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Original Article

Clinical study on polycystic ovary syndrome treated with Diane-35 and Pioglitazone

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Abstract: Objective: To observe the effects of Diane-35 and pioglitazone on endocrine, blood lipid, and blood glucose metabolism in patients with polycystic ovary syndrome (PCOS). Methods: 70 PCOS patients were selected as subjects between January 2019 and January 2020 and were randomized into two groups. The control group was provided with Diane-35 for 1 tablet/day. The patients in the observation group took additional pioglitazone twice a day. The therapeutic effect of the two schemes was analyzed by observing hormone, blood lipid, and blood glucose levels. The body mass index (BMI), waist-hip ratio (WHR), and Ferriman-Gallwey score (F-G) of the two groups of patients at different time points were compared. Results: Compared with the control group, after pioglitazone treatment, a significant decrease was observed in the levels of various hormone factors. In the observation group (all $P<0.01$) and the observation group yielded lower levels of fasting blood glucose (FBG), fasting insulin (FIN), Homeostatic Model Assessment for Insulin Resistance (Homa IR), and Homeostatic Model Assessment for β-cell function (Homa B), as compared to the control group (all $P<0.01$). Additionally, compared with the control group, the high-density lipoprotein (HDL) levels in the observation group saw a spike ($P<0.01$). The low-density lipoprotein (LDL) levels witnessed a downturn ($P<0.01$). Immediately after treatment and 1 month after treatment, the BMI, WHR, and F-G scores of the two groups declined gradually, with lower WHR and F-G scores of the observation group than those of the control group ($P<0.01$). Conclusion: Diane-35 and pioglitazone can effectively improve the symptoms of sex hormone secretion, blood glucose, and blood lipid disorder in PCOS patients, which has high clinical application value.

Keywords: Diane-35, pioglitazone, polycystic ovary syndrome, sex hormone, blood glucose and lipids

Introduction

Polycystic ovary syndrome (PCOS) is a gynecological disease with an increasing incidence in recent years [1-3]. Due to the imbalance of hormone secretion, PCOS patients are often accompanied by various clinical symptoms such as obesity, hirsutism, and menstrual cycle disorders, which jeopardize the daily activities of the patients [4-6]. In addition, studies have pointed out a higher incidence of various gynecological diseases such as diabetes and hypertension in PCOS patients than healthy individuals [7, 8]. PCOS, the main cause of female infertility worldwide, has captured researchers' attention with its multi-system features, instead of being simply regarded as an ovarian disease. It is closely related to metabolic disorders and hypothalamic-pituitary-ovarian axis (HPOA) dysfunction. The syndrome can lead to hyperandrogenemia (HA), hyperinsulinemia/insulin resistance (IR), ratio imbalance of estrogen (E2), luteinizing hormone (LH), and follicle-stimulating hormone (FSH), infertility, cardiovascular disease, endometrial dysfunction, and obesity. In addition, interventions such as metformin, orlistat, hormonal contraceptives, GLP1 agonists, and vitamin D have been used to improve or reverse the pathological features of polycystic ovary syndrome, and the combination of drugs to treat PCOS is better than monotherapy [9-11]. Accordingly, it is of great significance to take effective clinical interventions for PCOS. This study used the Diane-35 plus pioglitazone to treat PCOS patients, with an aim to observe the effect of this regimen and provide a reference for the treatment of PCOS.

Table 1. Comparison of general data

Groups	Age (years)	BMI	waist-hip ratio	Course of disease (years)	Body weight (Kg)
Control group	28.05±6.96	26.41±1.09	0.86±0.07	3.15±3.21	55.32±6.92
Observation group	27.93±7.27	26.27±1.23	0.85±0.05	3.21±3.29	55.11±7.22
t	0.07	0.50	0.69	0.50	0.10
P	P>0.05	P>0.05	P>0.05	P>0.05	P>0.05

Materials and methods

General information

This study was authorized by the hospital ethics committee. Over a period of January 2019 to January 2020, 70 PCOS patients were selected as the research objects and were randomly divided into a control group and an observation group. This study strictly complied with the standards of the ethics committee with the ethics committee number of 2018-11-15. https://clinicaltrials.gov/, ClinicalTrials.gov Identifier: NCT04508644.

Patient screening criteria

Inclusion criteria: (1) Those with completed clinical data and definite disease history; (2) Those diagnosed with PCOS and exhibited overt clinical manifestations; (3) Those who voluntarily participated in the study (The patients and their family had a full understanding of the study); (4) Those who were conscious and signed an informed consent form accompanied by their families; (5) Those with no potential diseases that seriously affected the results of this study.

Exclusion criteria: patients (1) with abnormal adrenal or thyroid function; (2) with other potential chronic diseases; (3) who did not cooperate with follow-up after the clinical intervention.

Treatment methods

Control group: Patients in the control group took Diane-35 (Hubei Gedian Renfu Pharmaceutical Co., Ltd., H20056637) daily at a dose of 1 tablet/day, with 20 days as a course of treatment. The medication was continued on day 5 of menstruation after stopping the medication. The treatment continued for 5 courses.

Observation group: Patients in the observation group received additional pioglitazone (Sino-American Shanghai Squibb Pharmaceutical Co., Ltd., H20023370) based on the regimen of the control group. The patient took 2 tablets once, 2 times a day for 6 months.

Indicators observation

The changes in the levels of hormones, blood sugar, and blood lipids before and after treatment were detected. Hormonal indicators included LH, FSH, E2, and testosterone (TT). Insulin resistance indicators: fasting insulin (FIN) was measured by the chemiluminescence method. Fasting blood glucose (FBG) was measured by the glucose oxidase method. The insulin resistance index (Homeostatic Model Assessment for Insulin Resistance (Homa IR) = FIN × FBS/22.5) and the insulin secretion index [Homeostatic Model Assessment for β-cell function (Homa B) = 20 × FIN/(FBS-3.5)] with the steady-state model (Homa mode1) were calculated to comprehensively evaluate the degree of insulin resistance in peripheral tissues. Blood lipid indicators include cholesterol (CHO), triacylglycerol (TG), low density lipoprotein (LDL), and high density lipoprotein (HDL). BMI, WHR, and F-G of the two groups of patients at different time points were compared.

Data analysis

The data in this study were processed using SPSS 20.0. The count data were expressed as number (n, %) and tested using χ^2, and the measurement data was tested using t-test and displayed in the form of (mean ± standard deviation). P<0.05 indicated that there were statistical differences between the groups.

Results

Comparison of general information

The two groups witnessed no great disparity in general information, as shown in **Table 1** (P>0.05).

Comparison of hormone levels

The sex hormone levels of the two groups are shown in **Tables 2** and **3**. After treatment, the

Table 2. Comparison of LH and FSH Levels between two groups of patients

	LH (U/L)		FSH (U/L)	
	Control group	Observation group	Control group	Observation group
Before treatment	13.92±2.21	13.89±2.07	6.71±1.31	6.67±1.25
After treatment	11.96±2.17	7.32±1.09a	6.49±1.46	4.09±1.12b
t	3.74	16.61	0.66	9.09
P	<0.01	<0.01	0.51	<0.01

Note: a and b indicate a significant difference between the two groups in hormones before and after treatment (a: t = 11.30, P<0.01; b: t = 7.72, P<0.01).

Table 3. Comparison of TT and E2 levels between the two groups

	TT (nmol/L)		E2 (pmol/L)	
	Control group	Observation group	Control group	Observation group
Before treatment	2.39±0.49	1.73±0.21	123.96±6.10	121.72±5.00
After treatment	2.37±0.43	1.22±0.11a	124.12±6.09	109.97±5.09b
t	7.32	15.33	1.68	10.55
P	<0.01	<0.01	0.10	<0.01

Note: a and b indicate a significant difference in hormones between the two groups before and after treatment (a: t = 12.73, P<0.01; b: t = 9.74, P<0.01).

Table 4. Comparison of FBG, FIN, Homa IR, and Homa B between the two groups

Group	Time	FBS (mmol/L)	FIN (mIU/L/)	Homa IR	Homa B
control group	before treatment	5.27±0.52	23.95±6.12	1.68±0.34	5.96±0.47
	after treatment	5.17±0.57	21.89±5.27	1.61±0.29	5.91±0.44
t		1.456	2.556	3.758	1.478
P		0.423	0.756	0.365	0.345
Observation group	before treatment	5.24±0.49	24.04±6.09	1.67±0.31	5.89±0.41
	after treatment	4.54±0.56a	13.27±4.1b	1.23±0.26c	5.40±0.61d
t		1.781	3.967	2.578	1.456
P		0.002	0.001	0.014	0.003

Note: a, b, c, d indicate a significant difference between the two groups after treatment (a: t = 11.73, P<0.01; b: t = 8.94, P<0.01; c: t = 7.64, P<0.01; d: t = 6.74, P<0.01).

levels of LH and E2 in the control group showed a significant decrease (P<0.01). The levels of FSH and TT did not change significantly (P>0.05). The levels of four hormones in the observation group after treatment all saw a slump (P<0.01). After taking pioglitazone, the levels of the four hormones in the observation group witnessed a greater decline than the control group (P<0.01).

Comparison of insulin-related indicators

Before treatment, the two groups did not present statistical difference with regard to FBG, FIN, Homa IR, and Homa B (P>0.05). After treatment, all indicators in the control group remained at the same level (P>0.05). The above indicators all down-regulated in patients of the observation group (P<0.05). See **Table 4**.

Comparison of CHO and TG levels

The CHO and TG levels of the two groups of patients before and after treatment are shown in **Figure 1**. After treatment, the level of TG in the control group decreased (P<0.01), and no marked change was identified in the level of CHO, while both indicators decreased significantly in the observation group (P<0.01). After taking pioglitazone, the levels of TG and CHO in the observation group were noticeably lower than those in the control group (P<0.01).

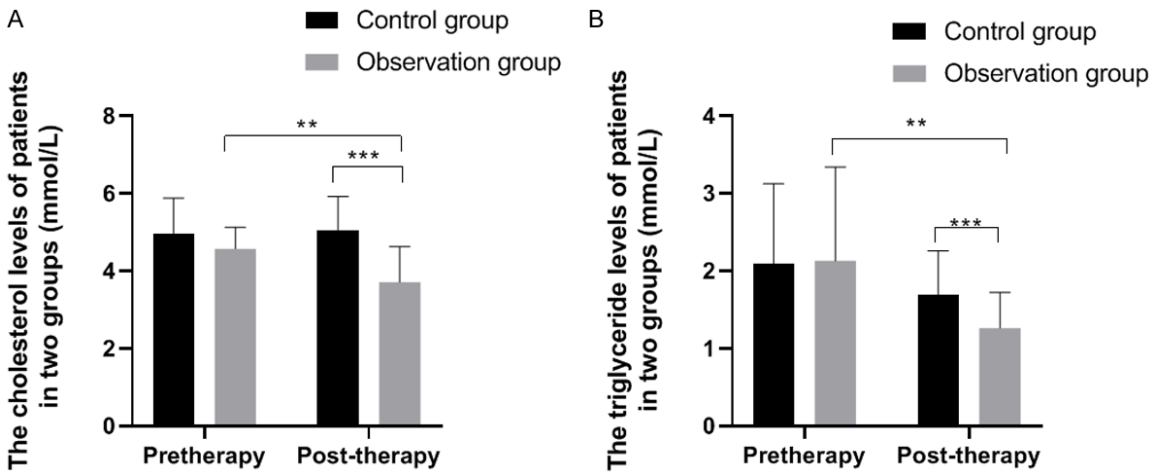

Figure 1. Comparison of CHO and TG levels between the two groups. Note: X: Treatment time. Y: (A) CHO level; (B) TG level. (A) The CHO levels of the control group before and after treatment were (4.97±0.91 mmol/L) and (5.03±0.89 mmol/L), while the CHO levels of the observation group before and after treatment were (4.57±0.55 mmol/L) and (3.71±0.91 mmol/L). ** and *** respectively indicate that the CHO levels of the observation group before and after treatment and between the two groups after treatment were significantly different (*: t = 4.78, P<0.01; **: t = 6.14, P<0.01). (B) The TG levels of the control group before and after treatment were (2.09±1.03 mmol/L) and (1.69±0.57 mmol/L), while the TG levels of the observation group before and after treatment were (2.13±1.21 mmol/L) and (1.26±0.46 mmol/L). ** and *** respectively indicate that the TG levels of the observation group before and after treatment and between the two groups after treatment were significantly different (*: t = 3.98, P<0.01; **: t = 3.47, P<0.01).

Comparison of HDL and LDL levels

The HDL and LDL levels of the two groups of patients before and after treatment are shown in **Figure 2**. After treatment, the level of LDL in the control group declined dramatically (P< 0.01), and no significant change was noticed in HDL. The LDL level was significantly decreased. HDL was significantly increased in the observation group (all P<0.01). After taking pioglitazone, LDL level was significantly lower. HDL was significantly higher in the observation group than those in the control group (all P<0.01).

BMI comparison

Figure 3 presented that BMI after treatment in both groups saw a trend of decrease (P<0.01). No evidence of statistical differences was found between the two groups before and after treatment (P>0.05).

WHR comparison

Immediately after treatment and 1 month after treatment, **Figure 4** displays a lower WHR level of the two groups than that before treatment, in which the observation group garnered a lower WHR level than that of the control group (P<0.01).

F-G score comparison

Immediately after treatment and 1 month after treatment, the F-G scores of the two groups of patients showed a clear trend of decline, with lower F-G scores of the observation group than those of the control group (P<0.01). See **Figure 5**.

Discussion

PCOS is a high-incidence gynecological disease that can cause various complications such as diabetes and hypertension, which seriously takes a toll on women's life and health [11, 12]. Currently, anti-androgen drugs such as Diane-35 are used to treat PCOS to drive down the level of male hormones in the body to alleviate the patient's symptoms and maintain their normal physiological activities [13-15]. Some critically ill patients usually exhibit symptoms such as dyslipidemia and aberrant blood sugar levels. It is formidable to substantially relieve their symptoms through mere anti-androgen therapy.

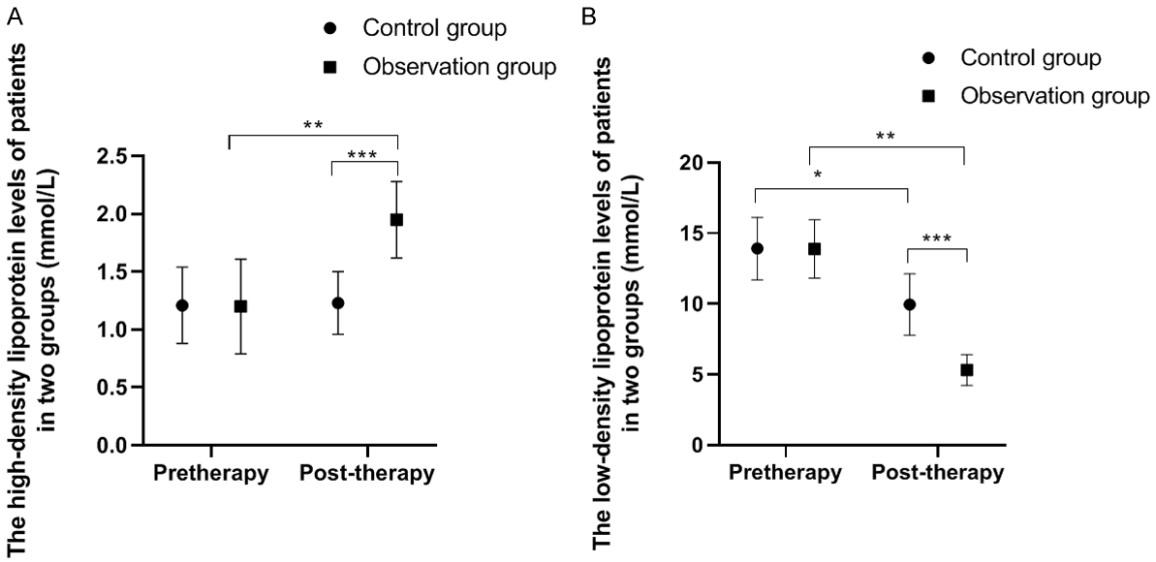

Figure 2. Comparison of HDL and LDL levels between the two groups. Note: X: Treatment time. Y: (A) Patient's HDL level; (B) Patient's LDL level. (A) The HDL levels of the control group before and after treatment were (1.21±0.33 mmol/L) and (1.23±0.27 mmol/L), while the HDL levels of the observation group before and after treatment were (1.20±0.41 mmol/L) and (1.95±0.33 mmol/L). There were significant differences in HDL levels in the observation group before and after treatment and between the two groups after treatment (t = 8.43, **P<0.01; t = 9.99, ***P<0.001). (B) The LDL levels of the control group before and after treatment were (13.29±2.21 mmol/L) and (9.96±2.17 mmol/L), while the LDL levels of the observation group before and after treatment were (13.89±2.07 mmol/L) and (5.32±1.09 mmol/L). The LDL levels of the observation group before and after treatment and between the two groups after treatment were significantly different (t = 24.62, *P<0.05; t = 21.67, **P<0.01; t = 11.30, ***P<0.001).

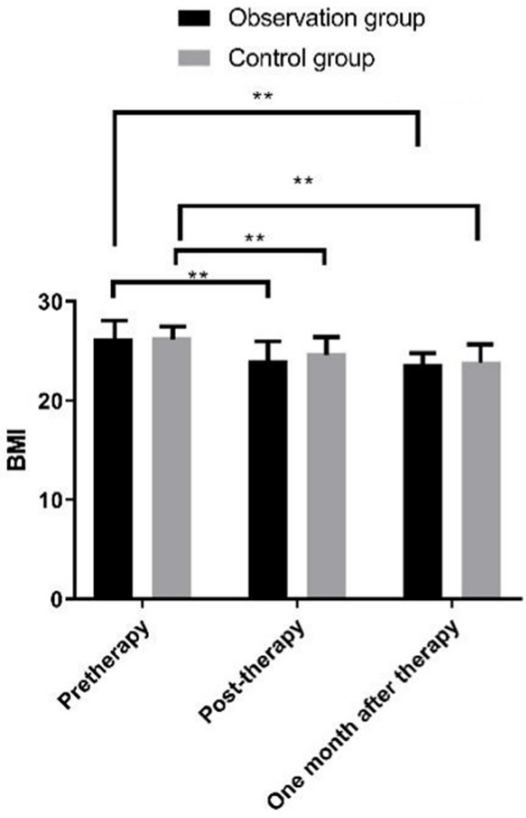

Figure 3. Comparison of BMI between the two groups of patients at different time points. Note: X: Treatment time. Y: BMI. After treatment, the BMI of observation group patients was (24.1±4.5) kg/m^2 lower than that before treatment (26.27±1.23) kg/m^2 (t = 1.357, **P<0.01); The BMI of the control group patients was (24.8±4.6) kg/m^2 lower than before treatment (26.41±1.09) kg/m^2 (t = 3.347, **P<0.01); One month after surgery, the BMI of the observation group patients was (23.3±2.5) kg/m^2 lower than that before treatment (26.27±1.23) kg/m^2 (t = 5.677, **P<0.01); The BMI of the control group patients was (23.9±4.6) kg/m^2 lower than that before treatment (26.41±1.09) kg/m^2 (t = 5.167, **P<0.01); There was no significant difference between the two groups before and after treatment (t = 7.548, 4.369, 4.555, P = 0.751, 0.548, 0.478).

In this study, after treatment with Diane-35, the secretion level of some hormones such as TT in the patient's body was significantly improved. The disorder of blood glucose and blood lipids showed no prominent mitigation. In the process of clinical intervention for patients, in addition to a single anti-androgen therapy, treatments for lowering blood sugar and blood lipids are imperative for such conditions. Pioglitazone is a biguanide drug that can

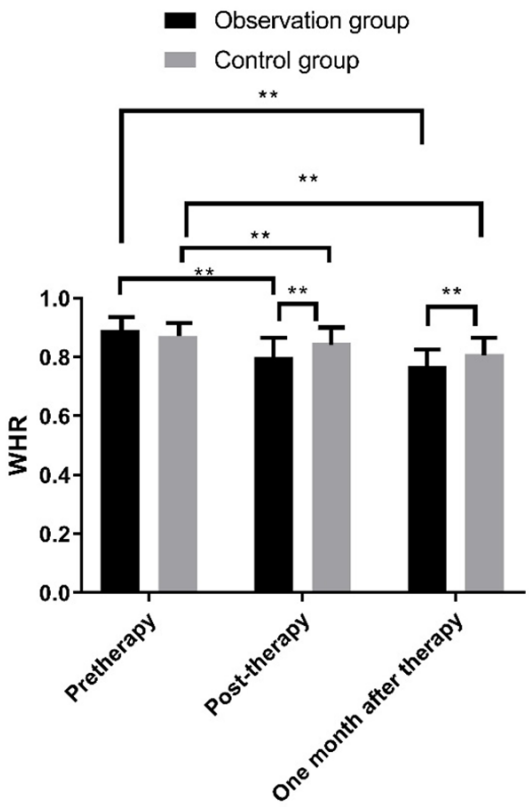

Figure 4. Comparison of WHR between the two groups of patients at different time points. Note: X: Treatment time. Y: WHR. After treatment, the WHR of the observation group patients was (0.80±0.11) lower than before treatment (0.89±0.12) (t = 2.547, **P<0.01); The WHR of the control group patients was (0.85±0.13) lower than before treatment (0.87±0.14) (t = 4.584, **P<0.01); One month after treatment, the WHR of the observation group patients was (0.73±0.08) lower than before treatment (0.89±0.12) (t = 2.747, **P<0.01); The WHR of the control group patients was (0.79±0.23) lower than before treatment (0.87±0.14) (t = 5.640, **P<0.01); Immediately after treatment and 1 month after treatment, the WHR of the observation group patients was lower than that of the control group patients (t = 7.478, 8.639, **P<0.01).

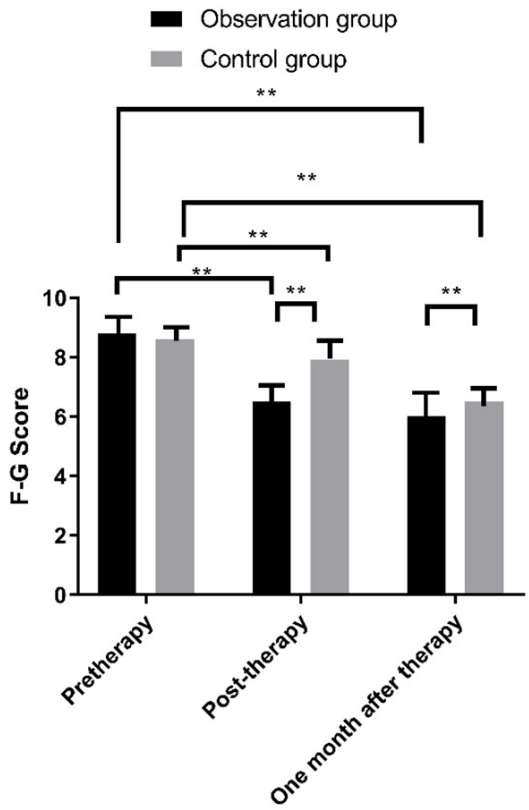

Figure 5. Comparison of F-C scores between the two groups of patients at different time points. Note: X: Treatment time. Y: F-C score. After treatment, the WHR of the observation group patients was (6.5±2.9) lower than that before treatment (8.8±3.5) (t = 3.517, **P<0.01); The WHR of the control group patients was (7.9±3.1) lower than before treatment (8.6±3.4) (t = 4.447, **P<0.01); One month after treatment, the WHR of the observation group patients was (6.0±1.9) lower than before treatment (8.8±3.5) (t = 2.517, **P<0.01); The WHR of the control group patients was (6.5±3.1) lower than before treatment (8.6±3.4) (t = 2.347, **P<0.01); Immediately after treatment and 1 month after treatment, the WHR of observation group patients was lower than that of Control group patients (t = 6.378, **P<0.01).

lower blood sugar by delaying the absorption of glucose by the stomach and intestines [16, 17]. This study compared patients receiving single Diane-35 treatment and patients taking additional pioglitazone. It showed different degrees of optimization in blood glucose and blood lipid levels 1 month after treatment. This showed that additional treatment with pioglitazone yields a positive effect on the improvement of the patient's internal environment. Studies have pointed out that pioglitazone can increase the sensitivity of adenosyl cyclase to insulin and drive down glucose synthesis by inhibiting liver gluconeogenesis, effectively lowering the patient's body's resistance to insulin [18]. We observed that 1 month after treatment with pioglitazone, the insulin level in the patient showed a remarkable improvement. The weakening of insulin resistance suggested that only a smaller amount of insulin is needed in the body to stabilize the patient's blood sugar level. This also plays a positive role in improving the patient's overall internal environment. Our study re-

vealed that compared with patients receiving single Diane-35 treatment, patients who took pioglitazone concurrently witnessed a remarkable improvement in the secretion of E2 and FSH and other sex hormones. Immediately after treatment and 1 month after treatment, the BMI, WHR, and F-G scores of the two groups decreased drastically compared with those before treatment. The observation group obtained lower WHR and F-G scores than the control group ($P<0.01$). It indicated that pioglitazone can not only maintain the patient's blood sugar stability but also played a positive role in controlling the patient's level of sex hormone secretion. In addition, Fonseka et al. [19-21] found that Diane-35 combined with pioglitazone can effectively improve the endocrine and blood sugar level of patients, and enjoy a satisfactory effect on PCOS. Cui et al. [20] also revealed that pioglitazone has a very significant effect on the treatment of PCOS. These studies confirmed the conclusions of this study. Diane-35 is an oral contraceptive that inhibits the secretion of LH, increases SHBG levels, reduces androgen secretion, blocks the response of peripheral target organs to androgens, lowers its biological effects, and achieves the purpose of treatment [22]. Studies have shown that Diane-35 may produce gastrointestinal discomforts such as nausea and vomiting. It can also lead to decreased insulin sensitivity, weight gain, and aggravation of obesity. Pioglitazone is widely recognized for correcting the IR of PCOS patients, improving the success rate of ovulation and the glucose balance disorder in the body. Concurrently it can predominantly make up for the deficiency of Diane-35 while enhancing the efficacy [23].

In summary, DIANE-35 combined with pioglitazone can effectively improve the symptoms of PCOS patients such as sex hormone secretion disorders and blood glucose and blood lipid disorders, and play a positive role in the rehabilitation of patients, which has high clinical applications value.

Disclosure of conflict of interest

None.

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