



## OLIGOMENORRHEA IN ADOLESCENT GIRLS: CLINICAL, HORMONAL AND IMMUNOLOGICAL FEATURES

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**✓ Resume**

*The article presents comparative data of clinical, hormonal and immunological features of adolescent girls with oligomenorrhea. There are given health characteristics of girls with oligomenorrhea and hormonal features of various forms of the disease have been given. The immune status features of the patients with oligomenorrhea have been revealed: an increase in IL-1, IL-6, a decrease in the content of CD3+ and CD4+ lymphocytes, an increase in CD8+, CD16+, CD20+, CD25 which have been compared with the control group.*

**Keywords:** oligomenorrhea, adolescent girls, hormonal features, cytokines, cellular immunity

## O'SMIRLIK DAVRIDA OLIGOMENOREYA: KLINIK, GORMONAL VA IMMUNOLOGIK KO'RSATKICHLAR

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**✓ Rezyume**

*Maqolada oligomenoreya tashxisi qo'yilgan o'smir qizlarning klinik, gormonal va immunologik ko'rsatkichlari bo'yicha qiyosiy ma'lumotlar keltirilgan. Oligomenoreya bilan og'rigan qizlarning sog'lig'i holatining xususiyatlari va kasallikning turli shakllarining gormonal xususiyatlari berilgan. Oligomenoreya bilan og'rigan bemorlarda immunitet holatining xususiyatlari aniqlandi: nazorat guruhiga nisbatan IL-1, IL-6 ning ko'payishi, CD3+ va CD4+ limfotsitlari miqdorining pasayishi, CD8+, CD16+, CD20+, CD25 ning ko'payishi.*

**Kalit so'zlar:** oligomenoreya, o'smir qizlar, gormonal xususiyatlar, sitokinlar, hujayra immuniteti

## ОЛИГОМЕНОРЕЯ В ПОДРОСТКОВОМ ВОЗРАСТЕ: КЛИНИКО-ГОРМОНАЛЬНЫЕ И ИММУНОЛОГИЧЕСКИЕ ПОКАЗАТЕЛИ

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**✓ Резюме**

*В статье приводятся сравнительные данные клинико-гормональных и иммунологических показателей у девушки-подростков с диагнозом олигоменорея. Даны характеристика состояния здоровья девушки с олигоменореей и гормональные особенности различных форм заболевания. Выявлены особенности иммунного статуса у пациенток с олигоменореей: увеличение IL-1, IL-6, снижение содержания CD3+ и CD4+ лимфоцитов, увеличение CD8+, CD16+, CD20+, CD25 по сравнению с группой контроля.*

**Ключевые слова:** олигоменорея, девушки-подростки, гормональные особенности, цитокины, клеточный иммунитет

## **Relevance**

The state of reproductive health of adolescent girls is considered as one of the most important indicators of the reproductive potential of the population. The results of numerous studies are demonstrating that modern adolescents are characterized by increasing of the frequency of diseases of reproductive system, which is due to a number of exogenous and endogenous factors. The causative factors of the increasing in the incidence of pathology of the reproductive system at a young age include changes in sexual and reproductive behavior, leading to an increase in the number of unwanted pregnancies, an increase in the number of cases of infection with sexually transmitted infections. At the same time, the frequency of manifest violations of menstrual function in the form of oligo-menorrhea increases. These trends are of serious concern, since the health of adolescents determines the health of expectant mothers, gynecological diseases in adolescence potentially increase the frequency of reproductive disorders in the active reproductive age [7].

Oligomenorrhea is a violation of the menstrual cycle, manifested by scanty and rare menstruation. The diagnosis of oligomenorrhea is established on the basis of clinical data - the duration of the menstrual cycle is more than 42 days and less than 6 months or less than 8 periods per year. Oligomenorrhea should be considered as a symptom, as a predictor of early reproductive disorders, requiring identification of the cause and therapeutic measures. The causative factors of oligomenorrhea are numerous, the impact of an unfavorable factor or their combination causes pathological changes in one of the parts of the reproductive system, which ultimately lead to ovarian failure in varying degrees of severity.

Currently, much attention is paid to the pathogenetic relationships of the endocrine and immune systems in the development of various pathological conditions of the body. It has been established that interleukins, interferons and prostaglandins are synthesized and produced in nervous and endocrine glands tissues, which were recently classified as immunospecific. At the same time, the cyclicity of hormonal changes in the reproductive system is reflected in the indicators of cellular and humoral immunity, which determines the age-related features of these fluctuations [2,5]. Paying the attention to the high incidence of oligomenorrhea in adolescent girls, it seems significant to study this pathology in conjunction with hormonal and immunological parameters.

**Purpose:** to compare clinical, hormonal and some immunological parameters of oligomenorrhea and normal menstrual cycle in adolescents.

## **Material and methods**

We were examined 155 adolescent girls at age of 15-19 years old, 105 of them had that menstrual dysfunction as oligomenorrhea, 50 adolescents with timely commencement of menarche and established menstrual cycle. To clarify the genesis of oligomenorrhea it were performed, the following studies: anamnesis, clinical anthropometry, assessment of sexual development, ultrasound of the pelvic organs, MRI of the brain or MSCT of the adrenal glands (according to indications). Hormonal studies were carried out by ELISA and included the determination of serum concentrations of follicle-stimulating (FSH), luteinizing (LH) hormones, prolactin, estradiol, TSH, testosterone, according to indications - adrenocorticotrophic hormone, cortisol, 17-OH-P. Blood sampling was carried out in the morning on an empty stomach from the cubital vein.

To study the role of cellular immunity and cytokine status in the genesis of oligomenorrhea in adolescent girls it were formed 2 clinical groups: the main group included 46 adolescent girls with clinical signs of oligomenorrhea and the second group included 20 healthy girls with a normal menstrual cycle. In patients of both groups, blood was taken from the cubital vein on the 3rd-5th day of the menstrual cycle, indicators of hormonal status were determined, a detailed immunogram was performed with the determination of IL-1, IL-6, tumor necrosis factor (TNF). Determination of the subpopulation composition of lymphocytes.

The state of the immune system was assessed by the expression of CD differentiation antigens. Expression of CD receptors was carried out in the rosette reaction using monoclonal antibodies of the LT series manufactured by Sorbent LLC (Russia), according to the method of Garib F.Yu. et al. (1995). Cytokine concentrations were determined in blood serum by enzyme-linked immunosorbent assay using test systems of Vector-Best JSC (Novosibirsk, Russia), in accordance with the manufacturer's recommendations. The result was expressed as a number in pg/ml. Comparison of two groups in terms

of a quantitative indicator having a normal distribution, provided that the variances were equal, was performed using Student's t-test.

When studying the anamnestic data, the value of the Fisher criterion (F) and the level of its significance (P) were determined, which amounted to 0.05.

### **Results and discussion**

Finding out the causes of oligo-amenorrhea, their correct assessment is necessary not only for choosing a method of treatment, but also for early diagnosis, prognosis of reproductive function and appropriate prevention. It is known that the development of oligomenorrhea in girls is facilitated by numerous factors: diseases of the reproductive system, endocrinopathy, intense physical activity, chronic stress, weight loss, and much more. In the studies, the relationship between the pathological course of pregnancy and childbirth and the violation of the puberty process was revealed, the role of perinatal and postnatal factors in the diseases development of the reproductive system was determined. It is likely that the pathogenetic effect of causative factors manifests itself depending on their combination, the influence of each factor individually is ambiguous.

A number of anamnestic and clinical data have been identified that we have statistically significant differences in the comparison groups (Table 1). A high frequency of menstrual dysfunction (late menarche, irregular cycles, early menopause) was found at mothers or close maternal relatives of girls with oligomenorrhea - 45.7% versus 5% in the comparison group. The survey showed that the girls mothers health status is an important factor: in particular, thyroid disease, reproductive disorders in history in girls mothers in the study group significantly exceeded those in the comparison group. Statistically significant factors determined the past viral diseases in the child, deviations in weight (both in the direction of excess and its lack), recurrent AUB in anamnesis, as well as surgical interventions on the ovaries ( $P<0.05$ ).

Oligomenorrhea acts as a symptomatic diagnosis. The data of hormonal studies made it possible to identify the etiological factor of oligomenorrhea in the examined girls. The most significant causative factors were emerging polycystic ovaries - 33.5%, thyroid pathology - 7.6%, hyperprolactinemia 10.5%, hypothalamic syndrome with overweight/obesity - 10.5%, adrenal hyperandrogenism - 9%, oligomenorrhea which developed as a result of surgical interventions on the ovaries - 3.8%. In almost every fifth patient (19%) with oligomenorrhea, the clinical and hormonal examination did not allow to establish the cause of the disorder, or elimination of the alleged causative factor did not lead to the normalization of menstrual function - in this case, the condition was regarded as idiopathic oligomenorrhea. Primary oligomenorrhea in general amounted to 47.4%, secondary oligomenorrhea was diagnosed in 52.6%.

The study of cellular immunity and cytokine status in girls with oligomenorrhea revealed some features. Based on the results of cellular immunity, it can be said that in these patients, against the background of a general increase in the relative and absolute number of total lymphocytes, a decrease in the percentage of CD3+ and CD4+ lymphocytes, an increase in the number of CD8+, CD20+, CD16+, as well as the CD25+ activation marker, prevailed, in contrast to the control group. The immunoregulation index (CD4/CD8) was therefore lowered in this group of patients.

Cytokines are involved in the regulation of sex hormone secretion, modulation of the ovulatory process, and the functioning of the corpus luteum. We have investigated the following cytokines: tumor necrosis factor, interleukin-1 and interleukin-6, which have a pleiotropic effect on ovarian function, as known. These cytokines, according to some authors, are found in the follicular fluid and are presumably produced by granulosa cells. Gonadotropic hormones closely interact with the secretion of cytokines. Depending on the phase of the menstrual cycle, the quantitative ratio of cytokines may change. It is known that the activation of the immune system, manifested by a high level of pro-inflammatory cytokines, and in particular IL-1, can cause a violation of the functional state of the hypothalamic-pituitary-ovarian system. We found a significant increase in the amount of IL-1 in the blood serum of adolescent girls with oligomenorrhea in relation to the comparison group. In addition, the increased production of IL-1 is explained by its participation in the stress response of the body, which is due to the stimulating effect on its level of glucocorticoids and proves the relationship between the immune and neuroendocrine systems. These provisions are confirmed in studies that have shown that IL-1 affects all levels of the hypothalamic-pituitary-adrenal system, increasing the production of Corticotropin-

releasing hormone, ACTH, glucocorticoids, LH releasing factor, and other hormones: growth hormone, FSH, LH, prolactin.

**Table 1. Comparative assessment of anamnestic data in comparison groups.**

Characteristics	Main group n=105	Control n=50	P	F
Menstrual irregularities in mother/close relatives	48 (45,7%)	3 (5%)	<0,001	0,00001
Preterm birth	13 (12,3%)	6(12%)	>0,05	1
Early pregnancy toxicosis	11 (10,4%)	5 (10%)	>0,05	0,9
Maternal thyroid disease	21 (20%)	3 (5%)	<0,05	0,03
Past childhood viral infections (mumps, measles, rubella)	18 (17,1%)	3 (5%)	<0,05	0,05
Frequent colds	24 (23%)	11 (22%)	>0,05	0,9
Head injury/ CNS disease	14 (13,3%)	6 (12%)	>0,05	1,0
Threat of abortion	9 (8,6%)	3 (5%)	<0,05	0,75
Maternal infertility	16 (15,2%)	3 (5%)	<0,05	0,12
Excess body weight	19 (18%)	3 (5%)	<0,05	0,05
Underweight	20 (19%)	3 (5%)	<0,05	0,05
AUB in anamnesis	15 (14,2%)	0	<0,05	0,002
Amenorrhea in anamnesis	10 (9,5%)	0	<0,05	0,03
Hirsutism	48 (45,7%)	13 (25%)	<0,05	0,02
Thyroid diseases	16 (15,2%)	3(5%)	<0,05	0,12
Acne	16 (15,2%)	8 (15%)	>0,05	1,0
Striae	26 (25%)	5 (10%)	<0,05	0,03
Hepatitis in anamnesis	15 (14,2%)	5 (10%)	>0,05	0,6
Operations at the ovaries	9 (8,6%)	1 (0,9%)	<0,05	0,16
Ovarian cysts in anamnesis	8 (7,6%)	3 (5%)	>0,05	1,0
Allergic reactions in anamnesis	21 (20%)	6 (12%)	>0,5	0,26

According to R. Mathur et al. [6], TNF- $\alpha$  is produced by activated macrophages, granulosa cells, has an acute dose-dependent vasodilation and is involved in the processes of atresia and luteolysis in the ovaries. As pointed out by a number of authors [3,4], such changes can be mediated by TNF. According to the literature [3], the concentration of TNF- $\alpha$  of patients with oligomenorrhea also exceeds the control values. The actions of TNF- $\alpha$  and IL-1 overlap to a large extent.

**Table 2 Some indicators of cellular immunity in the comparison groups**

Index	Control group n=20	Main group N=46
Leukocytes	6420,0±1082,69	6986±1082,69
Lymphocytes %	28,57±3,85	34,61±6,49*
abs lymphocytes	1856±399,65	2413±846,11*
CD3%	55,9±3,88	49,0±4,77*
CD3 abs	1032,55±208,27	1174,48±409,37
CD4%	35,40±2,95	31,7±1,26*
CD4 abs	659,7±161,88	772,35±329,11
CD8%	22,95±1,99	34,17±6,98*
CD8 abs	427,05±100,25	820,78±285,16*
CD4/CD8	1,54	0,92
CD20%	22,95±2,46	32,95±4,93*
CD20 abs	423,95±92,77	808,61±306,87*
CD16%	14,3±4,84	29,13±5,6*
CD25%	22,6±2,46	29,3±4,98*
CD95%	25,00±2,73	24,04±5,41
IL-1 $\beta$	18,51±4,03	26,19±3,75*
IL-6	13,78±3,8	32,67±14,53*
TNF- $\alpha$	17,17±4,06	27,84±6,25*

Note: \* $p<0,05$

As a result of our study, it was found that the level of IL-6 of girls with oligomenorrhea was also significantly higher than the values of the control group. Taking into account the main biological effect of IL-6, which is associated with its participation as a cofactor in the differentiation of B-lymphocytes, their maturation and transformation into plasma cells that secrete immunoglobulins, it can be assumed that excessive production of IL-6 is a compensatory reaction to maintain the level of immunoglobulins, in this group of patients. In a normally functioning organism, there is a certain balance of interaction between Th-1 and Th-2 helpers; however, a strong change in their activity under the influence of the hormonal system can lead to serious adverse consequences in the reproductive system.

### Conclusions

Thus, the conducted studies have shown that changes in the level of a number of hormones in oligomenorrhea also affect the synthesis of pro-inflammatory cytokines. The revealed clinical and hormonal characteristics and the accompanying changes in cellular immunity indicate the need for a detailed study of the possible interdependence of these processes, in particular in idiopathic oligomenorrhea.

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