



بسم الله الرحمن الرحيم

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**TNF- α , IFN- γ and TGF- β mRNA Expression
Correlation with IVF Success Rates in Women
with Recurrent Implantation Failure
Undergoing Treatment with Intra-lipid infusion**

Thesis

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List of Abbreviations

AF	: Accessory factor
AIDS	: Acquired Immune Deficiency Syndrome.
AMV-RT	: Avian Myeloblastosis Virus Reverse Transcriptase.
APA	: Anti-phospholipid antibodies
APC	: Antigen presenting cells
ART	: Assisted reproductive technique
BMI	: Body mass index
CBRC	: Cross-border reproductive care
cDNA	: complementary DNA.
CNS1	: Conserved noncoding sequence 1
CSF	: Colony stimulating factor
CTB	: Cytotrophoblast
CTLA4	: Cytotoxic T-lymphocyte antigen 4
DHSs	: Demographic and Health Surveys
DNA	: Deoxyribonucleic acid
dNTPs	: Deoxynucleotide triphosphate
E2	: Estradiol
ECM	: Extracellular matrix
EDTA	: Ethylene Diamine Tetraacetic Acid.
EPA	: Eicosapentaenoic acid
ESHRE	: European Society of Reproduction and Embryology
ET	: Embryo transfer
EVT	: Extra-villous trophoblast cells
FADD	: FAS-associated death domain
FAS	: Fatty acid synthesis
FET	: Frozen Embryos Transfer.
FSH	: Follicle stimulating hormone

GDNF	: Glial cell-derived neurotrophic factor
HCG	: Human Chorionic Gonadotropin
HIV	: Human immunodeficiency virus
HMG	: Human Menopausal Gonadotropin
HVEM	: herpes virus entry mediator.
ICPD	: International Conference on Population and Development
ICSI	: Intracytoplasmic Sperm Injection
IDO	: Indoleamine 2,3-dioxygenase
IFFS	: International federation of fertility societies
IFN	: Interferon
IFN- γ	: Interferon-gamma
IL	: Intralipid
IQR	: Interquartile range
IVF	: In vitro fertilization
IVFE	: Intravenous fat emulsion
IVIg	: Intravenous immunoglobulin
IVIG	: Intravenous immunoglobulin. G
KIR	: Killer-cell immunoglobulin-like receptors
LCIVF	: Low-cost IVF
LH	: Luteinizing hormone.
LIT	: Lymphocyte immunization therapy
M-CSF	: Monocytes colony stimulating factor
MMPs	: Matrix metallo-proteinases
mRNA	: Messenger ribonucleic acid
MUC-1	: Mucin
NK	: Natural killer
NKT	: Natural killer T
NS	: Non-significant
PBMC	: Peripheral blood mononuclear cells
PBS	: Phosphate Buffer Saline.
PD1	: Programmed Death-1

PE	: Pre-eclampsia
PPARs	: Peroxisome proliferator-activated receptors
RIF	: Recurrent implantation failure
RNA	: Ribonucleic acid
RNase	: Ribonuclease
RPL	: Recurrent pregnancy loss
RQ	: Relative Quantification
RTIs	: Reproductive tract infections
RT-PCR	: Real-time polymerase chain reaction
S	: Significant.
SD	: Standard deviation
sHLA	: Soluble human leukocyte antigen
sPIF	: Synthetic pre-implantation factor
STIs	: Sexually transmitted infections
TGF	: Transforming growth factor
TGF- β	: Transforming growth factor-beta
Th	: T helper
TNF	: Tumour necrosis factor
TNF- α	: Tumor necrosis factor-alpha
TNFR	: Tumor necrosis factor receptor.
TRADD:	Tumor necrosis factor receptor type 1-associated DEATH domain protein.
TSH	: Thyroid stimulating hormone.
uNk	: uterine natural killer cells.
VSMC	: Vascular smooth muscle cell
WHO	: World Health Organization
WOI	: Window of implantation.

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Abstract

This study aimed at assessing the correlations between gene expression of TNF- α , IFN- γ , TGF- β in peripheral lymphocytes from women suffering from repeated implantation failure before and after intravenous Intra-lipid (IL) therapy, and correlation between changes in gene expression with IL infusion and success rate of IVF cycles. Twenty-three women complaining of unexplained infertility without history of autoimmune disorders, or immunodeficient diseases were included. All women included aged <40 years, BMI <28 with history of recurrent IVF cycles failure, seeking medical advice for new IVF trial. All were average responders to induction of ovulation (≥ 5 oocytes in each cycle) with good quality embryos transferred to uterus at proper time. Included women received 200 ml of 10% IL slowly intravenously. Two venous blood samples were taken from all candidates, one before IL infusion and the second was at day of embryo transfer. The current study detected a significant reduction of expression in TNF- α and increased expression of TGF- β , while non-significant reduction in expression of IFN- γ after treatment. Significant associations between reduction of TNF- α , IFN- γ expression and positive clinical and ongoing pregnancy were observed, while increased TGF- β expression was associated with only positive ongoing pregnancy. In conclusion, IL therapy might have a positive impact on IVF pregnancy rates via alterations in peripheral cytokines expression mainly reduction of TNF- α mRNA expression and increased TGF- β mRNA expression.

Keywords: Intralipid Therapy, IVF failure, IFN- γ , TNF- α , TGF- β

Introduction

Pregnancy is a unique immunological challenge in which the antigenically distinct fetus and placenta develop in the uterus of the mother. For the conceptus to implant and for pregnancy to be maintained, the conceptus must protect itself from the maternal immune system. This involves a balance between maternal immune defence mechanisms and invasion by the allogenic trophoblast (*Noronha and Antczak, 2010*).

IVF (in vitro fertilization) success rates, the percentage of all IVF procedures which result in a favourable outcome, this outcome may represent the number of confirmed pregnancies (confirmed by serum Human Chorionic Gonadotrophin β -HCG), Also called the pregnancy rate (*Firouzabadi et al., 2016*).

Accordingly, different fertility centres practicing IVF may use different definitions for recurrent implantation failure (RIF), Recent definition of RIF is: failure of implantation in at least two consecutive IVF attempts, in which 1–2 embryos of high grade quality are transferred in each cycle (*Shufaro and Schenker, 2011*).

The process of implantation involves two main components, a healthy embryo that should have the potential to implant and a receptive endometrium that should enable implantation. The “cross-talk” between the embryo and the endometrium that finally leads to apposition, attachment and invasion of embryos is mandatory for successful implantation and subsequent normal placentation. These processes seem to