Changes in Tumor factor necrosis-α (TNF-α) in Patients with Severe Pre-Eclampsia before and after Termination

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By

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Introduction

Pre-eclampsia is a hypertensive and multiple system disorder unique to human pregnancy. Although the etiology of pre-eclampsia remains unknown, there are many proposed theories regarding the pathogenesis of the pre-eclamptic disease processes as: oxidative stress; abnormal trophoblast invasion; vascular endothelial dysfunction; genetic predisposition; dietary deficiencies; and defective immunological adaptation to pregnancy **(David et al., ٢٠٠٩).**

Pre-eclampsia is one of the most recognized clinical causes of high-risk pregnancies. Although pre-eclampsia affects about ١٪–٢٪ of pregnancies in some European countries, its prevalence can be up to ١٠٪–١٥٪ in some South American and African countries **(Sucak et al., ٢٠١٠).**

Pre-eclampsia has a greater genetic component determined by multiple genes, the number of genes involved in the susceptibility to develop pre-eclampsia increases rapidly. Nearly ٥٠ maternal genes have been analysed; most of these studies have been approaches to identify a genetic association, comparing the frequencies of genetic polymorphisms between cases and controls **(Norma, ٢٠٠٦).**

Conditions associated with oxidative stress, include, obesity, chronic hypertension and diabetes, where antioxidant reserves may be inadequate. These observations have led to trials of prophylactic effects of antioxidants, including Vitamins C And E and Selenium. A recent Cochrane review of seven randomized trials reported a ٣٩٪reduction in the risk of pre-eclampsia associated with oral antioxidant supplements **(Sally and Linda, ٢٠٠٦).**

A shallow trophoblast invasion is one of the mechanisms strongly affiliated to the pathogenesis of pre-eclampsia. It is claimed that shallow trophoblastic invasion might lead to poor placental vascularization that will result in both deficient anchoring in the matrix tissue and placental ischemia ending in the release of inflammatory cytokines in maternal circulation starting the process of pre-eclampsia **(Leif et al., ٢٠٠٥).**

The increased syncytiotrophoblast deportation in pre-eclampsia is probably explained by the presence syncytial sprouts that may be elongated on long pedicles. Cytotrophoblast proliferation and formation of these outgrowth lesions of syncytiotrophoblast may represent evidence of placental repair mechanisms. Pre-eclampsia is associated with glycogen accumulation in syncytiotrophoblast, which could be another expression of

increased syncytiotrophblast deportation and increased cytotrophoblast proliferation **(Gustaaf et al., ١٩٩٨).**

Dys-regulation of the maternal immune response towords the fetus might be the causal factor of shallow trophoblastic invasion **(Reza et al., ٢٠٠٧).**

It has been proved that in pre-eclamptic patients, there is up-regulation of Th١ activity with the abnormal release of increasing amounts of pro-inflammatory cytokines as IL-١٢ and TNF-α **(Jacek et al., ٢٠٠٢).**

And these pro-inflammatory cytokines might be the causal factor of generalized endothelial dysfunction that is characteristic to pre-eclampsia **(Reza et al., ٢٠٠٧).**

Inflammatory cytokines are known to be potent activators of vascular endothelial and have been proposed as mediators of endothelial dysfunction during pre-eclampsia **(Sazina et al., ٢٠٠٣).**

In normal pregnancy, particularly, at the maternal-fetal interface, anti-inflammatory cytokines produced by T helper (TH٢) cells predominate, regulating trophoblast cell growth, differentiation and invasion for embryo implantation and therefore, an appropriate balance between pro-(TH١) and anti (TH٢) inflammatory cytokines is thought to be crucial for determining the success or failure

of pregnancy. Endothelial dysfunction, present in pre-eclampsia, may cause abnormal immune (TH١) activation, causing disturbed balance between pro-inflammatory (tumor factor necrosis-α (TNF-α), interleukin (IL)-٦, IL-٢, IL-١β) and anti-inflammatory (IL-٤, IL-١٠, IL-١٣) cytokines, which compromises uteroplacental perfusion and perpetuates further vascular damage **(Archana et al., ٢٠١٠).**

Many pro-inflammatory cytokines and modulators are founded at increased levels in both circulation and placenta during pre-eclamptic pregnancy. Two of them tumor factor necrosis-α (TNF-α) and interleukine-١(IL-١) have both been implicated in pre-eclampsia pathophysiology, since they have the ability to stimulate structural and functional alternation in endothelial cells **(Henna et al., ٢٠٠٩; Henna et al., ٢٠٠٧).**

Tumour necrosis factor alpha (TNF-α) is a multifunctional pro-inflammatory cytokine that is involved in the pathogenesis of a large number of autoimmune and inflammatory human diseases **(Tanja et al., ٢٠٠٥).**

TNF-α is known to induce free radical generation, and mitochondrial superoxide radical production. Which is considered a key step in its cytotoxic action **(Yuping and Scott, ١٩٩٦).**

TNF-α has also been shown to affect early events in pregnancy, leading to failed trophoblast invasion and placentation **(Bauer et al., ٢٠٠٤).**

Tumour Factor Necrosis-α (TNF-α), has been hypothesized to be one of the pro-inflammatory cytokines incriminated in pre-eclampsia evidenced by." Firstly, plasma TNF-α has direct contact with the maternal endothelial cells in vivo. Secondly, elevated plasma concentrations of TNF-α have been observed in women with pre-eclampsia as compared to normal pregnant women **(Conrad et al., ١٩٩٧).**

Thirdly, chronic infusion of TNF-α into rats during late pregnancy results in a significant increase in renal vascular resistance and arterial pressure **(Alexander et al., ٢٠٠٢).**

Finally, TNF-α has been shown to up-regulate the expression of numerous molecules such as platelet-derived growth factor, cell adhesion molecules, endothelin-١, and plasminogen activator inhibitor-١ in endothelial cells, indicating their activation. These molecules have detrimental effects on the vasculature, and also characterize pre-eclamptic pregnancy **(Hung et al., ٢٠٠٤).**

Aim of Work

١. This study aimed at investigating the role of placenta in the pathogenesis of pre-eclampsia.

٢. It aimed at studying the hypothesis that placenta was the source of abnormal cytokines production in pre-eclamptic patients.

٣. It aimed at studying the level of (TNF-α) before and after termination (Removal of placenta) from maternal circulation.

Hypertensive Disorder with Pregnancy

Hypertensive disorders represent the most common medical complication of pregnancy, affecting ٦ to ٨ percent of gestations in the United States. In ٢٠٠٠, 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.

Chronic Hypertension

Chronic hypertension is defined as a blood pressure measurement of ١٤٠/٩٠ mm Hg or more on two occasions before ٢٠ weeks of gestation or persisting beyond ١٢ weeks postpartum **(Lawrence and Patricia, ٢٠٠٨).**

Gestational Hypertension

Gestational hypertension has replaced the term pregnancy-induced hypertension to describe women who develop hypertension without proteinuria after ٢٠ weeks of gestation **((Lawrence and Patricia, ٢٠٠٨).**

Preeclampsia

Preeclampsia is a multiorgan disease process of unknown etiology characterized by the development of hypertension and proteinuria after ٢٠ weeks of gestation **(Lawrence and Patricia, ٢٠٠٨).**

Pre –eclampsia superimposed on chronic hypertension

Establishment of proteinuria equal to or greater than ٣٠٠ mg in ٢٤hr urine in women had blood pressure equal to or higher than (١٤٠/٩٠ mmHg) before pregnancy or diagnosed before ٢٠th week of pregnancy but had no proteinuria **(Zareian, ٢٠٠٤).**

Eclampsia

Occurance of seizures in women with pre-eclampsia **(Zareian, ٢٠٠٤)**.

Pre-eclampsia

Definition

Pre-eclampsia (PE) is a multi-organ disorder defined as elevated blood pressure (>١٤٠/٩٠ mmHg) and proteinuria that may develop from ٢٠ weeks gestation. PE is the first cause of maternal death **(Idalia et al., ٢٠١١).**

Incidence and risk factors

Hypertensive disorders of pregnancy represent overall ١٠٪ of population births with ٧٪ of mild preeclampsia (or simple gestational hypertension) and ٣٪ of preeclampsia (hypertension and proteinuria or more rarely HELLP syndrome **(Pierre, ٢٠٠٢).**

Pre-eclampsia is twice as common in primigravid women as in women having second or later pregnancies. However, with a change of partner, the risk in a multiparous woman increases; this effect suggests that primipaternity ***(James,*** **٢٠٠٠).** Partners of men who were born to a pre-eclamptic pregnancy also had increased risk of developing pre-eclampsia **(Hege et al., ٢٠١٠).**

Li and Wi found that among women with no history of pre- eclampsia, a new father increased the risk of pre-eclampsia by ٣٠٪. However, in women who had had pre-eclampsia in a previous pregnancy a new father was associated with a non-significant ١٠-٣٠٪ decrease in risk **(Brenda and Kim, ٢٠٠١).**

The risk of pre-eclampsia in women with two or more induced abortions tended to be lower in both same paternity and new paternity pregnancies, as compared with primigravid women (١,٤٪ and ٢,٥٪ vs ٥,٥٪). Stratified analyses to further explore the impact of changed paternity

and gestational length at the time of the abortion on the pre-eclampsia risk were restricted by small numbers **(Lill et al., ٢٠٠٨).**

Multiple gestations were associated with an increased risk of pre-eclampsia (١٢٪) and with a lower recurrence of pregnancy. Yet, multiple gestations did not explain the association between primiparity and pre-eclampsia **(Sonia et al., ٢٠٠٩).**

The study reviewed by **(Thaís et al., ٢٠٠٨)**, obesity was observed to be an independent risk factor both for gestational hypertension (GH) and for pre-eclampsia superimposed on chronic hypertension (PESCH). The risk of PESCH and of GH among obese pregnant women was ٢٣,٩٤ and ١٧,٦٣ times that of non-obese pregnant women, respectively. This is a disturbing finding, since obesity is currently a growing public health problem, thus contributing to an increase in the incidence of hypertensive syndromes in pregnancy (HSP). Also **Chaturica et al,** have demonstrated a linear relationship between increasing BMI and pre-eclampsia amongest both overweight and obese women which is more pronounced amongest nulliparous women; It is estimated at each one-unit increase in BMI among nulliparous women confers a ٧٪ increase in risk for pre-eclampsia (٩٥٪ CI ١,٠٦, ١,٠٨) and a ٦٪ increase in risk

for early pre-eclampsia (٩٥٪ CI ١,٠٥, ١,٠٨) **(Chaturica et al., ٢٠١٠).**

The risk of preeclampsia is decreased by an estimated ٣٠٪ among smokers. This risk has been found in numerous populations **(Stephanie et al., ٢٠٠٩). Levine et al** have reported significant differences in these angiogenic factors predating the clinical manifestations of preeclampsia. Specifically, lower concentrations of placental growth factor (PlGF) have been noted, while soluble fms-like tyrosine kinase-١ (sFlt-١) concentrations are higher. Cigarette smoking may also influence these angiogenic factors with lower circulating sFlt-١ concentrations in nonpregnant smokers compared to nonsmokers. Recent evidence suggests that cigarette smoking in pregnant women may also lower maternal sFlt-١ concentrations. There is limited information on the effect of cigarette smoke exposure on maternal PlGF concentrations **(Arun et al., ٢٠٠٨).**

Risk factor for pre-eclampsia

- **Maternal age**

Preeclampsia occurs more frequently in women at the extremes of reproductive age.

- Younger women (<٢٠ y) have a slightly increased risk. Primigravid patients in particular seem to be predisposed.
- Older women (>٣٥ y) have a markedly increased risk **(Zina et al., ٢٠١٠).**

- **Race**

Black race: In the United States, the incidence of preeclampsia is ١,٨٪ among white women and ٣٪ in African Americans **(Zina et al., ٢٠١٠)**.

- **Familial**

A familial component, long recognized in the aetiology of preeclampsia, supports the hypothesis of a genetic origin. Different modes of inheritance were proposed over the years varying from single gene models to complex segregation involving both maternal and fetal genotypes **(Anne et al., ٢٠٠٨).**

Family history of hypertension reflects genetic and behavioral factors whereby women may be predisposed to an increased pre-eclampsia risk. Family history of chronic hypertension is a proxy measure for hereditary factors as well as common environmental or behavioral exposures that may underlie preeclampsia risk **(Uzma et al., ٢٠١٠).**

- **Dietary intake**

Associations between various dietary components and pre-eclampsia have been studied in case-control and prospective cohort studies and have shown increased risk of pre-eclampsia with high consumption of energy, added sugar (sugar-sweetened soft drinks), PUFA, and decreased risk of pre-eclampsia with high consumption of milk and high intake sufficient status of vitamin D **(Anne et al., ٢٠٠٩).**

- **Stress**

stress has been shown to stimulate the sympathetic nervous system, which in turn can modulate peripheral vascular resistance as well as the immune system during pregnancy and thus could be implicated in the development of pre-eclampsia (**Stéphanie et al., ٢٠٠٩).**

- **Diabetes, hydatidiform mole, and hydrops fetalis**

There seems to be a higher incidence of pre-eclampsia in women who have diabetes mellitus, although it has been suggested that this is largely associated with poorly controlled diabetes. The United Kingdom survey of diabetic pregnancies has suggested a figure of ١٢٪. Diabetes is complicated by hyperplacentosis where hypertrophy of the placenta and, in particular, hyperplasia of cytotrophoblastic tissue remains a feature associated with pre-eclampsia. This condition is also found in hydatidiform mole and hydrops fetalis, both of which are also associated with a high incidence of pre-eclampsia **(Symonds, ١٩٩٥).**