The Effect of Endometrial Scratch Injury on Clinical Pregnancy Rate in Women with Unexplained Infertility Undergoing IUI with Ovarian Stimulation

A Randomized Controlled Trial

Thesis

Submitted for partial fulfillment of the master degree in Obstetrics and Gynaecology

By

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✍ *Ameena Mahmoud Sultan*

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List of abbreviations

AFC	: Antral Follicle Count
AIs	: Aromatose Inhibitors
AMH	: Anti-Mullerian Hormone
APS	: Anti-Phospholipid Syndrome
ART	: Assissted reproductive Technologies
ASRM	: American Society of Reproductive Medicine
BMI	: Body Mass Index
CC	: Clomiphene Citrate
CCCT	: Clomiphene Citrate Challenge Test
CDC	: Centers for disease control and prevention
ESI	: Endometrial Scratch Injury
FAI	: Free Androgen Index
FSH	: Follicular Stimulating Hormone
GnRH	: Gonadotropin releasing hormone
HA	: Hupothalamic Amenorrhea
HCG	: Human Chorionic Gonadotropin
HIV	: Human Immunodefiency Virus
HMG	: Human Menopausal Gonadotropin
HP-HMG	: Highly Purified Human Menopausal Gonadotropin
HSG	: HystroSalpingography
HyCoSy	: Hystrosalpingo-Contrast Sonography
ICI	: Intra-Cervical Insemination
ICSI	: Intra-Cytoplasmic Sperm Injection
IL	: InterLeukin
IUAs	: Intra-Uterine Adhesions

List of abbreviations *(Cont ..)*

IUD	: Intrauterine Device
IUI	: Intra-Uterine Insemination
IVF	: In Vitro Fertilization
LEP	: Leptin
LH	: Leutinizing Hormone
LPD	: Leuteal Phase Defect
MRI	: Magnetic Resonance Imaging
NIH	: National institue of health
OHSS	: Ovarian hyperstimulation syndrome
PCOS	: Polycystic ovary syndrome
POI	: Primary ovarian insufficiency= premature ovarian faliure
rhFSH	: Recombinant human FSH
RIF	: Recurrent implantation faliure
RM	: Recurrent miscarriage
RPL	: Recurrent Pregnancy Loss
SERMs	: Selective estrogen receptor modulators
SHBG	: Sex hormone binding globulin
TNF-α	: Tumor necrosis factor alpha
TSH	: Thyroid stimulating hormone
uFSH	: Urinary FSH
uNK	: Uterine natural killer cells
WHO	: World health Organization

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PROTOCOL OF THESIS

AIM OF THE WORK

The objective of the present study is to evaluate the value of endometrial scratch injury (ESI) on clinical pregnancy rate in women undergoing intrauterine insemination (IUI) with ovarian stimulation for unexplained infertility.

Research Question:

In women with unexplained infertility undergoing intrauterine insemination (IUI) with ovarian stimulation, does endometrial scratch injury improve the clinical pregnancy rate?

Research Hypothesis:

In women with unexplained infertility undergoing intrauterine insemination (IUI) with ovarian stimulation, endometrial scratch injury may improve the clinical pregnancy rate.

PATIENTS AND METHODS

Setting

This study will be conducted at Ain-Shams maternity hospital,IVF unit.

Study Design

Randomized controlled clinical trial

Study Population

Patients will be selected according to Inclusion and Exclusion criteria:

Inclusion criteria:

The study will include couples with unexplained infertility and assigned for IUI with clomiphene citrate ovarian stimulation with the following criteria:

1. Normal semen analysis: The World Health Organization (WHO) has published revised lower reference limits for semen analyses. The following parameters represent the generally accepted 5 thpercentile: **(Cooper *et al., 2010)***
   - Volume : 1.5 mL
   - Sperm concentration : 15 million spermatozoa/mL
   - Morphology : 4 % normal forms
   - Progressive motility : 32 %

2. Documented ovulation: by mid-luteal phase serum progesterone level> 3 ng/ml, or sonographic evidence of documented ovulation **(*Wathen et al., 1984).***
3. Normal uterine cavity: by HSG and trans-vaginal ultrasonography **(*Soares et al., 2000).***
4. Normal tubal patency: by HSG and/or laparoscopy with chromotubation **(*Lim et al., 2011).***

Exclusion criteria:

1. Women aged more than 35 years.
2. Women with diminished ovarian reserve as denoted by a serum FSH > 10 mIU/ml or a serum AMH < 1 ng/ml.
3. Women with body mass index 35 kg/m2 or more.
4. Women who have clomiphene citrate (CC) resistance, or who had prior history of serious adverse effects with clomiphene citrate (CC) (blurring of vision, or severe OHSS).
5. Women with expected decreased endometrial receptivity (e.g. intra uterine abnormalities: adhesions or chronic endometritis).

Randomization, Allocation and Concealment

- Recruited women will be randomized into one of two groups:
  1. Group I, including women who will undergo endometrial scratch injury.
  2. Group II, including women who will not undergo endometrial scratch injury.

- Randomization is to be performed using computer-generated randomization system.
- Allocated groups will be labeled in serially-numbered opaque envelops that are only opened after recruitment.

Induction of Ovulation

- Induction of ovulation is performed by administration of CC 100 mg per day starting from cycle day 2 through cycle day 6.
- The patient is serially followed up by transvaginal sonography starting on cycle day 10.
- When a mature follicle size (≥ 18 mm) is achieved, ovulation is triggered by IM injection of hCG 10,000 IU.
- Serum hCG assays is checked 16 days after the day of triggering ovulation.

Endometrial Scratch Injury

- Endometrial scratch injury is performed on the same day of triggering ovulation.
- Endometrial scratch injury is performed using the IUI catheter [Sperm TRANSTM IUI catheter].
- Endometrial scratch technique is to be done similar to the technique of embryo transfer in in vitro fertilization (IVF) cycles by exposing the cervix using sterile speculum then the cervix was cleaned with sterile gauze moistened with saline. The thin catheter is then introduced through the internal os then the endometrium is gently scratched by moving the catheter up and down 3 times.

IUI

- The procedure is performed 36 hours after triggering ovulation.
- A specimen from husband's semen is analyzed, processed, prepared and loaded on the IUI catheter [Sperm TRANSTM IUI catheter].
- The IUI is performed under abdominal ultrasound guidance with a semi-filled urinary bladder.

Outcomes

- The primary outcome is clinical pregnancy rate defined as sonographic detection of viable intrauterine pregnancy.
- Secondary outcomes include:
  1. Biochemical pregnancy rate.
  2. Patient's discomfort and satisfaction.

Ethical Aspects

- The study protocol is in agreement to the Helsinki Declaration of Principles of Ethical Medical Research [last updated in Brazil, 2013].
- All participating women have to sign informed written consent after thorough explanation of the procedure and purpose of the study.
- Any participating woman has the right to withdraw from the study at any phase without being adversely impacted regarding the medical service she should receive.

Sample Size Justification

Sample size was calculated using EpiInfo version 7.0, setting the power at 80% and the type-1 error at 0.05. Data from a previous similar study ***(Maged et al., 2015)*** showed that the clinical pregnancy rates in women who underwent endometrial scratch injury with IUI and women who did not were 39% and 18.2%, respectively. Calculation according to these values produces a minimal sample size of 73 women in each group.

Statistical Methods

Statistical analysis is to be performed using SPSS for Windows version 20.0 and Microsoft Excel version 2010. Data are to be presented in terms of range, mean and standard deviation (for numeric parametric variables); range, median and interquartile range (for numeric non-parametric variables); and number and percentage (for categorical variables). Difference between two groups is to be analyzed using independent student's t-test (for numeric parametric variables); Mann-Whitney's U-test (for numeric non-parametric variables); and chi-squared test (for categorical variables). Association between the outcomes and measured variables is to be estimated using logistic regression analysis, and expressed in terms of odds ratios and their 95% confidence intervals. Significance level is set at 0.05.

Consent form

The patient's approval on participating in the study:

To answer the following questions:

Please put a circle around (Yes) or (No) knowing that it means that you completely understand the nature of the study and any problem that might accidentally happen during this study.

The patient's number in the study :	
The first letters of the patient's full name:	
The hospital number:	
I have read the associated illustrative guide.	Yes No
I can withdraw this approval at any time during the study.	Yes No
My withdrawal from the study (if happened) won't negatively affect the provided medical care.	Yes No
I had enough time asking about anything I want to know about the study.	Yes No
I do agree on participating in this study.	Yes No
The doctor's name :	Signature:
The patient's name :	Signature:

INTRODUCTION

In defining infertility, according to the International Committee for Monitoring Assisted Reproductive Technology and the World Health Organization, infertility is 'a disease of the reproductive system defined by the failure to achieve a clinical pregnancy after 12 months or more of regular unprotected sexual intercourse. ***(Zegers-Hochschild et al., 2009).***

Unexplained infertility refers to the absence of a definable cause for a couple's failure to achieve pregnancy after 12 months of attempting conception despite a thorough evaluation, or after six months in women 35 years and older ***(ASRM.,2008).***

Unexplained infertility is applied to 10% - 30% of couples seeking treatment for infertility ***(Collins and Van-Steirteghem, 2004).*** This incidence variation may be attributed to selection bias in referral-based infertility practices or may reflect other differences among study populations.

There are several possibilities of unexplained infertility; subtle changes in follicle development , ovulation, and the luteal phase, the male partner's semen with sperm concentration