Comparision of Letrozole with Timed Intercourse Versus Clomiphene Citrate with Intrauterine Insemination in Patients with Unexplained Infertility

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OBJECTIVE: To evaluate outcomes of patients with unexplained infertility who underwent letrozole (LET)–stimulated controlled ovarian stimulation (COS) with timed sexual intercourse (IC) as compared to patients treated with clomiphene citrate (CC) and intrauterine insemination (IUI).

STUDY DESIGN: A non-randomized, retrospective study where unexplained infertility patients (n=7,764) underwent a COS cycle with both LET and timed IC or with CC and IUI from January 2010–June 2014. One group consisted of patients who completed a COS cycle with LET and were instructed to have sexual IC. The other included patients were treated with CC and underwent IUI. Pregnancy rates (PRs) were compared between groups.

RESULTS: No statistical difference was observed in each group's age or serum follicule-stimulating hormone levels. A statistical significance in LET versus CC-stimulated groups was observed for mean endometrial thickness (8.3±1.7 vs. 7.9±1.8 mm) and follicular response (2.0±1.0 vs. 2.3± 1.3), respectively. Clinical PRs after timed IC were significantly higher in the LET versus CC-stimulated group (15.0% vs 11.8%). Clinical PRs after timed IUI were also significantly higher in the LET versus CC-stimulated group (12.3% vs 11.5%). Moreover, clinical PRs in LET with IC were significantly higher than CC with IUI (15.0% vs. 11.5%).

We suggest that physicians consider LET and timed IC rather than CC and IUI for … unexplained infertility.

CONCLUSION: Unexplained infertility patients who underwent LET stimulation with IC were found to have better pregnancy outcomes as compared to those who underwent timed IC or IUI with CC stimulation. (J Reprod Med 2016;61:000–000)

Keywords: artificial insemination; clomiphene; clomiphene citrate; fertility agents, female; in vitro fertilization; infertility; intercourse; intrauterine insemination; letrozole; pregnancy rates; unexplained infertility.

Nearly 30% of couples trying to conceive are diagnosed with unexplained infertility, and a uniform protocol of management has yet to be agreed upon. To a large extent, this has resulted in treatment regimens that are determined by physician preference.[1] A diagnosis of unexplained infertil-

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ity is typically made after confirmation of normal ovarian reserve and ovulatory markers, tubal patency, and partner semen analysis.[2] Controlled ovarian stimulation (COS) is generally considered a first-line treatment in patients with unexplained infertility, and several agents with different modes of action are commonly employed.

Two oral agents that have been widely used for COS are the selective estrogen receptor modulator clomiphene citrate (CC) and the third generation aromatase nonsteroidal inhibitor (AI) letrozole (LET). CC clomiphene citrate has been widely used worldwide, and it is the first choice in normogonadotropic oligo/amenorrheic infertility (World Health Organization [WHO] group 2).[3] CC is a nonsteroidal triphenylethylene derivative that exhibits both estrogenic agonist and antagonist properties, although its estrogenic agonist properties manifest only when endogenous estrogen levels are extremely low.[4] CC acts by binding to estrogen receptors (ERs) in the hypothalamus, causing a perceived drop in circulating estrogens, which increases gonadotropin secretion by the pituitary and subsequent ovulation.[5] Various adverse effects have been described, mainly secondary to its antiestrogenic action, including hot flashes, premenstrual syndrome–like symptoms, suboptimal endometrial thickness, and decreased cervical mucus production, all of which are also associated with reducing pregnancy rates. Lastly, CC is more likely to produce a multifollicular response, potentially increasing the multiple pregnancy rates.[6,7] Laterally with CC treatment, intrauterine insemination (IUI) has been widely used to circumvent the poor cervical mucus production, and human chorionic gonadotropin (hCG) trigger is typically employed in those cycles in an effort to appropriately time insemination procedures.[8,9] Nevertheless, although the routine use of timed IUI has been shown to be beneficial by numerous studies, overall outcomes remain ambiguous, with many previous reports not supporting its use.[10-15]

Letrozole is a potent, reversible AI approved by the FDA as a chemotherapeutic agent in postmenopausal women with metastatic cancer[16]; it has been used in reproductive medicine since 2001.[17] When aromatization of androgens is inhibited, the resulting reduction of circulating estrogens promotes the growth of ovarian follicles through the increased secretion of follicle-stimulating hormone (FSH), yielding a transient intraovarian androgenic environment. This appears to increase follicular sensitivity to FSH without antagonizing ERs, thus avoiding an antiestrogenic affection on the endometrial lining.[5] Although LET stimulation can result in some side effects such as hot flashes, muscle aches, and gastrointestinal disturbances,[19] the side effect profile is typically well tolerated. Furthermore, LET appears to cause fewer congenital abnormalities in comparison to CC.[18] Although both CC and LET have both been widely utilized for COS in IUI protocols, the choice of agent is largely a matter of physician discretion, and the current opinion favors LET to increase PRs.[20]

To date, several prospective, randomized studies and metaanalyses comparing these agents have contributed to our current knowledge base.[5-7] LET has appeared to be just as safe and effective as CC. However, small sample sizes (<100 patients) and conflicting studies have left physicians indefinite as to the significance and applicability of prior results. Recently, LET has been advocated as the optimal agent for ovulation induction due to an observed decrease in the frequency of its side effects, thus leading to an increasingly favorable attitude in its use for standard care in many centers. We previously conducted a retrospective analysis that compared LET versus CC efficacy combined with IUI in patients with unexplained infertility and demonstrated a trend towards higher PRs with LET usage.[21]

Given the fact that LET is associated with minimal antiestrogenic effects, we postulated that the use of IUI would not enhance the PR of LET cycles. In order to test this hypothesis, we compared reproductive outcomes in patients with unexplained infertility who underwent a LET cycle with timed sexual intercourse (IC) to those who underwent a CC cycle with timed IUI.

Materials and Methods

Patient Information

This observational, retrospective cohort study was performed at an academic, private fertility practice. We reviewed the electronic medical records of all patients undergoing treatment with CC or LET from January 2010 to June 2014. The choice of COS protocol was determined by the treating physician. Patients <40 years of age diagnosed with unexplained infertility (normal ovarian reserve screening [day 3 FSH ≤12.5 mUI/mL, day 3 estradiol ≤80 pg/mL, and AMH ≥1 ng/mL]) with partners having normal semen analysis according to WHO parameters[22] were included in the study. Only cycles

timed with r-hCG were included. Patients who had a canceled cycle or were still undergoing a treatment cycle were excluded from this analysis.

Ovulation Induction

Letrozole (Femara, Novartis, East Hanover, New Jersey) or CC (Clomid, Sanofi-Aventis, Bridgewater, New Jersey) were administered starting on cycle day 3 until cycle day 7 of a spontaneous or a progesterone-induced cycle. Initial dosages of 5 mg and 100 mg were used with LET and CC, respectively, until ovarian response was observed. Monitoring by transvaginal ultrasound was performed starting on cycle day 12 until a dominant follicle (≥20 mm) was observed, and then ovulation triggering medication was prescribed; endometrial thickness and pattern (I, II, or II) were recorded at this cycle time point. If no response was observed, the patient was monitored every 3–4 days until cycle day 21; if still no response was observed, the cycle was canceled. Ovulation was triggered with r-hCG (Ovidrel, EMD Serono, Rockland, Massachusetts), and 24–36 hours thereafter patients were either advised to have IC or were scheduled for IUI. A clinical pregnancy was determined by the presence of a gestational sac approximately 7–10 days following a positive pregnancy test by measuring serum β-hCG. Delivery rates were not available for all patients included in the study due to unavailability of information on all patients as it is not required in non-IVF patients by the Society of Assisted Reproductive Technologies (SART).

Study Outcomes

The primary outcome measure was PR per cycle. Secondary end points were the number of mature follicles (≥14 mm) and endometrial thickness (mm), as measured by transvaginal ultrasound on the day of hCG trigger.

Statistical Analyses

Statistical analyses were performed using the SPSS statistical package (IBM, Armonk, New York). Continuous variables were assessed by Student's *t* test or by Wilcoxon rank sum test if the data did not appear normally distributed. Categorical variables were assessed by χ^2 tests or two-tailed Fisher's exact tests in cases of small cell frequencies. A probability value (p value) of <0.05 was considered statistically significant.

Because of its retrospective nature informed consent was not necessary. The study protocol and analysis was approved by the Western Institutional Review Board.

Results

A total of 7,764 patients with unexplained infertility were included in the study: 2,430 included in the LET group and 5,334 in the CC group. No differences in the mean age of LET (33.4±4.2) and CC (33.5±4.3) groups were observed (Table I). The mean endometrial thickness on the day of hCG (LET=8.3 mm vs. CC=.9 mm) and mean number of mature follicles (LET=2.0±1 vs. CC=2.3±1.3) differed significantly (Table I). The overall clinical PR per cycle was significantly different between LET (13.3%) and CC (11.6%) cycles (Table I).

Letrozole IC Versus CC IC

The mean endometrial thickness and mean number of mature follicles on the day of hCG trigger for

Table I *Letrozole Versus CC*

	Letrozole (n=2,430)	CC (n=5,334)	p Value
Age, yrs.	33.4±4.2	33.5±4.3	NS
Endometrial thickness	8.3±1.7	7.9±1.8	<0.05
Endometrial pattern			
Type I	40.3%	30.5%	
Type II	53.9%	50.9%	
Type III	5.8%	18.6%	
FSH	8.0±4.0	7.7±3.5	NS
Follicles >14 mm	2.0±1.0	2.3±1.3	<0.00001
BMI	23.7±4.7	24.1±4.9	<0.001
Biochemical pregnancy rate	15.4% (375/2,430)	13.7% (733/5,334)	<0.05
Clinical pregnancy rate	13.3% (325/2,430)	11.6% (622/5,334)	<0.05

Table II *Letrozole IC Versus CC IC*

	Letrozole IC (n=918)	CC IC (n=1,742)	p Value
Endometrial thickness	8.2±1.9	7.8±1.8	<0.05
Follicles >14 mm	1.9±1.0	2.2±1.3	<0.00001
Biochemical pregnancy rate	17.4% (160/918)	13.6% (238/1,742)	<0.00001
Clinical pregnancy rate	15.03% (138/918)	11.8% (207/1,742)	<0.00001

CC and LET with IC cycles were found to both be significantly different (Table II). Further, the clinical PR per cycle was 15.0% in LET patients and 11.8% in CC patients, again reaching statistical significance (Table II).

Letrozole IUI Versus CC IUI

The mean endometrial thickness and mean number of mature follicles on the day of hCG trigger for CC and LET with IUI cycles were both found to be significantly different (Table III). Moreover, the clinical PR per cycle was 12.3% in LET patients and 11.5% in CC patients ($p<0.05$) (Table III).

Letrozole IC Versus CC IUI

Patients who underwent a LET cycle with IC were compared to patients who underwent a CC cycle with IUI. A significant difference was observed on the day of hCG trigger in the mean endometrial thickness and mean number of mature follicles between groups (Table IV). The clinical PR per cycle was significantly higher in LET with IC patients than in CC with IUI patients (15.0 and 11.5%, respectively) (Table IV).

Discussion

Despite the fact that CC treatment results in a high ovulatory response, PRs have remained relatively low, most likely the result of the medication's antiestrogenic effects. While CC use in ovulation induction cycles is effective and well established, COS is better accomplished with the utilization of gonadotropins. Letrozole has more recently been used as a COS agent and appears to be similar in efficacy to CC in the setting of unexplained infertility.[23]

Overall, our retrospective analysis demonstrates equivalent PR between both agents, with a trend toward higher success rates in LET cycles (Table I). The primary end point of this analysis was to determine if stimulation with LET with IC, thus without IUI, could be as effective as treatment with CC with IUI. Interestingly, based on these study parameters our study's results initially demonstrated that the procedure of IUI in unexplained infertility patients using LET did not enhance the chances of getting pregnant as compared to patients using CC. We analyzed each treatment agent when administered during a timed IC cycle and found that LET cycles showed higher PRs than did CC cycles (Table II). Next, we analyzed both agents when administered in a cycle with an IUI, and PRs were again higher in the LET group (Table III). Last, we compared the subgroup of LET-stimulated patients who had timed IC with those stimulated with CC and who underwent an IUI, and we were able to demonstrate that LET cycles with timed IC were more effective and higher pregnancy rates were achieved (Table IV).

Recent studies have suggested that LET may be a more attractive option as it offers a lower likelihood of decreasing infertility patients' endometrial thickness, a more frequent monofollicular response, and has a less severe side effect profile as

Table III *Letrozole IUI Versus CC IUI*

	Letrozole IUI (n=1,512)	CC IUI (n=3,592)	p Value
Endometrial thickness	8.3±1.6	7.9±1.8	<0.05
Follicles >14 mm	2.0±0.9	2.4±1.3	<0.00001
Biochemical pregnancy rate	14.2% (215/1,512)	13.7% (495/3,592)	<0.00001
Clinical pregnancy rate	12.3% (187/1,512)	11.5% (415/3,592)	<0.00001

Table IV *Letrozole IC Versus CC IUI*

	Letrozole IC (n=918)	CC IUI (n=3,592)	p Value
Endometrial thickness	8.2±1.9	7.9±1.8	<0.05
Follicles >14 mm	1.9±1.0	2.4±1.3	<0.0002
Biochemical pregnancy rate	17.4% (160/918)	13.7% (495/3,592)	<0.00001
Clinical pregnancy rate	15.03% (138/918)	11.5% (415/3,592)	<0.00001

compared to CC. A meta-analysis performed by He et al included 6 randomized controlled trials; their results found a greater endometrial thickness after LET stimulation when compared to CC cycles in 2 of the 6 trials included (Atay et al 2006, 8.4±0.18 vs. 5.2±0.12 mm; Aygen et al 2007, 10.4±1.4 vs. 6.8±0.5 mm) and no significant difference in another 2 (Bayar et al, 2006, and Dehbashi et al, 2009).[7] Similar findings were also reported in another meta-analysis by Polyzoz et al, with significantly increased endometrial thickness in 2 of the 5 trials included (Barroso et al, 2006, and Wu et al, 2007) and higher but not statistically significant thickness in 1 (Sipe et al, 2006).[6] Our study supports these results, as we also observed a greater endometrial thickness in the LET group as compared to the CC group in all subgroups analyzed (Tables I–IV). We also observed that patients who underwent CC treatment more frequently had a type III endometrium (5.8 vs. 18.6%) (Table I).

Regarding follicular maturation, the same meta-analysis authored by He et al reported a decreased average follicular response in LET stimulation as compared with CC groups (SMD −1.41, 95% CI −1.54 to −1.28; $p<0.00001$; heterogeneity $\chi^2=0.06$),[7] which was corroborated by our results, even when the basal antral follicle count was higher in LET patients (Tables I–IV). Alternately, in the meta-analysis authored by Polyzoz et al, no prominent trend was found in favor of AI or CC.[6] Both meta-analyses concluded LET to be equally as effective as CC yet asserted that LET usage leads to a monofollicular response more frequently than CC treatment does, therefore decreasing the risk of multiple pregnancies.

To our knowledge the only study to measure and report adverse effects secondary to CC use was published by Bhattacharya et al, in which patients randomized to CC treatment reported that the process of this treatment was more acceptable than those randomized to expectant management.[24] In the present study we did not evaluate the prevalence of adverse side effects from LET or CC treatment.

Although gonadotropin stimulation preceding IUI was considered the first option for idiopathic infertility, the lower cost, increased comfort, lower multiple pregnancy rates, and overall clinical acquiescence recognized by oral therapies with timed IC provides an alternative that attracts clinicians and patients alike. Clinicians have routinely recommended IUI to improve success rates when CC is utilized, as an undetermined fraction of patients will experience a significant compromise of cervical mucus production as a result of CC's antiestrogenic effect. Our study has demonstrated higher pregnancy rates with LET+IC than with CC+IUI, thus suggesting that IUI does not necessarily increase a couple's chance of success if they are being treated with LET and should only be recommended in aberrant cases such as male factor or cervical factor subfertility. In addition, it is not clear whether couples who failed a LET cycle with timed IC would benefit from further treatment with IUI instead of progressing to IVF.

Due to the high number of couples with unexplained infertility undergoing LET or CC cycles, there could potentially be substantial savings for patients if further studies substantiate our finding that IUI is not an essential component of LET cycles for the treatment of idiopathic infertility. Although both LET and CC are relatively inexpensive medications, LET is slightly more expensive than CC. Depending on the pharmacy used, a typical 5-day treatment regimen using generic CC may cost $15–$30 USD, while generic LET may cost $50–$150 USD. Because of the addition of the $300 for sperm sample processing and insemination procedure, CC/IUI costs patients nearly twice as much as LET/IC, making LET a more cost-effective option.

To our knowledge this study is one of the largest of its kind. A protocol based on LET and IC reduces the incidence of antiestrogenic effects, as evidenced by an increased endometrial thickness

and a trend toward pregnancy rates that were higher than those found in patients undergoing CC and IUI. We suggest that physicians consider LET and timed IC rather than CC and IUI for the treatment of unexplained infertility.

References

1. Practice Committee of the American Society for Reproductive Medicine: Effectiveness and treatment for unexplained infertility. Fertil Steril 2006;86:1001
2. Ray A, Shah A, Gudi A, et al: Unexplained infertility: An update and review of practice. Reprod Biomed Online 2012;24:591-602
3. Seli E, Arici A: Ovulation induction with clomiphene citrate. *In* UpToDate. Edited by RL Barbieri. Wolters Kluwer Health/UpToDate, Inc. Available at http://www.uptodate.com/contents/ovulation-induction-with-clomiphene-citrate. Accessed _____
4. Practice Committee of the American Society for Reproductive Medicine: Use of clomiphene citrate in infertile women: A committee opinion. Fertil Steril 2013;100:341-348
5. Requena A, Herrero J, Landeras J, et al: Use of letrozole in assisted reproduction: A systematic review and meta-analysis. Hum Reprod Update 2008;14:571-582
6. Polyzos NP, Tzioras S, Mauri D, et al: Treatment of unexplained infertility with aromatase inhibitors or clomiphene citrate: A systematic review and meta-analysis. Obstet Gynecol Survey 2008;63:472-479
7. He D, Jiang F: Meta-analysis of letrozole versus clomiphene citrate in PCOS. Reprod Biomed Online 2011;23:91-96
8. Zreik TG, García-Velasco JA, Habboosh MS, et al: Prospective, randomized, crossover study to evaluate the benefit of human chorionic gonadotropin-timed versus urinary luteinizing hormone-timed intrauterine inseminations in clomiphene citrate-stimulated treatment cycles. Fertil Steril 1999;71:1070-1074
9. Kosmas IP, Tatsioni A, Fatemi HM, et al: Human chorionic gonadotropin administration vs. luteinizing monitoring for intrauterine insemination timing, after administration of clomiphene citrate: A meta-analysis. Fertil Steril 2007;87:607-612
10. Veltman-Verhulst SM, Cohlen BJ, Hughes E, et al: Intrauterine insemination for unexplained subfertility. Cochrane Database Syst Rev 2012;(9):CD001838
11. Cohlen BJ, Vandekerckhove P, te Velde ER, et al: Timed intercourse versus intrauterine insemination with or without ovarian hyperstimulation for subfertility in men. Cochrane Database Syst Rev 2000;(2):CD000360
12. Helmerhorst FM, van Vliet HA, Gornas T, et al: IUI versus timed IC for cervical hostility in subfertile patients. Obstet Gynecol Surv 2006;61:402-414; quiz 423
13. Barros-Delgadillo JC, Martinez-Barrios E, Moreno-Aburto C, et al: [Intrauterine insemination versus programmed intercourse in cycles of controlled ovaric hyperstimulation]. [Article in Spanish] Ginecol Obstet Mex 2008;76:18-31
14. Abu Hashim H, Ombar O, Abd Elaal I: Intrauterine insemination versus timed intercourse with clomiphene citrate in polycystic ovary syndrome: A randomized controlled trial. Acta Obstet Gynecol Scand 2011;90:344-350
15. Check JH, Liss J, Bollendorf A: Intrauterine insemination (IUI) does not improve pregnancy rates in infertile couples where semen parameters are normal and postcoital tests are adequate. Clin Exp Obstet Gynecol 2013;40:33-34
16. Lamb HM, Adkins JC: Letrozole: A review of its use in postmenopausal women with advanced breast cancer. Drugs 1998;56:1125-1140
17. Fisher SA, Reid RL, Van Vugt DA, et al: A randomized double-blind comparison of the effects of clomiphene citrate and the aromatase inhibitor letrozole on ovulatory function in normal women. Fertil Steril 2002;78:280-285
18. Casper RF, Mohamed FM: Historical perspective of aromatase inhibitors for ovulation induction. Fertil Steril 2012;98:1352-1355
19. Tulandi T, Martin J, Al-Fadhli R, et al: Congenital malformations among 911 newborns conceived after infertility treatment with letrozole or clomiphene citrate. Fertil Steril 2006;85:1761-1765
20. Palatnik A, Strawn E, Szabo A, et al: What is the optimal follicular size before triggering ovulation in intrauterine insemination cycles with clomiphene citrate or letrozole? An analysis of 988 cycles. Fertil Steril 2012;97:1089-1094.e1-3
21. Mukherjee T, Whitehouse M, Lee JA, et al: The efficacy of insemination in letrozole versus clomiphene citrate treatment cycles. Fertil Steril ____;100:Suppl S261-000
22. Cooper TG, Noonan E, von Eckardstein S, et al: World Health Organization reference values for human semen characteristics. Hum Reprod Update 2010;16:231-245
23. Kar S: Current evidence supporting "letrozole" for ovulation induction. Hum Reprod Sci 2013;6:93-98
24. Bhattacharya S, Harrild K, Mollison J, et al: Clomiphene citrate or unstimulated intrauterine insemination compared with expectant management for unexplained infertility: Pragmatic randomised controlled trial. BMJ 2008;337:a716