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PECULIARITIES OF CARBOHYDRATE AND LIPID METABOLISM IN INFERTILE PATIENTS WITH CLOMIFEN-RESISTANT FORM OF POLYCYSTIC OVARIAN SYNDROME AND OBESITY

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Abstract

Medical ovulation induction with clomiphene citrate is currently the first line treatment for anovulatory women with PCOS. Clomiphene resistance (failure to ovulate after taking clomiphene) is common, occurring in approximately 15% to 40% of women with PCOS. Resistance is associated with an increased body mass index. **The aim** of the study was to elucidate the characteristics of carbohydrate and lipid metabolism in patients with clomiphene-resistant PCOS and obesity. **Material and methods.** A comprehensive examination of 97 infertile patients with PCOS with obesity and clomiphene-resistant PCOS and 46 conditionally healthy normoovulatory women of control group K with 18.5 ≤ body mass index (BMI) < 25 kg/m^2, without clinical or biochemical signs of hyperandrogenism, with ovarian volume less than 9 cm^3 and without previously known endocrine disease. Clinical-anamnestic, anthropometric, sonographic, immunochemical, enzyme-linked immunosorbent assay, colorimetric, statistical research methods are used. **Results and discussion.** It was found that the most characteristic features of carbohydrate metabolism disorders in clomiphene-resistant women with PCOS and obesity are increased levels of hypoglycemic index, C-peptide, glucose levels after 2 h in oral glucose tolerance test, HOMA index; and of lipid metabolism - an increase in atherogenic factor, triglycerides, total

cholesterol on the background of increased production of leptin and vaspin and decreased secretion of adiponectin, omentin and visfatin.. **Conclusions.** Visceral obesity plays an important role in the development of insulin resistance and hyperinsulinemia in infertile patients with clomiphene-resistant PCOS and obesity. This category of women in preconception training, before carrying out ovarian drilling or controlled ovarian stimulation, it is necessary to correct disorders of carbohydrate and lipid metabolism.

Key words: polycystic ovary syndrome; clomiphene-resistant form; obesity; hyperandrogenism; carbohydrate and lipid metabolism; adipokines.

Polycystic ovary syndrome (PCOS) is a common endocrine disorder that affects 9 to 18 percent of women in their reproductive life [11]. It is a complex and heterogeneous endocrine disease characterized by clinical or laboratorial hyperandrogenism, oligo-anovulation and metabolic abnormalities, including insulin resistance, excessive weight or obesity, type II diabetes, dyslipidemia and an increased risk of cardiovascular disease [20, 22, 24]. The most significant clinical manifestation of PCOS is hyperandrogenism. Androgen excess plays a prominent role in the development of metabolic disturbances associated with PCOS, with a discernible impact on key peripheral metabolic tissues, including the adipose, liver, pancreas, and muscle, and very prominently the brain, contributing to the constellation of metabolic complications of PCOS, from obesity to insulin resistance [7, 14, 19-21]. Obesity and insulin resistance aggravate the symptoms of hyperandrogenism, forming a vicious cycle that promotes PCOS development [7, 11, 13, 24]. These changes can underlie specific hormonal and reproductive changes, and thus potentially influence its clinical manifestations. PCOS is considered the leading cause of anovulatory infertility [10] and is therefore clinically associated with subfertility or infertility.

A number of treatment options, used alone or in conjunction with other medical therapies, are available for the treatment of subfertility associated with anovulation [5]. Medical ovulation induction with clomiphene citrate is currently the first line treatment for anovulatory women. Clomiphene citrate is an antioestrogen and competes for receptor-binding sites with endogenous oestrogens. Studies evaluating clomiphene citrate have shown an ovulation rate of 60% to 85% and a pregnancy rate of 30% to 50% after six ovulatory cycles, with an increased risk of multiple pregnancy (5% to 7%) [6]. Clomiphene resistance (failure to ovulate after taking clomiphene) is common, occurring in approximately 15% to 40% of women with PCOS [5]. Definitions of clomiphene resistance vary, but the National

Collaborating Centre for Women's and Children's Health/National Institute for Clinical Excellence (2013) definition is: "Anovulatory women who do not ovulate while receiving the 150 mg dose of clomiphene citrate" [15]. Resistance is associated with an increased body mass index.

The aim of the study: to elucidate the characteristics of carbohydrate and lipid metabolism in patients with clomiphene-resistant PCOS and obesity.

Material and methods

The work was performed from 2017-2021 at the Department of Obstetrics, Gynecology and Reproductology of the P.L. Shupyk National University of Health of Ukraine, on the basis of the Municipal Non-Profit Enterprise "Kyiv City Center of Reproductive and Perinatal Medicine" of the executive agency of the Kyiv City Council, Ukraine.

A comprehensive examination of 97 infertile patients of main groupe PCOS with obesity and clomiphene-resistant PCOS and 46 conditionally healthy normoovulatory women of control group K with 18.5 ≤ body mass index (BMI) < 25 kg / m^2, without clinical or biochemical signs of hyperandrogenism, with ovarian volume less than 9 cm^3 and without previously known endocrine disease. The study did not includes patients with PCOS who received medication in the form of hormonal drugs three months before the study, insulin sensitizers or corticosteroids. All subjects received information about the study protocol and signed a written informed consent.

The mass-growth data were evaluated to determine body weight, height and BMI according to the Kettle formula: BMI = m / h^2, where *m* is body weight, *h* is height.

According to the WHO classification of 1997 [16], the diagnosis of first-degree obesity was made for women with a BMI from 30 kg / m^2 to 34.99 kg / m^2, second-degree - from 35 kg / m^2 to 39.99 kg / m^2, third-degree - from 40 kg / m^2 and more.

Waist circumference was measured after removal of clothing from the abdomen, placed a centimeter at the top of the iliac crest and measured horizontally at the end of the landmark.

The severity of hirsutism was assessed by Ferriman D., Gallwey J.D. (1961) [9] on a 4-point scale according to the localization of hair in 9 zones. In each of the zones, the number of points according to the degree of hair growth was counted. The lowest number was calculated as the sum of points for all 9 zones.

Ultrasound was performed using expert ultrasound devices using transabdominal and transvaginal convex sensors with a frequency of 3.5 and 5 MHz according to standard methods.

Concentrations of hormones such as luteinizing (LH), follicle-stimulating (FSH), prolactin (PRL), free testosterone (T_f), androstenedione (AS), dehydroepiandrosterone sulfate (DHEAS), estradiol (E_2), progesterone (P_4), antimullerian hormone (AMH), insulin and cortisol in peripheral blood serum were investigated on an automatic analyzer Cobas e411 (Roche Diagnostic, Switzerland) using an electrochemiluminescent detection immunochemical method and Roche Diagnostic reagents (Switzerland) on the 2-3rd day of the menstrual cycle.

Plasma glucose levels were determined by the hexokinase method.

The index of insulin resistance (HOMA) was calculated by the formula: HOMA = (fasting blood glucose (mmol / l) × fasting insulin (μU / l)) / 22.5.

The level of C-peptide in venous blood was determined by immunochemical method with chemiluminescent detection using an analyzer and test systems Immulite (Siemens AG, Germany).

The oral glucose tolerance test (OGTT) consisted of measuring glucose levels before and after loading with glucose at a standard dose (75 g) on an empty stomach. The test was performed in the morning after 10-14 hours of fasting. The patient did not limit herself in water consumption. Smoking was prohibited on the day of the test. The original blood sample was taken on an empty stomach, then the patient took 75 g of glucose dissolved in 200 ml. The blood sample was taken again after 120 minutes - with normal tolerance the concentration of glucose in blood plasma 2 hours after exercise was less than 7.8 mmol / l. An increase in plasma glucose concentration 2 hours after exercise ≥ 7.8 mmol / l, but below 11.1 mmol / l indicated a violation of glucose tolerance [23].

To assess the results of OGTT was calculated hypoglycemic factor - the ratio of glucose concentration 2 hours after exercise to its concentration on an empty stomach. Normally, this ratio should be less than 1.3 [23].

The enzymatic colorimetric method, analyzer and test of the Cobas 6000 system were used to assess the concentration of total cholesterol, triglycerides, high-density lipoprotein (HDL) and low-density lipoprotein (LDL) in the blood serum, Roche Diagnostics (Switzerland).

The atherogenic factor was calculated by the formula: atherogenic factor = (total cholesterol - HDL) / HDL. The norm of the atherogenic coefficient was considered to be its level ≤ 3 [1].

Serum adiponectin levels were measured by ELISA using test systems Mediagnost GmbH (Germany), visfatin - test systems Cusabio (China), leptin - test systems Diagnostics Biochem Canada Inc (Canada), omentine - test systems Human Omentin-1 ELISA company BioVendor (Czech Republic), vaspin - a set of reagents Human / Mouse / Rat Vaspin Enzyme Immunoassay Kit manufactured by RayBio® (Georgia), 17-oxyprogesterone (17-OP) - test systems EUROIMMUN, Demeditec (Germany).

Statistical processing of the obtained digital data was performed using the methods of analytical and variational statistics. The analysis of quantitative indicators was analyzed using the arithmetic mean (M) and the standard deviation error (± SE). Student's T-test was used to compare the parameters. The comparison of quantitative parameters was based on a preliminary assessment of the normality of data distribution according to the Shapiro-Wilk test. Given the different sample sizes, Glass's delta was used to measure the effect size for the T-test.

The closeness of the correlations between the results of the research was determined from the results of the calculation of the corresponding coefficients: for the results of the study, expressed in parametric units, - by the linear Brave-Pearson correlation coefficient.

The study was approved by the Ethics Committee of the Odessa National Medical University and performed in accordance with the Declaration of Helsinki. All participants gave written informed consent to participate in this study.

Results and discussion

The age of the examined women ranged from 22 to 35 years and averaged in the group with PCOS - 27.06±0.28 years, in the control group - 26.93±0.58 years, statistically significantly did not differ between groups.

The average weight of patients with PCOS (95.93±1.14 kg) exceeded that in group K (57.57±1.17 kg) 1.67 times ($p<0.01$, Glass's delta 5,994), mass index body (36.20±0.44 vs. 21.80±0.44 kg / m^2) - 1.66 times ($p<0.01$, Glass's delta 5,926). The waist circumference of patients with PCOS (96.47±1.05 cm) was 1.41 times greater than that of women in group K (68.33±0.48 cm) ($p<0.01$, Glass's 10,823), circumference hips (105.06±0.84 vs. 91.00±0.72 cm) - 1.15 times ($p <0.01$, Glass's delta 26.569), and the ratio of waist circumference / hip circumference (91.00±0,72 vs. 0.75±0.01) - 1.22 times ($p<0.01$, Glass's delta 3,400). In

90.32% of women with PCOS, the ratio of waist circumference / hip circumference was more than 0.8, in 9.68% of people - from 0.7 to 0.8. In the control group, the ratio of waist circumference / hip circumference in 13.33% of cases was less than 0.7, in 70.00% of people - from 0.7 to 0.8, in 16.67% of women - more than 0.8 .

Women with PCOS had excessive hair growth in all areas of the "hormonal" Feriman-Galway scale compared with those surveyed in the control group, the average hirsut number (10.65 ± 0.26 points) exceeded that in the control group (2.63 ± 0.31 points) 4.04 times ($p<0.01$, Glass's delta 4,690). Hair growth in women with PCOS in zones A, B, C, D, E, F, G, H, I probably did not differ and exceeded that in patients of the control group on average: in zone A - in 2,13, B - in 3.55, C - in 3.15, D - in 2.90, E - in 3.02, F - in 7.47, G - in 4.26, H - in 6.29, I - in 9,40 times, i.e. the most characteristic of the surveyed women with PCOS was the presence of excessive growth of downy hair in the areas of the waist, back, shoulder and back of the thighs.

The study of menstrual function revealed that the average age of menarche in patients with PCOS (13.13 ± 0.13 years) was probably higher than in the control (12.57 ± 0.16 years) ($p <0.01$, Glass's delta 0.622). In most patients with PCOS, menstruation was irregular, and therefore the average number of menstrual cycles in the last year was 6.65 ± 0.28 and was less than that in the control (12.77 ± 0.15) at 1.80 times ($p <0.01$, Glass's delta 7.286). Delayed menstruation in women with PCOS ranged from 0 to 1,095 days, averaging 102.90 ± 13.90 days.

The duration of menstrual bleeding in the group with PCOS (6.10 ± 0.08 days) exceeded that in group K (5.37 ± 0.23) 1.14 times ($p<0.01$, Glass's delta 0.584). The average duration of the menstrual cycle in the group with PCOS (48.74 ± 3.27 days) was 1.70 times greater than that in group K (28.70 ± 0.34 days) ($p <0.01$, Glass's delta 10,774).

In all patients of the control group, menstrual cycles were ovulatory, which was confirmed by basal temperature charts and ovulation tests, while in patients with PCOS, menstrual cycles were overwhelmingly anovulatory.

All surveyed women with clomiphene-resistant PCOS and obesity suffered from primary infertility, its duration ranged from 1 to 14 years and averaged 6.24± 0.31 years.

At ultrasound of the pelvic organs in all examined patients with PCOS, the ovaries had at least 12 cystic inclusions with a diameter of 2-9 mm on the periphery or throughout the ovary. The ultrasound picture did not change during the menstrual cycle, dominant follicles and corpora lutea were not registered. All ovaries in the groups with PCOS were bilaterally

enlarged and statistically significantly exceeded similar control values. The average volume of the right ovary (16.38 ± 0.62 cm^3) in PCOS exceeded that in the control (3.93 ± 1.08 cm^3) 4.17 times (p<0.01, Glass's delta 13,833), the left ovary (14.71 ± 0.37 cm^3 vs. 3.72 ± 0.52 cm^3) - 3.95 times (p<0.01, Glass's delta 12,632).

The initial basal level of adenohypophysis hormones in patients with clomiphene-resistant PCOS and obesity was characterized by an increase in LH production by 1.89 times (9.99 ± 0.23 vs. 5.30 ± 0.18 IU / l, p<0.01, Glass's delta 4,835), FSH - 1.23 times (5.94 ± 0.11 vs. 4.85 ± 0.09 IU / l, p<0.01, Glass's delta 2,180), an increase in the ratio of LH / FSH in 1.55 times (1.71 ± 0.04 vs. 1.11 ± 0.08, p<0.01, Glass's delta 2,400) against the background of the level of PRL, which had no significant differences with a similar indicator of group K (10.45 ± 0.28 vs. 9.15 ± 0.53 ng / ml, p>0.05, Glass's delta 0.444).

Analysis of sex steroid levels showed that on the 2-3rd day of the menstrual cycle in the surveyed women with PCOS there was an increase in the average concentration of E_2 in the serum by 1.49 times (61.90 ± 2.23 vs. 41.59 ± 2.33 pg / ml, p<0.01, Glass's delta 1,593). The level of P_4 on the 2-3rd day of the menstrual cycle was increased 1.97 times (1.43 ± 0.10 vs. 0.73 ± 0.07 ng / ml, p<0.01, Glass's delta 1,842), and on the 21st day decreased by 2.99 times (4.55 ± 0.31 vs. 13.59 ± 0.35 ng / ml, p<0.01, Glass's delta 4,660). The basal serum T_f content in patients with PCOS exceeded that in group K by 2.24 times (3.51 ± 0.12 vs. 1.57 ± 0.12 pg / ml, p<0.01, Glass's delta 2,985). Changes in the levels of sex steroids occurred against the background of a decrease in serum levels of globulin, which binds sex steroids, 1.68 times (31.03 ± 0.67 vs. 52.23 ± 2.10 nmol / l, p<0.01, Glass's delta 1,840).

In women with clomiphene-resistant PCOS and obesity, there was an increase in the production of adrenal hormones, such as AS in 1.88 times (2.97 ± 0.11 vs. 1.58 ± 0.06 ng / ml, p<0.01, Glass's delta 4,212), DHEAS - 2.88 times (281.61 ± 13.14 vs. 97.76 ± 5.97 μg / dl, p<0.01, Glass's delta 5,621), 17-OP - 2, 44 times (1.49 ± 0.05 vs. 0.61 ± 0.02 ng / mL, p<0.01, Glass's delta 7.333).

The average amount of cortisol in the serum of peripheral blood of the examined patients with PCOS (12.90 ± 0.44 μg / dl) was within the physiological norm and probably did not differ from the control index (13.74 ± 0.85 μg / dl, p>0,05, Glass's delta 0,181). The average level of serum AMH in patients with PCOS (4.77 ± 0.14 ng / ml) was 2.94 times higher than in the control (2.31 ± 0.05 ng / ml, p<0.01, Glass's delta 9,840). Patients with clomiphene-resistant form of PCOS and obesity were characterized by vitamin D deficiency,

which was manifested by a decrease in 25 (OH) D by 1.56 times (17.69 ± 0.88 vs. 27.67 ± 1.25 ng / ml, p<0,01, Glass's delta 1,457).

Analysis of carbohydrate metabolism showed that in clomiphene-resistant patients with PCOS and obesity, the level of immunoreactive insulin on an empty stomach exceeded that in the control group by 3.80 times (19.66 ± 0.34 vs. 5.17 ± 0.58 μIU / ml, p<0.01, Glass's delta 4,571), fasting glucose - 1.13 times (5.35 ± 0.09 vs. 4.73 ± 0.09 mmol / l, p<0.01, Glass's delta 1,240), glucose after 2 h at PGTT - 1.88 times (9.05 ± 0.12 vs. 1.10 ± 0.12 mmol / l, p<0.01, Glass's delta 8.460), HOMA index - 4.24 times (4.65 ± 0.10 vs. 1.10 ± 0.12, p<0.01, Glass's delta 5.221), the level of C-peptide - 3.18 times (4.50 ± 0.25 vs. 1, 41 ± 0.02, p<0.01, Glass's delta 23,769) (Table 1).

Table 1 - Baseline levels of carbohydrate metabolism of patients in the study groups, M±SE

Group	Fasting insulin, μIU / ml	Fasting glucose, mmol / l	OGTT, glucose after 2 hours, mmol / l	HOMA index	C-peptide, ng / ml
PCOS, n=97	19,66±0,34 [k]	5,35±0,09 [k]	9,05±0,12 [k]	4,65±0,10 [k]	4,50±0,25 [k]
K, n=30	5,17±0,58	4,73±0,09	4,82±0,09	1,10±0,12	1,41±0,02
Note. [k] is the probable statistical difference with group K (p<0,05).					

The hypoglycemic index in the group with PCOS exceeded that in the control by 1.68 times (1.72±0.02 vs. 1.02±0.01, p <0.01, Glass's delta 70.000) and was in group I - 1.74±0.04 (p<0.01), in group II - 1.75±0.05 (p<0.01), in group III - 1.66±0.03 (p<0,01), probably did not differ between these groups.

The HOMA index in PCOS and obesity was positively correlated with fasting glycemia (r = 0.53; p<0.01), BMI (r = 0.49; p<0.01), waist circumference (r = 0.47; p< 0.01), the ratio of waist circumference / hip circumference (r = 0.31; p <0.05), the content of triglycerides in the blood (r = 0.27; p<0.05). Direct correlations of fasting serum insulin levels with fasting blood glucose (r = 0.32; p<0.01), BMI (r = 0.53; p <0.01), waist circumference (r = 0.51; p<0,01), the ratio of waist circumference / hip circumference (r = 0,28; p<0,01), the content of triglycerides in the blood (r = 0,27; p <0,05), the HOMA index (r = 0, 88; p<0.01) were also determined.

Dyslipidemia in the group of women with PCOS was manifested by an increase in

total cholesterol by 2.15 times (5.54±0.08 vs. 2.58±0.08 mmol / l, p<0.01, Glass's delta 6,727), LDL - in 1.68 times (3.77±0.04 vs. 2.24±0.06 mmol / l, p<0.01, Glass's delta 4,636), triglycerides - 2.03 times (1.65±0.02 against 0.81±0.02 mmol / l, p<0.01, Glass's delta 7.0), the coefficient of atherogenicity - 5.36 times (4.09±0.10 against 0.76±0.07, p<0.01, Glass's delta 8,763) against the background of a decrease in HDL content by 1.35 times (p<0.01, Glass's delta 1,727) (Table 2).

Table 2 - Baseline levels of lipid metabolism in patients of the study groups, M±SE

Group	Cholesterol, mmol / l	HDL, mmol / l	LDL, mmol / l	Triglycerides, mmol / l	Coefficient atherogenicity
PCOS, n=97	5,54±0,08 [k]	1,11±0,01 [k]	3,77±0,04 [k]	1,65±0,02 [k]	4,09±0,10 [k]
K, n=30	2,58±0,08	1,49±0,04	2,24±0,06	0,81±0,02	0,76±0,07
Note. [k] is the probable statistical difference with group K (p<0,05).					

Disadipokinemia in patients with clomiphene-resistant PCOS and obesity was manifested by a decrease in adiponectin levels by 5.59 times (3.39±0.29 vs. 18.98±1.16 μg / ml, p<0.01, Glass's delta 2,447) , visfatin - 5.50 times (4.48±0.37 vs. 24.66±1.45 μg / ml, p<0.01, Glass's delta 2,538), omentin - 1.36 times (235.75 ±18.51 vs. 237.62±33.28 ng/ml, p<0.01, Glass's delta 0.796) against the background of an increase in leptin production by 2.37 times (37.86±2.07 vs. 15.96±0,70 ng/ml, p<0.01, Glass's delta 5,748) and vaspin 2.74 times (528,09±41,46 vs. 192,66±11,80 ng / ml, p<0,01, Glass's delta 5,188) (Table 3).

Table 3 - The level of serum adipokines in patients of the study groups, M±SE

Group	Adiponectin, μg / ml	Visfatin, μg / ml	Leptin, ng / ml	Omentin, ng / ml	Vaspin, ng / ml
PCOS, n=97	3,39±0,29 [k]	4,48±0,37 [k]	37,86±2,07 [k]	235,75±18,51 [k]	528,09±41,46 [k]
K, n=30	18,98±1,16	24,66±1,45	15,96±0,70	321,74±19,71	192,66±11,80
Note. [k] is the probable statistical difference with group K (p<0,05).					

Negative correlations of adiponectin levels with the level of insulin in the blood (r = -0.51; p<0.01) and the HOMA index (r = -0.48; p<0.01) were revealed, which indicates the role of insulin resistance in reducing the level adiponectin in PCOS and obesity. In women

with PCOS and obesity, direct correlations were found between leptin levels and BMI ($r = 0.53$; $p<0.01$) and waist circumference / hip circumference ratio ($r = 0.61$; $p<0.01$), blood insulin levels ($r = 0.57$; $p<0.01$) and HOMA index ($r = 0.68$; $p<0.01$); negative correlations of visfatin level with BMI ($r = -0.49$; $p <0.01$) and waist circumference / hip circumference ratio ($r = -0.53$; $p<0.01$), blood insulin level ($r = -0.541$; $p<0.01$) and HOMA index ($r = -0.53$; $p<0.01$); inverse correlations of omentin level with total cholesterol ($r = -0.42$; $p<0.05$), atherogenic coefficient ($r = -0.45$; $p<0.05$) and insulin level ($r = -0 , 46$; $p<0,05$), HOMA index ($r = -0,43$; $p<0,05$), as well as a direct correlation between the content of omentin and adiponectin in the blood ($r = 0,68$; $p<0.01$). Direct correlations of the level of vaspin with BMI ($r = 0,0,58$; $p<0,01$) and the ratio of waist circumference / hip circumference ($r = 0,0,59$; $p<0,01$), the level of insulin in blood ($r = 0.63$; $p<0.01$) and HOMA index ($r = 0.70$; $p<0.01$).

A differential pattern of fat distribution exists between males and females. While females tend to store fat predominantly in the subcutaneous adipose depots and especially in the gluteal and femoral fat pads, males accumulate fat in the visceral depots [4, 20]. However, this pattern of fat accumulation is altered in hyperandrogenic women with PCOS. Clinical studies documented that women with PCOS exhibited increased global adiposity [8] and thickness of the intraperitoneal and mesenteric fat depots compared with control women [3]. The thickness of the intraperitoneal fat depots in these patients was positively correlated with circulating androgen levels, suggesting that androgen excess masculinizes the pattern of fat distribution, favoring visceral fat accumulation [3]. Additional findings have supported the role of androgens in body fat distribution in females, promoting increased visceral adiposity [20].

This alteration in regional fat distribution induced by androgens may have detrimental metabolic implications for PCOS patients, since increased visceral adiposity is considered a risk factor for the development of metabolic syndrome [12] and may contribute to aggravating metabolic abnormalities linked to this endocrinopathy.

Recent findings demonstrated that intra-adipose androgen production by the enzyme AKR1C3 plays a prominent role in adipose tissue dysfunction in PCOS [17, 20]. This enzyme catalyzes the conversion of androstenedione to testosterone and is abundantly expressed in the adipose tissue. Studies of patients with PCOS showed increased local androgen production by AKR1C3 and lipid accumulation in the adipose tissue leading to lipotoxicity, insulin resistance, and compensatory hyperinsulinemia [17]. Interestingly, *in vitro* experiments showed that insulin upregulates AKR1C3 expression, which may exacerbate intra-adipose

androgen production and generate a vicious cycle in the adipose tissue that may increase the metabolic risk in PCOS patients [17].

Androgens have also been shown to modulate adipokine production in the adipose tissue. Adiponectin is an adipocyte-derived adipokine with insulin-sensitizing features. An array of *in vitro* and *in vivo* studies have documented the ability of androgens to reduce circulating adiponectin levels [20], an effect that has been postulated as a key factor contributing to insulin resistance in PCOS women. In keeping with the beneficial effects of adiponectin on insulin sensitivity and metabolic health in PCOS, a recent report in mice showed that the overexpression of this adipokine in the adipose tissue prevents metabolic derangements linked to continuous exposure to DHT but had only minor effects on the reproductive profile in a mouse model of PCOS [2]. In addition to their effects on adiponectin levels, androgens also reduce circulating levels of other adipokines such as omentin-1. This adipokine also has insulin-sensitizing properties and its circulating levels have been negatively correlated with free testosterone levels in obese patients with PCOS [18]. Collectively, these findings demonstrated that hyperandrogenism attenuates adipokine levels with insulin-sensitizing properties that may have detrimental consequences on insulin sensitivity in women with PCOS.

Conclusions

Peculiarities of metabolism in patients with clomiphene-resistant form of PCOS and obesity are dyslipidemia and adipose tissue dysfunction, which is manifested by changes in the secretion of adipokines such as adiponectin, visfatin, leptin, omentin, vaspin. The expression of insulin-sensitizing adipokines varies depending on the amount of adipose tissue. With an excess of visceral fat, adipocytes trigger signals that promote the development of diabetogenic and atherogenic profile of serum.

The most characteristic features of carbohydrate metabolism disorders in clomiphene-resistant women with PCOS and obesity are increased levels of hypoglycemic index, C-peptide, glucose levels after 2 h in oral glucose tolerance test, HOMA index; and lipid metabolism - an increase in atherogenicity, triglycerides, total cholesterol on the background of increased production of leptin and vaspin and decreased secretion of adiponectin, omentin and visfatin.

Visceral obesity plays an important role in the development of insulin resistance and hyperinsulinemia in infertile patients with clomiphene-resistant PCOS and obesity.This category of women in preconception training, before carrying out ovarian drilling or

controlled ovarian stimulation, it is necessary to correct disorders of carbohydrate and lipid metabolism.

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