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EFFECT OF CHLORMADINONE-CONTAINING CONTRACEPTIVES ON CARBOHYDRATE AND LIPID METABOLISM IN WOMEN WITH METABOLIC SYNDROME

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ABSTRACT

Today, the overweight problem is one of the most critical health problems worldwide. The World Health Organization views obesity as an epidemic affecting millions of people. Historically, in studies of the efficacy and safety of various contraception methods, obese patients were excluded from the sample due to a theoretically higher risk of developing complications. However, the degree of increased risk has not been definitively established. Also, it is known that obesity can cause the development of anovulation and oligomenorrhea. Still, according to recent studies, it has been shown that the majority of obese patients have regular ovulation and need to use contraceptives. In this regard, the feasibility and safety of using certain methods of contraception in a patient with obesity should be decided individually, taking into account all the components of a woman's somatic status and her desire to have children in the future. Hormonal contraception is currently an essential element of the family planning system. Oral contraceptives are contraindicated in patients with severe obesity but can be used in those women who are slightly overweight. In general, the problem of using hormonal contraceptives (produced in various dosage forms) in the group of obese women has several aspects. The question is discussed that excess body weight may distort the drug's pharmacodynamics and pharmacokinetics and, consequently, decrease the contraceptive effect.

Another problem is the risks of hormonal contraception in obesity and metabolic syndrome. The study of the state of carbohydrate and lipid metabolism in women with impaired lipid metabolism against the background of hormonal contraception is relevant. It can help clarify the indications, contraindications, conditions for the use of hormonal contraception.

Keywords: metabolic syndrome, obesity, contraception, hormonal contraceptives, metabolism

I. INTRODUCTION

The World Health Organization declared that obesity became a global epidemic and posed a serious threat to public health in 1997. According to WHO research, 50-75 % of the population aged 35-64 years are overweight, and among women of reproductive age, obesity is two times more common. Obesity can be considered as an extreme factor affecting the reproductive function of women. Violation of the function of the sex glands is observed in 46-96 % of obese women. According to V. P. Smetnik (2000), the main cause of disorders in the reproductive system in obesity is the effect of insulin on the ovaries. Insulin, being a synergist of Luteinizing Hormone (LH), promotes the activation of the theca cells' functions and the hormone-producing stroma. An increase in androgens' intrafollicular content disrupts follicles' growth, promotes the development of hyperandrogenic anovulation and endometrial hyperplasia. Insulin Resistance (IR) is manifested in women by anovulation, Polycystic vary syndrome (PCOS), virilization, and hyperplastic processes in hormone-dependent organs and tissues.

Polycystic ovary syndrome (PCOS) is a widespread endocrine disease among women of reproductive age [1]. This syndrome is characterized by insulin resistance, moderate obesity, irregular menstruation or amenorrhea, and signs of an excess of androgens (for example, hirsutism, acne) [2-5]. Combined oral contraceptives pills (COCP), preferably with antiandrogenic properties, are commonly used to correct the menstrual cycle and symptoms of androgen excess associated with PCOS [6,7]. However, COCP can also cause insulin resistance and glucose intolerance [8-10]. Thus, there is a concern that COCP may further exacerbate underlying metabolic dysfunction and insulin resistance in women with PCOS [11]. It is especially true for obese women with PCOS who have insulin resistance associated with both PCOS and overweight [12].

Data on the effect of COCP on carbohydrate metabolism in overweight women and PCOS are contradictory. Studies with COCP containing antiandrogen-cyproterone acetate have shown no effect on insulin sensitivity or exacerbation of insulin resistance and decreased glucose tolerance [13-16]. Studies with COCP with low androgen levels-desogestrel showed decreased glucose tolerance and insulin resistance [11, 17]. A recent meta-analysis of studies examining the relationship between the use of COCP and metabolic changes showed that the use of COCP has no significant effect on fasting glucose or insulin levels [18]. However, when using COCP with different types of progestins, considerable heterogeneity was revealed. Body mass index (BMI) was a contributing factor in fasting glucose and insulin resistance changes.

The absence of a control group is a standard limitation of most studies evaluating COCP's metabolic effects in women with PCOS. It can cause insulin resistance and glucose intolerance even in women without PCOS [8-10]. Whether women with PCOS were more susceptible than women without this pathology was evaluated in only two studies. One study evaluated norethindrone-containing COCP in women with PCOS compared to a control group with a comparable BMI [19]. After three months of using it, a decrease in the insulin sensitivity index was observed in both groups. It is unknown whether this data can be applied to low-dose antiandrogenic COCP, which are often used in treating women with PCOS. Another study evaluated low-dose COCP containing norgestimate, the outcome of which was no change in insulin sensitivity in thin women with PCOS and women in the control group [20]. This study established the effect of frequently used low-dose COCP (30 mcg Ethinyl estradiol and 2 mg chlormadinone acetate) with an antiandrogenic effect on carbohydrate and lipid metabolism in women with and without PCOS. Women in the main and control groups were overweight according to BMI. The reason for choosing this COCP is that it was studied. A safety profile was established with no significant deterioration in the picture of fasting insulin, glucose and glycolized hemoglobin.

The purpose of the study is to determine the metabolic effects of chlormadinone-containing COCP in overweight women.

II. MATERIALS AND METHODS

The subject of the study was 30 women who were overweight or obese. Group 1 included ten women with metabolic syndrome and PCOS, and group 2 included 20 obese women without PCOS. The modified Rotterdam criteria determined PCOS after excluding other endocrine diseases [25]. In this study, all women with PCOS had clinical or biochemical signs of hyperandrogenism, amenorrhea. The control group consisted of regularly menstruating women. The exclusion criteria for both groups were similar and included the following: pregnancy, contraindications to COCP (for example, a history of thromboembolism, blood pressure > 140/90 mmHg, liver disease), diabetes mellitus, tobacco use and use of hormonal contraceptives, insulin, antiandrogens, glucocorticoids, hypotensive or antilipidemic agents within the last three months.

The studies were conducted in the follicular phase of the menstrual cycle. After 12 hours of fasting, vital signs, height, weight, fasting serum lipids, insulin, and glucose were obtained in both groups. A two-hour oral glucose tolerance test was performed with a 75 g glucose load, with glucose and insulin levels determined every 15 minutes. The next day, the participants started taking COCP (Ethinyl estradiol 30 mcg and chlormadinone acetate 2 mg). Participants in both groups were followed up prospectively for three months. The age of the examined patients ranged from 20 to 27 years (Table 1).

Laboratory tests

Serum and plasma were stored at -80 ° C before analysis. The oxidative method measured the serum glucose level (YSI 2300 STAT Plus analyzer; Yellow Springs Instruments). Serum insulin levels were measured by enzyme-linked immunosorbent assay (enzyme-linked immunosorbent assay (ELISA); ALPHA Diagnostics).

Serum testosterone was measured using ELISA. In both groups, the tests were performed twice. The coefficients of variation were <10%.

III. RESULTS

Three months after using COCP (belara) in the control group, there was a small but statistically significant increase in fasting insulin, glucose and a statistically significant decrease in insulin sensitivity compared to the baseline level (Table 2). Women of Group 1 with PCOS already had an unfavourable baseline glucose metabolism profile compared to overweight women without PCOS. Although a similar deterioration in these parameters was observed in group 1 with PCOS after three months of COCP use, the changes in women with PCOS from the initial to three months period did not reach significance.

Both in women with PCOS and women without this pathology, the level of total cholesterol increased significantly after three months of taking COCP (Table 2). However, only women in the second group comparison had a significant increase in the level of high-density lipoprotein cholesterol. Women in group 2 also had a considerable increase in low-density lipoprotein (LDL), but they had a lower LDL cholesterol level at baseline than women with PCOS, at 10 mg/dl. Even after a significant increase, LDL cholesterol levels after treatment with COCP were still lower than in women with PCOS.

Age of the examined patients and body mass index indicators

Table 1

Parameters	Women of the first group with PCOS (n=10)	Group of comparison (n=20)	p
Age	24.3± 4.4	21.8± 3.8	0.1175
BMI (kg/m ²)	32.6± 7.2	31.3± 8.8	0.7008
Anamnesis diabete	2 (20%)	4 (20%)	1.0000

Indicators of the effect of COCP on carbohydrate and lipid metabolism in the examined patients

Table 2

Parameters	Women with PCOS (n=10)		Group of comparison (n=20)		P-value (initial comparisons between groups)	P-value (comparing the effect of COCP between groups)
	initial	After three months	initial	After three months		
Total Testosterone (ng/dl)	57.6± 38.9	22.5± 19.9	25.5 ± 12.9	19.7± 9.4	0.0021	0.8769
Free Testosterone (ng/dl)	8.1 ± 8.5	3.5± 4.4	4.4± 2.5	1.7± 0.8	0.0822	0.3785
Fasting insulin (mkEd/ml)	7.9(4.8-13.1)	8.7(6.3-12.1)	4.7(3.5-6.4)	5.6(4.3-7.4)	0.0495	0.6336
Fasting glucose (mg/dl)	88.7± 6.6	88.1± 7.0	84.1± 4.9	84.3± 6.0	0.0393	0.6543
Oral Glucose Tolerance Test (mg/dl)	119± 29.0	124± 27.9	111 ± 20.3	114 ± 27.7	0.3921	0.8144
Homeostatic model assessment (HOMA)-IR Index	0.73 ± 0.49	0.60± 0.35	1.21 ± 0.61	1.01± 0.58	0.0397	0.6234
Systolic Blood Pressure (SBP) (mmHg)	117± 10.5	117± 9.88	116 ± 14.8	116± 14.8	0.8655	0.8316

Diastolic Blood Pressure (DBP)(mmHg)	69±6.3	70±6.1	72 ± 7.7	72±7.9	0.2448	0.5006
Body Mass Index (BMI)(kg/m ²)	32.6±7.2	32.5±6.9	31.3 ± 8.8	31.3±8.9	0.7008	0.7352
Waistcircumference (cm)	97.4±13.6	96.2±16.1	87.8 ± 19.8	89.4±18.6	0.1806	0.3056
Waisttohipratio	0.84(0.80-0.88)	0.81(0.75-0.87)	0.75 (0.70 - 0.80)	0.78 (0.75 - 0.81)	0.0198	0.0955
Totalcholesterol (mg/dl)	168 ± 24.0	182 ± 25.4	161 ± 27.0	182 ± 24.6	0.452	0.2173
Low-density lipoprotein (LDL)(mg/dl)	100 ± 16.6	107 ± 19.7	90 ± 22.0	102 ± 25.6	0.2398	0.5785
Triglycerides (mg/dl)	116 (90.0-137.8)	136(93.3-198.5)	66 (52.8-83.1)	76(59.4-98.0)	0.0044	0.6599
High-densitylipoprotein (HDL)	45 ± 8.9	48 ± 7.8	53 ± 11.9	61 ± 12.6	0.0947	0.0882

IV. DISCUSSION

This work aimed to determine COCP's metabolic effects containing chlormadinone acetate in women with metabolic syndrome with PCOS and without this pathology for three months. Women with PCOS were more insulin-resistant, had higher fasting insulin and glucose levels at baseline. After three months of using COCP, a significant decrease in glucose tolerance was found in women with PCOS compared to women in the control group. After three months, there was no significant difference between the two groups in other metabolic parameters.

The decrease in glucose tolerance in women with PCOS after using COCP seems to be primarily associated with a decrease in beta-cell function, not with a deterioration in insulin resistance. It is not surprising because women with PCOS were already significantly more resistant to insulin at the initial stage. It was expected that COCP could not further exacerbate this insulin resistance. Insulin resistance already present at baseline, combined with reduced beta-cell function during treatment with COCP, could lead to greater glucose intolerance in women with PCOS than women in the control group.

In this study, insulin resistance did not significantly worsen in women with PCOS during COCP use. Baseline obesity in women with PCOS may explain the lack of further worsening of insulin resistance during treatment. The effect of obesity is further confirmed by a meta-analysis evaluating the association between COCP and metabolic changes in women with PCOS [18].

When comparing the lipid profile in the groups with PCOS and the comparison group at baseline, the only significant difference was the higher triglyceride content in the group of women with PCOS (116 (90.0–137.8) mg/dl) compared with the group of women without PCOS - 66 (52.8– 83.1) mg/dl ($p=0.02$). After three cycles of using chlormadinone acetate, no significant differences in lipid parameters were found between them.

At the initial stage, there was no significant difference between the two groups in blood pressure parameters. Also, there was no negative effect of chlormadinone acetate on these indicators after three cycles of using COCP. It demonstrates a limited or complete absence of the impact of low-dose chlormadinone-containing COCP on blood pressure.

V. CONCLUSION

Thus, a comparative analysis of the effect of a low-dose antiandrogenic COCP containing chlormadinone acetate on glucose metabolism in women with and without PCOS showed that the administration of the drug to overweight/obese women caused a significant deterioration in glucose tolerance in women of group 1 with PCOS compared to women of the comparison group.

However, in women with PCOS, when using COCP, there was no decrease in insulin sensitivity. In contrast, this indicator in women of the comparison group without PCOS tended to decrease compared to the baseline level.

Further research is needed to include many normal and overweight women and PCOS over a more extended period to develop criteria for the acceptability of hormonal contraceptive use in overweight/obese women and PCOS.

CONFLICT OF INTERESTS AND CONTRIBUTION OF AUTHORS

The authors declare the absence of apparent and potential conflicts of interest related to this article's publication and report on each author's contribution.

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