INTRODUCTION

Preeclampsia represents an important cause of maternal as well as perinatal morbidity and mortality. Inspite of its relevant epidemiologic impact, the complete pathogenesis of this disease still remains unclear, underlining a multifactorial etiology ***(Duckitt et al., 2005).*** The typical clinical manifestations of preeclampsia, including hypertension, proteinuria, and the varying degrees of ischemic peripheral organ damage, which typically arise in the third trimester of gestation, might be late phenomena of the complex process of embryo implantation. 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. Leading to the dimissal of inflammatory factors in the systemic maternal circulation ***(Khong et al., 1986; Meekins et al., 1994).***

Endothelial dysfunction has been hypothesized to be part of an excessive maternal inflammatory response to pregnancy ***(Redman et al., 2005).***

Complement activation, activated circulating leukocytes, increased release of reactive oxygen species, and increased levels of various inflammatory cytokines in preeclampsia all agree with this hypothesis ***(Redman et al., 2005; Haeger et al., 1992).***

Pentraxin 3 (PTX3), tumor necrosis factor stimulated gene-14 belongs to the same family as C-reactive protein (CRP) or serum amyloid P component (SAP) and consists of 381 amino acids. The C-terminus is highly homologous to SAP and CRP whereas the N-terminus doesn't show any homology to other proteins. The according gene is organized into three exons and is extremely evolutionarily conserved from horseshoe crab to human. Responding to proinflammatory stimuli CRP, SAP and PTX3 are produced by various tissues. It is also expressed in tissues undergoing cell death. PTX3 then interacts with several growth factors, extra cellular matrix components and certain pathogens but is also involved in the activation of the complement system and facilitates pathogen recognition by phagocytes ***(Simon et al., 2009).***

During pregnancy, PTX3 is increasingly expressed in amniotic epithelium, chorionic mesoderm, trophoblast terminal villi, and perivascular stroma of placentae. Scientists have showed that in case of a future preeclampsia the PTX3 plasma levels are even more increased in all three trimesters ***(Cetin I, et al., 2006; Quirini et al., 2006).***

So far no studies that combine PTX3 with other potential markers have been performed. Thus we were encouraged to try

to explore the uses of this novel marker in the field of obstetrics, in order to help in the evolution of a new medical era in which we can prevent as well as prognose the great mystery of preeclampsia.

AIM OF THE WORK

The aim of this work is to compare between serum levels of Pentraxin 3 in mild and severe preeclampsia versus normotensive pregnancies in order to speculate a possible role of this novel vascular inflammatory marker in the pathogenesis and evaluation of preeclampsia.

HYPERTENSIVE DISORDERS OF PREGNANCY

Hypertensive disorders are one of the most common medical complications of pregnancy and affects both maternal and fetal health. Hypertensive disorders occur in 5% to 10 % of all pregnancies ***(Solomon and Seely, 2006).***

Hypertensive disorders in pregnancy remain one of the leading causes of maternal death world wide (about 15% to 20% of maternal deaths in developing as well as developed nations) ***(Brown et al., 2006).***

Pre-eclampsia was defined as the development of blood pressure>140/90 after 20 weeks of gestation occurring in women with no prior history of HTN or renal disease whose blood pressure returned to normal within 3 months postpartum, Plus the presence of proteinuria>300mg/day or more than +2 on a voided or +1 on catheterized random urine specimen ***(Gifford et al., 2000).***

Pre-eclampsia and eclampsia has been called the "disease of theories". Although it is a relatively common entity and has been the subject of a large body of research, the search for an inciting agent and a unifying pathophysiological mechanism has generated more questions than answers. Even the definition of the disease has been a source of controversy. Nevertheless,

research has yielded a great deal of information that has markedly improved maternal and fetal outcomes, and work continues to enhance efforts at prevention of this often devastating condition ***(NHBPEPWG, 1990).***

Table (1): Classification of hypertensive disorders complicating pregnancy ***(Gifford et al., 2000).***

Gestational Hypertension	• Increased blood pressure (≥140 mm Hg systolic or >90 mmHg diastolic pressure) first diagnosed after 20 weeks gestation and not accompanied by proteinuria. • BP returns to normal <12 weeks post partum. Final diagnosis made only post-partum. • It may have epigastric pain or thrombocytopenia.
Pre-eclampsia	**Minimum criteria** • New-onset hypertension(≥140/90mmHg) and proteinuria (excretion> 0.3g in 24 hours) after 20 weeks gestation in a previously normotensive woman. **Increased certainty of pre-eclamspsia:** • BP ≥160/110mmHg. • Proteinuria 2g/24h. • Serum creatinine>1.2mg/dl • Platelet<100.000/mm³. • Increased LDH. • Elevated ALT or AST. • Persistant epigastric pain.
Eclampsia	• Seizures that cannot be attributed to other causes in a woman with pre-eclampsia.
Pre-eclampsia superimposed on chronic hypertension	• New-onset or acutely worse proteinuria(≥300mg/24), sudden increase in blood pressure, thrombocytopenia (<100.000mm³), or elevated liver enzymes after 20 weeks gestation in women with pre-existing hypertension.
Chronic hypertension	• BP ≥140/90mmHg present before pregnancy or first diagnosed before 20 weeks gestation. • Hypertension does not resolve by 12 weeks postpartum.

Incidence and Risk Factors:

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

Risk factors of PE include:

Age and Parity:

Young maternal age, nulliparity, and twin pregnancies are associated with a threefold relative risk. 85% of all cases of PE occur in primi-gravidas. Other risk factors associated with a relative risk include multiparous women conceiving by a new partner (***Duckitt and Harrington, 2005).***

Racial factors:

The incidence increases in black races(8.5%)than in white ones (6.2%) which is mostly due to genetic factors ***(Samadi et al., 2001).***

Familial factors:

Review of risk factors aids the understanding of theories regarding mode of inheritance. Daughters and sisters of pre-eclamptic women have more than a fourfold relative risk for the development of PE ***(Walker, 1998).***

Obesity:

PE increases from 4.3% for women with the body mass index <19.8kg/m² to 13.3% in those >35kg/m² ***(Cunningham et al., 2005).***

Pre-existing medical disease:

Medical conditions with the potential to cause micro vascular disease (e.g. diabetes mellitus, chronic hypertension, renal, vascular and connective tissue disorders), antiphospholipid antibody syndrome, and nephropathy ***(Duckitt and Harrington, 2005).***

Cigarette smoking:

For unknown reasons, pregnant smokers have a decreased incidence of PE ***(Conde-Agudelo et al., 1999).***

Hyperplacentosis:

It is an increase in weight and consequently functions of the placenta due to increased number or size of its tissue mass. It may occur in multiple pregnancies, hydatiform mole and hydrops fetalis ***(Gorzelak et al., 2000).***

Dietary habits:

The malnutrition increases the incidence of PE ***(Jaramillo et al., 2001).***

Recurrence:

In general, the recurrence risk of preeclampsia in a woman whose previous pregnancy was complicated by pre-eclampsia near term is approximately 10%. If a woman had severe pre-eclampsia (including HELLP syndrome and/or eclampsia), she has 20% risk of developing pre-eclampsia sometime in her subsequent pregnancy ***(Sibai et al., 1994).*** If a woman had HELLP syndrome or eclampsia, the recurrence risk of HELLP syndrome and eclampsia are 5% and 2%, respectively ***(Sullivan et al., 1994).*** The recurrence rate rises the earlier the disease manifested during the index pregnancy. If pre-eclampsia presents clinically before 30 weeks gestation, the recurrence rate may be as high as 40% ***(Chesley, 1978*)**.

Pathophysiology:

A two stage model of preeclampsia (PE) has been proposed as a means of addressing its pathophysiology ***(Nejatizadeh et al., 2008).***

The first stage:

During normal placentation, cytotrophoblast cells cross the placental-maternal bridges and invade the maternal deciduas and adjacent spiral arteries. They replace the maternal endothelium in the spiral arteries and then invade the media,

with resulting destruction of the elastic, muscular and neural tissues. The cytotrophoblast cells become incorporated into the wall of the vessels. These changes create a low resistance to flow and absence of maternal vasomotor control, leading to an enormous increase in blood supply to the growing fetus. By the 20^{th} week of gestation, this process is more or less complete ***(Nejatizadeh et al., 2008).***

In the preclinical stage of (PE), the endovascular cytotrophoblast invasion is restricted, resulting in impaired arterial remodeling (shallow placentation) ***(Redman and Sargent, 2005).*** The etiology of shallow placentation is unknown, but maternal- fetal immune adaptation could be a main cause ***(Roberts and Lain, 2002).***

In the deciduas, trophoblast cells are confronted by natural killer cells **(*Redman and Sargent, 2005)***.During normal pregnancy, these immune cells probably facilitate deep invasion of the trophoblast cells into the myometrial segments and promote extensive spiral artery remodeling. Killer immunoglobulin receptors (KIRs) or natural killer cells interact with specific trophoblast cell markers and this interaction may influence the trophoblast invasion ***(Nejatizadeh et al., 2008).***

The natural killer cells also have a role in producing several cytokines that are implicated in angiogenesis and

vascular stability, including vascular endothelial growth factor (VEGF) and placental growth factor (PIGF) ***(Moffett and Loke, 2004).***

The second stage:

The clinical features of PE appear to arise from a generalized systemic inflammatory response, of which endothelial dysfunction is a prominent component ***(Wang et al., 2004).*** The endothelial dysfunction can give rise to vasospasm due to a decrease in production and activity of vasodilator prostaglandins, especially prostacycline and nitric oxide, but also by causing an increased sensitivity to pressor agents ***(Sibai et al., 2005).***

Endothelial dysfunction can also give rise to activation of the coagulation cascade, with formation of occlusive microthrombi and a loss of fluid from the intravascular space ***(Roberts and Lain, 2002)***. All these components contribute to a reduced perfusion, which is seen in virtually in any organ (uterus included) examined in women with PE ***(Roberts et al., 2003).***

In the kidney, endothelial damage results in proteinuria and produces the characteristic pathological lesion glomerular endotheliosis. Glomerular endotheliosis is characterized by generalized swelling and vascuolization of the endothelial cells. Although once considered pathegnomonic for PE, recent studies

have shown that mild glomerular endotheliosis may also occur in a significant percentage of normal pregnancies at term, but is more severe in Pre-eclampsia ***(Strevens et al., 2003).***

The linkage between the two stages:

The first stage in the 2 stage model is completed before the 20th week and prior to the appearance of clinical signs. In the second and third trimesters of pregnancy, the placenta requires increasing access to the maternal blood supply. As a result of the first stage, leading to a reduced uterine perfusion, the placenta becomes increasingly hypoxic. This hypoxic and dysfunctional placenta is considered to release factors into the maternal circulation that eventually cause the clinical features of PE ***(Chaiworapongsa et al., 2004).***

These released factors act as the linkage between the two stages and their identification could hopefully enable the development of therapies for prevention of the clinical stage development ***(Chaiworapongsa et al., 2004).***

Early- onset and late-onset pre-eclampsia:

PE is clinically a heterogeneous disease and major differences are observed between early-onset and late-onset disease. In a recent study of placental morphology, placentas

from women with early-onset(less than 34 weeks) and late-onset PE (more than 34 weeks) were studied separately ***(Egbor et al., 2006).***

An abnormal placental morphology was found in early-onset disease, whereas placentas from late-onset disease were morphologically similar to those from gestational age matched controls. This result is an agreement with studies of findings on second trimester Doppler ultrasound of the uterine arteries, where increased impedance was more associated with early-than with late-onset disease ***(Valensise et al., 2008).***

Diagnosis

Symptoms:

As pre-eclampsia pathophysiology involves multisystem affection so there are diverse presentations, we classify it according to system affection as the following:

Cerebral:

Headache, dizziness, tinnitus, drowsiness and altered consciousness are common in severe pre-eclampsia and almost invariably precede an eclamptic convulsion. These symptoms indicate poor cerebral perfusion ***(Sibai et al., 2003)***.

Visual:

Symptoms may include blurred vision, diplopia, scotomata, blindness as a result of retinal arterial spasm, edema and retinal detachment. The pathophysiology of these symptoms can also be vasospasm, ischemia and hemorrhage in the occipital cortex ***(Brown et al., 1988).***

Gastrointestinal:

Nausea, vomiting, and epigastric or right upper quadrant pain and hematemesis are caused by distension of Glisson's capsule by edema and hemorrhage. These are symptoms of severe pre-eclampsia and can precede hepatic rupture and convulsions ***(Cunningham et al., 2001)***.

Renal:

Oliguria, anuria and hematuria are symptoms of severe pre-eclampsia that may be caused by renal artery vasospasm ***(ACOG, 2002).***

Signs:

Blood Pressure:

High blood pressure is the hallmark of gestational hypertension. Blood pressure is taken with the patient in an upright position, after a 10 minute rest period. A mercury sphygmomanometer is preferred ***(ACOG, 2002).***

Blood pressure should be taken in a sitting position in a semireclining position in hospitalized patients. The right arm should be used for the measurement, and the arm should be placed in a horizontal position at heart level. The increase in blood pressure reflects the arteriolar vasospasm that is basic to preeclasmpsia ***(Sibai, 1990).***

Hypertension in pregnancy is most typically diagnosed by the presence of an absolute blood pressure ≥ 140mmHg systolic and /or ≥ 90mmHg diastolic. Previously the definition included a rise in blood pressure from preconceptionor first trimester values of more than 25-30 mmHg systolic and/or 15 mmHg diastolic. It is uncertain how these discriminate levels of blood pressure were chosen ***(Mark, 2002).***

Proteinuria:

In early pre-eclampsia, proteinuria is minimal. Proteinuria develops as the disease progresses and usually occurs after the development of hypertension and weight gain **(*Cunningham et al., 2001).*** However, proteinuria accompanied by hypertension is the most reliable indicator of fetal morbidity and mortality ***(Tervila et al., 2002)***.

Urine protein levels are affected by several factors and fluctuate in the same patient from hour to hour **(*Lindheimer* et *al., 2010)***. Therefore, a semi quantitative assay is unreliable, and