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Use of an aromatase inhibitor for induction of ovulation in patients with an inadequate response to clomiphene citrate

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Objective: To use aromatase inhibition for induction of ovulation in women in whom clomiphene citrate (CC) treatment was unsuccessful.

Design: Prospective trial in infertility patients treated with CC.

Setting: Two tertiary-referral infertility clinics associated with the Division of Reproductive Sciences, University of Toronto.

Patient(s): Twelve patients with anovulatory polycystic ovary syndrome (PCOS) and 10 patients with ovulatory infertility, all of whom had previously received CC with an inadequate outcome (no ovulation and/or endometrial thickness of ≤0.5 cm).

Intervention(s): The aromatase inhibitor letrozole was given orally in a dose of 2.5 mg on days 3–7 after menses.

Main Outcome Measure(s): Occurrence of ovulation, endometrial thickness, and pregnancy rates.

Result(s): With CC treatment in patients with PCOS, ovulation occurred in 8 of 18 cycles (44.4%), and all ovulatory cycles for the women included in this study had endometrial thickness of ≤0.5 cm. In 10 ovulatory patients, 15 CC cycles resulted in a mean number of 2.5 mature follicles, but all cycles had endometrial thickness of ≤0.5 cm on the day of hCG administration. With letrozole treatment in the same patients with PCOS, ovulation occurred in 9 of 12 cycles (75%) and pregnancy was achieved in 3 patients (25%). In the 10 patients with ovulatory infertility, letrozole treatment resulted in a mean number of 2.3 mature follicles and mean endometrial thickness of 0.8 cm. Pregnancy was achieved in 1 patient (10%).

Conclusion(s): Oral administration of the aromatase inhibitor letrozole is effective for ovulation induction in anovulatory infertility and for increased follicle recruitment in ovulatory infertility. Letrozole appears to avoid the unfavorable effects on the endometrium frequently seen with antiestrogen use for ovulation induction. (Fertil Steril® 2001;75:305–9. ©2001 by American Society for Reproductive Medicine.)

Key Words: Aromatase inhibitors, letrozole, clomiphene citrate, PCOS, ovulation, infertility

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In women with World Health Organization type II anovulatory infertility, the treatment of first choice for the induction of ovulation is an antiestrogen, most commonly clomiphene citrate (CC) (1, 2). However, 20%–25% of women are resistant to CC and do not ovulate. In addition, clinical data have revealed a discrepancy between ovulation and conception rates during CC treatment and a higher than expected incidence of miscarriage in conception cycles (3–6). These observations have been attributed to the antiestrogenic mechanism of action of CC, which involves long-lasting estrogen receptor (ER) depletion. It also appears that CC accumulates in the body because of its long half-life (7). As a result, CC may have a negative effect on the quality and quantity of cervical mucus (8), on endometrial development (9), and on other as yet undetermined fertility factors (10, 11).

After failure of CC, gonadotropin preparations such as hMG or pure FSH have been used as a second-line treatment for ovulation induction. In women with polycystic ovary syndrome (PCOS), because of the high sensitivity of the ovaries to gonadotropin stimulation, treatment with hMG or pure FSH is difficult to control and characteristically induces several ovulatory follicles, leading to the risk of multiple pregnancies and ovarian hyperstimulation

syndrome (OHSS) (12). Therefore, a simple oral treatment that could be used without risk of hyperstimulation and with minimal monitoring would be the preferred therapy.

In addition, although it has been established that pregnancy rates for women who take CC are lower than expected on the basis of ovulation rates, CC therapy is widely administered to induce multiple ovulation in ovulatory women suffering from unexplained infertility. In these women, CC is anticipated to improve the outcome of infertility treatment by increasing the number of oocytes available for fertilization (13). However, the use of CC in unexplained infertility may be complicated because of antiestrogenic effects on endometrial development. For these reasons, a simple, inexpensive, and safe alternative to CC for use in normally ovulatory women is also required.

We hypothesized that it may be possible to mimic the action of CC without depletion of ERs by administration of an aromatase inhibitor in the early part of the menstrual cycle. This would result in release of the hypothalamic/pituitary axis from estrogenic negative feedback, increasing gonadotropin secretion and resulting in stimulation of ovarian follicle development. A group of new, highly selective aromatase inhibitors has been approved for use in postmenopausal women with breast cancer to suppress estrogen production. These aromatase inhibitors have a relatively short half-life compared with CC and therefore would be eliminated from the body rapidly (14, 15). In addition, because ER down-regulation does not occur, no adverse effects on estrogen target tissues, as observed in CC-treated cycles, would be expected.

In the present study, we present our preliminary experience with the use of the aromatase inhibitor letrozole in a selected group of women who demonstrated failure to ovulate or adverse endometrial effects after treatment with CC.

MATERIALS AND METHODS

Twenty-two patients who attended the outpatient clinics of the Reproductive Biology Unit at the University Health Network, Toronto General Hospital, and the Toronto Center for Advanced Reproductive Technology participated in this study. Both clinics are part of the Division of Reproductive Sciences, Department of Obstetrics and Gynecology, University of Toronto.

We obtained approval from the University of Toronto research ethics committee to use the aromatase inhibitor letrozole in women who failed to respond adequately to CC. We defined inadequate response to CC as unsuccessful ovulation induction, determined by serial ultrasound and serum E_2 and LH monitoring, or ovulation with a very thin endometrium ($\leq$0.5 cm) on the day of the LH surge or when hCG would normally be administered. Patients who failed to respond adequately to CC were offered the option of trying letrozole as an alternative treatment for induction of ovulation or to supplement ovulation.

The study patients consisted of two groups. Group 1 included 12 patients who had anovulatory infertility as a result of PCOS. PCOS was diagnosed according to National Institutes of Health consensus criteria (16). The second group included 10 ovulatory patients who had unexplained infertility (7 patients), male factor infertility (2 patients), and endometriosis (1 patient) who were being monitored for intrauterine insemination or timed intercourse.

All patients had received CC in a total of 33 previous stimulation cycles. CC was used for induction of ovulation in anovulatory patients with PCOS (18 CC cycles) and for superovulation in ovulatory patients (15 CC cycles). Inadequate response to CC was defined as failure of ovulation (10 cycles) or ovulation with an endometrial thickness of $\leq$0.5 cm (23 cycles). Inadequate endometrial thickness despite ovulation was seen in 8 cycles in 8 patients with PCOS and in all 15 cycles in the 10 ovulatory patients. The remaining 4 patients with PCOS tried CC for 10 cycles, all of which were anovulatory. In these 10 cycles in which ovulation failed to occur, CC was given in a dose of 50–100 mg/d for 5 days starting on day 3 or 5 of the menstrual cycle, depending on the preference of the attending physician.

The 22 study patients then completed one letrozole cycle each. In all patients, letrozole (Femara; Novartis, East Hanover, NJ) treatment was given orally at least 2 months after the last CC cycle, in a dose of 2.5 mg/d, from days 3 to 7 of the menstrual cycle. A 2-month washout period before the letrozole cycles was used to eliminate any posttreatment effect of CC. Patients were followed by follicular monitoring with transvaginal ultrasound and serial measurements of estrogen and LH starting on day 7 of the menstrual cycle, and according to the growth of the follicles thereafter (usually every other day).

Endometrial thickness was assessed as we have described previously (9) and as performed routinely in our clinic for the last 10 years. Briefly, the endometrial thickness was measured at the greatest diameter perpendicular to the midsagittal plane in the fundal region, including both layers of the endometrial cavity. The image was oriented so that the endometrial canal and the cervical canal were visualized in the same plane to ensure measurement through the center of the endometrium.

We administered hCG (10,000 IU SC, Profasi; Serono, Oakville, Ontario, Canada) to trigger ovulation when at least one mature follicle ($\geq$2.0 cm) developed, followed by timed intercourse or intrauterine insemination. In patients receiving ovulation induction for intrauterine insemination or timed intercourse in whom an LH surge is detected, our clinic policy is to administer hCG to supplement the surge. Identical criteria were used for administration of hCG in both the CC- and letrozole-treated cycles.

TABLE 1

Characteristics of letrozole and CC treatment cycles in anovulatory patients with PCOS.

Variable	Mean value for letrozole treatment (± SD)	Mean value for CC treatment (± SD)	*P* value	Range for letrozole treatment	Range for CC treatment	Median for letrozole treatment	Median for CC treatment
Day of hCG administration	14.2 ± 2.1	14.8 ± 2.7	NS	12–18	11–19	14	14
Endometrial thickness (cm) on day of hCG	0.81 ± 0.14	0.62 ± 0.25	<.01	0.7–1.1	0.3–1.2	0.8	0.6
Follicles >1.5 cm on day of hCG	2.1 ± 0.93	1.9 ± 1.6	NS	1–4	1–5	2	2
E_2 (pmol/L) on day of hCG	962 ± 654	1,638 ± 1,406	<.01	344–2,347	178–5,210	844	1,174
E_2 per mature follicle (pmol/L)	444 ± 256	830 ± 279	<.01	172–786	278–1,174	347	917
LH on day of hCG (IU/L)	22 ± 22	19 ± 14	NS	6–66	5.6–43	9.6	10.1

Note: Letrozole gave 9 ovulatory cycles among a total of 12 cycles; CC gave 8 ovulatory cycles among a total of 18 cycles. NS = not significant.

Mitwally. Letrozole for induction of ovulation. Fertil Steril 2001.

Results of letrozole and CC treatment cycles were described as means ± SD, range, and median of each variable for anovulatory patients with PCOS and ovulatory patients. Where appropriate, a group *t*-test or Student's *t*-test was used to compare data. The statistical tests were performed with GraphPad Prism Version 3 software (GraphPad Software Inc., San Diego, CA).

RESULTS

Patients in the first group (12 patients with PCOS) had 18 CC cycles. Patients were scheduled for timed intercourse in 16 cycles and intrauterine insemination in 2 cycles. Ovulation occurred in 8 cycles (44.4%) with an endometrial thickness of ≤0.5 cm. The remaining 10 CC cycles were anovulatory. No pregnancy was achieved in any of the ovulatory cycles. Each patient subsequently received 1 letrozole treatment cycle. Ten of the 12 patients with PCOS were scheduled for timed intercourse and the remaining 2 for intrauterine insemination. During letrozole treatment, ovulation occurred in 9 patients (75%), including 3 of the 4 patients who were anovulatory with CC. Pregnancy was achieved in 3 cycles (25%), 2 of which were singleton clinical pregnancies and 1 of which was a chemical pregnancy. All 3 pregnancies resulted from timed intercourse cycles. Table 1 shows the characteristics of the CC and letrozole treatment cycles in anovulatory patients with PCOS.

Patients in the second group (10 patients) had 15 CC cycles. Ovulation occurred in all cycles. The mean number of follicles measuring >1.5 cm on the day of hCG administration was 2.5 follicles (range, 1–5). However, the endometrial thickness was ≤0.5 cm in all cycles, and no pregnancy was achieved. Each patient subsequently received one letrozole treatment cycle. During letrozole treatment, ovulation occurred in all cycles. The mean number of follicles measuring >1.5 cm on the day of hCG administration was 2.3 (range, 1–4). Follicles of >1.5 cm on the day of hCG administration were distributed as follows: One patient had 1 follicle, 6 patients had 2 follicles each, 2 patients had 3 follicles each, and 1 patient had 4 follicles. A singleton clinical pregnancy (10%) resulted from timed intrauterine insemination in one couple with unexplained infertility who developed 2 follicles of >1.5 cm. Table 2 shows the characteristics of the CC and letrozole treatment cycles in the group of 10 ovulatory patients.

On the day of hCG administration in patients with PCOS, the mean serum E_2 concentration was 962 pmol/L in letrozole treatment cycles, versus 1,638 pmol/L in CC treatment cycles. In ovulatory patients, the serum E_2 level was 719 pmol/L in letrozole treatment cycles versus 3,003 pmol/L in CC treatment cycles. Mean endometrial thicknesses on the day of hCG administration in patients with PCOS and ovulatory patients was 0.81 and 0.89 cm with letrozole, compared with 0.62 and 0.52 cm in CC treatment cycles, respectively.

At the time of writing, the three clinical pregnancies had resulted in a normal live birth and two ongoing singleton pregnancies.

DISCUSSION

CC is the most commonly prescribed medication for ovulation induction. It is believed that CC initiates or augments ovulation by blocking negative feedback of endogenous estrogen at the level of the hypothalamus and pituitary, promoting an increase in the pulsatile release of LH and FSH (12, 17). A considerable body of experimental evidence suggests that, in addition to its desirable central action of stimulating a transient increase in gonadotropin secretion, CC

TABLE 2

Characteristics of letrozole and CC treatment cycles in ovulatory patients.

Variable	Mean value for letrozole treatment (± SD)	Mean value for CC treatment (± SD)	*P* value	Range for letrozole treatment	Range for CC treatment	Median for letrozole treatment	Median for CC treatment
Day of hCG administration	11.6 ± 2.6	10.5 ± 1.6	NS	8–16	8–13	12	10
Endometrial thickness (cm) on day of hCG	0.89 ± 0.12	0.5 ± 0.1	<.001	0.7–1.1	0.3–0.6	0.9	0.5
Follicles >1.5 cm on day of hCG	2.3 ± 0.8	2.5 ± 1	NS	1–4	1–5	2	2
E_2 (pmol/L) on day of hCG	719 ± 411	3,003 ± 1,422	<.001	357–1,674	559–6,782	548	2,756
E_2 per mature follicle (pmol/L)	344 ± 217	1,366 ± 683	<.001	136–837	280–2,755	257	1,378
LH on day of hCG (IU/L)	17 ± 14	13 ± 7	NS	3.6–40	3–29	8	12.7

Note: Letrozole = 10 cycles; CC = 15 cycles. NS = not significant.

Mitwally. Letrozole for induction of ovulation. Fertil Steril 2001.

may have other unintended and potentially detrimental effects on peripheral estrogen target tissues (18).

Letrozole (4,4′-[1H-1, 2, 4-triazol-1-ylmethylene]-bis-benzonitrile) is a specific, reversible, nonsteroidal aromatase inhibitor that suppresses estrogen biosynthesis. It is currently administered orally to postmenopausal patients with advanced breast cancer to reduce the estrogen produced by peripheral androgen aromatization. Continuous administration of letrozole up to 5 mg/d produced marked suppression of E_2, estrone, and estrone sulfate, with very few side effects (14, 15). The disposition of letrozole in healthy postmenopausal women is characterized by steady-state plasma concentrations in 4–8 hours and a half-life of approximately 45 hours. The absolute systemic bioavailability of letrozole after oral administration was 100% compared with the same dose given IV (19).

We hypothesized that letrozole administration in the early part of the menstrual cycle would release the pituitary/hypothalamic axis from estrogenic negative feedback, similar to the effect of CC but without ER down-regulation and the adverse endometrial and cervical mucus effects seen with CC. The subsequent increase in gonadotropin secretion could stimulate ovarian follicle development, as reported previously in the Bonnet monkey (20). In addition, letrozole is eliminated from the body rapidly (half-life of 45 hours). In the letrozole-treated cycles, the endometrium was of adequate thickness to allow implantation even though estrogen levels were two- to threefold lower than observed in CC cycles. This observation supports the absence of any direct antiestrogenic effects of letrozole on the endometrium. The rapid elimination and reversibility of letrozole appeared to allow the endometrium to respond well to rising estrogen levels in the late follicular phase.

Further research in our program is ongoing to determine whether other mechanisms could be acting to initiate and stimulate follicle development in letrozole-treated cycles. One alternative hypothesis is that letrozole may act locally in the ovary to increase follicular sensitivity to FSH. This may result from accumulation of intraovarian androgens because conversion of androgen substrate to estrogen is blocked. Recent data support a stimulatory role for androgens in early follicular growth in primates, in contrast to the inhibitory effect observed in rodents (21). Testosterone was found to augment follicular FSH receptor expression in primates, which suggests that androgens promote follicular growth and estrogen biosynthesis indirectly by amplifying FSH effects (22–24). In addition, androgen accumulation in the follicle may stimulate insulin-like growth factor, along with other endocrine and paracrine factors, which may synergize with FSH to promote folliculogenesis (25–27).

Women with ovulatory disorders who are resistant to standard doses of CC generally become candidates for gonadotropin therapy. However, severe OHSS and the high risk of multiple pregnancy are major disadvantages of gonadotropin treatment, especially in young women with PCOS. Some investigators have proposed combined CC and low-dose glucocorticoid therapy for the treatment of CC-resistant anovulation (28–31). Although this form of therapy can be successful in women with hyperandrogenism, a disadvantage is the potential for glucocorticoid-related side effects. Other investigators have described the use of extended duration and higher doses of CC (32–35).

We report the novel use of the aromatase inhibitor letrozole for inducing ovulation in anovulatory women with PCOS and for augmenting ovulation in ovulatory infertile women. In a group of women with PCOS who did not have an adequate response to CC, ovulation occurred in 75% of letrozole treatment cycles and clinical pregnancy was achieved in 17% of the cycles. In the group of ovulatory

women, ovulation was augmented and more than one mature follicle was obtained in 9 of 10 patients (90%).

Because patients were scheduled for timed intercourse or intrauterine insemination of washed sperm, hCG was used to trigger ovulation or to supplement the LH surge when at least one follicle measured ≥2.0 cm. This same criterion was applied to both CC and letrozole cycles. Compared with CC, letrozole produced a significantly thicker endometrium on the day of hCG administration despite the significantly lower E_2 levels in both patients with PCOS and the ovulatory patients. This observation confirms the deleterious effect of CC on endometrial growth that is believed to be due to depletion of endometrial ERs. No apparent adverse effect on the endometrium was seen with letrozole treatment.

In summary, the results of this preliminary study suggest that the aromatase inhibitor letrozole is an orally effective, inexpensive method for stimulating follicular development. Aromatase inhibitors have potential as alternatives to, or even replacements for, CC as a first-line treatment for ovulation induction in anovulatory infertility and for augmentation of ovulation in ovulatory infertility patients.

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