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Open Access Original Article

Crescent Journal of Medical and Biological Sciences
Vol. 6, No. 2, April 2019, x–x
eISSN 2148-9696

Comparing Naltrexone and Metformin Pretreatment for Inducing Ovulation in Patients With Polycystic Ovary Syndrome in Intrauterine Insemination Cycles

Afsun Zarei, Bahia Namavar Jahromi, Gooya Madadi, Mahshid Alborzi*, Pardis Bakhshaei

Abstract

Objectives: Polycystic ovary syndrome (PCOS) is a common endocrine disorder among women. Hyperinsulinemia and insulin resistance are normally observed in PCOS patients and metformin is used to treat this disease. The evidence indicates that the opioid system plays a role in the pathogenesis of the PCOS. Based on the above-mentioned explanation, the present study evaluated the role of opioid antagonist (naltrexone) in PCOS-induced infertility compared to metformin.

Material and Methods: Totally, 120 patients afflicted with PCOS were assigned to three groups based on Rotterdam diagnostic criteria, with a body mass index (BMI) of 25-30 kg/m^2. The first group received naltrexone (50 mg/d) for 8 weeks. In addition, the second group were injected with metformin 1000 and then 1500 mg/d for the first and seventh weeks, respectively. Finally, the third group entered the intrauterine insemination (IUI) without prior therapeutic treatment. Then, the groups were compared in terms of the amount of estradiol produced per day of human chorionic gonadotropin injection and the total amount of gonadotropin needed, the number and size of the adult follicles, the number of days of taking the drug, and incidence of pregnancy-induced abo

Results: Based on the results, the mean of infertility duration was not significant among the three groups ($P=0.782$). Further, the mean fasting insulin level between the metformin and control groups represented a significant difference ($P=0.045$). The average number of days to trigger patients in the 3 groups was not significant ($P=0.346$). Although the average number of follicles between metformin and naltrexone groups was not significant, it was higher in the naltrexone group. Finally, the average BMI of the naltrexone group after the treatment was lower compared to before treatment ($P\leq 0.001$).

Conclusions: In general, the number of receiving days and the dose of the drug in the naltrexone group was lower compared to the metformin group. Furthermore, the number of mature follicles in both ovaries and the serum estradiol level in the naltrexone group was higher compared to the metformin group.

Keywords: Naltrexone, Polycystic ovary syndrome, Metformin

Introduction

Polycystic ovary syndrome (PCOS) is considered a prevalent endocrine disease among women which includes 87% of outpatient referrals caused by oligomenorrhea and 26% of amenorrhea complaint and 18% of all causes of infertility (1-4).

Based on Rotterdam modified diagnostic criteria, diagnosis of polycystic ovarian syndrome requires at least 2 of the following indexes:

- Lack of ovulation or ovulation in a long-time interval;
- Clinical or chemical signs of androgenism;
- Sonographic findings predicting PCOS;

Abandonment other etiologies such as adrenal congenital hyperplasia, androgen releasing tumors and Cushing's syndrome (5). Diagnostic criteria for PCOS in sonography can be described based on Rotterdam Consensus (2013) as detecting 12 or more numbers of the follicle with the size of 2-9 mm or increased ovarian size above 10 cm^3 founded in vaginal sonography (5,6). Patients suffering from PCOS encounter increased concentrations of luteinizing hormone (LH). However, follicle-stimulating hormone (FSH) rises at unconsidered amounts (7) and this causes a higher proportion of LH against FSH in these patients. Therefore, increased secretion of androgen from the theca layer leads to this unbalanced proportion of LH/FSH (8).

Recently, more attention has been paid to patients' metabolic changes. Peripheral resistance against insulin is a characteristic of many PCOS patients (9). Almost 50% of PCOS patients face with insulin resistance as a result of fat storage in the abdominal wall (10) which thus can cause metabolic syndrome and type 2 diabetes mellitus (11). However, insulin resistance is reported in PCOS patients without obesity. Responsible molecular mechanism for

Received 21 March 2018, **Accepted** 19 November 2018, **Available online** 20 June 2022

[1]Infertility Research Center, Department of Obstetrics and Gynecology, Shiraz University of Medical Sciences, Shiraz, Iran.
***Corresponding Author:** Mahshid Alborzi, Tel: +9177913221, Email: alborzimah@gmail.com

insulin resistance in PCOS patients is defined as a disorder in the post-receptor signaling pathway in fatty and skeletal muscle cells (12). It is found that the signaling pathway deficit can cause selective resistance against insulin and then affect the function of insulin (13). Glucose-stimulated insulin releasing disorder has recently been highlighted as an important mechanism (14).

Various evidence emphasizes that the opioid system plays a remarkable role in the pathogenesis of PCOS. The function of such a system is altered in central and peripheral forms (15,16). Opioids can lead to altered and abnormal patterns of gonadotropin secretion cycle and interfere with metabolic balance in PCOS patients (17,18). Moreover, insulin receptors are found on the surface of opioid secreting cells of the pituitary gland (19). Additionally, beta-endorphins are important neurotransmitters of the hypothalamus which have an inhibitory effect on GnRH secretion (20). Although consuming opioids as inhibitory neurotransmitters is common among PCOS patients, it can have stimulatory effects on LH secretion and this controversial effect is observed in both human and animal cases (21-23). In addition, LH response to gonadotropin-releasing hormone (GnRH) agonist normal as a result of long-term use of the opioid antagonists.

Based on the findings of an animal case study, beta-endorphin can stimulate the release of insulin and glucagon (24). Therefore, an abnormal opioid system somewhat can be responsible for hyperinsulinemia and resistance to insulin occur in PCOS patients due to the increased peripheral level of beta-endorphins (25). Several studies demonstrated that opioid antagonists increase ovulation (26) while they decrease insulin response during glucose stimulation test (OGTT) in PCOS patients who suffer from hyperinsulinemia (26, 27).

Reparative hyperinsulinemia and insulin resistance contribute to the pathogenesis of PCO. A large body of research evaluated the effects of drugs on increasing body sensitivity to insulin including metformin. Hyperinsulinemia is normally accompanied by hyperandrogenemia. The current study investigated the effect of an opioid antagonist (naltrexone) on the treatment of infertility which is resulted from PCOS.

Materials and Methods

The present prospective and randomized interval clinical trial included 120 patients suffering from PCOS who referred to Shiraz Ghadir Mother and Child Hospital for infertility treatment. These patients, whose body mass index (BMI) ranged from 25 to 30 based on Rotterdam criteria and were insulin resistant, were scheduled to undergo intrauterine insemination (IUI).

The patients were divided into 3 groups. Naltrexone at the dose of 50mg was administered to the first group per day for 8 weeks. In addition, the second group was prescribed metformin at the dose of 1000 mg/d and then 1500 mg/d for the first and next 7 weeks, respectively, and then the patients entered the IUI cycle. Further, the third group entered the IUI cycle without receiving any drug. IUI process was identically implemented for all 3 groups. The clomiphene citrate (100 mg/d) and gonadotropin (75 mg/d) were administered to the patients since the fifth to ninth day of menstruation cycle and eighth day of the cycle. Next, the first ultrasonography was performed on the 10th day of the cycle and then the dose of the drug was adjusted.

Finally, all the groups were compared in terms of the produced estradiol at the day of human chorionic gonadotropin injection, the total amount of needed gonadotropin, the number and size of the matured follicles, drug receiving days count, conceiving pregnancies, and the rate of abortion.

Inclusion criteria were containing 3 groups of 40 patients with PCO who were afflicted with PCOS based on diagnostic criteria of Rotterdam, having BMI ranging between 25 and 30 kg/m^2, being resistant to insulin (HOMA-IR) >3, and being randomly selected and organized in 3 groups. The study was initiated after obtaining informed consent.

Exclusion criteria included those patients who were unable to complete the cycle of using the administered medications during the 8 weeks.

Statistical Analysis

The average of the differences and pairwise comparisons among the groups were conducted using the Kruskal-Wallis and Mann-Whitney tests, respectively.

Results

Based on the findings, the total age average of the patients was 27.92 ± 4.53 and that of the individual groups were 28.26 ± 4.57 (control group), 28.987 ± 5.10 (metformin-treated group), and 26.32 ± 3.29 (naltrexone-treated group), respectively (P = 0.57).

Furthermore, the total BMI, as well as BMI for each of the control, metformin, and naltrexone groups were estimated 26.70 ± 4.44, 27.16 ± 4.57, 27.29 ± 5.12, and 25.53 ± 3.12 kg/m^2, respectively (P = 0.599). Moreover, the mean duration of infertility of the whole patients was 4.53 ± 2.48 years while for the individual groups it was 4.76 ± 2.32, 4.36 ± 2.44, and 4.61 ± 2.06 years, respectively (P = 0.782).

As regards the level of mean fasting insulin, statistically meaningful differences were observed among the groups (Table 1). Metformin and control groups demonstrated a clear difference in this respect (P = 0.045). Table 2 presents the hormone level differences between the 3 groups.

Totally, the average HOMA index of the patients was calculated 3.45 ± 1.20 while it was estimated 3.63 ± 1.19, 3.21 ± 1.21, and 3.52 ± 1.19 for the control, metformin, and naltrexone groups, respectively (P = 0.75).

Additionally, the average number of the days to trigger the patients was totally 8.11 ± 2.09 days whereas it was

Table 1. Divided Hormone Level of Patients in 3 Groups of the Study

		Number	Average	SD	Min	Max	*P*
FBS level mg/dL	Control group	46	91.46	6/40	75	110	0.287
	Metformin	44	90.18	6/84	68	103	
	Naltrexone	40	87.95	8/63	64	98	
	Total	120	89.95	7/38	64	110	
Fasting Insulin level, mIU/L	Control group	46	15.92	5.52	10.12	37	0.045
	Metformin	44	14.13	5.77	9.01	34.1	
	Naltrexone	40	16.48	7.61	9.14	36.1	
	Total	120	15.49	6.34	9.01	37	
FSH level, IU/mL	Control group	46	7.79	13.12	2.1	91	0.560
	Metformin	40	5.26	2.52	1.5	12	
	Naltrexone	39	4.85	2.18	0.9	10.6	
	Total	125	6.06	8.23	0.9	91	
TSH level mIU/L	Control group	44	2.69	2.08	0.8	13.53	0.995
	Metformin	42	2.52	1.59	0.02	6.2	
	Naltrexone	34	2.55	1.63	0.1	7.5	
	Total	120	2.59	1.78	0.02	13.53	
LH level, IU/mL	Control group	46	6.03	4.85	1	23.4	0.102
	Metformin	40	5.25	3.84	0.2	19.6	
	Naltrexone	38	7.93	6.73	0.7	37	
	Total	124	6.36	5.30	0.2	37	
Prolactin level, ng/mL	Control group	44	18.5	14.96	3.8	95	0.216
	Metformin	44	26.31	57.51	0.7	392	
	Naltrexone	36	21.21	37.62	1	229.4	
	Total	124	22.06	40.60	0.7	392	
Testosterone level, ng/dL	Control group	33	0.70	0.69	0.2	4.3	0.360
	Metformin	29	1.79	6.20	0.2	34	
	Naltrexone	32	0.96	1.09	0.25	6.1	
	Total	94	1.12	3.51	0.2	34	
AMH level, ng/mL	Control group	46	5.85	5.79	0.25	30.24	0.156
	Metformin	43	6.08	4.72	0.4	21	
	Naltrexone	34	7.30	4.96	1	19.3	
	Total	123	6.33	5.20	0.25	30.24	

SD: Standard deviation; FBS: Fetal bovine serum; FSH: Follicle stimulating hormone; TSH: Thyroid stimulating hormone; LH: Luteinizing hormone; AMH: Anti-Mullerian hormone.

8.37 ± 2.36, 8.36 ± 1.85, and 7.44 ± 1.89 days for the control, metformin, and naltrexone groups, respectively ($P = 0.066$). In addition, the average amount of consumed gonadotropin was 3.90 ± 2.38 in total. However, it was estimated 4.17 ± 2.29, 4.05 ± 2.80, and 3.37 ± 1.90 for control, metformin, and naltrexone groups, respectively ($P = 0.346$).

The average number of the follicle in 2 ovaries of the entire patients was 3.83 ± 3.07 while it was 4.54 ± 2.81 (control), 2.76 ± 2.11 (metformin), and 4.06 ± 3.93 (naltrexone) for the individual groups, respectively ($P = 0.002$). Further, differences were found between the patients of control and metformin groups in this regard ($P = 0.001$). In other words, the average count of follicles of 2 ovaries was higher in the naltrexone group compare to the metformin group. Approximately 26.1% (n = 12), 31.6% (n = 12), and 25% (n = 10) of the patients in control, metformin, and naltrexone groups became pregnant, respectively ($P = 0.783$).

Table 2. Distribution of the Consumed Gonadotropins in Patients of the Treatment Groups

	n	Mean	SD	Minimum	Maximum
Control group	46	4.17	2.29	1	12
Metformin	41	4.05	2.80	1	14
Naltrexone	35	3.37	1.90	1	7
Total	122	3.90	2.38	1	14

Further, the total mean of the level of estradiol was 274.61 ± 217.97 pg/mL before the triggering while the mean of estradiol level was 261.83 ± 159.10, 264.68 ± 215.2, and 303.86 ± 286.09 pg/mL for the control, metformin, and naltrexone groups, respectively ($P = 0.517$).Eventually, the mean number of consumed gonadotropins in the

entire patients, as well as the control, metformin, and naltrexone groups was 3.90 ± 2.38, 2.27 ± 4.17, 4.05 ± 2.80, and 3.37 ± 1.90, respectively. However, the mean number of the consumed gonadotropins in the treatment groups was not statistically significant ($P = 0.346$).

The average BMI calculated for the naltrexone group was 25.53 ± 3.12 and 24.38 ± 2.84 kg/m^2 before and after the treatment, respectively ($P < 0.001$).

Discussion

The current study attempted to compare the effect of naltrexone and metformin medications on the induction of ovulation in patients with PCOS who underwent intrauterine insemination. The results indicated that naltrexone has no advantage regarding ovulation induction in patients with PCOS compared to metformin. Furthermore, the number of obtained follicles in the metformin group was significantly higher compared to the other 2 groups. In other words, there were no meaningful differences between the naltrexone and control groups respecting the number of follicles. Accordingly, naltrexone therapy seems to have no effect on the obtained follicle number.

Previous studies demonstrated that naltrexone therapy can affect the endogenous opioid system of body disturbed in patients with PCOS. Moreover, a decrease in opioid secretion can improve the thalamic function. Additionally, a decrease in LH secretion while an increase in GnRH secretion result in improving the follicle production in patients with the polycystic ovarian syndrome (26-28). However, the results of the current study contradict those of the above studies. In fact, the duration of naltrexone therapy was longer in the above-mentioned studies. Conversely, metformin significantly improved follicular development, this is probably due to the decreased insulin resistance among the patients (29-31). Although the mean level of fasting insulin was lower in the metformin-related group compared to the other groups and thus it can justify the above-mentioned mechanism.

As regards the average BMI and average infertility duration, at first, no differences were observed among the 3 groups. However, the average BMI of the naltrexone group significantly decreased after the treatment. In addition, the average weight loss was 3.4 kg among the patients of the naltrexone group. It should be noted that 8-week and short-time treatments failed to result in losing the weight at this amount in overweight patients and those with endocrinal disorders. Therefore, there were probably other mechanisms affecting the weight loss including the recommended exercises and dietary regime reported by several patients. It is noteworthy that the effect of low dose and long-term use of naltrexone on weight loss is confirmed in overweight patients. Further, based on the reports, naltrexone has the same effect as obesity drugs (32). However, the effect of naltrexone on weight loss of the cases in the present study could not precisely be investigated.

Investigating the endocrinal changes in patients at 8th week after the treatment was one of the most important strength points of the current study. The blood levels of hormones such as estradiol, anti-Müllerian hormone (AMH), fasting insulin, thyroid stimulating hormone (TSH), LH, FSH, and prolactin were estimated after drug treatment. Ahmad et al (16) found that 6-month naltrexone therapy can lead to a decrease in fasting insulin, LH, FSH, and testosterone level in patients with infertility and polycystic ovarian syndrome. They further reported that the effect of naltrexone on opioid receptors existing in pituitary gland was the main cause of this mechanism. Furthermore, several other studies highlighted similar results. Of course, all the studies regarding endocrinal effects were performed using a long-term treatment with naltrexone (26, 28, 32) and no research is found with lower than six-month use of naltrexone therapy.

Using naltrexone therapy in a period lower than 8 months seems to be insufficient for affecting the hypothalamic-pituitary-ovarian endocrinal system. In fact, the effect of long-term naltrexone therapy on the endocrine system was confirmed in previous research. Therefore, given the above-mentioned issue, the present study proposed an appropriate template for other simple future studies to investigate the effects of long-term naltrexone treatment in patients. The results of the current study revealed that short-term (8 weeks) treatment by naltrexone and metformin have no priority in positively affecting the follicle-related hormones compared to the control group.

Finally, the number of receiving days and the dose of the drug in the naltrexone group was found to be lower compared to the metformin group. Conversely, the number of mature follicles in both ovaries and the serum estradiol level in the naltrexone group were higher compared to the metformin group. However, they were not statistically significant, which is possibly due to small sample size.

Conflict of Interests

Authors have no conflict of interests.

Ethical Issues

This study was approved by the Ethics Committee of Shiraz University of Medical Sciences under the ethical code: ct 90-5912 and written informed consent was obtained from the patients for voluntary participation after explaining the aims and methods of the study.

Financial Support

he authors gratefully acknowledge the efforts of the Deupty Reserch of Shiraz University of medical sciences (Iran) during the study period (grant no: 5912).

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