

Comparison of HOMA-IR, Uterine and Spiral Artery Resistance and Endometrium in PCOS Patient with Clomiphene Citrate and Naltrexone Treatment

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ABSTRACT

Clomiphene citrate become the first-line treatment in ovulatory PCOS patients, but only for ovulation induction. Naltrexone can restore menstrual regularity, induce ovulation, and reduce LH/FSH ratio, and testosterone levels. This study was to compare HOMA-IR, uterine and spiral artery resistance, endometrium thickness and trilaminar pattern after naltrexone or clomiphene citrate administration in PCOS patients. This study used pre dan post test control group design in PCOS patients according to Rotterdam criteria. Population was divided into two groups, one receiving naltrexon for 5 days in 50 mg/day, 100 mg/day, and 150 mg/day for first, second and third cycle, and another group received clomiphene citrate of the same doses and periods. Both underwent fasting blood glucose and insulin examination on day 3 and 12 of menstrual cycle and USG TVS doppler on day 12. Patients with dominant follicle on day 12 of menstrual cycle were excluded. We compared decreased values of HOMA-IR, uterine and spiral artery resistance, endometrium thickness and trilaminar pattern. Between naltrexone and clomiphene citrate group, we found significant differences in HOMA-IR values ($p = 0.023$), and uterine artery resistance ($p = 0.039$) and pulsatile indexes ($p = 0.02$), while there was no significant difference in spiral arteries resistance index ($p = 0.952$), endometrial thickness on day 12 ($p = 0.305$), and trilaminar endometrium pattern ($p = 0.395$). In conclusion, compared to clomiphene citrate, naltrexone produces remarkable changes in uterine arteries resistance and HOMA-IR value, while its effect on endometrial thickness, trilaminar pattern, and spiral arteries resistance index is average. (MOG 2013;21:94-99)

Keyword: PCOS, naltrexone, clomiphene citrate, HOMA-IR, resistance, endometrium.

ABSTRAK

Klomifen sitrat menjadi pengobatan lini pertama pada pasien PCOS, tetapi hanya untuk induksi ovulasi. Naltrekson dapat mengembalikan keteraturan menstruasi, menginduksi ovulasi, mengurangi rasio LH/FSH, dan kadar testosteron. Penelitian ini membandingkan HOMA-IR, resistensi arteri uterus dan spiral, ketebalan endometrium dan pola trilaminar setelah pemberian naltrekson atau klomifen sitrat pada pasien PCOS. Penelitian ini menggunakan pre and post test control group design pada pasien PCOS menurut kriteria Rotterdam. Populasi dibagi dua kelompok, satu menerima naltrexon selama 5 hari sebanyak 50 mg/hari, 100 mg/hari, dan 150 mg/hari untuk siklus pertama, kedua dan ketiga. Kelompok lain menerima klomifen sitrat pada dosis dan jangka waktu yang sama. Keduanya menjalani pemeriksaan glukosa darah puasa dan insulin pada hari 3 dan 12 dari siklus menstruasi dan USG TVS doppler pada hari 12. Pasien dengan folikel dominan pada hari 12 dari siklus menstruasi dikeluarkan. Dibandingkan penurunan nilai HOMA-IR, resistensi arteri uterus dan spiral, ketebalan endometrium dan pola trilaminar. Antara kelompok naltrekson dan klomifen sitrat, didapatkan perbedaan signifikan pada nilai HOMA-IR ($p = 0,023$), dan resistensi arteri uterus ($p = 0.039$) dan indeks pulsatil ($p = 0,02$), sedangkan tidak ada perbedaan signifikan pada indeks resistensi arteri spiral ($p = 0,952$), ketebalan endometrium pada hari ke 12 ($p = 0,305$), dan pola trilaminar endometrium ($p = 0,395$). Kesimpulannya, dibandingkan dengan klomifen sitrat, naltrekson menghasilkan lebih banyak perubahan resistensi arteri uterus dan nilai HOMA-IR, namun tidak pada ketebalan endometrium, pola trilaminar, dan indeks resistensi arteri spiral. (MOG 2013;21:94-99)

Kata kunci: endometrium, naltrekson, klomifen sitrat, HOMA-IR, resistensi

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INTRODUCTION

Polycystic Ovary Syndrome (PCOS) is a heterogeneous disease with unclear etiology, which affects 6 -10% of women of reproductive age. Clinical and biochemical picture of each individual manifest variably, namely the presence of polycystic ovaries and hyperandrogenism, changes in gonadotropin secretion

and chronic an-ovulation, and these are the main clinical signs of PCOS. Medical treatment of PCOS can be divided into four components, the handling of the menstrual cycle, hirsutism, infertility and response to insulin resistance. The incidence of insulin resistance in PCOS patients ranges from 50-70%.¹

Clomiphene citrate become the first-line treatment in anovulatory PCOS patients. However, the use of clomiphene citrate is only for induction of ovulation, which is as anti-estrogens, and does not address the basic/cause of the pathogenesis of PCOS as hyperinsulin and hyperandrogen. Success rate of clomiphene citrate ovulation is $\pm 70\%$, but the pregnancy success rate is only 30-40%. Various hypotheses were developed for evaluation of imbalance between the incidence of ovulation and pregnancy. Several studies demonstrated that clomiphene citrate have anti-estrogen effects that play a role in the endometrium.² Endometrial thickness and trilaminar pattern can be used as an evaluation for uterine receptivity. Besides, better endometrial vascularity will allegedly increase the chance of pregnancy. Use of Doppler ultrasonography to evaluate the uterine arteries, spiral arteries, and the arteries subendometrial can be used for evaluation of the endometrial response.³

In PCOS patients, we can also found an increase in uterine artery resistance than normal people. It is associated with high levels of androgens that activate specific receptors on the wall of the artery, the collagen and elastin deposits smooth muscle cells which have effect as vasoconstrictors. This condition makes the uterus decreased perfusion and is suspected to be the cause of the high incidence of abortion in PCOS patients.⁴

β - Endorphins hypothalamic system regulators have a various role functions, including reproduction. In patients with PCOS there is an increased of central opioid tone that can be suppressed by the opioid antagonist. Naltrexone (μ -opioid receptor antagonist), can restore menstrual regularity, induce ovulation, and reduce the ratio of LH/FSH, and testosterone levels.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 compare HOMA-IR, uterine and spiral artery resistance, endometrium thickness and endometrium trilaminar pattern after administration of naltrexone or clomiphene citrate in PCOS patients.

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 fasting glucose and fasting examined insulin on day-3. And on day-12 both examined groups fasting glucose, fasting insulin and TVS Doppler to measure endometrial thickness, trilaminar pattern, spiral artery resistance index, resistance index and pulsatile index of uterine artery. Patients with dominant follicle on day 12 of the menstrual cycle was excluded in the next cycle. Researchers compared to HOMA-IR, uterine and spiral artery resistance, endometrium thickness and endometrium trilaminar pattern between the two groups. The data were recorded in the data collection form designed specifically for this study. 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. Table 1 shows the age of the study subjects naltrexone group did not differ significantly ($p = 0.635$) with a group of clomiphene citrate and body mass index naltrexone group of study subjects did not differ significantly ($p = 0.977$) in the control group clomiphene citrate. Table 2 shows the analysis of changes in HOMA-IR values obtained significant difference ($p = 0.023$) between the naltrexone group (2.3 ± 2.2) with clomiphene citrate group (0.37 ± 0.9). Table 3 shows significant differences ($p = 0.039$) between uterine artery resistance index in naltrexone group (0.85 ± 0.08) and clomiphene citrate (0.91 ± 0.10), and found significant differences ($p = 0.02$) from the uterine arteries pulsatile index between naltrexone group (1.91 ± 0.45) and clomiphene citrate (2.39 ± 0.41).

Table 1. Research Subject Characteristic

Group	Age	<i>p</i> value	BMI	<i>p</i> value
Naltrexone	28,4 ± 1,35	0,635	30,8 ± 2,89	0,977
Clomiphen citrate	28,8 ± 1,37		30,3 ± 2,06	

Mann-Whitney non parametric test

Table 2. HOMA-IR value changes

	HOMA-IR	P value	HOMA-IR	P value	HOMA-IR	P value
	Day-3		Day-12		changes	
Naltrexone	7,5±3,2	0,758	5,2±1,3	0,88	2,3±2,2	0,023
Clomiphen citrate	6,8 ±2,1		6,4±1,8		0,37±0,9	

Mann-Whitney non parametric test

Table 3. Resistance of uterine artery in 12th day of menstrual cycle

	Naltrexone	Clomiphen citrate	<i>p</i> value
RI	0,85±0,08	0,91±0,10	0,039 ^a
PI	1,91±0,45	2,39±0,41	0,02 ^b

Mann-Whitney non parametric test(a), T test (b),

Table 4. Comparison of endometrial quality in naltrexone and clomiphen citrate group

Variables	Naltrexone (n=18)		Clomiphen citrate (n=20)		<i>P</i>
	Mean (mm)	N(%)	Mean(mm)	N (%)	
Endometrial thickness	7,9±1,1(5,8-10,4)		7,5±1,1(5,4 - 9,6)		0,305 ^a
- < 7 mm		3 (16,7)		7(35)	0,278 ^b
- ≥ 7 mm		15 (83,3)		13(65)	
Spiral artery resistance index	0,62±0,1		0,64±0,06		0,952 ^c
- ≤ 0,55		2 (11,1)		1 (5)	0,595 ^b
- > 0,55		16 (88,9)		19(95)	
Endometrial quality					
-Good quality		2 (11,1)		1 (5)	0,595 ^b
- Poor quality		16 (88,9)		19 (95)	
Trilaminar pattern		4 (22,2)		2(10)	0,395 ^b

^a T test^b Fisher's exact test^c Mann-Whitney

Table 4 shows the endometrial thickness in 12th day of naltrexone group study subjects did not differ significantly ($p = 0.305$) with a group of clomiphene citrate. Endometrial thickness ≥ 7 mm on the 12th day naltrexone group of study subjects did not differ significantly ($p = 0.278$) with clomiphene citrate group. There is no significant difference in resistance index of spiral arteries between naltrexone and clomiphene citrate ($p = 0.952$). And the spiral arteries $RI \leq 0.55$ naltrexone and clomiphene citrate group was not

significant ($p = 0.595$). The results of analysis trilaminar endometrium pattern obtained no significant difference ($p = 0.395$) between the naltrexone group (22.2%) with clomiphene citrate group (10%).

DISCUSSION

This study aimed to learn the effect of naltrexone as an alternative therapy in patients with PCOS. The effect

Table 5. Comparison in group with folicel preovulation

Variable	Naltrexone (n=3)		Clomiphene citrate (n=4)		P
	Mean (mm)	N(%)	Mean(mm)	N (%)	
Endometrial thickness	7,9±2,3		6,9±1,8		0,48 ^a
- ≥ 7 mm		2(63,3)		1(25)	0,486 ^b
Spiral artery resistance index	0,58±0,08		0,69±0,2		0,289 ^a
- ≤ 0,55		1 (33,3)		0 (0)	0,595 ^b
Uterine artery Resistance-Resistance index					
-Pulsatile index	0,85±0,13		0,9±0,19		0,285 ^a
	1,77±0,35		2,77±0,62		0,077 ^a

^a Mann-Whitney^b Fisher's exact test

that occurs because of naltrexone compared with the effects of clomiphene citrate as a first-line therapy in anovulatory PCOS. Treatment success rate clomiphene citrate ovulation $\pm 70\%$, but the success rate is only 30-40% pregnancy. Imbalance between the incidence of ovulation and pregnancy is suspected because of clomiphene citrate has the effect of anti-estrogen that made thin endometrium. Changes in endometrial thickness and trilaminar pattern can be used as a parameter to evaluate uterine receptivity. It is assume a better endometrial vascularity will increase the chances of pregnancy. Use of Doppler ultrasonography to evaluate the uterine arteries, spiral arteries, and the arteries subendometrial can be used for evaluation of the endometrial response.³ In PCOS patients obtained an increase in uterine artery resistance than normal people. This is related to androgen levels. This condition makes perfusion to uterine decreased and endometrial vascularity will also affect this.⁶ 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

From the analysis result showed significant differences impairment HOMA-IR ($p = 0.023$) between the naltrexone group (2.3 ± 2.2) and clomiphene citrate (0.37 ± 0.9). Naltrexone effects on the pancreas decrease insulin production, while increasing hepatic clearance of insulin resulting in lower levels of insulin in the circulation.⁷ In the group with a BMI > 30 kg/m² compared to BMI < 30 kg/m² found impairment HOMA-IR value greater. It probably depends on the levels of β -endorphin, β -endorphin levels in which obese patients are higher than non-obese patients. In PCOS women with central obesity and insulin resistance hiperandrogen values higher than non central

obesity, but it is also found differences in the levels of β -endorphin levels were higher in obese than non-obese central. It is assumed that differences in the expression of the opioid system in obese women with PCOS on the terms of the distribution of body fat affects the success of naltrexone therapy with insulin resistance.⁸ Clomiphene citrate does not have metabolic effects in PCOS patients, so you do not get change in value of HOMA-IR after clomiphene citrate therapy, this corresponds well with studies conducted by Memon et al.⁹

In uterine artery vascular obtained significant differences ($p = 0.039$) resistance index naltrexone group (0.85 ± 0.08) compared with clomiphene citrate group (0.91 ± 0.10) and significant differences in pulsatile index ($p = 0.02$) between the naltrexone group (1.91 ± 0.45) and clomiphene citrate (2.39 ± 0.41). In group formed preovulation follicles, uterine artery resistance of naltrexone group was better than clomiphene citrate group, although not statistically significant. The act of clomiphene citrate as anti estrogen did not affect metabolic factors in PCOS, such as increased levels of androgens. Where androgen activates specific receptors on the wall of the artery, the collagen and elastin deposits smooth muscle cells that are vasoconstrictors. Besides anti-estrogen clomiphene citrate effects can be local to the uterus. Estradiol work on specific receptors on uterine artery walls releasing nitric oxide, a potent vasodilator that causes vasodilation and increased blood flow.¹⁰ Central effects of the naltrexone would reduce levels of pituitary LH. LH levels are down will affect ovarian theca cell androgen production decreases so. Naltrexone affects carbohydrate metabolism by lowering insulin levels. Where insulin levels down will increase levels of SHBG and lower free androgen levels. Besides insulin levels will increase IGFBP-I levels. Increased IGFBP will

enhance circulation and local IGF activity in ovarian androgen production, which lowers the theca cells. Androgens vasoconstriction suspected of having direct effect on blood vessels, and fibrotic processes mediated by androgen-dependent collagen and elastin deposits on smooth muscle. So the decline in androgen levels can improve uterine perfusion.¹¹

Research found a greater success rate of pregnancy in patients with RI sub endometrial blood flow low to moderate ($RI \leq 0.55$).⁴ From the results of the study found no significant differences in the spiral arteries resistance index ($p = 0.952$) in the naltrexone group (0.62 ± 0.1) and clomiphene citrate (0.64 ± 0.06). On naltrexone group subject the spiral arteries $RI \leq 0.55$ more (11.5%) compared with clomiphene citrate group subjects (5%), although no statistically significant differences found. On group forming preovulatory follicles, resistance of spiral arteries in naltrexone group was better than that in clomiphene citrate group, although not statistically significant ($p=0.289$). Anti-estrogen effects of clomiphene citrate can be local to the blood vessels. Where estradiol work on a specific artery wall receptor it will release nitric oxide, a potent vasodilator that causes vasodilation and increased blood flow. Although uterine artery vascular resistance found in the naltrexone group better than clomiphene citrate group, the endometrial spiral artery vascular resistance was not significantly different. This may be due to blood flow to the endometrium not only supplied by the uterine arteries. In addition, some factors are also thought to affect the vascularization of the endometrium, such as endometrial E2 levels.¹²

In this study, endometrial thickness on day 12 of the menstrual cycle in the naltrexone group (7.9 ± 1.1 mm) thicker than clomiphene citrate group (7.5 ± 1.1 mm), although no statistically significant differences found. Pregnancy does not occur in endometrial thickness of less than 7 mm,^{13,14} although some studies found implantation endometrium of pregnancy can occur in less than 6mm. In the naltrexone group subjects ≥ 7 mm endometrium thick on day 12 of the menstrual cycle much more (83.3%) compared with clomiphene citrate group subjects (65%), although no statistically significant differences found. In group formed preovulation follicles, endometrial thickness naltrexone group better than clomiphene citrate group, although not statistically significant ($p=0.48$). Clomiphene citrate able to bind to estrogen receptors located throughout the body including the receptor located in the hypothalamus and pituitary. Due to the antiestrogenic effect of clomiphene citrate makes the endometrium become thin.¹⁵ The lacking endometrium thickness in clomiphene citrate group was due to the depletion of estrogen receptors resulting in lower growth in the

proliferative phase of endometrium lining, besides clomiphene citrate persists in the body for a long half-life (several weeks) and excess of this will slow leads to accumulation of antiestrogenic effects on drug delivery triggers ovulation in the next cycle.¹⁶

When compared to the quality of the endometrium with parameter endometrial thickness and resistance index spiral arteries, where it says good quality if endometrial thickness ≥ 7 mm and spiral arteries resistance index ≤ 0.55 , the quality of the endometrium on naltrexone group was not significantly different when compared with clomiphene citrate group.

Endometrium pattern associated with pregnancy success rate, where the picture of trilaminar pattern have higher pregnancy rate than the homogeneous pattern. Endometrium trilaminar pattern occur in late follicular phase and the growth affect by hormone levels. In the early proliferative phase endometrium pattern looks homogeneous. Changes homogeneous pattern of the early phase of a trilaminar in the late proliferative phase endometrium increases receptivity. Although the biochemical changes that cause changes in the picture is still unclear.¹⁷

CONCLUSION

The decline in the value of HOMA-IR PCOS patients by administering naltrexone better than clomiphene citrate. Resistance and pulsatile index of uterine artery in PCOS patients by administering naltrexone better than clomiphene citrate. There were no significant differences in the spiral arteries resistance index in PCOS patients by administering naltrexone compared to clomiphene citrate. There were no significant differences in endometrial thickness and trilaminar pattern in PCOS patients by administering naltrexone compared to clomiphene citrate.

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