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ABSTRACT

of the dissertation for the degree of Doctor of Philosophy

THE ROLE OF AUTO-ANTIBODIES IN ETIOLOGY OF OLIGOMENOREIA IN THE REPRODUCTIVE AGE

Speciality: 3215.01 - Obstetrics and Gynecology

Field of science: Medicine

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GENERAL CHARACTERISTICS OF THE STUDY

The actuality and processing degree of the subject. Menstrual problems take great place in life of each woman. Prevalence of menstrual dysfunctions in developing countries covers nearly 5-15% of women of childbearing age, in older women it reaches a higher percentage [1,2].

According to various studies, the prevalence of oligomenorrhea worldwide has increased significantly and reached to 12-15.3% in recent decades, in infertile women this index is isə 10-20[3,4]. Therefore, the diagnosis and treatment of menstrual disorders is very important.

Numerous studies, clinical observations showed the role of autoimmune processes in the development of oligomenorrhea. Autoimmune processes cause pathological changes in human organs and tissues. There is a violation of thyroid status and an increase in the level of antiovarian antibodies (AOA) in the blood in the form of hypothyroidism and autoimmune thyropathy in women suffering from oligomenorrhea[5].

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[1]Луценко, Л.А. Патология щитовидной железы у женщин репродуктивного возраста: преконцепционная подготовка и тактика ведения во время беременности //Internationaljournalofendocrinology, - 2015.2 (66), - с. 111-116.

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Antiovarian antibodies are antibodies formed against ovarian tissue. The pathological level of this antibody is observed in patients suffering from premature ovarian failure, hormonal imbalance, unexplained infertility and inflammatory diseases of the small pelvic organs. According to various sources, the existing frequency of antiovarian antibodies is changes between 51.85% and 73.3%[6].

The normal functioning of the thyroid gland is very important for normal menstrual cycle, because the reproductive system and the thyroid gland are interconnected[7]. Disfunction of thyroid gland can seriously affect the female reproductive system and that is why menstrual irregularities are very common in women with thyroid dysfunction [8]. Studies confirm connection between menstrual disfunction and hyper- or hypothyroidism[9]. Prevalence of menstrual disfunction in women with initial hypothyroidism is more common for 3 times among the general population than women of reproductive age and according to some researchers is 23.4-70%[7,8]. Functional disorders of the thyroid gland affects changes in ovarian function, menstrual disorders (especially oligomenorrhea) and the functioning of the reproductive system[7,10]. At the same time, the complexity of the pathogenesis of thyroid hypofunction affecting the reproductive system is noted. Connec-

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[7]Сметник, А.А., Сазонова, А.И. Влияние щитовидной железы и ее патологии на репродуктивную функцию женщин // Акушерство и гинекология, - 2019. № 3, - с. 46-52.

[8]Khatiwada, S. Pattern of Thyroid Dysfunction in Women with Menstrual Disorders / S.Khatiwada, S.Gautam, R.KC [et al.] // Ann. Clin. Chem. Lab. Med, - 2016. 2(1), - p. 3-6.

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tion between menstrual cycle and thyroid hormone levels is functioning mainly by thyrotropin-releasing hormone, which directly affects the ovaries and thyroid dysfunction, and by stimulating the synthesis of thyroid-stimulating hormone (TSH) in pituitary cells, can change globulin levels which binds sex hormones and therefore, it causes menstrual irregularities [7,8,10].

It is known that, deficiency of thyroid hormones is observed in hypothyroidism, and this leads to changes in the synthesis, transport, metabolism and peripheral effects of sex hormones. In this case, the metabolism of androgens and estrogens is disrupted.[7,11,12]

The thyroid gland is an important endocrine gland that affects the reproductive system and, autoimmune thyroiditis consists 5-7% among its pathologies. In case of autoimmune thyroiditis pathological increase in the level of anti-TPO (antibodies synthesized against thyroid peroxidase enzyme), anti-TG (antibodies against thyroglobulin) factors in the blood. Recent researches show that the role of autoantibodies in menstrual disorders, infertility and miscarriage is 30-50% [13]. Existence of connection between infertility and antithyroid antibodies proves the relevance of the given study once again. Despite numerous scientific studies to determine this pathology there are unresolved questions in the etiopathy of oligomenorrhea. The level of antibodies against the ovarian tissue in the blood-AOA, anti-TPO, anti-TG antibodies against enzymes synthesized in the thyroid gland are being studied along with various hormonal tests for the assessment of oligomenorrhea in reproductive age (19-45 years). Although this type of

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[11] Нажмутдинова, Д.К., Рахимбердиева, З.А., Максудова, Д.Р. Взаимосвязь аутоиммунного тиреоидита с нарушенной репродуктивной функцией у женщин фертильного возраста // Евразийский Союз Ученых (ЕСУ), - 2017. 2(35), - с. 31-34.

[12] Yadav, P., Arora, G. Prevalence of hypothyroidism in reproductive age group in rural population of Haryana and its effects on menstrual disturbances // Int J Reprod Contracept Obstet Gynecol, - 2021. 10, - p. 567-70.

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research works are conducted, Assessment of the role of autoimmune processes in the etiopathogenesis of oligomenorrhea remains unstudied.

In our researches we have systematically reviewed studies conducted till now and in the assessment of this pathology we want to examine the complex determination of AOA, anti-TPO, anti-TG and the severity of the pathology depending on the amount in the blood.

We consider that, achieved results of our study will be very important for determining the severity of the pathology and the correct choice of treatment tactics.

The object and subject of the study

The objects of the study were women of reproductive age (19-45 years) with oligomenorrhea and non-oligomenorrhea. The subjects of the study were studying of the amount of antiovarian antibodies (AOA), antibodies to thyroid peroxidase (AB-TPO) and antibodies to thyroglobulin (AB-TG) in the blood and their interaction with each other and the functional state of the ovaries.

The purpose of the study

Studying of the effect of autoimmune processes on ovarian dysfunction in women with oligomenorrhea.

Objectives of the study:

1. To assess anamnestic and clinical, hormonal, USE features and ultrasound of the reproductive system and thyroid gland in women of reproductive age with oligomenorrhea.
2. Assessment of ovarian function by AOA, anti-TPO and anti-TG factors in women with oligomenorrhea.
3. Comparative assessment of AOA, anti-TPO and anti-TG levels in different age groups of women with oligomenorrhea.
4. To study the correlation between antiovarian antibodies, anti-TPO and anti-TG in women with oligomenorrhea.
5. Development of an algorithm that allows to assess ovarian dysfunction depending on the level of autoimmune markers -AOA, anti-TPO and anti-TG in women with oligomenorrhea.

Methods of the study. Gynecological examination – gynecological examination of all women; Determination of structural changes in

the genitals and thyroid gland by USE examination; endocrine status-determination of FSH, LH, estradiol, prolactin, DHEA-S, TSH, free T3, free T4, free testosterone; AOA, anti-TPO, anti-TG ELISA immunoenzyme test for specific study. 160 women involved in the study (main group - 110 women of reproductive age with oligomenorrhea; control group - 50 healthy women) will be divided into groups based on the results of laboratory tests, physical (gynecological examination) and instrumental (USM) anamnestic data.

Main provisions of the dissertation to be defended:

- Anamnesis features, anthropometric indicators, ovarian and uterine USM, thyroid USE and USM-Doppler in women of reproductive age with oligomenorrhea.
- Blood test of hormones that reflect the function of the ovaries, thyroid hormones and autoantibodies in women with oligomenorrhea.
- Identification of mutual correlation relations between antibodies and between antibodies and hormones.
- Diagnostic algorithm consisting of 3 stages for the diagnosis of autoimmune changes in women with oligomenorrhea.

Scientific novelty of the study:

- The effect of autoimmune processes on the etiopathogenesis of oligomenorrhea has been studied;
- The effect of anti-TPO, anti-TG factors along with AOA on the mechanism of oligomenorrhea was comprehensively assessed;
- The severity of ovarian dysfunction depending on the ratio of AOA, anti-TPO and anti-TG markers was assessed;
- Algorithm for assessment of ovarian function in women of reproductive age depending on the level of autoimmune markers has been developed.

Practical significance of the study:

In women with oligomenorrhea olan xəstələrdə rhe role of autoimmune processes in the formation of this pathology is determined by the identification of markers AOA, anti-TPO and anti-TQ.

The achieved results of scientific resesrach work will help obstetricians-gynecologists, endocrinologists and reproductive specialists

to chose examination and treatment tactics for patients with oligomenorrhea.

Approbation of the dissertation work:

Basic provisions of the dissertation work have been reported in scientific-practical conferences: The I International Congress on Obstetrics and Gynecology on "Innovative Technologies in Obstetrics and Gynecology" held by the Public Association for the Development of Gynecology and Perinatology (November 8-9, 2018, Baku); the XLV International scientific-practical conference on "New approaches and current research in modern medicine" (March 2021, Moscow); International Conference on "Progressive processes of world scientific thinking in the research of the XXI century" (May 2021, Kazan).

Materials of the dissertation have been reported and discussed in the meeting of the Scientific Council of the Public Legal Entity "Scientific Research Institute of Obstetrics and Gynecology" held on July 01, 2021 (01.07.2021, protocol №7) and in a Scientific Seminar of the Azerbaijan State Advanced Training Institute for Doctors named after A.Aliyev (March 02, 2022, protocol №6).

Published works: 11 scientific articles on subject of the dissertation have been published. 8 of them are articles, 3- thesis and conference materials, also 2 articles and 2 thesis have been published.

Application of results of the dissertation work: The results of the dissertation are included to the treatment process of the Scientific Research Institute of Obstetrics and Gynecology.

The name of organization where the dissertation work was conducted: the Public Legal Entity Scientific Research Institute of Obstetrics and Gynecology.

Volume and structure of the dissertation. The dissertation is presented in form of text consisting of 146 pages printed in computer and it is consisting of parts such as introduction (10208 symbols), literature review (50871 symbols), research materials and methods (15520 symbols), chapters III (20886), IV(29298 symbols) and V personal results (10088 symbols), final (37545 symbols), results (2254 symbols), practical recommendations (605 symbols). 226 texts

were included to the list of bibliography. 9 of them are locals, 8 are Turkish, 61 are from near abroad and 148 are from far abroad. The dissertation also includes 17 graphs, 32 tables, 3 schemes and 1 figure.

The total volume of the dissertation by symbols (excluding spaces, title page, table of contents, graphs, diagrams, figures, bibliography and abbreviated terms) – is 177275 symbols.

MATERIALS AND METHODS OF THE STUDY

The character of the study is prospective. Women applied to the Scientific Research Institute of Obstetrics and Gynecology during 2015-2018 years were involved in the study on a voluntary basis. All patients were informed about the study, were examined on the basis of consent.

Criteria for including to the main group:

- Not younger than 19 and not older than 45 yesrs
- Disorders of the menstrual cycle in the form of primary and secondary oligomenorrhea;
- The duration of the menstrual cycle is from 43 days to 6 months;
- The interval between menstrual cycles is more than 35 days;
- The duration of the menstruation is 1-3 days;
- Normohonadotropic insufficiency of the ovaries;
- Absence of non-specific and specific gynecological diseases (gonorrhea, tuberculosis, pale treponema, chlamydia, etc.).

Exception criteria:

- Congenital malformations;
- Congenital dysfunction of the adrenal cortex, hypothalamic-pituitary insufficiency, with chromosomal abnormalities;
- Presence of organic diseases of the thyroid gland;
- Acute or chronic diseases of the small pelvic organsnin;
- Existance of severe somatic pathologies (ischemic heart disease, angina pectoris, chronic renal failure), diseases of the blood and hematopoietic organs, severe thrombophilia;

- Existance of new derivatives.

Women from the control group have been examined during prophylactic visits. No impairment of menstrual function was reported in women of this group, regular ovulatory cycle was observed in every 28-30 days, pregnancy resulting in alive and premature birth is in the medical history, complicated obstetric and gynecological history and severe somatic pathology were not recorded.

Criteria for including to the control group:

- Not younger than 19 and not older than 45 years;
- Continuous stages of sexual maturity;
- Regular menstrual cycle;
- Normal physical and sexual maturity;
- Presence of female-type hair groth and absence of symptoms of hyperandrogenism;
- Body weight index is between 18.6 – 24.9 kg/m^2;
- Duraton of menstrual bleeding is 3-5 days;
- Absence of specific inflammatory diseases of the gynecological organs;
- History of abortion and childbirth, maintaining reproductive function;
- Absence of non-specific inflammatory processes of small pelvic organs;
- Absence of chromosomal and monogenic pathologies in the anamnesis.

10 women with oligomenorrhea-type menstrual disorders have been included to the main group.

The women included in the main group were divided into 3 subgroups:

- I subgroup – 57 women with oligomenorrhea.
- II subgroup – 31 women with oligomenorrhea diagnosed with hyperprolactinemia.
- III subgroup– 22 women with oligomenorrhea diagnosed with early ovarian failure.

The control group was consisting of reproductively healthy 50 women without oligomenorrhea.

The social and living conditions were satisfactory in respectively, 93.6% and 94.0% of women included to the main and control groups. 50 (36.4%) women in the main have high education, 56 (50.9%) patients have secondary education and 14 (12.7%) patients have incomplete secondary education, in control group this indicators were respectively 17 (34.0%), 26 (52.0%) and 7 (14.0%) women.

Housewives were dominating in the main and control groups. Thus, 29 (50.9%) patients did not work in the first subgroup, 20 (64.5%) in the second subgroup, 14 (63.6%) in the third subgroup, and 27 (54.0%) women in the control group.

It was detected during the study that 50.5% (n = 56) of women in the main group had primary oligomenorrhea and 49.5% (n = 54) patients had secondary oligomenorrhea. 8 (16.0%) women in the control group are not married, 11 (22.0%) are pregnant for the first time, 10 (20.0%) are re-pregnant, 11(22.0%) are primogenitures, 10 (20.0%) were with repeated childbirth.

Clinical-laboratory and instrumental examinations were conducted for all women. The plan of study included the following: collection of anamnesis, physical examination, ultrasound examination of small pelvic organs and thyroid gland (USE) + doppler.

Levels of honadotropic (LH, FSH), luteotropic (prolactin), steroids (estradiol, testosterone, dehydroepiandrosterone-sulfate - DHEA-S), thyrotropic (T3, T4, TTH) hormones in the blood serum were tested by Human GmbH (Germany) and determined by the ELISA method. Determination of follicle-stimulating hormone (FSH), luteinizing hormone (LH), prolactin (PL), estradiol, total testosterone, T3, T4, TTH in blood serum was conducted in the early follicular phase of the menstrual cycle Immulite 1000 analyzer (Siemens, Germany). Antiovarian antibodies (AOA), anti-thyroglobulin (AB-TG) and anti-thyroperoxidase (AB-TPO) antibodies were detected in blood serum by ORA using ORGenTec Diagnostics (Germany) test systems. Measurements were performed on Cobas 6000 e-601 analyzer (Roche, Diagnostics, Basil).

Statistical analysis of the achieved results was conducting by using Microsoft “Statistica” software in Excel release 16 (StatSoft, USA). Indicators were expressed in the form of average ± standard deviation (SD), absolute numbers and percentages. The student's t-criterion was calculated. The correlation coefficient was calculated according Pearson. Also, the determination coefficient (R2) was determined in Excel. The dispersion of variance (variability) was estimated as Y by means of coefficient of determination. This is explained by X in a simple line regression model [14]. Statistical indicators were considered significant at $p < 0.05$ level.

RESULTS OF PERSONAL RESEARCH

Clinical and ultrasound indicators of patients. In patients of the main and control groups the age difference was not statistically significant. The average ages of women in control group with oligomenorrhea respectively were 31.39±6.05 and 30.52±5.92 years (p=0.918, t=0.10). The average ages in subgroups I, II and III, respectively were 30.0±2.46, 35.2±1.06 and 29.8±1.87 years. As it is given in the Table 3.1.1., most patients in the I subgroup were 19-25 years old (33.3%), in the II subgroup - 31-35 years old (29.0%) and 36-40 years old (29.0%) and 26-30 years old (40.9%) in the III subgroup. The patients with oligomenorrhea had a higher history of hypertension (8.2%) and diabetes mellitus (9.1%), somatic diseases - rheumatism (13.6%), metabolic changes (10.9%), hirsutism (54, 5%), gynecological diseases - ovarian polycystic syndrome (14.5%) and ovarian follicular cysts (12.7%) were more common while collecting anamnesis. Spontaneous miscarriages (7.3%) and premature births (20.9%) were also observed.

The norm was observed in 11 of 57 patients in the I subgroup, 46 women suffered from obesity, 26 of them had 1st degree obesity and 20 women had 2nd degree obesity. In 6 women of 10 women examined in the II subgroup the norm was observed, 26 women suffered from

[14]Сергиенко, В.И., Бондарева, И.Б. Математическая статистика в клинических исследованиях. 2-е изд., перераб. и доп. Москва: ГЭОТАР, - 2006. - 304 с.

obesity, 15 of them had 1st degree obesity and 10 women had 2nd degree obesity. The norm was observed in 3 of 22 women in the III subgroup, the obesity was detected in 16 patients, 16 of them were with 1st degree obesity and 3 women with 2nd degree obesity. In the control group consisting of 50 examined women the norm was detected in 31 patients, 19 women had 1st degree obesity. Thus, in the main group the norm was in 20 (18.2%) patients, obesity in 90 (81.8%) patients. At the same time, I and II degree obesity was respectively observed in 57 (51.8%) and 33 women (30.0%).

The study detected excessive hair in 60 (54.5%) women in the main group and absence of such condition in the control group. The first degree of hirsutism was observed in54 (49.1%) patients, II degree in 6 (5.4%) patients. In 45.5% of women with oligomenorrhea (n=50) hair growth was normal. Thus, mild hirsutism predominated among the examined patients.

Galactorrhea was diagnosed in totally 28 (25.4%) patients. Besides it, galactorrhea was observed in 20 patients among women with hyperprolactinemia in the II subgroup and this was 64.5% of all patients in the subgroup (n=31), galactorrhea was observed in 8 women in groups with normal prolactin levels. 7 of 28 patients with galactorrhea, were spontaneous and women declared it independently. In most cases – in 21 patients galactorrhea was detected only by pressure on the mammary glands.

In patients of the I, II and III subgroups menstrual cycle was observed to be less than norm, this was less than in the control group respectively for 3.7 times ($t = 2.71$, $p = 0.008$), 1.5 times ($t = 1.28$, $p = 0.205$) and 2.5 times ($t = 2.19$, $p = 0.032$).

In 56 (50.5%) examined women primary oligomenorrhea was diagnosed, the remaining 54 (49.5%) patients had secondary oligomenorrhea. In the main group, gynecological diseases were diagnosed in 62 (56.36%) patients, this is higher than in the control group for 57.42% ($p < 0.05$).

Ultrasound data of the uterus show that, sizes in women from I, II and III subgroups, does not differ statistically from the values of the control group. Only in women of the III subgroup uterine length was

short (p = 0.001, t = 3.56), and endometrial thickness (p = 0.048, t = 2.01) was statistically significantly lower than the control group. While analysing the ultrasound data if the uterus, its length and width were 3.99 ± 0.19 cm (control - 4.54 ± 0.21 cm, p = 0.055, t = 1.94) and 4.51 ± 0.11 cm (control - 4, respectively). 80 ± 0.16 cm, p = 0.138, t = 1.49) in a group of patients with primary oligomenorrhea (n = 56). In the group of patients with secondary oligomenorrhea (n=54) the length of the uterus was 3.82 ± 0.22 cm (p = 0.020, t = 2.37), the width of the uterus was 4.33 ± 0.33 cm (p = 0.202, t = 1.28). As can be seen, the length of the uterus in patients with primary and secondary oligomenorrhea was statistically significantly lower than the control indicator, although the width of the uterus was low, it was not statistically significant.

Measuring the front and back parts of the uterus showed that in the group with primary oligomenorrhea this indicator was averagely 3.40 ± 0.31 cm, which was slightly lower than the control indicator (control - 3.56 ± 0.18 cm, p = 0.656, t = 0.4), in the group with secondary oligomenorrhea it was 3.28 ± 0.47 cm (p = 0.579, t = 0.56). Endometrial thickness was also lower in women with primary and secondary oligomenorrhea than in the control group, was 11.8 ± 1.1 mm (p = 0.217, t = 1.24) and 9.41 ± 1.07 mm (p = 0.122, t = 1.56) respectively, against the control group in which it was 9.78 ± 1.20 mm.

Right ovarian volume in subgroups I and II did not differ significantly from each other, as well as from the control indicator. This indicator was 2.8 times lower compared to the control value in subgroup III (t-criterion = 3.45, p = 0.001), and, 2.8 times (t-criterion = 3.32, p = 0.001) and decreased 2.6 times (t-critical. = 3.30, p = 0.002) lower compared to subgroups I and II, respectively. The same situation was observed with regard to the left ovary.

In women of subgroup III, statistically significantly lower indicators compared to subgroups I and II were observed – they were respectively 3.0 times (t-critical. = 3.45, p = 0.001), 3.2 times (t-critical. = 3.27, p = 0.002) and 3.3 times (t-crit. = 4.25, p = 0.001). Comparative analysis of the average number of antral follicles in women in the study groups did not reveal significant differences.

According to USE results, the width of the ovarian stroma in the main group was 16.46 ± 3.25 mm, in the control group - 8.97 ± 1.16 mm (p = 0.031, t = 2.17), this was more for 45.5% than in the control group. The total number of follicles was determined as 18.92 ± 1.57 in the main group and as 13.88 ± 1.62 in the control group (p = 0.027, t = 2.23), and it was more for 26.64%. The number of follicles with a diameter of 2-5 mm and 6-9 mm in the main group was respectively 12.23 ± 1.77 mm and 7.12 ± 1.41 mm, and was 10.12 ± 1.14 mm and 4.82 ± 1.06 mm in the control group. No statistically significant difference was found here. Thus, the difference in the number of follicles with a diameter of 2-5 mm and 6-9 mm with the main and control groups was 17.2% (p = 0.032, t = 0.99) and 32.30% (p = 0.194, t = 1.30), respectively. The results of sonography showed an increase in the volume and structure of the thyroid gland in 40 (36.4%) of 110 patients.

Assessment of functional condition of the ovaries in women of fertile age with oligomenorrhea. In women with oligomenorrhea the mean LH level was higher than the control level for 51.75% (p = 0.048, t = 2.00), LH / FSH ratio - 44.28% (p = 0.007, t = 2.74), total testosterone - 39.09% (p = 0.149, t = 1.45), AMH level - 33.86% (p = 0.048, t = 1.99). At the same time, the concentration of FSH and estradiol in the main group decreased by 24.64% (p = 0.236, t = 1.19) and 59.36% (p = 0.163, t = 1.40), respectively. Blood TSH levels in the main group of patients ranged from 0.3 to 6.6 BV / ml (0.3-4.2 BV / ml in the control group). Thus, the quantity of TSH in the blood in the main group was on average 22.2% higher than in the control group. The normal TSH level was detected in 60.0% (n = 66) of patients, increased TSH level - in 30.0% (n = 33) of patients and decreased TSH level - in 10.0% (n = 11) of patients in the main group; this indicators were respectively 78.0% (n=39), 20.0% (n=10) and 2.0% (n=1) in the control group. T3 levels in blood in patients of the main group ranged from 1.8 to 6.9 nmol / l (2.7-6.4 nmol / l in the control group), and T4 levels in the main group ranged from 8.1 to 27.4 nmol / l (9.7–25.6 nmol / l in the control group). Statistically insignificant differences

were noted between the groups in terms of the composition of hormones T3 (p = 0.981) and T4 (p = 0.979). The T3 / T4 ratio did not differ statistically from the control group. The minimum value of the T3 / T4 ratio in the main group was 0.06, the maximum ratio was 0.9, in the control group it was respectively 0.11 and 0.57.

Serum concentrations of FSH, dehydroepian-drosterone sulfate (DHEA-S) and estradiol averagely decreased in patients with oligomenorrhea in comparison with the control group. At the same time, the levels of FSH and DHEA-S in the III subgroup of the study slightly exceeded the average value of these hormones in the control group, as in the I and II subgroups. Estradiol levels decreased in all groups, especially in the III subgroup, but the difference was not significant. Concentrations of LH, prolactin, total testosterone, AMH, and TSH in blood serum of women with oligomenorrhea increased compared to the control group. Thus, in women of the I, II and III subgroups LH levels 50.79% (p = 0.085, t-critical = 1.74), 55.79% (p = 0.006, t-critical = 2.82) and 47.9% (p, respectively) of the control indicator. = 0.053, t-critical = 1.96) was averagely higher. The LH / FSH ratio increased significantly in subgroup II by 56.28% (p = 0.005, t-critical = 2.87) compared to the control group. A statistically significant increase in AMH levels was observed in patients in subgroup II – 34.0% (p = 0.05, t-critical. = 1.94). The average increase in TSH level in all subgroups was vrespectively 34.02% (p = 0.367, t-critical. = 0.91), 37.25% (p = 0.312, t-critical= 1.02), and 36.95% (p = 0.276, t-critical. = 1.10) compared with the control group. The differences between the subgroups were statistically insignificant. In women in the I subgroup T3 and T4 hormone levels increased insignificantly compared to the control group, and was decreased in the III subgroup. The concentrations of T3 and T4 did not differ significantly from the control value in the II subgroup.

The levels of BWI, TSH hormone were increased in women with diagnosed hypothyroidism (n = 33). In patients of the control group BWI was averagely high for 14.3% in the I subgroup, for 17.1%– in the II subgroup and for 17.0% in the III subgroup. However, the increase in TSH was statistically significant. Thus, in women of the first

subgroup, the concentration of this hormone was averagely 52.33% (p = 0.053, t = 1.97) higher than the control group, 49.61% (p = 0.054, t = 1.96) - in the second group, and in subgroup III it was 50.77% (p = 0.052, t = 1.98) higher. Thus, noted during the study statistically significant changes were noted in LH, AMH levels and LH / FSH ratio in subgroup II and LH level in subgroup III. Analysis of thyroid hormone detected hypothyroidism in 33 (30.0%) women, including 14 (12.7%) in subgroup I, 9 (8.2%) in subgroup II and 8 (9.1%) in subgroup III.

LH levels and LH / FSH ratios were significantly higher than the control values for respectively 50.79% (p = 0.052) and 52.66% (p = 0.045) in the group of women with primary oligomenorrhea. In the group of women with secondary oligomenorrhea LH levels and LH / FSH ratios exceeded the control value by 61.9% (p = 0.001) and 66.67% (p = 0.046), respectively. At the same time, there was no statistically significant difference between groups of patients with primary and secondary oligomenorrhea. Statistical analysis showed a significant increase in AMH levels in patients with primary and secondary oligomenorrhea for respectively of 33.86% (p = 0.049) and 34.17% (p = 0.052) in comparison with the control value.

Prolactin, testosterone, and TSH concentrations exceeded control values by an average of 4.9% (p = 808), 38.33% (p = 0.163), and 34.36% (p = 0.355), respectively in the group of women with primary oligomenorrhea; in the group of women with secondary the difference with the control group was respectively 6.16% (p=0.726), 39.34% (p=0.115) and 37.36% (p=0.303). In the group of women with primary oligomenorrhea the average levels of DHEA-S and estradiol decreased by 3.13% (p = 0.923) and 56.67% (p = 0.113), respectively, i9n comparison with control values; in the group of women with secondary oligomenorrhea these indexes were respectively lower for 6.45% (p = 0.862) and 56.67% (p = 0.089). There was actually no difference between groups of patients with oligomenorrhea. In women with primary oligomenorrhea T3 content was 4.88% higher than the control value (p = 0.875), but T4 levels are not practically different from control values. In patients with secondary oligomenorrhea, levels of T3 and T4 hormones were 9.11% (p = 0.747) and 5.12% (p = 0.846) higher,

respectively, compared with control levels. According to the achieved results, a weak correlation was observed for all hormone pairs studied in women with oligomenorrhea. At the same time, the difference in the correlation between sex hormones, thyroid hormones and TSH and the control group was minimal, only in the control group the difference in the correlation coefficient of FSH with T3 was found, here the relationship between these hormones was weak and indirect in oligomenorrheal groups, and moderate and straight in control group. The analysis showed that, there is a weak positive relationship between FSH-TSH, thyroid hormones estradiol and TSH, testosterone and T3 and TSH in oligomenorrheal groups. The association of LH with all studied hormones was negative.

The study showed a statistically significant increase in antibodies in patients with oligomenorrhea (Table 1).

Table 1

Consentration of antibodies in blood in main control groups

Indicator	Main group (n=110)	Control group (n=50)	t- criterion	P
AB-TG, BV/ml	124,12±37,87 (0,11-5085,0)	35,75±8,57 (1,50-196,20)	2,28	0,024
AB-ATO, BV/ml	196,17±55,76 (0,9-6240,0)	27,71±7,13 (2,30-172,60)	3,00	0,003
AOA, ng/ml	6,36±1,14 (0-106,70)	3,06±1,16 (1,20-8,50)	2,03	0,044

The amount of antibodies examined in the thyroid gland and ovaries in the main group of patients was higher than in the control group. Thus, the level of AB-TG was statistically 3.5 times higher than the control indicator (t-criterion = 2.28, p = 0.024), AB-TPO - 7.1 times (t-criterion = 3.0, p = 0.003). The concentration of circulating AOA in the blood of women in the main group was 2.1 times higher (t-critical=2.03, p=0.044). At the same time, no AOA was found in the blood of 2 (1.8%) patients with oligomenorrhea oliqomenoreyalı. So, according to the obtained examination results in 110 examined women with oligomenorrhea no changes were found in the thyroid gland in 37

(33.6%) women, symptoms of autoimmune thyroiditis were found in 40 (36.4%) patients and hypothyroidism in 33 (30.0%) patients.

The maximum value of AB-TG and AB-TPO is recorded in the group of patients with symptoms of autoimmune thyroiditis, and this is 37.41% higher than in the group of women with no changes in the thyroid gland ($t = 0.40$, $p = 0.688$). At the same time, there was no significant difference in AB-TG levels between groups with symptoms of hypothyroidism and no changes in the thyroid gland ($t=0.05$, $p=0.962$). We supposed that, maximum levels of AB-TPO will be observed in patients with symptoms of autoimmune thyroiditis. The highest levels of AOA in the blood were found in patients with symptoms of autoimmune thyroiditis and hypothyroidism, and this was higher than in women with oligomenorrhea with unchanged thyroid gland for respectively 29.92% ($t = 0.28$, $p = 0.783$) and 44.72% ($t = 0.41$, $p = 0.683$). But no statistically significant differences were found as the result of the comparative analysis.

We analyzed the AB-TG and AB-TPO levels of AOA and antibodies in women with oligomenorrhea and concomitant gynecological diseases within the frames of the given study. As the result of the comparative analysis we detected that AOA quantity in women with oligomenorrhea without concomitant gynecological diseases was higher for respectively 26.0%, 12.24%, 45.94% ($p <0.05$) and 52.27% ($p <0.05$) than in women with hirsutism, polycystic ovary syndrome, uterine fibroids and ovarian follicular cysts. The maximum level of AB-TPO has been detected in the group of women with polycystic ovary syndrome. In comparison with the group of women without concomitant diseases the AB-TPO level was 6.4 times higher ($p <0.001$) in this group. Compared to the AB-TPO level in the group of women with oligomenorrhea and without concomitant diseases, this figure was statistically higher for respectively 5.0 times ($p <0.05$) and 4.8 times ($p <0.001$), in the group of women with hirsutism and uterine fibroids. AB-TPO levels in patients with ovarian follicular cysts, at the same time in patients with oligomenorrhea who do not have other diseases the value of this enzyme was not practically different, and was 11.0% higher in women with autoimmune thyroiditis.

The AB-TG level in the blood was also recorded in patients with disease-free oligomenorrhea, like AB-TPO. In patients with ovarian follicular cysts, on whom the value of AB-TG was detected, the maximum level of these antibodies was 6.3 times higher than in the group of women without oligomenorrhea ($p < 0.001$). In groups of women with symptoms of autoimmune thyroiditis, uterine fibroids and hirsutism the amount of AB-TG exceeded the level of antibodies in the group without diseases by 3.7 times ($p < 0.01$), 1.9 times ($p < 0.05$) and 1.7 times ($p < 0.05$), respectively. AB-TG levels in the blood of patients with polycystic ovary syndrome, was 1.2 times higher than in women without oligomenorrhea.

AB-TG levels were mostly determined in subgroups I and II in comparison with the control group. Thus, in subgroups I and II, the amount of AB-TG was respectively 3.3 times ($t = 2.0$, $p = 0.048$) and 3.2 times ($t = 2.08$, $p = 0.041$) higher. However, the level of these antibodies did not differ significantly between groups of women with oligomenorrhea.

Comparing of the average values of AB-TPO showed that their amount was more in all three subgroups, than in the control indicator, however, a statistically significant difference was identified only in subgroup III. Thus, the level of AB-TPO in patients of subgroup I was higher for 2.9 times ($t = 1.06$, $p = 0.291$) compared to the control group and for 3.2 times ($t = 1.48$, $p = 0.142$) compared with subgroup II. It was 7.0 times more than the third subgroup ($t = 4.03$, $p = 0.001$). The analysis among subgroups showed that, in women of the III subgroup (with oligomenorrhea and early ovarian failure) The amount of AB-TPO was, respectively, 2.4 times ($t = 1.75$, $p = 0.085$) and 2.2 times ($t = 1.81$, $p = 0.076$) higher than in subgroups I and II.

According to our research, the amount of AOA in the blood of women in I, II and III subgroups was more than the control indicator for respectively 2.1 times ($t = 0.63$, $p = 0.533$), 1.3 times ($t = 0.46$, $p = 0.644$) and 2.6 times ($t = 1.12$, $p = 0.266$).

During the study we assessed the transport of AOA, AB-TPO and AB-TG antibodies in women of different age groups with oligomenorrhea: there were 56 women in the 19-30 age group (control group, n =

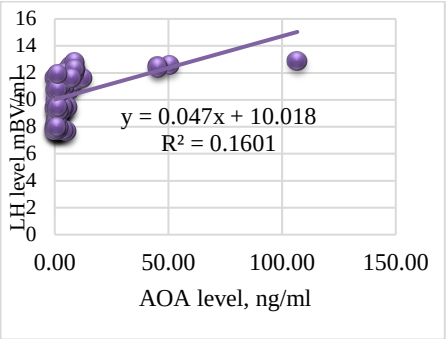
28), 44 women in the 31-40 age group (control group, n = 16) and 10 women in the 41-45 age group (control group, n = 6). The average ages of examined patients in each group were respectively 25.39±2.23 years (control - 25.11±2.84 years), 35.93±2.22 (control - 34.23±2.25 years) and 43.0±1.4 years (control - 42.3±42.3 years). Frequent carriers of AB-TG are patients from 41-45 age group, the carriers of AB-TPO and AOA were women in the age group of 31-40, respectively. According to the results of statistical analysis, there was no significant difference in the average values of the levels of these antibodies between the groups.

Studies of antibody concentrations have shown that, increased titre of antibodies TQ was detected in 23.2% of patients in the age group of 19-30 years to, TPO – in 8.9% of patients and AOA – in 8.9% of patients, in the age group of 31-40 years, carrying of AB-TG, AB-TPO and AOA was determined in 15.9% of cases, respectively. In elderly patients (41-45 years), high AOA titre was recorded in 10.0% of patients, AB-TG - 30.0% of patients and AB-TPO - 20.0 % of patients.

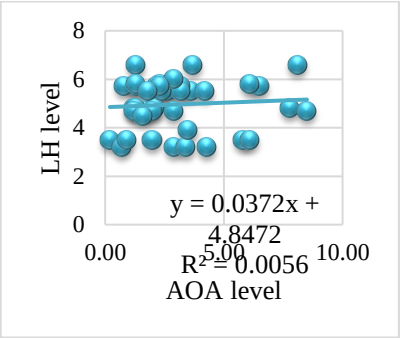
Assessment of interaction of antiovarian and thyroid antibodies in women of reproductive age with oligomenorrhea. Analysis showed that, the dependence of the indicators was statistically insignificant and weak. However, in the main group, antibodies were associated with thyroid hormones only positively, but in the control group, negative connections also were found. A very weak positive correlation was detected between AB-TPO and AB-TG in the main group, in comparison with it positive correlation between AB-TPO and AB-TG was very weak. Correlation between these antibodies also was weak in the control group and in both cases, the relationship was statistically insignificant. A weak correlation was also observed between AB-TG ($r = +0.199$, $p > 0.05$) and AB-TPO ($r = +0.096$, $p > 0.05$) in the main and control groups. A weak positive correlation with the AB-TG and T3 / T4 ratio was observed, A weak negative relationship between AB-TPO and T3 / T4 was found. In the control group, the correlation between these indicators was weak and negative.

Calculating of correlation between detected direct weak relation between them ($r=+0.212$, $p=0.033$). In women with oligomenorrhea in

anamnesis direct, weak correlation of AOA, AB-TG and AB-TPO was associated. AOA, all hormones which has statistically important correlation have been studied in women with oligomenorrhea and significant connection with LH levels (Charter 1) have been detected.



A



B

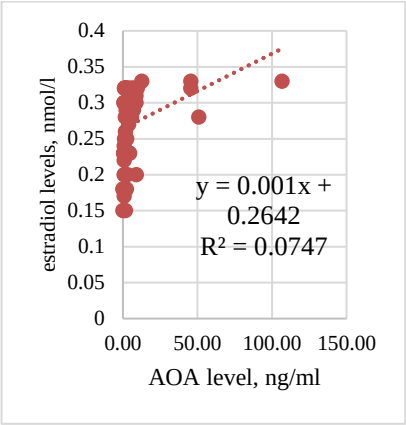
Charter 1. Correlation of AOA with LH levels in the blood in women from the main (A) and control (B) groups

The determination coefficient in the main group (R^2) was16.0%, 0.56% in the control group, and it showed increasing of OAO ratio by increasing of LH concentration in blood.

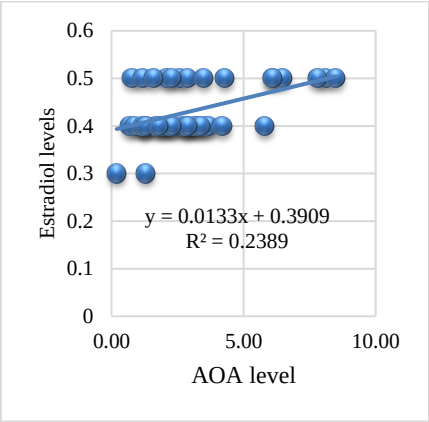
In women with oligomenorrhea (main group) a noticeable cotrrelation between AOA and estradiol was detected (r=+0.534, p=0.001) (Charter 2).

Besides LH and estradiol, AOA was significantly correlated with AMH. At this case the coefficient R^2, shows changes in the correlation of AOA with AMH during oligomenorrhea. Thus, this ratio was 42.03% in the control group and 10.36% in the main group.

Dislike this, AOA was weakly correlated with total testosterone levels. Comparison of R2 with 17.36% ratios in the control group and 2.5% ratios in the main group, decrease in the correlation between the main group with an increase in total testosterone and AOA was observed.



A



B

Charter 2. Correlation of AOA with estradiol levels in the blood in women from the main (A) and control (B) groups

According to the achieved results, AOA was weakly correlated with FSH. Conducted correlation analysis showed a cause-and-effect correlation between AOA and LH, as well as with estradiol and AMH in women with a history of oligomenorrhea of fertile age.

During the study we searched the correlation of AB-TG with hormones that reflect the functional state of the ovaries (Table 2).

In women of the main group there was very weak and statistically insignificant relation between AB-TG and hormones. In women without oligomenorrhea (the control group), A very weak correlation was observed except the association of AB-TG with total testosterone and AMH, where a significant inverse correlation was noted.

Table 2.

Hormone correlation coefficient (r) of AB-TG in women in the research groups

Hormone	Main group (n=110)	Control group (n=50)
FSH	+0,032 p=0,758	-0,055 p>0,05
LH	+0,031 p=0,758	+0,025 p>0,05
Estradiol	+0,086	+0,114

	p=0,398	p>0,05
Total testosterone	+0,081 p=0,428	-0,327 p>0,05
AMH	-0,055 p=0,590	-0,360 p>0,05

In the main and control groups AB-TPO, was associated with a weak, statistically insignificant correlation with hormones that reflect the functional state of the ovary (Table 3).

Table 3.

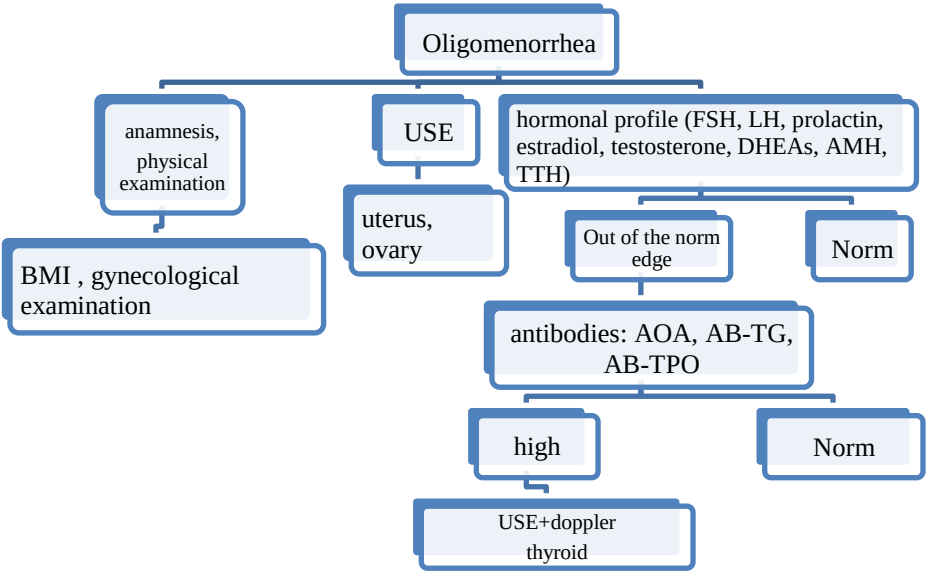
The correlation coefficient (r) of AB-TPO with hormones in women from study groups

Hormone	Main group (n=110)	Control group (n=50)
FSH	O,024 p=0,590	0,066 p>0,05
LH	-0,039 p=0,703	-0,108 p>0,05
Estradiol	-0,048 p=0,636	+0,232 p>0,05
Total testosterone	+0,083 p=0,419	-0,133 p>0.05
AMH	0,024 p=0,818	-0,039 p>0,05

Thus, we achieved statistically significant correlation coefficients between AOA and hormones and a statistically insignificant relationship between AC-T and AB-TPO and the functional status of the ovaries. In addition to the interaction of both signs, üçüncü amillərin də təsir göstərə biləcəyindən irəli gələrək, we do not exclude out the effect of a significant change between AB-TG and AB-TPO indicators, thinking that third factors may also play a role. For example, in the main group the minimum value of AB-TG was 0.11 BV/ml and maximum value was 5085.0 BV/ml, the minimum value of AB-TPO was 0.9 BV/ml, and maximum value was 6240.0 BV/ml.

According to the achieved results, we have developed an algorithm for the diagnosis of autoimmune changes in patients of reproductive age with oligomenorrhea (Scheme). Using of the introduced

complex of diagnostic methods and proposed algorithm will help you choose the optimal and different tactics for treatment of patients of reproductive age with oligomenorrhea.



Scheme 3. Algorithm for diagnosing of autoimmune changes in women of reproductive age with oligomenorrhea

Thus, as a thyroid dysfunction is one of important reasons of menstrual disorders assessment of thyroid gland should be part of a number of studies conducted in women with menstrual disorders, especially with oligomenorrhea.

CONCLUSION

1. In anamnesis of women with oligomenorrhea of reproductive age those with hypertension (8.2%) and diabetes mellitus (9.1%) in heredity were more common. Rheumatism (13.6%) was more common somatic disease, polycystic ovarian syndrome (14.5%), hyperandrogenism (35.5%), and ovarian follicular cysts (12.7%) were more common ginecological diseases. Ovarian volume decreased by an average of 3.3 times (p = 0.001) in women with early ovarian failure and oligomenorrhea. Instrumental-laboratory complex examination of the thyroid gland revealed signs of autoimmune thyroiditis in 36.4% of cases, signs of hypothyroidism in 30.0% of women with oligomenorrhea.
2. The level of AB-TG in blood of women with oligomenorrhea was more than the control indicator 3.5 times (t=2.28, p=0.024), AB-TPO – 7.1 times (t=3.0, p=0.003), AOA- 2.1 times (t =2,03, p=0,044).
3. AB-TG - 23.2%, AB-TPO - 8.9% and AOA - 8.9% was observed in patients aged between 19-30 years, transportation of AB-TG, AB-TPO and AOA in 31-40 age group was detected in 15.9% of cases. In elder patients (41-45 years old) high AOA titre was observed in 10.0% of cases, AB-TG - in 30.0% and AB-TPO - in 20.0% of cases.
4. In women with oligomenorrhea AOA had positive correlation with hormones that reflect the functional state of the ovaries: with FSH - r=0.214 (p=0.034), R^2- 0.32%; with LH - r=0.605 (p=0.001), R^2 – 16.0%; with estradiol – r=0.534 (p=0.001), R^2- 7.47%; with total testosterone - r=0.272 (p=0.007), R^2-2.5%; with AMH - r=0.538 (p=0.001), R^2-10.36%. At the same time, the interaction with thyroid hormones was weak and statistically insignificant. A very weak positive correlation was established between AB-TPO and AB-TG. A direct, weak, statistically significant correlation between AOA and AB-TPO (r = +0.212, p = 0.033) was detected. Weak, statistically insignificant correlation between AOA, AB-TG, and AB-TPO thyroid hormones was detected.
5. The algorithm designed to diagnose autoimmune changes in

women of fertile age with oligomenorrhea includes: collection of detailed anamnesis, anthropometric indicators (BWI, ginecology examination), USE of the uterus and ovaries and laboratory tests: examination of serum FSH, LH, prolactin, estradiol, testosterone, DHEAs, AMH, TTH. Detection of AOA, AB-TPO and AB-TG antibodies in the blood. USE and USE-Doppler of the thyroid gland in cases of high titre.

PRACTICAL RECOMMENDATIONS

1. It is advisable to apply the three stage algorithm for diagnosing autoimmune changes in women of reproductive age with oligomenorrhea in anamnesis:
   a) Collecting of detailed medical history, anthropometric measurements, uterine examination, USM of the uterus and ovaries, examination of serum FSH, LH, prolactin, estradiol, testosterone, DHEAs, AMH, TTH hormones in the first stage,
   b) Detecting of antibodies AOA, AB-TPO and AB-TG in blood in the second stage,
   c) USE and USE-doppler examination of the thyroid gland in the third stage.
2. The efficiency of proposed algorithm depends on identification of autoimmune processes in the ovary.

List of published scientific articles on the topic of the dissertation

1. Qurbanova, C.F., İbadullayeva-Adıgözəlova, K.P., Rzayeva G. Reproduktiv yaş dövründə oliqomenoreyanın etiologiyasında müxtəlif autoantitellərin rolu // - Bakı: Müasir ginekologiya və prinatologiyanın actual məsələləri, 2017. Cild 4, №1,- s. 52-53
2. Ибадуллаева-Адыгезалова, К.Р. Оценка уровня антител к яичникам и щитовидной железе у женщин репродуктивного возраста с олигоменореей// - Украина:Вестник проблем биологии и медицины, 2020.№2 (156), - с.73-77.
3. İbadullayeva-Adıgözəlova, K.P. Oliqomenoreya ilə reproduktiv yaşda olan xəstələrdə autoimmun dəyişikliklərin diaqnostikası // - Bakı: Müasir ginekologiya və prinatologiyanın actual məsələləri, 2021. Cild 8, №1, s. 28-34
4. Adygezalova, K.P., Gurbanova, J.F. The Role Ovarian Index in Formation of Oligomenorrhea in Women with Autoimmunity // Journal of Gynecology Research Reviews & Reports. 2021, 3(1), 4 p.
5. Qurbanova, C.F., İbadullayeva-Adıgözəlova, K.P. Oliqomenoreya olan qadınlarda antiovarian anticisimlərin honadotrop və steroid hormonları ilə assosiasiyası // - Bakı: Azərbaycan təbabətinin müasir nailiyyətləri, 2021. №1,- s. 60-65
6. Qurbanova, C.F., İbadullayeva-Adıgözəlova, K.P. Oliqomenoreya ilə fertil yaşda olan qadinlarda tiroid anticismlərinin tiroid hormonlari ilə qarşılıqlı əlaqəsi //- Bakı: Elm və tibb, Ə.Əliyev ad. Elmi praktik jurnal, 2021. №2 (24) - s. 52-53
7. İbadullayeva-Adıgözəlova, K.P. Reproduktiv yaşda olan oliqomenoreyalı qadınlarda hipotalamus-hipofiz-yumurtalıq sisteminin funksional vəziyyətinin və yumurtalıq ehtiyatının qiymətləndirilməsi // - Bakı: Sağlamlıq, 2021. №2,- s. 78-83
8. Ибадуллаева-Адыгезалова, К.Р. Корреляционная оценка половых и тиреоидных гормонов у пациенток с первичной олигоменореей в анамнезе // - Перм: Пермский медицинский журнал, 2021. Т.38, №6, - с.52-58

9. İbadullayeva-Adıgözəlova, K.P. Oligomenoreyalı qadınlarda antiovarian anticismlərin səviyyəsi // Əziz Məmmədkərim oğlu Əliyevin doğum gününə həsr olunmuş elmi-praktiki konfransın məcmuəsi, - Bakı: 2021, - s. 103-104
10. Ibadullayeva-Adygezalova, K.P., Results of testing thyroid antibodies in women with oliqomenorrhea // Обмен научными знаниями в условиях глобализации.Сорник научных трудов. Россия, Казань, 2021. – с. 154-155
11. Ибадуллаева-Адыгезалова, К.Р., Курбанова, Д.Ф. Ассоциация антиовариальных антител со стероидными гормонами у женщин с олигоменореей // Современная медицина: новые подходы и актуальные исследования, - Интернаука. Москва: 2021. №2(41), - с. 7-12

LIST OF ABBREVIATIONS

AIT	autoimmune thyroiditis
AB-TG	antibodies to thyroglobulin
AB-TPO	antibodies to thyroperoxidase
AOA	antiovarian antibodies
FSH	follicle-stimulating hormone
LH	luteinizing hormone
T3	triyodtironin
T4	tiroksin
TG	thyroglobulin
TPO	thyroid peroxidase
TSH	thyroid stimulating hormone
USE	ultrasound examination

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