RECUPERABILIDADE DO SISTEMA REPRODUTIVO EM PACIENTES COM HIPERANDROGENISMO CONCOMITANTE

RECOVERABILITY OF REPRODUCTIVE SYSTEM IN PATIENTS WITH CONCOMITANT HYPERANDROGENISM

ВОЗМОЖНОСТИ ВОССТАНОВЛЕНИЯ РЕПРОДУКТИВНОЙ СИСТЕМЫ У БОЛЬНЫХ С СОЧЕТАННОЙ ФОРМОЙ ГИПЕРАНДРОГЕНИИ

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RESUMO

O hiperandrogenismo adrenal (HA) exerce um efeito negativo sobre o sistema reprodutivo das mulheres (SR), enquanto o HA ovariano é pré-condicionado pelo estado anovulatório. Há opiniões contraditórias sobre a influência de diferentes androgênios nas funções do sistema reprodutivo das mulheres. Os principais critérios de avaliação e importância desses fatores permanecem indefinidos. A HA combinada é uma das principais causas patogênicas de disfunções menstruais e reprodutivas. O estado de anovulação provoca um aumento no nível dos andrógenos principais, e a deficiência da fase lútea é uma consequência do impacto negativo do AH. A terapia baseada em patogênese individual permite recuperar a ovulação e assegurar a gravidez contra um pano de fundo de normalização do metabolismo androgênico e outros indicadores do funcionamento do sistema reprodutivo. Os critérios para diagnósticos diferenciais dos estados hiperandrogênicos e avaliação das disfunções reprodutivas permitem encontrar um padrão de tratamento individual.

Palavras-chave: *hiperandrogenismo, anovulação, deficiência da fase lútea, síndrome dos ovários policísticos, testosterona, diidrotestosterona, infertilidade*

ABSTRACT

Adrenal hyperandrogenism (HA) exerts a negative effect on the women's reproductive system (RS), while ovarian HA is preconditioned by the anovulation state. There are contradictory opinions on the influence of different androgens on the functions of women's reproductive system. The main criteria of the assessment and importance of these factors remain undefined. Combined HA is one of the leading pathogenic causes of menstrual and reproductive dysfunctions. Anovulation state causes an increase in the level of the main androgens, and the luteal phase deficiency is a consequence of the negative impact of HA. Individual pathogenesis-based therapy, allows recovering ovulation and securing pregnancy against a background of normalization of androgen metabolism and other indicators of the reproductive system functioning. The criteria for differential diagnostics of hyperandrogenic states and assessment of reproductive dysfunctions allows finding an individual treatment pattern.

Keywords: *hyperandrogenism, anovulation, luteal phase deficiency, polycystic ovary syndrome, testosterone, dihydrotestosterone, infertility*

АННОТАЦИЯ

Сочетанная форма гиперандрогении является одной из ведущих патогенетических причин развития нарушений менструальной и репродуктивной функций организма. Состояние ановуляции обуславливает повышение уровня основных андрогенов, а недостаточность лютеиновой фазы является

следствием негативного влияния гиперандрогении. Проведение индивидуальной, патогенетически - обоснованной терапии с учетом состояния репродуктивной системы, позволяет добиться восстановления овуляторных циклов и наступления беременности на фоне нормализации показателей метаболизма андрогенов и других показателей функционирования репродуктивной системы.

Ключевые слова: *гиперандрогения, ановуляция, НЛФ, поликистозные яичники, тестостерон, дигидротестостерон, бесплодие.*

INTRODUCTION

One of the urgent problems of today's gynaecological endocrinology is early detection of women's reproductive dysfunctions.

Hyperandrogenism (HA) remains among the leading causes of reproductive system pathology; it is found in 10 – 20% of all women of reproductive age.

The incidence of HA within the structure of gynaecological disorders is as much as 1,3 – 4% (1, 2). Scientific literature contains a variety of definitions of "hyperandrogenism", but most often this term is used for designating a set of symptoms of disorders associated with specific and metabolic effects of androgens in the female body due to pathological biosynthesis, transport, and metabolism of androgens (3, 4). HA syndrome is one of the most widespread causes for female reproductive disorders - oligomenorrhea, anovulation and, as a result, infertility (5, 6). Besides, HA is manifested by complex symptoms of skin/skin appendages lesions (hirsutism, acne, alopecia, seborrhoea), collectively referred to as "androgen-dependent dermopathy". It is common knowledge that in the female body, androgens are produced by both ovaries and adrenal glands (7). Detection of the source of HA is quite problematic, and diagnosis of a specific clinical form of HA is also difficult due to the polymorphism of this pathology and prevalence of its combined forms. However, distinguishing a particular HA form is definitely essential for detecting the source of HA and prescribing an adequate (in terms of pathogenesis) therapy (8). As of today, the most common pathology leading to the development of the HA syndrome is considered to be polycystic ovary syndrome (PCOS). PCOS is regarded as a poly-glandular, poly-etiologic and poly-symptomatic pathology, whose pathogenesis can be caused by disorders in both central and peripheral parts of the reproductive system. In many studies, it was established that about 10% of women with PCOS also demonstrate symptoms of congenital adrenal hyperplasia (CAH) (9). It must be admitted that the ever-rising interest in the study of this pathology is limited by a number of difficulties, which include heterogeneity and polymorphism of HA; this leads to considerable differences in diagnostic approaches, interpretation of diagnostic results or clinical evidence, specifics of the course of disease and choice of treatment tactics. Until now, the question of the cross-effects of the HA syndrome in the female body and reproductive system disorders remains disputed. International scientific literature still lacks statistically significant data on the dynamics of steroid hormones (estrogens and androgens) metabolism taking into account various indicators of reproductive system activity. All these data are usually related to attempts of making a diagnosis in indeterminate cases. At that, the clinical picture of combined HA greatly varies from case to case and may not correspond to current standard diagnostic criteria of certain diseases.

All stated above support the urgency of the problem and persuade of a need to improve the methods of examining HA patients, to search for optimal diagnostic criteria helping to identify a specific HA form, which is surely important for conducting an efficient pathogenesis-related therapy.

The goal of the study is to make a comprehensive assessment of the reproductive system state and improvement of the principles of menstrual/reproductive function recovery in patients with a combined form of HA, to determine the correlation between the main indicators of steroid hormones taking for different disorders of the reproductive system - corpus luteum insufficiency and anovulation.

MATERIALS AND METHODS

This paper presents the results of

examination and treatment of 105 women, including the control group. The patients were from 19 to 37 years old, the mean age was 27.39±0.75 years. 70 of them had symptoms of androgen-dependent dermopathy, with laboratory results indicative of HA, i.e. higher levels of free testosterone (FT) and total testosterone (TT), higher levels of androstenedione (An) and dihydrotestosterone (DHT). Combined HA was detected by signs of both adrenic HA (increased DHEAS, 17-OHP and reduced cortisol (C)) and ovarian HA (LH > 10 mIU/ml, LH/FSH > 2, ovarian volume > 9 cm^3, opsomenorrhea and primary infertility).

When selecting patients for all study groups, we excluded from consideration:
- thyroid diseases;
- hyperprolactinemia;
- Cushing's disease;
- serious extragenital pathologies;
- hormone-active androgen-producing tumors of ovaries and adrenal glands;
- pathologies of the hemostasis system (genetic and acquired forms of thrombophilia).

The assessment of the patients' state was carried out in compliance with a set of the HA diagnostic criteria:
- Stage 1. Assessment of clinical HA symptoms: the signs of androgen-dependent dermopathy of different intensity (acne, hirsutism, alopecia, etc.);
- Stage 2. Evaluation of HA laboratory criteria: increase in the level of the main androgens — TT, FT, An, and DHT;
- Stage 3. Differential diagnostics of the HA form (source): adrenal, ovarian or combined.

This research clearly determined only criteria for PCOS diagnostics, including clinical criteria (luteal phase deficiency and infertility), laboratory criteria (the LH level > 10 IU/l on days 5-7 of the menstrual cycle) and instrumental criteria (the ovarian volume increase > 9-10 cm^3, detected by ultrasonic scanning of the pelvic organs) (10).

The patient groups were formed only on the basis of laboratory-confirmed combined HA and the criteria of reproductive system functional activity – accomplished ovulation. The forms of the patients' reproductive disorder (luteal phase deficiency and anovulation) were defined after the results of the ultrasound and tests of hormones in the peripheral blood. The level of estradiol (E2) in peripheral blood on days 21-23 of the cycle defined the hormonal criteria of the reproductive disorder type: E2 < 350 pmol/l – hypoestrogenic, E2 > 750 pmol/l – hyperestrogenic, at the concentration of E2 between 350 - 750 pmol/l and 16 < P < 30 nmol/l – normoestrogenic or hypoprogesterone types.

Assessments of the reproductive function of patients with combined HA (CHA) were carried out on days 5 – 7 and 21 – 23 of the menstrual cycle, which made it possible to divide the patients into two groups depending on the form of their reproductive disorder:

Group I CHA+A: 33 women aged 19 – 37 (mean age 26.67±1.01 days unit) with anovulatory disorder of the reproductive system (with the menstrual cycle less than 21 or more than 35 days, endometrial thickness less than 6 mm or more than 12 mm, absence of yellow body in the ovaries, progesterone level < 15.9 nmol/l on days 21 – 23 of the menstrual cycle).

Group II CHA+LPD: 37 women aged 20 – 38 (mean age 28.24±1.12 days unit) with luteal phase deficiency (the menstrual cycle of 21 – 26 days, the duration of the yellow body phase less than 10 days, sonographically measured endometrial thickness less than 10 mm and the size of the yellow body less than 20 mm, progesterone level 16 – 30 nmol/l on days 21 – 23 of the menstrual cycle).

The control group was comprised of 35 apparently healthy women of a reproductive age (28.32±1.52 years old) having a regular ovulatory menstrual cycle of 28 – 30 days, with no symptoms of HA.

When analyzing anamnestic data and the results of the physical examination, we considered the following parameters: age, the state of the menstrual and reproductive functions, family history, anthropometric data, pelvis ultrasound, hormonal and non-hormonal state. The pelvic ultrasound was performed for all the patients in a standard way, in dynamic range, using the SonoAce-8000 Live equipment produced by Medison (Korea), with abdominal and vaginal sensors of 3.5 MHz, 5 MHz, and 7.5 MHz respectively. The hormonal panel tests were also performed in the course of the menstrual cycle, on days 5 – 7 and 21 – 23, assessing the level of secretion of peptide and steroid sex hormones. All the patients were examined for non-hormonal homeostasis to reveal disorders of lipid and carbohydrate metabolism.

For successful treatment of menstrual and

reproduction disorders, as the first stage of ovulation stimulation in the cases of combined HA, we implemented a therapy with combined oral contraceptives (COCs) containing progestogens dienogest and drospirenone. As a hormonal support for the luteal phase of the menstrual cycle, we prescribed natural micronized progesterone in the total daily dose of 200–300 mg, and an analog of the endogenous progesterone, dydrogesterone, 10 – 14 days with the total daily dose of 10 – 20 mg. In order to reduce the manifestations of androgen-dependent dermopathy and treat the hormonal dysregulations, we administered dexamethasone in an individual daily dose of 0,125 – 0,5 mg. The treatment results were evaluated in 3, 6 and 9 months. Statistical processing of the obtained data was carried out in Microsoft Excel (Microsoft, USA), SPSS–9.0 and Epi-info 6.0, with the use of parametric and non-parametric methods. The parameters defined in the study were: mean value (M), standard deviation (σ), mean value error (m), and percentage in the data series (%). After checking the normal distribution of data, we used parametric methods (Student's t-test). For correlation analysis of the parameters, we used Pearson correlation method. The critical value of significance for all criteria was assumed to be equal to 0.05. The differences were taken to be significant at $P < 0,05$ and highly significant at $P < 0,01$.

RESULTS

Russian and foreign researchers strongly recommend assessing the reproductive system state only after eliminating all the cases of serious physical, endocrine and infectious diseases, which often cause menstrual and reproductive dysfunctions, because adequate work of all levels of the reproductive system is possible only under the conditions of physical and mental/emotional comfort, i.e. in a healthy female organism. Determination of only one marker — TT — is not, in our view, a sufficient criterion of HA diagnosis, so HA can be confirmed only after simultaneous testing for all other elements actively participating in the metabolism of androgens (TT, FT, An, DHT); they should be measured dynamically in the course of the menstrual cycle, in combination with clinical data and the assessment of the reproductive system functional status. HA states evaluated on days 5–7 of the menstrual cycle can be more evident in patients with a prevalent ovarian component, because of a considerable increase in the levels of the main androgens. The obtained results are in line with the opinion of some researchers (11) who consider a hypothesis of the role of adrenarche in the ovarian HA genesis Higher levels of androgens are the results of anovulation; at that, progressive increase in the levels of sex steroids exacerbates the anovulatory state.

In 69.2% of patients with CHA+A, the ovarian volume is increased (14,23±1,16 cm^3, $P < 0,01$), while the follicular structure on days 5–7 of the menstrual cycle includes follicles sized 8–10 mm in diameter (8,37±0,62 mm on average), which produce both estrogens and androgens to an equal degree, therewith supporting the normo-estrogenic anovulatory state (12,13). The clinical manifestations of reproductive system disorder in the group of patients with CHA+A include serious dysfunctions: the menstrual (opsomenorrhea — 60,6%, amenorrhea — 9,1%) and the reproductive one (infertility — 72,9%).To treat patients with CHA+A, we initially followed the simplest possible pattern of ovulatory stimulation by modern neutral metabolic COCs or the COCs that are not the derivatives of 19-norsteroids, since the latter exacerbates the HA state in the patients with CHA. Administering COCs, which contain such progestagens as dienogest and drospirenone, allows reducing the functional capacity of the ovaries and the LH level due to the recovery of the central regulatory component of the reproductive system, as well as avoiding negative effects on the general metabolism and the metabolism of androgens. The duration of treatment is individual for each clinical case and primarily depends on normalization of androgen metabolism indicators and normalization of the reproductive organs state, as well as on the reduction in the LH level and the LH/FSH ratio during the first three months of therapy. The treatment should last for at least 4–6 months since this type of therapy has only a limited effect. Thus, the treatment led to a considerable reduction in the main androgens levels. The decrease in the LH concentration 5,19±1,12 mIU/ml and the values of LH/FSH 0,97±0,21 ($P < 0,05$) correlated with the decrease in testosterone concentration and ovarian volume (8,79±1,34 cm^3, $P < 0,05$) due to the suppression of LH-dependent synthesis of androgens. Besides, we revealed a strong direct correlation between the LH level on the one hand, and ovarian volume and the An level on the other hand (14 - 16).

In patients with CHA+LPD, the prevalent

component is abnormal steroidogenesis in adrenal glands. The increased functional capacity of the adrenal component gives rise to a resemblance of an unpronounced HA, which is seen as a slight increase in the main androgens levels. The hyperandrogenic state has a suppressive effect upon the growth and development of follicles in the ovaries, which causes a shrinkage of the preovulatory follicle down to 16,84±0,74 mm, ($P < 0,05$) on days 11–15 of the menstrual cycle, a shift of ovulation (days 16 – 18), low functional capacity of the yellow body — 17,53±0,57 mm ($P < 0.05$), a change in hormonal parameters (a decrease of the E2 level on days 5–7 — 157,77±16,12 pmol/l ($P < 0,05$), and a change in the P level on days 21–23 to 31,79±2,27 nmol/l, ($P < 0,01$). Apart from this, patients with CHA+LPD have typical insignificant dysfunctions of the reproductive system - menstrual dysfunctions in the form of dysmenorrhoea — 29,7%, premenstrual syndrome (PMS) — 53%, and metrorrhagia — 43% of all patients; they are clinical criteria of luteal phase deficiency.

In patients with LPD, we revealed a high incidence of reproductive losses — 32,4%, which was caused by miscarriage found in every fourth patient and progressed like a non-developing pregnancy till weeks 8–9 of gestation. It is common knowledge that this state is associated with the low functional capacity of the yellow body; chorionic gonadotrophin, whose important role consists in preventing regression and stimulating the work of the yellow body, starts to exert its effect only from days 12–14 after insemination. This statement proves a need for progestogenic therapy to ensure recovery of the yellow body functional capacity and, as a consequence, to maintain a wanted pregnancy (17, 18). The positive effect of this treatment pattern relies on normalization of folliculogenesis in the ovaries, which manifests itself in the growth of the preovulatory follicle (20,97±1,32 mm, $P < 0,05$) and the appearance of a functionally active yellow body (21,36±0,78 mm, $P < 0,05$). This treatment pattern led to the onset of pregnancy in 68,3% of the cases considered.

DISCUSSION

The therapy of CHA+LPD patients continued only until normalization of the level of androgens. The treatment combining hormonal contraceptives and progestogens made it possible to normalize the reproductive system function, increase the estradiol activity during the menstrual cycle and make the yellow body active.

The treatment of LPD and stimulation of ovulation in the CHA+A patients were conducted in accordance with the conventional scheme. Stage 1 involved prescription of COCs for 4 – 6 - 8 months. The exact duration of the course depended on normalization of the main indicators of PCOS: LH < 8, ovarian volume < 8 cm^3. In case of inefficiency after 4-6 months, the next stage (Stage 2) included stimulation of ovulation with Clostilbegyt (Clomiphene) in the daily dosage of 50 mg from day 5 till day 9 of the cycle; the course was repeated 2 - 3 times. Stage 3 included the use of gonadotropins (recombinant FSH) in the daily dose of 100 IU, combined with stimulation of physiological ovulation. When the reproductive system state was normalized, we determined the steroid profile parameters and evaluated the levels of estradiol and the main androgens (TT, FT, An, and DHT).

In case of the recovery of ovulatory cycles, the patients with anovulation and CHA are recommended to continue a therapy similar to that for patients with LPD - in order to normalize the functional capacity of the yellow body and the parameters of androgenic pathobolism, because, in accordance with the results of our study, some of the patients with CHA+A were moving to the CHA+LFD group (78,6%). Besides, the therapy in the CHA+A group helped to reduce the incidence of menstrual disorders; the most severe form of the dysfunction, amenorrhea, was not detected in any of the patients after the treatment (being 9,1% prior to it). Opsomenorrhea manifestations decreased to 12,4%. In case of preparing for pregnancy and infertility treatment, the therapy should continue to be given until pregnancy. The post-treatment fertility indicator (onset of pregnancy) for the patients from this group of CHA reached 66,7%; the mean duration of therapy was 7,62±0,64 months.

E2 belongs to the most biologically active compounds, its indicator is the key criterion determining the functional capacity of a female reproductive system (19). This fact can be confirmed by the results of our study, whereby in patients with CHA+LPD we revealed a hypo-estrogenic state (157,77±16,12 pmol/l) on days 5–7 that exacerbated the hyperandrogenic state. A low E2 level in patients with CHA+LPD determines high figures of the ratio between androgens and estrogens, which is clinically manifested as pronounced skin symptoms of a real HA (acne — 43%, hirsutism — 11,43±0,65

points). The results of these relations evaluation on days 5–7 of the menstrual cycle in the CHA+LPD group demonstrated higher values for the ratio DHT/E2 (10,51±1,02, P < 0,01) in comparison with the group of patients with CHA+A (DHT/E2 = 9,49±0.77). This parameter appreciably decreased in the second group (to 3.12±0,28, P < 0,01) and remained unaltered for the first group (8,87±1,78, P < 0,01) in the course of the menstrual cycle. It should be noted that in the course of the menstrual cycle, these values reduced almost two times due to a significant increase in E2 – 559,28±37,84 pmol/l (P < 0.01) (Figure 1).

According to the results of our study, in the course of a pathogenetic therapy, patients with CHA+LPD demonstrated a statistically significant decrease in the androgens levels and a noticeable rise in the E2 level (Figure 2).

Patients with a luteal phase deficiency require individual correction of their hyperandrogenic state by a therapy in combination with progestogens and natural progesterone analogs via a pattern standard for LPD cases (20). What confirms this statement in the first place is the fact that patients with an HA and infertility demonstrated both delayed ovulation periods (the mean duration of the menstrual cycle is 40,15±3,79 days) and the syndrome of an ovulating follicle, which can be detected only through ultrasound monitoring of folliculogenesis. The positive effect of this treatment pattern is reflected in the following processes: normalization of folliculogenesis in the ovaries, namely, the growth of the preovulatory follicle, the appearance of a functionally active yellow body, an increase in the E2 level on days 5–7 of the menstrual cycle and in the P level on days 21–23 (83,8%), and also the onset of pregnancy (68,4%). In the group of CHA+LPD patients undergoing pathogenetic therapy, we observed a statistically significant reduction in the following parameters: TT, FT, An, and DHT, as well as a noticeable increase in the E2 level both on days 5–7 and days 21–23 of the menstrual cycle, which was practically the same as in the control group. In addition to the considerable increase in the E2 level and reduction in the androgens level, we revealed a statistically significant decrease of their ratio values, which had a clinical manifestation in a better skin health (Figure 2).

The results of our study show that pregnancy started only in the cases of normalization of all androgen metabolism indicators (TT, FT, DHT, and An) and their ratios to estrogens (TT/E2, DHT/E2) in the fertility cycle. In early gestation (weeks 5–8), maintenance of pregnancy is possible only if the androgens levels are decreasing, while the concentrations of E2 and human chorionic gonadotrophin are rising. The results of this study give grounds to claim that the most important parameters in terms of diagnostics and treatment control are the indicators of the main androgens (TT, FT, An and DHT), the indicators of estradiol and progesterone measured dynamically during the menstrual cycle, as well as their ratio. Thus, it should be noted that hormone correction of diagnosed reproductive dysfunctions in both groups with CHA, with regard to androgen metabolism indicators and change in the hemostasis system, allows achieving normalization of hormonal values, menstrual function, and a sustained recovery of the reproductive system functional capacity.

CONCLUSIONS:

For patients with CHA+A, it is typical to demonstrate pronounced menstrual (opsomenorrhea with menstrual delays up to 2 months, and/or amenorrhea) and reproductive (hormonal infertility) dysfunctions; enlargement of ovaries > 9 cm3; an increase in the value of LH/FSH > 2 and in the main androgens levels (TT, FT, An). Androgen levels in patients with anovulation were greatly different from those in the control group both on days 5 – 7 and 21 – 23 of the menstrual cycle. Their level of E2 was not statistically changing in the course of the menstrual cycle, which, taking into account the low level of progesterone, confirms the presence of an anovulatory state.

Increased androgens levels in patients with CHA+A result from anovulation; besides, a progressive increase in the levels of sex steroids during the menstrual cycle exacerbates the anovulatory state, which manifests itself as the increased LH level and LH/FSH ratio, enlargement of ovaries with follicles sized 8 – 10 mm in diameter and absence of any dynamic changes of the E2 level and the value of P.

Patients with CHA+LPD tend to show such characteristics as minor menstrual dysfunctions (delayed ovulation). In their cases, miscarriage is caused by the lower functional activity of the yellow body, by changes of

hormonal parameters as well as by a pronounced hyperandrogenic state. The androgenic indicators in patients with LPD (tested on days 5 – 7 of the menstrual cycle) were practically similar to those of patients having anovulation (TT, FT, An, DHT) (21). However, in the course of the menstrual cycle, these indicators were close to the values of the control group, while the E2 and P levels became twice higher, which is the evidence of anovulatory cycle (Figure 1).

The hyperandrogenic state of patients with CHA+LPD has a suppressive effect upon the growth and development of follicles in the ovaries, which causes shrinkage of preovulatory follicles, a shift of ovulation, a low functional capacity of the yellow body, and a change in hormonal parameters (reduction of the E2 level on days 5 – 7 of the menstrual cycle and a decrease in the P level on days 21 – 23).

The efficacy of the treatment aimed at ensuring a functional recovery of the reproductive system in women with HA depends on the precise differential diagnosis of the HA character and on the state of the reproductive system.

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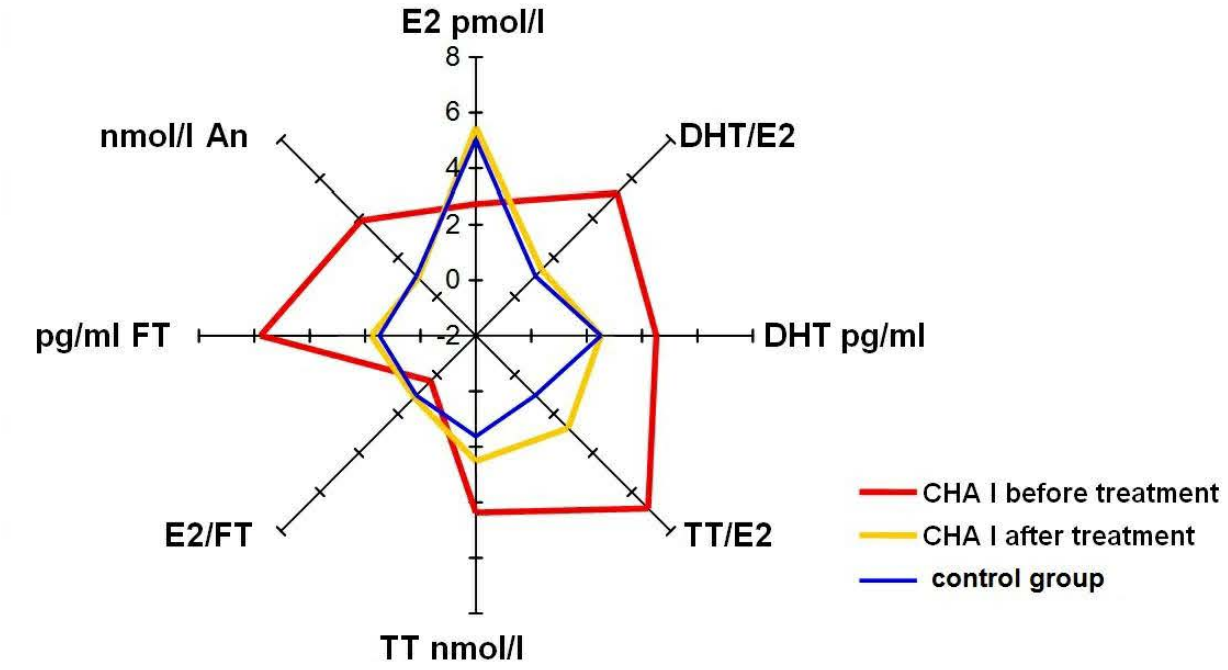
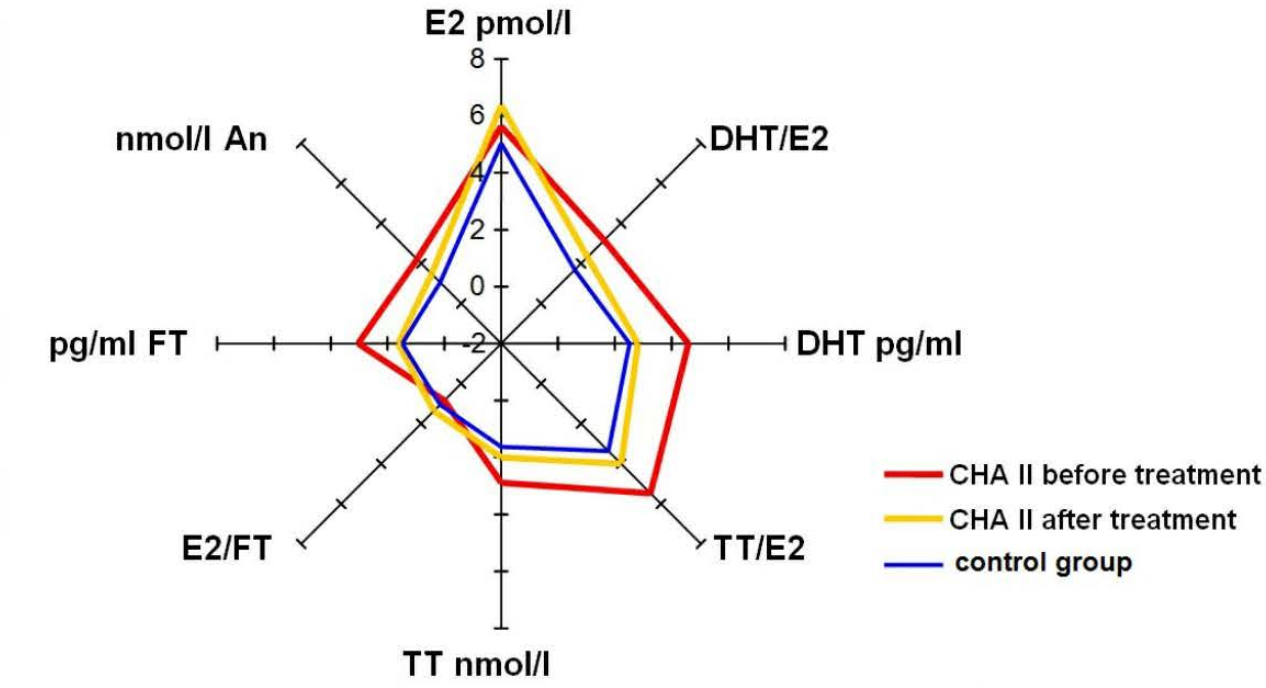
Figure 1. Steroid hormone indicators and their ratios in the group of patients with CHA and anovulation, before and after treatment, days 21–23 of the cycle.



CHA — combined hyperandrogenism; An — androstenedione; DHT — dihydrotestosterone; E2 — estradiol; FT — free testosterone; TT — total testosterone.

Figure 2. Steroid hormone indicators and their ratios in the group of patients with CHA and LPD before and after treatment, days 21–23 of the cycle.



CHA+LPD — combined hyperandrogenism + luteal phase deficiency; An — androstenedione; DHT — dihydrotestosterone; E2 — estradiol; FT — free testosterone; TT — total testosterone.