

# The Efficacy of Letrozole in Women with a Poor Endometrial Response to Clomiphene Citrate

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## 클로미펜에 불량한 자궁내막 발달을 보이는 여성에서 레트로졸의 유용성

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**목적:** 클로미펜을 이용한 배란유도 주기에서 불량한 자궁내막 발달을 보이는 불임 여성에서 레트로졸의 효용성을 알아보고자 하였다.

**연구방법:** 2004년 3월부터 2009년 8월까지 분당서울대학교병원에서 클로미펜을 이용한 배란유도 주기에서 자궁내막 두께가 6.5 mm 이하여서 다음 주기에 레트로졸을 사용하였던 18명의 불임 여성을 선정하였다. 환자들의 평균 연령은 30.7±2.8세, 불임 기간은 33.1±26.6개월이었다. 불임의 인자는 자궁내막증이 1명, 다낭성난소증후군이 5명, 원인불명의 불임증이 12명이었다. 레트로졸은 2.5 mg의 용량으로 월경 3~5일 사이에 시작하여 5일간 투여하였다.

**결과:** 이전 클로미펜 사용시와 비교하였을 때 레트로졸 주기에서 우성난포의 개수는 더 적었으나 (1.1±0.3 vs. 2.2±1.5,  $p=0.011$ ) 자궁내막 두께는 유의하게 증가하였으며 (8.4±1.7 mm vs. 5.8±0.5 mm,  $p<0.001$ ) 자궁내막 패턴 중 type C의 빈도는 이전 클로미펜 주기에서 50%이었던 것이 레트로졸 사용시 94.4%로 유의한 증가를 보였다 ( $p=0.036$ ). 레트로졸을 이용한 배란 유도 주기에서 임신율은 11.1%였다.

**결론:** 얇은 자궁내막 발달을 보였던 클로미펜 주기에 비해 레트로졸 사용시 자궁내막이 좀 더 두꺼워지고 패턴이 호전되는 것으로 보아 클로미펜에 불량한 자궁내막을 보이는 여성에서 이차 선택약제로 레트로졸의 사용은 유용한 방법으로 사료된다.

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**중심단어:** 레트로졸, 클로미펜, 배란유도, 자궁내막

Although clomiphene citrate (CC) has been used widely as an ovulation-inducing agent in women with ovulatory disorder or unexplained infertility, its anti-estrogenic property can cause detrimental effects on endometrium or cervical mucus in 15~50% of the CC users.<sup>1,2</sup> In addition, 20~25% of women with polycystic

ovary syndrome (PCOS) are refractory to CC despite administration of higher dose. Aromatase inhibitors, as an alternative ovulation-inducing agent, are first introduced in 2001 by Mitwally et al. in CC-refractory cases.<sup>3</sup> Since aromatase inhibitors do not bind to estrogen receptor, it can be expected to have no anti-estrogenic effect.<sup>4,6</sup> It can be also advantageous that aromatase inhibitors have a relatively short half-life (~45 hours) and a few side effects; they usually induce mono-follicular ovulation, thus eliminating ovarian hyperstimulation syndrome

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(OHSS) and multi-fetal gestations.<sup>7</sup>

There have been four randomized controlled trials (RCTs) comparing directly the efficacy between aromatase inhibitor (letrozole) and CC as a first-line ovulation-inducing agent in women with PCOS.<sup>8~11</sup> A recent meta-analysis including these four RCTs denoted that letrozole has a similar ovulation and pregnancy rate compared with CC, hence it appears not to be superior to CC.<sup>12</sup> However, use of letrozole yielded a higher ovulation (54.6%) and pregnancy rate (25%) in CC-refractory women.<sup>6</sup> Use of letrozole also showed similar outcomes to CC + metformin in women failed to ovulate by using CC alone.<sup>13</sup> A recent report indicates that letrozole is superior to CC 150 mg in PCOS women who failed to ovulate by the use of CC 100 mg.<sup>14</sup> Therefore, letrozole is favored in women failed to ovulate by CC; moreover, it clearly reduces multi-fetal gestations and does not induce anti-estrogenic effect.<sup>15,16</sup>

There have been mixing results with regards the effect of aromatase inhibitors on the endometrium; someone reported a superiority of letrozole,<sup>8,10</sup> or others did not.<sup>9,11</sup> Use of aromatase inhibitors has been recommended in cases with thin endometrium after the use of CC, but there have been no direct evidences regarding its efficacy. In the present study, we investigated the efficacy of letrozole use in women with poor endometrial response to CC.

## MATERIALS AND METHODS

We retrospectively selected eighteen women in whom poor endometrial response to CC was noted and letrozole used in a subsequent cycle during March 2004 to August 2009 at the Seoul National University Bundang Hospital. The mean age of the women was  $30.7 \pm 2.8$  years (range 28~37) and the mean duration of infertility was  $33.1 \pm 26.6$  months. Eight women had primary infertility. The infertility factors were identified as corrected endo-

metriosis (n=1), PCOS (n=5), and unexplained (n=11). One patient had undergone a laparoscopic surgery due to bilateral endometriomas, but had no evidence of endometriosis at the time of ovulation induction. Among the women with unexplained infertility, two women had undergone hysteroscopic resection of submucosal myomas and two had undergone hysteroscopic polypectomy.

In the previous CC cycle, 50~100 mg of CC (Clomiphene<sup>®</sup>, Youngpoong Pharma.) was administered for 5 days. The mean number of the previous CC cycle was  $1.2 \pm 0.5$ ; one cycle (n=15), two cycles (n=2), and three cycles (n=1). One to six mature follicles ( $\geq 15$  mm) were observed in all of the women except one in whom only one follicle with 13 mm in diameter was observed. However, all of the women had a thin endometrium ( $\leq 6.5$  mm) at the time of LH surge or triggering (mean 5.8 mm, range 4.4~6.5 mm). In the subsequent cycle, letrozole (Femara<sup>®</sup>, Novartis) 2.5 mg was administered for 5 days in all of the women. When mature follicles reached 18 mm or more, ovulation was triggered by urinary hCG (IVF-C<sup>®</sup>, IBSA) 5,000 IU or recombinant hCG (Ovidrel<sup>®</sup>, Serono) 250  $\mu$ g and then encouraged coitus 1~2 days later. Endometrial thickness was measured by using transvaginal ultrasonography; on uterine longitudinal view, distance between both myometrial-endometrial junctions was measured (from outer margin of hyper-echoic stripe). Endometrial pattern was classified as three types using the criteria suggested by Gonen et al. (type A: entirely homogeneous, hyper-echogenic pattern without a central echogenic line, type B: intermediate iso-echogenic pattern with the same reflectivity as the surrounding myometrium and a non-prominent or absent central echogenic line, and type C: a multilayered 'triple-line' endometrium consisting of a prominent outer and central hyper-echogenic line and inner hypo-echogenic or black region).<sup>17</sup>

Data were presented as mean  $\pm$  S.D. and analyzed

**Table 1.** Outcomes of ovulation induction in previous clomiphene and subsequent letrozole cycle in eighteen women

	Letrozole cycle (n=18)	Range	Previous clomiphene cycle (n=18)	Range	P
Duration of ovulation induction	12.2±1.4	10~15	12.9±1.7	11~17	NS
At triggering or LH surge day					
No. of follicles ≥15 mm	1.1±0.3	1~2	2.2±1.5	0~6	0.011
Endometrial thickness (mm)	8.4±1.7	5.8~12.0	5.8±0.5	4.4~6.5	<0.001
Endometrial pattern					
A	0		5		0.036
B	1		4		
C	17		9		

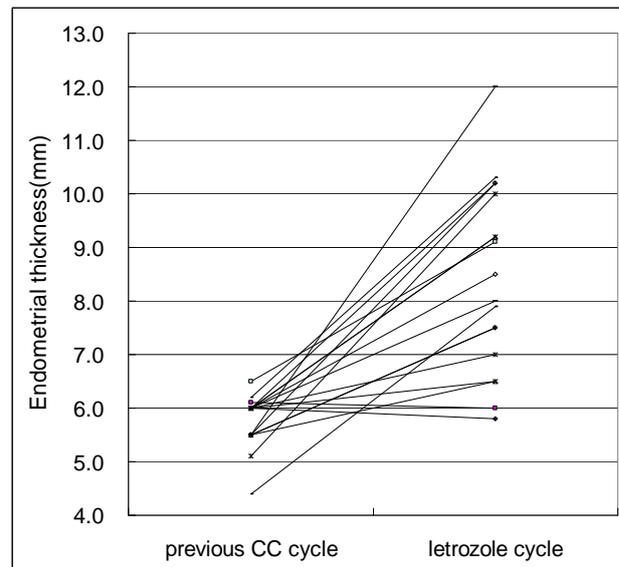
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using MedCalc Software (ver. 6.10, Mariakerke, Belgium). The paired Student's t-test was used to compare the means and Chi-square test was used to compare the proportions. A *p* value less than 0.05 was considered as statistically significant.

## RESULTS

In the subsequent letrozole cycles, time to ovulation was similar, but the number of mature follicle was significantly lower and the endometrial thickness at triggering or LH surge day was significantly higher when compared with the previous CC cycles (Table 1). Individual endometrial thickness in the previous CC and the subsequent letrozole cycle in eighteen women were illustrated in Figure 1. In the subsequent letrozole cycles, endometrial thickness was rather decreased in two women and was still less than 7 mm in four women. The two women who showed decreased endometrial thickness had a history of previous hysteroscopic resection of submucosal myomas.

The incidence of 'type C' endometrium was 50% in the previous CC cycle, but this was increased to 94.4% after the use of letrozole. Among five women showed 'type A' in the previous CC cycle, 'type B' was noted in



**Figure 1.** Individual endometrial thickness at triggering or LH surge day in previous clomiphene (CC) and subsequent letrozole cycle in eighteen women

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one and 'type C' was noted in four women. All of the four women, in whom 'type B' showed in the previous CC cycle, were changed to 'type C'. Two women were pregnant after the use of letrozole hence the pregnancy rate was 11.1%; the endometrium was changed from 5.1 mm ('type A') to 10.0 mm ('type C') in one woman,

**Table 2.** Prospective, randomized studies on comparison of the efficacy of aromatase inhibitors versus clomiphene citrate (CC) as a first-line treatment for ovulation induction in women with polycystic ovary syndrome

Author (year) <sup>ref. no.</sup>	Comparison groups	Number of cycles	Ovulation rate	Pregnancy rate	*EMT (mm)
Atay (2006) <sup>8</sup>	Letrozole 2.5 mg	51	82.4% <sup>†</sup>	21.6% <sup>†</sup>	8.4 <sup>†</sup>
	CC 100 mg	55	63.6%	9.1%	5.2
Bayar (2006) <sup>9</sup>	Letrozole 2.5 mg	99	65.7%	9.1%	8.0
	CC 100 mg	95	74.7%	7.4%	8.0
Sohrabvand (2006) <sup>10</sup>	Letrozole 2.5 mg + metformin	29	90.6%	19%	8.2 <sup>†</sup>
	CC 100 mg + metformin	30	80.6%	7%	5.5
Badawy (2009) <sup>11</sup>	Letrozole 5 mg	540	67.5%	15.1%	8.1 <sup>†</sup>
	CC 100 mg	523	70.9%	17.9%	9.2
Badawy (2009) <sup>32</sup>	Anastrozole 1 mg	115	67.9%	10.2%	10.1 <sup>†</sup>
	CC 100 mg	101	68.6%	7.9%	8.2

\*EMT: endometrial thickness, <sup>†</sup> $p < 0.05$ .

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and from 6.0 mm ('type B') to 6.5 mm ('type C') on the other women.

## DISCUSSION

There have been four RCTs comparing directly the efficacy between aromatase inhibitor and CC as a first-line ovulation-inducing agent in women with PCOS (Table 2). Atay et al. reported a significantly higher ovulation and pregnancy rate in letrozole group, but this was not confirmed in other trials. In Sohrabvand' study, only CC-refractory women were included, and they compared the efficacy between CC + metformin and letrozole + metformin.<sup>10</sup> In CC-refractory women, letrozole alone was reported to have similar outcome compared with CC + metformin,<sup>13</sup> hence a superiority of letrozole over CC was not evident in Sohrabvand' study. Badawy et al. reported a large-scaled trial, but they used letrozole 5 mg, unlike other trials.<sup>11</sup> Although they reported similar ovulation and pregnancy rate, the endometria were rather thinner in letrozole group. A

recent meta-analysis<sup>12</sup> and two review articles<sup>16,18</sup> pointed out that more studies are needed to confirm the efficacy of aromatase inhibitor as a first-line ovulation-inducing agent in women with PCOS.

Aromatase inhibitors are first introduced in 2001 as an alternative in women showing inappropriate response to CC.<sup>3</sup> Inappropriate response to CC was defined by failed ovulation or poor endometrial response (<5 mm) after use of CC 50~100 mg. In twelve PCOS women, eight ovulated cycles were noted amongst 18 cycles, but endometrial thickness was less than 5 mm in all of CC cycles. In ten women with unexplained infertility and/or mild male factor, average 2.5 mature follicles was observed, but endometrial thickness was less than 5 mm in all of CC cycles. After use of letrozole 2.5 mg, nine out of 12 PCOS women were ovulated. Mean endometrial thickness was 8.1 mm and three women were pregnant. In ten women with unexplained infertility, average 2.3 mature follicles was observed and mean endometrial thickness was 8.9 mm after use of letrozole.

Thereafter, Begum et al. reported that letrozole yielded

mature follicles in 90% women who showed inadequate response to poor ovulation to CC; the endometrial thickness was significantly higher (9.4 mm vs. 5.8 mm) and the pregnancy rate was 26%.<sup>19</sup> Among 44 PCOS women refractory to six times CC trials up to 150 mg, ovulation occurred in 24 women and pregnancy was established in six women.<sup>6</sup> High body mass index, amenorrhea, and old age have been known to be the factors related with CC-resistant,<sup>20</sup> however, no factors were identified as predicting ovulation when letrozole used.<sup>6</sup>

Use of letrozole showed similar outcomes to CC + metformin in women failed to ovulate by using CC alone.<sup>13</sup> In 64 PCOS women failed to ovulate by using CC 100 mg, use of letrozole (7.5 mg) was superior to CC 150 mg (ovulation 62.5% vs. 37.5%; pregnancy rate 40.6% vs. 18.8%).<sup>14</sup> In that study, a relatively high dose of letrozole was used. In general, 2.5 mg or 5 mg of letrozole has been known to be appropriate for 5-day administration and the dose more than 5 mg may hamper adequate endometrial development. However, high dose letrozole appears to be safe in CC-resistant PCOS women because Begum' study demonstrated good endometrial development after use of letrozole (mean endometrial thickness: 10.4 mm in letrozole group, 9.0 mm in CC group).

In 218 PCOS women who failed to ovulate by using CC 100 mg, administration of letrozole 5 mg showed similar outcomes between 5- and 10-day administration, but follicle number and pregnancy rate was significantly higher in 10-day administration group (17.4% vs. 12.4%).<sup>21</sup> Taken together, letrozole could be successfully used in CC-resistant PCOS women, although it is not recommended as a first-line choice.

Since our study was focused on endometrial thickness, instead of ovulation, the characteristics of the study subjects were different with those in the study by Mitwally.<sup>3</sup> Our study subjects had endometrial thickness

6.5 mm or less despite adequate ovulation after the use of CC. In general, women having endometrial thickness less than 6 mm are less likely pregnant,<sup>22,23</sup> and it should be 7 mm or more for successful implantation.<sup>24~26</sup> The criteria of thin endometrium was 6.5 mm in our study and we attempted to investigate whether the use of letrozole is useful as a second-line therapy in infertile women showing a poor endometrial development at previous ovulation induction cycle by using CC. As a result, the use of letrozole yielded an improvement of endometrial development despite lower number of follicles; hence we concluded that letrozole is useful as a second-line therapy.

In 64 women with unexplained infertility who failed to conceive by using at least three times CC trials, administration of letrozole 5 mg in the next cycle resulted in an improvement of endometrial development, which is consistent with our result.<sup>27</sup>

Several trials have been made to compare aromatase inhibitors with CC as a first-line therapy in women with unexplained infertility. Earlier report indicated that letrozole 2.5 mg resulted in fewer follicle but thicker endometrium when compared with CC 100 mg.<sup>28</sup> A recent large-scaled prospective trial denoted that pregnancy, multi-fetal pregnancy, and abortion rates were similar between groups with letrozole 5 mg, anastrozole 1 mg, and CC 100 mg.<sup>29</sup> Those results were consistent with a previous meta-analysis.<sup>30</sup> In women with unexplained infertility, dose of letrozole appears not to be correlated with clinical outcomes.<sup>31</sup>

There were few studies about anastrozole. In PCOS women, use of anastrozole 1 mg had similar ovulation and pregnancy rate when compared with CC 100 mg, but endometria were thicker in anastrozole group, as shown in Table 2.<sup>32</sup> In CC-resistant PCOS women, use of anastrozole 1 mg resulted in more thin endometrium (6.5 mm vs. 8.2 mm), lower ovulation (60% vs. 84.4%) and pregnancy rate (16.6% vs. 27%) when compared

with letrozole 2.5 mg.<sup>33</sup> However, in a subsequent study, endometria were more thick (10.2 mm vs. 9.1 mm) in anastrozole group and similar ovulation (63.4% vs. 62%) and pregnancy rate (15.1% vs. 12.2%) was noted between anastrozole and letrozole.<sup>34</sup>

Debate on the safety of letrozole has been emerged after publication of one abstract presented in the Annual Meeting of the American Society for Reproductive Medicine (2005). Based on the data from Montreal Fertility Center, malformation rate was 4.7% amongst 150 babies conceived after use of letrozole for two years. In contrast, malformation rate was 1.8% among 36,050 newborns delivered by low-risk mothers at the St. Mary Hospital during the past 10 years. Although the overall rates did not differ statistically, two heart anomalies and three musculoskeletal anomalies were identified in letrozole group and this was significantly higher when compared with control group.<sup>35</sup> Thereafter, Novartis company (brand name: Femara) recommended that letrozole should not be used for ovulation induction. However, it has been criticized that control group is inappropriate because non-infertility women and low-risk mothers were included in control group. Furthermore, it was problematic because female age (letrozole: 35.2, control: 30.5 years) and multi-fetal pregnancy rates were different between the two groups.<sup>36</sup>

Several studies have been published regarding non-increasing malformation rate by using letrozole. A large-scaled retrospective study (data collected from five centers in Canada) denoted that use of letrozole did not increase malformation and major malformation rate; 2.4% and 1.2% in letrozole group, 4.8% and 3.0% in CC group.<sup>37</sup> In that study, heart anomaly was significantly lower in letrozole group (0.2% vs. 1.8%,  $p=0.02$ ). In a subsequent study, lower malformation rate was observed in letrozole group (0%) compared with CC group (2.6%) or natural pregnancy (3.2%).<sup>38</sup> It assumed to be safe because aromatase inhibitors have a short half-life (~45

hours) and usually used during 5 days in early follicular phase.<sup>12,36,39</sup> However, this topic should be further clarified.

Thin endometrium could be resulted from Asherman's syndrome, endometritis, and use of oral contraceptives, as well as anti-estrogenic effect of CC (mainly impact of zu-clomiphene form).<sup>40</sup> The strategies for thin endometrium include low dose aspirin, intravaginal sildenafil, vitamin E, and/or pentoxifylline, but the striking evidences are still lacking. In our study, the authors feel that use of letrozole appears to be an effective strategy for second-line treatment in women with inadequate endometrial response to CC. Use of letrozole was associated with more thick and improved endometrium than previous CC cycles in which thin endometrium was identified. Our study has a limit because endometrial status in the natural cycle was not described. Since four women had endometrial thickness less than 7 mm despite the use of letrozole, further investigations will be needed to clarify the etiology.

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= Abstract =

**Objective:** To examine the efficacy of letrozole in infertile women showing a poor endometrial development at previous ovulation induction cycle by using clomiphene citrate.

**Methods:** Eighteen infertile women were selected who showed a poor endometrial development (endometrial thickness  $\leq 6.5$  mm) after clomiphene treatment (50~100 mg) as ovulation induction for timed coitus. The mean age of the patients was  $30.7 \pm 2.8$  years old and the mean duration of infertility was  $33.1 \pm 26.6$  months. The infertility factors were identified as corrected endometriosis (n=1), polycystic ovary syndrome (n=5) and unexplained (n=12). Letrozole was given orally in a dose of 2.5 mg for 5 days starting 3~5 of menstrual cycle.

**Results:** The number of follicles was significantly lower in the letrozole cycle when compared with previous clomiphene cycle ( $1.1 \pm 0.3$  vs.  $2.2 \pm 1.5$ ,  $p=0.011$ ). The endometrial thickness (mm) at the time of triggering or LH surge was significantly greater in the letrozole cycle ( $8.4 \pm 1.7$  vs.  $5.8 \pm 0.5$ ,  $p<0.001$ ). The endometrial pattern 'type C' was significantly higher in the letrozole cycle (94.4% vs. 50%,  $p=0.036$ ). The pregnancy was achieved in 11.1% of the letrozole cycle.

**Conclusion:** Use of letrozole was associated with more thick and improved endometrium than previous clomiphene cycles in which thin endometrium was identified. Use of letrozole appears to be an effective strategy for second-line treatment in women with inadequate endometrial response to clomiphene.

**Key Words:** Letrozole, Clomiphene, Ovulation induction, Endometrium

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