PERIPHERAL NATURAL KILLER CELLS (CD56) AND PREECLAMPSIA

Thesis

Submitted for Partial Fulfillment of M.Sc. Degree
In Obstetrics and Gynecology

Prepared By

Ahmed Abu El-Magd Sleem
M.B.,B.Ch.
Ain Shams University 2003

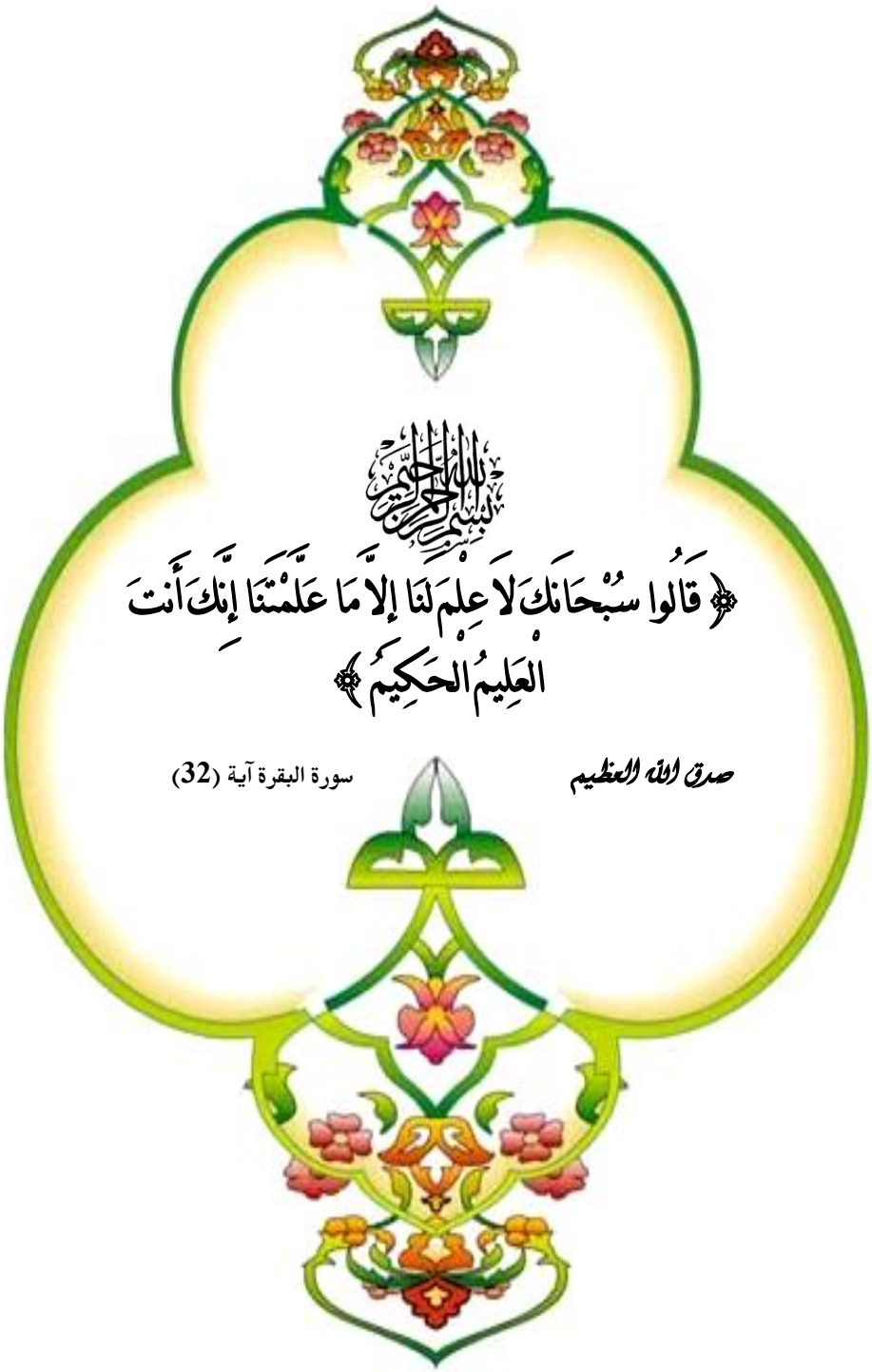
Supervised By

Dr. Hisham Mohammed Fathi
Professor of obstetric and gynecology
Ain Shams University

Dr. Ihab fouad Serag Eldin Allam
Assistant professor of obstetric and gynecology
Ain Shams University

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

Faculty of Medicine
Ain Shams University
2014



بسم الله الرحمن الرحيم

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

صدق الله العظيم

سورة البقرة آية (32)

Acknowledgement

First of all thanks to **ALLAH** who gives us the gift of knowledge and understand.

Words do fail to express my deepest gratitude and appreciation to **Dr. Hisham Mohammed Fathi,** Professor of obstetric and gynecology, Ain Shams University, for his excellent guidance, powerful support, supervision and help through out the accomplishment of this study. I owe him more than I can express for all his big efforts in bringing this work to light.

It is a great honour for me to take this opportunity to express my most profound gratitude , deep respect and appreciation to **Dr. Ihab Fouad Serag Eldin Allam,** Assistant professor of obstetric and gynecology, Ain Shams University, for the immeasurable time and effort devoted for the revision, encouragement and correction of the manuscript. I owe him more than I can express for all the so long time he spent in revising every detail.

I am deeply indebted and grateful to **Dr. Mostafa Fouad Gomaa,** Lecturer of Obstetrics and Gynecology, Ain Shams University, who offered much of his time and advice through my work in this study. His kind assistance, great support and sincere cooperation have affected the outcome of this work.

Ahmed Abu El-Magd Sleem

List of Contents

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 histocomptability 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**

List of Tables

List of Figures

Peripheral Natural Killer Cells (CD56) and Preeclampsia

Protocol submitted for partial fulfillment of M.SC degree
In obstetrics and gynecology

Prepared by

Ahmed Abu El-Magd Sleem

MB.B.CH
Ain Shams University
2003

Supervised By

Dr. Hisham Mohammed Fathi
Professor of obstetric and gynecology
Ain Shams University

Dr. Ehab fouad Serag eldin allam
Assistant professor of obstetric and gynecology
Ain Shams University

Dr. Mostafa Fouad gomaa
Lecturer of Obstetrics and Gynecology
Ain Shams University

Faculty of Medicine
Ain Shams University
2010

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 ***(HawkiJL, 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 (Th_1) compared with that of women who remain normotensive ***(Bardeguez and associates, 1991).*** This Th_1/Th_2 imbalance, with Th_2 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, 2oo7).***

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 ≥ 160mm.hg or a diastolic B.p. of ≥ 110mm .hg.
- proteinurea measured as +3 or mor dipstick or 24 h urin collect of ≥ 5mg.
- urin output ≤ 30 ml/hr for 24 h not responding to 500 ml I V F.