

# **CHANGES OF INTERLEUKIN- $\gamma$ IN PATIENT OF SEVER PREECLAMPSIA BEFORE AND AFTER TERMINATION**

## ***Thesis***

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## *Lists of Abbreviations*

<b>1<sup>st</sup></b>	First.....
<b>2<sup>nd</sup></b>	Second.....
<b>&lt;</b>	Less than.....
<b>&gt;</b>	More than.....
<b><math>\alpha</math></b>	Alpha.....
<b><math>\gamma</math></b>	Gama.....
<b>Ang</b>	Angioprotiens gene.....
<b>APLABS</b>	Auto immune phospholipids antibodies.....
<b>ALT</b>	Alanin transferase.....
<b>AST</b>	Aspartate transferase.....
<b>B</b>	Beta.....
<b>Bp</b>	Bood pressure.....
<b>BMI</b>	Body mass index.....
<b>CBC</b>	Complete blood count.....
<b>Cm</b>	Centimter.....
<b>CS</b>	Cesarean section.....
<b>CT</b>	Coputerized tomography.....
<b>DOC</b>	Deoxycorticosterone.....
<b>DM</b>	Diabetes mellitus.....



<b>F.H.S</b>	Fetal heart sound.....
<b>FFAs</b>	Free fatty acids .....
<b>HIF-<math>\alpha</math></b>	Hypoxia-inducible factor- $\alpha$ .....
<b>Hr</b>	Hour.....
<b>IL-<math>\gamma</math></b>	Interleukin- $\gamma$ .....
<b>IL-<math>\delta</math></b>	Interleukin- $\delta$ .....
<b>IL-<math>\beta</math></b>	Interleukin- $\beta$ .....
<b>I/R</b>	ischaemia–reperfusion.....
<b>IV</b>	Intravenous.....
<b>IU</b>	International unit.....
<b>Kg</b>	Kilogram.....
<b>Mcg</b>	Microgram.....
<b>Mg</b>	Milligram.....
<b>ML</b>	Millilitre.....
<b>Mm</b>	Millimeter.....
<b>NO</b>	Nitous oxide.....
<b>OFR</b>	O $\cdot$ free radicals.....
<b>PG <math>\gamma</math></b>	Prostaglandine $\gamma$
<b>PIGF</b>	placental growth factor.....
<b>PROM</b>	Premature rupture of membrane.....

<b>RAS</b>	Renin angiotensin system.....
<b>SLE</b>	Systemic lupus erythromatosis.....
<b>TGF-<math>\gamma</math> <math>\beta</math></b>	Transforming growth factor beta $\gamma$ .....
<b>TNF-<math>\alpha</math></b>	Tumor necrosing factor alpha.....
<b>Th</b>	T- helper.....
<b>Th<math>\gamma</math></b>	T- helper type $\gamma$ .....
<b>Th<math>\gamma</math></b>	T- helper type $\gamma$ .....
<b>US</b>	Ultra sound.....
<b>U/L</b>	Unit per litre.....
<b>VD</b>	Vaginal delivery.....
<b>VEGF</b>	Vascular endothelial growth factor.....
<b>WHO</b>	World Health Organization.....

## Introduction

**P**re-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., 2009).

**Pre-eclampsia** is one of the most recognized clinical causes of high-risk pregnancies. Although pre-eclampsia affects about 1%–2% of pregnancies in some European countries, its prevalence can be up to 10%–15% in some South American and African countries (Sucak et al., 2010).

**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 50 maternal genes have been analyzed; most of these studies have been approaches to identify a genetic association, comparing the frequencies of genetic polymorphisms between cases and controls (Norma, 2006).

**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 39% reduction in the risk of pre-eclampsia associated with oral antioxidant supplements (**Sally and Linda, 2006**).

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., 2005**).

**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 syncytiotrophoblast deportation and increased cytotrophoblast proliferation (**Gustaaf et al., 1998**).

**Dys-regulation** of the maternal immune response towards the fetus might be the causal factor of shallow trophoblastic invasion (**Reza et al., ۲۰۰۷**).

It has been proved that in pre-eclamptic patients, there is up-regulation of Th<sup>۱</sup> activity with the abnormal release of increasing amounts of pro-inflammatory cytokines as IL-۱۲ and TNF- $\alpha$  (**Jacek et al., ۲۰۰۲**).

And these pro-inflammatory cytokines might be the causal factor of generalized endothelial dysfunction that is characteristic to pre-eclampsia (**Reza et al., ۲۰۰۷**).

**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., ۲۰۰۳**).

**In** normal pregnancy, particularly, at the maternal-fetal interface, anti-inflammatory cytokines produced by T helper (TH<sup>۲</sup>) cells predominate, regulating trophoblast cell growth, differentiation and invasion for embryo implantation and therefore, an appropriate balance between pro-(TH<sup>۱</sup>) and anti (TH<sup>۲</sup>) 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 (TH<sup>۱</sup>) activation, causing disturbed balance between pro-inflammatory (tumor factor necrosis- $\alpha$  (TNF-A), interleukin (IL)-۶, IL-۲, IL-۱ $\beta$ ) and anti-inflammatory (IL- $\xi$ ,

IL-10, IL-13) cytokines, which compromises uteroplacental perfusion and perpetuates further vascular damage (**Archana et al., 2010**).

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- $\alpha$  (TNF- $\alpha$ ) and interleukin-1 (IL-1) have both been implicated in pre-eclampsia pathophysiology, since they have the ability to stimulate structural and functional alternation in endothelial cells (**Hanna Peterson., 2010**).

**Interleukin-6** is TH1 cytokine and has been shown to induce lymphocyte proliferation, and T-cell, B-cell differentiation, and to stimulate hepatic acute phase proteins (**Robin, 2009**).

Cytokines known to play important role in maintenance Of normal pregnancy as well as development of pathological status. There is a hypothesis of altered immune response in preeclampsia and suggests that dysregulation of cytokine expression occurs in preeclampsia with increase levels of pro-inflammatory cytokines. Inadequate trophoblast invasion and failure of physiological remodeling of spiral arteries of placenta in preeclampsia stimulate over production of inflammatory Th1 cytokines (interleukin-6) causing endothelial damage. Chronic infusion of interleukin-6 into normal pregnancy rates has been

to significantly increase arterial pressure and impair renal hemodynamics.

There is a significant negative correlation was observed between levels of endothelial nitrous oxide and interleukin- $\gamma$  (i.e. decrease endothelial nitrous oxide levels with increase interleukin- $\gamma$  levels.) which indicates that interleukin- $\gamma$  might be a possible mediator of increase vascular resistance during preeclampsia (**Archana, 2010**).