Changes in Interleukin–٨ in Patients of Severe Pre-Eclampsia Before & After Termination

Thesis

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Presented by

Mohamed Mohey El–Din Zaki
M.B.,B.Ch. (٢٠٠٢) Sohag University

Supervised by

Prof. Dr. Walied Hetlar Ahmed Tantawy
Professor of Obstetrics and Gynecology
Faculty of Medicine, Ain Shams University

Ass. Prof. Ahmed Hamdy Nagib Abdel Rahman
Assistant Professor of Obstetrics and Gynecology
Faculty of Medicine, Ain Shams University

Dr. Mostafa Fouad Gomaa
Lecturer of Obstetrics and Gynecology
Faculty of Medicine, Ain Shams University

Faculty of Medicine
Ain Shams University
٢٠١٢

التباين فى عامل انترلوكن – ٨ فى المرضى المصابين بتسمم الحمل قبل و بعد الولادة

رسالة

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تحت إشراف

أ.د. وليد هتلـر احمـد طنطـاوى
استاذ امراض النساء و التوليد – جامعة عين شمس

د. احمد حمدى نجيب عبد الرحمن
استاذ مساعد امراض النساء و التوليد – جامعة عين شمس

د. مصطفـى فـؤاد جمعـة
مدرس امراض النساء و التوليد – جامعة عين شمس

كلية الطب
جامعة عين شمس
٢٠١٢

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Mohamed Mohey El –Din

Contents

List of Abbreviations

Abbreviation	Full Meaning
ALT	: Alanine transaminase
AST	: Aspartate transaminase
AT١-B٢	: Angiotensin II receptor type ١ and bradykinin B٢ receptor
BMI	: Body mass index
CD	: Cluster of differentiation
Eng	: Endoglin
GFR	: Glomerular filtration rate
HELLP	: Hemolysis , elevated liver enzymes , low platelet count
HLA	: Human leucocyte antigen
IFN	: Interferon
ICU	:Intensive care unit
IL	: Interleukin
IL٢R α	: IL -٢ receptor alpha
MHC	: Major histocompatibility complex
NICU	: Neonate intensive care unit
NK cells	: Natural killer cells
NO	: Nitric oxide
NOS	: Nitric oxide synthase
PGI٢	: Prostaglandin I ٢
PlGF	: Placental growth factor
ROS	: Reactive oxygen species
RPF	: Renal plasma flow
sEng	: Soluble endoglin
SFlt١	: Soluble fms-like tyrosine kinase ١
SLE	:Systemic lupus erythematosis
SOD	: Superoxide dismutase
TCR	: T cell receptor
TGFB٣	: Transforming growth factor B٣
Thl	: T-helper type ١
Th٢	: T-helper type ٢
TNF α	: Tumor necrosis factor alpha
TX A٢	: Thromboxane A٢
VEGR	: Vascular endothelial growth factor

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Introduction

Preeclampsia is a heterogeneous disorder affecting ٣–٥٪ 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, ٢٠٠٥).***

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., ٢٠٠٥).***

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., ٢٠٠٥).***

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 ١ (Thl) or type ٢ (Th٢). It is generally agreed that preeclampsia is associated with both local and systemic changes in type ١/type ٢ 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 Th١ cytokines, interleukin (IL)-٢, IL-١٢, and IFN-γ. On the other hand, they exhibit low spontaneous or phytohemaglutinin-induced expression of the Th٢ cytokines IL-١٠ and IL-٥ ***(Jonsson et al., ٢٠٠٥).***

Inflammatory cytokines are peptide mediators of endothelial cell activation and dysfunction and have been

speculated to have a role in the pathogenesis of preeclampsia because of their endothelial effect ***(Matthiesen et al., ٢٠٠٥).***

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, ٢٠٠٦)***

Interleukin-٨ (IL-٨) is a major neutrophil chemoattractant. It has been found in endothelial cells and regulates endothelial cell proliferation, angiogenesis, tumor growth and participates in graft rejection and placental infection ***(Li et al., ٢٠٠٣)***.

Interleukin-٨ (IL-٨) is a strong neutrophil chemoattractant and activator, and it is necessary for monocyte recruitment to the vascular endothelium. IL-٨ / neutrophil-activating peptide-١ (NAP-١) selectivity stimulates the ability of neutrophil and T-lymphocytes to invade injured or inflamed tissue. Study

findings indicate that (IL-٨) may participate in the pathogenesis of adult respiratory distress syndrome, bacterial infections, graft rejections, glomerulonephritis, and placental infection. The property of (IL-٨) to stimulate movement of neutrophils across endothelial monolayers in vitro supports the concept of a central role of this molecule in the accumulation of neutrophils in inflammatory lesions in vivo ***(Marzena et al., ٢٠٠٧)***

Aim of Work

١) It aims at testing the hypothesis that placenta is the source of abnormal cytokines production in pre-eclamptic patients.

٢) To study the level of (IL-٨) before and after termination (Removal of the placenta) from the maternal circulation.

Preeclampsia

Preeclampsia is an unique 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., ٢٠٠٥).***

Preeclampsia is a pregnancy specific syndrome of reduced organ perfusion secondary to vasospasm and endothelial activation **(*Cunningham et al., ٢٠٠٥*)**, characterized by increased blood pressure and proteinuria presenting after ٢٠ weeks of gestation in a previously healthy women ***(Davey and MacGillivray, ١٩٨٨)***.

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., ٢٠٠٣).***

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