeclampsia ***(Kim et al., 2001).***

4- Racial factors:

The incidence of preeclampsia is more common in black races (8.5%) than in white one (6.2%). This is mostly due to genetic factor that relates the underlying chronic hypertension ***(Mulroz et al., 2000).***

5- Obesity:

A systematic review reported that, at antenatal looking, a BMI>35kg/m2, systolic blood pressure 130 mmHg, or diastolic blood pressure 80 mmHg were predictive of development of preeclampsia ***(Duckitt and Harrington, 2005).***

6- Dietary Habits:

There is a strong relationship between the incidence of preeclampsia and malnutrition and this explains the higher incidence in low class people ***(Ross, 2000).***

7- Smoking:

Although smoking during pregnancy causes a variety of adverse pregnancy outcomes, ironically, it has consistently been associated with reduced risk of hypertension during pregnancy ***(Bainbridge et al., 2005).***

PATHOGENESIS

The pathophysiology of preeclampsia likely involves both maternal and fetal/placental factors. Abnormalities in the development of placental vasculature early in pregnancy may result in relative placental under perfusion, hypoxia and ischemia, which then leads to release of antiangiogenic factors into the maternal circulation that alters maternal systemic endothelial function and cause hypertension and other manifestations of the disease. However, the molecular basis for placental dysregulation of these pathogenic factors remains unknown, and the role of angiogenic proteins in early placental vascular development are under investigation.

1-Abnormal development of the placenta:

The critical role of the placenta in the pathophysiology of preeclampsia is supported by epidemiologic and experimental data that show:

- Placental tissue is necessary for development of the disease, but the fetus is not ***(Moore-Maxwell et al., 2004; Matsuo et al., 2007).***
- Preeclampsia is always cured after delivery of the placenta.

Examination of human placentas at various stages of gestation in women with normal pregnancies, as well as those with preeclampsia, has led to an understanding of normal

placental morphology and pathologic changes in the uteroplacental circulation that are likely to be relevant to preeclampsia.

2-Abnormal remodeling of spiral arteries:

In normal pregnancies, the cytotrophoblast cells of the developing placenta migrate through the decidua and part of the myometrium to invade both the endothelium and highly muscular tunica media of the maternal spiral arteries, the terminal branches of the uterine artery that supply blood to the developing fetus and placenta (figure 1). As a result, these vessels undergo transformation from small muscular arterioles to large capacitance vessels of low resistance, thus greatly facilitating blood flow to the placenta compared with other areas of the uterus ***(Zhou et al., 1997; Zhou et al., 1993).*** Remodeling of the spiral arteries probably begins in the late first trimester and is completed by 18 to 20 weeks of gestation, although the exact gestational age at which trophoblast invasion of these arteries ceases is unclear.

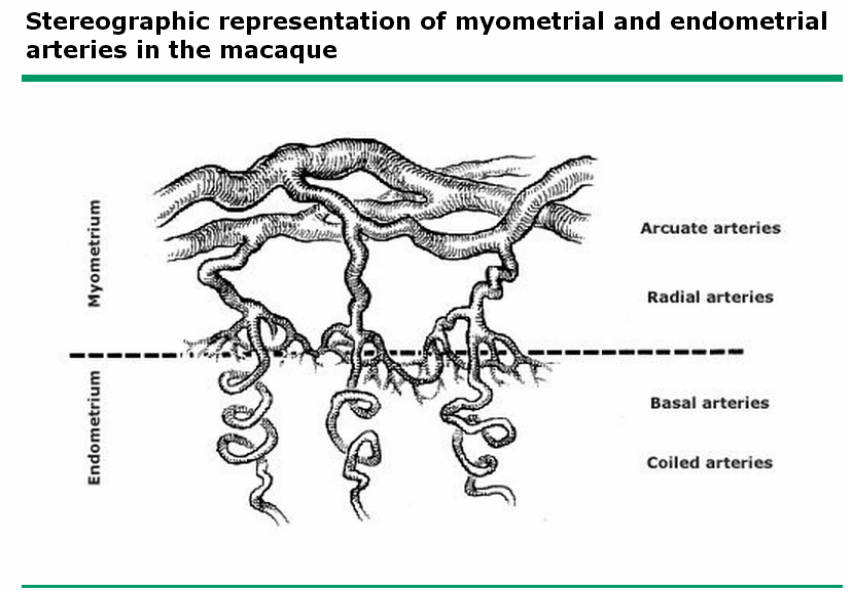

Figure (1): Parts of myometrial arcuate arteries from which myometrial radial arteries course toward the endometrium. There are found larger endometrial coiled arteries and smaller endometrial basal arteries ***From Okkels and Engle. Acta Pathol Microbiol Scand 15:150, 1930. Reproduced with permission from: Pritchard, JA, MacDonald, PC. Williams Obstetrics, 16th Edition, Appleton-Century-Crofts, New York 1980. Copyright © 1980 McGraw Hill. p.25.***

By comparison, in preeclampsia, cytotrophoblast cells infiltrate the decidual portion of the spiral arteries, but fail to penetrate the myometrial segment ***(Roberts et al., 1993; Meekins et al., 1994).*** 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 (figure 2 and figure 3). This defect in deep placentation has been associated with development of multiple adverse pregnancy

outcomes, including second trimester fetal death, placental infarcts, abruptio placentae, preeclampsia with or without intrauterine growth restriction, intrauterine growth restriction without maternal hypertension, premature rupture of membranes, and preterm labor ***(Brosens et al., 2011).***

It is not known why the normal sequence of events in development of the uteroplacental circulation does not occur in some pregnancies. Vascular, environmental, immunological, and genetic factors all appear to play a role ***(Ilekis et al., 2007).*** These factors will be reviewed in the following discussion.

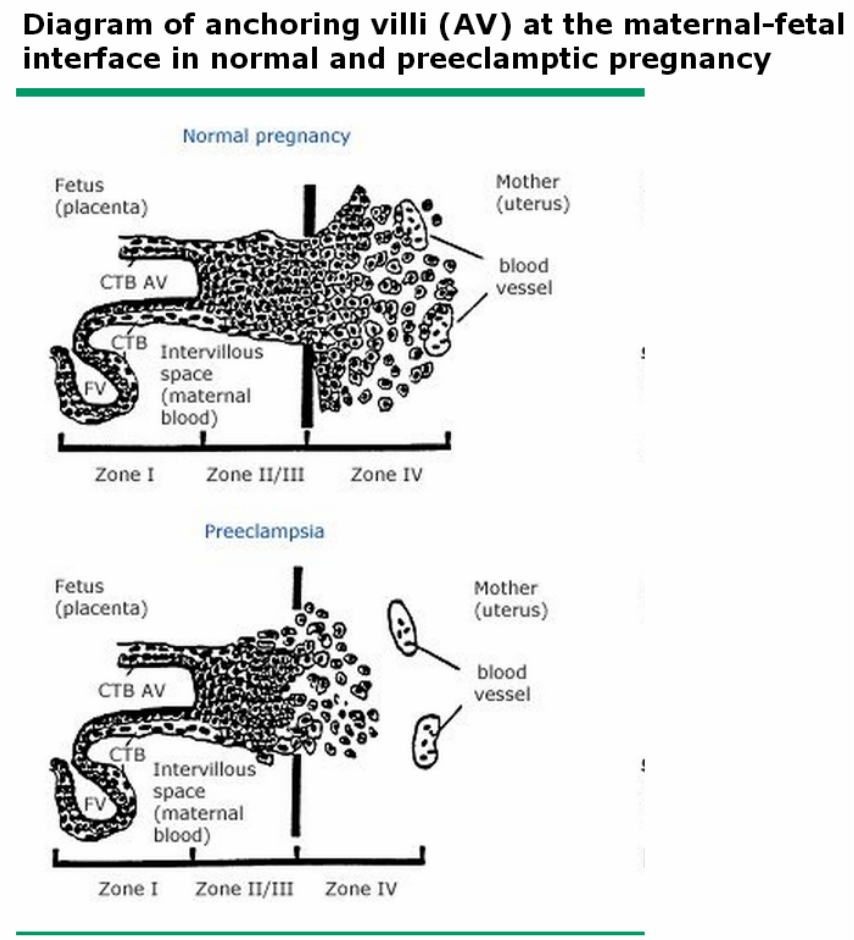

Figure (2): The floating villi (FV) are in the intervillous space in direct contact with the maternal blood. In normal pregnancy, invasive cytotrophoblasts (CTB) form cell columns (zone II/III) and invade maternal decidua and vasculature (zone IV). During the differentiation along the invasive path, the cytotrophoblasts dramatically alter their expression of various molecules, such as integrins. In preeclampsia, the invasive cytotrophoblasts fail to differentiate along the invasive pathway and do not gain access to spiral arteries. *Courtesy of Kee-Hak Lim, MD.*

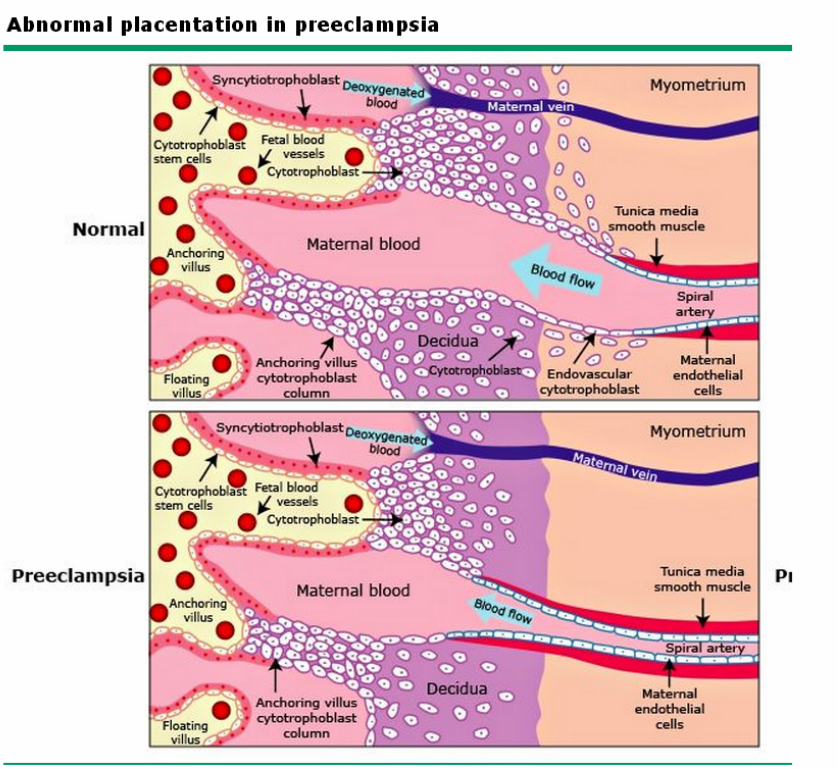

Figure (3): Exchange of oxygen, nutrients, and waste products between the fetus and mother depends on adequate placental perfusion by maternal vessels. In normal placental development, invasive cytotrophoblasts of fetal origin invade the maternal spiral arteries, transforming them from small-caliber 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 "pseudovasculogenesis" or "vascular mimicry" (Upper panel). 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 (Lower panel).
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3-Defective trophoblast differentiation:

Defective differentiation of trophoblast is one possible mechanism responsible for defective trophoblast invasion of the spiral arteries ***(Huppertz et al., 2008).*** 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 I major histocompatibility complex molecule, HLA-G ***(Cross et al., 1994; Lim et al., 1997).*** During normal differentiation, invading trophoblasts alter their adhesion molecule expression from those that are characteristic of epithelial cells (integrin alpha6/beta1, alphav/beta5, and E-cadherin) to those of endothelial cells (integrin alpha1/beta1, alphav/beta3 and VE-cadherin), a process referred to as pseudo-vasculogenesis ***(Zhou et al., 1997).*** Trophoblasts obtained from women with preeclampsia do not show upregulated adhesion molecule expression or pseudo-vasculogenesis. The resulting impaired placentation and accompanying ischemia are thought to be the primary events leading to placental release of soluble factors that cause systemic endothelial dysfunction resulting in the preeclamptic phenotype.

4-Hypoperfusion, hypoxia, ischemia:

Hypoperfusion appears to be both a cause and a consequence of abnormal placental development. A causal