LETROZOLE VERSUS CLOMIPHENE CITRATE FOR OVULATION INDUCTION IN WOMEN WITH POLYCYSTIC OVARY SYNDROME

Thesis
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List of Abbreviations

ACTH	Adreno Cortico Trophic Hormone
AIs	Aromatase inhibitors
AMH	AntiMullerian hormone
ART's	Assisted reproductive techniques
BMI	Body Mass Index
CC	Clomiphene citrate
COH	Controlled ovarian hyperstimulation
COH-IUI	Controlled ovarian hyperstimulation and intrauterine insemination
DHEA	Dehydroepiandrosterone
ER	Estrogen receptors
ESHRE	European society for human reproduction and embryology
FSH	Follicle stimulating hormone
GnRhA	Gonadotropin releasing hormone analogues
hCG	Human chorionic gonadotropins
hMG	Human menapausal gonadotropin
HSG	Hystero salpingography
ICSI	Intra cytoplasmic sperm injection
IGF-1	Insulin like Growth Factor 1
IU	International unit
IUI	Intrauterine insemination
IVF	In vitro fertilization
IVF-ET	In vitro fertilization and embryo transfer
LH	Luteinizing hormone
OHSS	Ovarian Hyperstimulation Syndrome

PCOS	Polycystic Ovary Syndrome
SD	Standerd Deviation
TSH	Thyroid stimulating hormone
WHO	World health organization

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ABSTRACT

Background: The aim of the current study was to compare the efficacy of Letrozole and Clomiphene citrate, as a first line treatment for induction of ovulation in cases of polycystic ovary syndrome.

Methods: this study was randomized comparative study involving (80) Egyptian women were diagnosed as having Polycystic ovary syndrome attending Ain Shams University Maternity Hospital (Infertility out-patient clinic). During the initial visit, anthropometric measurements and baseline investigations were performed. Patients were randomized to 5.0 mg Letrozole daily (40 Patients) or 100 mg Clomiphene citrate (40 Patients) from the third until the eighth day of menstruation. Serial transvaginal scans were performed to see the dominant follicles, endometrial thickness and number of follicles. Transvaginal scans were performed serially to look for evidence of ovulation.

Results: The subjects were homogenously distributed. The difference between Letrozole and Clomiphene citrate for ovulation rate was 35 (87.5%) versus 24 (60%). Patients taking Letrozole exhibited a mean endometrial thickness (ET) at mid cycle of menses (Day 11-D14) of 9.2 mm (SD 2.37) versus 8.4 mm (SD 1.61) for patients taking Clomiphene citrate, and these differences were statistically significant ($P < 0.0001$). In terms of pregnancy rate, Letrozole facilitated pregnancy induction in 15 patients (37.5%) versus 6 patients (15%) for Clomiphene citrate, this was statistically significant ($P = 0.02$). More dominant follicles exhibiting a mono-follicular morphology were observed in patients treated with Letrozole compared to patients treated with Clomiphene citrate, with a mono-follicular dominant follicle observed in 18 (45%) versus 11 (27.5%) patients, respectively.

Conclusion: Letrozole provided a more efficient stimulation compared to Clomiphene citrate in terms of ovulation induction, thickening of the endometrial lining and achievement of a successful pregnancy.

Keywords: Polycystic Ovarian Syndrome; Ovulation Induction; Clomiphene Citrate; Letrozole.

Introduction

Ovulation is the central event in the reproduction cycle. Anovulatory dysfunction is a common problem and is responsible for about 40% of female infertility. Polycystic ovarian syndrome (PCOS) with abnormalities in the metabolism of androgens and estrogen and in the control of androgen production, remains one of its leading causes **(Badawy, et al., 2009).**

Using modified Rotterdam criteria to diagnose the polycystic ovary syndrome. Accordingly, all participating women had ovulatory dysfunction combined with hyperandrogenism (on the basis of hirsutism or an elevated testosterone level), polycystic ovaries (defined by an increased number of small antral follicles [≥12 follicles that were <10 mm in diameter] or an increased individual ovarian volume [>10 cm3] in one ovary), or both **(Legro, et al., 2014).**

Using the modified Rotterdam criteria a clinical diagnosis of Polycystic ovarian syndrome (PCOS) is easily reached and most often treatment can be initiated following a few basic investigations and exclusion of the male factor problem **(Hum Reprod, 2008).**

The polycystic ovary syndrome, which is diagnosed on the basis of hyperandrogenism, oligo-ovulation with associated oligomenorrhea, and polycystic ovaries on ultrasonography, affects 5 to 10% of reproductive age women and is the most common cause of anovulatory infertility **(Legro, et al., 2010).**

For more than four decades, clomiphene citrate has been the first line therapy for induction of ovulation in women with anovulatory infertility and for super-ovulation in couples with unexplained infertility. It is orally administered, available and is inexpensive **(Hum Reprod, 2009).**

Because of its long half-life (two weeks), clomiphene citrate accumulates in the body and may have a negative effect on the quality and quantity of cervical mucus, endometrial development, which may cause implantation failure, luteal phase defects (LPD) and significant

thinning of the endometrium. Clomiphene citrate resistance together with side effects like multi-follicular development and cyst formation are areas of concern. The desire for an effective alternative persists **(Kamath, et al., 2010).**

Clomiphene has drawbacks, including its overall poor efficacy , a relatively high multiple-pregnancy rate (3 to 8%) as compared with the rate associated with unassisted conception (<1%), and an undesirable side-effect profile, including mood changes and hot flushes. Failure either to ovulate (Clomiphene resistance), **(Legro, et al., 2007),** or to conceive with ovulation (Clomiphene failure) often results in the use of more expensive treatment options for infertility that may be associated with higher multiple-pregnancy rates and an increased risk of the ovarian hyper-stimulation syndrome **(Kamphuis, et al., 2014).**

The development of effective, simple, and safe treatments for infertility is an important public health goal **(Badawy, et al., 2008).**

In contrast to clomiphene, letrozole at the customary dose of 2.5 mg elicits a mono-follicular response and does not adversely affect either the endometrium or cervical mucus, due to an absence of a peripheral estrogen receptor blockage **(Polyzos, et al., 2009).**

The often asked question, whether it is better than clomiphene citrate as a first line treatment option remains unanswered and a clear answer would have important clinical implications for infertility specialists **(Kamath & George, 2011).**

Letrozole has now been in use as an ovulation induction agent for more than a decade. Even though emerging evidence suggests that it is an effective ovulation induction agent, comparable if not better than clomiphene **(Kamath & George, 2011).**

Aromatase inhibitors, which block estrogen synthesis, directly affect hypothalamic–pituitary–ovarian function and theoretically might increase pregnancy rates **(Casper & Mitwally, 2006)**.

Potential advantages of aromatase inhibitors over selective estrogen receptor modulators include a more physiologic hormonal stimulation of

the endometrium, a lower multiple-pregnancy rate through single-follicle recruitment, a better side-effect profile with fewer vasomotor and mood symptoms, and more rapid clearance, thus reducing the chances of peri-conceptional exposure **(Casper & Mitwally, 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 **(Bayar, et al., 2006).**

Letrozole is rapidly absorbed from the gastrointestinal tract (GIT) and excreted by the kidney. The elimination half-life of letrozole is about 2 days **(Al-Omari, et al., 2001).**

Aim of the work

The aim of the current study is to compare the efficacy of clomiphene citrate and letrozole, as a first line treatment for induction of ovulation in cases of polycystic ovary syndrome.

Patients and Methods

Study Site
Ain Shams University Maternity Hospital Infertility out-patient clinic.

Study Design
This study will be a randomized comparative study.

Study Population
Women will be distributed into two groups.

Group (L)
This group will include forty (40) women with polycystic ovary syndrome will take letrozole 5 mg / day starting on day 3 till day 7 of the menstrual cycle.

Group (C)
This group will include forty (40) women with polycystic ovary syndrome will take clomiphene citrate 100 mg / day starting on day 3 till day 7 of the menstrual cycle.

RESEARCH HYPOTHESIS

In women with polycystic ovary syndrome and undergoing induction of ovulation Letrozole may be effective as clomiphene citrate in induction of ovulation.

RESEARCH QUESTION

In women with polycystic ovary syndrome does letrozole effective as clomiphene citrate in induction of ovulation?

Inclusion Criteria:

1- Age: between 20-35 years.

2- Period of infertility more than one year (primary or secondary).

3- Diagnosis of (PCOS): Modified Rotterdam criteria will be used to diagnose the polycystic ovary syndrome which requires the presence of two out of the following three variables:

(1) Oligo- ovulation and/ or an ovulation**.**
(2) Clinical or biochemical signs of hyperandrogenism: hirsutism **(ESHRE/ASRM 2013)** or an elevated testosterone level **(LEGRO, 2010).**
(3) Polycystic ovaries (12 follicles that were <10mm in diameter) or an increased individual ovarian volume (> 10 cm) in one ovary or both.

4- No treatment was taken for induction of ovulation during the last 2 months prior to the inclusion in the study.

5- Serum level of FSH (< 10 mIU/mL) in the early follicular phase.

6- Two patent fallopian tubes and a normal uterine cavity will be documented by a recent (within 6 months) hysterosalpingography or laparoscopy.

7- Recent (within 3 months) semen analysis of the husband with normal semen parameters **(Rothmann, et al., 2013).**

Exclusion Criteria:
1- History of pelvic surgery.
2- Women with infertility factors other than polycystic ovary syndrome.

Methodology

This study will be conducted in Ain Shams University Maternity hospital (Infertility outpatient clinic).

After being approved by the medical ethics committee. the study will be randomized comparative study consisting of (80) Egyptian women will be diagnosed as having Polycystic ovary syndrome.

Women will be distributed into two groups with randomization sheet:

Group (L): (n=40) Letrozole **(Femara; Novartis, East Hanover, NJ)** will be given orally in a dose of 5 mg/day for 5 days starting from the third day of menstrual bleeding.