

EFFECT OF ETHINYL ESTRADIOL CYPROTERONE COMBINED WITH METFORMIN ON CLINICAL OUTCOME AND COMPLICATIONS OF PATIENTS WITH POLYCYSTIC OVARY SYNDROME INFERTILITY

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ABSTRACT

Purpose: To investigate the effect of Ethinyl Estradiol Cyproterone combined with Metformin in the treatment of infertility with polycystic ovary syndrome and its impact on complications, and provide reference value for clinical treatment. 112 patients admitted to our hospital from January 2016 to January 1818 were randomly divided into study group and control group. In the control group, 56 cases were given ethinyl estradiol progesterone orally; 56 cases in the study group, and Metformin was added orally on the above basis. The changes of endocrine level, blood lipid level and general condition of the two groups were recorded before and after treatment. The ovulation pregnancy and complications were compared between the two groups. **Result:** Before treatment, there was no significant difference in endocrine level between the two groups ($P > 0.05$). After treatment, the LH of the study group was (9.18 ± 1.05) U/L, T was (49.32 ± 5.31) $\mu\text{g/L}$, and INS was $(8.45) \pm 0.89$ U/L, FPG was (4.25 ± 0.49) mmol/L, and HOMA-IR was (1.75 ± 0.29) , compared with the control group ($P < 0.05$). After treatment, the TC of the study group was (3.48 ± 0.65) mmol/L, TG was (1.17 ± 0.31) mmol/L, and LDL-C was (2.05 ± 0.39) mmol/L, which was significantly lower than the control group. The indexes were higher than the control group, and the difference was statistically significant ($P < 0.05$). Before treatment, there was no significant difference in body general indicators between the two groups ($P > 0.05$). After treatment, the BMI of the study group was (20.03 ± 2.07) Kg/m², WHR was (0.72 ± 0.11) , the hairy score was (1.05 ± 0.19) , and the acne score was (2.35 ± 0.39) , compared with the control group ($P < 0.05$). Among the study group, the periodic ovulation rate was 91.03%, the ovulation rate was 75.22%, and the pregnancy rate was 37.5%, which was significantly different from the control group of 75, 58.14% and 17.86% ($P < 0.05$). Among the patients in the study group, 1 patient had elevated blood pressure, 1 patient had dizziness headache, and 1 patient had ovarian stimulation syndrome. The complication rate was 5.36%, which was significantly lower than that of the control group (28.57%). The difference was statistically significant ($P < 0.05$). **Conclusion:** Combined drug use can effectively improve the endocrine hormone level, blood lipid level and body general index of the patients, which is conducive to the improvement of ovulation rate and pregnancy success rate, as well as the improvement of patients' quality of life and family relations. In addition, with less adverse reactions, the drug safety is high, which is worthy of clinical application.

KEYWORDS: P - COS; Infertility; Ethinyl estradiol Cyproterone; Metformin.

Polycystic ovary syndrome (p-cos) is a complex endocrine disease, mainly presenting with no ovulation, abnormal menstruation, hairy, insulin resistance, abnormal lipid metabolism (obesity) and other symptoms, which is one of the main causes of female infertility (see figure 1). The disease is most common in women of childbearing age. If the treatment is not timely and the treatment method is not reasonable, the probability of infertility is extremely high, which has a great impact on the quality of life and family relationship of patients. Related studies indicated that^[1-3], the clinical incidence of polycystic ovary syndrome type infertility in women of childbearing age was close to 5%. Therefore, reasonable and effective treatment methods should be

actively sought to improve the endocrine and metabolic abnormalities of patients, so as to improve the pregnancy rate and reduce complications. However, in the conventional treatment, ethinyl estradiol Cyproterone is often administered orally, which has the effect of anti-androgen and anti-gonadotropin, and can improve the clinical performance of patients to a certain extent, but the effect is poor in the improvement of insulin resistance, which is difficult to popularize and apply.^[4] In this study, 112 cases of patients admitted to our hospital from January 2016 to January 2018 were selected to evaluate the clinical value of the combined use of Metformin in order to make application contributions to

further improving the pregnancy rate of patients. Detailed information will be reported as follows:

1. MATERIALS AND METHODS

1.1 General Information

112 patients admitted to our hospital from January 2016 to January 1818 were randomly divided into study group and control group. The study group of 56 patients, all female, aged 24-39 years, mean age (30.17 ± 2.59) years, duration of 3 years -8 years, mean disease duration (6.12 ± 2.37) years, body mass index (BMI) 18-30 The mean BMI (25.16 ± 2.31); 56 patients in the control group, all female, aged 25-37 years, mean age (30.26 ± 2.63) years, duration of disease 3 years-9 years, mean disease duration (6.45 ± 2.39) years, Body mass index (BMI) 19-31, mean BMI (25.20 ± 2.29). Baseline data were comparable between the two groups ($P > 0.05$).

Case inclusion criteria^[5-6]: (1) were diagnosed by B-ultrasound; (2) approved by the hospital ethics committee; (3) signed informed consent. Case exclusion criteria: (1) those with endocrine diseases (such as Cushing's syndrome, thyroid disease, etc.); (2) those with cardiovascular and cerebrovascular diseases or liver and kidney dysfunction; (3) those who have recently taken hormones or allergies; (4) Those with severe cognitive dysfunction or mental disorders; (5) unable to cooperate with the investigator.

1.2 Methods

1.2.1 Control group: On the basis of perfect routine examination and symptomatic supportive treatment, simply give Da Ying-35 (manufacturing company: Bayer Pharmaceutical Co., Ltd. J20100003) orally, 1 tablet per night, continue to take 3 weeks, then stop the drug, to retreat On the 5th day of sexual bleeding, the next cycle of treatment was continued for 3 cycles.

1.2.2 Study group: On the basis of the control group, add Metformin (manufacturing company: Chengdu Hengrui Pharmaceutical Co., Ltd. H20080697), 3 times a day, 500mg each time, continue to take 3 menstrual cycles. Both groups of patients received 50-100 mg of clomiphene in the 4th month after administration. The follicle size was measured after 12 days of treatment. When a single 18 mm or more or two 16 mm or more diameter follicles were injected, human chorionic gonadotropin (HCG) was injected at 10,000 IU. And the same room the next day.

Table 1: Comparison of endocrine levels before and after treatment ($x \pm s$).

Index	Study group (n=56)		Control group (n=56)	
	Before treatment	After	Before	After
LH (U/L)	$13.20 \pm 1.39^{\#}$	$9.18 \pm 1.05^{##}$	13.17 ± 1.40	12.05 ± 1.16
T ($\mu\text{g/L}$)	$70.01 \pm 7.39^{\#}$	$49.32 \pm 5.31^{##}$	70.02 ± 7.45	56.19 ± 6.03
INS (U/L)	$20.10 \pm 4.37^{\#}$	$8.45 \pm 0.89^{##}$	20.07 ± 4.39	12.57 ± 1.31
FPG (mmol/L)	$7.70 \pm 1.03^{\#}$	$4.25 \pm 0.49^{##}$	7.68 ± 1.02	5.71 ± 0.89
HOMA-IR	$4.97 \pm 0.66^{\#}$	$1.75 \pm 0.29^{##}$	5.01 ± 0.63	2.23 ± 0.58

Note, # compared with pre-treatment, t were 0.114, 0.007, 0.036, 0.103, 0.328, $P > 0.05$; ## compared with after treatment, t were 13.727, 6.399, 19.467, 10.754, 5.539, $P < 0.05$.

3 Observation indicators^[7-9]

1.3.1 Endocrine level test: Fasting peripheral venous blood was collected before and after treatment (days 2-4 days of menstrual cramps). Detection method: chemiluminescence, endocrine level test indicators: luteinizing hormone (LH), follicle stimulating hormone (FSH), testosterone (T), insulin (INS), fasting blood glucose (FPG), and insulin resistance (HOMA-IR).

1.3.2 Blood lipid level test: Fasting peripheral venous blood was collected before and after treatment (2-5 days of menstrual cramps). Detection method: oxidase method.

1.3.3 General detection of body characteristics: Before and after treatment, the detection indicators include: body mass index (BMI), waist-to-hip ratio (WHR), hairy condition (assessed by FG score table, see Figure 2), hemorrhoids (using hemorrhoids) Comprehensive sub-meter evaluation).

1.3.4 Ovulation Pregnancy and Complications: The ovulation status and pregnancy status of the two groups were recorded. Complications included elevated blood pressure, headache and dizziness, and ovarian stimulation syndrome.

1.4 Statistical processing

SPSS 17.0 software was used for data analysis. The counts of complications and other data were expressed by rate. The chi-square test, endocrine, blood lipids, general conditions and other measurement data were expressed by ($\bar{x} \pm s$). Using t test, $P < 0.05$ was used. Statistical significance.

2 RESULTS

2.1 Comparison of endocrine levels before and after treatment

As can be seen from Table 1, there was no significant difference in endocrine level between the two groups before treatment ($P > 0.05$). After treatment, the LH of the study group was (9.18 ± 1.05) U/L and T was (49.32 ± 5.31) $\mu\text{g/L}$. INS was (8.45 ± 0.89) U/L, FPG was (4.25 ± 0.49) mmol/L, and HOMA-IR was (1.75 ± 0.29), compared with the control group ($P < 0.05$).

2.2 Comparison of blood lipid levels before and after treatment

As can be seen from Table 2, there was no significant difference in blood lipid levels between the two groups before treatment ($P>0.05$); after treatment, the study group TC was (3.48 ± 0.65) mmol/L, and TG was

(1.17 ± 0.31) mmol/L. LDL-C was (2.05 ± 0.39) mmol/L, which was significantly lower than that of the control group. The other indexes were higher than the control group. The difference was statistically significant ($P<0.05$).

Table 2: Comparison of blood lipid levels before and after treatment ($\bar{x}\pm s$).

Index	Study group (n=56)		Control group (n=56)	
	Before treatment	After	Before	After
TC (mmol/L)	5.30±0.79 [#]	3.48±0.65 ^{##}	5.27±0.80	4.25±0.76
TG (mmol/L)	1.51±0.39 [#]	1.17±0.31 ^{##}	1.52±0.41	1.52±0.43
HDL-C (mmol/L)	1.40±0.37 [#]	1.75±0.19 ^{##}	1.41±0.39	1.47±0.31
LDL-C (mmol/L)	2.87±0.43 [#]	2.05±0.39 ^{##}	2.88±0.42	2.51±0.49
ApoA (g/L)	1.07±0.26 [#]	1.45±0.59 ^{##}	1.09±0.27	1.20±0.48
Apo (g/L)	0.47±0.05	0.75±0.13	0.46±0.06	0.53±0.10

Note, # compared with pre-treatment, t is 0.200, 0.132, 0.139, 0.124, 0.399, 0.958, $P>0.05$; ## compared with post-treatment, t is 5.762, 4.941, 5.763, 5.497, 2.460, 10.038, $P<0.05$.

2.3 Comparison of general conditions before and after treatment

As can be seen from Table 3, there was no significant difference between the two groups ($P>0.05$). After treatment, the BMI of the study group was (20.03 ± 2.07)

Kg/m², WHR was (0.72 ± 0.11) , and the hairy score was obtained. The score of (1.05 ± 0.19) and acne was (2.35 ± 0.39) , which was compared with the control group ($P<0.05$).

Table 3: Comparison of general conditions before and after treatment ($\bar{x}\pm s$).

Index	Study group (n=56)		Control group (n=56)	
	Before treatment	After	Before	After
BMI (Kg/m ²)	25.16±2.31 [#]	20.03±2.07 ^{##}	25.20±2.29	25.05±2.16
WHR	0.81±0.10 [#]	0.72±0.11 ^{##}	0.82±0.11	0.83±0.13
Hairy score	4.20±0.47 [#]	1.05±0.19 ^{##}	4.17±0.49	2.77±0.51
Acne score	5.17±0.76 [#]	2.35±0.39 ^{##}	5.20±0.75	3.83±0.68

Note, # compared with pre-treatment, t were 0.092, 0.503, 0.331, 0.210, $P>0.05$; ## compared with post-treatment, t were 12.557, 4.834, 23.650, 14.128, $P<0.05$.

2.4 Comparison of ovulation and pregnancy between the two groups

As can be seen from Table 4, the patients in the study group had a periodic ovulation rate of 91.03%, an

ovulation rate of 75.22%, and a pregnancy rate of 37.5%, which was statistically significant (75, 58.14%, and 17.86% in the control group). <0.05).

Table 4: Comparison of ovulation and pregnancy between the two groups [n(%)].

Group	CaseNo. (n)	Number of follicular cycles	Number of ovulation cycles	Cycle ovulation rate (%)	Number of dominant follicles	Number of ovulation	Ovulation rate (%)	Pregnancy rate (%)
Study group	56	156	142	91.03	339	255	75.22	21(37.5)
Control group	56	156	117	75	301	175	58.14	10(17.86)
x ²				13.092			20.334	4.460
P				<0.01			<0.01	<0.05

2.5 Comparison of complications

As shown in table 5, 1 patient in the study group showed increased blood pressure, 1 patient with dizziness and headache, and 1 patient with ovarian stimulation syndrome. The incidence of complications was 5.36%, significantly lower than 28.57% in the control group, and the difference was statistically significant ($P<0.05$).

Table 5: Comparison of complications [n (%)].

Group	Case number (n)	High blood pressure	Dizziness, headache,	Ovarian stimulation syndrome	Incidence rate (%)
Study group	56	1	1	1	3 (5.36)
Control group	56	5	6	5	16 (28.57)
χ^2					10.004
<i>P</i>					<0.01

3. DISCUSSION

PCOS has the characteristics of heterogeneity, progressive development and inability to cure. If not treated properly, it can seriously affect the normal quality of life of patients. At present, there are many studies on the pathogenesis of polycystic ovary syndrome, but there is no unified statement (see Figure 3). Most scholars believe that^[10-15], when women have endocrine disorders, hyperandrogenemia, elevated luteinizing hormone levels and hyperinsulinemia can occur, and elevated androgen can inhibit follicular maturation, interfere with the development of follicles, resulting in follicular atresia, thereby inducing polycystic changes in the ovary. Other studies have also pointed out that^[16-17], excessive levels of androgen in women can lead to dysfunction of the hypothalamic-pituitary-ovarian system, increase the level of luteinizing hormone, which in turn leads to increased synthesis of androgen levels, forming a vicious circle. Therefore, the key to its clinical treatment should focus on reducing androgen levels and luteinizing hormone levels, while reducing insulin resistance. The ethinyl estradiol Cyproterone is a third-generation oral contraceptive with the main chemical components including ethinyl estradiol and Cyproterone, which have anti-androgenic and anti-gonadotropin levels.^[18] According to research by Lau Zhiying^[19], ethinyl estradiol can increase the level of sex hormone-binding globulin and inhibit testosterone levels, thereby indirectly reducing the level of T; in addition, it can inhibit luteinizing hormone secretion and reduce androgen levels. In addition, Cyproterone has a strong anti-androgenic effect, which can significantly improve endocrine disorders, and has positive significance for improving women's irregular menstruation, improving endometrial status and increasing pregnancy rate.^[20] The results of this study showed that after using ethinyl estradiol Cyproterone, the endocrine level, blood lipid level and general condition of the two groups were significantly improved compared with before treatment. It is suggested that the clinical manifestations of the drug are basically consistent with the theoretical research.

According to relevant studies^[21], increased insulin secretion can lead to luteinizing hormone secretion, thereby inhibiting the liver's synthesis of sex hormone binding protein and insulin binding protein, leading to continuous increase of androgen level. In the academic world, hyperinsulinemia is generally considered as the initial factor of polycystic ovary syndrome. Thus, another key focus of treatment for the disease is a decrease in insulin levels. And Metformin belongs to

biguanidine class hypoglycemic drug, hypoglycemic effect is affirmative. It can effectively promote the use and decomposition of glucose in body tissue cells. At the same time, it can also inhibit the allogenic process of liver glycogen and reduce the decomposition and release of liver glycogen. Related studies have pointed out^[22] that Metformin can inhibit the absorption of glucose by intestinal cell wall, and has no obvious hypoglycemic effect on normal population, so the drug safety is very high. Zhao songqing et al.^[23] pointed out that combined medication can effectively optimize the hormone level of patients and reduce hyperlipidemia, and the insulin resistance level is (1.78 + 0.32) after treatment, which is significantly better than single medication, and has positive significance for the rehabilitation of diseases and the improvement of pregnancy success rate.

In this paper, a satisfactory result was obtained by using the above two drugs in combination. The results of this study showed that there was no significant difference in endocrine level between the two groups before treatment ($P>0.05$). After treatment, the LH of the study group was (9.18±1.05) U/L and T was (49.32±5.31) µg/L and INS were (8.45±0.89) U/L, FPG was (4.25±0.49) mmol/L, and HOMA-IR was (1.75±0.29), which was compared with the control group ($P<0.05$). It is suggested that the improvement of endocrine hormone levels in the study group is more significant, which may be related to the decrease of insulin levels after co-administration of Metformin and the control of androgen levels. Another group of studies showed that there was no significant difference in blood lipid levels between the two groups before treatment ($P>0.05$). After treatment, the study group had TC (3.48±0.65) mmol/L and TG (1.17±0.31) mmol/L and LDL-C were (2.05±0.39) mmol/L, which were significantly lower than the control group. The other indexes were higher than the control group. The difference was statistically significant ($P<0.05$). Before treatment, there was no significant difference in body general indicators between the two groups ($P>0.05$). After treatment, the BMI of the study group was (20.03±2.07) Kg/m², WHR was (0.72±0.11), the hairy score was (1.05±0.19), and the acne score was (2.35±0.39), compared with the control group ($P<0.05$). It is suggested that the combination therapy can effectively reduce the body fat level, improve the general condition of the body, and help to improve the ovulation rate and the success rate of pregnancy. The last group of data showed that the patients in the study group had a periodic ovulation rate of 91.03%, an ovulation rate of 75.22%, and a pregnancy rate of 37.5%, which was

significantly different from the control group of 75, 58.14%, and 17.86%. $P < 0.05$). Among the patients in the study group, 1 patient had elevated blood pressure, 1 patient had dizziness headache, and 1 patient had ovarian stimulation syndrome. The complication rate was 5.36%, which was significantly lower than that of the control group (28.57%). The difference was statistically significant ($P < 0.05$). It is suggested that the ovulation rate and pregnancy success rate are higher after combined use, and the safety of medication is better. It is basically consistent with the above research conclusions.

In summary, the combination of drugs can effectively improve the patient's endocrine hormone levels, blood lipid levels and general body indicators, which is conducive to ovulation rate and pregnancy success rate improvement, help improve patients' quality of life and family relationships, and less adverse reactions, medication It is safe and worthy of clinical application. However, it is worth noting that the research volume is still small, and the research conclusion may be deviated from the actual situation. It should be further explored and analyzed after increasing the research sample, in order to provide more reference for clinical treatment.

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