The Effect of Day 6 Endometrial Injury of the Same ICSI Cycle on the Pregnancy Rate

(Randomized Controlled Trial)

Thesis

Submitted for Partial Fulfillment of Master Degree
in Obstetrics and Gynecology

By

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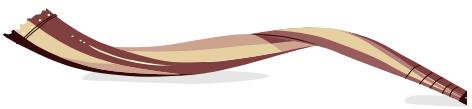

Rasha Arafat

List of Abbreviations

Abb.	Full term
AFC	Antral follicle count
AH	Assisted hatching
AMH	Anti-Müllerian hormone
Ang-1	Angiopoietin-1
APC	Antigen presenting cells
ART	Assisted reproductive technique
ASRM	American Society for Reproductive Medicine
BMI	Body mass index
CAM	Cell adhesion molecule
cAMP	Cyclic adenosine monophosphate
CCCT	Clomiphene citrate challenge test
CG	Chorionic gonadotrophin
CL	Corpus luteum
CLC	Cardiotropin-like cytokine
CLF	Cytokine-like factor
CNTF	Ciliary neurotropic factor
COH	Controlled ovarian hyperstimulation
Col	Collagens
CSF-1	Colonystimulating factor-1
CT	Cardiotrophin
DBD	DNA-binding domain
DCS	Dendrtic cells
DET	Double-embryo transfer
DHEA	Dehydroepiandrosterone
DOR	Diminished ovarian reserve
E2	Serum estradiol
ECF	Endometrial cavity fluid
EFORT	Exogenous FSH ovarian reserve test

Abb.	Full term
EGF	Epidermal growth factor
eNOS	Endothelial nitric oxide synthase
ERE	Estrogen response elements
ERR	Estrogen receptor related
ESC	Endometrial stromal cell
ESR	Estrogen receptors
EST	Estrogen sulphotransferase
ET	Embryo transfer
EVT	Extravillous trophoblast cells
FGF7	Fibroblast growth factors-7
FISH	Fluorescence *in situ* hybridization
FN	Fibronectin
FSH	Follicle-stimulating hormone
GAST	GnRH agonist stimulation test
GIFT	Gamete intrafallopian transfer
GnRH	Gonadotrophin-releasing hormone
GnRHa	Gonadotropin releasing hormone agonist
GPRCs	G protein coupled receptors
HAI-1	Hepatocyte growth factor activator inhibitor type I
HBD	Hormone-binding domain
HB-EGF	Heparin-binding epidermal growth factor
HCG	Human chorionic gonadotropine
HGF	Hepatocyte growth factor
HLA	Human leukocyte antigen
HLA	Human leukocyte antigen
hMG	human Menopausal gonadotropine
hPL	Human placental lactogen
HSD	Hydroxysteroid dehydrogenases
ICSI	Intracytoplasmic sperm injection
IFN	Interferon

Abb.	Full term
IGFBP-1	Insulin-like growth factor binding protein-1
IGF-BPs	Insulin like growth factor binding proteins
IGF-I	Insulin-like growth factor-1
IL-1	interleukin-1
IL-6	Interleukin-6
IVF	*In vitro* fertilization
JAK	Janus kinase
KLRC1	Killer cell lectin-like receptor subfamily C, member 1
KLRD1	Killer cell lectin-like receptor subfamily D, member 1
LBD	Ligand binding domain
LH	Luteinizing hormone
LIF	Leukaemia inhibitory factor
LN	Laminin
MESA	Microsurgical epididmal sperm aspiration
MHC	Major histocompatibility complex
MMPs	Matrix metalloproteinases
MOS	Macrophage
MUC-1	Mucin-1
NK	Natural killer
NO	Nitric oxide
NOS	NO synthase
NR	Nuclear receptors
OHSS	Overian hyperstimulation syndrom
OSM	Oncostatin M
P	Progesterone
PA	Plasminogen activator.,.
PAI	Plasminogen activator inhibitor
PAI-1	Plasminogen activator inhibitor-1
PCOS	Polycystic ovary syndrome
PCOS	Polycystic ovary syndrome

Abb.	Full term
PCR	POLYMERASE chain reaction
PCT	Post coital test
PGD	Pre-implantation genetic diagnosis
PGS	Preimplantation genetic screening
PKA	Protein kinase
PP14	Placental protein 14
PR	Progesterone receptor
PRs	Progesterone receptors
PSV	Peak systolic velocity
rFSH	Recombinant follicle stimulating hormone
SART	Society for Assisted Reproductive Technologies
SER	Smooth endoplasmic reticulum
SERMs	Selective estrogen receptor modulators
SET	Single- embryo transfer
SFRE	Steroidogenic factor-1 response elements
sGE	Superficial glandular epithelia
SHBG	Sex hormone-binding globulin
SOCS	Suppressors of cytokine signalling
StAR	Steroid acute regulatory protein
STAT	Signal transducer and activator of transcription
STS	Steroid sulfatase
TAF	transcriptional activation function
TESE	Testicular sperm extraction
TET	Tubal embryo transfer
TGFβ1	Transforming growth factor β1
Th	T helper cell
TIMPs	Tissue inhibitors of matrix metalloproteinases
TNF	Tumor necrosis factor
UBF	*Uterine blood flow*
uFSH	Urinary follicle stimulating hormone

Abb.	Full term
uNK	Uterine natural killer
uPA	Urokinase-type plasminogen activator
VEGF	Vascular endothelial growth factor
VN	Vitronectin
VSMC	Vascular smooth muscle cells
woi	window of implantation
ZIFT	Zygote intrafallopian transfer

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Introduction

In assisted reproductive technology, procedures for culturing and transferring embryos have been continually improved over the last two decades. Yet the clinical pregnancy rate has not substantially improved over the last ten years (currently only 32.4~33.0% per IVF transfer as reported by ESHRE in 2010) [(1)] and many patients have suffered repeated implantation failure even in the most successful In vitro fertilization (IVF) clinics. Although no practical solutions for repeated implantation failure have emerged, an improved ability to control the endometrial environment for implantation promises to have a significant, positive impact on IVF outcomes [(2)]

Although many fertility disorders have been overcome by a variety of assisted reproductive techniques, implantation remains the rate-limiting step for the success of in vitro fertilization (IVF). Implantation of the embryo, which is a prerequisite for successful pregnancy, can only take place in a receptive uterus. In humans, the uterus becomes receptive during the midsecretory phase of the menstrual cycle (days 19 to 23), commonly known as the window of implantation (WOI). It is assumed that inadequate uterine receptivity is responsible for approximately two-thirds of implantation failures [(3)]

A key determinant of treatment success is implantation of the embryo, which depends on two factors: the quality of the embryo and the receptivity of the

endometrium. It has been shown that endometrial receptivity could be modulated by a multitude of signaling molecules, including prostaglandins[4] growth factors, cytokines, chemokines, integrins, leukemia inhibitory factor[5] [6] Wnt family ligands [7] and E-cadherin [8]

The optimal window for endometrial receptivity is relatively narrow and implantation is unlikely to occur even when good quality embryos are transferred into the uterus outside this time. One of the proposed interventions designed to improve endometrial receptivity is physical injury to the endometrium and early reports suggest that it could improve the rates of implantation (27.7% versus 14.2%, $P < 0.001$), clinical pregnancy (66.7% versus 30.3%, $P < 0.001$), and live birth (48.9% versus 23.6%, $P = 0.016$) [9]

The underlying mechanism of how endometrial injury improves endometrial receptivity remains unknown. Three hypotheses have been made. The first is that local injury to the endometrium induces endometrial decidualization, which increases the probability of implantation of a replaced embryo [10]

This hypothesis is based on the observation of induction of decidual tissue formation which mimics the endometrial changes of early pregnancy after mechanical endometrial stimulation with a microcurette in guinea pigs [11]

The second is that endometrial healing following injury is associated with a significant increase in the