

A Safe and Effective Contraceptive Method for Women with Obesity in the Postpartum Period

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Abstract Aim. The purpose of this study is to determine the safety of using of drospirenone-containing combined oral contraceptive (OC) in overweight/obese women of reproductive age. **Material and methods.** The study included 65 women of reproductive age who were prescribed OC with 30 µg of ethinyl estradiol and 3 mg of drospirenone for 3 months for therapeutic and preventive purposes. The main parameters evaluated were lipid and carbohydrate metabolism. **Results.** According to the results of the study, a favorable effect of low-dose OC pills on body weight and lipid profile was revealed without significant changes in carbohydrate metabolism. **Conclusion.** Therefore, this method of contraception may be recommended for overweight/obese patients to control fertility in the postpartum period.

Keywords Obesity, Combined oral contraception, Lipid spectrum, Insulin resistance

1. Introduction

Metabolic syndrome (MS), also known as syndrome X, dysmetabolic syndrome, insulin resistance syndrome, as well as obesity syndrome, “abundance syndrome” [1], according to WHO, is a pathological condition characterized by abdominal obesity, decreased tissue sensitivity to insulin and a combination of metabolic, hormonal and clinical disorders, which are the main causes of the development of chronic non-infectious diseases. This is a condition when the body suffers from four ailments: arterial hypertension, obesity, coronary heart disease (CHD) and type 2 diabetes (T2D). This syndrome, due to its danger, was called the “deadly quartet”. The reason for this is the development of such complications as vascular atherosclerosis, the development of fatty liver disease and, as a result, cirrhosis, heart attack and stroke, decreased potency and polycystic ovary syndrome (PCOS). Obesity is the main criteria for MS and its external manifestation. The results of WHO statistics show that about 1.7 billion people in the world are overweight, and by 2025 the world's obese population will reach 300 million. At the same time, women of reproductive age account for about 25% from it. Obesity, which has overwhelmed most of the developed countries of the world and represents a new “non-infectious” global epidemic, is considered as one of the reasons for the steady deterioration of the reproductive potential of modern humanity. Obesity is

a complex of multifactorial problems that are in close pathogenetic relationship with insulin resistance, which, acting synergistically, often lead to reproductive dysfunction. [5]. According to the results of many studies, obese patients have such reproductive dysfunctions as an irregular menstrual cycle, hypomenstrual syndrome, secondary amenorrhea, acyclic bleeding due to hyperplastic processes in the endometrium (63% of women), a high incidence of infertility (2 times more often than in populations). In the initial stage of the disease, the vast majority of patients experience ovulatory cycles. In obese women with menstrual disorders like hypomenstrual syndrome, the frequency of ovulatory cycles can reach 34% [2]. It has been scientifically proven that in women with overweight/obesity in adipose tissue, aromatase activity progresses and gradually gives rise to excessive conversion of androgens into estrogens, which is the cause of chronic hyperestrogenemia.

Consequently, in girls with obesity, menarche occurs early, and the timing of the onset of menopause in women with long-term obesity is postponed, and therefore patients in this group need contraception for a long time. An estimated 44% of pregnancies worldwide are unintended [3], and it has been assessed that many of these pregnancies are among obese women [4]. Obese women may avoid contraception due to concerns that hormones may cause further weight gain. Therefore, it is extremely important for clinicians to solve the issue of contraception in these patients in order to prevent unwanted pregnancy and an increased risk of gestational and obstetric complications [5,6]. At the present time, pharmaceutical activity is so developed that there is a huge selection of contraceptive methods. Currently, the main task of the doctor, in addition to the effective and safe prevention

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of unintended pregnancy, is to prevent the side effects of the chosen method on carbohydrate and lipid metabolism, the blood coagulation system, the cardiovascular system and the activity of other organs involved in the vicious circle of metabolic disorders. Particular importance belongs also to the successful weight loss to improve the overall health and quality of life of the patient. The above points to the need for careful selection of an effective and reliable contraceptive for overweight women with assessment a benefit /risks for each specific fertility control method. It is necessary to focus on highly effective methods of contraception, which include combined oral contraceptives (COCs). For a long time, doctors have been particularly wary when prescribing hormonal contraceptives to overweight/obese women, because the risk of complications is especially high. However, even a physiological pregnancy (which is very rare in the case of obesity), as well as abortion, in comparison with the use of modern and highly effective methods of hormonal contraception, potentiate a greater risk of occurrence and deterioration of metabolic disorders in this category of patients. The negative attitude towards the prescribing of COCs to obese women is due to the fact that taking high-dose contraceptives (the dose of ethinylestradiol is more than 35 µg with the progestogen component of I and II generations) in a number of women led to weight gain and nowadays such pills not recommended for contraception. The development and putting of modern COCs into clinical practice has led to an expansion of the category of women for whom hormonal contraception has become acceptable. The above side effects are not detected in modern hormonal contraceptives with lower doses of estrogens and III generation progestogens. The main contraceptive effect in COCs belongs to the gestagen. It is known that all progestogens, depending on the derivative, are divided into 3 groups (derivatives of progesterone, testosterone and spironolactone). In obesity, it is recommended to use progestogens, derivatives of progesterone or spironolactone (drospirenone), which have a neutral effect on the metabolism of carbohydrate, lipid metabolism and the hemocoagulation/fibrinolysis system. F. Guang-Sheng et al conducted an open, randomized, placebo-controlled, multicenter comparative study of 768 healthy women in need of contraception, in order to identify the efficacy and safety of combined oral contraceptives containing 30 µg ethinyl estradiol + 3 mg drospirenone (n=573) and 30 µg ethinylestradiol + 150 mg desogestrel (n=195) for 13 cycles. Weight, height and BMI were assessed at each visit. The authors indicate that there was a significant decrease in mean weight (-0.28 kg) in the group of women taking oral contraceptives containing 30 µg of ethinyl estradiol and 3 mg of drospirenone (n=573); in addition, in this group there was a more favorable effect of taking this contraceptive on premenstrual symptoms [10]. Drospirenone is similar to spironolactone, but surpasses the latter in terms of the severity of the antiminerlocorticoid effect. This fact has particular importance because aldosterone is involved in the formation of excess adipose tissue. Thus, for overweight

women planning contraception, it is advisable to recommend the use of drospirenone-containing oral contraceptives.

These drugs provide reliable contraception, are well tolerated and safe to use, and their antiminerlocorticoid and antiandrogenic effects help to normalize body weight and prevent the transition of overweight to obesity. The use of testosterone derivatives (levonorgestrel, desogestrel, gestaden, etc.) is undesirable due to the fact that obesity is often accompanied by ovarian hyperandrogenism. Dienogest (a gestagen of the last, IV generation) is exception and does not have an ethynyl group in position 17- α , combines the advantages of progesterone derivatives and 19-norsteroids, activates only progesterone receptors and does not have androgenic, estrogenic or glucocorticoid effects, which is very important when choosing contraception in overweight and obese women.

Moreover, estrogens of oral contraceptives have a positive effect on fat metabolism by increasing the content of high-density lipoprotein (HDL) and reducing the level of low-density lipoprotein (LDL). In addition, synthetic estradiol (ethinylestradiol) has more pronounced estrogenic properties than natural, and can be used in overweight/obese women, as it has more resistance to liver metabolism.

The aim of our investigation was to study the effect of drospirenone-containing combined oral contraceptive (30 µg of ethinyl estradiol and 3 mg of drospirenone) on possible changes in anthropometric parameters, lipid profile and insulin resistance in overweight/obese women of reproductive age.

2. Material and Research Methods

The work was performed on the basis of the private clinic "Zurriyot-shifo" in the Urgench city. The study included 65 overweight/obese women of reproductive age who applied for outpatient care in the period 2020-2022 and who, for therapeutic and contraceptive purposes were prescribed oral contraceptive pills (OC pills) with 30 µg of ethinyl estradiol (EE) and 3 mg of drospirenone (DRSP) for 3 months. Inclusion criteria: the main criteria is central obesity (waist circumference (WC) in women is 80 cm or more) and reproductive age (from 18 to 44 years). Exclusion criteria: the presence of standard contraindications to the use of OC pills and organic damage of the hypothalamic-pituitary region, adrenal glands. The main parameters assessed in the study were general and gynecological examination, anthropometric parameters (age, height, body weight, WC, calculation of body mass index (BMI)), clinical parameters (blood pressure (BP), heart rate), lipid profile, indicators of carbohydrate metabolism. Normoglycemia was determined at glucose levels less than 5.6 mmol/l on an empty stomach. For each patient, the insulin resistance index (HOMA-IR) was determined. Basal hyperinsulinemia was diagnosed at an insulin level >25.0 µU/l, and insulin resistance (IR) was diagnosed at a HOMA value >3.0. Venous blood sampling for all biochemical studies was performed by venipuncture on an empty stomach, 12-14 hours after the last meal and 3

days after alcohol intake. Serum lipids were determined before the intake and after stopping OC pills (after 3 months).

3. Results and Discussion

During the study, 65 patients from 19 to 42 years old (mean age was 28.9 ± 6.1 years) who applied for outpatient care with various gynecological problems were examined. The vast majority of them live in rural areas - 40 (61.5%) and are housewives - 44 (67.7%). Among them, 39 patients were diagnosed with PCOS, 32 patients suffered from infertility, and 22 patients had functional hyperprolactinemia. In addition, 14 overweight/obese women had a history of blighted ovum and 14 patients were diagnosed with adenomyosis. Menstrual disorders occurred in 34 (52.3%) women, among them secondary oligomenorrhea was more common in 22 patients (33.8%) (Table 1).

Table 1. Gynecological diseases detected in overweight/obese women

Diseases	Frequency of occurrence	
	n	Rate, %
Infertility-1	24	36,9±6,0
Infertility-2	8	12,3±4,1
PCOS	39	60,0±6,1
Functional hyperprolactinemia	22	33,8±5,9
Adenomyosis	14	21,5±5,1
Blighted ovum	14	21,5±5,1
Myoma	2	3,1±2,2
Candidosis	6	9,2±3,6
Follicular cyst	-	-
Endometrial cyst	1	1,5±1,5
Endocervix cyst	2	3,1±2,2
Bilateral adnexitis	4	6,2±3,0
Paraovarian cyst	1	1,5±1,5
Hypoplasia of the uterus 1 degree	2	3,1±2,2
Hypoplasia of the uterus 2 degree	2	3,1±2,2
Salpingitis	2	3,1±2,2
Abnormal uterine bleeding	2	3,1±2,2
Spontaneous miscarriage	2	3,1±2,2
Primary oligomenorrhea	2	3,1±2,2
Secondary oligomenorrhea	22	33,8±5,9
Hyperpolymenorrhea	6	9,2±3,6
Dysmenorrhea	24	36,9±6,0
Polymenorrhea	2	3,1±2,2
Secondary amenorrhea	2	3,1±2,2

Among the 65 women, there were 32 patients (49.2%) with obesity class I, 17 (26.2%) - with obesity class II, 6 patients (9.2%) - with obesity class III, and 10 (15.4%) - were overweight. According to the study, the average BMI was 33.98 ± 0.55 kg/m². Initially, 25 (38.5 %) patients with arterial hypertension (AH) stage I and 1 (1.5%) patient with

AH stage II were identified among the studied patients, and the mean statistical indicators of systolic blood pressure (SBP) and diastolic blood pressure (DBP) were 126.6 ± 1.8 and $82, 8 \pm 1.3$ mm Hg respectively. By analyzing anthropometric parameters of examined women, we did not find a significant difference in body weight initially and after 3 months of taking OC pills (Table 2). In this case, OC with DRSP showed a significantly better effect on body weight (weight loss by 2.4%), probably due to its antiminerlocorticoid effect. Given the fact that weight gain with traditional OC pills is the main cause of hormonophobia and drug discontinuation, it can be concluded that OC containing 30 µg EE and 3 mg DRSP, due to the ability to reduce body weight and prevent weight gain, as well as favorable effect on the lipid profile, is the most acceptable OC option for women seeking to maintain a stable body weight.

Table 2. Dynamics of anthropometric parameters of patients with overweight/obesity taking 30 µg EE/3 mg DRSP

Parameters	Initially	After 3 months	P
Height (cm)	159,85±0,75	159,85±0,75	>0,05
Weight (kg)	86,80±1,53	84,75±1,39	>0,05
BMI (kg/m ²)	33,98±0,55	33,20±0,50	>0,05
Waist (cm)	98,14±1,19	95,58±1,06	>0,05

In the study of fasting insulin and blood glucose, as well as an indirect indicator of the sensitivity of insulin receptors in tissues (HOMA index), a slight increase in these indicators was revealed (by 12,7%, 7,1% and 16,2% respectively). Despite these changes, fasting glucose and insulin levels remained within normal limits (Table 3).

Table 3. Dynamics of carbohydrate metabolism in overweight/obese patients taking 30 µg EE/3 mg DRSP

Indicators of carbohydrate metabolism	Initially	After 3 months	P
Fasting blood glucose, mmol/l	4,9±0,16	5,25±0,35	>0,05
Fasting insulin	17,3±1,6	19,5±0,92	>0,05
HOMA index	4,13±0,40	4,8±0,23	>0,05

According to the results of lipid profile assessment (Table 4), an increase in triglyceride levels by 15% was revealed after taking drospirenone-containing OC. Moreover, after 3 months of taking OC pills patients showed a positive trend towards lower of atherogenic low-density lipoprotein (LDL) by 4,5%, very-low-density lipoprotein (VLDL) by 13,1% and an increase in antiatherogenic high-density lipoprotein (HDL) by 9%, while total cholesterol remained almost at the same levels (~5 mmol/l). This, in turn, favorably affects the atherogenic coefficient (AC) by decreasing from 3,36 to 2,97 for 3 months. It is considered that AC is better predictor of cardiovascular risk and indicate an atherogenic risk. Therefore, taking a drospirenone-containing OC in overweight and obese women does not have a statistically significant negative effect on the development of cardiovascular complications.

Table 4. Dynamics of lipid spectrum parameters in overweight/obese patients taking 30 µg EE/3 mg DRSP

Indicators of fat metabolism	Initially	After 3 months	p
Total cholesterol (mmol/l)	5,13±0,6	5,08±0,57	>0,05
Triglycerides (mmol/l)	1,6±0,084	1,84±0,080	<0,05
LDL (mmol/l)	3,3±0,15	3,15±0,14	>0,05
VLDL (mmol/l)	0,38±0,023	0,33±0,016	>0,05
HDL	1,22±0,052	1,33±0,054	>0,05
AC	3,36±0,16	2,97±0,13	<0,05

In addition, the use of OC pills by patients for 12 weeks did not show adversely affect to the parameters of the cardiovascular system (systolic and diastolic blood pressure, pulse (PS)) (Table 5). According to our study mean SBP of patients after 3 months accounts for 118,9±1,3 mmHg and pulse rate also was within the normal range - 79,8±0,64 beats per minute.

Table 5. Trends in blood pressure and heart rate in overweight/obese patients taking 30 µg EE/3 mg DPRP

Parameters	Initially	After 3 months	P
SBP (mmHg)	126,6±1,8	118,9±1,3	<0,01
DBP (mmHg)	82,8±1,3	73,7±0,94	<0,001
Pulse (beats per minute)	81,2±1,1	79,8±0,64	>0,05

In an objective study, clinical manifestations of hyperandrogenism (acne, hirsutism) were observed in 46.2% of cases. While taking a low-dose OC pills by the end of the 12th week clinical cure of acne was achieved in 24 (80%) patients (Table 6).

Table 6. Dynamics of acne and hirsutism recovery against the background of taking 30 µg EE/3 mg DRSP

Parameters	Initially		After 3 months		p
	N	Rate, %	N	Rate, %	
Acne	30	46,2±6,2	6	9,2±3,6	<0,001
Hirsutism	30	46,2±6,2	30	46,2±6,2	>0,05

4. Conclusions

Our data suggest that a low-dose OC containing 30 µg of ethinylestradiol and 3 mg of drospirenone can be recommended to patients with overweight and obesity because weight gain, severe disorders in the lipid profile and an increase in blood pressure are not predicted. Additional control should be carried out in patients with impaired carbohydrate metabolism. An increase in the HOMA index makes one cautious when prescribing OC pills in patients

with clinical manifestations of insulin resistance. To sum up, life threatening complications may be revealed after conducting further study with the inclusion of a large number of overweight/obese women, who take OC pills for a longer period.

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