ORIGINAL ARTICLE

Recoverability of reproductive system in patients with concomitant hyperandrogenism

SAIDOVA, R. A.

ABSTRACT

Aim: To find out whether the influence of hyperandrogenic states on women's reproductive system depend on the source of the hyperandrogenism.
Design: The study was carried out from 2003 to 2010. 105 women were examined and treated in the study. As criteria of participants' inclusion, the clinical symptoms of hyperandrogenism were regarded: hirsutism, acne, and other signs of androgen-dependent dermopathy. At the next stage, laboratory criteria of hyperandrogenism were assessed: concentrations of total and free testosterone, androstenedione, dihydrotestosterone, and other hormones in the course of the menstrual cycle.
Methods: The hormonal panel tests were performed in the course of the menstrual cycle, assessing the level of secretion of peptide and steroid sex hormones. In addition to measuring quantitative indicators of these hormones, the qualitative indicators of such relation as progesterone/estradiol, total testosterone/estradiol, dihydrotestosterone/estradiol, estradiol/free testosterone, luteinizing hormone/follicle-stimulating hormone were considered. In order to exclude the cases of thyroid gland pathology, the levels of thyroid gland hormones in blood were tested. All the patients were examined for the non-hormonal homeostasis to reveal disorders of lipid storage and carbohydrate metabolism. The obtained data were statistically processed involving parametric and non-parametric methods.
Results: Adrenic hyperandrogenism exerts a negative effect on the processes of folliculogenesis, while ovarian hyperandrogenism is preconditioned by the anovulation state and can be stopped virtually completely with recovery of ovulation.
Conclusion: 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 hyperandrogenism. Individual pathogenesis-based therapy, considering the condition of the reproductive system, allows recovering ovulation and securing pregnancy against a background of normalization of androgen metabolism and other indicators of the functioning of the reproductive system.
Keywords: Hyperandrogenism, anovulation, luteal phase deficiency, androgens, infertility

INTRODUCTION

One of the urgent problems of today's gynaecological endocrinology is the early detection of women's reproductive dysfunctions in population. Hyperandrogenism (HA) remains among the leading causes for reproductive system pathology, which is found in 10–20% of all fertile age women of reproductive age.

The incidence of HA within the pattern structure of gynaecological disorders is as much as 1.3–4%[3,9,12]. In the literature we find a variety of definitions for the termof "hyperandrogenism", but most often the word is used for designating a set of symptomssyndrome pertaining toof disorders in the area of specific and metabolic effects of androgens in a female organism caused by the pathology of androgens biosynthesis, transportfer and metabolism[5,18,19,20]of androgen. The hHyperandrogenicsm syndrome is one of the most widespread causes for female reproductive disorders such as oligomenorrhea, anovulation and, as a consequence of themresult, infertility[9,13]. In addition to that, HA is presents in a complex of signs ofpointing to dermatoses and cutaneous appendage lesions (hirsutism, acne, alopecia, seborrhoea), collectively referred to as ""androgen-dependent dermopathy"[1,4,14]. It is common knowledge that in the female organismwomen androgens are produced in two places: inby both ovaries and in adrenal glands[10,12]. Detection of the source of HA presents considerable difficultiesposes great problems, while and diagnosis of a concrete clinical form of HA is a challenge, which is due to the polymorphism of the studied pathology and to the prevalence of its concomitant forms. Yet, distinguishing a particular form of HA is, beyond any doubt, essential for detecting the source of HA and prescribing an adequate, pathogenetically substantiated therapy[1,9,15]. As of today, the most common

Department of Obstetrics and Gynaecology, Medical and Preventive Faculty, I. M. Sechenov First State Medical University, 8 Trubetskaya str., 119991 Moscow, Russia
Correspondence to Dr. Saidova R.A. Tel: +74992480553, E-mail: editor3@academicpapers.org

pathology leading to the development of the HA syndrome is ~~regarded~~ considered to be polycystic ovary syndrome (PCOS). PCOS is ~~viewed~~ regarded as a pluriglandular, polygenic and polysymptomatic pathology, whose pathogenesis can be caused by disorders in both ~~the~~ central and peripheral parts of the reproductive system[8,13]. In many studies it has been established that about 10% of women having PCOS also demonstrate symptoms of congenital adrenal hyperplasia (CAH)[1,6,16]. ~~We have to~~It must be admitted that the ever-rising interest in the study of this pathology is limited by a number of difficulties, ~~to~~ which ~~belong such ones as~~include ~~HA's~~ heterogeneity and polymorphism of HA; this leads to considerable differences in diagnostic approaches, in the ~~analysis~~ treatment of ~~examination data~~diagnostic results and interpretation of clinical evidence, specifics of~~in~~ the course of disease~~'s characteristics~~ and ~~specification~~ choice of treatment policy. Until now, ~~much disputed has been and remains~~ the question of the cross-effects of the HA syndrome in a female organism and ~~of~~ reproductive system disorders remains disputed.

All ~~of the~~stated above ~~is only to confirm~~support the urgency of the problem and ~~to additionally convince us~~persuade of a need to improve our methods of examining HA patients, to search for optimal diagnostic criteria helping us identify precisely the form of HA, which surely is essential for prescribing an efficient~~,~~ pathogenetic therapy.

Goal of the study ~~=~~ was a comprehensive assessment of the state of the reproductive system and perfection of the principles of menstrual/reproductive function's recovery in patients with a combined form of HA.

MATERIALS AND METHODS

In this paper we present the results of an examination and treatment of 105 women, including the reference group, aged 19–37 y/o (mean age 27.39±0.75 years), 70 of whom had symptoms of androgen-dependent dermopathy, with laboratory results ~~proving~~ indicative of HA, i.e. increased levels of free testosterone (FT) and total testosterone (TT), increased levels of androstenedione (An) and dihydrotestosterone (DHT). Revealing a concomitant HA that shows evidence of both adrenic ~~HA~~ (increased DHEAS, 17-OHP and reduced cortisol (C)) and ovarian HA (LH >10mIU/L, LH/FSH >2, ~~ovaries'~~ ovarian volume > 9 cm^3, opsomenorrhea and primary sterility) makes it possible to determine the tactics of treatment.

When selecting research subjects for all study groups, we ~~withdrew~~ exclude ~~the cases of~~from consideration:

- thyroid disorders;
- hyperprolactinemia;
- Cushing disease;
- serious extragenital pathologies;
- hormonally active androgen-producing tumours of ovaries and adrenal glands;
- pathologies of the haemostasis system (genetic and acquired forms of thrombophilia)

The assessment of the patients'~~:~~ condition was carried out in compliance with a set of the HA diagnostic criteria:

- i~~I~~nitially, clinical symptoms of HA are assessed: the signs of androgen-dependent dermopathy of different intensity (acne, hirsutism, alopecia, etc.);
- t~~T~~hen the laboratory criteria of HA are assessed: increases in the level of the main androgens ~~—~~ TT, TF, An, and DHT;
- a~~A~~t last, a differential diagnostics~~is~~ of the source of HA is run~~made~~: adrenal, ovarian or concomitant.

Assessments of the reproductive function of patients with concomitant HA 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 ~~subject to~~depending on the form of their reproductive disorder:

Group I~~:~~ CHA+A:~~-~~ 33 women aged 19–37 (mean age 26.67±1.01) with anovular disorder of the reproductive system (menstrual cycle < 21 or > 35 days, endometrial thickness less than 6 mm or more than 12 mm, no yellow body in the ovaries, progesterone (P) level <15,9 nM/l on days 21–23 of the menstrual cycle).

Group II CHA+LPD:~~-~~ 37 women aged 20–38 y/o (mean age— 28.24±1.12) with luteal phase deficiency (menstrual cycle is~~-~~ 21–26 days, the length of the yellow body phase is~~-~~ less than 10 days; sonographically measured endometrial thickness is~~-~~ less than 10 mm and the size of yellow body ~~—~~ less than 20 mm; P level is~~-~~ 16–30 nM/l on days 21–23 of the menstrual cycle).

The reference group was comprised of 35 apparently healthy women of a fertile age (28.32±1.52 y/o) having a regular ovulatory menstrual cycle of 28–30 days with no symptoms of HA.

When analysing anamnestic data and the results of the physical examination, we considered the following parameters: age, ~~the status of~~ menstrual and reproductive functions, family history, anthropometric data including Ferriman-Gallwey hirsutism score, pelvic ultrasound, hormonal and non-hormonal state. The pelvic ultrasound was ~~done~~ performed for~~to~~ all the patients ~~as per~~in a standard way~~routine~~, dynamically, using the Sono-Ace-8000

Live equipment produced by 'Medison' (Korea), with two sensors, – abdominal and vaginal, at frequencies of, respectively, 5 MHz and 7.5 MHz, respectively. On days 5–7 of the menstrual cycle we assessed: womb size, ovarianes' volume, endometrial thickness, the number and size of follicles; we also registered paraplasms, if any; on days 21–23 of the cycle we measured the size of the yellow body and endometrial echo. Examinations of tThe hormonal panel tests were also done performed in the course of the menstrual cycle, on days 5–7 and 21–23, assessing the level of secretion of peptide sex hormones (follicle-stimulating hormone (FSH), luteinizing hormone (LH), prolactin) and steroid sex hormones: estradiol (E2), P, TT, TF, An, DHT, –17-hydroxyprogesterone (17-OHP), dehydroepiandrosterone sulphate (DHEAS), C, as well as sex steroid-binding globulin (SSBG). In addition to measuring quantitative indicators of these hormones, we considered the qualitative indicators of such relation as P/E2, GT/E2, DHT/E2, E2/FT, LH/FSH. In order to reject exclude the cases of thyroid gland pathology, we tested the levels of thyroid gland hormones in blood. All the patients were examined for tThe assessment of the non-/hormonal control of homeostasis was done on all the patients with the aim ofto revealing disorders of lipid storage and carbohydrate metabolism. The study of the haemostasis system was done performed at initial examinationpresentation and, dynamically, in the course of the treatment in 1, /3, and /6 months; it was aimed at diagnosing thrombophilic states (activated partial thromboplastin time, APPT, thrombocytes aggregation with different aggregation stimulators, fibrin monomers soluble complex, FMSC, D-dimer, and TAT complexes). The study was carried out using enzyme immunoassay and the 'Boehnringer ELISA-Photometr' spectrophotometer. For patients with pelvic inflammatory diseases, in order to specify the diagnosis, microbiological assays were taken from the posterior vaginal vault and the cervical canal, with control-ed tests taken in 3–4 weeks after termination of the therapy and during three menstrual cycles.

In order to correctFor the successful treatment of menstrual and reproduction disorders, and also as the first phase stage of stimulating ovulation in cases of concomitant HA, we implementedadministered a therapy by useconsisting of combined oral contraceptives (COCs) which containinged progestagens – dienogest and drospirenone, Janin et Jess («Bayer Shering Pharma»), Germany). As a hormonal support for the luteal phase of the menstrual cycle, we prescribed natural micronized progesterone – 'Outrogestan' 100 mg (Laboratoires BESINS INTERNATIONAL, France) in the total daily dose of 200–300 mg, and an analogue of the endogenous progesterone, – dydrogesterone 'Duphaston' («Solvay Pharma», Netherlands), – 10–14 days' regimen inwith the total daily dose of 10–20 mg. In order to reduce the manifestations of androgen-dependent dermopathy and also by way of correctingtreat the hormonal dysregulations, we administered dexamethasone in an individual daily dose of 0.125–0.5 mg. The outcomes of the treatment were evaluated in 3, /6, and /9 months. For sThe obtained data were statistically processeding of the datawith «SPSS–9.0 involving parametric and non-parametric methods». Differences between the groups of the patients were taken to be significant at $p < 0.05$.

RESULTS

Researches done by Russian and foreign colleagues in Russia and other countries strongly suggest that the assessment of the reproductive system status is to be carried outassessed only after withdrawal from the study of all the cases of serious physical, hormonal and infectious diseases which often are the causes for menstrual and reproductive dysfunctions are excluded from the study, because the adequate work of all levels and planes of the reproductive system is possible only under the conditions of physical and mental/emotional comfort, i.e. in a healthy female organism. Testing for only one marker – TT – is not, in our view, a sufficient criterion of HA, so making judgements about the presence of HA is can be postulated justified only after a simultaneous study of all substances actively participating in the metabolism of androgens (GT, FT, An, DHT) dynamically in the course of the menstrual cycle, in combination with clinical evidence and the assessment of the functional status of the reproductive system. Hyperandrogenic states assessed on days 5–7 of the menstrual cycle can seem more pronounced in patients with a prevalent ovarian component, because a of a considerable increase in the main androgens levels of the main androgens is detected: TT (3.75±0.31 nM/l, $p<0.05$), FT (6.03±1.12 pg/ml, $p<0.01$) and An. (16.27±5.24 nM/l, $p<0.01$). At the same time, we havethere are relatively standard values for the levels of E2=169.82±9.63 pmol/l ($p<0.05$) and DHT=318.29±30.59 pg/ml ($p<0,05$), which makes the real HA less significant. Besides, HA in the group of patients with a prevalence of the ovarian component is determined,results first and foremost, by from the anovulation state, which is confirmed by tests done on days 21–23 of the menstrual cycle: the level of P=2.32±0.41 nmol/l, ($p<0.01$), while the level of E2=275.19±26.6 pmol/l on days 21–23 and

169.82±9.63 pmol/l, (p<0.05) on days 5–7 of the menstrual cycle. The levels of the main androgens, – GT, FT, An, and DHT, – remained persistently high and practically the same as these evidence obtained on days 5–7 of the menstrual cycle. Having considered the levels of androgens and E2 individually, we also assessed their ratios (GT/E2, DHT/E2, and E2/FT), which were largely in excess of those from the reference group. At the same time, the maximum value for GT/E2 was detected in the group with CHA+A — 23.75±1.46 nmol/l, (p<0.05). The relation E2/FT's value was reliably low both in the group with CHA+A — 16.27±5.24 (p<0.01) and in the group with CHA+LPD — 14.15±1.43 (p<0.01); however, the reasons for such a low E2/FT were different: in the group with CHA+A, it was due to the pronounced increase of FT, while in the group with CHA+LFD, the reason was due to hyperestrogenism on days 5–7 of the menstrual cycle. The evidence found do agreeresults are in line with the opinion of some colleagues [5, 11, 12] who considering a hypothesis as to theof the role of adrenarche in the genesis of ovarian HA genesis. According to the hypothesis which ,assumes that the reticular zone of the adrenal cortex is being overstimulated, which leads to the intensified secretion of androgens and, consequently, to the extraglandular production of estrogens. The latter, in its turn, causes the increase in LH/FSH and the concomitant intensification of the secretion of androgens in the ovaries.

DISCUSSION

The increased levels of androgens are the results of anovulation, at the same time the progressive increase in the levels of sex steroids exacerbates the anovulatory state, which manifests itself as the rise in the LH value (9.12±0.76 mIU/l, p<0.01) and in the LH/FSH ratio (1.61±0.13, p<0.05), which rises two-fold to reach 2.99±0.32 (p<0,01) in the course of the menstrual cycle. Patients having CHA+A, in 69.2% of all cases demonstrate the increased volume of ovaries (14.23±1.16 cm^3, p<0.01), while the follicular ovaries apparatus on days 5–7 of the menstrual cycle contains follicles sized 8–10 mm in diameter (on average 8.37±0.62 mm) which release both estrogens and androgens to an equal degree, therewith supporting the normal-estrogen anovulatory state [6, 16, 17]. The clinical manifestationsaspects of reproductive disorder in the group of patients having CHA+A are manifested ininclude serious dysfunctions: the menstrual (opsomenorrhea — 60.6%, amenorrhea — 9.1%) and the reproductive one (sterility — 72.9%).

To treat patients having CHA+A we used, to start with, the simplest possible regimen of ovulatory stimulation by modern neutral metabolic COCs or the COCs which are not the derivatives of 19-norsteroids, because givingsince the latter exacerbate the HA state these medication toin the patients with CHA exacerbates the HA state. Administering COCs which contain such progestagens as dienogest and drospirenone allows us to both reduce the functional capacity of the ovaries and the LH level of LH due to the recovery of the central regulatory component of the reproductive system, and to avoid a detrimental effect upon the general metabolism and the metabolism of androgens as a whole. The length of treatment in each case of clinical observation is determined individually and depends, in the first place, by on the normalization of androgen metabolism indicators and of the state of reproductive system organs, and also by on the reduction in the LH level and the LH/FSH ratio during the first three months of therapy. If this type of therapy demonstrates has only a limited effect, the extent of exposuretreatment must be last minimum at least 4–6 months.

Thus, under pressure ofin the therapytreatment, we observe a considerable reduction in the main androgens levels of the main androgenswas observed: TT (2.16±0.24 nmol/l, p<0.01), FT (1.03±0.29 pg/ml, p<0.01), An (6.37±0.42 nmol/l, p<0.05), and и DHT (210.32±22.57 pg/l, p<0.05), which the values being were practically equal to those in the reference group. In connection with normalization of the reproductive system's central regulatory component of reproductive system and recovery of the active ovulatory menstrual cycles, we observed a considerable increase in the level of E2=547.24±55.38 pmol/l, (p<0.05) on days 21–23 of the menstrual cycle, and a reliable reduction in the relations: GT/E2=10.86±1.79 (p<0.05), DHT/E2=4.82±1.43 (p<0.05). Lowering of the LH concentration 5.19±1.12 mIU/l and of the values of LH/FSH 0.97±0.21 (p<0.05), which correlated with the decrease in testosterone concentration and ovarianes' volume (8.79±1.34 cm^3, p<0.05) due to the suppression of LH-dependent synthesis of androgens. In addition to this, we revealed a strong and direct correlation between the LH level on the one hand, and the ovarian volume of ovaries and the level of An level on the other[2].

In case of the recovery of ovulatory cycles, for patients having anovulation with underlying CHA, continuing it is indicated to carry on with the therapy similar to thate one administered to patients with LPD is indicated, in order to normalize the functional capacity of the yellow body and the parameters of pathobolism of androgens, because, in accordance with the results of our study, some of the patients with CHA+A moved to the CHA+LFD group (78.6%).

In addition to this, the therapy in the CHA+A group being administered, the incidence of menstrual disorders fell; at the same time, 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 only 12.4%. In case of preparing for pregnancy and infertility treatment, the therapy should continue to be given until the onset of pregnancy symptoms. The post-treatment fertility indicators of the patients in this group of CHA manifested themselves in the beginning of pregnancy for 66.7% of the women, the mean length of therapy having been 7.62±0.64 months.

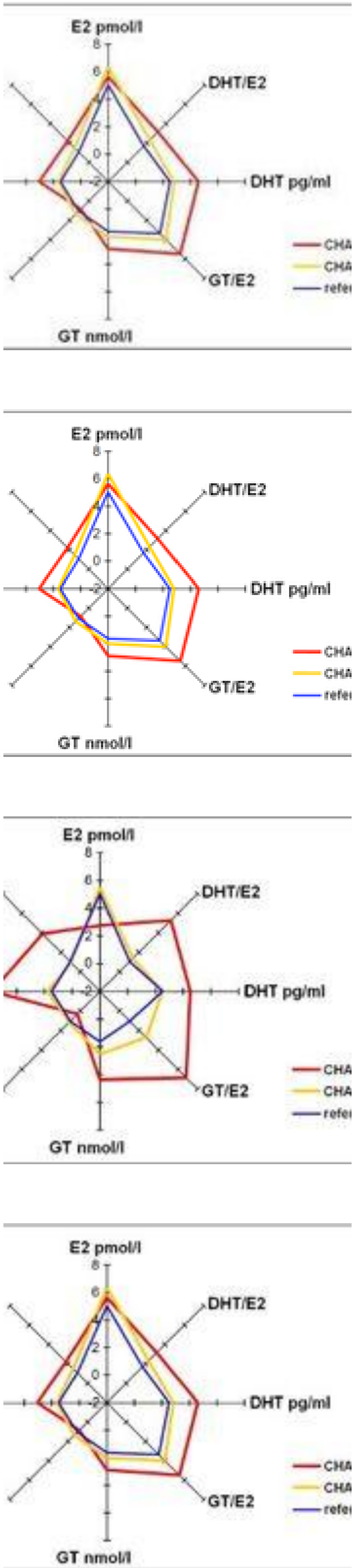
In patients having CHA+LPD, the prevalent component is the dysfunction of steroidogenesis in adrenal glands. The increased functional capacity of the adrenal component gives the appearance of an unpronounced HA, which manifests itself as an insignificant rise in the main androgensthe levels of the main androgens: TT (2.97±0,26 nmol/l, p<0.05), FT (3.21±0.18 pg/ml, p<0.05), An (10.67±0.53 nmol/l, p<0.05), and as a pronounced increase in the DHT level of DHT (448.17±11.49 pg/ml, p<0.01), the latter having a tendencywhich tends to rise in the course of the menstrual cycle DHT (458.52±20.29 pg/ml).

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 of the menstrual cycle), low functional capacity of the yellow body – 17.53±0.57 mm, (p<0.05), and a change in hormonal parameters (a fall of the E2 level on days 5–7 of the menstrual cycle – 157.77±16.12 pmol/l (p<0.05), and a decrease in the P level of P on days 21–23 of the menstrual cycle down to 31.79±2.27 nmol/l, (p<0.01)). Since patients with LPD demonstrated a prevalence of the adrenal component of HA, it seems reasonable to assess the parameters of sex steroid precursors: DHEAS and 17-OHP which were reliably in excess of the values detected in CHA+A patients. So, as the results of this study show, the level of DHEAS level was 7.19±0.87 mkmol/l (p<0.01), while the revealed value for 17-OHP was 5,76±0,24 nmol/l, which in the course of the menstrual cycle increased to 10.98±1.46 nmol/l (p<0.01). This nearly two-fold increase in the level of 17-OHP level in the course of the menstrual cycle was caused, in our view, by the rise in P concentration on days 21–23 of the menstrual cycle, which is actively released by the yellow body becoming eventually a link in the metabolism of the chain of androgens. Apart from this, it is typical of patients with CHA+LPD to have insignificant dysfunctions of the reproductive system, i.e.: menstrual dysfunctions in the form of dysmenorrhoea – 29.7%, premenstrual syndrome (PMS) – 53%, and metrorrhagia – 43% of all patients, which are clinical criteria of luteal phase deficiency.

E2 belongs to the most biologically active compounds, its indicator is the key criterion determining the functional capacity of a female reproductive system [4, 8]. This fact has been confirmed by the results of our study, whereby in patients with CHA+LPD we revealed a hyperestrogenic state (157.77±16.12 pmol/l) on days 5–7 of the menstrual cycle whichthat exacerbated the hyperandrogenic state. A low level of E2 level in patients having CHA+LPD determines high figures of the ratio between androgens and oestrogens, which has a clinical manifestation in pronounced skin symptoms of a real HA (acne – 43%, hirsutism – =11.43±0.65 points). The results of the assessment of these relations on days 5–7 of the menstrual cycle in the group having CHA+LPD demonstrated higher values for the ratio DHT/E2=10.51±1.02 (p<0.01) in comparison with the group of patients having CHA+A DHT/E2=9.49±0.77, which level 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. The lowest level of E2/FT=14,15±1,43, with respect to the reference group evidence (39.57±2.08, p<0.01). The GT/E2 ratio was 21.46±3.42 nmol/l, which is practically the same as that of the group with CHA+A and reliably higher than the reference group data – 6,74±0,38 (p<0,01). It should be noted that in the course of the menstrual cycle there took place a nearly two-fold reduction in these values due to a pronounced increase in this parameter: E2=559.28±37.84 pmol/l (p<0.01) (Fig. 1).

Figure 1.
An — androstenedione; CHA — concomitant hyperandrogenism; DHT — dihydrotestosterone; E2 — estradiol; FT — free testosterone; TT — total testosterone.

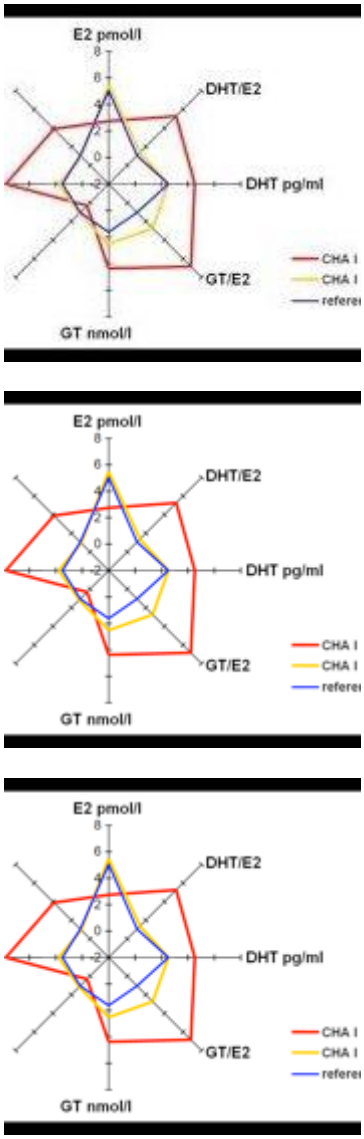
Fig. 1: Steroid hormone indicators and their ratios in the group of patients having CHA+Anovulation, before and after treatment, days 21–23 of the cycle.



For patients having LPD, we revealed a high incidence of reproductive losses — 32.4%, which was caused by the habitual miscarriage (HM) found in every fourth patient; this HM progressed like a non-developing pregnancy till weeks 8–9 of gestation. It is a common knowledge that this state is linked to a low functional capacity of the yellow body; at the same time, chorionic gonadotrophin, ~~–~~ whose important role ~~it is to~~consists in preventing regression and stimulating~~e~~ the work of the yellow body, ~~-~~ starts to exert its effect only from days 12–14 after insemination. This~~e~~ ~~above~~ statement ~~confirms~~ proves a need for ~~that a~~ progestogenic therapy ~~is necessary~~ to ensure recovery of the functional capacity of the yellow body and, as a consequence, the maintenance of a wanted pregnancy. The positive effect of this treatment regimen 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±0.78mm, p<0.05), with an increase in the ~~level of~~ E2 level (219.54±25.53 pmol/l, p<0.05) on days 5–7 of the menstrual cycle and a rise in the value of P (44.73±4.28 nmol/l, p<0.05) on days 21–23 of the menstrual cycle, and also ~~by~~ in the ~~start~~ beginning of pregnancy (68.3%).

According to the results of our study, ~~under pressure of~~in the course of a pathogenetic therapy ~~being administered~~, patients having CHA+LPD demonstrated a reliable decrease in the ~~levels of~~ androgens levels and a pronounced rise in the E2 level ~~of E2~~ 219.54±25.53 pmol/l on days 5–7 and 630.33±53.54 pmol/l on days 21–23 of the menstrual cycle, which was practically the same as those values for healthy non-hirsute women in the population. The ~~level of~~ TT level fell to 2.21±0.18 nmol/l (p<0.05); the FT level ~~of FT~~ was as much as 1.14±0.16 pg/ml, (p<0.01); the An level ~~of An~~ decreased and was no more than 6.32±0.83 nmol/l, (p<0.05); the DHT value reliably fell to 292.57±17.42 pmg/ml, (p<0.05) but still was in excess of the general population figures. Having in mind the significant decrease in the ~~level of~~ E2 level and a reliable fall of androgen values, we also observed a reduction in such relations as GT/E2 and DHT/E2, which clinically manifested itself in a better skin health (acne — in 22.3% of the patients and the intensity of hirsutism — 9.46±1.17 points) (Fig. 2).

Fig. 2: Steroid hormone indicators and their ratios in the group of patients having CHA+LPD before and after treatment, days 21–23 of the cycle.
An — androstenedione; CHA+LPD — concomitant hyperandrogenism + luteal phase deficiency; DHT — dihydrotestosterone; E2 — estradiol; FT — free testosterone; TT — total testosterone.



Patients with a luteal phase deficiency are in need of individual correction of their hyperandrogenic state in combination with a therapy by progestagens, the analogues of natural P, administered via a regimen that is standard for LPD cases. What confirms this statement in the first place is the fact that patients with an HA and sterility demonstrated both delayed ovulation periods (the mean length of the menstrual cycle is 40.15±3.79 days) and the syndrome of anovulating follicle, whose diagnosis is possiblewhich can be detected only through ultrasound monitoring of folliculogenesis. The positive effect of this treatment regimen relies on 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 level of E2 level on days 5–7 of the menstrual cycle and in the P level of P on days 21–23 of the menstrual cycle (83.8%), and also the start beginning of pregnancy (68.4%). In the group of patients having CHA+LPD, the pathogenetic therapy being administered, we observed a reliable reduction in the following values: GT, FT, An, and DHT, as well as a pronounced increase in the E2 level of E2 both on days 5–7 and days 21–23 of the menstrual cycle, which is practically the same as in the reference group. With due regard to the considerable increase in the E2 level of E2 and reduction in the androgens level of androgens, we revealed a reliable fall of their ratio values, which had a clinical manifestation in a better skin health (Fig. 2).

As the results of our study show, pregnancy started only in cases where a normalization of all androgen metabolism indicators took place (GT, FT, DHT, and An) along with their ratio to oestrogens (GT/E2, DHT/E2) in the fertility cycle. In the early stages of pregnancy (weeks 5–8 of gestation), the its maintenance of pregnancy is possible only if the levels of androgens levels are falling, at the background of a dynamic rise inwhile the concentrations of E2 and human chorionic gonadotrophin, HCG, are rising.

Thus, it should be noted that conducting a hormone correction of the diagnosed reproductive dysfunctions in both groups with CHA, with regard to the values of androgen metabolism indicators and to a change in the haemostasis system, allows us to achieve a normalization of the hormonal panel values and of the menstrual function, along with a sustained recovery of the reproductive system's functional capacity of the reproductive system.

CONCLUSION

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 cm^3; an increase in the value of LH/FSH > 2 and in the levels of the main androgens levels (GT, FT, An). Androgen levels in patients having anovulation were greatly different from these levels of androgens in the control group both on days 5–7 and 21–23 of the menstrual cycle; at the same time, the level of E2 in the course of the menstrual cycle did not change in a statistically significant manner, which in combination with a low P level of progesterone only confirms the presence of an anovulatory state.

Increased androgens levels of androgens in patients having CHA+A are the result froms of anovulation; at the same time, a progressive increase in the levels of sex steroids exacerbates the anovulatory state, which manifests itself as the

increased LH level ~~of LH~~, as the enlargement of ovaries with follicles sized 8–10 mm in diameter, and as the absence of any dynamic changes of the E2 level and the value of P^{21}.

Patients with CHA+LPD tend to exhibit such characteristics as minor menstrual dysfunctions (delayed ovulation); habitual miscarriage caused by the lowering of functional activity of the yellow body and by changes of hormonal parameters (a lower level of E2 157.77±16.12 pmol/l on days 5–7 of the menstrual cycle, and a reduction in P on days 21–23 ~~of the menstrual cycle~~ – 31.79 nmol/l); and also as a pronounced hyperandrogenic state[7]. Patients having LPD demonstrated androgenic indicators – tested on days 5–7 of the menstrual cycle – being ~~as~~ practically the same as those of patients having anovulation (GT, FT, An, DHT); in the course of the menstrual cycle, however, these indicators approximated to the values of the reference group, while the E2 and P levels rose twice, which is the evidence of an ovulatory cycle in action (Fig. 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 a shrinkage of the preovulatory follicle, a shift of ovulation, a low functional capacity of the yellow body, and a change in hormonal parameters (a fall of the E2 level on days 5–7 of the menstrual cycle and a decrease in the P level ~~of P~~ on days 21–23 ~~of the menstrual cycle~~).

The efficacy of the treatment aimed at ensuring a functional recovery of the reproductive system in women having HA ~~is~~ depend~~sent~~ on the precision of the differential diagnosis of the nature HA ~~and of its nature,~~ and on the ~~condition~~ state of the reproductive system.

REFERENCES

1. Arutunyan, E. M. Osnovnye printsipy diagnostiki i gormonal'noi korrektsii nadpochechnikovoi giperandrogenii u bolnykh s vrozhdennoi disfunktsiei kory nadpochechnikov [Diagnosis and hormonal correction of adrenal hyperandrogenism in patients with adrenogenital syndrome: basic principles]. PhD in medicine thesis. Moscow: I. M. Sechenov First State Medical University, 2009.
2. Carmina, E. Ovarian and adrenal hyperandrogenism. Ann. N Y Acad. Sci., 2006, 1092, p. 130-137.
3. Chernukha, G. E. Giperandrogenii i printsipy ikh terapii u zhenshch reproduktivnogo vozrasta [Forms of hyperandrogenism and principles of their treatment in women of reproductive age]. Meditsina, 2004, 3, s. 17-20.
4. Dobrokhotova, Yu. E., Dzhobava, E. M., Ragimova, Z. E., Gerasimovich, M. Yu. Sindrom giperandrogenii v praktike akushera-ginekologa, dermatologa i endokrinologa [Hyperandrogenism syndrome in the practice of obstetrician-gynaecologist, dermatologist, and endocrinologist]. Moscow: GEOTAR-MEDIA, 2009, 101 s.
5. Durinyan, E. R. Steroidogenez v nadpochechnikakh pri sindrome polikistoznykh yaichnikov [Steroidogenesis in adrenal glands at polycystic ovarian syndrome]. Problemy reprodukcii, 1997, 3, s. 18-22.
6. Guseynova, Z. S. Osobennosti profilaktiki sindroma poteri ploda u beremennykh s giperandrogeniei [Prevention of the fetal loss syndrome in pregnant women having hyperandrogenism]. PhD in medicine thesis. Moscow: I. M. Sechenov First State Medical University, 2011.
7. Islamova, Sh. N. Osnovnye printsipy differentsialnoy diagnostiki i taktiki vedeniya bolnykh s sochetannoi formoy giperandrogenii [Differential diagnosis and management of patients with concomitant hyperandrogenism: basic principles]. PhD in medicine thesis. Moscow: I. M. Sechenov First State Medical University, 2011.
8. Kulakov, V. I., Nazarenko, T. A., Kuzmichev, L. N., et al. Sravnitelnaya otsenka metodov lecheniya besplodiya u zhenshchin s SPKYa [Comparative assessment of therapies for infertility in women with the polycystic ovary syndrome]. Zhurnal ros. akushera i ginekologa, 2004, 1, s. 23-28.
9. Manukhin, I. B., Tumilovich, L. G., Gevorkyan, M. A. Klinicheskie lektsii po ginekologicheskoy endokrinologii [Clinical lectures on gynaecological endocrinology]. Moscow: GEOTAR-MEDIA, 2006, 316 s.
10. Moran, C., Azziz, R. 21-hydroxylase-deficient nonclassic adrenal hyperplasia: the great pretender. Semin Reprod Med., 2003, 21, p. 295-300.
11. Nazarenko, T. A. Zhenskoe besplodie, obuslovlennoe narusheniyami protsessa ovuljatsii: klinika, diagnostika i lechenie [Female infertility caused by ovulatory dysfunctions: clinical evidence, diagnosis, treatmen]. Abstract of Dr.habil. of medicine thesis. Moscow: Russian Scientific Centre for Obstetrics, Gynaecology and Perinatology, 1998.
12. Ovsyannikova, T. V., Fanchenko, N. D., Speranskaya, N. V., Glazkova, O. I. Osobennosti funktsii kory nadpochechnikov u bolnykh s khronicheskoy anovulyatsiey i giperandrogeniey [Specific characteristics of the adrenal cortex's functioning in patients with chronic anovulation and hyperandrogenism]. Problemy reprodukcii, 2001, 1, s. 30-35.
13. Pershina, E. V. Otsenka i printsipy korrektsii narusheniy reproduktivnoy sistemy u bolnykh s sochetannoy formoy giperandrogeniy [Reproductive system disorders in patients with concomitant hyperandrogenism: assessment and basic principles of correction]. PhD in medicine thesis. Moscow: I. M. Sechenov First State Medical University, 2011.
14. Rebora, A. Pathogenesis of androgenetic alopecia. Journal of the American Academy of Dermatology, 2004, 50, p. 777-779.
15. Saidova, R. A., Arutyunyan, E. M., Pershina, E. V., et al. Osnovnye printsipy lecheniya bolnykh s razlichnymi formami giperandrogeniy [Basic principles for treatment of patients having different forms of hyperandrogenism]. Zhurnal akusherstva i zhenskikh bolezney, 2009, 1, s. 84-91.
16. Saidova, R. A., Makatsariya, A. D. Izbrannye lektsii po ginekologii [Selected lectures on gynaecology]. Moscow: Triada-X, 2005, 256 s.
17. Saidova, R. A., Vorobyeva, E. V., Monastyrnaya, O. A. Znachenie otsenki sostoyaniya reproduktivnoy sistemy v lechenii besplodiya zhenshchin pozdnego reproduktivnogo vozrasta [The importance of reproductive system status assessment for the treatment of infertile women in late reproductive age]. Ginekologiya, 2012, 14, 2, s. 69-74.
18. Serov, V. N., Prilepskaya, V. N., Ovsyannikova, T. V. Ginekologicheskaja jendokrinologija [Gynaecological endocrinology]. 2nd ed. Moscow: MedPress, 2006, 520 s.
19. Smetnik, V. P., Tumilovich, L. G. Neoperativnaya ginekologiya [Non-operative treatment in gynaecology]. Moscow: Medical Press Agency, 2005, 629 s.
20. Vikhlyaeva, E. M. (ed). Rukovodstvo po endokrinnoy ginekologii [Gynaecological endocrinology: a manual]. Moscow: Meditsinskoe informatsionnoe agentstvo, 1997, 768 s.
21. Vorobyeva, E. V. Otsenka sostoyaniya reproduktivnoi sistemy

v optimizatsii printsipov lecheniya endokrinnykh form besplodiya u zhenshchin pozdnego reproduktivnogo vozrasta [Assessment of the reproductive system status and its role in improving the strategy of treating endocrine forms of infertility in late reproductive-age women]. PhD in medicine thesis. Moscow: I. M. Sechenov First State Medical University, 2012.