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NEUROENDOCRINE AND AUTONOMIC MECHANISMS OF MENSTRUAL CYCLE DISORDERS IN ADOLESCENT GIRLS: PROGNOSTIC ASSESSMENT USING ROC-ANALYSIS

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Abstract.

Menstrual cycle disorders (MCD) in adolescent girls frequently co-occur with autonomic dysfunction (AD), forming a persistent clinico-functional complex that compromises quality of life and increases the risk of chronic reproductive and psychosomatic disorders.

Objective. *To investigate the clinical and diagnostic interdependence of autonomic dysfunction and menstrual cycle disorders in adolescent girls, identifying clinical and functional markers of autonomic regulation associated with the pattern and severity of menstrual irregularities.*

Materials and methods. *The study cohort comprised 79 adolescent girls aged 13-18 years presenting with MCD and signs of AD (study group), alongside 29 apparently healthy adolescents serving as controls. Autonomic status was evaluated using the Wayne scale and the Kerdo index. All patients underwent pelvic ultrasonography; brain magnetic resonance imaging was performed when clinically indicated Hormonal evaluation included thyroid-stimulating hormone, prolactin, luteinizing hormone, follicle-stimulating hormone, and testosterone levels. Receiver operating characteristic (ROC) analysis was employed. The study was conducted following the ethical principles for biomedical research, and the protocol was approved by the Local Ethics Committee of Samarkand State Medical University. All procedures were performed in accordance with the 2013 revision of the Declaration of Helsinki of the World Medical Association. Written informed consent was obtained from all participants or their legal representatives prior to enrollment. Patient data confidentiality was strictly maintained throughout the study. Statistical analyses were performed using the Statistica and SPSS software packages, with statistical significance set at $p < 0.05$. This work was conducted as part of the research program of Samarkand State Medical University, titled «Optimization of early diagnostic, therapeutic, and preventive strategies for pathological conditions affecting public health in the Samarkand Region» (2022-2026).*

Results. *Asthenic complaints were reported by 63.3% of patients in the study group compared with 13.8% in the control group ($p < 0,001$). Ovarian abnormalities were detected by ultrasonography in 57.0% of patients. Elevated prolactin levels were recorded in 32.9%, thyroid-stimulating hormone abnormalities in 29.1%, and increased testosterone concentrations in 24.1% of cases. Receiver operating characteristic analysis indicated that the Wayne scale (area under the curve [AUC] = 0.82; 95% confidence interval [CI]: 0.73-0.91) and the Kerdo index (AUC = 0.79; 95% CI: 0.69-0.88) exhibited the highest prognostic value. These findings corroborate the predominant role of the autonomic nervous system and neuroendocrine mechanisms in the pathogenesis of menstrual cycle disorders in adolescent girls. The severity of clinical and autonomic manifestations was significantly greater in the study group than in the control group, underscoring the significance of autonomic dysfunction as a primary pathogenetic factor of reproductive disorders during adolescence. Instrumental and laboratory data demonstrated a close association between functional alterations in autonomic regulation and hormonal disturbances of the hypothalamic-pituitary-ovarian and thyroid axes. The absence of structural alterations in the hypothalamic-pituitary region on magnetic resonance imaging among the examined patients emphasizes the predominantly functional nature of the identified disorders. The substantial prognostic value of hormonal and ultrasonographic parameters justifies their inclusion in a comprehensive diagnostic algorithm for adolescents presenting with this condition.*

Conclusions. *Autonomic dysfunction and neuroendocrine dysregulation play a pivotal role in the development and progression of menstrual cycle disorders in adolescent girls. The Wayne scale and the Kerdo index serve as informative prognostic tools with high sensitivity and specificity. An integrative diagnostic approach incorporating clinical, autonomic, hormonal, and instrumental data is justified for this patient population.*

Keywords: *Adolescent Girls; Menstrual Cycle Disorders; Autonomic Dysfunction; Neuroendocrine Regulation; Hormonal Profile; ROC analysis.*

Introduction

Menstrual cycle disorders (MCD) in adolescent girls represent a pressing issue in adolescent gynecology and pediatric neurology, as they frequently co-occur with autonomic dysfunction (AD), forming a persistent clinico-functional complex that compromises quality of life and increases the risk of chronification of pain and psychosomatic disorders [1, 4, 7].

The prevalence of menstrual disorders among adolescents remains high, with dysmenorrhea and premenstrual symptoms representing the most frequent manifestations and reaching prevalence rates of double-digit percentages or higher [2]; in certain clinical cohorts, the proportion of adolescents presenting with menstrual complaints exceeds 90% [3]. Neurovegetative mechanisms underlying dysmenorrhea and MCD are actively investigated in the global literature. Evidence indicates that a subset of patients exhibits signs of autonomic imbalance, including alterations in heart rate variability [5], thereby supporting the concept of autonomic nervous system involvement in the pathogenesis and severity of clinical symptoms. Findings concerning autonomic dysfunction across specific menstrual disorder phenotypes, however, remain inconsistent, varying according to age, phenotype, and the assessment methods utilized for autonomic regulation [6].

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Puberty constitutes a vulnerable developmental stage for the onset of autonomic disturbances, which frequently precipitate MCD. In the Republic of Uzbekistan, this issue is of particular significance given the increasing incidence of menstrual function disorders among adolescent girls and the persistent need for comprehensive diagnostic models that integrate endocrine and autonomic mechanisms [10, 11]. Critical questions regarding the diagnostic markers with the highest prognostic value and the establishment of a reproducible diagnostic pathway for adolescents presenting with concurrent AD and MCD remain unresolved despite considerable interest in this subject [12, 13].

Study objective.

To investigate the clinical and diagnostic interdependence of autonomic dysfunction and menstrual cycle disorders in adolescent girls, identifying clinical and functional markers of autonomic regulation associated with the pattern and severity of menstrual irregularities.

Materials and methods

The study cohort comprised adolescent girls presenting with clinical manifestations of MCD accompanied by signs of autonomic insufficiency or dysfunction. These patients were managed in both outpatient and inpatient settings at the Multidisciplinary Clinic of Samarkand State Medical University (comprising the outpatient department, the Department of Pediatric Neurology, and the Pediatric Somatic Department) and the Multidisciplinary Children's Hospital of Samarkand (including the Departments of Pediatric Gynecology, Pediatric Neurology, and Pediatric Somatic Medicine).

The study cohort comprised 79 patients aged 13-18 years, with the observation period spanning 2024-2025. Inclusion criteria encompassed clinical manifestations of MCD concurrent with symptoms of AD, an MCD duration exceeding 6 months prior to enrollment or primary amenorrhea, diagnoses corresponding to International Classification of Diseases, Tenth Revision (ICD-10) codes N91–N94 for menstrual cycle disorders and G90 for autonomic nervous system disorders, and written informed consent obtained from the patients or their parents. Exclusion criteria comprised acute or severe neurological diseases, inflammatory and autoimmune diseases in the exacerbation stage, oncological pathologies, acute infectious processes, severe decompensated somatic conditions, and congenital or severe gynecological developmental anomalies.

Patients in the study group were stratified by the severity of clinical manifestations into those with mild disturbances (n = 34; 43.0%) and those with moderate disturbances (n = 45; 57.0%). Evaluation of autonomic tone using the Kerdo index revealed sympathicotonia in 38 patients (48.1%), vagotonia in 26 (32.9%), and a mixed type in 15 (19.0%). The control group consisted of 29 age-matched apparently healthy adolescent girls.

The severity of AD was assessed using the Wayne scale, while autonomic tone was evaluated via the Kerdo index. All patients underwent pelvic ultrasonography to evaluate ovarian dimensions, ovarian structure, and endometrial thickness. Brain magnetic resonance imaging (MRI) with targeted visualization of the sella turcica was performed in cases of severe MCD concurrent with AD. Hormonal profiling included the measurement of thyroid-stimulating hormone, prolactin, luteinizing hormone, follicle-stimulating hormone, and testosterone levels. Receiver operating characteristic (ROC) analysis was employed to evaluate the prognostic value of these parameters.

The study was conducted following the ethical principles for biomedical research, and the protocol was approved by the Local Ethics Committee of Samarkand State Medical University. All procedures were performed in accordance with the 2013 revision of the Declaration of Helsinki of the World Medical Association. Written informed consent was obtained from all participants or their legal representatives prior to enrollment. Patient data confidentiality was strictly maintained throughout the study.

Statistical analyses were performed using the Statistica and SPSS software packages. Quantitative variables are expressed as mean ± standard deviation (SD) or median with interquartile range (IQR). Qualitative variables are presented as absolute frequencies and percentages. Intergroup comparisons were conducted using the Mann–Whitney U test, the Kruskal–Wallis test, and the Pearson chi-square test. Correlation analysis was performed using the Spearman rank correlation coefficient (r), and receiver operating characteristic (ROC) analysis was employed to determine the area under the curve (AUC), sensitivity, and specificity, with statistical significance established at $p < 0.05$.

This work was conducted as part of the research program of Samarkand State Medical University entitled «Optimization of early diagnostic, therapeutic, and preventive strategies for pathological conditions affecting public health in the Samarkand Region» (2022-2026).

Results and discussion

Clinical evaluation indicated that adolescent girls in the study group reported emotional lability, increased fatigability, headaches, palpitations, dizziness, and sleep disturbances significantly more frequently than their counterparts in the control group. Clinical signs of autonomic lability were identified in 58.2% of the patients in the study group, compared with only 10.3% of the controls ($p < 0.001$) (Table 1).

Pelvic ultrasonography revealed structural and functional ovarian alterations in 45 (57.0%) patients in the study group, compared with isolated cases in the control group (6.9%; $p < 0.001$). The most frequently observed findings included multifollicular ovarian morphology, ovarian size asymmetry, and endometrial thickness discordant with the menstrual cycle phase.

Brain magnetic resonance imaging (T1-weighted images, sagittal plane) revealed no gross focal or space-occupying lesions in the examined adolescent girls. The cortical and subcortical structures were normally formed; the pituitary gland was normally positioned, maintaining its typical shape, with smooth contours, a homogeneous structure, and dimensions consistent with age-specific norms; no evidence of space-occupying lesions or deformation of the sella turcica was observed. The absence of structural alterations in the hypothalamic-pituitary region underscores the predominantly functional nature of the identified neuroendocrine disturbances.

Table 1

Clinical and autonomic manifestations in the examined adolescent girls

Parameter	Study group (n=79)	Control group (n=29)	p
Asthenic complaints, n (%)	50 (63.3%)	4 (13.8%)	<0.001
Headaches, n (%)	42 (53.2%)	5 (17.2%)	0.001
Sleep disturbances, n (%)	37 (46.8%)	3 (10.3%)	<0.001
Palpitations, n (%)	31 (39.2%)	2 (6.9%)	0.002
Orthostatic instability, n (%)	29 (36.7%)	1 (3.4%)	<0.001
Autonomic lability (clinical), n (%)	46 (58.2%)	3 (10.3%)	<0.001

Note: Differences were evaluated using the Pearson χ^2-test

Evaluation of the hormonal profile revealed significantly higher rates of pituitary and thyroid hormone level deviations in the study group. Elevated prolactin levels were recorded in 32.9% of patients, thyroid-stimulating hormone (TSH) abnormalities in 29.1%, and increased testosterone concentrations in 24.1%, whereas such alterations were confined to isolated cases in the control group ($p < 0.05$) (Table 2).

Table 2

Instrumental and laboratory parameters in the examined patients

Parameter	Study group (n=79)	Control group (n=29)	p
Ovarian abnormalities detected by ultrasonography, n (%)	45 (57.0%)	2 (6.9%)	<0.001
Elevated prolactin, n (%)	26 (32.9%)	1 (3.4%)	0.001
TSH abnormalities, n (%)	23 (29.1%)	1 (3.4%)	0.003
Elevated testosterone, n (%)	19 (24.1%)	0	0.004
Moderate/severe autonomic dysfunction, n (%)	52 (65.8%)	4 (13.8%)	<0.001

Note: the Pearson χ^2-test; statistical significance was set at $p < 0.05$.

Correlation analysis revealed significant associations between the severity of AD and both laboratory and instrumental parameters. Positive correlations were identified between the total Wayne scale score and prolactin levels ($r = 0.52$; $p = 0.002$) and between the Kerdo index and ultrasonographic evidence of ovarian dysfunction ($r = 0.47$; $p = 0.004$). An inverse correlation was observed between thyroid-stimulating hormone levels and menstrual cycle regularity ($r = –0.44$; $p = 0.006$) (Table 3).

Table 3

Correlations among clinical, hormonal, and autonomic parameters

Parameters	r	p
Wayne scale ↔ prolactin	0.52	0.002
Kerdo index ↔ ovarian abnormalities detected by ultrasonography	0.47	0.004
TSH ↔ menstrual cycle regularity	–0.44	0.006
Autonomic score ↔ severity of clinical complaints	0.56	<0.001

Note: r denotes the Spearman correlation coefficient.

To evaluate the prognostic value of clinical, functional, hormonal, and instrumental parameters in the development of severe MCD in adolescent girls, ROC analysis was performed. An unfavorable outcome was defined as the presence of persistent, clinically significant MCD concurrent with moderate or severe AD. The highest prognostic value was demonstrated by the Wayne scale scores and the Kerdo index, whereas prolactin and TSH levels, along with ultrasonographic evidence of structural and functional ovarian alterations, contributed substantially to the predictive model (Table 4).

Table 4

Results of ROC analysis for predicting menstrual cycle disorders in adolescent girls

Parameter	AUC	95% CI	Sensitivity, %	Specificity, %
Wayne scale (points)	0.82	0.73-0.91	78.5	75.9
Kerdo index	0.79	0.69-0.88	74.1	72.4
Prolactin	0.76	0.66-0.86	70.3	69.0
TSH	0.73	0.62-0.84	68.4	65.5
Testosterone	0.71	0.60-0.82	66.7	62.1
ovarian abnormalities detected by ultrasonography	0.78	0.68-0.88	72.6	71.8
MRI (sella turcica alterations)	0.69	0.57-0.81	61.9	66.7

Note: AUC denotes the area under the ROC curve; CI indicates confidence interval. AUC values ≥ 0.70 were considered indicative of good prognostic value. Statistical significance was set at $p < 0.05$.

These findings corroborate the predominant role of the autonomic nervous system and neuroendocrine mechanisms in the pathogenesis of MCD in adolescent girls. The severity of clinical and autonomic manifestations was significantly greater in the study group than in the control group, a finding consistent with contemporary literature identifying AD as a primary pathogenetic factor in adolescent reproductive disorders [14]. A close association between functional alterations in autonomic regulation and hormonal disturbances of the hypothalamic-pituitary-ovarian and thyroid axes was established through instrumental and laboratory evaluations [15].

The absence of structural alterations in the hypothalamic-pituitary region on magnetic resonance imaging among the examined patients underscores the predominantly functional nature of the identified disorders [16]. The high AUC values for the Wayne scale and the Kerdo index indicate the potential utility of autonomic dysfunction parameters as early risk markers for an unfavorable course of menstrual cycle disorders [17, 18]. The substantial prognostic value of specific hormonal and ultrasonographic parameters justifies their integration into a comprehensive diagnostic algorithm for adolescents presenting with this condition.

Conclusions

1. Autonomic dysfunction and neuroendocrine dysregulation play a pivotal role in the development and progression of menstrual cycle disorders in adolescent girls: autonomic lability was identified in 58.2% of the study group, elevated prolactin in 32.9%, thyroid-stimulating hormone abnormalities in 29.1%, and increased testosterone concentrations in 24.1%.

2. ROC analysis identified the Wayne scale (area under the curve [AUC] = 0.82) and the Kerdo index (AUC = 0.79) as the most informative prognostic parameters for an unfavorable course of menstrual cycle disorders, demonstrating high sensitivity (78.5% and 74.1%, respectively) and specificity (75.9% and 72.4%, respectively).

3. An integrative diagnostic approach incorporating clinical, autonomic, hormonal, and instrumental data is justified for adolescent girls presenting with concurrent autonomic dysfunction and menstrual cycle disorders, facilitating the transition from a descriptive assessment to a prognostically oriented observation model.

Future research directions. Multicenter prospective studies with expanded cohorts are warranted to validate the developed prognostic models. Longitudinal follow-up of these patients is of particular interest to evaluate the impact of the identified autonomic and neuroendocrine disturbances on reproductive health in adulthood. The development of personalized diagnostic and management algorithms for adolescents with menstrual cycle disorders and autonomic dysfunction, incorporating the identified predictors such as the Wayne scale and Kerdo index scores, is recommended to enable timely risk stratification and optimize rehabilitation programs.

Author contributions. N. Abdullayeva: conceptualization, scientific supervision, study design, critical analysis of the results, and final manuscript editing; A. Dzjurabekova: study design, organization of the clinical examination, data interpretation, and manuscript editing; D. Kenjaeva: clinical data collection, statistical analysis, and preparation of the initial manuscript draft; J. K. Ismatov: statistical analysis and preparation of the initial manuscript draft.

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НЕЙРОЕНДОКРИННІ ТА ВЕГЕТАТИВНІ МЕХАНІЗМИ ПОРУШЕНЬ МЕНСТРУАЛЬНОГО ЦИКЛУ У ДІВЧАТОК-ПІДЛІТКІВ ІЗ ПРОГНОСТИЧНОЮ ОЦІНКОЮ НА ОСНОВІ ROC-АНАЛІЗУ

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Резюме.

Порушення менструального циклу (ПМЦ) у дівчат-підлітків нерідко поєднуються з вегетативною дисфункцією (ВД), формуючи стійкий клініко-функціональний комплекс, що знижує якість життя та підвищує ризик хронізації репродуктивних і психосоматичних розладів.

Мета. Вивчення клініко-діагностичної взаємозалежності вегетативної дисфункції та порушень менструального циклу у дівчат-підлітків з виявленням клінічних і функціональних маркерів автономної регуляції, асоційованих з характером і вираженістю менструальних порушень.

Матеріали та методи. Обстежено 79 дівчат-підлітків у віці 13-18 років з НМЦ та ознаками ВД (основна група) і 29 відносно здорових підлітків (контрольна група). Оцінка вегетативного статусу проводилася за шкалою Вейна та індексом Кердо. Усім пацієнткам виконувалося УЗД органів малого таза, за показаннями – МРТ головного мозку. Гормональне обстеження включало ТТГ, пролактин, ЛГ, ФСГ та тестостерон. Застосовувався ROC-аналіз. Дослідження проведено відповідно до етичних принципів біомедичних досліджень; протокол дослідження схвалено локальним етичним комітетом Самаркандського державного медичного університету. Усі процедури проводилися відповідно до принципів Гельсінської декларації Всесвітньої медичної асоціації (редакція 2013 року). Письмову інформовану згоду було отримано від усіх учасниць або їхніх законних представників до включення в дослідження. Конфіденційність персональних даних пацієнток була повністю дотримана на всіх етапах дослідження. Статистичний аналіз проводився з використанням пакетів Statistica та SPSS при рівні значущості $p < 0,05$. Робота виконана в рамках плану науково-дослідних робіт Самаркандського державного медичного університету за темою «Удосконалення методів ранньої діагностики, лікування та профілактики патологічних станів, що впливають на здоров'я населення Самаркандської області» (2022-2026 рр.).

Результати. Астенічні скарги виявлені у 63,3% пацієнток основної групи проти 13,8% у контрольній групі ($p<0,001$). УЗД-зміни яєчників виявлені у 57,0% пацієнток. Підвищення пролактину зареєстровано у 32,9%, відхилення ТТГ – у 29,1%, підвищення тестостерону – у 24,1%. За даними ROC-аналізу найбільшу прогностичну значимість показали шкала Вейна (AUC=0,82; 95% ДІ: 0,73-0,91) та індекс Кердо (AUC=0,79; 95% ДІ: 0,69-0,88). Отримані результати підтверджують провідну роль ВНС та нейроендокринних механізмів у формуванні НМЦ у дівчаток-підлітків. Вираженість клінічних та вегетативних проявів в основній групі достовірно перевищувала аналогічні показники контрольної групи, що підтверджує значущість ВД як одного з ключових патогенетичних факторів репродуктивних порушень у підлітковому віці. Інструментальні та лабораторні дані продемонстрували тісний взаємозв'язок між функціональними змінами вегетативної регуляції та гормональними порушеннями гіпоталамо-гіпофізарно-яєчникової та тиреоїдної осей. Відсутність структурних змін гіпоталамо-гіпофізарної області за даними МРТ у обстежених пацієнток підкреслює переважно функціональний характер виявлених порушень. Істотна прогностична значимість гормональних та ультразвукових показників обґрунтовує їх включення до комплексного діагностичного алгоритму для підлітків із даною патологією.

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Висновки. Вегетативна дисфункція та нейроендокринна дисрегуляція відіграють ключову роль у формуванні та прогресуванні НМЦ у дівчаток-підлітків. Шкала Вейна та індекс Кердо є інформативними прогностичними інструментами з високою чутливістю та специфічністю. Для даної категорії пацієнток обґрунтований інтегративний діагностичний підхід з урахуванням клінічних, вегетативних, гормональних та інструментальних даних.

Ключові слова: дівчатка-підлітки; порушення менструального циклу; вегетативна дисфункція; нейроендокринна регуляція; гормональний профіль; ROC-аналіз.

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