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Review Article

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The Role of Drospirenone in The Treatment of Obesity with Hyperandrogenism

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Summary

The article is devoted to the problem of the effect of excess body weight and obesity on the level of androgens in a woman's body and the method of treatment of menstrual dysfunction resulting from exposure to adipose tissue.

Keywords: Drospirenone, Hyperandrogenism, Obesity, Menstrual Cycle.

The problem of obesity in modern society is becoming truly large-scale - out of 7.5 billion people living on earth, about 1.2 billion suffer from this disease. According to epidemiological forecasts, while maintaining the existing rate of increase in obesity, it is assumed that by 2025 it will suffer from 30% to 50% of the population of economically developed countries. Obesity is not just an excess of body fat, it is a complex pathology, which is currently regarded as a chronic recurrent disease that contributes to the manifestation and development of many concomitant diseases that shorten the life span of a person and worsen its quality [1]. When analyzing epidemiological data not only in our country, but also in the world, it can be concluded that despite a large number of new developments, both in diet therapy and in drug treatment, the number of obese patients is growing in all age groups [2].

adults with obesity > 18	men	women
USA	32,6	34,7
The United Kingdom of Great Britain and Northern Ireland	26,9	29,2
Germany	21,9	18,5
France	23,8	24
Russia	20,3	27,4
China	5,9	8

WHO 2015.,

In the course of numerous studies, scientists have found that the presence of obesity in a woman reduces her fertility. This is especially true in women with abdominal obesity. At the same time, in the initial stages of the disease, most patients have ovulatory cycles. According to foreign researchers, up to 30% of women with abdominal obesity and up to 80% with gluteofemoral obesity have a regular menstrual cycle and are capable of conceiving. In obese women, against the background of menstrual dysfunctions of the oligomenorrhea type, accounting for up to 80% in the structure of menstrual irregularities, the frequency of ovulatory cycles can reach 34% [3]. Against the background of obesity, as a rule, girls have earlier menarche, and the timing of menopause in chronic obesity, due to relative hyperestrogenism, is postponed, and these patients need contraception longer.

When assessing the reproductive health of obese patients, it must be remembered that this contingent of women is characterized by a high incidence of complications after abortion, a higher incidence of ovarian and breast cancer, miscarriage (fetal malnutrition, gestosis, etc.), as well as complications in childbirth. and the postpartum period, therefore, these patients need a careful selection of differentiated methods of contraception.

The development and introduction into clinical practice of modern combined oral contraceptives contributes to an increase in the number of women for whom hormonal contraception is not only a family planning method, but also a therapeutic agent. In particular, by the method of correcting hyperandrogenic states, it is rational to choose combined oral contraceptives containing a gestagenic component with a proven antiandrogenic effect.

These drugs perform the function of therapy for hyperandrogenism and regulation of the menstrual cycle.

Menstrual dysfunction associated with obesity is the most common symptom of women of reproductive age, affecting about 45% of this population. Often this condition is accompanied by metabolic disorders, hyperandrogenism, and eating disorders. In these clinical conditions, there is a combination of symptoms characterizing PCOS and obesity. This contingent of women occupies a special place, because not all patients with PCOS are obese, and not all obese women have menstrual irregularities and anovulation [4].

Observing for a long time the patients with overweight and obesity and emerging anovulatory infertility, as a consequence of this, we noted that the main role in the clinical picture of anovulation is played by hyperandrogenism. Symptoms of hyperandrogenism and anovulation clinically demonstrate bipolar ovarian disorders: hyperactivity of androgen-secreting theca cells and inability of granulosa cells to grow a dominant follicle. In the case of obese patients, it is adipose tissue, as a consequence of hyperphagia, that is the source of hyperinsulinemia and insulin resistance. For the physiological functioning of adipose tissue, the nature of its distribution is of great importance. In women with normal hormonal homeostasis, the accumulation of adipose tissue occurs in the subcutaneous tissue according to the gynoid type. With endocrine changes, when the balance of sex steroids in a woman shifts towards androgens, the formation of an android type of obesity with excessive accumulation of visceral fat is possible [5].

Visceral fat is more sensitive to catechus olamines, is less sensitive to insulin compared to subcutaneous fat, triglycerides are more easily released from it. Visceral adipose tissue is better supplied with blood, its adipocytes have a high density of beta-adrenergic receptors (stimulation of lipolysis) with a relatively low density of alpha-adrenergic receptors (suppression of lipolysis). Intensive lipolysis of visceral fat leads to an increase in free fatty acids in the bloodstream, which causes metabolic disturbances characteristic of abdominal obesity. The high metabolic activity of visceral fat becomes the cause of many disorders, and therefore it is visceral obesity that is associated with a high risk of endocrine and metabolic disorders, which are based on insulin resistance and, as a consequence, hyperinsulinemia [6, 7].

In addition, the metabolic aspects of the formation of anovulation partly depend on genetic characteristics, partly provoked by hormonal imbalance, mainly hyperandrogenism. The adipose tissue contains enzymes: aromatase and 5alpha-reductase. Aromatase converts androgens to estrogens. With obesity, aromatase is present in excess, therefore estrogens are constantly formed in high concentrations, which leads to a violation of the ovulation process. A tonic increase in the level of estrogens in the early follicular phase, formed as a result of peripheral conversion of androgens, through a positive feedback mechanism, affects the pituitary gland. The increased release of biologically active luteinizing hormone leads to the stimulation of androgen production by the ovarian stroma. The androgens formed in high concentrations are additional precursors for subsequent aromatization and conversion into estrogens in adipocytes - this is how the "vicious circle" is closed. In turn, an excessive amount of 5alpha-reductase, which converts testosterone and dihydrotestosterone, increases the production of the latter, which enhances the effects of hyperandrogenism [8].

In the history of the creation of progestogenic components of COCs, three main directions can be distinguished:

- Derivatives of testosterone (19-norsteroids)

1. Containing the ethynyl group at C-17
- Estrana (1st generation) - norethisterone, norethinodrel, linestrenol, tibolone.
- Gonans (2nd generation) - norgestrel, levonorgestrel.
- (3rd generation) - desogestrel, gestodene, norgestimate.

2. Does not contain ethynyl group dienogest
- Derivatives of progesterone chlormadinone, cyproterone (acetate), dydrogesterone, medroxyprogesterone.
- Derivatives of spironolactone drospirenone.

Drospirenone was introduced for medical use in combined oral contraceptives in 2000. It is widely used worldwide as a component of combined oral contraceptives and hormone replacement therapy. Drospirenone, also known as 1,2-dihydrospirrenone, is a synthetic steroid of 17alpha-spironolactone. It is analogous to other spironolactones (Figure 1), such as spironolactone, canrenone, spirenone. At the same time, drospirenone is an antagonist of androgen receptors, a biological target of androgens such as testosterone and dihydrotestosterone. It has about 65% affinity for the synthetic anabolic steroid Metrabolone for androgen receptors [9]. The drug is more effective as an antiandrogen compared to spironolactone, but less effective than cyproterone acetate and accounts for only 35% of it. To date, it has been proven that one of the effects of drospirenone is a suppressive effect on the production of 5alpha-reductase. 5alpha-reductase is an enzyme that converts testosterone to dihydrotestosterone. Thus, drospirenone has three parallel antiandrogenic effects: progestogenic, blocking androgen receptors, and blocking effect on dihydrotestosterone synthesis (Figure 2) [10].

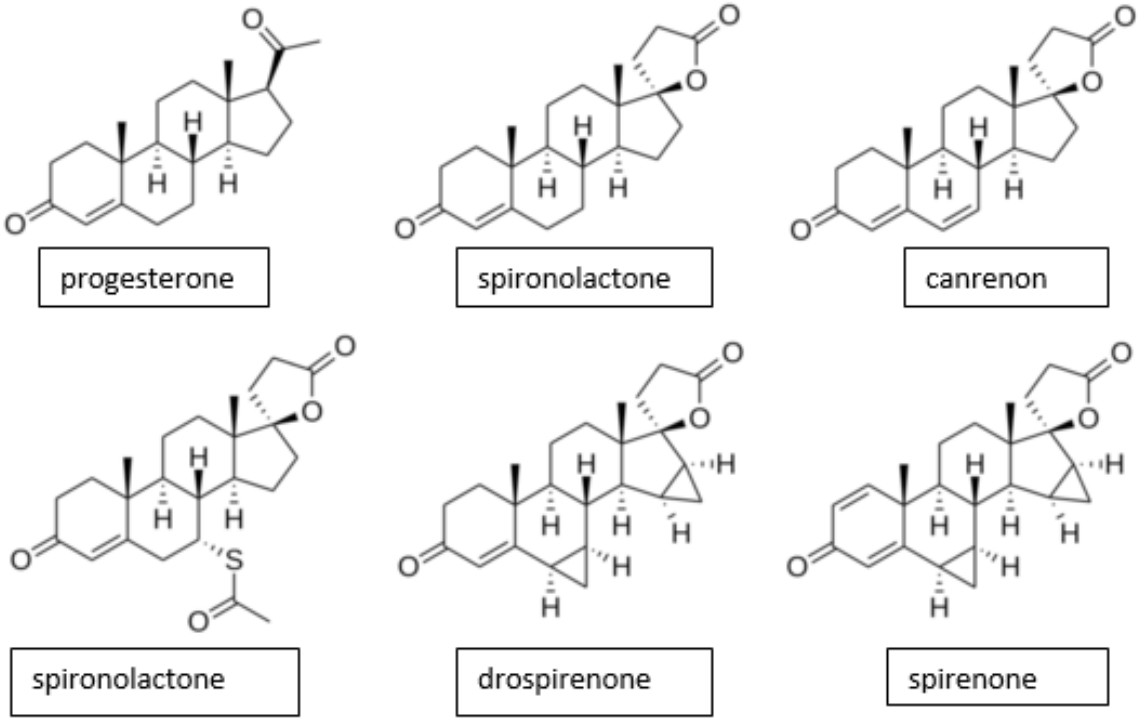

Figure 1

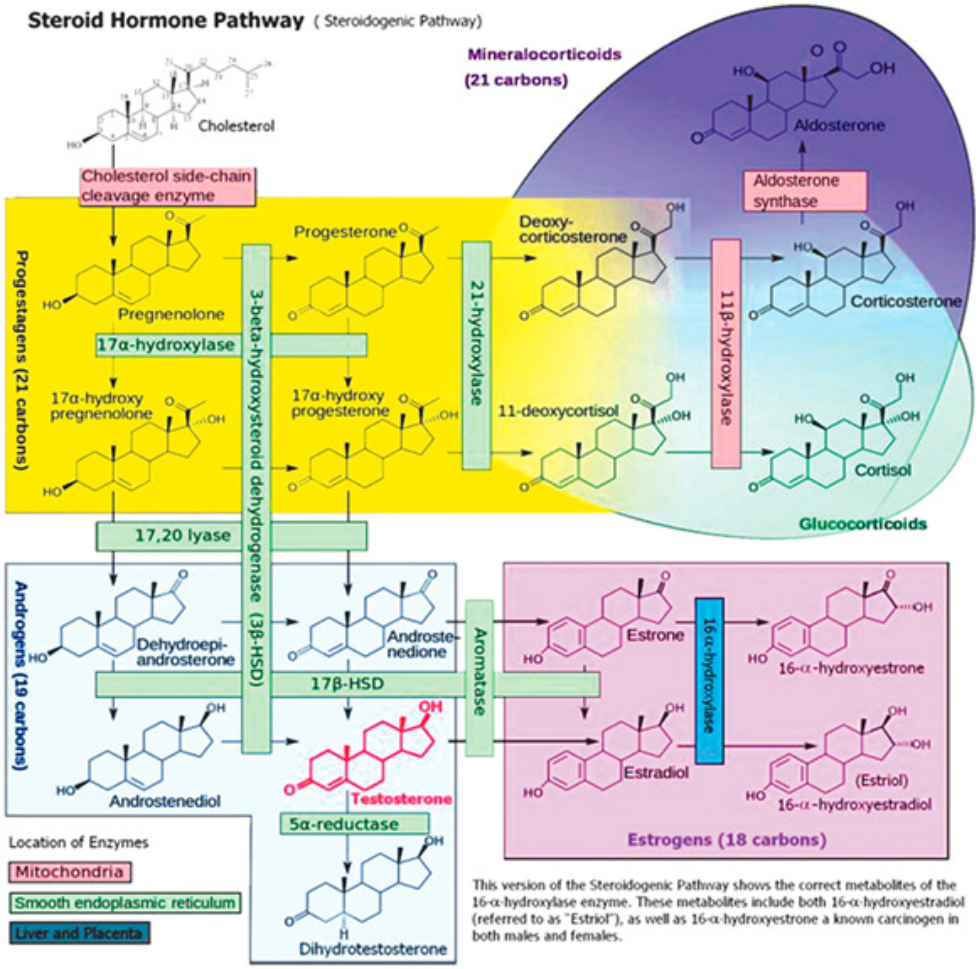

Figure 2

To assess the change in androgen levels, weight loss and the effect on the regularity of menstruation, we conducted a study in which 156 patients with menstrual irregularities took part.

1. The age of the patients was 18 - 33 years, the average age was 24.6 + 4.2 years.
2. Menstrual irregularities: oligomenorrhea 57.7%; amenorrhea 23.1%; acyclic bleeding 19.2%; regular menstruation 0%.
3. The average level of androgens before the start of the study: androstenedione 23.7 nmol / l; testosterone 3.9 nmol / l; dihydrotestosterone 4.32 nmol / l. (diagram 1, 2)
4. The average body weight was 98.8 + 18.8 kg; the average body mass index is 31.4 + 6.2 kg / m^2.

All patients were prescribed a combined oral contraceptive containing 20μg of ethinylestradiol and 3 mg of drospirenone, as well as training in methods of rational nutrition, moderate physical activity, and keeping a diary of observation and menstrual calendar. COCs were taken for 12 cycles. After the end of the contraceptive intake, the patients were followed up for another 12 cycles. After 24 months from the beginning of COC prima, the menstrual calendar was analyzed, anthropometry was performed I also took blood serum samples for androgens.

1. Menstrual cycle: oligomenorrhea 34.6%; amenorrhea 3.8%; acyclic bleeding 0%; regular menstruation 61.5%.
2. A decrease in body weight by at least 5% (P <0.001) in 63.2% of patients; 33.1% have a decrease in body weight> 10%.
3. The average level of androgens after 24 cycles from the beginning of the study: androstenedione 7.57 nmol / l; testosterone 0.45 nmol / l; dihydrotestosterone 1.24 nmol / l. (Diagram 1, 2).

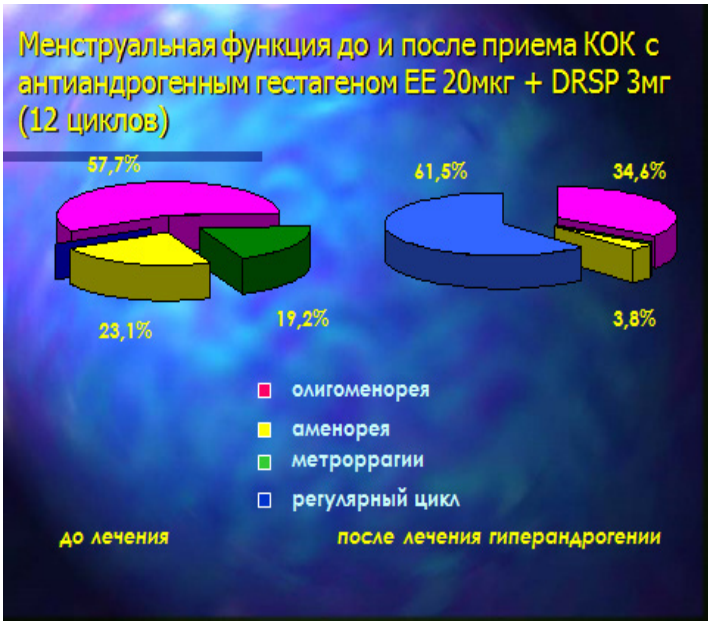

Chart 1

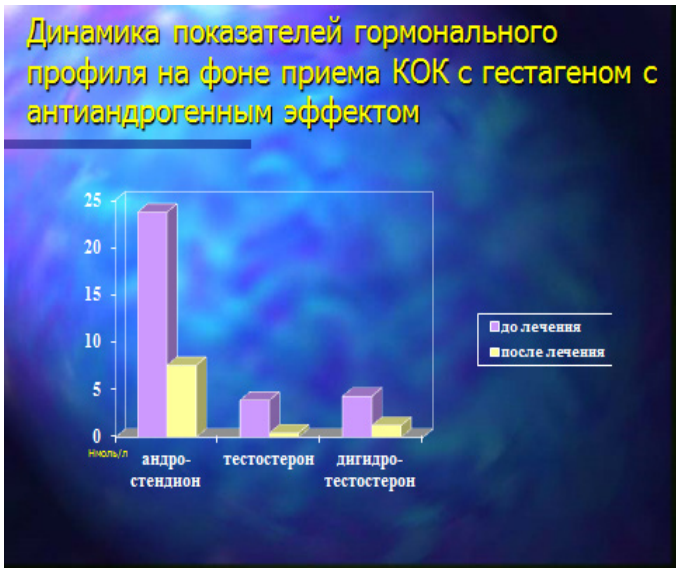

Chart 2.

Reference values: androstenedione - 1.6 - 19.0 nmol / l; testosterone - 0.52 - 1.72 nmol / l; dihydrotestosterone - 0.08 - 1.56 nmol / l.

Based on the results of the study, it was concluded that drospirenone-containing combined oral contraceptives have not only a contraceptive, but also a therapeutic effect in the treatment of antiandrogenic conditions. There was a direct correlation between the percentage of body weight loss and a decrease in androgen levels. Thus, a wide range of therapeutic effects of drospirenone is possible due to its antiandrogenic and antimineralocorticoid activity, and this is applicable both for contraception and for the treatment of menstrual irregularities against the background of overweight and hyperandrogenism in women of reproductive age.

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