



شبكة المعلومات الجامعية
التوثيق الإلكتروني والميكروفيلم

بسم الله الرحمن الرحيم



MONA MAGHRABY



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شبكة المعلومات الجامعية التوثيق الإلكتروني والميكروفيلم



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التوثيق الإلكتروني والميكروفيلم

جامعة عين شمس

التوثيق الإلكتروني والميكروفيلم

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MONA MAGHRABY



Efficacy of Sequential Embryo Transfer in Improving Pregnancy Rate in Women with Repeated Unexplained Implantation Failure

Thesis

*Submitted for Partial Fulfillment of
Master Degree in Obstetrics & Gynecology*

By

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List of Abbreviations

Abb.	Full term
AFC	Antral follicle count
AMH	Antimüllerian hormone
APA	Anti-phospholipid antibodies syndrome
BMI	Body mass index
CAT	Chlamydia antibody tests
DHEA	Dehydro epi and rostenedione
EIM	ESHRE IVF monitoring
ELISA	Enzyme-linked immunosorbent assay
FSH	Follicle stimulating hormone
FSH	Follicle-stimulating hormone
G-CSF	Granulocyte colony-stimulating factor
hCG	Human chorionic gonadotropin
HLA	Human leukocyte antigen
HSG	Hystero-salpingogram
ICSI	Intracytoplasmic Sperm Injection
IF	Immunofluorescence
IFN- γ	Interferon- γ
IL1 β	IL1 -beta
IL2	Interleukin 2
IQR	Inter-quartile range
IVF	In vitro fertilization
IVF-ET	In vitro fertilization and embryo transfer
IVIG	Intravenous immunoglobulins
IVM-MII	In vitro-matured metaphase II
MHC	Major histocompatibility complex
MI	Metaphase I
MIF	Micro-immunofluorescence
MIP	Maximal implantation potential
MTHFR	Methylene tetrahydrofolate reductase
NICE	National Institute for Health and Care Excellence
NSAIDs	Nonsteroidal anti-inflammatory drugs
OC	Oocyte cryopreservation

List of Abbreviations cont...

Abb.	Full term
<i>OHSS</i>	<i>Ovarian hyper stimulation syndrome</i>
<i>OR</i>	<i>Ovarian reserve</i>
<i>PBMCs</i>	<i>Peripheral blood mononuclear cells</i>
<i>PCOS</i>	<i>Polycystic ovary syndrome</i>
<i>PESE</i>	<i>Sperms will be extracted from epididymis</i>
<i>PGD</i>	<i>Preimplantation genetic diagnosis</i>
<i>PID</i>	<i>Pelvic inflammatory disease</i>
<i>PIO</i>	<i>Progesterone-in-oil</i>
<i>pNK</i>	<i>Peripheral</i>
<i>rFSH</i>	<i>Recombinant FSH</i>
<i>RIF</i>	<i>Repeated implantation failure</i>
<i>rLH</i>	<i>Recombinant Luteinizing hormone</i>
<i>SIS</i>	<i>Saline Infusion Sonohysterography</i>
<i>SPSS</i>	<i>Statistical Package for Social Science</i>
<i>TFI</i>	<i>Tubal factor infertility</i>
<i>TGFβ₁</i>	<i>Transforming Growth Factor-beta 1</i>
<i>TH1:TH2</i>	<i>T helper 1:T helper 2</i>
<i>uNK</i>	<i>Uterine natural killer cells</i>
<i>US</i>	<i>Ultrasonography</i>
<i>WOI</i>	<i>Window of implantation</i>

**PROTOCOL OF A THESIS FOR PARTIAL FULFILMENT OF
MASTER DEGREE IN OBSTETRICS & GYNECOLOGY**

**Title of the Protocol: Efficacy of sequential embryo transfer in
improving pregnancy rate in women with
repeated unexplained implantation failure**

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**What is already known on this subject? AND
What does this study add?**

Effect of sequential embryo transfer on pregnancy rate in cases with repeated implantation failure.

Prospective clinical interventional randomized controlled trial.

Sequential ET may be used to improve pregnancy outcomes in patients with repeated IVF–ET failures. However, the efficacy of this procedure is still a matter of debate.

1.INTRODUCTION/ REVIEW

Repeated implantation failure (RIF) is determined when transferred embryos fail to implant following several in vitro fertilization (IVF) treatment cycles. However, there are no formal criteria defining the number of failed cycles or the total number of embryos transferred in these IVF attempts. Accordingly, different fertility centers practicing IVF may use different definitions for RIF (**Shufaro et al., 2011**).

Considering the current success rate of IVF treatments and the mean number of embryos transferred in each cycle, it is recommended to define RIF as failure of implantation in at least three consecutive IVF attempts, in which 1–2 embryos of high grade quality are transferred in each cycle. Repeated IVF–embryo transfer failures may occur for a variety of reasons typically include reduced endometrial receptivity secondary to uterine cavity anomalies, thin endometrium, abnormal changes in adhesion molecules expression and embryonic developmental abnormalities, such as low embryo quality due to a poor culture environment and genetic factors. Improving the clinical pregnancy rate in these patients is a challenge faced by clinicians and improving endometrial receptivity is essential to increase the success rate (**Simon et al., 2012**).

Successful embryo implantation could be considered as a result of the intimate communication between the embryo and maternal endometrium. These two worlds need to be in full synchronization in a specific time-frame, called “Window of implantation” (WOI). In this period, lasting approximately two days, a 6–8 day human embryo has a chance to be attached into the surface endometrial layer, composed of epithelial cells and to be implanted into the stromal cell layer (**Fritz et al.,**

2014).

Finding the best moment in the menstrual cycle for embryo transfer is a crucial step in overcoming the infertility problems in patients with repeated implantation failures (RIF). Displacement of the WOI during the midluteal phase occurs in at least 25% of RIF patients. Some authors report even higher incidence of more than 30% out-of-phase endometrium in patients with implantation failures. Most of them were found to have their WOI shifted later in the cycle and the endometrium of these women was characterized as preceptive. Changing the time of embryo transfer is a reasonable solution in these cases. However, this approach is not sufficient in those conditions where patients have variable WOI (Mitri et al., 2016).

Blastocyst transfer is an approach aiming to improve the IVF/ET in repeated IVF/ET failures. However, the results of this approach depend on the number of fertilized oocytes and the quality of the fertilized embryos. Ledee-Bataille et al. reported similar implantation rate of day 3 embryos vs day 5 embryos in prospective randomized study. Moreover, cancelation of the entire treatment cycle can happen due to failure of the embryos to develop to blastocyst stage with unfavorable emotional and economic consequences. Thus, sequential transfer approach has the advantage of blastocyst transfer without exposing the whole cycle to the risk of cancelation (Ledee-Bataille et al., 2004).

2.AIM / OBJECTIVES

Research hypothesis:

Sequential embryo transfer among women less than 40 years with repeated unexplained implantation failure will not improve the pregnancy rate.

Question of the study:

DOES SEQUENTIAL EMBRYO TRANSFER IMPROVE PREGNANCY RATE IN PATIENTS WITH REPEATED UNEXPLAINED IMPLANTATION FAILURE?

The aim of the study to compare the pregnancy rate between two groups of women with repeated unexplained implantation failure,

one group undergo sequential embryo transfer on day 3 and day 5, the other one undergo embryo transfer on day 3.

Primary outcomes:

The primary outcome measure is:

- Ongoing pregnancy: the patients' proportion that their pregnancy continued beyond 12 weeks.

Secondary outcomes:

- (1) Clinical pregnancy rate: the patients' proportion with viable FHB (Beta HCG and US).
- (2) Implantation rate: is the proportion of gestational sacs seen on the ultrasound divided by the total number of embryos transferred.
- (3) Biochemical pregnancy as the detection of hCG in blood or urine without subsequent clinical signs of pregnancy.
- (4) Early pregnancy loss is the patients' proportion with their pregnancy failed to develop before 12 weeks of gestation.

3.METHODOLOGY:

Patients and Methods

- **Study design:**
A randomized controlled clinical trial.
- **Site of the study:**
IVF Unit, Ain Shams University Maternity Hospital.
- **Time of the study:**
From September, 2019 till end of the study.

Study Population:

Group A: women undergoing sequential embryo transfer at day 3 and day 5