MINIMAL STIMULATION PROTOCOL VERSUS GONADOTROPINS STIMULATION FOR OVULATION - INDUCTION IN CLOMIPHENE CITRATE RESISTANT PATIENTS

Thesis

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List Of Abbreviation

AIs	Aromatase inhibitors
ART	Assisted reproductive technology
BBT	Basal body temperature
BMI	Body mass index
CC	Clomiphene citrate
CCCT	Clomiphene citrate challenge test
COH	Controlled ovarian hyperstimulation
CT	Computerized tomography
DEX	Dexamethasone
DHEAS	Dehydroepiandrosterone sulfate
DVT	Deep venous thrombosis
E2	Estradiol
FSH	Follicle- stimulating hormone
GH	Growth hormone
GnRH-a	Gonadotropin releasing hormone agonist
HCG	Human chorionic gonadotropin
HDL	High density lipoprotein
HMG	Human menopausal gonadotropin
HSG	Hysterosalpingography
IGF	Insulin growth factor
IM	Intramuscular
IUI	Intrauterine insemination
IVF-ET	In vitro fertilization-embryo transfer
LDL	Low-density lipoprotein

LH	Luteinising hormone
LPD	Luteal phase defect
LUF	Luteinized unruptured follicle syndrome
MRI	Magnatic resonance image
MSP	Minimal stimulation protocol
NS	Non significant
OHSS	Ovarian hyperstimulation syndrome
PCOS	Polycystic ovary syndrome
$PGF_{2\alpha}$	prostaglandin $F_{2\alpha}$
POF	Premature ovarian failure
PRL	Prolactin
PRs	Pregnancy rates
rFSH	Recombinant follicle-stimulating hormone
S	Significant
SHBG	Sex hormone binding globulin
SSRIs	Selective serotonin re-uptake inhibitors
TSH	Thyroid stimulating hormone
Us	Ultrasound
WHO	World health organization

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INTRODUCTION

Infertility is defined as the inability to establish pregnancy within a specific period of time; usually 1 year ***(Sciarra, 1994)*** with unprotected intercourse. It affects nearly 10-15% of couples which makes it an important component of practices of many physicians.

Failure to ovulate is the major problem in nearly 40% of women with infertility ***(Stubi Field, 1984)*** and is observed by folliculometry and serum progesterone in the 21st day of menstrual cycle.

Clomiphene citrate acts by blocking negative feed back of endogenous estrogen at the level of hypothalamus and pituitary, promoting an increase pulsatile release of LH and FSH ***(Kettle et al., 1993)***.

However, 20-25 % of women are resistant to Clomiphene citrate and do not ovulate. In addition there is a discrepancy between ovulation and conception rates during Clomiphene citrate treatment and a higher than expected incidence of miscarriage in conception cycle ***(Frank et al., 1985)***.

Low ovarian response may be a result of diminished ovarian reserve, which can be due to advanced age, prior

ovarian surgery and environmental and genetic factors. Also other factors such as endometriosis and pelvic infection may impair ovarian function. However in most patients, low ovarian response remains unexplained ***(Mitwally and Casper, 2001)***.

Clomiphene citrate is the treatment of choice for the anovulatory infertile women with polycystic ovarian syndrome, but only 75% of patient responds positively ***(Poslon et al., 1989)***. Clomiphene citrate resistance was defined as failure to ovulate to a dose schedule of 200 mg / day for five days ***(George et al., 2003)***.

Ovulation induction with gonadotropins is the standard treatment for Clomiphene citrate resistance women ***(Polson et al., 1995)***; however this is expensive and has added risks of ovarian hyperstimulation and multiple pregnancies.

Recently, a new regimen of Clomiphene citrate with gonadotropin was used in ovulation induction with ***(Dhaliwal et al., 2002)*** or without ***(Houmard et al., 2002)*** intra-uterine insemination and super ovulation in invitro fertilization with or without intra-cytoplasmic sperm injection ***(Sophonsritsuk et al., 2005)***. This was termed minimal stimulation protocol. Minimal stimulation protocol is given in the form of Clomiphene citrate started between 3^{rd} – 7^{th} day of the cycle, human menopausal gonadotropin given in the 9^{th} day of the

cycle, and HCG injection on the day of follicular maturation (dominant follicule $\geq$ 18 mm).

Minimal stimulation protocol appears to be a cost effective method in ovulation - induction requiring less monitoring having less side effects and leading to satisfactory pregnancy results in unexplained infertility undergoing intrauterine insemination ***(Dhaliwal et al., 2002)*** and in invitro fertilization ***(Hurst et al., 2002).***

So this study was performed to test the potential benefits of this new induction protocol in cases of Clomiphene citrate resistance.

AIM OF THE WORK

This study was performed to compare between minimal stimulation protocol and gonadotropins in inducing ovulation in Clomiphene citrate resistant patients

INFERTILITY

Definition:

Infertility is defined as inability to establish pregnancy within a specific period of time; usually one year with unprotected intercourse ***(Sciarra, 1994)***. In contrast to sterility, infertility is not an irreversible state. The term primary infertility is applied to the couple who has never achieved a pregnancy; secondary infertility implies that at least one previous conception has taken place ***(Rein and Barbieri, 1999)***.

Possible Etiologies:

These include:

1. Ovarian and endocrine factors.
2. Uterine factor.
3. Peritoneal factors.
4. Tubal factor.
5. Immune factors.
6. Cervical factors.
7. Male factor.
8. Embryological factors.
9. Infection.

(Mishell et al., 1997).

While the factors and problems listed above can be identified by medical tests, a wide variety of other factors may be affecting fertility. As example, people with some genetic disorders (such as cystic fibrosis) are more likely to experience fertility problems. Several lifestyle factors, general health and chemical exposure issues can affect the ability to conceive particularly smoking, obesity and stress ***(Cahill and Wardle, 2002)***.

Evaluation of Infertile Couple:

(McClure and Thompson, 1997)

The approach in the infertile couple should begin with a detailed medical, sexual and social history followed by physical examination of both partners. The sequence of investigation should be ordered so that the simple, least invasive and most productive tests are completed first.

Evaluation of male infertility:

Diagnostic test for male factors:

1. ***Semen analysis:***
    - Sperm variables (density, motility, morphology):
    - Seminal fluid variables (volume, PH).
    - Other cells or bacteria (pus cells, round cells).

2. Sperm cell properties:

- Movement characteristics (video micrography).
- Membrane integrity (hyper 'osmotic swelling').
- Biochemical properties (acrosin concentration).

3. Sperm cell function:

- In vivo mucus penetration (postcoital test).
- In vitro mucus penetration.
- Fertilizing capacity (sperm-hamster egg penetration).

Table 1: Semen analysis: Reference values on at least two occasions.

Ejaculate volume	**1.5-5.0 ml**
pH	**> 7.2**
Sperm concentration	**> 20 million/ml**
Total sperm number	**> 40 million/ejaculate**
Percent motility	**> 50%**
Forward progression	**> 2 (scale 0-4)**
Normal morphology	**> 50% normal***
	> 30% normal**
	> 14% normal***
Sperm agglutination	**< 2 (scale 0-3)**
Viscosity	**< 3 (scale 0-4)**

* World Health Organization, 1987.
** World Health Organization, 1992.
***Kruger (Tygerberg) Strict Criteria, World Health Organization, 1999.

Evaluation of female infertility:

Medical History:

Important points in it:

1. Sexual dysfunction: Dyspareunia and Vaginismus, coital frequency, orgasm.
2. Endocrine: Menstrual pattern, hirsutism, Acne, oily skin, weight changes, eating disorders, galactorrhea and thyroid symptoms.
3. Uterine and tubal, pelvic or abdominal surgery.
4. Pelvic infection, pelvic pain, dysmenorrhea or sexually transmitted diseases.
5. Cervical factor: Mucous secretion, conization, cautarization.
6. Ovulation cascade: Dysmenorrhea.
7. Previous obstetric history: Pregnancy loss, Puerperal sepsis.
8. Contraception: Hormonal, intrauterine contraceptive device.

Surgical history:

The surgical history should focus on the pelvis because any surgery on the reproductive organs, bowel, or bladder can cause pelvic inflammation, adhesions, and tubal damage.

Physical examination:

Once the history is taken the patient should be examined. This examination should cover all the systems with particular attention to the reproductive system. The height and weight are