

Comparison of the Number and Size of the Dominant Follicles with Estradiol Levels on PCOS with Naltrexone and Clomiphene Citrate Therapy

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ABSTRACT

The success rate of clomiphene citrate, the first-line therapy in PCOS, is only 30-40% pregnancy. Naltrexone combination with clomiphene citrate produced improved endocrine and metabolic changes in PCOS. This study compared the number, size dominant follicle and estradiol levels in PCOS after naltrexone and clomiphene citrate therapy. This was an experimental study with pre and post test control group design, performed in PCOS patients by Rotterdam criteria. The population was divided into treatment group receiving naltrexone for 5 days from menstrual cycle day 3 to 7 in a dose of 50, 100, and 150 mg/day for first, second, and third cycle, and control group receiving clomiphene citrate for 5 days in a dose of 50, 100, and 150 mg/day for third cycle. Serum estradiol and TVS were measured in both to find dominant follicles on day 3 and 12 of menstrual cycle. Number, dominant follicle size with estradiol level were compared. Regarding dominant follicle, in naltrexone group, from 18 cycles, 3 subjects had it in first cycle. In clomifene citrate group, from 20 cycles, it was found in 2 in first cycle and 2 in third cycle. Mann-Whitney test showed dominant follicle size had no significant differences ($p = 0.400$) between naltrexon (19.70 ± 2.261) and clomiphene citrate (18.45 ± 2.017) group. Estradiol levels in subjects with dominant follicle showed no significant differences ($p = 0.057$) between naltrexon (260.7 ± 11.51) and clomiphene citrate group (272.4 ± 2.92). In conclusion, number and size of dominant follicle and estradiol levels did not differ significantly in both groups. (MOG 2013;21:89-93)

Keywords: PCOS, naltrexone, clomiphene citrate, estradiol, follicle

ABSTRAK

Tingkat keberhasilan klomifen sitrat, terapi lini pertama pada PCOS, hanya 30-40% kehamilan. Kombinasi naltrekson dengan klomifen sitrat menghasilkan peningkatan endokrin dan perubahan metabolik pada PCOS. Penelitian ini membandingkan jumlah, ukuran folikel dominan dan kadar estradiol dalam PCOS setelah terapi naltrekson dan klomifen sitrat. Penelitian ini merupakan penelitian eksperimental dengan pre and post test control group design, dilakukan pada pasien PCOS dengan kriteria Rotterdam. Populasi dibagi menjadi kelompok perlakuan penerima naltrekson selama 5 hari dari siklus menstruasi hari 3-7 dalam dosis 50, 100, dan 150 mg/hari untuk siklus pertama, kedua, dan ketiga, dan kelompok kontrol yang menerima klomifen sitrat selama 5 hari dalam dosis 50, 100, dan 150 mg/hari selama siklus ketiga. Estradiol serum dan TVS diukur pada kedua kelompok untuk menemukan folikel dominan pada hari 3 dan 12 siklus menstruasi. Diperbandingkan jumlah, ukuran folikel dominan dengan kadar estradiol. Dalam kelompok naltrekson, dari 18 siklus, 3 subyek memiliki folikel dominan di siklus pertama. Dalam kelompok klomifen sitrat, dari 20 siklus, 2 subyek mendapatkan folikel dominan pada siklus pertama dan 2 pada siklus ketiga. Uji Mann-Whitney menunjukkan ukuran folikel dominan memiliki perbedaan signifikan ($p = 0.400$) antara kelompok naltrekson (19.70 ± 2.261) dan klomifen sitrat (18.45 ± 2.017). Kadar estradiol pada subyek dengan folikel dominan menunjukkan tidak ada perbedaan signifikan ($p = 0.057$) antara kelompok naltrekson (260.7 ± 11.51) dan klomifen sitrat (272.4 ± 2.92). Kesimpulannya, jumlah dan ukuran folikel dominan serta kadar estradiol tidak berbeda secara signifikan pada kedua kelompok. (MOG 2013;21:89-93)

Kata kunci: PCOS, naltrekson, klomifen sitrat, estradiol, folikel

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INTRODUCTION

Polycystic Ovary Syndrome (PCOS) is the most ovulatory disorders experienced by women in their reproductive ages.¹ Around approximately 4-12% of women suffer from this disorder. Until now the main cause, diagnosis, clinical implications and treatment

caused is still being debated.² Infertility or menstrual disorders in general is a major complaint that encourages people come to the reproductive endocrinology clinic, usually starts since menarche and diverse forms, ranging from the delayed menarche, amenorrhea, oligomenorrhea to abnormal uterine bleeding and it is associated with anovulation. Some alternative therapies have been proven and used but the

fact remains that there are still many people with PCOS who experienced failure of ovulation problems, especially with the low pregnancy rate or miscarriage rate significantly. Clomiphene citrate as a first-line therapy with anovulation in PCOS achieve ovulation success rate around 70%, but the success rate is only 30-40% pregnancy. Clomiphene citrate has an effect on endometrial thickness affecting endometrial receptivity. This fact opens research opportunities to seek other therapies that can solve problems and improve the quality of oocyte ovulation in patients with PCOS.

Endogenous opioids (β -endorphin) has been identified to have an influence on the pathogenesis of obesity and PCOS. The β -endorphin could affect appetite, behavior and feelings known to the central effects. Likewise peripheral effects have been shown to affect the metabolism of carbohydrate systems, insulin resistance and maturation follicle.^{3,4} Inhibition of both acute or chronic opioid system significantly lowers the oral glucose tolerance test results in patients with PCOS who hyperinsulinemia.⁵

Inhibition of β -endorphin can be done with the anti-opioid. This has been demonstrated with the use of naltrexone as an anti-opioid drug addiction to help eliminate and prevent the recurrence of opioids. Anti opioid well known that naloxone and naltrexone.^{6,7} Research conducted by Ahmed et al (2008) showed that administration of naltrexone combination with clomiphene citrate showed some clinical parameters improved endocrine and metabolic changes in patients with PCOS.⁵ In this study, the authors try to do more research on the effects of naltrexone as an anti-opioid in patients with PCOS, by comparing the total and size of the dominant follicles and estradiol levels in patients with PCOS who have received naltrexone or clomiphene citrate.

MATERIALS AND METHODS

An experimental research design with pre and post test control group design. Feasibility of Conduct obtained from the ethical committee for research at the Faculty of Medicine, University of Airlangga, Surabaya. Performed in humans with PCOS by Rotterdam criteria. The population was divided into two groups who received naltrexone for 5 days (day 3 to day 7 of the menstrual cycle) at a dose of 50 mg/day for first cycle, 100 mg/day for the second cycle and 150

mg/day for the third cycle and who received clomiphene citrate for 5 days at a dose of 50 mg/day untuk first cycle, 100 mg/day for the second cycle and 150 mg/day for the third cycle. In both groups examined serum estradiol and TVS to measure the follicles on day-3 and day-12. Patients with dominant follicle on day 12 of the menstrual cycle was excluded in the next cycle. Researchers compared the total and size of the dominant follicles and estradiol levels between the two groups.

The data were recorded in the data collection form designed specifically for this study. To see the difference in the total and size of the dominant follicles and estradiol levels in patients with PCOS, first tested for normality, when the normal distribution using the t test, when abnormal distribution will be non-parametric test Mann-Whitney. To facilitate statistical calculations will be used SPSS software tools

RESULTS

During the period from March 2012 to August 2012 the number of subjects that we have collected for 16 patients with division 8 subjects as the control group (clomiphene citrate) with a total of 20 cycles and 8 subjects as the treatment group (naltrexone) with a total of 18 cycles. In the control group 2 subjects obtained by examination of the dominant follicle on day 12 the first cycle, whereas the treatment group obtained three subjects with a dominant follicle on day 12 the first cycle. In the second cycle of the dominant follicle formation was not obtained in both groups, whereas the third cycle 2 subjects obtained by examination of the formation of the dominant follicle on day 12 in the control group (clomiphene citrate) without the formation of the dominant follicle in the treatment group (naltrexone). Table 1 shows the age of the subject of this research did not differ significantly ($p = 0.439$) for the both group. Similarly, body mass index of the subject treatment groups (naltrexone) did not differ significantly ($p = 0.725$) in the control group (clomiphene citrate). Table 3 shows the cross-sectional size of the dominant follicle-12 days in subjects who formed the dominant follicle was not found significant differences ($p = 0.400$) between the groups naltrexon with clomiphene citrate. Table 5 shows the results of the analysis of differences in estradiol-12 days in subjects who formed the dominant follicle was not found significant differences ($p = 0.057$) between the groups naltrexon with clomiphene citrate.

Table 1. Characteristics of subjects

Group	Age (y.o)	p Value	BMI (kg/m ²)	p Value
Naltrexone	28.4 ± 1.35	0.439	31.0 ± 2.73	0.725
Clomiphene citrate	28.8 ± 1.37		30.3 ± 2.06	

Non parametric test of *Mann-Whitney*

Table 2. The number and size of dominant follicle (Day 12)

Group	Cycle-1 (mm)*	Cycle-2 (mm)	Cycle-3 (mm)*	Total (cycle)
Naltrexone	21.6	-	-	3 (16.66%)
	18.2			
	20.3			
Clomiphene citrate	21.4	-	18.3	4 (20%)
	18.2		18.1	

Table 3. The difference in cross-sectional size of the dominant follicle in subjects who formed the dominant follicle

Group	The size of dominant follicle Days 12(mm)	p Value
Naltrexone	19.70±2.261	0.400
Clomiphene citrate	18.45±2.017	

Non parametric test of *Mann-Whitney*

Table 4. The difference in cross-sectional estradiol levels (day 12) in subjects who formed the dominant follicle

Group	Cycle-1 (pg/mL)	Mean (pg/mL)	Cycle-2 (pg/mL)	Mean (pg/mL)	Cycle-3 (pg/mL)	Mean (pg/mL)
Naltrexone	247.56	266.73	-	-	-	-
	266.39					
	268.43					
Clomiphene citrate	270.23	272.44	-	-	275.79	272.77
	273.97				269.76	

Table 5. Estradiol level means in subjects who formed the dominant follicle

Group	Estradiol serum (day 12) (pg/mL)	p Value
Naltrexone	260.7±11.51	0.057
CC	272.4 ± 2.92	

Non parametric test of *Mann-Whitney*

DISCUSSION

This study aimed to study the effect of naltrexone as a treatment alternative in patients with anovulatory PCOS. The effect that occurs because of naltrexone compared with the effects of clomiphene citrate as a first-line therapy in anovulatory PCOS have shown to increase the incidence of ovulation by 70-80%, but the pregnancy rate is only around 30-40%. Some of the factors that influence the success of clomiphene citrate ovulation induction in cases of PCOS are obese, hiperandrogenemia, age and insulin resistance. Research conducted by Ahmed et al (2008) showed that administration of naltrexone as an anti-opioid combination with clomiphene citrate showed some clinical parameters improved endocrine and metabolic changes in patients with PCOS.⁵ Besides the central and peripheral effects of naltrexone is a basic improvement of ovulation in PCOS.

This research used the size of dominant follicles and estradiol levels as a parameter of impending ovulation. As it is known at the beginning of the cycle, estradiol levels low will trigger the secretion of gonadotropins. LH stimulate androgen synthesis in theca cells, and androgen into estrogen changed by FSH in granulosa cells (two cell theory). At the beginning of the cycle, FSH addition to trigger the synthesis of estrogen also causes cell proliferation so that the follicle grows larger granulosa, with estrogens stimulate the synthesis of FSH receptor in granulosa cells and triggers the secretion of inhibin and activin by granulosa cells. Impact of gonadotropin stimulation (FSH and LH) causes the growth of multiple follicles and estradiol secretion increased slowly. On days 5-7 of the menstrual cycle, estradiol levels were high enough with inhibin-B suppress FSH secretion, but not LH. FSH secretion decreased on days 5-7 less impact several follicles will undergo atresia ready and will grow to be the dominant follicle continues to grow. The dominant follicle continues to grow will lead to increased secretion of estradiol, and in approximately cycle day 12, the levels are high enough around 200 pg/mL will provide feedback so that the resulting surge in LH FSH surge that followed. FSH surges with estrogen triggers the formation of LH receptors on cells and followed luteinizing granulosa imperfect ensued which resulted in increased secretion of progesterone surge in gonadotropins who was instrumental in the process of ovulation.⁸

In general, the women in particular in patients with PCOS, ovarian reserve declines with increasing age.⁹ Ovarian reserve in women of the same age is not always the same. Besides age will lead to a decline in

ovarian sensitivity to gonadotropin stimulation. Changes in ovarian cellular level, the main cause of the decrease in sensitivity.⁸

Metabolic abnormalities that occur in patients with PCOS strongly correlated with the amount of body mass index in these patients. The greater the body mass index of more severe metabolic abnormalities were found.¹⁰ Clomiphene citrate able to bind to estrogen receptors are located throughout the human body in a much longer time than estrogen. This resulted in FSH window open longer so that clomiphene citrate may produce more stout dominant follicle.⁸ Naltrexone as previously described to have central and peripheral effects, which can improve some metabolic conditions are changed in patients with PCOS and could further lead to the formation of the dominant follicle.³ Inhibition of opioid system with naltrexone hyperinsulinemia in PCOS who showed improvement due to decreased levels of glycogen regulation insulindalam circulation.^{11,12}

The dominant follicle continues to grow will lead to increased secretion of estradiol, and approximately day 12 of the menstrual cycle, the levels are high enough, 200 pg/mL will provide positive feedback on LH secretion, causing a surge of LH which will be followed by a surge of FSH followed imperfect luteinization of granulosa cells. This causes a slight increase secretion of progesterone that triggers gonadotropin surge plays an important role in the process of ovulation, oocyte maturation and rupture of the follicle wall.⁸ Estradiol plays a critical role in the growth and development of follicles either through local effects on granulosa cells or by setting positive and negative feedback on the secretion of FSH and LH. Preparation of two-cell theory to explain the formation of the complex of follicular estradiol.¹³

CONCLUSIONS

There were no significant differences between patients with PCOS dominant follicles in size by administering naltrexone compared to clomiphene citrate. There were no significant differences in estradiol levels by administering naltrexone patients with PCOS compared to clomiphene citrate. There were no significant differences between patients with PCOS dominant follicles in size by administering naltrexone compared to clomiphene citrate.

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