RECENT ADVANCES IN ASSISITED REPRODUCTIVE TECHNOLOGY

ESSAY

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ABSTRACT

The knowledge of reproductive medicine has expanded rapidly since the birth of Louise Brown, the first baby to be conceived by in vitro fertilization, which was performed by Professors Steptoe and Edwards in Bournhall, England, in 1978.In vitro fertilization means the fertilization of an oocyte with sperm outside the body. Several drugs are used to hyperstimulate the ovaries : Clomiphene citrate,Gonadotropins ,GnRH agonists, GnRH antagonists, and recently aromatase inhibitors. Many methods have been described for the retrieval (pick-up) of oocytes IVF. Laparoscopic and ultrasound guided transvaginal retrieval.Preimplantation genetic diagnosis (PGD) is now the field for research in order to increase the rate of implantation .The embryo transfer (ET) process represents the culmination of the IVF cycles.Blastocyst transfer would provide a better synchrony between the uterine endometrium and the embryo.Cryopreservation allows the storage of supernumerary embryos while oocytes, ovarian tissues and testicular tissue are still under trial.

Key Words: In vitro fertilization - Controled ovarian Hyperstimulation – Oocyte retival-Sperm retrival- endometrial receptivity- Embryo Transfer –Preimplantation Genetic Diagnosis-Cryopreservation.

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DEDICATION

To the memory of

My father

And to my
lovely mother
and to my deer
husband Ahmed
for their
support and
helh
And to my
beloved son
fawzy

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LIST OF ABBREVIATIONS

- ART Assisted reproductive technologies
- ACTH Adrenocorticothyrotropin hormone
- ASRM American Society for Reproductive Medicine
- BT Blastosyst Transfer
- CC Clomiphene citrate
- CCC Clomiphene citrate challenge test
- CGH Comparative genomic hypridization
- COH Controlled ovarian hyperstimulation
- DXM Dexamethasone
- DHEAS Dehydroepianderostiendione sulphate
- dUPT Deoxynuclieotidyl transferase biotin
- E2 Estradiol
- ECM Extracellular matrix
- EGF Endometrial Growth Factor
- ET Embryo transfer
- FDA Food and Drug Administration
- FbM follitropin alfa
- FISH Flurorescence Insitu Hybridization
- FSH Follicle-stimulating hormone
- GIFT Gamete intrafallopian transfer
- GnRH Gonadotropin releasing hormone
- GnRH a Gonadotropin releasing hormone agonisit
- GV Germinal vesicle
- HB-EGF Heparin-binding EGF-like growth factor
- HCG Human chorionic gonadotropins
- HMG Human menopausal gonadotropin
- HP-FSH Highly purified Follicle-stimulating hormone
- ICSI Intracytoplasmic sperm injection
- IUI Intrauterine Insemination
- IGF Insulin-like growth factor
- IGF-BPs IGF binding proteins
- IL Interleukin
- IVF In vitro fertilization
- LH Luteinizing hormone
- LIF Leukemia inhibitory factor
- LPD Luteal phase defect
- MESA Microsurgical epididymal sperm aspiration

- M II Metaphase II
- M-FISH Multicolour Flurorescence Insitu Hybridization
- MUC-1 Mucin-1
- NIVF Natural cycle IVF
- NS No significant
- NSADs Non Steroidal Anti-inflammatory Drugs
- OHSS Ovarian hyperstimulation syndrome
- OC Oral contraceptive
- OPU Oocyte Pick Up
- OR Ovarian Reserve
- P Progesterone
- PCOS Polycystic ovarian syndrome
- PCR Polymeraze Chain Reaction
- PGD Preimplantation Genetic Diagnosis
- PGs Preimplantation Genetic Screening
- POST Peritoneal Oocyte and Sperm Transfer
- PR Pregnancy Rate
- RCT Randomized controlled Trial
- r-hFSH Recombinant human Follicle-stimulating hormone
- r-hLH Recombinant human Luteinizing hormone
- SART Society for assisted reproductive technology
- SBT Single Blastosyst Transfer
- SEM Scanning electron microscopy
- SKYFISH Spectral Karyotyping Flurorescence Insitu Hybridization
- TESE Testicular sperm extraction
- TET Tubal embryo transfer
- Th T-helper
- US Ultrasonography
- ZIFT Zygote intra-fallopian transfer

Assisted reproductive techniques (ART)

The first in vitro fertilization (IVF) pregnancy was ectopic and the first child , Louise Brown was conceived in a natural IVF cycle ***(Steptoe and Edwards ,1978)***

Assisted reproductive technologies (ART) encompass all techniques involving direct manipulation of oocytes outside the body. The first and still most common form of ART is in vitro fertilization (IVF), but there are other related techniques within ART ***(Speroff and Fritz, 2005)***.

IVF: *In Vitro Fertilization*: extraction of oocytes, fertilization in the laboratory, transcervical transfer of embryos into the uterus.

GIFT: *Gamete Intrafallopian Transfer*: the placement of oocytes and sperm into the fallopian tube.

ZIFT: *Zygote Intrafallopian Transfer*: the placement of fertilized oocytes into the fallopian tube.

TET: *Tubal Embryo Transfer*: the placement of cleaving embryos into the fallopian tube.

POST: *Peritoneal Oocyte and Sperm Transfer*: the placement of oocytes and sperm into the pelvic cavity.

In addition, techniques of sperm retrieval and sperm injection are now part of the assisted reproductive technology

ICSI: Intracytoplasmic Sperm Injection (of a single spermatozoon).

TESE: Testicular Sperm Extraction.

MESA: Microsurgical Epididymal Sperm Aspiration.

Components:

A typical ART cycle has the following main components: ***(Yao and Schust, 2002)***:

- Downregulation using gonadotropin releasing hormone (GnRH) agonist.
- Controlled ovarian hyperstimulation (COH) using gonadotropins with follicular monitoring using transvaginal ultrasound and assessment of serum estradiol level.
- Oocyte maturation using hCG.
- Oocyte retrieval.
- Fertilization by IVF, ICSI or GIFT.
- In vitro embryo culture (except in GIFT).
- Luteal support or endometrial preparation using progesterone supplementation.
- Transfer of fresh embryos with possible cryopreservation of excess embryos.
- First trimester pregnancy monitoring.

Patient Selection for IVF:

The initial experience with in vitro fertilization involved women with tubal disease, but early in the 1980s, the treatment was extended to individuals with male factor infertility, unexplained infertility, endometriosis, and immunologic causes for infertility ***(Sauer et al., 1955)***.

IVF is the treatment of choice for patients with severe distal tubal disease, proximal obstruction (especially after 6 months have elapsed following cannulation or balloon tuboplasty), and for patients who have failed to achieve pregnancy within 2 years after tubal surgery or when tubal obstruction persists after surgery. Large hydrosalpinges can reduce the success rate with IVF, and removal is recommended prior to treatment ***(Strandell et al., 1994)***.

Whereas IVF can overcome a number of the barriers to fertility, it suffers the same limitation as does in vivo fertilization when it comes to age. Beyond the simple effect of age on oocyte quality, there also is a negative influence on IVF success from decreased ovarian responsiveness ***(speroff et al., 1999).***

I. CLOMIPHENE CITRATE (CC): (Clomid)

CHEMICAL NATURE:

It is an orally active non steroidal agent chemically related to diethylstilbestrol. Chemical name is 2-[p-(2-chloro-l,2-diphenyl-vinyl) phenoxy] triethylamine dihydrogen citrate. Clomiphene is a racemic mixture of its two stereochemical isomers, originally described as the cis and trans-isomers ***(Speroff et al.,1999).***

MECHANISM OF ACTION:

Being similar to estrogen, it binds to estrogen receptors (nuclear receptors) for long periods of time, for weeks rather than hours, depleting receptor concentrations interfering with receptor recycling ***(Clark et al 1982).*** It modifies hypothalamic activity by affecting the concentration of intracellular estrogen receptors. So the hypothalamic-pituitary axis will be blind to endogenous level of estrogen so GnRH secretion is activated (negative feedback is diminished),

leading to FSH and LH pulse frequency increases in women with normal cycles (but not amplitude). On the other hand, administrafion of CC in anovulatory women will cause an increase in gonadotropin pulse amplitude ***(Speroff et al., 2005)*.**

DOSE AND ADMINISTRATION:

Standard Therapy

CC is administered orally, typically starting on the third to day after the onset of spontaneous or progestin-induced menstruation ovulation rates, conception rates, and pregnancy outcome similar regardless whether treatment begins on cycle day 3, 4, or 5 ***(Wu CH,and Winkel ,1989)***.

Treatment typically begins with a single 50-mg daily for 5 consecutive days, increasing by 50-mg increments in subsequent cycles until ovulation is induced effective dose of CC ranges from 50 mg/day to 250 mg although doses in excess of 100 mg/day are not approved the Food and Drug Administration (FDA). Lower dose (e.g., 12.5 mg/day to 25 mg/day) deserve a trial in who