

PERIPHERAL NATURAL KILLER CELLS (CD56) AND PREECLAMPSIA

Thesis

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In Obstetrics and Gynecology*

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بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ

﴿قَالُوا سُبْحَانَكَ لَا عِلْمَ لَنَا إِلَّا مَا عَلَّمْتَنَا إِنَّكَ أَنْتَ
الْعَلِيمُ الْحَكِيمُ﴾

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صدق الله العظيم



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✍ Ahmed Abu El-Magd Sleem

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List of Abbreviations

ADCC	Antibody dependent cellular cytotoxicity
APC	Allophycocyanin
AT1-AA.....	Angiotensin II type 1 receptor autoantibodies
CTCM	Mplete tissue culture medium
CXCL	Chemokine ligand
dNK	Decidual NK
eNK	Endometrial
ET-1	Endothelin-1
EVTs	Extravillous trophoblasts
GM-CSF.....	Granulocyte – macrophage colony – stimulating factor
HIF	Hypoxia induced factors
HLA	Human leukocyte antigen
IFN-γ.....	Interferon-γ
IFN-γ	Immunoregulatory cytokines such as interferon-γ
IGG1	Immunoglobulin
IL-2.....	Interleukin-1
IP-10.....	Inducible protein-10
IUFD	Intra uterine fetal death
KARs	Killing activating receptors
KDR	Kinase domain region
KIR	Killer immunoglobulin-like receptors
KIRs	Killer inhibitory receptors

List of Abbreviations (Cont...)

LDL	Low-density lipoprotein
M-CSF	Macrophage colony – stimulating factor
MHC	Major histocompatibility complex
NCAM	Neural cell adhesion molecule
NK	Natural killer
NK cells	Natural killer cells
NK	Natural killer
NO	Nitric oxide
NO₂--	Nitrogen dioxide
ONOO-	Peroxynitrite anion
PBL	Peripheral blood lymphocytes
PBMC	Peripheral blood mononuclear cells
PBMCs	Peripheral blood mononuclear cells
PE	phycoerythrin
PLGF	Placental growth factor
PROM	Pre mature rupture of membranes
ROS	Reactive oxygen species
RPL	Recurrent pregnancy loss
RUPP	Reduced uterine perfusion pressure
sEng.....	Soluble endoglin
sFlt-1	Soluble fms-like tyrosine kinase-1
SOD	Superoxide dismutase

List of Abbreviations (Cont...)

TGF	Transforming growth factor
Th 1	T helper 1
Th 2	T helper 2
Th	T-helper
TNF-α	Tumour necrosis factor-α
TPR	Total peripheral resistance
TX.....	Thromboxane
u NK.....	Uterine NK
VEGF	Vascular endothelial growth factor

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Introduction

Pre-eclampsia is the commonest medical condition in obstetrics, affecting 5-10% of all pregnancies. It is the major cause of maternal mortality, and a substantial cause of neonatal morbidity and mortality (**HawkiJJL, 2002**).

The etiology of preeclampsia is unknown. At present, 4 hypotheses are the subject of extensive investigation, as follows:

- (1) Placental ischemia-Increased trophoblast deportation, as a consequence of ischemia, may inflict endothelial cell dysfunction.
- (2) Very low-density lipoprotein versus toxicity-preventing activity-In compensation for increased energy demand during pregnancy.
- (3) Immune maladaptation-Interaction between decidual leukocytes and invading cytotrophoblast cells is essential for normal trophoblast invasion and development.
- (4) Genetic imprinting-Development of preeclampsia may be based on a single recessive gene or a dominant gene with incomplete penetrance (**Dekker and Sibai, 1998**).

There is circumstantial evidence to support the theory that preeclampsia is immune mediated. Certainly the microscopic changes at the maternal-placental interface are suggestive of acute graft rejection (*Labarrere, 1988*).

Dekker and Sibai (1998) have reviewed the possible role of immune maladaptation in the pathophysiology of preeclampsia. Beginning in the early second trimester, women destined to develop preeclampsia have a significantly lower proportion of helper T cells (Th₁) compared with that of women who remain normotensive (*Bardeguet and associates, 1991*). This Th₁/Th₂ imbalance, with Th₂ dominance, may be mediated by adenosine, which is found in higher serum levels in preeclamptic compared with normotensive women (*Yoneyama and co-workers, 2002*). These helper T lymphocytes secrete specific cytokines that promote implantation, and their dysfunction may favor preeclampsia (*Hayashi and associates, 2004; Whitecar and colleagues, 2001*).

Natural killer cells (or NK cells) are a type of cytotoxic lymphocyte that constitute a major component of the innate immune system (*Roitt, 2001*).

Human NK cells divided into CD56 (dim) and CD56(bright) subsets. These two types of NK cells respond to different types of stimuli, with CD16⁺ CD56 (dim) NK cells having direct cytotoxic ability and CD16⁻ CD56(bright) NK

cells having mainly an immunoregulatory function (***Harlin et others, 2007***).

An Accumulating evidence from animal models, genetic studies, and isolated decidual leukocytes suggests that decidual natural killer (NK) cells supply factors necessary for development and arterial modification of the maternal-fetal interface. This beneficial role of NK cells to normal placentation may shed light on the cause of the placental pathologies observed in pre-eclampsia

(Goldman, 2008).

Further studies investigated types 1 and 2 lymphocyte populations in normal pregnancy and pre-eclampsia using stable surface markers for type 1 (IL-18 receptor) and type 2 (ST2L, IL-1receptor family). The results using this technique showed that the predominant changes (a decreased type 1/type 2 ratio in normal pregnancy which is reversed in pre-eclampsia) were in the NK CD56bright NK CD56dim and NKT (CD3/CD56+) populations rather than Th and Tc cells

(Borzychowskiet al., 2005).

These changes occur from the first trimester onwards, but are more apparent later in gestation. This is supported by the finding that expression of IFN7 by CD4+ and CD8+ T cells did not differ between normal pregnant and pre-eclamptic women, but the levels were higher in NK cells in pre-eclampsia (***Darmochwal-Kolarz et al., 2002***).

Aim of work

- 1- To test the immunological hypothesis of preeclampsia etiology
- 2- To study the relationship between peripheral natural killer cells (CD56) and preeclampsia

Patients and Methods

This study is a case control study will be held at Ain Shams University maternity hospital in period between November 2010 and April 2011.

In the study 160 pregnant women will be recruited and divided in to 2 groups as following

- 1- Group A will include 80 normal primigravida with GA not less than 24 weeks with no antenatal complications recruited from the antenatal care clinics of Ain Shams University hospital.
- 2- Group B will include 80 patient with the following criteria

Inclusion criteria:

- 1- Primigravid
- 2- Diagnosed as sever preeclampsia by one of the following
 - Sustained systolic B.p of $\geq 160\text{mm.hg}$ or a diastolic B.p. of $\geq 110\text{mm .hg}$.
 - proteinurea measured as +3 or mor dipstick or 24 h urin collect of $\geq 5\text{mg}$.
 - urin output $\leq 30\text{ ml/hr}$ for 24 h not responding to 500 ml I V F.