SERUM LEVEL OF INTERLEUKIN-16 IN PREECLAMPSIA

Thesis

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Shimaa Gaballa

Dedicated to

My Parents

Contents

List of Abbreviations

Abbreviation	Full Meaning
ALT	: Alanine transaminase
AST	: Aspartate transaminase
AT1-B2	: Angiotensin II receptor type 1 and bradykinin B2 receptor
CD	: Cluster of differentiation
Eng	: Endoglin
GFR	: Glomerular filtration rate
HELLP	: Hemolysis , elevated liver enzymes , low platelet count
HLA	: Human leucocyte antigen
IFN	: Interferon
IL	: Interleukin
IL2R α	: IL -2 receptor alpha
MHC	: Major histocompatibility complex
NIL-16	: Neuronal form of IL-16
NK cells	: Natural killer cells
NO	: Nitric oxide
NOS	: Nitric oxide synthase
PGI2	: Prostaglandin I 2
PlGF	: Placental growth factor
ROS	: Reactive oxygen species
RPF	: Renal plasma flow
sEng	: Soluble endoglin
SFlt1	: Soluble fms-like tyrosine kinase 1
SOD	: Superoxide dismutase
TCR	: T cell receptor
TGFB3	: Transforming growth factor B3
Thl	: T-helper type 1
Th2	: T-helper type 2
TNF α	: Tumor necrosis factor alpha
TX A2	: Thromboxane A2
VEGR	: Vascular endothelial growth factor

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Introduction

Preeclampsia is a heterogeneous disorder affecting 3–5% of pregnancies and a major cause of obstetric morbidity and mortality worldwide. For the fetus, preeclampsia can result in small-for-gestational-age infancy, preterm delivery, hypoxic neurologic injury or death. For the mother, complications of preeclampsia include renal failure, HELLP syndrome (hemolysis, elevated liver enzymes, and low platelet count), seizures, liver failure, stroke or death. Women with preeclampsia often later develop cardiovascular disease and hypertension, another source of significant morbidity ***(Redman and Sargent, 2005).***

While the initial events involved in the pathogenesis of pre-eclampsia are still a mystery, recent developments have begun to elucidate molecular mechanisms behind its manifestations. Scientists have postulated many theories regarding its cause, but the pathogenesis remains poorly understood ***(Saftlas et al., 2005).***

An abnormally developed, hypoxic placenta and endothelial dysfunction are important themes. Further, there seems to be a tip in the balance of angiogenesis versus antiangiogenesis, with favoring of the latter in pre-eclampsia. The mechanism of endothelial activation is unknown but may result from inflammatory cytokines produced by the placenta caused by ischemia or injury of the endothelium. Serum levels

of several cytokines have been reported to be altered and the alterations in cytokine levels were thought to participate the pathogenesis of preeclampsia ***(Matthiesen et al., 2005).***

Cytokines are small immunologic "hormones" that recruit other immune cells, cause oxidative stress, and may contribute the endothelial damage. Several studies have implicated abnormal levels of cytokines in preeclampsia, but the pattern of cytokine expression and a possible role in its pathogenesis remains controversial. Cytokine responses are generally characterized as T-helper type 1 (Thl) or type 2 (Th2). It is generally agreed that preeclampsia is associated with both local and systemic changes in type 1/type 2 cytokine balance compared to normal pregnancy. Decidual lymphocytes and peripheral blood mononuclear cells from patients with preeclampsia are generally primed to synthesize high levels of the Th1 cytokines, interleukin (IL)-2, IL-12, and IFN-γ . On the other hand, they exhibit low spontaneous or phytohemaglutinin-induced expression of the Th2 cytokines IL-10 and IL-5 ***(Jonsson et al., 2005).***

Inflammatory cytokines are peptide mediators of endothelial cell activation and dysfunction and have been speculated to have arole in the pathogenesis of preeclampsia because of their endothelial effect ***(Matthiesen et al., 2005).***

Whereas these findings initially lead to the conclusion that a maternal T lymphocyte- mediated cytotoxic reaction against the fetal allograft was possibly associated with, and may

be the cause of preeclampsia, it is now believed that such a cytokine environment rather reflects the state of exaggerated inflammation that characterizes the disease. Monocytes and granulocytes present an activated pattern of leukocyte adhesion molecules on their surface and show an increased incidence of basal or induced oxidative stress response compared to their counterparts from normal pregnancy. Spontaneous monocytic cytokine expression is higher in preeclampsia in comparison with normal pregnancy ***(Luppi and Deloia, 2006).***

Interleukin-16 was initially described as a T-lymphocyte chemoattractant using cluster of differentiation type 4 (CD4) as its receptor. IL-16 stimulates the production of proinflammatory cytokines such as IL-6, tumor necrosis factor alpha (TNF-α), IL-1 alpha and IL-15 by monocytes, and upregulation of IL -2 receptor alpha (IL-2R alpha) on T cells. In addition, IL-16 inhibits IL-4 and IL-5 release from T cells and thus impairs Th2 immunity ***(Pinsonneault et al., 2001).***

Interleukin -16 is expressed in numerous normal human tissues and cell types, including activated monocytes, dendritic cells and fibroblasts ***(Lynch et al., 2003).***

On the other hand, serum level of IL -16 is increased in inflammatory conditions, such as systemic lupus erythematousus, rheumatoid arthritis, allergic diseases and inflammatory bowel disease ***(Karaki et al, 2005 and Seegert & Schreiber, 2000).***

In addition, a bias towards Th1 immunity exists in preeclampsia ***(Saito and Sakai, 2003)***, while IL-16 alters the Th1/Th2 balance by inhibiting Th2 immunity ***(Pinsonneault et al., 2001).***

Aim of the Work

The purpose of the current study is to evaluate the relationship between the serum level of interleukin -16 and preeclampsia in pregnant females.

I - Preeclampsia

Preeclampsia is a serious complication of the second half of human pregnancy, which can have harmful effects on the immediate and long-term health of the mother and the baby ***(Sibai et al., 2005).***

This disease is characterized by multiple maternal disturbances, among which the more prominent symptoms are de novo hypertension, proteinuria, and edema. Additional metabolic dysfunctions may be present, such as activation of the clotting system, impaired liver function, renal failure or pulmonary edema, in particular, in cases of severe, early onset disease ***(Von-Dadelszen et al., 2003).***

In the absence of intervention, preeclampsia can progress in generalized convulsions or eclampsia. The symptoms resolve only once the placenta is removed, and thus, preeclampsia remains one of the most common reasons for induced preterm delivery. While the etiology of the disorder is still elusive, it is quite clear that it requires a placenta to develop. Risk factors are known and include primiparity, multiple pregnancies, a previous history of preeclampsia, and chronic medical conditions such as obesity, hypertension, vascular disease, or diabetes ***(Duckitt and Harrington, 2005).***

However, there is no definitive predictive factor and no preventive treatment available so far. There may undoubtedly

be a genetic component at the basis of some cases of preeclampsia, at least in those with a familial history ***(Laivuori, 2007).***

However, such a genetic cause has not been convincingly demonstrated until now, most likely because polymorphisms in not only one but in several genes are likely to predispose to the development of this complex multifactorial disease. On the other hand, recent work clearly reveals that immune maladaptation and overt activation of the maternal innate immune system are involved in preeclampsia ***(Sargent et al., 2006).***

Remarkably, although the maternal symptoms of preeclampsia appear very heterogeneous at first sight, they can all be ascribed to a generalized endothelium dysfunction , which is undeniably part of this exaggerated systemic inflammatory response to pregnancy ***(Redman and Sargent,2003).***

Historical Background

Since the 18th century, preeclampsia has been known and termed under such headings as puerperal convulsions,puerperal nephritis and albuminuria, puerperal albuminuria and convulsions, eclampsia, toxemia and preeclamptic toxemia and as pregnancy associated hypertension or hypertensive disease in pregnancy ***(Chesley, 1976)***.