We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

6,300

Open access books available

172,000

International authors and editors

190M

Downloads

Our authors are among the

154

Countries delivered to

TOP 1%

most cited scientists

12.2%

Contributors from top 500 universities

WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com

Effect of Aromatase Inhibitors versus Clomiphene Citrate for Ovulation Induction in Infertile Women with Ovulatory Dysfunction (PCO)

Hassan S.O. Abduljabbar, Magda Hagraas and Rania Magadmy

Abstract

A RCT conducted to assess the efficacy of letrozole as an ovulation induction agent in infertile women, and to compare the effectiveness of letrozole with the current standard agent, clomiphene citrate given for three successive cycles on the induction of ovulation. Forty-five infertile women with anovulation included, the subjects were randomly divided into two groups; subjects were allocated to either CC (100) or letrozole (5 mg) daily—5 days starting on the third day of menses, for 3 months. On stimulation day 12 subjects, serum estradiol and transvaginal sonography to document the number of follicles was done. On stimulation day 21 subjects, serum progesterone and ultrasound for the thickness of endometrium was done. Participants were followed-up monthly. Results revealed that the mean number of follicles reaching >18 mm and endometrial thickness in the letrozole comparable to those receiving clomiphene citrate. Letrozole showed lower estradiol level compared to Clomiphene citrate ($P < 0.05$). Ovulation occurred in 84.4%, 78.1% in the letrozole and clomiphene citrate, respectively, and pregnancy rate is 18.8% in the letrozole group compared to 15% in the clomiphene citrate group. In conclusion, there was no significant increase in the number of follicles, endometrial thickness and pregnancy rate induced by letrozole compared with clomiphene citrate.

Keywords: infertility, anovulation, letrozole, clomiphene citrate

1. Introduction

Many controversies surround the treatment of infertile women with polycystic ovary syndrome (PCOS). Before any intervention is initiated, pre-conceptional counselling should be provided emphasizing the importance of lifestyle, especially weight reduction and exercise in overweight women, smoking, and alcohol consumption [1].

The recommended first-line treatment for ovulation induction remains the anti-estrogen clomiphene citrate (CC). Recommended second-line intervention, should CC fail to result in pregnancy, is either exogenous gonadotropins or laparoscopic ovarian surgery (LOS). The use of exogenous gonadotropins is associated with

increased chances for multiple pregnancies, and, therefore, intense monitoring of ovarian response is required. Laparoscopic ovarian surgery alone is usually effective in less than 50% of women, and additional ovulation induction medication is required under those circumstances. Recommended third-line treatment is in vitro fertilization (IVF) [1].

Aromatase inhibitors act not only by decreasing circulating levels of estrogen, but also by directly blocking local estrogen production in the breast tumor.

In premenopausal women, it causes an increase in gonadotropin secretion because of the reduced negative feedback of estrogen to the pituitary.

It also leads to ovarian stimulation, an increase in ovarian size, which may result in ovarian cysts in premenopausal females [2].

Kafy and Tulandi [3] found that letrozole in a dose of 5 mg daily for 5 days is associated with a thicker endometrium and a better pregnancy rate. It is as effective as gonadotropin but yet less expensive. Moreover, induction of ovulation with FSH injections is carried with relative risks of multiple gestations and severe ovarian hyperstimulation syndrome [4]. The benefit of the use of aromatase inhibitors has not yet been proven in large studies [5].

Gregoriou et al. [6] stated that ovarian stimulation with letrozole is associated with acceptable pregnancy rates compared with gonadotropin with significant less cost, risks, and patient inconvenience. In addition, suggests that clomiphene suppresses endometrial receptivity more than letrozole, and they concluded that letrozole might be an appropriate drug for ovulation induction. Fortunately, Badawy et al. [7] documented safety of letrozole and clomiphene citrate for both the mother and fetuses.

Yet, the benefit of the use of aromatase inhibitors has not yet been proven in large studies, and further randomized-controlled studies are warranted to define more clearly the efficacy and safety of letrozole in human reproduction.

2. Material and methods

Condition phase: Infertility due to anovulation.

Intervention: Patients were assigned to the letrozole or clomiphene citrate. Patients were enrolled and followed-up. The Ethics Committee of the King Abdulaziz University Hospital approved this study. Written informed consent was obtained from each patient.

Study design: Treatment, randomized, double-blind, efficacy study comparing letrozole versus clomifene citrate for ovulation induction.

Setting: A university teaching hospital.

Primary outcome measures: Ovulation rate, number of growing and mature follicles during treatment, serum estradiol level, serum progesterone level, endometrial thickness.

Secondary outcome measures: Hyperstimulation, miscarriage rate, multiple pregnancy rate, and ectopic pregnancy trial population: 44 infertile females were assigned to the study according to certain inclusion criteria.

Inclusion criteria

1. Age: 25–40, BMI < 30.
2. Infertility due to anovulation.

3. No recent (within 3 months) treatment for induction of ovulation.
4. Normal semen analysis.
5. Proven patency of at least one fallopian tube.
6. Had no other pelvic pathology.

Exclusion criteria

1. Inability to give informed consent
2. Hypersensitivity to letrozole or clomiphene citrate
3. Excess prolactin levels
4. Other causes of infertility
5. Absence of any inclusion criteria.

This double-blind randomized-controlled trial was conducted in 44 infertile patients attending the Department of Obstetrics and Gynecology, King Abdulaziz University Hospital, Jeddah over a period of 1 year. Forty-four infertile women, aged between 25 and 40 years with infertility for 2 years or more, of unprotected coitus without conception in patients who have never conceived before, because of anovulation related to PCOS, were recruited for study after obtaining informed consents from the couples. PCOS diagnosis required the presence of two of three criteria, i.e., oligomenorrhea and/or anovulation, clinical and biochemical signs of hyperandrogenism, and/or polycystic ovaries on ultrasound. Couples with any other significant subfertility factor in either of the partner detected by pre-recruitment investigations were not included in this study. The Ethics Committee of the King Abdulaziz University Hospital approved this study.

All patients were screened for the hormonal profile, including the follicle-stimulating hormone, luteinizing hormone, prolactin, thyroid-stimulating hormone, estradiol, a pelvic ultrasound for confirmation of polycystic changes in the ovary, hysterosalpingography to determine tubal patency, Semen analysis in the patient's partner to rule out malefactor.

Computer-assisted randomization was done and concealment was ensured. The candidates were randomly divided into two groups. Patients were allocated to either group (I), where patients received 5 mg of letrozole once daily (Femara[®], Novartis, Basel, Switzerland), or group (II), where patients received 100 mg of CC once daily (Clomid[®], Sanofi Aventis, France), for 5 days starting on day 3 of menses, for the first, second, and third month. Follow-up of ovulation and endometrial thickness was monitored by transvaginal ultrasonographic folliculometry by the same operator by the same observer. Timed intercourse was advised 24 h after measuring dominant follicle of >18 mm till 12 h post ovulation.

Subjects returned to the clinic on stimulation day 12 for blood sampling to analyze estradiol and were undergone transvaginal sonography to document on the number of follicles (Note: Stimulation day 1 equals the first day of study drug).

Blood sampling was repeated on stimulation day 21 for the analysis of serum progesterone. Ovulation was confirmed by a progesterone level 10 ng/mL. If the results of the progesterone test indicate that the patient has not ovulated, the subject was brought back 1–2 days later for a repeat progesterone test. Also, ultrasound for assessment of the thickness of the endometrium was done.

In ovulatory cycles, a pregnancy test was performed 3 days post missed period. Subjects with a positive pregnancy test were supplemented with micronized progesterone vaginally. Participants were evaluated for three courses of intervention.

Subjects may be allowed to continue for up to two additional treatment cycles if they failed to achieve clinical pregnancy in their first treatment cycle, and did not experience other mandatory withdrawal condition. A follow-up visit was arranged for each group every month at the second day of menstruation until 3 months after recruitment or at any time during the trial if the pregnancy was achieved.

2.1 Statistical analysis

The data were analyzed with the Statistical Program SPSS version 16. Descriptive statistics comprised the mean and standard deviation (SD), analytical statistics comprised the t-test to make comparisons between independent quantitative means, and the Anova test to make comparisons between the different groups. *P* value < 0.05 was significant. Pearson correlation was done between different parameters.

3. Results

Results obtained during the term of the project and data analysis. Patients were randomized so as, 24 women of mean age (30.2 ± 4.3) years received letrozole; whereas, 20 women of mean age (29.8 ± 4.7) years received clomiphene citrate. Group (I) had a body mass index of (28.2 ± 2.1); whereas, group (II) had a body mass index of (27.4 ± 2.2). There was no significant difference between the groups as regard age or body mass index (*P* > 0.05) (**Table 1**) and the baseline hormonal profiles of the two groups (**Table 2**).

There was no significant statistical difference between letrozole group and the clomiphene citrate group concerning the following hormones: serum FSH day 2 (5.5 ± 1.9 versus 5.9 ± 1.5 IU/ml), serum LH day 2 (4.1 ± 2.4 versus 4.4 ± 2.3 mIU/ml), and serum E2 day 2 (53.1 ± 11.4 versus 50.9 ± 15 pmol/L).

	Age	BMI
Letrozole (n = 24)	30.2 ± 4.3	28.2 ± 2.1
Clomiphene citrate (n = 20)	29.8 ± 4.7	27.4 ± 2.2
Significance	NS	NS

Significant change: *P* < 0.05.

Table 1.
Baseline parameters of the study groups.

	FSH	LH	TSH	Prolactin	Estradiol
	IU/ml	mIU/ml	uIU/m	mIU/L	pmol/L
Letrozole (n = 24)	5.5 ± 1.9	4.1 ± 2.4	1.9 ± 0.1	12.2 ± 2.6	53.1 ± 11.4
Clomiphene citrate (n = 20)	5.9 ± 1.5	4.4 ± 2.3	2.0 ± 0.2	13.4 ± 1.6	50.9 ± 15
Significance	NS	NS	NS	NS	NS

Significant change: *P* < 0.05.

Table 2.
Baseline hormonal parameters of the study groups.

The primary outcome measures were a number of mature follicles and endometrial thickness (in mm); secondary outcome measures were the pregnancy rate and miscarriage rate. The number of follicles showed no statistically significant ($P > 0.05$) difference between the groups (5.8 ± 3.6 for Group I versus 3.2 ± 3.3 in Group II) in cycle I. Endometrial thickness showed no statistically significant ($P > 0.05$) difference (9.07 ± 0.3 for Group I versus 4.08 ± 0.3 cm for Group II) (**Table 3**).

The mean number of follicles reaching >18 mm was significantly higher in patients who received letrozole (4.5 ± 4.5) than in those receiving clomiphene citrate (3.6 ± 3.6), although this difference was found non-significant. Letrozole and clomiphene citrate showing no significant difference ($P > 0.05$) as regards the endometrial thickness (1.1 ± 0.2 versus 1.2 ± 0.2) (**Table 3**). There is an insignificant difference between clomiphene citrate and letrozole as regard endometrial thickness and number of follicles through the 3 cycles. Clomiphene citrate significantly increased estradiol and progesterone levels compared to letrozole in cycle 1 and cycle 3 (**Tables 3–5**).

	Estradiol	Progesterone	Follicles	Endometrium	Pregnancy
	pmol/L	mol/L	Number	Thickness (cm)	Rate
Letrozole (n = 24)	$4.5 \pm 455.7^*$	47.6 ± 34.4	4.5 ± 4.5	$1.1.2 \pm 0.2$	2.0
CC (n = 20)	2.5 ± 2127.6	62.2 ± 62.8	3.6 ± 3.6	1.2 ± 0.2	1.9 ± 0.2
Significance	0.001	0.017	0.820	0.724	0.030

CC = clomiphene citrate.
Significant change: $P < 0.05$.

Table 3.
Effect of letrozole versus clomiphene citrate on estradiol, progesterone, no. of follicles and endometrial thickness in cycle 1.

	Estradiol	Progesterone	Follicles	Endometrium	Pregnancy
	pmol/L	mol/L	Number	Thickness (cm)	Rate
Letrozole (n = 24)	$4.2 \pm 656.7^*$	39.6 ± 31.1	$5.8 \pm 3.6^*$	1.07 ± 0.3	1.8 ± 0.3
CC (n = 20)	1.5 ± 904.5	48.9 ± 57.1	3.2 ± 3.3	$1.08 \pm .3$	2.0 ± 0.2
Significance	0.25	0.14	0.46	0.81	0.02

CC = clomiphene citrate.
Significant change: $P < 0.05$.

Table 4.
Effect of letrozole versus clomiphene citrate on estradiol, progesterone, no. of follicles and endometrial thickness in cycle 2.

	Estradiol	Progesterone	Follicles	Endometrium	Pregnancy
	pmol/L	mol/L	Number	Thickness (cm)	Rate
Letrozole (n = 24)	3.9 ± 349.09	36.8 ± 26	5.1 ± 4.8	1.05 ± 0.2	2.0 ± 0.3
CC (n = 20)	4.08 ± 5443.4	51.3 ± 68.5	1.3 ± 1.5	1.09 ± 0.4	2.0 ± 0.2
Significance	0.007	0.05	0.26	0.10	NS

CC = clomiphene citrate.
Significant change: $P < 0.05$.

Table 5.
Effect of Letrozole versus clomiphene citrate on estradiol, progesterone, no. of follicles and endometrial thickness in cycle 3.

	No. of pregnancy	Miscarriage
Letrozole (n = 24)	4	0
Clomiphene citrate (n = 20)	3	0
Significance	0.49	NS

Significant change: P < 0.05.

Table 6.
Effect of letrozole versus clomiphene citrate on number of pregnancies pregnancy and miscarriages in the 3 cycles.

A comparison of the number of pregnancies achieved in the groups showed insignificant statistical difference ($P < 0.05$). No multiple pregnancies occurred in both groups (**Table 6**).

Anova between the 3 cycles revealed that there is no significant difference between estradiol, progesterone levels, number of follicles, and endometrial thickness. Post Hoc Tests also revealed insignificant differences between the outcomes in the 3 cycles.

4. Discussion

Detailed scientific discussions of the results obtained during the term of the project, and related past results obtained in the field of this research area. Although clomiphene citrate is considered the first-line drug for ovulation induction in women with PCOS, a significant proportion of women do not respond to this treatment [8]. Letrozole, a third-generation aromatase inhibitor, is suggested for ovulation induction [9].

Letrozole initiates ovulation by decreasing the conversion of androstenedione and testosterone to estrogen in the ovary. The inhibition of estrogen production, in turn, increases GnRH release and pituitary follicle-stimulating hormone (FSH) synthesis [10]. Clomiphene citrate acts by blocking the negative feedback of endogenous estrogen at the level of the hypothalamus and pituitary gland and promoting an increase in the pulsatile release of luteinizing hormone and follicle-stimulating hormone. However, clomiphene citrate has an antagonistic effect on the endometrium and may reduce endometrial thickness [11].

The results of this prospective randomized study showed that letrozole was as effective as clomiphene citrate for induction of ovulation with an insignificant change in the number of mature follicles and endometrial thickness. Atay et al. [8] reported that letrozole and clomiphene citrate were effective for ovulation induction in PCOS, but in contrast to the present study, they found greater endometrial thickness in the letrozole group.

In the present study, clomiphene citrate significantly increased estradiol and progesterone levels compared to letrozole in cycle one and cycle 3. Badawy et al. [7] found that levels of serum estradiol and progesterone were statistically significantly higher in the clomiphene citrate group compared to letrozole.

The hormonal changes could be explained by clomiphene citrate (CC) binds to estrogen receptors (ERs) for an extended period of time due to its structural similarity to estrogen. This will deplete ER concentrations. The antiestrogenic effect on the hypothalamus and the pituitary is believed to be the main mechanism of action for ovarian stimulation. Depletion of hypothalamic ERs prevents correct interpretation of circulating estrogen levels; estrogen concentrations are falsely perceived as low leading to reduced estrogen-negative feedback on GnRH production and

subsequent increased gonadotropin (FSH and LH) secretion. The rise of FSH promotes growth of ovarian follicles and ovulation in anovulatory women. It is believed that the hypothalamus is the main site of action because in normally ovulatory women, CC treatment was found to increase GnRH pulse frequency [12].

Letrozole block estrogen-negative feedback, without depletion of ERs as occurs with CC. Inhibition of aromatization will block estrogen production from all sources and release the hypothalamic/pituitary axis from estrogenic negative feedback. The resultant increase in gonadotropin secretion will stimulate growth of ovarian follicles [13].

5. Conclusions and recommendations

Letrozole in patients with PCOS is as effective as clomiphene citrate in inducing ovulation; letrozole had a comparable effect to clomiphene citrate on endometrial thickness and number of follicles.

Acknowledgements

We thank Amani Al-Mars, Laila Al-Tonesy, Hala Al-Tayeb, and Amina Saleh for their contribution in collecting data.

Conflicts of interest

The authors of this paper report no conflicts of interest.

Author details

Hassan S.O. Abduljabbar^{1*}, Magda Hagra^{1,2} and Rania Magadmy³

¹ Faculty of Medicine, King Abdulaziz University, Kingdom of Saudi Arabia

² Faculty of Medicine, Suez Canal University, Egypt

³ Clinical Trial Unit, King Fahd Medical Research Centre, King Abdulaziz University, Kingdom of Saudi Arabia

*Address all correspondence to: profaj17@yahoo.com

IntechOpen

© 2020 The Author(s). Licensee IntechOpen. This chapter is distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/3.0>), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

References

- [1] Thessaloniki ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group. Consensus on infertility treatment related to polycystic ovary syndrome. *Human Reproduction*. 2008;**23**(3):462-477. DOI: 10.1093/humrep/dem426. Erratum in: *Hum Reprod*. 2008;**23**(6):1474. PMID: 18308833
- [2] Jermy K, Luise C, Bourne T. The characterization of common ovarian cysts in premenopausal women. *Ultrasound in Obstetrics and Gynecology*. 2001;**17**(2):140-144
- [3] Kafy S, Tulandi T. New advances in ovulation induction. *Current Opinion in Obstetrics and Gynecology*. 2007;**19**(3):248-252
- [4] Nader S. Ovulation induction in polycystic ovary syndrome. *Minerva Ginecologica*. 2008;**60**(1):53-61. Review
- [5] Hart R. PCOS and infertility. *Panminerva Medica*. 2008;**50**(4):305-314. Review
- [6] Gregoriou MD, Nikos F, Vlahos MD. Randomized controlled trial comparing superovulation with letrozole versus recombinant follicle-stimulating hormone combined with intrauterine insemination for couples with unexplained infertility who had failed clomiphene citrate stimulation and intrauterine insemination. *Fertility and Sterility*. 2008;**90**(3):678-683. DOI: 10.1016/j.fertnstert.2007.06.099
- [7] Badawy A, Shokeir T, Allam AF, Abdelhady H. Pregnancy outcome after ovulation induction with aromatase inhibitors or clomiphene citrate in unexplained infertility. *Acta Obstetrica et Gynecologica Scandinavica*. 2009;**88**(2):187-191. DOI: 10.1080/00016340802638199
- [8] Atay V, Cam C, Muhcu M, Cam M, Karateke A. Comparison of letrozole and clomiphene citrate in women with polycystic ovaries undergoing ovarian stimulation. *The Journal of International Medical Research*. 2006;**34**(1):73-76
- [9] Ekerhovd E. Ovulation induction by means of letrozole. *Tidsskrift for den Norske Lægeforening*. 2009;**129**(5):412-415. DOI: 10.4045/tidsskr.08.0129. Review. Norwegian
- [10] Ohno Y, Fujimoto Y. Endometrial oestrogen and progesterone receptors and their relationship to sonographic appearance of the endometrium. *Human Reproduction Update*. 1998;**4**(5):560-564. Review
- [11] Nakamura Y, Ono M, Yoshida Y, Sugino N, Ueda K, Kato H. Effects of clomiphene citrate on the endometrial thickness and echogenic pattern of the endometrium. *Fertility and Sterility*. 1997;**67**(2):256-260
- [12] Kerin JF, Liu JH, Phillipou G, Yen SS. Evidence for a hypothalamic site of action of clomiphene citrate in women. *The Journal of Clinical Endocrinology and Metabolism*. 1985;**61**(2):265-268
- [13] Kamath MS, George K. Letrozole or clomiphene citrate as first line for anovulatory infertility: A debate. *Reproductive Biology and Endocrinology*. 2011;**9**:86. DOI: 10.1186/1477-7827-9-86