

RESEARCH ARTICLE

The Effectiveness of Clomiphene Citrate and Letrozole for Ovulation Induction Related to Endometrial Thickness and Number of Dominant Follicle

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Abstract

The aim of the study is to know the effectiveness of clomiphene citrate and letrozole for ovulation related to endometrial thickness and number of dominant follicle. Study design was cross sectional based on medical records of women who underwent ovulation induction from January 2011-May 2015. A number of 143 anovulation women were divided into clomiphene citrate 50mg, clomiphene citrate 100 mg, letrozole 2.5mg and letrozole 5mg. Each group received the agent daily on 3rd-7th day of menstrual cycle. On 12th day of menstrual cycle, the transvaginal ultrasound was performed to measure endometrial thickness and dominant follicle number. From all subjects, 45 subjects (31.5%) were in 50mg clomiphene citrate groups, 29 subjects (20.3%) in 100mg clomiphene citrate group, 23 subjects (16.1%) in 2,5mg letrozole group, and 46 subjects (32.2%) in 5mg letrozole group. Subjects who received letrozole had thicker endometrium compared to clomiphene citrate ($p < 0.05$). Different doses were not associated with endometrial thickness between subjects who received either letrozole or clomiphene citrate. In addition, subjects receiving letrozole had higher proportion of having trilaminar endometrium morphology. We did not observe the difference in total number of dominant follicle between groups. It is concluded that letrozole is more effective than clomiphene citrate in terms of endometrial thickness but not for number of dominant follicles.

Keywords: clomiphene citrate, letrozole, ovulation induction, endometrial thickness, dominant follicle

Efektivitas Induksi Ovulasi Klomifen Sitrat dan Letrozol dalam Hal Ketebalan Endometrium dan Jumlah Folikel Dominan

Abstrak

Studi ini bertujuan untuk menilai efektivitas induksi ovulasi klomifen sitrat dan letrozol dalam hal ketebalan endometrium dan jumlah folikel dominan pada perempuan yang tidak berovulasi. Desain studi adalah potong lintang menggunakan rekam medik pasien yang menjalani induksi ovulasi pada bulan Januari 2011-Mei 2015. Sebanyak 143 perempuan yang tidak berovulasi dibagi dalam kelompok yang mendapat klomifen sitrat 50mg, klomifen sitrat 100mg, letrozol 2.5mg dan letrozol 5mg. Setiap kelompok mendapat obat induksi ovulasi antara hari ke-3 sampai hari ke-7 siklus haid. Pada hari ke-12 siklus haid dilakukan ultrasonografi transvaginal untuk mengukur ketebalan endometrium dan jumlah folikel dominan. Sebanyak 45 subyek (31,5%) mendapat klomifen sitrat 50mg, 29 subyek (20,3%) mendapat klomifen sitrat 100mg, 23 subyek (16,1%) mendapat letrozol 2,5mg dan 46 subyek (32,2%) mendapat letrozol 5mg. Subyek yang mendapat letrozol memiliki endometrium yang lebih tebal dibandingkan kelompok klomifen sitrat ($p < 0,05$). Dosis yang berbeda tidak berhubungan dengan ketebalan endometrium baik pada kelompok klomifen sitrat maupun letrozol. Kelompok yang mendapat letrozol lebih banyak memiliki gambaran morfologi endometrium trilaminar. Tidak dijumpai perbedaan bermakna dalam jumlah folikel di antara semua kelompok. Disimpulkan letrozol lebih efektif dibandingkan klomifen sitrat dalam hal ketebalan endometrium tetapi tidak untuk jumlah folikel dominan.

Kata kunci: klomifen sitrat, letrozol, induksi ovulasi, ketebalan endometrium, folikel dominan.

Introduction

World Health Organization (WHO) had declared infertility as a health problem on 30th November 2009. Infertility has a definition as a reproductive system disease marked by the inability of achieving pregnancy after 12 months or more periods of sexual intercourse without the use of contraception.^{1,2} It occurred on about 10-15% spouses at reproductive age in the United States (6% in North America and 3.1% in South & Middle America), 3% in Middle East, 10.1% in Africa, 4.8% in Asia and Oceania, 2.9% in India, 2.9% in Philippines, 1.9% in Bangladesh, and 3.4% in Indonesia.³⁻⁵

Infertility caused by female factors accounted for 28.6% to 57.5% of all cases.⁶⁻¹⁰ WHO explained that anovulation infertility caused by ovulation dysfunction (WHO anovulation infertility classification class 2) appeared on 80% of cases.¹¹ One of the treatment to cure this condition is by ovulation induction to stimulate mature oocyte.¹² All this time, ovulation induction agent commonly used in Indonesia is clomiphene citrate. It has a relatively high ovulation success rate, approximately 50-75%, but the conception success rate is just about 10-40%.¹³⁻¹⁵ The unconformity between ovulation and conception rate of this drug is caused by the anti-estrogen effect of clomiphene citrate which caused the thinning of endometrium layer and reducing endometrium exogenicity.¹⁵⁻²⁰ Dehbashi *et al*¹⁶ reported that the administration of clomiphene citrate affected endometrium thickness, but not its exogenicity. Gonen *et al*¹⁷ found that the administration of clomiphene citrate was actually affecting endometrium thickness and exogenicity, and there was a conformity between endometrial thickness, exogenicity, and pregnancy rate. A study by Rinaldi *et al*¹⁸ concluded that pregnancy rate was higher in the group with an endometrium thicker than 10 cm. Therefore, the anti-estrogen effect of clomiphene citrate was suspected as the cause of the ovulation-conception number unconformity.¹⁵

The other promising ovulation inducing agents other than clomiphene citrate is letrozole. Letrozole is an aromatase inhibitor commonly used in breast cancer treatment. Aromatase inhibitor reduces estrogen level in breast cancer patients and inhibiting the growth of the cancer.²¹ The use of letrozole as an ovulation inducing agents is promising and will improve ovulation-conception rate unconformity found on clomiphene citrate administration because letrozole has no anti-estrogen effect like clomiphene citrate.¹⁵ Begum *et al*²² proved that the endometrial layer was thicker on letrozole administration

compared to clomiphene citrate ($9.03 \pm 0.89\text{mm}$ vs $10.37 \pm 1.2\text{mm}$; $p < 0.05$). However, there were different results such as the study by Badawy *et al*,²⁴ obtaining different result on endometrial thickness between clomiphene citrate and letrozole ($9.2 \pm 0.7\text{mm}$ vs $8.1 \pm 0.2\text{mm}$; $p < 0.05$). Disappointing result was also reported by Dehbashi *et al*,²³ where the endometrial thickness on either clomiphene citrate and letrozole did not show any significant difference ($7.12 \pm 2.01\text{mm}$ vs $6.44 \pm 1.68\text{mm}$; $p > 0.05$). Although there were differences on endometrial thickness, letrozole is still considered as a promising drug because of the absence of anti-estrogenic effect. Therefore, this study is aimed to know the effectiveness of clomiphene citrate and letrozole for ovulation induction related to endometrial thickness and the number of dominant follicles between the administration of 50mg to 100mg of clomiphene citrate with 2,5mg to 5mg of letrozole.

Methods

This is a cross sectional study using medical records of patients receiving either 50mg clomiphene citrate, 100mg clomiphene citrate, 2.5mg letrozole, or 5mg letrozole at dr. Cipto Mangunkusumo National Hospital, Jakarta from January 2011–May 2015. Every treatment groups received the agent daily on 3rd-7th day of menstrual cycle. The inclusion criteria of the samples were women who met the diagnostic criteria for anovulation infertility, receiving either 50 mg clomiphene citrate, 100mg clomiphene citrate, 2.5mg letrozole or 5mg letrozole therapy, and have a complete USG medical record. On 12th day of menstrual cycle, transvaginal ultrasound examination was performed to measure endometrial thickness and dominant follicle number. Ultrasonography examination was performed by expert in reproductive endocrinology. Smokers and patients receiving both clomiphene citrate and letrozole at the same time were excluded.

All numerical values were tested for their distribution normality using Kolmogorov-smirnov or Shapiro-wilk tests. Normally distributed data were expressed as mean \pm standard deviation whereas non-normally distributed data were expressed as median (minimum-maximum). The comparison of numerical variables between groups were tested using one-way ANOVA and Kruskal Wallis. Independent t-test or Mann-Whitney were used for post-hoc analysis between groups. All p values < 0.05 were considered statistically significant. Statistical analysis were performed using Statistical Package for Social Science (SPSS) for windows version 22.

License to use the medical records of patients at RSCM had been coordinated with related parties and had been approved by the Health Research Ethics Committee of the Faculty of Medicine, Universitas Indonesia Number 245 / UN2.F1 / ETIK / 2015 on 30 March 2015.

Endometrial Thickness, Morphology, and Number of Dominant Follicle

There was a significant difference on endometrial thickness on late-follicular phase ($p < 0.001$) between women receiving clomiphene citrate and letrozole. However, there were no significant differences on the comparison of women receiving 2.5mg letrozole

Table 1. Subject Characteristics between Groups Received Clomiphene and Letrozole (n=143)

Characteristics	Clomiphene		Letrozole	
	50mg (n=45)	100mg (n=29)	2.5mg (n=23)	5mg (n=46)
Age (year)	33.29 \pm 4.5	33.76 \pm 5.24	34.97 \pm 5.1	34.11 \pm 4.06
BMI (kg/m ²)	22.2 (17.7-40.1)	23.63 \pm 3.77	23.9 \pm 3.47	23.1 \pm 3.47
Duration of infertility (year)	3 (1-13)	3 (1-13)	5 (1-10)	3 (1-13)

Data were presented as mean \pm standard deviation or median (minimum-maximum)

Table 2. Etiology of Infertility between Groups Received Ovulation Induction

Etiology	Clomiphene		Letrozole	
	50mg (n=45)	100mg (n=29)	2,5mg (n=23)	5mg (n=46)
Male factor	11 (24.4%)	7 (24.1%)	8 (34.8%)	17 (37.0%)
Female factor	18 (40.0%)	6 (20.7%)	8 (34.8%)	14 (30.4%)
Idiopathic	16 (35.6%)	16 (55.2%)	7 (30.4%)	15 (32.6%)

Results

Subjects' Characteristics

A number of 143 patients were recruited in this study. Subjects were grouped based on their treatment: 45 patients on clomiphene citrate 50mg group, 29 patients in clomiphene citrate 100mg group, 23 patients in letrozole 2.5mg group, and 46 patients in letrozole 5mg group. Characteristics of the subjects were presented in Table 1. We classified patient's causes of infertility either male, female or idiopathic factor as shown in Table 2. There was no difference in causes of infertility in four groups.

against women receiving 5mg letrozole and between women receiving 50mg clomiphene citrate and 100mg clomiphene citrate ($p > 0.005$).

Trilaminar endometrial morphology was higher in women receiving 2.5mg and 5mg letrozole compared to those administered with 50mg and 100mg clomiphene citrate (14% and 23.1%). There was no significant difference on follicle numbers between women receiving clomiphene citrate and letrozole (Table 3).

Table 3. Endometrial Thickness, Morphology, and Number of Dominant Follicle after Ovulation Induction

Outcome Variables	Clomiphene		Letrozole		p
	50mg (n=45)	100mg (n=29)	2,5mg (n=23)	5mg (n=46)	
Endometrial thickness (mm) ^{a,b,c,d}	9 (5-20)	8 (4.3-17)	12 (11-16)	11 (8-18)	<0.001*
Number of dominant follicle (n,%)	1 (0-3)	1 (0-2)	1 (1-2)	1 (0-3)	0.664
Endometrial morphology (n,%)					
Thin	14 (9.8%)	4 (2.8%)	0	1 (0.7%)	<0.001
Intermediate	13 (9.1%)	12 (8.4%)	3 (2.1%)	12 (8.4%)	
Trilaminar	18 (12.6%)	13 (9.1%)	20 (14%)	33 (23.1%)	

*Kruskal Wallis

Post-hoc analysis with Mann-Whitney test with $p < 0.05$ between: ^aclomiphene citrate 50mg dan letrozole 2.5mg, ^{ba}clomiphene 50mg and letrozole 5mg, ^{ca}clomiphene 100mg and letrozole 2.5mg, and ^{da}clomiphene 100mg and letrozole 5mg.

Discussion

This study compared endometrial thickness, morphology, and number of dominant follicle between groups receiving different doses of either clomiphene citrate or letrozole. This study confirmed the difference of endometrial thickness and endometrium morphology between these two different type of induction agents. This was similar with previous study: letrozole yielded thicker endometrium, thus preferable for successful pregnancy.²² However, a contrary result was noted from Maryati *et al*²⁴ study among Indonesian population with similar setting. Besides, Casper and Mitwally²⁵ reported that there was no difference in the number of dominant follicle between groups.

To date, clomiphene citrate is the most prescribed induction agent. However, there was a rising question about its efficacy. Although ovulation rate was quite high, the pregnancy rate was still low. This probably due to endometrial thickness and nontrilaminar morphology. Letrozole has become a center of attention as it has anti-estrogenic effect.²⁶

This study found that there was no difference in the given doses of induction agent. Previous report by Fadhli *et al*²⁷ found a thicker endometrium with 5mg letrozole compared to 2.5mg letrozole. Previously, successful rate in patients who took letrozole was higher than clomiphene citrate. As clomiphene citrate remains a gold standard for therapy, Begum *et al*²² found that letrozole could become a solution if they failed with clomiphene citrate.

Endometrial thickness is an important factor for successful pregnancy after induction. However, there is a controversy on its role due to different results in many trials. In a meta-analysis, there was no difference in pregnancy rate and ovulatory cycles between letrozole and clomiphene citrate.²⁸ Remohi *et al*²⁹ stated that estradiol level correlated with endometrial thickness. Also, endometrial thickness correlated with implantation. However, those parameters were not a good predictors for pregnancy. There were another factors attributed for successful pregnancy, including vasculature of the subendometrium and intraendometrium.³⁰ The main limitation encountered in this study was

unequal sample size between all groups. Besides, we could not report the effects of each treatment regarding with the neonatal outcomes.

Conclusions

This study supported that letrozole was associated with thicker endometrium and trilaminar morphology of endometrium. However, there was no significance difference in the number of dominant follicle. Further study on its efficacy toward pregnancy rate between different doses of clomiphene citrate and letrozole among Indonesian population is needed.

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