Clomiphene citrate or aromatase inhibitors for superovulation in women with unexplained infertility undergoing intrauterine insemination: a prospective randomized trial

Ahmed Badawy, M.D., Abubaker Elnashar, M.D., and Mohamed Totony, M.D.

Objective: To compare clomiphene citrate (CC) and letrozole used for superovulation before intrauterine insemination (IUI) in unexplained infertility.

Design: Prospective randomized trial.

Setting: A university teaching hospital and a private practice setting.

Patient(s): Four hundred and twelve infertile women with unexplained infertility. For each patient, four cycles were included in the study: CC and letrozole cycles.

Intervention(s): Patients were randomized to treatment with 100 mg of CC daily (207 patients, 404 cycles) or 5 mg of letrozole daily (205 patients, 400 cycles) for 5 days starting on day 3 of menses. The IUI was done 36 ± 4 hours after human chorionic gonadotropin (hCG) injection.

Main Outcome Measure(s): Number of follicles, serum estradiol level, serum progesterone level, endometrial thickness, and pregnancy and miscarriage rates.

Result(s): The total number of follicles during stimulation was statistically significantly greater in the CC group (3.1 ± 0.36 vs. 1.6 ± 0.41). There was no statistically significant difference in pretreatment endometrial thickness between the two groups or endometrial thickness at the time of hCG administration. Serum E2 and progesterone concentrations were statistically significantly higher in the CC group. The days to hCG injection were similar in both groups. Pregnancy occurred in 73 out of 205 patients (400 cycles) in the letrozole group (37.6% and 19.3%, respectively) and 78 out of 207 patients (404 cycles) (35.6% and 18.2%, respectively) in the CC group; the differences were not statistically significant. Two twin pregnancies occurred in the CC group.

Conclusion(s): This study found no superiority between letrozole and CC for inducing ovulation in women with unexplained infertility before IUI. (Fertil Steril® 2008; ■ ■ ■ ■ ©2008 by American Society for Reproductive Medicine.)

Key Words: ■ ■ ■ ■

Intrauterine insemination (IUI) is widely used in treating couples with mild male factor infertility, minimal to mild endometriosis, and unexplained infertility. Intrauterine insemination gained popularity because of its simplicity, noninvasiveness, and reported cost effectiveness. Despite many studies about IUI, some fundamental essentials of the IUI used for patients with unexplained infertility are still controversial. Many randomized controlled trials have found that superovulation plus IUI significantly increased pregnancy rates compared with IUI alone (1–3). Nevertheless, the National Institute for Clinical Excellence (NICE) recommended that ovarian stimulation should not be offered in patients with unexplained infertility, even though it is associated with higher pregnancy rates than unstimulated intrauterine insemination, because it carries a risk of multiple pregnancies.

Nor is there consensus regarding the most favorable ovarian stimulation protocol. To achieve mild ovarian hyperstimulation, various drugs have been used: clomiphene citrate (CC), aromatase inhibitors, human menopausal gonadotropins, and purified or recombinant follicle-stimulating hormone (FSH). A systematic review of five randomized controlled trials compared oral (antiestrogens) and injectable (gonadotropins) drugs for stimulated IUI in couples with unexplained fertility problems and found no significant difference in live birth rates per couple although the pregnancy rate seemed to be higher with gonadotropins (4). Hence, oral agents might be the suitable for ovarian stimulation, and they are not far from achieving the goals of the procedure.

To the best of our knowledge, no studies have examined pregnancy rates with oral agents such as CC and aromatase inhibitors used for superovulation before IUI, and the issue surrounding which oral drug for ovarian stimulation is optimum before IUI cycles remains unresolved. In view of this uncertainty, we compared CC and letrozole used for superovulation in a prospective randomized controlled trial.

MATERIALS AND METHODS

From January 2004 to December 2007, 412 couples (women younger than 40 years) with unexplained infertility completed their first cycle of stimulation using either CC (n=207) or letrozole (n=205).
CC and letrozole for IUI

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Statistical Analysis

Data were statistically analyzed using the SPSS computer package (SPSS Inc., Chicago, IL) by Student’s t-test. Proportions were analyzed using the chi-square test. Results were expressed as mean and standard error of the mean. $P<0.05$ was considered statistically significant. Sample size calculation, before the study, showed that each arm should contain at least 203 patients to have 80% power of the study at 95% confidence interval (CI) when a 15% difference in pregnancy rate was expected between the two groups.

RESULTS

The study comprised 412 women (804 cycles) in total. The mean number of cycles per woman was 1.95 in both groups. There were no statistically significant differences between the two groups as regards age, duration of infertility, body weight, height, and body mass index (BMI) (Table 1). The total number of follicles during stimulation was statistically significantly greater in the CC group (3.1 ± 0.36 vs. 1.6 ± 0.41). There was no statistically significant difference in pretreatment endometrial thickness between the two groups or in endometrial thickness at the time of hCG administration. Serum E2 and progesterone concentrations were statistically significantly higher in the CC group. The days to hCG injection were similar in both groups (Table 2). Pregnancy occurred in 73 of 205 patients (400 cycles) in the letrozole group (35.6% and 18.2%, respectively) and 78 of 207 patients (404 cycles) (37.6% and 19.3%, respectively) in the CC group; the differences were not statistically significant. Two twin pregnancies occurred in the CC group and none in the letrozole group. No higher order pregnancies or cases of ovarian hyperstimulation syndrome occurred in either group. Miscarriage occurred in 11 letrozole patients (14.4%) and 12 CC patients (16.2%); the difference between groups was not statistically significant.

DISCUSSION

The underlying principle for superovulation in women with unexplained infertility, who by definition have regular ovulatory menstrual cycles, is to augment the probability of pregnancy by increasing the number of oocytes on hand for fertilization. The goal is to prevail over a possible flaw in ovulatory function that is not uncovered by conformist testing. When used in conjunction with IUI to increase the density of motile sperm available to these oocytes, the likelihood of pregnancy may be further increased.

Compared with natural cycle IUI, ovarian hyperstimulation may perk up treatment outcomes for couples with unexplained and mild male subfertility (1–3). However, there is still a dispute about which drug should be the first choice for ovarian hyperstimulation. Studies comparing the efficacy of oral agents with different types of gonadotropins in IUI
programs have produced conflicting results (7–12). That is, IUI cycles with human menopausal gonadotropin stimulation have shown slightly higher but not statistically significantly different pregnancy rates than cycles stimulated with CC (7, 9). When compared with gonadotropins, oral agents may offer similar pregnancy rates in IUI as well as reducing the costs and potential side effects of treatment such as multiple births and ovarian hyperstimulation syndrome.

Letrozole is a third-generation aromatase inhibitor. Blocking estrogen production by inhibiting aromatization stops the conversion of androstenedione and testosterone to estrogen in the ovary. This hypoestrogenic state releases the hypothalamic–pituitary axis from estrogenic negative feedback, which in turn increases FSH secretion and the development of ovarian follicles. Since the early reports by Mitwally and Casper (13), many studies have weighed aromatase inhibitors as ovulatory agents in various indications with contradictory results (14–16). Recently, Polyzos et al. (15), in a meta-analysis, seriously questioned the value of letrozole versus CC in ovulation induction in patients with polycystic ovary syndrome.

As gonadotropin therapy is the mainstay of most forms of infertility treatment, many reports have examined gonadotropin injection and intrauterine insemination (IUI) used alone or in combination with oral agents in various indications (18–20). To the best of our knowledge, there are no studies comparing aromatase inhibitors and CC alone in an IUI program for couples with unexplained infertility. In our study, the total number of follicles during stimulation was greater in the CC group (1.6 ± 0.41 vs. 3.1 ± 0.36). Serum E2 and progesterone concentrations were statistically significantly higher in the CC group. The days to hCG injection were similar in both groups. It can be argued that clomiphene citrate results in central estrogen receptor depletion for a lengthy time because of its greater half-time for clearance (2 weeks). As a consequence, supraphysiologic levels of estrogen can occur without central suppression of FSH because the normal estrogen receptor–mediated feedback mechanisms are blocked. This results in multiple follicle growth and higher multiple pregnancy rates with CC than are found in letrozole cycles. In this study, only two twin pregnancies occurred in the CC group. No higher order

**TABLE 1**

<table>
<thead>
<tr>
<th>Characteristics of the patients.</th>
<th>Letrozole group (n = 205)</th>
<th>CC group (n = 207)</th>
<th>t</th>
<th>P valuea</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of cycles</td>
<td>400</td>
<td>404</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>29.1 ± 3.01</td>
<td>28.3 ± 2.81</td>
<td>2.05</td>
<td>.68</td>
</tr>
<tr>
<td>Parity</td>
<td>0.3 ± 0.1</td>
<td>0.4 ± 0.1</td>
<td>3.42</td>
<td>.11</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>160.3 ± 5.1</td>
<td>163.3 ± 4.9</td>
<td>2.63</td>
<td>.44</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>68.3 ± 6.4</td>
<td>72.1 ± 5.2</td>
<td>2.24</td>
<td>.071</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>26.6 ± 3.1</td>
<td>28.1 ± 3.8</td>
<td>1.98</td>
<td>.72</td>
</tr>
</tbody>
</table>

a None of the differences were statistically significant (P > .05).


**TABLE 2**

<table>
<thead>
<tr>
<th>Outcome in letrozole and clomiphene citrate (CC) groups.</th>
<th>Letrozole group (n = 205)</th>
<th>CC group (n = 207)</th>
<th>t</th>
<th>P valuea</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of follicles &gt;18 mm</td>
<td>1.6 ± 0.41</td>
<td>3.1 ± 0.36</td>
<td>4.4</td>
<td>.045a</td>
</tr>
<tr>
<td>Pretreatment endometrial thickness</td>
<td>4.7 ± 0.4</td>
<td>4.4 ± 0.6</td>
<td>1.41</td>
<td>.52</td>
</tr>
<tr>
<td>Endometrial thickness at hCG (mm)</td>
<td>9.3 ± 0.4</td>
<td>9.2 ± 0.6</td>
<td>2.40</td>
<td>.08a</td>
</tr>
<tr>
<td>Serum E2 (pg/mL)</td>
<td>289.1 ± 64.2</td>
<td>410 ± 81.2</td>
<td>3.12</td>
<td>.024a</td>
</tr>
<tr>
<td>Serum progesterone (ng/mL)</td>
<td>8.2 ± 0.9</td>
<td>11.4 ± 1.1</td>
<td>6.30</td>
<td>.023a</td>
</tr>
<tr>
<td>Days to hCG injection (days)</td>
<td>12.1 ± 1.38</td>
<td>10.5 ± 2.52</td>
<td>4.90</td>
<td>.080</td>
</tr>
<tr>
<td>Pregnancy/cycle</td>
<td>76/400 (19.0%)</td>
<td>74/404 (18.3%)</td>
<td>1.88</td>
<td>.78</td>
</tr>
<tr>
<td>Pregnancy/patient</td>
<td>76/205 (37.07%)</td>
<td>74/207 (35.7%)</td>
<td>2.3</td>
<td>.31</td>
</tr>
<tr>
<td>Miscarriage/patient</td>
<td>11 (14.4%)</td>
<td>12 (16.2%)</td>
<td>1.53</td>
<td>.42</td>
</tr>
</tbody>
</table>

a Statistically significant difference: P < .05.

pregnancies or cases of ovarian hyperstimulation syndrome occurred in either group.

In our study, we found no statistically significant difference in the pretreatment endometrial thickness between the two groups or the endometrial thickness at the time of hCG administration. The high estrogen level from multiple follicular growths might compensate for the alleged antiestrogenic effect of CC on the endometrium, but there is little to no compelling evidence to support this idea. Limited endometrial proliferation has been observed in some CC-treated patients (21), but the effect is minor or not at all evident in the large majority of women (22–24). Although some studies have suggested that fecundity may relate to endometrial thickness, others have failed to demonstrate any significant correlation. Indeed, CC has been shown to inhibit steroid hormone production by cultured avian, ovine (25), and human granulosa/luteal cells (26), but estrogen and progesterone levels in CC-induced cycles are typically significantly higher, not lower, than in spontaneous cycles. Adverse effects of CC on mouse ovum fertilization and embryo development have been demonstrated in vitro (27), but circulating levels of CC never reach the concentrations required to produce these effects, even after several consecutive treatment cycles (28).

Taken together, the available evidence and accumulated clinical experience suggest that any adverse antiestrogenic effects of CC present no major obstacle in the majority of treated women, as found in our study. Pregnancy occurred in 76 of 400 cycles in the letrozole group (18.2%) and 78 of 404 cycles (19.3%) in the CC group; the difference was not statistically significant. It is also of note that the cost of letrozole per cycle is much higher than CC, especially when higher doses of letrozole are required (500 vs. 5 Egyptian pounds, respectively).

In addition, the safety of letrozole has been seriously questioned after an abstract presented at the 2005 American Society for Reproductive Medicine (ASRM) meeting examined 130 letrozole pregnancies compared with a large control group of spontaneous conceptions. It suggested that the use of letrozole for infertility treatment might be associated with a higher risk of congenital cardiac malformations in the newborns (29). As a result of that study, on November 17, 2005, Novartis Pharmaceutical, the manufacturer, issued a statement to physicians in Canada and worldwide advising that the use of letrozole in premenopausal women, specifically for ovulation induction, is contraindicated (30). There is no evidence that the exposure of oocytes to letrozole can increase birth defects. A recent study on aromatase-overexpressing mice showed that when these animals were treated with high doses of letrozole for 6 weeks and allowed to conceive 2 weeks later, there was no difference between treated and control animals in terms of litter size, birth weight, and anomalies (31). Mitwally et al. (32) reported favorable pregnancy outcomes and low multiple gestation rates of aromatase inhibitors for ovarian stimulation. A more recent multicenter retrospective study in Canada by Tulandi et al. (33) on pregnancy outcome after letrozole induction of ovulation concluded that the concern about letrozole use for ovulation induction was unproven.

Our study found no superiority of either letrozole or CC for inducing ovulation in women with unexplained infertility before IUI. We found that CC provided a similar pregnancy rate with no statistically significant increase in multiple pregnancies or miscarriage rates. Because the economic aspects of infertility management are of utmost importance, especially in economically disadvantaged regions, CC may be the optimum choice for an oral agent in an IUI program.

REFERENCES


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