Optimizing Embryo Transfer In Assisted Reproduction

THESIS

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بسم الله الرحمن الرحيم

" قالوا سبحانك لا علم لنا الا ما علمتنا انك انت العليم الحكيم"

صدق الله العظيم

الاية (٣٢) من سورة البقرة

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Abstract

Since the birth of Louise Browen the first IVF child in July 1978 and the birth of the first ICSI child in January 1992, many couples with longstanding female factor or male infertility can be helped to overcome their infertility resulting in a birth of a child . The final and ultimate goal of all infertility treatments has been to give the large population on infertile couples a chance to fulfill their childwish and experience the happiness of having a healthy child ***(Van-Steirteghem et al., 2002)***.

In vitro fertilization (IVF) means the fertilization of an oocyte with a sperm outside the body . IVF treatment involves the collection of mature oocytes, their fertilization and cultivation as embryos and their subsequent transfer to the uterus ***(Rabe et al., 2000) .***

IVF is generally indicated for cases of severe infertility including tubal factor, endometriosis, and male factor infertility and recommended for all refractory infertility conditions ***(Marcelle, 2005) .***

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Key words: Optimizing Embryo - Transfer - Assisted Reproduction

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LIST OF ABBREVIATIONS

ACOG: American Committee of Obstetrics and Gynaecology.

AH: assisted hatching

ART: Asisted Repeoductive Technology.

ASRM: American Society for Reproductive Medicine

CGH: Comparative genomic hybridization

CPR: Clinical pregnancy rate

ECM: Extracellular matrix

ESHRE: European Society for Human Reproduction and Embryology.

ET: Embryo transfer

FISH: Fluorescent in situ hybridization

FSH: Follicular stimulating hormone

GES: Graduated embryo score

GV: Germinal vesicle

HAS: Human serum albumin

HB-EGF: heparin-binding EGF-like growth factor

HCG: Human chorionic gonadotropin

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HLA: Human leucocytic antigen

HMG: Human memopausal gonadotropin

ICM: Inner cell mass

ICSI: Intracytoplasmic sperm injection

IGFBP-1: binding protein-1 .

IVF: In vitro fertilization.

LH: luteinizing hormone

MCES: The mean cumulative embryo score

MPR: Multiple pregnancy rate

MUC-1: Mucin 1.

NIVF : natural cycle IVF

NSAIDs: Non steroidal anti-inflammatory drugs

OHSS: Ovarian hyperstimulation syndrome

PCR: Polymerase chain reaction

PGD: preimplantation genetic diagnosis

PN : pronuclei

PR: pregnancy rate

RCTs: Randomized controlled trials

SART: Society for Assisted Reproductive Technology

SBT: Single Blastocyst Transfer

SET: Single embryo transfer

SSS: Synthetic serum substitute

TE: Trophectoderm

XO: Crossing over

ZP: Zona Pellucida

INTRODUCTION

Since the birth of Louise Browen the first IVF child in July 1978 & the birth of the first ICSI child in January 1992 many couples with longstanding female factor or male infertility can be helped to overcome their infertility resulting in a birth of a child . The final and ultimate goal of all infertility treatments has been to give the large population on infertile couples a chance to fulfill their childwish and experience the happiness of having a healthy child ***(Van-Steirteghem et al ; 2002)***.

Indeed , at that time Patrick Steptoe was visionary when he said " this is the first time we have solved all the problems at once . We are at the end of the beginning – not the beginning of the end " . Remarkable advances have since been made in every step involved in assisted reproductive techniques and this is reflected in the increase in pregnancy rates reported world-wide ***(Karande and Gleicher , 2003) .***

Assisted reproductive technologies (ART) involve laboratory preparation of gametes , artificially bringing them together and hence enhancing fertility by either bypassing an absolute obstruction to fertilization , or boosting a fecundity above that expected without treatment ***(Hamilton , 2007) .***

In vitro fertilization (IVF) means the fertilization of an oocyte with a sperm outside the body . IVF treatment involves the collection of mature oocytes , their fertilization and cultivation as embryos and their subsequent transfer to the uterus ***(Rabe et al ; 2000) .***

IVF is generally indicated for cases of severe infertility including tubal factor , endometriosis , and male factor infertility and recommended for all refractory infertility conditions ***(Marcelle , 2005) .***

Currently , IVF treatment is well established in the contemporary management of infertility and currently accounts for 1 % of the total births in the UK ***(ESHRE ,2004) .***

Clinical components of IVF include ovarian stimulation , oocyte retrieval,

sperm preparation , in vitro fertilization and finally embryo transfer ***(Hoddleston and Hornstein, 2005)***

Embryo transfer (ET) is the final and most crucial step in IVF . About 80% of patients undergoing IVF reach the ET stage , but only a small proportion of them achieve pregnancy . The pregnancy rate after ET is dependant upon multiple factors including embryo quality , endometrial receptivity and the technique of ET itself ***(Mansour and Aboulghar , 2002)***

According to **the embryo quality** , an attempt is made to transfer embryos with high quality to increase their chance of implantation . Embryos are evaluated by morphologic criteria which include cell number , degree of fragmentation and symmetry of individual balstomeres , as well as performing preimplantation genetic diagnosis (PGD) ***(Hoddleston and Hornstein , 2005) .***

Preimplantation genetic diagnosis (PGD) describes a number of techniques for preconceptional genetic evaluation of embryos resulting from IVF , and can be used to detect numerical and structural abnormalities to identify oocytes or embryos with inherited single gene disorders or to determine gender ***(Magli et al ; 2003)***

It has been claimed that 5-day embryo culture could improve implantation rate and make single blastocyst transfer (SBT) acceptable in selected IVF patients ***(Gardner et al ; 2004) .***

Elective single embryo transfer (SET), combined with subsequent transfer of frozen/thawed embryos , can maintain high pregnancy rate with a dramatic decrease in multiple pregnancy rate . It has been argued that in the near future , SET should be the default policy for good prognosis IVF/ICSI patients ***(Bergh C , 2005) .***

The implantation of human embryo into **the receptive endometrium** is a critical event in the establishment of pregnancy ***(Daftary GS et al ; 2006)***

Endometrial receptivity is defined as " the temporally and spatially unique set of circumstances that allow for successful implantation of the embryo ***(Attar E et al ; 2006).***

These circumstances include biochemical markers (adhesion molecules , cytokines , growth factors , immune markers and others) and morphological markers (pinopodes , epithelial tight junction changes and apoptosis) ***(Cicinelli et al ; 2008).***

In addition , among potential uterine predictors for implantation measurable by ultrasound are endometrial thickness and volume , endometrial pattern and endometrial blood flow ***(Schild et al ; 2000) .***

Many strategies aiming to improve **embryo transfer techniques** and thereby IVF/ET outcome . Randomized control trials (RCT) have shown that ultrasound guidance and the use of soft catheters instead of firm ones , embryo deposition in the mid cavity of the uterus , 2 cm below the fundus and a trial (mock ET) were associated with higher pregnancy rates . Further studies are needed to evaluate the necessity of a full bladder , flushing the cervical canal before ET , the best transfer medium , the best position of the patient and the benefit of analgesia or anesthesia in these techniques ***(Sallam et al ; 2005) .***

In addition , various medications have been proposed and used after ET in an attempt to improve the outcome of IVF and ICSI . In a RCT vaginal progesterone administration starting on the day of oocyte retrieval decreased the frequency of uterine contraction and increase the implantation rate ***(Baruffi et al ; 2003) .*** Also , It was found that administration of low dose baby aspirin increases the implantation and pregnancy rates ***(Waldenstrom et al ; 2004)***

Aim of this work is to study the advances of optimizing embryo transfer in assisted reproduction . We will study the effect of certain embryo transfer and post-transfer measures on the outcome of pregnancy in hundred selective cases having ICSI .

PHYSIOLOGY of CONCEPTION

Review of Literature

PHYSIOLOGY OF CONCEPTION

Gamete is a cell that fuses with another gamete during fertilization (conception) in organisms that reproduce sexually. In species which produce two morphologically distinct types of gametes, and in which each individual produces only one type, a female is any individual which produces the larger type of gamete called (an ovum) and a male produces the smaller tadpole-like type called (a sperm) ***(Dusenbery et al., 2009).***

Gametes carry half the genetic information of an individual, one chromosome of each type. In humans an ovum can only carry X chromosome (of the X and Y chromosomes) where as a sperm can carry either an X or a Y ***(Xu et al., 1997).***

In contrast to a gamete, the diploid somatic cells of an individual contain one copy of the chromosome set from the sperm and one copy of the chromosome set from the egg; that is, the cells of the offspring have genes expressing characteristics of both the father and the mother. A gamete`s chromosomes are not exact duplicates of either of the sets of chromosomes carried in the somatic cells of the individual that produced the gametes. They can be hybrids produced through crossover (a form of genetic recombination) of chromosomes, which takes place in meiosis. This hybridization has a random element, and the chromosomes tend to be a little different in every gamete that an individual produces**.** ***(Randerson et al., 2001).***

Mitosis

Mitosis is the process by which a cell separates the chromosomes in its cell nucleus, into two identical sets, in two daughter nuclei. It is generally followed immediately by cytokinesis, which divides the nuclei, cytoplasm, organelles and cell membrane into two daughter cells containing roughly equal shares of these cellular components. Mitosis and cytokinesis together define the mitotic (M) phase of the cell cycle-division of the mother cell into two daughter cells, genetically identical to each other and to their parent cell ***(Rubenstein et al., 2008).***

The stages of the cell cycle can be broken down into five stages: Interphase, Prophase, Metaphase, Anaphase, Telophase (Fig. 1).