CHANGES IN SEXUAL FUNCTIONING IN WOMEN OF REPRODUCTIVE AGE WITH INFERTILITY AND DIMINISHED OVARIAN RESERVE

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Androgens play a key role in the physiology of the female body and the reproductive system. Androgen receptor expression in the various tissues points to the importance of androgens in the regulation of the female sexual and social functioning. The study aimed to evaluate sexual functioning in women with infertility and diminished ovarian reserve (DOR) using the Female Sexual Functioning Index questionnaire (FSFI). A cross-sectional study of 496 patients with infertility and DOR assessed the degree of sexual dysfunction in conjunction with the changes in the androgenic profiles as indicated by the androstenedione levels in the blood serum. Women with infertility and DOR were significantly more likely to report changes in sexual functioning, including a decrease in libido and in the quality and frequency of sexual relations. Furthermore, patients with normal androstenedione levels generally significantly outscored patients with decreased androstenedione levels (average questionnaire scores 21.2 ± 7.2 and 15.17 ± 3.0 respectively), indicating a lesser degree of sexual dysfunction in the former group; on the other hand, the latter group reported increased pain and decreased attraction, arousal, lubrication, orgasm, and satisfaction. Hormonal profile changes in patients with DOR, including decreased androstenedione levels, significantly impact sexual functioning, and their detection in clinical practice will allow to objectify complaints at an earlier state in order to assess the severity of sexual dysfunction and determine further personalized management tactics.

Keywords: androgens, androgen deficiency, reproductive age, infertility, diminished ovarian reserve, ART, questionnaire, sexual dysfunction, FSFI

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ВЛИЯНИЕ ГОРМОНАЛЬНОГО СТАТУСА НА СЕКСУАЛЬНУЮ АКТИВНОСТЬ ЖЕНЩИН РЕПРОДУКТИВНОГО ВОЗРАСТА С БЕСПЛОДИЕМ

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Андрогены играют одну из ключевых ролей в физиологии женского организма и репродуктивной системы. Экспрессия андрогенных рецепторов в различных тканях свидетельствует о важной роли андрогенов в регуляции сексуального и социального функционирования женщин. Целью исследования было оценить сексуальное функционирование у женщин с бесплодием и сниженным овариальным резервом (СОР) по результатам опросника «Индекс женской сексуальной функции» (Female Sexual Function Index, FSFI). В одномоментном исследовании у 496 пациенток с бесплодием и СОР провели оценку нарушений сексуального функционирования и их взаимосвязи с изменениями андрогенного профиля, основанного на концентрации андростендиона в сыворотке крови. Женщины с бесплодием при СОР статистически значимо чаще отмечали изменение сексуального функционирования, в том числе снижение способности и частоты сексуальных отношений, либидо. Для женщин с бесплодием и измененным овариальным резервом с нормальным уровнем андростендиона характерен суммарно больший общий балл (21,2 ± 7,2), что говорит о меньшей степени выраженности нарушений сексуального функционирования по сравнению с группой со сниженным уровнем андрогенов, средний балл в которой статистически значимо ниже (15,17 ± 3,0). Кроме того, наблюдаются снижение влечения, возбуждения, удовлетворения, оргазма, любрикации и увеличение болевых ощущений. Изменение гормонального профиля у пациенток с СОР и снижением уровня андрогенов вносит значимый вклад в сексуальное функционирование, и его выявление в клинической практике позволит на более раннем этапе провести объективизацию жалоб и оценить выраженность сексуальных нарушений у молодых женщин с бесплодием с целью определения дальнейшей персонифицированной тактики ведения.

Ключевые слова: андрогены, андрогенный дефицит, репродуктивный возраст, бесплодие, сниженный овариальный резерв, ВРТ, опросник, сексуальное функционирование, FSFI

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Many modern women prioritize career development and then partner choice in their lifestyle; the decision to have a child is made later in life, by the age of 35–38 years, as dictated by changes in levels of reproductively significant hormones before the occurrence of disturbances in the menstrual rhythm. This hormonal profile change clinically manifests by the age of 40 years. It is associated with changes in folliculogenesis and contributes to the structure of infertility [1], which is defined by the inability to achieve pregnancy after at least a year of regular sexual intercourse. In women with diminished ovarian reserve (DOR), changes in sexual functioning are associated with the anti-Müllerian hormone (AMH) levels.

Androgens, which form certain behavioral features including sexual functioning, most prominently so in males, play a major role in folliculogenesis. The production of androgens under the influence of the luteinizing hormone (LH) stimulates the appearance of follicle-stimulating hormone (FSH) receptors on granulosa cells. The process of differentiation and maturation

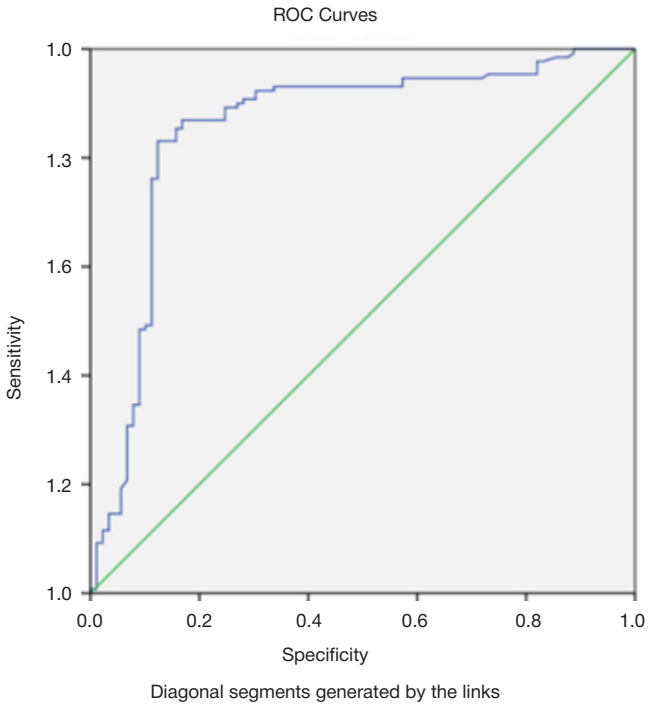

Fig. ROC curve for androstenedione

of follicles, especially in FSH-dependent early antral stages, likewise involves androgens [2].

Expression of androgen receptors (AR) in the various tissues, such as the central nervous system and reproductive organs, indicates the importance of androgens in the regulation of the female sexual and social functioning. Gonadectomy leads to changes in hippocampal neuroplasticity, depressive behavior, and suppression of sexual motivation.

The brain is among the main targets for sex hormones, both for estradiol as a central modulator of sexual desire, and for testosterone, the so-called "king" of sexuality. Androgens are instrumental in maintaining all phases of sexual functioning and significantly impact many neural and behavioral functions through both genomic and non-genomic effects [3].

ARs in the medial preoptic region of the hypothalamus, the region of the brain that regulates sexual behavior, have a high affinity for dihydrotestosterone (DHT). The neuroendocrine mechanisms underlying the effect of testosterone on female sexual functioning are studied through direct stimulation of ARs or through conversion of androgens to estrogens and subsequent binding to estrogen receptors [4].

Androstenedione (A) is a precursor of androgens (including testosterone) and estrogens in the body. Due to the difficulties in determining the level of androgens and the absence of lower reference values in women of reproductive age, focus on androstenedione levels is an acceptable approach to androgenic profile analysis in patients with DOR.

The Female Sexual Function Index questionnaire (FSFI) is commonly used to assess sexual functioning in women, and allows assessment of the severity of sexual dysfunction caused by low androgen levels [5, 6].

All of the above led to the current study, which aimed to assess the severity of sexual dysfunction in patients with infertility and DOR with psychodiagnostic testing.

METHODS

The cross-sectional study with a parallel group design enrolled 496 female patients aged 18–42 years with confirmed infertility and DOR. Exclusion criteria: surgical menopause (bilateral oophorectomy or hysterectomy); hormone-producing tumors; body mass index (BMI) ≤ 18 kg/m^2 or ≥ 30 kg/m^2; HIV and other immunodeficiency conditions; rheumatic diseases; immunomodulatory therapy; glucocorticoids, combined oral contraceptives, other hormonal drugs; intrauterine contraception; oncological diseases; pregnancy and lactation. Medical history collection accounted for current age, age of menopause onset in the mother, and BMI.

The hormonal profile was determined by immunochemiluminescent analysis (ICLA). ROC analysis was performed for all hormones, with AUC > 0.6 as the primary criterion for prognostic significance. The sensitivity and specificity of the models were calculated using logistic regression for use as prognostic factors for low androgen levels. The concentration of androstenedione turned out to be the most prognostically significant parameter (cut off point = 7.034) (see Fig.).

Patients were assigned into groups depending on A levels based on the results of the hormone analysis: group 1 — 256 women with reduced A levels (≤ 7.0 nmol/l), group 2 — 240 women with normal A levels (> 7.0 nmol/l).

Female sexual functioning was assessed in six domains: attraction, arousal, lubrication, orgasm, satisfaction, and pain. Domain-specific scores were calculated for each domain by multiplying the initial score (0(1)–5) by a factor, with the sum of scores in all six domains as the total score. Each patient answered the questionnaire twice with an interval of one month in order to confirm the result. The threshold value for healthy women with no sexual dysfunction is 29 points; a low total score corresponds to more pronounced sexual dysfunction [5, 6].

Statistical data processing was performed using the statistical software package Statistica V10 (StatSoft Inc.; USA). The type of quantitative data distribution was determined using the Kolmogorov-Smirnov test and graphical analysis of the data before conducting comparative analysis. For normal data distribution, the mean value (M) with standard deviation (SD) was calculated; the differences between the two groups were assessed with t-test. For data distribution patterns differing from normal, the median and interquartile range were determined; the differences between the two groups were assessed with the Mann–Whitney U test. The differences were considered statistically significant at $p < 0.05$.

RESULTS

The study participants were women of reproductive age with infertility and DOR who applied to achieve pregnancy in the IVF/ICSI program at the Kulakov National Medical Research Center for Obstetrics, Gynecology and Perinatology, Moscow, Russia. The average age of the women was 37.3 ± 2.4 years. All patients had a regular menstrual cycle with the average duration of 27.4 ± 2.1 days. All patients demonstrated a high level of intelligence and social responsibility.

30% of the patients had a history of surgical interventions (appendectomy or diagnostic laparoscopy, including linked with tubal-peritoneal factor). One in three patients noted a history of ureaplasma parvum while providing information on past inflammatory and infectious diseases of the genital organs. On average, more than three programs of assisted reproductive technologies (ART) (IVF and cryoprotocol) terminating with a negative result at the stage of hormonal verification of pregnancy were noted in medical history. The duration of infertility was 6.8 ± 5.9 years; 349/496 (70.6%) patients had primary infertility. 2.7 ± 2.2 ART cycles were performed. A history of pregnancies ending in childbirth was noted in 49/147 (33.3%) patients;

Table 1. Hormonal characteristics of patients in the study group

n = 496	A ≤ 7.0 nmol/l (*n* = 256)	A > 7 nmol/l (*n* = 240)	*p*
LH, mIU/ml	5.3 (2.8–8.3)	5.1 (3.2–9.8)	0.112
FSH, mIU/ml	7.9 (6.3–9.5)	6.7 (4.6–8.8)	0.1009
T_{tot}, nmol/l	0.7 (0.5; 1.2)	1.1 (0.6; 1.7)	0.0586
T_{fr}, pg/ml	1.7 (0.6; 2.1)	2.1 (0.7; 3.3)	0.4696
DHT, pg/ml	294 (152; 554)	269 (201.5; 422.0)	0.0768
DHEAS, μmol/l	4.5 (2.4; 6.8)	4.6 (2.6; 7.7)	0.2019
17-OP, nmol/l*	2.2 (1.0; 4.3)	3.15 (2.3; 3.8)	0.0174
A, nmol/l*	4.5 (2.5; 7.0)	8.9 (7.1; 11.6)	< 0.001
AMH, ng/ml*	1.0 (0.4; 4.2)	2.7 (1.3; 5.6)	< 0.001

Note: data presented as median (lower and upper quartile); * — Mann–Whitney test, $p < 0.05$; LH — luteinizing hormone; FSH — follicle-stimulating hormone; T_{tot} — total testosterone; T_{fr} — free testosterone; DHT — dihydrotestosterone; DHEAS - dehydroepiandrosterone sulfate; 17-OP — 17-hydroxyprogesterone; A — androstenedione; AMH — anti-Müllerian hormone.

medical abortion for various indications in 28/147 (19%) patients; pregnancy terminations in the early stages (6–7 weeks gestation) in 52/147 (35.4%) patients. BMI in patients was 24.6 ± 5.4 kg/m^2.

The hormonal profile analysis revealed statistically significant differences in 17-OP, A, and AMH levels between the study groups (Table 1).

All patients were tested to assess sexual functioning. Women with infertility and DOR at A > 7.0 nmol/l generally scored higher (21.2 ± 7.2), indicating a lesser degree of sexual dysfunction. In the group with A ≤ 7.0 nmol/l, the average score was significantly lower (15.17 ± 3.0). Domain-specific scores for attraction, arousal, lubrication, orgasm, and satisfaction were higher in the former study group; the domain-specific score for pain was higher in the latter study group.

The questionnaire data links laboratory-confirmed A < 7,0 nmol/l to sexual dysfunction in women with infertility and DOR (Table 2).

DISCUSSION

The study aimed to determine the severity and prevalence of sexual dysfunction in patients of reproductive age with infertility and DOR.

The tissues with androgen receptors, including those in the nervous system, are the first to respond to changes in androgen levels, which corresponds to the areas of sexual dysfunction identified in our study, such as decrease in libido, in amount and quality of orgasms, and in satisfaction with intercourse [7].

Female sexual dysfunction is multifaceted; its occurence depends on the age and ethnicity of the woman. In a study of 1749 patients aged 18-59 years, sexual dysfunction was found more often in women (43%) than in men (31%) [8]. With the rhythm of the menstrual cycle remaining the same, the number of antral follicles and AMH decreases, and estrogen levels depend on the presence of a leading follicle. Hypoestrogenism occurs close to the menopausal period, while a reduced level of androgens, in particular dehydroepiandrosterone (DHEA), manifests long before the onset of menopause. Numerous studies show a reduced level of DHEA (which has weak androgenic activity and is involved in sex hormone synthesis) observed in women as young as 30 years [9].

Reduced synthesis of sex steroids in the blood serum, as an additional component to the sexual dysfunction, further aggravates the psychological discomfort of a woman [10]. We show that sexual dysfunction is more common in patients with low androgen levels. In particular, problems in all domains covered by the FSFI questionnaire, including decrease in arousal and libido, are significantly more frequent. These results are consistent with those of another study where low androgen levels were found in post-menopausal women and linked with a decrease in libido with a relative preservation of physiological mechanisms of sexual function [11].

In our study, decrease in sexual functioning correlated with low levels of AMH, 17-OP, and androsteneodine. Similarly, a study of women with hypoactive sexual dysfunction revealed significantly lower levels of two testosterone precursors, A and DHEA-C. Other authors likewise associate the existing relationship between low androgen levels and sexual desire with DHEAS levels [12].

Use of estrogens as part of menopausal hormone therapy (MHT) in postmenopausal women is associated with slight improvement in sexual functioning without effect on libido [13], while in a randomized placebo-controlled study during combined MHT with testosterone medications in postmenopausal women, resulting normalization of levels

Table 2. Comparative assessment of the women's sexual functioning according to the FSFI questionnaire data (M ± SD)

	A ≤ 7.0 nmol/l (*n* = 256)	A > 7 nmol/l (*n* = 240)	*p*
Attraction*	2.58 ± 0.95	3.45 ± 1.55	0.003
Arousal*	2.15 ± 0.8	2.98 ± 1.39	0.003
Lubrication*	2.88 ± 0.49	3.96 ± 0.87	< 0.001
Orgasm*	2.4 ± 0.8	3.48 ± 1.36	< 0.001
Satisfaction*	2.68 ± 0.98	3.54 ± 1.43	0.002
Pain*	2.45 ± 1.0	3.79 ± 1.26	< 0.001
Total*	15.17 ± 3.0	21.2 ± 7.2	< 0.001

Note: * — Student's *t*-test, $p < 0,05$.

of total and free testosterone was linked to improved sexual functioning, including sexual satisfaction, general well-being, and mood [14], which also confirms the role of androgens in maintaining sexual functioning.

Decreased levels of androgens contribute significantly (possibly decisively) to impaired sexual functioning. It is not always possible to determine the early changes in the androgenic profile using only laboratory data, since clinical diagnosis is generally retrospective, when the changes are already pronounced [15]. The probable decrease in the concentration of sexual receptors may also narrow the window of therapeutic possibilities.

CONCLUSIONS

Psychodiagnostic testing conducted in women of reproductive age with infertility and DOR using the FSFI questionnaire allows to identify changes in sexual functioning and can be considered a method for early assessment of androgen levels. The impaired sexual functioning in women with infertility and DOR is associated with a physiological decrease in the levels of androstenedione as a testosterone and estradiol precursor and is pathogenetically explained by a decrease in the functional activity of the ovaries and low androgen levels. Further research into timely personalized treatment strategies is required.

References

1. Kirschner AA, Bardin CW. Androgen production and metabolism in normal and virilized women. Metabolism. 1972; 21 (7): 667–88. DOI: 10.1016/0026-0495(72)90090-x.
2. Lenie S, Smitz J. Functional AR signaling is evident in an in vitro mouse follicle culture bioassay that encompasses most stages of folliculogenesis. Biol Reprod. 2009; 80 (4): 685–95. DOI: 10.1095/biolreprod.107.067280. Epub 2008 Dec 10. PMID: 19074005.
3. Bramen JE, Hranilovich JA, Dahl RE, Chen J, Rosso C, Forbes EE, et al. Sex matters during adolescence: testosterone-related cortical thickness maturation differs between boys and girls. PLoS One. 2012; 7 (3): e33850. DOI: 10.1371/journal.pone.0033850. Epub 2012 Mar 29. PMID: 22479458; PMCID: PMC3315517.
4. Cappelletti M, Wallen K. Increasing women's sexual desire: the comparative effectiveness of estrogens and androgens. Horm Behav. 2016; 78: 178–93. DOI: 10.1016/j.yhbeh.2015.11.003. Epub 2015 Nov 14.
5. Rosen R, Brown C, Heiman J, Leiblum S, Meston C, Shabsigh R, et al. The Female Sexual Function Index (FSFI): a multidimensional self-report instrument for the assessment of female sexual function. J Sex Marital Ther. 2000; 26 (2): 191–208. DOI: 10.1080/009262300278597. PMID: 10782451.
6. Stenyaeva NN, Khritinin DF, Chausov AA. Ginekologicheskie zabolevaniya kak prediktory zhenskoj seksual'noj disfunkcii. Ginekologiya. 2021: 2. Russian.
7. Poletti A, Martini L. Androgen-activating enzymes in the central nervous system. J Steroid Biochem Mol Biol. 1999; 69 (1–6): 117–22. DOI: 10.1016/s0960-0760(98)00150-2. PMID: 10418985.
8. Laumann EO, Paik A, Rosen RC. Sexual dysfunction in the United States: prevalence and predictors. JAMA. 1999; 281: 537–44.
9. Goncharov NP, Dedov II, Gavisova AA, Sukhikh GT. Ehndokrinnaya sistema cheloveka v razlichnye periody ego zhizni. M.: Izdatel'stvo Adamant, 2020. Russian.
10. Graziottin A, Serafini A, Palacios S. Aetiology, diagnostic algorithms and prognosis of female sexual dysfunction. Maturitas. 2009; 63 (2): 128–34. DOI: 10.1016/j.maturitas.2009.04.007. Epub 2009 Jun 2. PMID: 19493639.
11. Bemesderfer S. A revised psychoanalytic view of menopause. J Am Psychoanal Assoc. 1996; 44 Suppl: 351–69. PMID: 9170070.
12. Worboys S, Kotsopoulos D, Teede H, McGrath B, Davis SR. Evidence that parenteral testosterone therapy may improve endothelium-dependent and -independent vasodilation in postmenopausal women already receiving estrogen. J Clin Endocrinol Metab. 2001; 86 (1): 158–61. DOI: 10.1210/jcem.86.1.7103. PMID: 11231994.
13. Nastri CO, Lara LA, Ferriani RA, Rosa-E-Silva AC, Figueiredo JB, Martins WP. Hormone therapy for sexual function in perimenopausal and postmenopausal women. Cochrane Database Syst Rev. 2013; (6): CD009672. DOI: 10.1002/14651858.CD009672.pub2. PMID: 23737033.
14. Davis SR, Goldstat R, Papalia MA, Shah S, Kulkarni J, Donath S, et al. Effects of aromatase inhibition on sexual function and well-being in postmenopausal women treated with testosterone: a randomized, placebo-controlled trial. Menopause. 2006; 13 (1): 37–45. DOI: 10.1097/01.gme.0000168061.32917.83. PMID: 16607097.
15. Bachmann G, Bancrofti J, Braunstein G, Burger H, Davis S, Dennesrtein L. Female androgen insufficiency: the Princeton consensus statement on definition, classification, and assessment. Fertil Steril. 2002; 77 (4): 660–5. DOI: 10.1016/s0015-0282(02)02969-2.

Литература

1. Kirschner AA, Bardin CW. Androgen production and metabolism in normal and virilized women. Metabolism. 1972; 21 (7): 667–88. DOI: 10.1016/0026-0495(72)90090-x.
2. Lenie S, Smitz J. Functional AR signaling is evident in an in vitro mouse follicle culture bioassay that encompasses most stages of folliculogenesis. Biol Reprod. 2009; 80 (4): 685–95. DOI: 10.1095/biolreprod.107.067280. Epub 2008 Dec 10. PMID: 19074005.
3. Bramen JE, Hranilovich JA, Dahl RE, Chen J, Rosso C, Forbes EE, et al. Sex matters during adolescence: testosterone-related cortical thickness maturation differs between boys and girls. PLoS One. 2012; 7 (3): e33850. DOI: 10.1371/journal.pone.0033850. Epub 2012 Mar 29. PMID: 22479458; PMCID: PMC3315517.
4. Cappelletti M, Wallen K. Increasing women's sexual desire: the comparative effectiveness of estrogens and androgens. Horm Behav. 2016; 78: 178–93. DOI: 10.1016/j.yhbeh.2015.11.003. Epub 2015 Nov 14.
5. Rosen R, Brown C, Heiman J, Leiblum S, Meston C, Shabsigh R, et al. The Female Sexual Function Index (FSFI): a multidimensional self-report instrument for the assessment of female sexual function. J Sex Marital Ther. 2000; 26 (2): 191–208. DOI: 10.1080/009262300278597. PMID: 10782451.
6. Стеняева Н. Н., Хритинин Д. Ф., Чаусов А. А. Гинекологические заболевания как предикторы женской сексуальной дисфункции. Гинекология. 2021: 2.
7. Poletti A, Martini L. Androgen-activating enzymes in the central nervous system. J Steroid Biochem Mol Biol. 1999; 69 (1–6): 117–22. DOI: 10.1016/s0960-0760(98)00150-2. PMID: 10418985.
8. Laumann EO, Paik A, Rosen RC. Sexual dysfunction in the United States: prevalence and predictors. JAMA. 1999; 281: 537–44.
9. Гончаров Н. П., Дедов И. И., Гависова А. А., Сухих Г. Т. Эндокринная система человека в различные периоды его жизни. М.: Издательство АдамантЪ, 2020.
10. Graziottin A, Serafini A, Palacios S. Aetiology, diagnostic algorithms and prognosis of female sexual dysfunction. Maturitas. 2009; 63 (2): 128–34. DOI: 10.1016/j.maturitas.2009.04.007. Epub 2009 Jun 2. PMID: 19493639.
11. Bemesderfer S. A revised psychoanalytic view of menopause. J Am Psychoanal Assoc. 1996; 44 Suppl: 351–69. PMID: 9170070.

12. Worboys S, Kotsopoulos D, Teede H, McGrath B, Davis SR. Evidence that parenteral testosterone therapy may improve endothelium-dependent and -independent vasodilation in postmenopausal women already receiving estrogen. J Clin Endocrinol Metab. 2001; 86 (1): 158–61. DOI: 10.1210/jcem.86.1.7103. PMID: 11231994.
13. Nastri CO, Lara LA, Ferriani RA, Rosa-E-Silva AC, Figueiredo JB, Martins WP. Hormone therapy for sexual function in perimenopausal and postmenopausal women. Cochrane Database Syst Rev. 2013; (6): CD009672. DOI: 10.1002/14651858.CD009672.pub2. PMID: 23737033.
14. Davis SR, Goldstat R, Papalia MA, Shah S, Kulkarni J, Donath S, et al. Effects of aromatase inhibition on sexual function and well-being in postmenopausal women treated with testosterone: a randomized, placebo-controlled trial. Menopause. 2006; 13 (1): 37–45. DOI: 10.1097/01.gme.0000168061.32917.83. PMID: 16607097.
15. Bachmann G, Bancrofti J, Braunstein G, Burger H, Davis S, Dennesrtein L. Female androgen insufficiency: the Princeton consensus statement on definition, classification, and assessment. Fertil Steril. 2002; 77 (4): 660–5. DOI: 10.1016/s0015-0282(02)02969-2.