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Research Article

EFFICACY OF LETROZOLE AND CLOMIPHENE IN PATIENTS WITH MULTIPLE-CAUSE INFERTILITY UNDERGOING INTRAUTERINE INSEMINATION

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ABSTRACT

What is known: Clomiphene is commonly used in infertility treatment prior to intrauterine insemination (IUI). In treatment failure, exogenous gonadotropins are used as a second-line treatment, but are associated with a higher risk of ovarian hyperstimulation syndrome and multiple gestations. Letrozole has been introduced as a new oral treatment option.

Objectives: This study evaluated the efficacy of these two drugs in infertile patients who underwent IUI.

Methods: A total of 127 patients who received either letrozole (2.5 -7.5 mg daily) or clomiphene (50-200 mg daily) and underwent IUI at the medical centre between 1 January 2004 and 31 January 2011 were included in this retrospective study. Parameters measured were the endometrium thickness, follicle size, number of follicles ≥ 18 mm, ovulation, pregnancy, miscarriage and full term pregnancy rates as well as adverse events.

Results: The rate of endometrium growth was higher in the letrozole group (0.95 ± 0.66 mm/day vs. 0.48 ± 0.70 mm/day, p=0.029) and the endometrium thickness on day 12 and day 13 of cycle was also higher in the letrozole group (10.094 0 ± 1.69 mm vs. 8.973 ± 1.70, p=0.025). Although the number of dominant follicles was lower (1.33 ± 0.50 vs. 2.32 ± 1.11, p=0.001), ovulation rates was higher in the letrozole group (97.83% vs. 85.12%, p=0.05). The pregnancy rates were similar in the letrozole and clomiphene group (4.35% vs. 3.70%, p = 0.768), but the miscarriage rates were higher in the clomiphene group.

What is new: The study included Malaysian patients with multiple-causes infertility.

Conclusion: Letrozole is shown to produce higher rate of endometrium growth, thicker endometrium and produce higher ovulation relative to clomiphene. Although pregnancy rates were similar in both groups, clomiphene may be associated with risks of miscarriages.

Keywords*:* Letrozole, Clomiphene, Infertility, Intrauterine insemination (IUI), Follicular development, Endometrium thickness.

INTRODUCTION

The incidence of infertility is rising worldwide, including in Malaysia. Couples are considered infertile if they do not conceive after one year of unprotected intercourse. Clomiphene is commonly used in infertility. However, 20-25% women fail to respond to clomiphene treatment and do not ovulate[1]. Subsequent to clomiphene failure, exogenous gonadotropins have been used as a second-line treatment, but they are expensive, inconvenient, and associated with a higher risk of ovarian hyperstimulation syndrome as well as multiple gestations[2].

Letrozole has been introduced as a new oral treatment option and is associated with higher rates of pregnancy or having same pregnancy rates as compared to clomiphene[3-6]. There is no local data comparing the effectiveness of clomiphene and letrozole. The goal of this study was to compare the efficacy of letrozole and clomiphene in patients with infertility. The objectives include comparing the rate of endometrium growth, follicle growth, follicle size, endometrium thickness, ovulation, pregnancy, miscarriage, full term pregnancy rates, number of dominant follicles (≥ 18 mm), and adverse events between patients on letrozole and clomiphene.

METHODS

Study Design

A retrospective study was conducted at the Universiti Kebangsaan Malaysia Medical Centre using the data of patients on clomiphene or letrozole who underwent intrauterine insemination (IUI) from 1 January 2004 until 31 January 2011. Patients received either clomiphene or letrozole daily for five days beginning from day 2 until day 6 of the menstrual cycle. Follicular development and endometrium thickness were monitored by transvaginal ultrasound from day 6 onwards. Follicles were considered as mature when it attained a mean diameter ≥ 18 mm by averaging inner two diameters of the follicle. Follicular size and endometrium thickness on day 12 and day 13 of cycle were measured. When at least one mature follicle was observed, a single injection of 10,000 IU of human chrorionic gonadotrophin (hCG) was given to trigger ovulation. The IUI was performed 36 hours after hCG application around day 14 of cycle. Ovulation was ascertained by observing rupture of the follicles by transvaginal ultrasound. Pregnancy was diagnosed by positive urine pregnancy test and ultrasonography. Inclusion criteria for the subjects were patients below 35 years of age, diagnosed with infertility with intact hypothalamus and pituitary glands received either letrozole or clomiphene for the treatment of infertility and underwent IUI. Subjects were excluded if diagnosed with primary ovarian failure and older than 35 years. The study protocol was approved by the institutional research ethics committee (reference no. UKM 1.5.3.5/244/NF-003-2011)

Data Collection

Data were obtained from patients' medical records. The details of these patients were acquired from the follicular tracking form and were recorded in the data collection form. The primary outcome measures were the endometrium thickness (mm), size of follicle (mm) and number of follicles ≥ 18 mm. The secondary outcome measures were the occurrence of ovulation, pregnancy, miscarriage and full term pregnancy. Adverse events from letrozole or clomiphene were also recorded.

Statistical Analysis

SPSS version 18 was used to analyze the data. Student's t-test, Chi-square (χ^2) test, and Yates' correction χ^2 test were used

where applicable. Differences were considered statistically significant if p <0.05. Distributions of continuous variable data were assessed. For normally distributed data, Student's t-test was used and the results were expressed as mean ± standard deviation. For non-normally distributed data, non-parametric test (independent sample Mann-Whitley U test) was used and the results were expressed as median with an interquartile range. χ^2 test was used to compare the difference of norminal data in two independent groups.

RESULTS

Demographic Data

This study comprised a total of 127 patients. Patients' demographic data is shown in Table 1. The characteristics of the patients in the letrozole and clomiphene groups were similar in all aspects, except for a longer duration of infertility in the letrozole group.

Endometrium Growth throughout the Follicular Phase

The endometrium thickness in the letrozole and clomiphene group increased throughout the follicular phase (Figure 1). The endometrium thickness was significantly higher in the letrozole group on day 10 to day 13 of the cycle. There was a significant difference in the rate of endometrium growth between the letrozole and clomiphene group, 0.95 ± 0.66mm/day versus 0.48 ± 0.70 mm/day, respectively (p=0.029).

Follicle Growth during Follicular Phase

The follicle size increased throughout the follicular phase in both groups (Figure 2). The follicle size was significantly higher in the letrozole group on day 8 to day 9 of the cycle, but was similar in both groups during the late follicular phase. There was no difference in follicle growth rate between the letrozole and clomiphene group (n= 15, 1.97 ± 0.10mm/day versus n= 32, 1.70 ± 1.39 mm/day respectively, p=0.506).

Table 1: Demographic characteristics of patients with infertility who received either letrozole or clomiphene

Characteristics	Letrozole (n= 46)	CC (n= 81)	Statistics	P value
Age (years, mean ± SD)	30.80 ± 2.89	30.19 ± 2.76	t= 1.196	p=0.234
BMI (kg/m^2, mean ± SD)	23.80 ± 4.33	23.34 ± 4.09	t= 0.597	p=0.551
Duration of infertility (years, mean ± SD)	5.00 ± 2.41	4.09 ± 2.00	t= 2.296	p=0.023*
Race				
Malay	40 (86.96%)	68 (83.95%)	χ^2=0.208	p=0.648
Non Malay	6 (13.04%)	13 (16.05%)		
Causes of infertility				
Anovulation	2 (4.35%)	3 (3.70%)	Yates' χ^2=0.087	p=0.768
PCOS	12 (26.09%)	16 (19.75%)	χ^2=0.685	p=0.408
Endometriosis	4 (8.70%)	9 (11.11%)	Yates' χ^2=0.016	p=0.899
Tubal factor	5 (10.87%)	6 (7.41%)	Yates' χ^2=0.115	p=0.735
Male factor	8 (17.39%)	18 (22.22%)	χ^2=0.421	p=0.517
Unexplained	10 (21.74%)	21 (25.93%)	χ^2=0.279	p=0.598
PCOS + Male factor	2 (4.35%)	0 (0%)	Yates' χ^2=0.083	p=0.773
PCOS + Tubal factor	1 (2.17%)	2 (2.47%)	Yates' χ^2=0.253	p=0.615
PCOS + Endometriosis	1 (2.17%)	0 (0%)	Yates' χ^2=0.083	p=0.773
Male factor + Tubal factor	1 (2.17%)	4 (4.94%)	Yates' χ^2=0.087	p=0.768
Anovulation + Tubal factor	0 (0%)	1 (1.23%)	Yates' χ^2=0.083	p=0.773
Tubal factor + endometriosis	0 (0%)	1 (1.23%)	Yates' χ^2=0.083	p=0.773

* p < 0.05 denotes statistical significance

Values are the number of patients (with percentage)

BMI = body mass index; PCOS = polycystic ovarian syndrome; CC = clomiphene

t = student t test; χ^2 = chi square test; Yates' χ^2 = Yates' correction chi square test

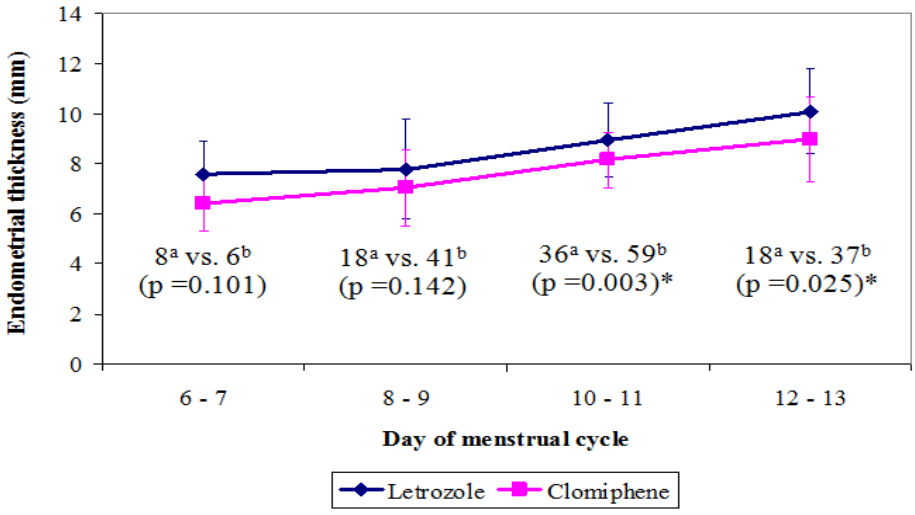

Fig. 1: The growth of endometrium throughout the follicular phase after taking letrozole or clomiphene for five days from day 2 until day 6 of menstrual cycle.

* p<0.05 denotes statistical significance

n^a = number of patients in letrozole group who underwent transvaginal ultrasound

n^b = number of patients in clomiphene group who underwent transvaginal ultrasound

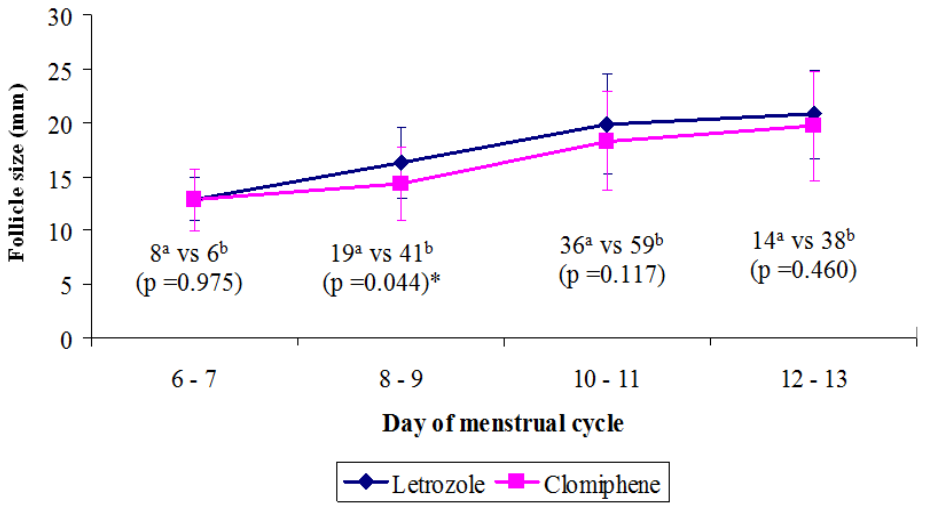

Fig. 2: The growth of follicle throughout the follicular phase after taking letrozole or clomiphene for five days from day 2 until day 6 of menstrual cycle

* p<0.05 denotes statistical significance

n^a = number of patients in letrozole group who underwent transvaginal ultrasound

n^b = number of patients in clomiphene group who underwent transvaginal ultrasound

Table 2: Endometrium thickness, follicle size and number of dominant follicles on day 12 and 13 of cycle in patients with infertility who received either letrozole or clomiphene

Parameters	Letrozole	CC	Statistics	P value
Endometrium thickness (mm) on day 12-13	10.094 ± 1.69[a]	8.973 ± 1.70[b]	t= 2.299	p=0.025*
Follicle size (mm) on day 12-13	20.79 ± 4.08[c]	19.66 ± 5.09[d]	t=0.744	p=0.460
No of follicles ± 18 mm on day 12 - 13	1.33 ± 0.50[e]	2.32 ± 1.11[f]	t=3.559	p=0.001*

* p < 0.05 denotes statistical significance

Values are mean ± SD, except for the total patients develop follicles ≥ 18 mm by day 13, which are the number of patients (with percentage)

CC = clomiphene

t = student t test

n^a = 18 (total number of patients in letrozole group for measurement of endometrium thickness on day 12-13 of cycle)

n^b = 37 (total number of patients in CC group for measurement of endometrium thickness on day 12-13 of cycle)

n^c = 14 (total number of patients in letrozole group for measurement of follicle size on day 12-13 of cycle)

n^d = 38 (total number of patients in CC group for measurement of follicle size on day 12-13 of cycle)

n^e = 9 (total number of patients in letrozole group for measurement of no of follicle ≥ 18 mm on day 12-13 of cycle)

n^f = 25 (total number of patients in CC group for measurement of no of follicle ≥ 18 mm on day 12- 13 of cycle)

Table 3: Outcome of ovulation induction and adverse event in patients with infertility who received either letrozole or clomiphene

Parameters	Letrozole (n= 46)	CC (n= 81)	Statistics	P value
Ovulation	45 (97.83%)	69 (85.12%)	Yates' χ^2=3.819	p=0.050*
Pregnancy	2 (4.35%)	3 (3.70%)	Yates' χ^2=0.087	p=0.768
Miscarriage	0 (0%)	2 (66.67%)	Yates' χ^2=0.111	p=0.739
Full term pregnancy	2 (4.35%)	1 (1.23%)	Yates' χ^2=0.253	p=0.615
Adverse event				
Abdominal pain	0 (0%)	1 (1.23%)	Yates' χ^2=0.083	p=0.773
OHSS	0 (0%)	1 (1.23 %)	Yates' χ^2=0.083	p=0.773
Birth defect	0 (0%)	0 (0%)		

* p < 0.05 denotes statistical significance

Values are the number of patients (with percentage)

OHSS = ovarian hyperstimulation syndrome

Yates' χ^2 = Yates' correction chi square test

Endometrium Thickness and Number of Dominant Follicle

The endometrial thickness on day 12-13 of the cycle was significantly higher in the letrozole group (Table 2). The total number of dominant follicles (≥ 18 mm) on day 12 – 13 of the cycle was significantly higher in the clomiphene group.

Outcome of Ovulation Induction and Adverse Events

The ovulation rate in the letrozole group was significantly higher (Table 3). Pregnancy rates were similar in the letrozole and clomiphene group (4.35 % vs. 3.70%, p=0.768). However, two out of three pregnancies in the clomiphene group resulted in a miscarriage (66.67%). The number of pregnancies reaching term in the letrozole group was 4.34% compared to 1.23% in the clomiphene group. Abdominal pain (one case) and ovarian hyperstimulation syndrome (one case) were reported in the clomiphene group.

DISCUSSION

Comparison of Endometrium Thickness

Adequate endometrial development is essential for pregnancy to occur. Before ovulation, the endometrium must be able grow to a thick and glandular layer rich with blood vessels to provide optimal environment for the implantation of the embryo. The estrogen receptors in the endometrium play an important role in the thickening of the uterus.

In the present study, the letrozole group had significantly higher rate of endometrium growth and thicker endometrium on day 12-13 of the cycle compared to the clomiphene group. This is possibly due to the different mechanisms of action of these two drugs. Letrozole has no effects on estrogen receptors and acts by decreasing the conversion of androstenedione and testosterone to estrogens in the ovary, hence does not exert any negative effect on the endometrium[2]. In contrast, clomiphene has anti-estrogenic effects, and the depletion of estrogen receptors causes the reduction of the endometrium growth[7-9]. The difference in half life of these two drugs may also have effect on the endometrium thickness. Letrozole has a relatively short half-life (approximately 45 hours) and was given for 5 days from day 2 to day 6 of the menstrual cycle in the present study, allowing rapid elimination from the body and complete endometrial recovery by day 12 to 13 of cycle before implantation. On the other hand, clomiphene has a relatively long half-life (two weeks) causing prolonged effects of endometrial estrogen receptors depletion which may lead to endometrial thinning[10].

It is believed that pregnancy rates would be higher when the endometrium thickness reaches ≥ 9 mm during late follicular phase of cycle[11]. Therefore, the target endometrium thickness on day 12 and 13 of cycle in the present study was ≥ 9 mm[11]. However, the mean endometrium thickness in the clomiphene group was only 8.973 ± 1.70mm. This may have affected the pregnancy rate in this group.

Comparison of Follicle Size

Follicle size has influence on oocyte maturation, fertilization, and embryo quality. Our results show that the follicle size was significantly greater in the letrozole group on day 8 to day 9 of the cycle. Letrozole directly blocks estrogen production, unlike clomiphene which blocks the estrogen receptor.This may allow higher initial release of FSH in the letrozole group[12] and hence producing greater follicle size on day 8 to day 9 of the cycle compared to the clomiphene group. It is speculated that letrozole may cause accumulation of androgens that normally converts to estrogens in the ovary. The androgens may raise the follicular sensitivity to FSH by increasing the follicular FSH receptor expression or stimulating the insulin-like growth factor I (IGF-I) to promote folliculogenesis[13,14].

During late follicular phase (on day 12 to 13 of cycle), both groups in the present study had similar size follicles. It is believed that both letrozole and clomiphene play a role in promoting folliculogenesis. These drugs create an estrogen deficient environment, therefore releasing the hypothalamic–pituitary axis from estrogenic negative feedback, which in turn increases the FSH which stimulates the growth of ovarian follicles[2]. Interestingly, although letrozole suppresses the estrogen level for shorter period of time than clomiphene (due to its half life of 45 hours compared to 2 weeks in clomiphene), the follicle size was no different with clomiphene group. This is possibly related to the effects of androgen in the letrozole group which raises the follicular sensitivity to FSH, causing the growth of follicle[15].

The follicle ≥18mm (known as dominant follicle) is most likely to have a mature oocyte that is capable of fertilization[16]. In the present study, the follicle size was similar on day 12 and 13 in both letrozole and clomiphene group (20.79 ± 4.08mm versus 19.66 ± 5.09 mm). This indicated that both groups have similar efficacy in producing the follicle ≥ 18 mm during the late follicular phase.

Comparison of Total Number Follicle > 18 mm (Dominant Follicle) on Day 12 and 13 of Cycles

The increased number of follicles ≥ 18 mm (dominant follicle) on day 12 and 13 may increase the rate of ovulation. However, the higher number of dominant follicles on ovulation may increase the risk of multiple pregnancies and ovarian hyperstimulation syndrome (OHSS). Multiple pregnancies in assisted reproductive treatment cycles are not encouraged because the perinatal mortality rates are 4-fold higher for twins and 6-fold higher for triplets than for singletons (ESHRE 2000). In ovulatory infertility, especially polycystic ovary syndrome (PCOS), a dominant monofollicular development during ovulation is desirable.

The total number of dominant follicles on day 12 and 13 of cycle was significantly higher in the clomiphene group compared to letrozole group (2.32 ± 1.11 versus 1.33 ± 0.50). Our results are consistent with Fisher et al, and Atay et al.[4,17]. It is believed that the relatively longer half life of clomiphene (two weeks), leads to the development of more dominant follicles. Although clomiphene was given for five days on day 2 until day 6 of cycle in the present study, the long half life of clomiphene may cause depletion of central estrogen receptor for an extended duration, resulting in the continued secretion of FSH from the pituitary throughout the follicular phase, eventually leading to the development of multiple follicles. This may increase the risk of ovarian hyperstimulation and multiple pregnancies (7-11%) in clomiphene patients[18-20].

On the other hand, letrozole has a relatively short half life (45 hours). Letrozole may block the estrogen production in the early phase of follicular when letrozole was given for 5 days on day 2 until day 6 of cycle. The effects of letrozole during late follicular phase may be extremely low or absent. The hypothalamus is able to respond to the normal physiologic estrogen feedback, which in turn reduces the secretion of FSH from the pituitary because production of estrogen is not blocked by letrozole during the late follicular phase. This may cause atresia of other smaller follicles. As a result, a dominant monofollicular development during ovulation occurs in most of the letrozole patients. This may lower the risk of multiple pregnancies and OHSS in letrozole patients compared to clomiphene patients[4].

Ovulation, Pregnancy, Miscarriage and Full Term Pregnancy Rates

When a dominant follicle develops, ovulation must occur in order to release the oocyte for fertilization. In the present study, the ovulation rate in the letrozole group was significantly higher than the clomiphene group (97.83% versus 85.12%). Our result showed that the letrozole group has higher ovulation rates, although the number of dominant follicles was lower than clomiphene group.

The pregnancy rate was 4.35 % in the letrozole group compared with 3.70% in the clomiphene group. Although the pregnancy rates in both groups were similar, two out of three pregnancies ended up in miscarriage in the clomiphene group, but none in the letrozole group.

Several factors may affect the pregnancy outcome of the letrozole group in the present study. Firstly, the letrozole group had significantly longer duration of infertility than clomiphene upon diagnosis. Longer duration of infertility in letrozole group may

decrease the chances of achieving pregnancy[21]. Secondly, letrozole was used in those who failed the clomiphene treatment. Therefore, the infertility is more difficult to treat, and may influence the pregnancy rate in the letrozole group.

In the clomiphene group, the miscarriage rates were higher, but not statistically significant, which might be due to the sample size. The miscarriages in the clomiphene group are possibly due to the thinning of endometrium, as seen in the present study. Besides, clomiphene was found to reduce the uterine blood flow during the early luteal phase and the stage of implantation. This may explain the increased miscarriages in the clomiphene group[22].

This study found that although clomiphene is associated with a higher risk of miscarriage, both drug groups were associated with similar pregnancy rates. Al-Fozan et al. found superovulation and IUI with letrozole and clomiphene were associated with similar pregnancy rates (11.5% vs 8.9%), but the miscarriage rate was higher with clomiphene (36.6%)[23]. Davar et al. also found similar pregnancy rates in letrozole (9.5%) and clomiphene (5.7%) in unexplained or mild male factor infertility, but the miscarriage rate was higher with clomiphene (66.6%) compared to letrozole (25%)[24]. However, in comparison, the pregnancy rates of letrozole (4.35%) and clomiphene (3.70%) in our study were lower. This could be because 10.87% of letrozole patients and 9.88% of clomiphene patients in our study had combined causes of infertility compared to both previous studies where patients had only one cause of infertility (unexplained or mild male factor infertility). The patients in our study also had a longer duration of infertility (5.00 ± 2.41 years in letrozole group and 4.09 ± 2.00 years in clomiphene group) compared with patients in Al-Fozan et al. study (2.6 ± 0.2 years in letrozole group versus 2.9 ± 0.3 years in clomiphene group)[23]. The patients in our study were also older (30.80 ± 2.89 years old in letrozole versus 30.19 ± 2.76 years old in clomiphene) compared with patients in Davar et al. (29 ± 2.9 years old in letrozole versus 25.7 ± 3.8 years old in clomiphene)[24]. All these factors may have affected the pregnancy outcome of this study.

Adverse Events

None of the patients from the letrozole group reported any adverse effects. In the clomiphene group, one patient complained of abdominal pain while another was diagnosed with mild OHSS. OHSS is a potentially life-threatening complication and patients may begin with symptoms of abdominal bloating, nausea, vomiting and diarrhea with subsequent progression to lethargy, complete loss of appetite, shortness of breath and ascites[25].

Occurrence of OHSS could be related to the development of multiple follicles in clomiphene, due to its relatively long half life (2 weeks), as seen in our study. Following ovulation, these multiple follicles undergo luteinization, which may cause excessive release of vascular endothelial growth factor (VEGF). VEGF may increase the capillary permeability, resulting in a massive fluid shift, abdominal ascites, hydrothorax, edema, hydropericardium in OHSS patients[26]. The patient diagnosed with OHSS in the present study had two dominant follicles during the late follicular phase. This showed that clomiphene (which has higher risk for developing multiple follicles) has a higher potential for OHSS compared to letrozole.

In the present study, no birth defects were reported among patients with full term pregnancies in the letrozole and clomiphene group. A multicentre retrospective study in Canada involving 911 newborns from women who conceived following clomiphene and letrozole treatment found that there was no difference in the overall rates of major and minor congenital malformations among the 2 groups. However, it appeared that congenital cardiac anomaly was less frequent in the letrozole group. To date, there is no data to prove letrozole is teratogenic[27]. In the present study, letrozole was administered at the beginning of the cycle (starting on day 2 to day 6 of cycle) for five days during the follicular phase. Letrozole has a relatively short half life (approximately 45 hours), hence the drug exposure during the peri-ovulatory and luteal phases of the cycle might be extremely low or absent[10].

Limitations

This study was a retrospective observational study. Unlike clinical trials, patients were not randomized and the choice of treatment was based on physician preference.

CONCLUSION

This study showed that the rate of endometrium growth and the endometrium thickness on day 12 and 13 of cycle was significantly higher in the letrozole group. The follicle size was significantly higher in the letrozole group on day 8 to day 9 of the cycle, but was similar in both groups during day 12 and 13 of cycle. The rate of follicle growth was similar in letrozole and clomiphene group. The total number of dominant follicles (≥ 18 mm) on days 12 – 13 of the cycle was significantly lower in the letrozole group.

The ovulation rate in the letrozole group was significantly higher than in the clomiphene group. Pregnancy rates were similar in the letrozole group and the clomiphene group, but the clomiphene group may be associated with a higher risk of miscarriage. The full term pregnancies in the letrozole group were almost two folds higher in the letrozole group, although the differences were not statistically significant. Clomiphene may be associated with adverse events including abdominal pain and OHSS, but none was observed in the letrozole group.

These findings demonstrated that letrozole was more effective than clomiphene in establishing a thicker endometrium and higher ovulation rates. The pregnancy rates were similar in both groups, but clomiphene may be associated with higher risks of miscarriages.

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