Role of Letrozole versus Clomiphene Citrate for Ovulation Induction in Infertile Women

Thesis
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By
Nahla Ibrahim El-Awady (M.B.B.Ch)
Resident of Obstetrics and Gynecology
Maadi Armed Forces Medical Compound

Supervisors

Prof. Dr. Shrief Mohammed Habib
Professor of Obstetrics and Gynecology
Faculty of Medicine - Ain Shams University

Dr. Mohammed Hussain Mostafa
Lecturer of Obstetrics and Gynecology
Faculty of Medicine - Ain Shams University

Faculty of Medicine
Ain Shams University
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بسم الله الرحمن الرحيم

"قَالُوا سُبْحَانَكَ لاَ عِلْمَ لَنَا
إِلاَّ مَا عَلَّمْتَنَا إِنَّكَ أَنتَ الْعَلِيمُ الْحَكِيمُ"

صدق الله العظيم

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List of Abbreviations

17b-HSD	17b-hydroxysteroid dehydrogenase	LPD	Luteal Phase Defect
ACTH	Adrenocorticotropic Hormone	LOD	Laparoscopic Ovarian Drilling
AES	Androgen Excess Society	MFO	Multifollicular Ovary
AFS	American Fertility Society	MPA	Medroxyprogesterone Acetate
AIs	Aromatase Inhibitors	NCEP	National Cholesterol Education Program
ART	Assisted Reproduction Techniques	NETA	Norethindrone Acetate
ASRM	American Society for Reproductive Medicine	NGF	Nerve Growth Factor.
BBT	Basal body temperature	NICHD	National Institute Of Child Health And Human Development
BMD	Bone Mineral Density	PCOM	Polycystic Ovary Syndrome - Multicystic
BMI	Body Mass Index	PCOS	Polycystic Ovary Syndrome
CA125	Cancer Antigen 125	PCT	Postcoital Test
CC	Clomiphene Citrate	PGE2	Prostaglandin E2
CI	Confidence Interval	PGF2a	Prostaglandin F2a
COCs	Combination Oral Contraceptives	PP14	Placental Protein 14
COH	Controlled Ovarian Hyper stimulation	PSN	Presacral Neurectomy
COX-	Cyclooxygenase Isoenzymes 1 / 2	RANTES	Regulated On Activation, Normal T-Cell Expressed And Secreted
CPP	Chronic Pelvic Pain	RCOG	Royal College Of Obstetrician And Gynecologist
DMPA	Depot Medroxyprogesterone Acetate	SART	Society For Assisted Reproductive Technology Registry
E1	Estrone	SHBG	Sex Hormone Binding Globulin
E2	Estradiol	SPRMs	Selective Progesterone-Receptor Modulators
EDCs	Endocrine Disrupting Chemicals	TCDD	2,3,7,8 Tetrachlorodibenzo-P-Dioxin
EGF	Epidermal Growth Factor	TNFα	Tumor Necrosis Factor A
ESHRE	European Society For Human Reproduction And Embryology	TVS	Transvaginal
FSH	Follicle-Stimulating Hormone	VEGF	Vascular Endothelial Growth Factor
GIFT	Gamete intra-fallopian transfer	VLDL	Very Low Density Lipoprotein
HDL	High Density Lipoprotein	WHO	World Health Organization
HFEA	Human Fertilization Embryology Authority	ZIFT	Zygote Intra-fallopian Transfer
HOMP	High-Order Multiple Pregnancies		
ICAM-*1*	Intercellular Adhesion Molecule-1		
ICSI	Intra Cytoplasmic Sperm Injection		
IGF	Insulin-Like Growth Factors		
IGF	Insulin Like Growth Factor		
IL-1	Interleukin-1		
IL-6	Interleukin-6		
IUD	Intrauterine Device		
IUI	Intrauterine Insemination		
17b-HSD	17b-hydroxysteroid dehydrogenase		
IVF	In Vitro Fertilization		
LH	Luteinizing Hormone		

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INTRODUCTION

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AIM OF THE WORK

Introduction

Infertility is defined as failure to achieve clinical pregnancy after 12 months or more of regular unprotected sexual intercourse **(Zegers-Hochschild et al., 2009)**. Ovulation dysfunction represents one of the most common problems in couples presenting for infertility evaluation **(Branigan, 2003).**

Interational surveys indicate that 11% of nulliparous married women younger than 29 years have nonovulatory infertility and that rate increases to 27% of nulliparous married women aged 40 to 44 years **(Chandra A et al., 2005)**. Ovulatory dysfunction is one of the major causes of infertility, affecting 25% of couples with infertility. One of the leading causes of ovulatory dysfunction is polycystic ovarian syndrome (PCOS) ***(*Kamath and Goerge, 2011*)***, which is heralded as one of the most common endocrine disorders occurring in women **(Lujan et al, 2008)**.

On the other hand, Endometriosis plays an important role in female factor infertility**.** Some women with endometriosis experience painful symptoms and/or infertility, while others have no symptoms at all (**Eskenazi et al., 2001, Meuleman, et al., 2009).** The exact prevalence of endometriosis is unknown but estimates range from 2 to 10% within the general female population but up to 50% in infertile women (**ESHRE, 2013)**.

Infertility in many couples has multiple etiologies, however, in approximately 25% of couples, they have no identifiable cause for their subfertility following a routine evaluation and the infertility is labelled unexplained **(Kamath & Bhattacharya, 2012).**

A variety of medications can be used to induce ovulation in women with ovulatory dysfunction & the empiric treatment of women with unexplained infertility (**A Propst & Bates, 2012**).

The most common initial ovulation induction medication is clomiphene citrate (CC), however, it is not equally successful in all situations (**Badawy et al, 2007**). Failure to respond to clomiphene citrate occurs in up to 20% of cases which may require the use of injectable gonadotropines as a second line (**Mitwally and Casper, 2001**). The drawbacks of this approach include its high cost, the potentially life threatening ovarian hyperstimulation syndrome and the significant risk of high order multiple gestations (**Holzer et al., 2006**).

In addition, studies have shown a significant difference between rate of ovulation and pregnancy and a higher abortion rate in patients undergoing clomiphene citrate therapy. Thus, the use of a simple oral drug, as a safe alternative to Clomiphen citrate, can produce a new horizon in ovulation induction (**Kamath and George, 2011**).

Letrozole is a newly designed selective aromatase inhibitor, which can be used to induce ovulation in infertile women (**F.Sohrabvand et al., 2006**).

Letrozole is a third generation selective aromatase inhibitor (AI), which is indicated for the treatment of postmenopausal women with hormone-receptor-positive or unknown breast cancer (**Holzer et al., 2006**). It is rapidly absorbed from the gastrointestinal tract and excreted by the kidney. The elimination half-life of letrozole is about 2 days (**Mitwally and Casper, 2001**).

AIs prevent the Androgen-Estrogen conversion and therefore interfere with the negative feedback at the level of the hypothalamus-pituitary. The increased pituitary gonadotropin output will in turn stimulate the ovaries (**Mitwally et al., 2005)**. Also, they act locally in the ovary to increase follicular sensitivity to FSH. This may result from accumulation of intraovarian androgens, since conversion of androgen substrate to estrogen is blocked. Other studies support a stimulatory role for androgens in early follicular growth (**Al-Omari et al., 2001; Metawie, 2001)**.

In some studies, letrozole in contrast to C.C is better as it increases endometrial thickness by up regulation of estrogen receptors, so it increases pregnancy rate and also it decreases incidence of multiple pregnancy **(Fatemi et al., 2003; Mitwally et al., 2005)**. AIs is reported to be effective in inducing ovulation, increasing pregnancy rate, improving uterine environment and endometrial development with favorable cervical mucus **(Mitwally et al., 2005)**.

Aim of the work

- To evaluate the efficacy of Letrozole in ovulation induction in infertile women.
- Comparing the outcomes of Letrozole with those of clomiphene citrate.

REVIEW OF LITERATURE

UNEXPLAINED INFERTILITY

Unexplained infertility, sometimes also called idiopathic infertility, refers to failure to conceive in a couple for whom no definitive cause for infertility can be found. Usually, the duration of infertility is more than two years. The incidence of unexplained infertility varies in different studies but is usually 10-20 **% (Aboulghar et al., 2002).**

The basic infertility work-up includes demonstration of:

1) Ovulation and normal luteal phase.

2) Patent fallopian tubes.

3) Normal findings in semen analysis.

(WHO; Guzick et al. 1994; ASRM 2006, Alexander & A Dorkas,2008).

Speculations on possible underlying causes

Several theories have been tendered on the aetiology of unexplained infertility (Table 1). Diminished ovarian reserve, as shown by elevated serum follicle-stimulating hormone (FSH) level, may be one cause **(Cahill et al. 1995; Blacker et al. 1997; Luborsky et al. 2000)** and can result in alterations to other hormonal levels. Both the serum estradiol levels in follicular phase and the E2/P ratio have been shown to be elevated in women with unexplained infertility, suggesting altered folliculogenesis **(Blacker et al. 1997; Leach et al. 1997;Z Godinjak&N Bilalovic,2014)** and an absent midcycle elevation of the hormone prolactin, which is present in fertile women **(Subramanian et al. 1997**).

Another possible explanation is an impaired luteal phase, with a shorter luteal phase or a decreased peak serum progesterone level **(Li et al. 1990; Guzick et al. 1994; Blacker et al. 1997; Leach et al. 1997)**. Impaired luteal phase has been demonstrated in about 30% of women with unexplained infertility. Among women aged 40-45 years, the rate of impaired luteal phase is higher than among women aged 20-29, as is also the incidence of unexplained infertility (**Rodin et al. 1994; Miller et al. 1999)**. Both increased and decreased follicular LH-pulse frequency and a lower FSH/LH ratio or decreased midfollicular FSH have been postulated to induce impaired luteal phase, which may primarily be due to a functional imbalance in the hypothalamus **(Nakajima and Gibson 1991**).

Besides hormonal factors, gamete dysfunction may contribute to unexplained infertility. Altered folliculogenesis, impaired oocyte maturation, reduced oocyte quality and defects in gamete interaction have all been suggested (**Gabrielsen et al.**

1996; Blacker et al. 1997; Omland et al. 2001). One theory suggests that a failure in the natural ovum pickup mechanism by the fallopian tube may occur in these women, although this is difficult to verify (**Ahmad-Thabet 2000**). The presence of sperm-immobilizing antibodies is associated with immunological infertility in women with unexplained infertility (**H. Shibahara et al., 2009).**

Abnormal uterine artery blood flow might be associated with unexplained infertility (**Goswamy et al. 1988; Kupesic and Kurjak 1993; Steer et al., 1994)**. Increased uterine artery impedance in midluteal phase or an abnormal flow in spiral arteries would impair the implantation process, and have been suggested as possible mechanisms for infertility **(Kupesic and Kurjak 1993; Steer et al., 1994).**

Theory/Clinical finding	Mechanism	Study
Pituitary and/or follicular dysfunction		
FSH elevation	diminished ovarian reserve	Blacker et al. 1997
LH fall	impaired follicular development	Omland et al. 2001
poor ovulation	impaired/ short luteal phase	Rodin et al. 1994; Blacker et al. 1997
oestrogen elevation	altered folliculogenesis	Blacker et al. 1997; Leach et al. 1997
abnormal prolactin	absent mid-cycle prolactin rise and impaired oocyte development	Subramanian et al. 1997
pituitary-ovarian dysfunction	impaired follicular development	Cahill et al. 1995
impaired follicular development	impaired ovulation and increased risk of LUF	Blacker et al. 1997 Omland et al. 1998
Gamete dysfunction		
Oocyte dysfunction		
decreased oocyte function	reduced oocyte quality	Blacker et al. 1997; Omland et al. 2001
impaired oocyte transport	impaired ovum pick-up and impaired tubal transport	Ahmad-Thabet 2000 Omland et al. 1998
impaired oocyte-sperm interaction	impaired fertilization	Blacker et al. 1997; Omland et al. 2001
Sperm dysfunction		
impaired penetration of cervical mucus	impaired fertilization	Hull et al. 1998
impaired penetration of zona pellucida	impaired fertilization	Takeuchi et al. 2000; Hull et al. 1998
impaired penetration of ooplasmic membrane	impaired fertilization	Takeuchi et al. 2000; Hull et al. 1998
Alterations in endometrial function		
subclinical infection	impaired implantation	Kundsin et al. 1987
suboptimal expression of integrins and pinopods	impaired endometrial development and switch in the window of implantation	Omland et al. 2001 Lessey et al. 1995
Immunological factors		
elevated concentrations of: ovarian antibodies	ovarian failure	Luborsky et al. 2000
anti-spermatozoal antibodies	impaired fertilization	Luborsky et al. 2000
anti-cardiolipin antibodies	increased uterine artery resistance	Battaglia et al. 1998

Table (1): Theories about the etiology of unexplained infertility (Isaksson, 2002).

Management of unexplained infertility:

The Practice Committee of the American Society for Reproductive Medicine (**ASRM**) has published guidelines for a standard infertility evaluation **(Alexander Q & Dorkas, 2008**). It includes a semen analysis, assessment of ovulation, a hysterosalpingogram, and, if indicated, tests for ovarian reserve and laparoscopy. When the results of a standard infertility evaluation are normal, practitioners assign a diagnosis of unexplained infertility. Although estimates vary, the likelihood that all such test results for an infertile couple are normal (ie, that the couple has unexplained infertility) is approximately 15% to 30% **(ASRM, 2006**).

Assessment of Male Infertility:

Male factor infertility is the only cause of infertility in approximately 30% of couples and a contributing factor in another 20% to 30% (**Kolettis, 2003).** Assessment of the infertile couple includes evaluation of the male partner by history, examination, and semen analysis **(Alexander Q & Dorkas, 2008**).

Important elements of the history include prior paternity, a history of cryptorchidism, medical and surgical history, sexual dysfunction, and any use of medications, tobacco, alcohol, or illicit drugs. On the physical examination, testicular abnormalities such as a varicocele or absence of the vas deferens can be detected **(Alexander Q & Dorkas, 2008)**.

If the semen analysis is abnormal, it should be repeated after at least 1 month by a laboratory that adheres to World Health Organization (WHO) guidelines. (Table 2).

PARAMETER	WHO 1999	WHO 2010
Volume	2 ML	1.5 ML
Concentration	20 MILLION/ML	15 MILLION/ML
Progressive Motility	50%	32%
Normal Forms	14%	4%

Table (2): World Health Organization criteria for a normal semen analysis (Cooper, TG et al 2010).

Assessment of Ovulation

Ovulatory defects are present in 40% of infertile women and in approximately 15% of couples with infertility (**ASRM, 2006).** Often a defect in ovulatory function manifests itself in menstrual disturbances and can be identified by history in the majority of women. A patient with menstrual abnormalities should be investigated for underlying causes such as polycystic ovarian syndrome, thyroid disease, hyperprolactinemia, and hypothalamic causes secondary to weight changes. Eumenorrhea (normal menstrual cycles by history) is a highly accurate marker of

ovulation and anovulatory levels of serum progesterone (> 3 ng/mL) are found in only a very small minority of eumenorrheic patients (**Malcolm & Cumming, 2003).**

Methods used to evaluate ovulation include:

- The presence of regular menses and moliminal symptoms before menses is a sign that the woman is ovulatory. The luteal phase following ovulation to menses is typically 14 days, regardless of the length of time between menses. Ovulation typically occurs on day 10 of a 24-day menstrual cycle, day 14 of a 28-day menstrual cycle, and day 21 of a 35-day menstrual cycle **(A Propst & Bates, 2012).**

- Basal body temperature (BBT) recordings:
  An inexpensive method of detecting ovulation (**ASRM, 2006)**. The body temperature will increase slightly after ovulation in response to an increase in endogenous progesterone. Although BBT recordings are the least costly tool in a reliable patient, they are difficult to interpret and often frustrating for the patient **(Alexander Q & Dorkas, 2008)**.

- Urinary luteinizing hormone (LH) ovulation predictor kits:
  It detects the endogenous LH surge that occurs 36 to 48 hours before ovulation. This method seems to be an easy and reliable method that patients are compliant with. Testing should begin 4 days before expected ovulation, based on the cycle length **(ASRM, 2008).** They are useful for women who do not have very long menstrual cycles. Digital and nondigital ovulation predictor kits are available. The digital kits are more expensive but easier to interpret and are preferred by volunteers over the nondigital kits (**Tomlinson et al., 2008).** An additional advantage, they can be used by couples to appropriately time intercourse **(Alexander Q & Dorkas, 2008)**. This finding raises the possibility that a subset of unexplained infertility may be caused by poorly timed intercourse **(A Propst & Bates, 2012).**

- Mid luteal serum progesterone testing:
  Mid luteal progesterone levels are measured around day 21 in women with regular (28 day) cycles. However, they are often poorly timed if they are drawn on cycle day 21 in women with irregular menses. In such women it is better to use an ovulation kit and measure the progesterone levels 7 to 8 days after the LH surge is detected. Serum progesterone levels higher than 3 ng/mL suggest that ovulation has occurred and levels higher than 10 ng/mL are optimum **(Alexander Q & Dorkas, 2008)**.

- Endometrial biopsy
  To assess for secretory endometrial development. (***Coutifaris C et al., 2004***).