The Role of Tumor Necrosis Factor-308 Polymorphism on Pregnancy Rate in Women Undergoing Intracytoplasmic Sperm Injection Program

Thesis

Submitted for Partial Fulfillment of MD
In Obstetrics and Gynecology

By

Khaled Hamed Ahmed Gabr
MSc. in Obstetrics and Gynecology, Ain Shams University, May 2009
Specialist in Obstetrics and Gynecology
In El Mahalla General Hospital

Under supervision of

Professor/ Hatem Hussein El Gamal
Professor of Obstetrics and Gynecology
Faculty of Medicine - Ain Shams University

Professor / Nashwa El Saied Hassan
Professor of Obstetrics and Gynecology
Faculty of Medicine - Ain Shams University

Dr/ Ahmed El Sayed Hassan El Bohoty
Assistant Professor in Obstetrics and Gynecology
Faculty of Medicine - Ain Shams University

Dr/ Amr Helmy Yehia
Assistant Professor in Obstetrics and Gynecology
Faculty of Medicine - Ain Shams University

Dr/ Nesrine Aly Mohamed
Assistant Professor in Clinical Pathology
Faculty of Medicine - Ain Shams University

Faculty of Medicine
Ain Shams University
2019

Acknowledgement

First of all, all gratitude is due to God almighty for blessing this work, until it has reached its end, as a part of his generous help, throughout my life.

Really I can hardly find the words to express my gratitude to Prof.Hatem EL Gamal, Professor of Obstetrics & Gynecology, faculty of medicine, Ain Shams University, for his supervision, continuous help, encouragement throughout this work and tremendous effort he has done in the meticulous revision of the whole work. It is a great honor to work under his guidance and supervision.

I would like also to express my sincere appreciation and gratitude to Prof. Nashwa El said, Professor of Obstetrics & Gynecology Ain Shams University, for her continuous directions and support throughout the whole work.

I would like to express my deepest gratitude and sincere thanks to Dr. Ahmed Elsayed El bohoty, **Assistant Professor** *in Obstetrics & Gynecology Faculty of Medicine - Ain Shams University for suggesting and planning this work, his instructive supervision, continuous guidance, unlimited help and unfailing support, valuable instructions throughout the work and final revision of the manuscript.*

I would like also to express my sincere appreciation and gratitude to ***Dr, Amr Helmy Yehia****,* ***Assistant Professor*** *in Obstetrics & Gynecology Ain Shams University, for his continuous directions and support throughout the whole work.*

I would like also to express my sincere appreciation and gratitude to ***Dr, Nesrine Aly Mohamed****,* ***Assistant Professor*** *in clinical pathology Ain Shams University, for her continuous directions and support throughout the whole work.*

I am also grateful to ***all staff members in the*** *assisted reproductive unit- Ain Shams University for her help in performing this work.*

Finally I owe too much for ***my family, my wife and my daughter*** *for continuous encouragement and support all through this work and* my life.

Khaled Hamed Ahmed Gabr

بسم الله الرحمن الرحيم

وقُلِ اعْمَلُوا فَسَيَرَى اللَّهُ عَمَلَكُمْ وَرَسُولُهُ وَالْمُؤْمِنُونَ

صدق الله العظيم

سورة التوبة آية (١٠٥)

Abstract

Background: Multiple pregnancies are frequent after the use of Assisted Reproductive Technologies. The presence of the TNF-308A allele is associated with high implantation and multiple pregnancy rates in women without known infertility factors after ovarian hyperstimulation with exogenous FSH. **Aim of the Work:** to evaluate the effect of tumor necrosis factor-308 genotypes (A and G) on embryo implantation and clinical pregnancy rates in women undergoing ICSI. **Patients and Methods:** This prospective observational cohort study was conducted at the Assisted Reproduction Technology Unit (ARTU) of Ain Shams University Maternity Hospital on 100 infertile women who were planned to perform ICSI due to tubal factor after obtaining an informed written consent from each patient. **Results:** Out of the 100 patients included in the study; 46 patients had positive serum ß-hCG 2 weeks after embryo transfer but only 38 patients of them had intra uterine gestational sac (s) with positive fetal pulsations by u/s scan 2 weeks later. There was a statistically significant correlation between TNF-308 AA + AG genotype and implantation rate 27.2% (P value: <0.001). The predictive value of serum TNF-308 genotypes for both chemical and clinical pregnancy rates, after applying multivariable binary logistic regression analysis were showed that, TNF-308 AA+ AG allele, and a grade 1 embryo were independent predictors of both chemical and clinical pregnancy rates., the results showed that, TNF-308 AA + AG allele, was the only independent predictor of clinical pregnancy. **Conclusion:** There is an association between the TNF-308 A allele and a high implantation and pregnancy rates. These data indicate that the serumTNF-308 A/G polymorphism may be a potential non-invasive biomarker for implantation and subsequently pregnancy in patients undergoing ICSI.

Key words: Tumor Necrosis Factor-308 Polymorphism, Pregnancy Rate, Intracytoplasmic Sperm Injection Program

List of Contents

List of Abbreviations

AP-1	:	Activator protein-1
APC	:	Antigen-presenting cells
ART	:	Assisted Reproductive Technology
ASK-1	:	Apoptosis-signaling kinase-1
CAMs	:	Cell adhesion molecules
cIAP1	:	Cellular inhibitor of apoptosis protein 1
COX	:	Cyclooxygenase
cPLA2	:	Cytosolic phospholipase A2
CRD	:	Carbohydrate recognition domain
DIC	:	Disseminated intravascular coagulation
ECM	:	Extracellular matrix
ELISA	:	Enzyme Linked Immunosorbent Assay
ERK	:	Extracellular regulated kinases
ET	:	Embryo transfer
Etk	:	Endothelial/epithelial kinase
EVT	:	Extravillous trophoblast
FADD	:	FAS-associated death domain protein
FAS	:	Fibroblast associated cell surface
FSH	:	Follicle stimulating hormone
GM-CSF	:	Granulocyte macrophage- colony stimulating factor
GnRH	:	Gonadotrophin releasing hormone
hCG	:	Human chorionic gonadotrophin
HLAs	:	Human leucocyte antigens
HMG	:	Human menopausal gonadotrophin
HSPGs	:	Heparin sulphate proteoglycans

List of Abbreviations (Cont.)

ICAM	:	Intracellular adhesion molecule
ICSI	:	Intra cytoplasmic sperm injection
IGFBP1	:	Insulin –like growth factor binding protein 1
INFγ	:	Interferon-γ
IVF	:	In vitro fertilization
IκB	:	Inhibitor of kB
JNK	:	c-Jun N-terminal kinase
KDA	:	Kilo Dalton
LH	:	Luteinizing hormone
LIF	:	Leukaemia inhibitor factor
LTs	:	Leukotrienases
MAP	:	Mitogen activated protein
MEKK	:	MAP kinase kinase kinase
MHC	:	Major histocompatibility complex
MMP	:	Matrix metalloproteinase
MUC-I	:	Mucin- 1
NFκB	:	Nuclear factor kappa B
NK	:	Natural killer
OPN	:	Osteopontin
PAI-1	:	Plasminogen activator inhibitor 1
PGEs	:	Prostaglandine E synthase
PGI2	:	Prostacycline
PGs	:	Prostaglandins
PI3K	:	Phosphoinositid-3-kinase
PI3K-AKT	:	PI3K-activated tyrosine kinase

List of Abbreviations (Cont.)

PR	:	Progesterone receptor
RIP	:	Serine/threonine kinase receptor interacting protein
SNPs	:	Single nucleotide polymorphisms
SODD	:	Silencer of death domain
TAC	:	TNF-∝ converting enzyme
Th1	:	T helper 1
Th2	:	T helper 2
TIMP	:	Tissue inhibitor of matrix metalloproteinase
TNF-∝	:	Tumor necrosis factor alpha
TNFR	:	TNF-∝ receptor
tPA	:	Tissue plasminogen activator
TRADD	:	TNFR associated death domain
tTG	:	Tissue transglutaminase
TV U/S	:	Transvaginal ultrasound
TXA	:	Thromboxanes
uNK	:	Uterine Natural killer
uPA	:	Urokinase-type plasminogen activator
vEGF	:	Vascular endothelial growth factor
WOI	:	Window of implantation
XAF1	:	XIAP associated factor 1
XIAP	:	X-linked inhibitor of apoptosis.

List of Figures

List of Figures (Cont.)

List of Tables

List of Tables (Cont.)

The Role of Tumor Necrosis Factor-308 Polymorphism on Pregnancy Rate in Women Undergoing Intracytoplasmic Sperm Injection Program

Thesis

Submitted for Partial Fulfillment of MD
In Obstetrics and Gynecology

By

Khaled Hamed Ahmed Gabr
MSc. in Obstetrics and Gynecology, Ain Shams University, May 2009
Specialist in Obstetrics and Gynecology
In El Mahalla General Hospital

Under supervision of

Professor/ Hatem El Gamal
Professor of Obstetrics and Gynecology
Faculty of Medicine - Ain Shams University

Dr/ Nashwa El Saied Hassan
Assistant Professor of Obstetrics and Gynecology
Faculty of Medicine - Ain Shams University

Dr/ Ahmed El Sayed Hassan El bohoty
Lecturer in Obstetrics and Gynecology
Faculty of Medicine - Ain Shams University

Dr/ Amr Helmy Yehia
Lecturer in Obstetrics and Gynecology
Faculty of Medicine - Ain Shams University

Dr/ Nesrine ALy
Lecturer in Clinical Pathology
Faculty of Medicine - Ain Shams University

Faculty of Medicine
Ain Shams University
2014

Introduction

Implantation is a process requiring the delicate interaction between the embryo and a receptive endometrium, this complex interaction requires a harmonized dialogue between embryonic and maternal tissues ***(Simon et al., 2000 and Aghajanova et al., 2008).***

The three stages of implantation are: apposition, adhesion, and invasion. Apposition describes trophoblast cells adhering to the receptive endometrial wall. Adhesion to the basal lamina and stromal extracellular matrix occurs in the presence of specific hormones, cytokines, and adhesion molecules. Once the blastocyst is anchored to the endometrial wall, it will become enclosed by an outer layer of syncytiotrophoblast, and an inner layer of cytotrophoblast. As the syncytiotrophoblast erodes the endometrial wall, the blastocyst will burrow into it and implantation will occur ***(Ganong, 2005).***

The priming of the endometrium to optimize the window of implantation phase has been a subject of interest for decades, and much work has gone into understanding the preparation and capability of the endometrial wall to create a suitable environment for the interaction with the blastcyst. While an embryo factor accounts for one third of implantation failures, lack of uterine receptivity explains approximately two thirds of implantation failures ***(Ledee-Bataille et al., 2002 and Achach, 2006).***

Expression of proteins, cytokines ,and peptides serve as biomarkers for maximal endometrial receptivity, and detection ,investigation of these biochemical markers during the implantation phase is an area of research receiving much interest and may serve to establish future treatments to help maximize the effectiveness of assisted reproductive techniques in the near future ***(Cavagna and Mantese, 2003).***