The Effects of Endometrial Scratching on Intrauterine Insemination Outcome in Patients with Unexplained Infertility: A Randomized Clinical Trial

Thesis

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BY

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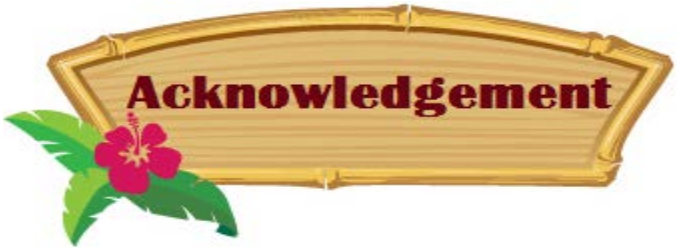

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List of Abbreviations

Abbreviation	Meaning
ACL	Anticardiolipin
APL	Antiphospholipid
CG	Chorionic Gonadotropin
cGAMP	Cyclic Guanosine Monophosphate
COH	Controlled Ovarian Hyperstimulation
CT	Cytotrophoblast
DCs	Dendritic cell
E2	Estradiol
ECM	Extracellular Matrix
EE	Endometrial Epithelium

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Abbreviation	Meaning
EGF	Epidermal growth factor
ESC	Endometrial Stromal Cell
EVCT	Extra Villous Cytotrophoblast
FSP	Fallopian tube sperm perfusion
FSH	Follicular Stimulating Hormone
GnRH	Gonadotropin Releasing Hormone
Groa	Chemokine Growth Related Oncogene (a)
HCG	Human Chorionic Gonadotropin
HESCS	Human endometrial stromal cells
HLA-G	Human leukocyte antigen G
HMG	Human Menopausal gonadotropin
ICSI	Intracytoplasmic Sperm Injection
IGFBP-1	Insulin Like Growth Factor Binding Protein

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Abbreviation	Meaning
IL	Interleukin
ITGa6	Integrin a 6
IUI	Intrauterine Insemination
IVF	In-Vitro Fertilization
LAC	Lupus Anticoagulant
LH	Luteinizing Hormone
LIF	Leukemia Inhibitory Factor
MHC	Major histocompatibility complex
NK	Natural Killer
OPN	Osteopontin
PI	Pulstile Index
PL	Placental Lactogen
RI	Resistant Index

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Abbreviation	Meaning
RIF	Recurrent Implantation Failure
SEM	Scanning Electric Microscope
ST	Syncytiotrophoblast
LEI	Local Endometrial Injury
TE	Trophoectoderm
TNF	Tumor Necrosis Factor
TPA	Tissue Plasminogen Activator
UPA	Urokinase Plasminogen Activator
UI	Unexplained Infertility
UNK	Uterine Natural Killer Cells
WOI	Window of Implantation
ZP	Zona Pellucida

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Introduction

Unexplained infertility (UI) is a term used to describe infertile couples in whom standard investigations, including semen analysis, tests of ovulation and tubal patency, have failed to detect any gross abnormality [(1).]

It is a diagnosis of exclusion, almost 30-40% of infertile couples would suffer from this type of subfertility. [(2)] A diversity of causes had been hypothesized to explain the condition. Cervical, uterine, ovulatory, peritoneal, immunological, endocrinological, genetic defects and reproductive physiology disturbances had been continuously suggested as potential causative factors. [(3, 4)]

Interventions for managing unexplained infertility had been widely practiced. These interventions include expectant management, intrauterine insemination (IUI) with ovarian stimulation and in vitro fertilization.[(5)] In humans, the uterus becomes receptive during the midsecretory phase of the menstrual cycle (days 19-23), commonly known as the window of implantation (WOI). [(6)]

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It is assumed that inadequate uterine receptivity is responsible for approximately two–thirds of implantation failures. [7] Since an impairment of endometrial receptivity may be a cause of subfertility in a group of couples diagnosed with unexplained infertility. [8, 9, 10]

Endometrial scratching has been suggested to boost embryo implantation following recurrent implantation failure after IVF. [11, 12] Endometrial scratching could have a favorable endometrial healing effect on the implantation process by releasing of biochemical mediators [11] such as endometrial proinflammatory cytokines (interleukin-6, leukemia inhibitory factor and tumor necrosis factor) that characterize early implantation. [13] These cytokines can be secreted by the endometrial cells and cells of the immune system. Decidual leukocytes infiltrate the implantation site, of these cells 65% to 70% are uterine - specific natural killer cells [13] which have been shown to be essential for the establishment of an adequate decidua. [14, 15] An additional 10% to 20% of the decidual leukocytes consist of macrophage and dendritic cells [16, 17] which remain in the decidua throughout pregnancy and secrete growth factors, chemokines, and cytokines regulating blastocyst implantation, angiogenesis, placental development, and decidual homeostasis. [18, 19]

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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 increase the probability of implantation of a replaced embryo. **(20)**

This hypotheses 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 micro curette in guinea pigs. **(21)**

The second is that the endometrial healing following injury is associated with a significant increase in the secretion of cytokins, interleukins, growth factors and macrophages and dendritic cells, all of which are beneficial to embryo implantation. **(20, 22)**

The third is that endometrial maturation is abnormally advanced when controlled ovarian stimulation is performed during ART. **(23)**

Intra-uterine insemination (IUI) is a very common procedure which is done during the treatment of infertility. This is a simple procedure and does not need hospitalization. In this procedure, sperms which have undergone certain laboratory process are introduced into the woman’s uterus (womb) at around the time of ovulation (i.e. release of the egg from ovum), with the aim of conception and pregnancy.

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Implantation rates are still low after ART and controlled ovarian stimulation, and despite the great improvements in fertilization procedures, during the implantation period, the endometrium undergoes transition and acquires an appropriate morphological and functional state under the influence of ovarian steroids, which facilitate the attachment of blastocyst. In addition progesterone and estrogen are the dominant hormonal modulators of endometrial development. Progesterone is essential for implantation and pregnancy maintenance in all mammals, whereas the requirement for estrogen in species specific **(24).**

Aim of the Work

To compare the effect of endometrial scratching/non scratching on the results of IUI in cases with unexplained infertility regarding to both chemical and clinical pregnancy.