

## Risk Factors for Reproductive Disorders in Adolescent Girls

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**Abstract:** The article presents clinical and laboratory analytical data on the occurrence of reproductive disorders in adolescent girls. Risk factors for menstrual disorders have been identified. Polymorbidity of the premorbid background was shown, which was more aggravated in patients with the manifestation of disorders in the form of uterine bleeding. The need for a comprehensive differentiated approach to the treatment of patients with menstrual disorders has been established.

**Keywords:** puberty, risk factors, dysmenorrhea, premorbid background, inflammation, sex hormones.

Negative trends towards an increase in the incidence of both somatic and gynecological diseases among adolescent girls have a negative impact on the formation of the female reproductive system. The premorbid background of patients becomes polymorbid due to a variety of chronic diseases and morphofunctional abnormalities, which is largely a "fertile ground" for the development of various disorders of the immature reproductive system - menstrual function disorders occur, from amenorrhea to uterine bleeding [1,3]. However, many questions regarding the mechanisms of occurrence and development of these reproductive disorders in adolescent girls have not been studied, management tactics are diverse, the available single reports need additions and clarifications, and, consequently, in-depth study of the problem. The purpose of our study is to study risk factors and links in the pathogenesis of menstrual function disorders in adolescent girls.

**Research materials and methods:** To achieve the intended goal, we identified girls with reproductive disorders (n=110) during preventive examinations (2020-2023) (n=900). The age of the subjects ranged from 10 to 19 years ( $14.8 \pm 1.3$ g). In accordance with the intended purpose of the study, the examined teenage girls were divided into two comparative groups: Group 1 – primary amenorrhea, hypomenstrual syndrome (n=55), Group 2 – uterine bleeding during puberty (n=55). The control group consisted of teenage girls with a normal menstrual cycle (n=20). The criteria for inclusion in and exclusion from the study corresponded to those generally accepted in gynecological practice for pubertal uterine bleeding and amenorrhea (hypomenstrual syndrome).

The physical and sexual development of teenage girls was studied using generally accepted methods and standards for diagnosing gynecological diseases in teenage girls. An objective assessment of sexual development was carried out using the common Tanner method, which includes the following elements: stages of development of the mammary glands (Ma), stages of development of pubic hair (Pb) and in the armpits (Ax), age of first menstruation (Me). Laboratory and instrumental research methods were carried out: traditional general clinical blood tests, coagulogram, ultrasound examination of the uterus and appendages; bacteriological studies taking into account the sensitivity of the isolated microflora; determination of the levels of sex

hormones and cytokines (interleukins) in blood serum using the RANDOX Biochip Chemiluminescence analysis method according to the protocols of the manufacturers of reagent kits. If necessary, consultations with related specialists. Statistical processing of the material was carried out using modern programs Microsoft Excel 2013, Statistica and MedCalc.

All studies were conducted taking into account the requirements of the Helsinki Declaration of the World Association "Ethical Principles of Scientific and Medical Research with human participation", normative documents, according to the principles of evidence-based medicine.

### **Results of our own research.**

To clarify the mechanisms of development of reproductive disorders, determine their functional role in the chronology of the development of disorders of the reproductive system and menstrual function, we analyzed in detail the risk factors for their development. Analysis of the premorbid background in the examined patients revealed multisystem disorders, some of which are in the chronic stage. Almost every third patient of both groups had gastrointestinal tract infections (enterocolitis 32% and 36%, gastritis- 31% and 68%, respectively), hepatitis A (15% and 21%). Diseases of the upper respiratory tract (bronchitis, chronic tonsillitis, rhinosinusitis) It was noted in every fourth patient (23% and 29%, respectively), anemia – group 1 - 35% and -69% in patients of group N. In childhood and puberty, all the patients we examined suffered from inflammatory diseases and many childhood infections: measles (60%), infectious mumps (25%), scarlet fever (22%), whooping cough (17%), rubella (5%). The value of the infectious index in most cases exceeded the average population data, amounting to 5 or more diseases in one patient. It should be noted the high incidence of chronic tonsillitis with annual seasonal exacerbations in childhood and puberty (53% and 77%, respectively) of thyroid and genitourinary system diseases (cystitis, pyelonephritis) up to 35% in the compared groups. The somatic background turned out to be the most burdened in patients of group N, where the pathology of the hepatobiliary complex prevailed  $n = 69\%$ , in the 1st comparison group this pathology occurred in every third patient ( $n=31\%$ ). Neuroendocrine diseases were found in every second patient in all the compared groups (up to 48%). Kidney diseases (chronic pyelonephritis) and central nervous system pathology in the form of adolescent vegetative-vascular dystonia were found in (21% in patients of group 1 and 69% in patients of group N. A characteristic feature of extragenital diseases was their double or triple combination in one patient and the anemized background on which they developed. It should be noted that all of the above violations of puberty in the examined patients of the compared groups occurred against the background of inflammatory diseases of the pelvic organs: vulvovaginitis - 76%-84%, respectively; salpingoophoritis -26%-56%, respectively.

Also, to identify risk factors for emerging reproductive disorders, the mothers' medical history, the age of onset and the nature of the course of this pregnancy (by our patient), complications of this pregnancy and childbirth were studied in detail. A high incidence of anemia (38%), threatened miscarriage (48%), hypertensive disorders (6%), and diseases of the genitourinary system (11%) was noted. Intrauterine hypoxia and fetal asphyxia at birth were noted in 22%, reduced height and weight indicators - 19%. Metabolic endocrine diseases in mothers accounted for 21%: among them, thyroid gland pathology -16%, obesity -19%. Among other hereditary diseases, hypertension was noted - 6%, consanguineous marriage - 2%.

Thus, a comparative analysis of somatic pathology in the examined patients showed its aggravation in patients of both groups compared, however, in patients of group P, the premorbid background and heredity turned out to be more burdened, polymorbid. The transferred extragenital and genital diseases of inflammatory origin had a significant impact on the nature of the formation of menstrual function in patients of the compared groups.

To clarify the mechanisms of menstrual dysfunction in patients with normal and impaired sexual development, a comparative analysis of the clinical manifestations of the menstrual cycle in the examined patients was carried out.

By the time of the examination, menstrual irregularities were observed in all patients (groups 1 and N). The duration of menstrual irregularities ranged from five months to three years. During this period, 80% of patients did not go to a doctor, 20% of patients received treatment that turned out to be ineffective.

Comparative characteristics of menstrual dysfunction in the examined patients showed earlier (44%) or later (58%) menarche against the background of a long development of the menstrual cycle (88%). Patients of group 1 are characterized by a high frequency of an unsteady menstrual cycle, accompanied by severe pain (83%). Also, these patients are characterized by a tendency to develop secondary amenorrhea and oligo-opsomenorrhea (up to 91%). Patients of group P are characterized by heavy, long periods (10-18 days) from the moment of menarche (77%), their recurrence (44%).

The high frequency of premenstrual syndrome in the examined patients (31% and 63%, respectively), as well as the associated mammary gland pathology - functional mastopathy up to 30% in group II patients indicate a multiplicity of functional disorders in the completely unformed body of teenage girls.

Thus, a comparative analysis of the clinical manifestations of menstrual dysfunction in teenage girls showed the greatest burden in patients of group P, where there were risk factors in the form of a burdened somatic and gynecological history. The premorbid background turned out to be burdened by somatic and gynecological diseases of inflammatory origin, mainly in patients of group P, where the intensity of menstrual irregularities was higher.

All examined patients received anti-inflammatory treatment with antibiotics taking into account the antibiogram. Patients of group 1 additionally received traditional hormonal treatment with a drug containing an active substance equivalent to estradiol 2.00 mg and dydrogesterone 10 mg for a course of 3 months. Patients of group P additionally received hemostatic therapy with traditional sex steroid hormones (ethinyl estradiol 30 µg + desogestrel 0.75 µg) initially to stop bleeding, then to normalize the menstrual cycle in a cyclic mode for 3 months. The starting dose of hemostasis depended on the severity and duration of bleeding, the patient's weight, ranging from 2 to 4 tablets, followed by a transition to a cyclic regimen. The polymorbidity of the background dictated the need for consultation with related specialists (neurologist, endocrinologist), whose recommendations were taken into account when choosing adequate management tactics, and at the same time correction of the identified disorders was carried out. Positive dynamics were observed at 2 months of treatment, a persistent positive effect was observed at 3 months from the start of treatment.

Positive clinical dynamics were combined with laboratory and instrumental indicators. The concentration levels of sex hormones (estradiol, progesterone, FSH, LH) in the blood serum were studied.

The analysis of the hormonal profile before treatment in the examined patients showed diametrically divergent concentrations of sex hormones. The basal level of tropic hormones of the adenohypophysis in the control and main groups before the start of treatment corresponded to the reference normative values (FSH  $3.73 \pm 0.18$  IU/l; LH  $2.96 \pm 0.11$  IU/l) ( $p < .001$ ). However, the concentration of estradiol in the compared groups was diametrically opposite: in the group of patients with uterine bleeding, the concentration of estradiol  $189.9 \pm 7.3$  nmol/l was increased; in group 1 with amenorrhea, the estradiol level was reduced by  $131.5 \pm 5.1$  nmol/l, respectively, compared with the control of  $179.2 \pm 7.32$  nmol/l. The AMH value in the control group was  $2.4 \pm 0.03$  ng/ml, in the main groups  $1.85 \pm 0.05$  ng/ml,  $1.83 \pm 0.06$  ng/ml, respectively ( $p < 0.001$ ). The concentration of testosterone in both compared groups was higher than  $1.12 \pm 0.06$  nmol/l than in the control group  $0.84 \pm 0.04$  nmol/l. The obtained laboratory data indicated the presence of ovarian insufficiency in the examined patients of the main groups.

Ultrasound results in the control group corresponded to the age norm. However, in patients of the main groups before treatment, against the background of the normative sizes of the uterus, the M-echo on days 2-3 of the cycle showed different thickness of the endometrium: group 1 - a thin line of  $2.4 \pm 0.05$  mm, group II in the form of a wide line (endometrial hyperplasia).  $15.7 \pm 0.09$  mm, several single follicles (1-2) with a diameter of 2-3 mm and small pinpoint follicles in the amount of 6-9 with a diameter of 1-2 mm. There were no signs of ovulation in both groups of patients. These data indicate ovarian and uterine incompetence in patients of the main groups.

Hormonal profile indicators at the end of treatment showed positive dynamics in the levels of sex hormones: a decrease in the concentration of androgens in patients of the main groups to  $0.89 \pm 0.03$  nmol/l, a decrease in the level of estradiol to reference values in patients of group P  $181.3 \pm 2.1$  nmol/l, an increase in the concentration of estrogens in patients of group 1 up to  $169.6 \pm 8.3$  nmol/l, respectively, compared to the control  $179.2 \pm 7.32$  nmol/l. There was also a leveling of AMH levels to normative data:  $2.3 \pm 0.03$  ng/ml and  $2.21 \pm 0.02$  ng/ml ( $p < 0.0001$ ), respectively.

Ultrasound results after treatment in all patients of the main groups revealed positive changes in the form of a decrease in the size of the hyperplastic endometrium - a narrowing of the endometrial line of  $5.3 \pm 0.02$  mm in patients of group P, a slight increase in the thickness of the endometrium of  $5.1 \pm 0.05$  mm in patients of group 1. In both comparison groups, increased echogenicity of the endometrium was noted, which indicated the appearance of full secretion; healthy early antral follicles appeared in the ovaries in the amount of 4-5, fine grain disappeared. Visual ultrasound signs indicated a decrease in ovarian and uterine insufficiency and the appearance of ovarian capacity.

The hemostasiogram parameters did not reveal statistically significant differences in the compared groups in the dynamics of treatment: the blood clotting time before treatment began at 2.58 s. /end 3.45 sec. after treatment, blood clotting time began 2.44 s./end 3.27 s.

In parallel with the positive dynamics in laboratory and instrumental research methods, there was an improvement in clinical symptoms, stopping uterine bleeding in patients of group N, and the appearance of menstruation (meager) in patients of group 1. These data indicate the restoration of the rhythm of menstruation, the appearance of a two-phase menstrual cycle (65%).

Thus, a comprehensive assessment of the state of the reproductive function of a teenage girl with the identification of risk factors as predictors of menstrual dysfunction will allow us to differentially develop the most effective methods of correcting the disorders that have arisen, monitor the dynamics and predict the outcome of the disease.

### **Conclusions:**

1. Diseases of inflammatory origin (both genital and extragenital) have a negative impact on the formation of menstrual function in adolescent girls and act as triggers of reproductive disorders.
2. Complex differentiated treatment of menstrual cycle disorders (anti-inflammatory treatment + correction of the hormonal profile allows pathogenetically adequate restoration of folliculogenesis, normalization of the balance of the hormonal profile, which is clinically manifested by the restoration of the menstrual cycle.

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