

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**

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بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ

وَقَدْ أَعْمَلُوا فَسَيَرَى اللَّهُ عَمَلَكُمْ
وَرَسُولُهُ وَالْمُؤْمِنُونَ

صدق الله العظيم

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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 β -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 serum TNF-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

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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
INF γ	: Interferon- γ
IVF	: In vitro fertilization
I κ B	: Inhibitor of κ B
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
NF κ B	: Nuclear factor kappa B
NK	: Natural killer
OPN	: Osteopontin
PAI-1	: Plasminogen activator inhibitor 1
PGEs	: Prostaglandine E synthase
PGI ₂	: 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- α converting enzyme
Th1	: T helper 1
Th2	: T helper 2
TIMP	: Tissue inhibitor of matrix metalloproteinase
TNF- α	: Tumor necrosis factor alpha
TNFR	: TNF- α 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.

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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 blastocyst. 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*).