

Clomiphene Citrate and Anastrozole : Effects on Follicular Diameter and Endometrial Thickness in Polycystic Ovary Syndrome

Yashinta Sampeliling¹, Andi Mardiah Tahir², Eddy Hartono³, Firdaus Kasim⁴

^{1,2,3}Department of Obstetrics and Gynecology, Faculty of Medicine, Universitas Hasanuddin

⁴Faculty of Public Health, Universitas Hasanuddin, Dr. Wahidin Sudirohusodo General Hospital, Makassar

Abstract

Objective: To compare the effects of clomiphene citrate and anastrozole on follicular diameter and endometrial thickness in women with polycystic ovary syndrome (PCOS).

Methods: This prospective study was conducted at the private-practice setting. The study group consisted of 14 patients who received clomiphene citrate 50 mg and 14 patients received anastrozole 1 mg on day 3 of menstruation for 5 days. Follicular diameter and endometrial thickness were measured with transvaginal ultrasound on day 12 of menstruation.

Results: The mean diameter of follicles in the clomiphene citrate group was not significantly differ compared with anastrozole group (13.35 ± 4.72 mm vs 10.92 ± 4.29 mm; $p > .05$, respectively). A similar effect also observed in endometrial thickness for both study groups (8.51 ± 1.88 mm in anastrozole vs 7.49 ± 2.09 mm in clomiphene citrate; $p > .05$).

Conclusion: Clomiphene citrate and anastrozole were not significantly improved follicular diameter dan endometrial thickness in polycystic ovary syndrome.

Keywords : Clomiphene citrate, anastrozole, PCOS

1. INTRODUCTION

Polycystic ovary syndrome (PCOS) occurs in 15-20% of reproductive women according to the European Society for Human Reproduction and Embryology (ESHRE) and the American Society for Reproductive Medicine (ASRM). Fifty to seventy percents of PCOS cases are caused by insulin resistance.¹ This syndrome is characterized by chronic anovulation with exaggerated biochemical and/or clinical of androgens and without other diseases of the adrenal gland, thyroid or pituitary in similar features. Clinical features of this syndrome including menstrual dysfunction, hirsutism, acne, alopecia, obesity, infertility, increased libido, and high rates of miscarriage.² However, the etiology of PCOS remains unclear.

Selective estrogen receptor modulator (SERM) such as clomiphene citrate (CC) has been the first-line oral therapy for ovulation induction in PCOS for the past 40 years, but its

use is often associated with multiple gestations and ovarian hyperstimulation so that the Endocrine Society Clinical Practice Guideline recommends metformin as an adjunct therapy to prevent ovarian hyperstimulation.^{3,4} A long half-life of around 12 days lead to adverse peripheral anti-estrogenic effects such as decreased endometrial thickness and changes in cervical mucus although clinical significance is still debated.⁵ Aromatase inhibitors such as anastrozole as an alternative agent for ovulation induction could prevent the negative effects of CC because of anastrozole has shorter half-life and different mechanism of action from CC.⁶ To compare the effects of CC and anastrozole on follicular diameter and endometrial thickness in women with polycystic ovary syndrome (PCOS).

2. METHODS

This prospective study was conducted at a private obstetrician's practice in Makassar from March 2018 until March 2019. This study approved by the Medical Research Ethics Committee of Hasanuddin University/dr. Wahidin Sudirohusodo General Hospital. Women diagnosed with polycystic ovary syndrome based on Rotterdam criteria, reproductive age (20-35 years), wanting to have children and body mass index (BMI) normal (18-25 kg/m²) were eligible for this study. Women excluded when diagnosed with polycystic ovary syndrome accompanied by other diseases and had a history of therapy with other ovulation induction agents during the study such as FSH or HMG injection.

Patients were randomly received CC 50mg/day or anastrozole 1mg/day orally on day 3 of menstruation for 5 days. Follicular diameter and endometrial thickness measured with transvaginal ultrasound on day 3 and day 12 of menstrual cycle. Data were analyzed using independent t-test, Mann-Whitney test and Chi-square. A *p*-value <.05 was considered significant.

3. RESULTS

Our study performed on 28 women with PCOS consisting of 14 patients who received CC and 14 patients received anastrozole. The characteristics of these patients are shown in table 1. Women with PCOS in the clomiphene citrate group had an average age of 27.93 years, body mass index (BMI) 25.94 kg/m², length of marriage 4.5 years, and 85.7% primary infertile. The number of antral follicles in this group was 8 follicles. PCOS women in the anastrozole group had an average age of 29 years, BMI 25.85 kg/m², marriage duration 4.5 years, and all of the women were secondary infertile. Transvaginal ultrasound examination results in this group on day 3 of menstruation obtained 10 antral follicles. Further analysis shows no significant differences for all of the patient's characteristics (*p*>.05) between the study groups (Table 1).

In our study, the larger follicular diameter observed before the administration of CC compared with anastrozole and there were significant differences between the two study groups (*p*<.05). The diameter of the follicles is greater after the administration of CC compared with anastrozole. However, there were no significant differences between the two study groups (*p*>.05) (Table 2). Table 3 shows the comparison of endometrial thickness

between CC and anastrozole. Endometrial thickness was not significantly different ($p>.05$) between CC and anastrozole on day 12 of menstruation.

Table 1. Patients characteristics

Characteristics	Clomiphene citrate	Anastrozole	p
	(n=14)	(n=14)	
Age (years)	27.93±3.22	29.64±3.82	0.214*
Body mass index (kg/m ²)	25.94± 4.41	25.85± 4.05	0.958*
Married duration (years)	4.50±3.23	3.57±2.28	0.544**
Infertility			
Primary	12(85.7%)	14(100%)	0.481***
Secondary	2(14.3%)	0	
Antral follicles	8.21±1.98	10,21±3.68	0.096**

* *t-independent test*, ** *Mann Whitney test*, *** *Chi Square test*

Table 2. Follicular diameter before and after treatment

Treatment	Clomiphene citrate (n=14)	Anastrozole (n=14)	p
Day 3	8.85±3.17	6.48±1.68	0.048*
Day 12	13.35±4.72	10.92±4.29	0.138**

* *Mann- Whitney test*, ** *t-independent test*

Table 3. Endometrial thickness before and after treatment

Treatment	Clomiphene citrate (n=14)	Anastrozole (n=14)	p
Day 3	5.37±2.76	4.21±1.29	0.369*
Day 12	7.49±2.09	8.51±1,88	0.186**

* *Mann- Whitney test*, ** *t-independent test*

4. DISCUSSION

Clomiphene citrate (CC) is the most commonly used oral agent for ovulation induction and the first-line therapy for anovulatory PCOS.^{7,8} CC acts as a non-steroidal selective estrogen receptor (SERM) modulator so that it has both estrogen agonists and antagonists action. CC has been reported to successfully induce ovulation in 60-80% of PCOS patients. More than 70% of ovulating PCOS patients response at dose level 50 or 100 mg.⁹ However, some patients are not response to CC treatment for ovulation induction due to clomiphene resistance. This condition found in 15–20% of patients.¹⁰

Our study found the mean diameter of follicles in day 12 of menstruation was greater in the CC group compared with anastrozole group. Our findings are in agreement with the

previous study that shows no significant difference in the effect of CC and anastrozole in follicular development.¹¹ However, the results of the present study differ from the previous study that shows anastrozole in PCOS patients has better outcomes in mature follicles (>18 mm), significantly thicker endometrium, and slightly higher pregnancy rate compared with clomiphene citrate. Anastrozole might reduce multiple gestations or the risk of hyperstimulation syndrome.¹² Another study also observed mature follicles obtained after administration of letrozole compared with CC.¹³ In contrast, smaller follicular diameter obtained in anastrozole compared with letrozole treatment.¹⁴

Insulin resistance affects follicular development or folliculogenesis in PCOS. Although insulin resistance is not included in the PCOS diagnostic criteria; insulin resistance and hyperinsulinemia are central pathophysiologies in most women with PCOS results in folliculogenesis and abnormal steroidogenesis leading to anovulation.¹⁵ Study shows 85% of women with PCOS diagnosed based on Rotterdam criteria are affected by insulin resistance (75% of thin women and 95% of obese and overweight women) using the gold standard clamping technique and WHO criteria for insulin resistance.¹⁶ Insulin resistance increases polycystic through AMH dysregulation or the hyperandrogenemia pathway.¹⁷

The endometrial thickness on day 12 of menstruation show anastrozole group has thicker endometrium compared with CC although the difference was not significant in our study. Similar findings with our study in a previous study that thicker endometrium observed after the administration of CC.¹⁸ A significant thicker endometrium on ovulation induction obtained with CC compared with anastrozole.¹² However; fewer follicles, fewer mature follicles, lower estradiol (E2) levels, and thicker endometrium obtained in anastrozole 1mg compared with CC 100mg for 5 days combined with gonadotropins for ovulation induction.¹³ Endometrial thickness is not affected by ovulation induction with aromatase inhibitors.¹¹ To increase the effect of CC or anastrozole on follicular and endometrial development, gonadotropins could be use as the combination treatment with CC or anastrozole. Combination of this treatment might be safer in terms of lower risk of hyperstimulation and multiple gestations, especially for high risk women.¹⁹ If there is no pregnancy, IVF can be recommended.

The discrepancies between studies might be caused by discrepancies in the characteristics of the sample as age and BMI. In addition, the present study did not assess the insulin resistance of PCOS women. The limitation of this study is the minimal size of the samples. In addition, the assessment of ovarian stimulation only performed in one menstrual cycle. Another limitation is CC administration for patients with the thinner endometrial line of day 3 of menstruation whereas CC affects the estrogen receptor in endometrium and it is inadequate.

5. CONCLUSION

Clomiphene citrate and anastrozole were not significantly improved follicular diameter dan endometrial thickness in polycystic ovary syndrome.

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