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The Role Ovarian Index in Formation of Oligomenorrhea in Women with Autoimmunity

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ABSTRACT

Menstrual irregularities of the oligomenorrhea type may depend on the presence or absence of hormonal or metabolic disorders. Antiovarian antibodies to the ovaries (AOA) can be one of the causes of hormonal disorders and related menstrual disorders. The aim of the study was to assess the functional state of the ovaries in women with oligomenorrhea and to compare the presence of antiovarian antibodies (AOA) with a group of healthy fertile women.

Material and Methods: 105 patients of reproductive age with oligomenorrhea were examined. Control - 50 women of childbearing age with an undisturbed rhythm of menstruation. Body mass index was calculated, ultrasound was performed, LH, FSH, estradiol, total testosterone by immunochemiluminescent method, anti-Müllerian hormone (AMH) by ELISA, AOA by ELISA method were determined. Statistica software (Stat Soft, USA) was used for statistical analysis.

Results: The average age of patients with oligomenorrhea and the control group was 31.39 ± 6.05 and 30.52 ± 5.92 years. Body mass index averaged 25.59 ± 2.74 and 24.12 ± 2.77 kg / m^2, respectively, in the main and control groups. The volume of the ovaries in the main group was 13.22 ± 3.01, in the control group - 6.0 ± 1.26 ($p = 0.028$), the width of the stroma in the main group was 16.46 ± 3.25 mm, in the control group - 8.97 ± 1.16 mm ($p = 0.031$). The average LH level in women with oligomenorrhea was 51.75% higher than the control level ($p = 0.048$), the LH / FSH ratio was higher by 44.28% ($p = 0.007$), and the AMH value was higher by 33.86% ($p = 0.048$). The AOA level in the main group averaged 6.36 ± 1.14 ng / ml, in the control group - 3.06 ± 1.16 ng / ml ($p = 0.044$). In patients with oligomenorrhea, AOA correlated with all studied hormones by a statistically significant relationship, and a significant relationship was determined with the level of LH, AMH and estradiol. In contrast to the main group, in women with a normal menstrual cycle, AOA was correlated with a significant significant association with FSH, total testosterone, and a weak insignificant association with LH.

Conclusion: In women of reproductive age with oligomenorrhea, high levels of LH, AMH, LH / FSH and antiovarian antibodies are determined. Antiovarian antibodies to the ovaries in oligomenorrhea correlate with a direct, noticeable relationship with gonadotropic and steroid hormones. To identify the autoimmune process in patients with oligomenorrhea, it is necessary to determine antiovarian antibodies.

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Introduction

Menstrual irregularities are one of the most common reasons for visiting a gynecologist. According to the literature, the incidence of irregular menstruation varies from 5% to 35.6% and depends on age, place of residence, occupation, etc. [1, 2]. Irregular periods can be the result of hormonal imbalances and stress; these factors act as indicators and mediators of various health indicators in women. A type of menstrual dysfunction is oligomenorrhea, characterized by a reduction in the duration of menstruation (less than three days) and an increase in the interval between cycles (more than 40 days). The literature reports on the incidence of oligomenorrhea among women of fertile age in 12.5% of cases [3]. Oligomenorrhea has been reported to be associated with obesity, enlarged ovaries, and polycystic ovary morphology [4]. Oligomenorrhea has also been considered a risk factor for ovarian cancer, but research on this link is conflicting [5].

The clinical consequences of oligomenorrhea-type menstrual irregularities may depend on the presence or absence of concomitant problems, such as hormonal or metabolic disturbances.

One of the causes of hormonal disorders, and related menstrual disorders, can be antibodies to ovarian tissue - antiovarian antibodies (AOA). Autoimmunity is associated with an imbalance in the various components of the immune response and with the development of autoantibodies directed against normal self-antigens. Antibodies to multiple ovarian antigens have been proposed as markers of ovarian autoimmunity. The presence of these antibodies to various cellular components of the ovary can negatively affect conception, egg development, and the ability of the ovaries to produce steroid hormones in response to stimulation, disrupt the process of follicle maturation, and initiate their destruction [6]. Thus, the results of a number of studies indicate

the effect of autoimmunity on ovarian pathology. Antiovarian antibodies may be indicators of ovarian autoimmunity in patients with menstrual disorder. The aim of the study was to assess the functional state of the ovaries in women with oligomenorrhea and to compare the presence of antiovarian antibodies (AOA) with a group of healthy fertile women.

Materials and Methods

The study involved a total of 105 women of reproductive age. The study was conducted in accordance with the principles of the Declaration of Helsinki of the World Medical Association "Recommendations for physicians involved in biomedical research with human participation." [7]. All women who took part in the study signed an informed consent. The criteria for inclusion in the study were: - age 16-48; - the duration of the menstrual cycle from 43 days to 6 months; - the interval between menstruation is more than 35 days; - the duration of menstruation is 1-2 days. Exclusion criteria: - congenital anomalies; - congenital dysfunction of the adrenal cortex, hypothalamic-pituitary and ovarian insufficiency in combination with chromosomal abnormalities; - the presence of diseases of the thyroid gland, kidneys, diabetes; - diseases of the female pelvic organs; - neoplasms; - diseases of the blood and blood-forming organs; - pregnancy; - use of hormonal contraception.

The Control Group Consisted of 50 Women with an Undisturbed Rhythm of Menstruation

Primary oligomenorrhea was found in 52 (49.5%) patients, secondary oligomenorrhea - in 53 (50.5%) patients. The examination protocol included: collection of anamnesis, physical examination, calculation of body mass index (BMI) according to the formula: weight (kg) / height in m^2. Ovarian ultrasound was performed with a 7 MHz transvaginal convex probe on a Philips HD 6 apparatus (USA) on days 2-4 of menstruation. The study of follicle-stimulating hormone (FSH), luteinizing hormone (LH), estradiol, total testosterone was carried out in blood serum by the immunochemiluminescent method on an Immulite 1000 analyzer (Siemens, Germany) in the early follicular phase on the third day of the menstrual cycle. The concentration of anti-Müllerian hormone (AMH) in serum blood was determined by ELISA on a UniCel DxI 800 analyzer (Beckman Coulter, USA). The amount of AOA was determined in venous blood by solid-phase ELISA using the BIOSERV Ovary-Antibody-ELISA kit (BIOSERV Diagnostics GmbH, Germany). Statistical analysis of the results was carried out using Statistica software in Microsoft Excel release 6 (StatSoft, USA). Indicators were expressed as mean ± standard deviation (SD), absolute numbers and percentages. The study of differences in data for groups of patients was carried out using the Student's t-test. To assess the relationship between the studied parameters, the Spearman correlation analysis was used. Statistical scores were considered significant at $p < 0.05$.

Results

Patients of the main and control groups did not have significant differences in age. The average age of patients with oligomenorrhea and the control group was 31.39 ± 6.05 and 30.52 ± 5.92 years ($p = 0.918$, $t = 0.10$), respectively. Body mass index averaged 25.59 ± 2.74 and 24.12 ± 2.77 kg / m^2 ($p = 0.706$, $t = 0.38$), respectively, in the main and control groups. According to the anamnesis, the age of menarche in patients with oligomenorrhea was 13.27 ± 0.80 years, the control was 12.97 ± 0.72 ($p = 0.918$, $t = 0.10$). The duration of menstruation in the main group was 3.6 ± 0.68 days, in the control group 5.2 ± 1.32 days ($p = 0.283$, $t = 1.08$). The average number of pregnancies in the main group was 1.19 ± 1.18, in the control group - 1.67 ± 1.46 ($p = 0.798$, $t = 0.26$). In patients with oligomenorrhea, the number of deliveries averaged 0.63 ± 0.15, in the control group - 1.0 ± 0.10 ($p = 0.042$, $t = 2.05$), the number of abortions - 0.63 ± 0.15 and 0.38 ± 0.10 ($p = 0.049$, $t = 1.98$). Gynecological diseases in patients of the main group in comparison with the control group occurred more often by 47.63% ($p < 0.05$), and somatic diseases - by 8.47%.

According to ultrasound data, the volume of the ovaries in the main group was 13.22 ± 3.01, in the control group - 6.0 ± 1.26 ($p = 0.028$, $t = 2.21$), the width of the stroma in the main group was 16.46 ± 3.25 mm, in the group control - 8.97 ± 1.16 mm ($p = 0.031$, $t = 2.17$).

In the study of the hormonal profile in women of the main group in comparison with the control group, statistically significant changes were noted (Table 1).

Table 1: The Level of Hormones in Patients of the Examination Groups

Index	Main group (n=105)	Control group (n=50)	p	t-test
FSH, mIU / ml	5.16±0.75	6.38±0.70	0.236	1.19
LH, mIU / ml	10.28±2.41	4.96±1.13	0.048	2.00
LH / FSH	2.01±0,27	1.12±0.18	0.007	2.74
Estradiol, nmol / l	0.27±0.09	0.43±0.07	0.163	1.40
Total testosterone, nmol / l	2.43±0.56	1.48±0.34	0.149	1.45
AMH, ng / ml	6.38±0.86	4.22±0.66	0.048	1.99

The average LH level in women with oligomenorrhea was higher than the control level by 51.75% ($p = 0.048$, $t = 2.00$), the LH / FSH ratio - by 44.28% ($p = 0.007$, $t = 2.74$) and the AMH value - by 33.86% ($p = 0.048$, $t = 1.99$).

The AOA content in the main group varied from 0 to 106.70 ng / ml, which averaged 6.36 ± 1.14 ng / ml; in the control group, the AOA value varied from 0.20 to 8.50 ng / ml - on average 3.06 ± 1.16 ng / ml ($p = 0.044$, $t = 2.03$).

In the study of the correlation relationship between AOA and hormones in patients of both groups, direct relationships were determined (Table 2).

Table 2: Correlation Coefficient (R) of Aoa with Hormones in Patients of the Study Groups

Hormone	Main group (n=105)	Control group (n=50)
FSH	+0.214 p=0.034	+0.649 p<0.05
LH	+0.605 p=0.000	+0.109 p>0.05
Estradiol	+0.534 p=0.000	+0.469 p<0.05
Total testosterone	+0.272 p=0.007	+0.502 p<0.05
AMH	+0.538 p=0.000	+0.630 p<0.05

As can be seen (Table 2), in patients with oligomenorrhea, AOA correlated with all studied hormones by a statistically significant relationship, and a significant relationship was determined with the level of LH, AMH (Fig.) and estradiol. AOA correlated weakly

with FSH levels and total testosterone. In the control group, there was also a noticeable statistically significant correlation between AOA with estradiol and AMH. In contrast to the main group, in women with a normal menstrual cycle, AOA was correlated with a significant significant association with FSH, total testosterone, and a weak insignificant association with LH.

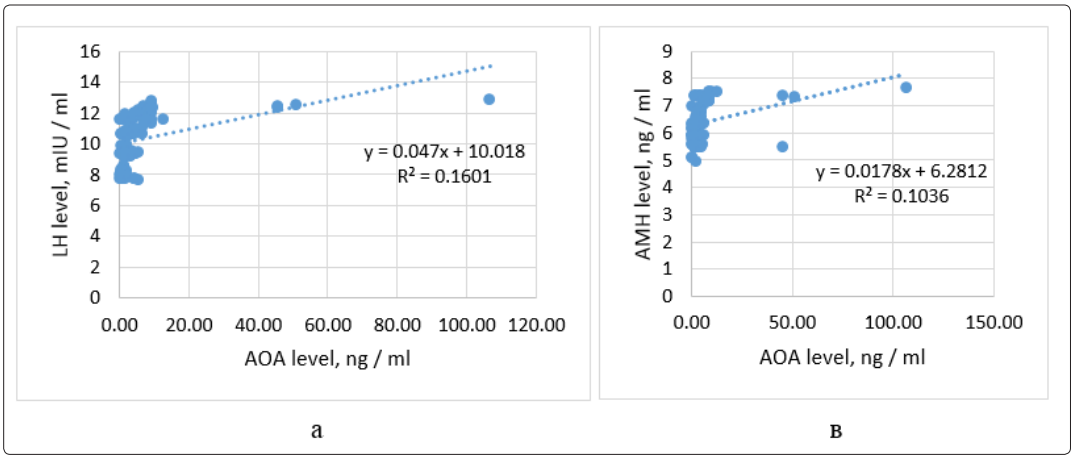

Figure: The correlation between AOA and LH level (a) and AMH (b) in women with oligomenorrhea

Discussion

Menstrual problems are one of the most common problems in women of childbearing age. In this study, we presented the results of assessing the ovarian hormonal profile and AOA content in women of reproductive age with oligomenorrhea. According to our data, women with oligomenorrhea of childbearing age, compared with women of a similar age with a normal menstrual cycle, had significantly high levels of LH, AMH, and the LH / FSH ratio, which confirms ovarian dysfunction in menstrual disorders. Researchers often note elevated LH levels in women with irregular menstrual periods [8, 9]. We note a decrease in the FSH content in patients with oligomenorrhea compared to the control group by 23.64% ($p > 0.05$), estradiol - by 59.26% ($p = 0.163$) and an increase in total testosterone by 39.09% ($p = 0.149$). Our results are comparable to those of other authors [8, 9]. The increase in total testosterone may be associated with a decrease in FSH levels. At the same time, an increase in the concentration of total testosterone is possibly the reason for an increase in the content of AMH [9]. It should be noted that, according to the literature, serum AMH levels are significantly associated with testosterone levels and oligo- or amenorrhea at the age of 16 and are a good indicator of oligomenorrhea in adolescence. An elevated AMH is likely to contribute to the development of polycystic ovary syndrome. [10].

We also evaluated the content of AOA and their relationship with the studied hormones. It should be noted that antibodies against the ovaries belong to a group of cells that are detected throughout the bloodstream. These cells are called "antibodies" because they actually work against certain functions of the ovaries. Usually antibodies are used by the body to fight invading bacteria and cells, however, sometimes the body mistakes its own cells for invading, and an example of this is antibodies against the ovaries [11, 12]. In women with oligomenorrhea, compared with the control group, there was a significant increase in the concentration of AOA to the ovarian tissue.

However, there are conflicting results regarding ovarian AOA levels. It has been established that autoimmune mechanisms, as well as increased production of multiple autoantibodies, are involved in disorders such as polycystic ovary syndrome [13, 14]. Studies have confirmed the high prevalence of AOA (30-67%) in patients with premature ovarian failure [6, 15]. Meanwhile, a number of studies report no difference in AOA levels between patients with polycystic ovary syndrome and healthy women [16, 17]. According to our results, AOA correlated with hormones in a significant straight line and, in general, a noticeable relationship. The association between AOA, which is considered a marker of autoimmunity, and gonadotropic, steroid hormones and AMH supports the hypothesis of an autoimmune etiology of menstrual disorders. It is reported that with autoimmune ovarian disease, the level of AOA increases, which are a highly specific serological marker and the main diagnostic criterion for autoimmune ovarian damage [18].

Thus, the pathogenetic role of antibodies to the ovaries is not fully defined. There is no consensus regarding AOA to the ovaries as a marker of ovarian autoimmunity. At the same time, since the presence of AOA is observed in women under 40 years of age with unexplained infertility and premature ovarian failure, it is believed that they are the cause of the onset and development of pathologies [19]. The authors believe that multiple targets are involved in ovarian autoimmunity, including ovarian cellular elements and oocyte-related antigens [20, 21]. Many studies evaluate only one target antigen, with the result that people with ovarian autoimmunity are not identified. Therefore, further prospective studies are needed to identify specific antigens.

Conclusion

In women of reproductive age with oligomenorrhea, high levels of LH, AMH, LH / FSH and antiovarian antibodies are determined. Antiovarian antibodies to the ovaries in oligomenorrhea correlate with a direct noticeable connection with gonadotropic and steroid hormones. To identify the autoimmune process in patients with oligomenorrhea, it is necessary to determine antiovarian antibodies.

Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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