Research Article

Letrozole 2.5 mg Shows Higher Endometrial Thickness Compared to 5 mg Letrozole in Ovulation Induction

Induksi Ovulasi dengan 2,5 mg Letrozole Menghasilkan Endometrium yang Lebih Tebal Dibandingkan 5 mg Letrozole

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Abstract

Objective: To compare the effects of ovulation induction with 2.5 mg letrozole to 5 mg letrozole by the number of mature follicles, endometrial morphology and endometrium thickness during the late follicular phase in infertility patient who successfully became pregnant.

Method: This was a cross sectional study. We collected the data of infertility patient who successfully became pregnant after receiving ovulation induction regiment of 2.5 mg and 5 mg letrozole.

Result: There mean number of follicles with diameter ≥ 18 mm was higher in group receiving 5 mg letrozole (1.64 SD ± 0.91) compared to group receiving 2.5 mg letrozole (1.37 SD ± 0.56) but statistically, there was no significant difference (p = 0.134). Endometrial thickness, which was measured by transvaginal ultrasound on the twelfth day of menstrual cycle, showed a significant difference (p = 0.023) between the groups. The endometrium was thicker in patients receiving 2.5 mg letrozole (7.83 mm SD ± 0.87) compared to patients receiving 5 mg letrozole (7.6 mm SD ± 1.10). The most common endometrium morphology found was triple line endometrium, both in group receiving 2.5 mg letrozole (65%) and in group receiving 5 mg letrozole (50%).

Conclusion: There was a significant difference in endometrial thickness between the pregnant patients who had received 5 mg of letrozole and 2.5 mg of letrozole for ovulation induction and the most common endometrium morphology and description was triple line endometrium in both research groups. But there was no significant difference between the number of ≥ 18 mm follicles on 2.5 mg doses and 5 mg doses of letrozole.

[Indones J Obstet Gynecol 2012; 36-3: 130-4]

Keywords: endometrium morphology, endometrium thickness, infertility, letrozole, ovarium follicles

Abstrak

***Tujuan**: Mengetahui efek induksi ovulasi dengan letrozole dosis 2,5 mg dibandingkan dengan dosis 5 mg terhadap jumlah folikel matur, morfologi endometrium dan tebal endometrium pada fase folikular akhir pada pasien infertilitas yang berhasil hamil.*

***Metode**: Penelitian ini menggunakan desain penelitian potong lintang. Data kasus-kasus pasien infertilitas yang berhasil hamil dengan menggunakan terapi induksi ovulasi letrozole 2,5 mg dan 5 mg dikumpulkan dan dianalisis.*

***Hasil**: Jumlah folikel dengan diameter ≥ 18 mm lebih banyak didapatkan pada dosis pemberian letrozole 5 mg (1,64 SD ± 0,91) dibandingkan dengan dosis pemberian letrozole 2,5 mg (1,37 SD ± 0,56) walaupun secara statistik tidak menunjukkan perbedaan secara bermakna (p = 0,134). Ketebalan endometrium yang diukur dengan ultrasonografi transvaginal pada hari kedua belas siklus menstruasi menunjukkan perbedaan secara bermakna (p = 0,023) di mana endometrium didapatkan lebih tebal pada pemberian dosis letrozole 2,5 mg (7,83 mm SD ± 0,87) dibandingkan dengan pemberian letrozole 5 mg (7,6 mm SD ± 1,10). Didapatkan morfologi endometrium yang paling sering ditemui adalah trilaminer di kedua kelompok penelitian yaitu 65% (letrozole 2,5 mg) dan 50% (letrozole 5 mg).*

***Kesimpulan**: Induksi ovulasi pada pasien infertilitas yang mendapat letrozole dan berhasil hamil memberikan perbedaan bermakna dalam hal ketebalan endometrium antara kelompok dosis letrozole 2,5 mg dan letrozole 5 mg. Tidak terdapat perbedaan bermakna antara jumlah folikel dengan diameter ≥ 18 mm pada kelompok letrozole 2,5 mg dan letrozole 5 mg dan morfologi endometrium terbanyak adalah gambaran trilaminer pada kedua kelompok dosis letrozole ini.*

[Maj Obstet Ginekol Indones 2012; 36-3: 130-4]

***Kata kunci**: folikel ovarium, infertilitas, ketebalan endometrium, letrozole, morfologi endometrium*

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INTRODUCTION

Debates on the issue of infertility ended on November 30 2009, when the World Health Organization (WHO) stated that infertility is a disease of the reproductive system and defined as failure of pregnancy after 12 months or more of sexual intercourse without contraception.[1,2] It occurs at around 10-15% of reproductive age couples in the United States, 5.4% in Europe, 3% in the Middle East, 10.1% in Africa, as well as 4.8% in Asia and Oceania.[3,4] Forty to fifty percent of infertility is caused by abnormalities in women with ovulation disorders in most cases (30-40%).[5,6]

Ovulation induction is one of the most important components in the management of ovulation disorders.[7,8] Clomiphene citrate (CC), an anti-estrogenic drug, is the first line of drug used in ovulation induction. Occurrence of ovulation in patients who received CC is ranged in about 80%. However, the pregnancy rate is only 25-40%,[9] and 10-30% of patients still experience anovulation even though they already had the maximum dose of clomiphene citrate. This condition is known as clomiphene citrate resistance. Aromatase Inhibitor (AI) is an alternative drug for ovulation induction that can be used in this circumstances.[10]

Aromatase inhibitor is one of the anti-estrogenic drug that is easy to use, relatively inexpensive, and have little side effects.[11] Letrozole (4.40-1 h -1,2.4-triazol-1ylmethylene-bis-benzonitrile) is a third generation of AI that inhibits the production of estradiol by declining the conversion rate of testosterone and androstenedion, thereby eliminating the negative feedback on the hypothalamus and pituitary gland of estradiol production.

Letrozole may be started until the third to seventh day of the menstrual cycle and cause the growth of single follicles because of the short half-time.[12,13] The optimal dose of letrozole dose for induction of ovulation until now has not yet been determined. Many studies reported using 2.5-7.5 mg/day of letrozole. Al-Fadhli et al compared the regiment of 2.5 mg doses and 5 mg letrozole, and found that the average number of mature follicles and the pregnancy rates were significantly higher in patients receiving 5 mg letrozole. On the other hand, higher dose of letrozole is associated with more inhibition of aromatase activity, thus keeping the levels of estradiol to be very low for adequate endometrial growths when ovulation.[15] It also had effects on the cervical mucus. This hypothesis led to the use of the 5 mg dose of letrozole for induction ovulation is associated with lower pregnancy rates.

Due to the above problem this research was carried out to assess the effect of ovulation induction with letrozole 2.5 mg dose compared with doses of 5 mg by examining the number of mature follicles and endometrial morphology in late follicular phase.

METHOD

Secondary data was obtained from patient's medical record. We collected data of infertility patients who successfully became pregnant with letrozole ovulation induction regime at the Moegni clinic, Jakarta from January 2008 to December 2010. The recapitulation, processing, and data analysis of this study were conducted from January to December 2011.

There was an analytical observational studies with cross-sectional design. We collected the data of infertility patients who successfully became pregnant after ovulation induction therapy with 2.5 mg and 5 mg letrozole. This data was used to get an overview of the dominant follicle, the thickness of the endometrium and endometrial morphology on late follicular phase.

All research data was recorded in the research form for the editing and coding process. Data was then tabulated and processed statistically using SPSS 17 for windows programs.

To see the characteristics of subjects, we conducted univariate descriptive analysis. To examine the relationship between infertility, the number of cycles of ovulation induction, the age factor, the amount of the dominant follicle, the thickness of the endometrium and endometrial echogenicity after 12 days of ovulation induction in infertility patients with 2.5 mg and 5 mg letrozole, we conducted an analysis with chi square test. If is not qualify for chi square then it was analyzed with Fisher test to obtain p value and confidence interval value.

After obtaining the results of bivariate analysis, the variables that have a significant relationship with $p<0.25$ will be further analyzed with advanced multivariate analysis to find out which independent variable affects the success of the pregnancy. Logistic regression analysis was performed to get the p value, the odd ratio and confidence interval.

RESULTS

From the data of medical record, we retrieved 123 patients who successfully became pregnant with letrozole regime. We finally obtained 88 subjects who fulfilled the criteria of inclusion and exclusion.

We gathered the results of anamnesis, physical examination, the transvaginal ultrasonography examination (TVS), laboratory test, sperm analysis and hysterosalphingografy (HSG).

The patient age was in the range of 21 to 43 years. Most of the subjects were in the age group

30-35 years (48.8%). All subject at least had a high school education, and 3.4% had graduated degree. Among the subjects, 42% had normal BMI (18-25), 34% was categorized as overweight, while the remaining 24% was categorized as obese. All subjects in this research had patent fallopian tube and normal sperm analysis result. The basic characteristics of the subject can be seen in Table 1.

Table 1. Characteristic of the subject

Variable	Frequency (n=88)	Percentage (%)
Aged		
18-25 years	7	7.9
26-29 years	15	17
30-35 years	43	48.8
36-40 years	19	22.5
> 40 years	4	4.5
Education		
High school	25	28.4
Diploma	30	34.1
Graduate	30	34.1
Postgraduate	3	3.4
BMI		
Underweight	0	0
Normal	37	42
Overweight	30	34
Obesity	21	24

Table 2 shows that the number of follicles with diameter ≥ 18 mm obtained in 5 mg doses of letrozole (1.64 ± SD 0.91) compared with 2.5 mg doses of letrozole (1.37 ± SD 0.56) and it showed no significant difference (p = 0.134).

Endometrial thickness as measured by TVS on day twelve of menstrual cycle showed a significant difference (p = 0.023), in which the endometrium was thicker in the group receiving 2.5 mg letrozole (7.83 mm SD ± 0.87) compared to the group receiving 5 mg doses of letrozole (7.6 mm SD ± 1.10). The result can be seen in Table 2.

For both group, endometrial morphology is also assessed with TVS on day twelve of the menstrual cycle. The result can be seen in Table 3.

The most commonly found morphology was the triple line in both study groups, 65% of subjects in group receiving 2.5 mg letrozole and 50% of subjects in group receiving 5 mg letrozole. Hyperechogenic - homogenic morphology were obtained more often in group receiving 5 mg letrozole (5.6%) compared with he group receiving 2.5 mg letrozole (1.9%). This difference is directly proportional to the thickness of the endometrium, which presented in most groups of 2.5 mg doses of letrozole.

From the aforementioned statistical test result, it can be concluded that the number of follicles with a diameter of ≥ 18 mm between the two groups did not differ significantly (p = 0.134)

Table 2. Comparison of the number of follicles and endometrium thickness on day twelve of menstrual cycle after the regiment of 2.5 mg and 5 mg letrozole.

	Groups	n	Mean	Std. Deviation	p
Number offollicles with diameter ≥ 18 mm	2.5 mg	52	1.37	.56	0.134
	5 mg	36	1.64	.91	
Endometrium thickness (mm)	2.5 mg	52	7.831	.87	0.023
	5 mg	36	7.600	1.10	

Table 3. Endometrium morphology on day twelve of menstrual cycle after therapy of 2.5 mg and 5 mg letrozole.

		Group				p
		2.5 mg		5 mg		
		n	%	n	%	
Endometrium morphology on day twelve of menstrual cycle	Hyperechogenic - homogenic	1	1.9	2	5.6	0.281
	Intermedia - Isoechogenic	17	32.6	16	44.4	
	Trilaminer	34	65	18	50	

(means when $p < 0.05$), but the difference is significant in terms of the thickness of the endometrium ($p = 0.023$) between the two study groups.

DISCUSSION

Letrozole, which was used as an ovulation induction regiment in this study, is one of the third generation aromatase inhibitor. It inhibits the production of estrogen by decreasing the conversion rate of testosterone and androstedione into estrogen in the ovaries. Ovulation induction is one of the most important components in the management ovulation disorders.[7,8]

Letrozole as an aromatase inhibitor (AI) is an anti-estrogen that is easy to use, relatively inexpensive, and has little side effect.[11] The optimal dose of letrozole for proper ovulation induction has not been determined yet. From a few studies showing the effectiveness of letrozole, some studies reported to use 2.5-7.5 mg letrozole per day.

There was no significant difference on the number of ≥ 18 mm follicle found in groups receiving 5 mg of letrozole (1.64 SD±0.91) compared to in group receiving 2.5 mg letrozole (1.37 SD±0.56) with p value of 0.134. On the study of Badawy[14] and Al-Fadhli,[15] they compared the result in patients receiving 2.5 mg and 5 mg letrozole, and they found no significant difference in the number of mature follicle between the groups. Success rate per cycle using letrozole according to research conducted by Badawy was higher in group receiving 2.5 mg letrozole (4.8%) compared to group receiving 5 mg letrozole (4.3%), although the difference was not statistically significant. On the other hand, the study by Al-Fadhli15 obtained pregnancy rate of 2.5% in group receiving 2.5 mg letrozole and 26.3% in group receiving 5 mg letrozole. It was associated with the average number of dominant follicles, which was higher in the group receiving 5 mg letrozole. But, along with the growing number of mature follicles, which was related to the doses given, there was also an increase in the onset of excessive ovarian stimulation syndrome caused by rising levels of estradiol resulting from the large number of mature follicles. Yet from the data collected, there is no patient who experience excessive ovarian stimulation syndrome.[14] The level of estradiol in mid luteal phase should be measured in order to see if there is a significant difference between the two groups in terms of its direct influence on the thickness of the endometrium and its effects on the incidence of excessive ovarian stimulation syndrome.

Endometrial thickness measured on day twelve of menstrual cycle was significantly different ($p = 0.023$). This could be related to the theory which stated that larger doses of letrozole are related to an inhibition of aromatase enzyme activity that makes the levels of estradiol too low to produce growth of adequate endometrium.[15] It also influences the condition of the cervical mucus. This hypothesis led to the use of the 5 mg dose of letrozole for induction ovulation is associated with lower pregnancy rates. However, the research of Tulandi et al showed different findings, where the thickness of the endometrium is higher in value on a 5 mg letrozole group (7.8 ± 0.3 mm) compared to 2.5 mg (7.6 ± 0.3 mm), although in the end they conclude a high success rate for pregnancy was not caused by endometrial thickness, but the conditions of superovulation where there were more dominant follicles formed in groups receiving 5 mg letrozole. Al Fadhli et al stated that the average number of mature (≥ 18 mm) follicles was significantly different ($p<0.005$) between the two groups and the success rate are directly proportional. The number of days required to reach a mature follicle is associated with increased doses of letrozole.[15]

Badawy[14] also found that the endometrium in the group receiving 5 mg letrozole was thinner than in the group receiving 2.5 mg letrozole. Al-Fadhli[15] acquired a different result, where the endometrial thickness was greater in the group receiving 5 mg letrozole (7.5 mm SD ± 0.3). In this study, we found that the endometrium is significantly thicker in group receiving 2.5 mg letrozole (7.83 mm ± SD 0.87) than in group receiving 5 mg letrozole (7.6 mm SD ± 1.10).

Previous studies stated that the differences in the thickness of the endometrium did not affect the success rate as long as endometrium thickness was ≥ 7 mm.

The examination of estradiol on day twelve cycles of menstruation, just before the hormone human chorionic gonadotropin (hCG) injected to trigger ovulation, should be performed. A study on estradiol levels measured before hCG injection found that that in the group with estradiol level of 1000-2000 pg/ml, the rate of good quality embryos development (73.6%) and high implantation and pregnancy rates (35.8%) were higher compared to

the group estradiol levels from 1000 to 2000 pg/ml.

We would also like to see whether there was a relationship between the number of dominant follicle and endometrial thickness because there were conflicting results from several researches regarding this matter. Badawy et al found that the number of dominant follicles is proportional with increased doses of letrozole. It was associated increased progesterone levels in mid luteal phase, thus the environment created in luteal phase was better and the risk of abortion in patients who successfully get pregnant decreased.[14]

Badawy et also stated that the changes in the thickness of the endometrium was associated with estradiol serum levels and an increase in the number of follicles. Another study stated that there was a correlation between levels of serum estradiol with endometrial thickness.

The number of pregnancy complications such as abortion was also higher in group receiving 5 mg letrozole (14.8%) compared to the group receiving 2.5 mg letrozole (12.1%).[14]

In this study, the most commonly found endometrium morphology was the triple line endometrium. A study suggested to delay embryo transfer in in-vitro fertilization procedure when a homogeneous hyperechoic pattern was found. A triple line endometrium and endometrial thickness of > 6 mm is associated with a high conception rate.[16]

CONCLUSION

There was a significant difference in regards of endometrial thickness between 2.5 mg and 5mg letrozole for ovulation induction. There was no significant difference between the number of follicles with diameter ≥ 18 mm on 2.5 mg doses and 5 mg doses of letrozole and most endometrium morphology and description are trilaminer in both research groups.

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