ISSN NO: 2770-2936
February, 2026

Cytokine Regulation In Pubertal Girls With Opsomenorrhea Across Different Body Mass Index Categories

T. M. Kamalov[1], D. A. Musakhodjaeva[2], Z. Sh. Azizova[2]
[1] Samarkand State Medical University
[2] Institute of Immunology and Human Genomics, Academy of Sciences of the Republic of Uzbekistan

Abstract.
Menstrual rhythm disturbances during puberty often reflect a combination of neuroendocrine immaturity and early forms of ovulatory dysfunction. In the context of abnormal body weight, inflammatory mechanisms may serve as an additional factor modulating reproductive regulation.
Aim. To determine the characteristics of serum levels of key cytokines in pubertal girls with opsomenorrhea across different body mass index (BMI) categories and to compare these parameters with those of a control group.
Materials and Methods. A cross-sectional comparative study was conducted in girls aged 12–18 years with menstrual cycle disorders, stratified by BMI using age- and sex-standardized measures. Participants with opsomenorrhea were analyzed within high- and low-BMI groups, while girls with normal BMI served as controls. Serum cytokine concentrations were assessed by solid-phase enzyme-linked immunosorbent assay, and statistical analysis was performed using nonparametric tests with adjustment for multiple comparisons.
Results. In girls with opsomenorrhea and high BMI, a pronounced pro-inflammatory profile was observed, characterized by increased IL-6 and TNF-α compared with controls. In the low-BMI group, IL-6 was elevated relative to controls, whereas TNF-α did not differ significantly. Decreased IL-10 compared with controls was noted in both groups and was most pronounced in girls with low BMI.
Keywords: opsomenorrhea; puberty; menstrual cycle; obesity; body mass index; inflammation; cytokines; ovulation.

Introduction

Menstrual rhythm disturbances during puberty represent a major component of adolescent gynecological complaints and may reflect both physiological immaturity of the hypothalamic–pituitary–ovarian axis and the emergence of pathological variants of ovulatory dysfunction [1]. In clinical studies addressing cycle disorders in adolescents, a cycle length of ≥35 and <90 days is commonly used as an operational definition of oligomenorrhea/opsomenorrhea [4].

In recent years, increasing evidence has linked nutritional status to menstrual regularity. Excess body weight and obesity are associated with a higher frequency of cycle disturbances, including prolonged intermenstrual intervals, particularly in the setting of metabolic dysregulation and PCOS-like phenotypes [7, 9]. Population-based data likewise support associations between BMI parameters and menstrual cycle characteristics in adolescence [11].

From a pathogenetic perspective, chronic low-grade inflammation is regarded as a key mechanism in individuals with elevated BMI, creating an immunometabolic milieu capable of affecting steroidogenesis, insulin sensitivity, and the regulation of ovulatory function [2]. IL-6 and TNF-α are traditionally considered systemic markers of this process, whereas IL-10 reflects anti-inflammatory restraint and the capacity of the immune system to limit inflammatory responses [5].

Despite the clear clinical relevance, data on the combination of opsomenorrhea and immunoinflammatory profiles in adolescents across BMI categories remain limited, and studies concurrently assessing pro-inflammatory (IL-6, TNF-α) and regulatory (IL-10) cytokines in age- and pubertal stage–matched groups are particularly scarce.

The aim of this study was to characterize serum levels of key pro-inflammatory cytokines and the regulatory cytokine IL-10 in pubertal girls with opsomenorrhea across different BMI categories and to compare these findings with those of a control group.

ISSN NO: 2770-2936
February, 2026

Materials and Methods

A cross-sectional comparative study was conducted. The main cohort included 118 adolescent girls aged 12–18 years with menstrual cycle disorders; the mean age was 14.6±0.52 years.

Participants were stratified by body mass index (BMI) into groups with high BMI (n=71), low BMI (n=47), and a control group with normal BMI (n=30). Mean BMI values were 27.6, 17.1, and 21.5, respectively. BMI was calculated as weight (kg)/height² (m²) and standardized for age and sex using the BMI-for-age Z-score (BMI-z). High BMI was defined as BMI-z ≥ +1.0 SD (overweight) and/or ≥ +2.0 SD (obesity), low BMI as BMI-z ≤ −2.0 SD, and normal BMI as BMI-z from −2.0 to +1.0 SD. BMI stratification was performed prior to cytokine profiling.

For the present analysis, girls with opsomenorrhea were identified within the main cohort. Opsomenorrhea was observed in 26.8% (n=19) of participants with high BMI and in 34.0% (n=16) of those with low BMI.

Clinical assessment included medical history and physical examination, pelvic ultrasound, and Doppler evaluation of uterine–ovarian blood flow. Brain MRI with visualization of the sellar region was performed when clinically indicated.

Laboratory assessment comprised a hormonal profile including follicle-stimulating hormone, luteinizing hormone, estradiol, prolactin, testosterone, thyroid-stimulating hormone, and free triiodothyronine and thyroxine. Immunological testing was performed in the Reproductive Immunology Laboratory of the Institute of Immunology and Human Genomics, Academy of Sciences of the Republic of Uzbekistan. Blood samples were obtained after clinical evaluation, collected in the morning after an overnight fast, centrifuged to separate serum, and stored at −20°C until analysis.

Serum levels of pro- and anti-inflammatory cytokines (IL-6, TNF-α, and IL-10) were measured using solid-phase enzyme-linked immunosorbent assay kits (Vector-Best, Russia) according to the manufacturer's instructions. Concentrations were quantified using calibration curves derived from optical density–concentration relationships for standard antigens and applied to study samples.

Statistical analysis was performed using Statistica 6.0. Quantitative data are presented as the median (Me) and interquartile range (Q1–Q3). Nonparametric methods were used for group comparisons. Three-group comparisons were performed using the Kruskal–Wallis test; when significant, post hoc pairwise comparisons were conducted using the Mann–Whitney U test with adjustment for multiple testing. Differences were considered statistically significant at $p<0.05$.

Results and Discussion

The establishment of the menstrual cycle and maturation of ovarian reserve in adolescent girls are determined not only by interactions within the neuroendocrine axis, but also by finely balanced immune processes in which cytokines act as mediators of intersystem regulation [1].

Assessment of serum cytokine levels in adolescent girls with opsomenorrhea across different BMI categories revealed BMI-dependent alterations in the cytokine profile, indicating enhanced inflammatory activity in the setting of metabolic imbalance. These findings suggest an association between impaired energy homeostasis, immunoinflammatory shifts, and features of reproductive function during pubertal development.

Table 1.

Serum cytokine concentrations in adolescent girls with opsomenorrhea across different BMI categories.

Parameter	Me, pg/mL	Q1 - Q3	*p-value*
Control group, n=30			
IL-6	9,37	8,17 - 10,91	-
TNF-α	15,39	9,84 - 19,74	
IL-10	4,88	3,91 - 5,85	
Girls with high BMI, n=19			

ISSN NO: 2770-2936
February, 2026

IL-6	33,85	29,63 - 41,48	*<0,001**
TNF-α	41,45	33,87 - 51,34	*<0,001**
IL-10	4,17	3,21 - 5,28	*<0,05**
Girls with low BMI, n=16			
IL-6	10,74	9,73 - 12,75	*<0,001**
TNF-α	17,54	12,45 - 22,33	*>0,05^*
IL-10	2,45	1,57 - 3,04	*<0,001**

***Note:** * statistically significant compared with the control group; ^ not significant compared with the control group. Me, median; Q1, 25th percentile; Q3, 75th percentile.*

Interleukin-6 (IL-6) is a pro-inflammatory cytokine involved in the regulation of immune responses, inflammation, and metabolism. It is produced by immune cells and adipocytes, as well as by ovarian and endometrial cells [10]. In the reproductive system, IL-6 participates in ovulation, folliculogenesis, and endometrial remodeling, and elevated levels have been associated with ovulatory dysfunction and menstrual cycle disturbances [3, 6].

Analysis of serum IL-6 demonstrated a statistically significant increase in girls with opsomenorrhea and high BMI compared with controls. The median value was 33.85 pg/mL (Q1–Q3 29.63–41.48) versus 9.37 pg/mL (Q1–Q3 8.17–10.91) in the control group ($p<0.001$). In the low-BMI group, the median IL-6 level was 10.74 pg/mL (Q1–Q3 9.73–12.75), which also differed from controls ($p<0.001$), although the magnitude of increase was substantially smaller than that observed in the high-BMI group.

In the high-BMI group, increased IL-6 is most plausibly related to inflammatory activity of adipose tissue and metabolic imbalance, which may be accompanied by insulin resistance and impaired ovulation. In the low-BMI group, a modest rise in IL-6 more likely reflects stress and energy deficiency, affecting neuroendocrine–immune regulation.

Tumor necrosis factor alpha (TNF-α) is one of the key pro-inflammatory cytokines [5]. Under physiological conditions it contributes to the regulation of inflammatory responses and tissue repair; however, excessive expression sustains chronic inflammation and disrupts tissue homeostasis. In the reproductive system, TNF-α may suppress hypothalamic–pituitary regulation, reduce LH and FSH secretion, inhibit steroidogenesis, and promote apoptosis of granulosa cells, thereby contributing to ovulatory dysfunction [8].

TNF-α levels were significantly higher in girls with opsomenorrhea and high BMI compared with controls. The median value was 41.45 pg/mL (Q1–Q3 33.87–51.34) versus 15.39 pg/mL (Q1–Q3 9.84–19.74) in the control group ($p<0.001$). In the low-BMI group, the median TNF-α level was 17.45 pg/mL (Q1–Q3 12.45–22.33), and the difference compared with controls did not reach statistical significance ($p>0.05$).

In the high-BMI group, elevated TNF-α is most likely linked to adipose tissue–driven inflammation and immunometabolic activation, which may be accompanied by insulin resistance and suppression of steroidogenesis and ovulation. In the low-BMI group, the absence of a significant increase in TNF-α suggests that menstrual disturbances are more commonly driven by functional neuroendocrine dysregulation rather than overt inflammatory activation.

Interleukin-10 (IL-10) is a key anti-inflammatory cytokine produced by regulatory T cells, monocytes/macrophages, and B lymphocytes. It limits inflammatory responses by suppressing the production of pro-inflammatory mediators (including TNF-α and IL-6) and reducing the activation of antigen-presenting cells, thereby maintaining immune homeostasis [8]. In the reproductive system, IL-10 contributes to the regulation of local inflammatory activity in the ovaries and endometrium and supports a favorable immune microenvironment for ovulation and cyclic endometrial remodeling [5].

Evaluation of the anti-inflammatory arm showed reduced IL-10 levels in both study groups compared with controls. In girls with high BMI, the median IL-10 concentration was 4.17 pg/mL (Q1–Q3 3.21–5.28)

ISSN NO: 2770-2936
February, 2026

versus 4.88 pg/mL (Q1–Q3 3.91–5.85) in the control group; the difference was statistically significant ($p<0.05$). The most pronounced and significant decrease was observed in the low-BMI group, with a median of 2.45 pg/mL (Q1–Q3 1.57–3.04) compared with controls ($p<0.001$).

A decrease in IL-10 indicates a relative insufficiency of anti-inflammatory regulation. In the high-BMI group, this is most plausibly related to sustained pro-inflammatory burden and attenuation of compensatory regulatory mechanisms. In the low-BMI group, reduced IL-10 is more likely driven by energy deficiency and stress-related immune dysregulation, resulting in diminished control over inflammatory reactions involved in cyclic endometrial processes.

In this cross-sectional comparative study of pubertal girls with opsomenorrhea, the frequency of this menstrual pattern was 26.8% in the high-BMI group and 34.0% in the low-BMI group. Serum markers demonstrated BMI-dependent immunoinflammatory shifts. High BMI was associated with a pronounced pro-inflammatory profile characterized by markedly increased IL-6 and TNF-α and a modest decrease in IL-10 compared with controls. In contrast, low BMI was associated with less prominent pro-inflammatory activation but a significant decrease in IL-10 compared with controls, suggesting insufficient anti-inflammatory regulation and potentially reduced resilience to inflammatory shifts accompanying cyclic endometrial remodeling.

Conclusions

1. In girls with opsomenorrhea and high BMI, IL-6 and TNF-α levels were significantly higher than in controls; median values were 33.85 and 41.45 pg/mL, respectively ($p<0.001$).
2. In the opsomenorrhea group with low BMI, IL-6 was significantly higher than in controls, whereas differences in TNF-α compared with controls were not statistically significant.
3. The anti-inflammatory arm in girls with opsomenorrhea was characterized by reduced IL-10 compared with controls in both BMI groups, with the most pronounced and significant decrease observed in the low-BMI group.

References

1. Anthon, *et al.* (2024). Menstrual Disorders in Adolescence: Diagnostic and Therapeutic Challenges. *Journal of Clinical Medicine, 13*(24), 7668. https://doi.org/10.3390/jcm13247668
2. Bekkering, S., Saner, C., Novakovic, B., Mansell, T., Longmore, D. K., McCallum, Z., Ponsonby, A.-L., Juonala, M., Netea, M. G., Sabin, M. A., Saffery, R., Riksen, N. P., & Burgner, D. P. (2024). Increased innate immune responses in adolescents with obesity and its relation to subclinical cardiovascular measures: An exploratory study. *iScience, 27*(5), 109762. https://doi.org/10.1016/j.isci.2024.109762
3. Brännström, M., & Enskog, A. (2002). Leukocyte networks and ovulation. *Journal of Reproductive Immunology, 57*(1–2), 47–60. https://doi.org/10.1016/S0165-0378(02)00009-8
4. Di Maio, S., *et al.* (2023). A multicenter ICET-A study on age at menarche and menstrual cycles in patients with transfusion-dependent thalassemia (TDT) who started early chelation therapy with different chelating agents. *Mediterranean Journal of Hematology and Infectious Diseases*.
5. Gul, A., & Yilmaz, R. (2024). Determination of inflammation by TNF-alpha and IL-10 levels in obese children and adolescents. *Nutrición Hospitalaria, 41*(4), 788–792. https://doi.org/10.20960/nh.05064
6. Hunter, C. A., & Jones, S. A. (2015). IL-6 as a keystone cytokine in health and disease. *Nature Immunology, 16*(5), 448–457. https://doi.org/10.1038/ni.3153
7. Itriyeva, K. (2022). The effects of obesity on the menstrual cycle. *Current Problems in Pediatric and Adolescent Health Care, 52*(8), 101241. https://doi.org/10.1016/j.cppeds.2022.101241
8. Scheller, J., Chalaris, A., Schmidt-Arras, D., & Rose-John, S. (2011). The pro- and anti-inflammatory properties of the cytokine interleukin-6. *Cytokine & Growth Factor Reviews*.
9. Svidinskaya, E. A., Ageev, M. B., Paleeva, N. V., Mukhaeva, V. A., & Sosnova, E. A. (2022). Menstrual dysfunction in adolescent girls who are overweight: A literature review. *V.F. Snegirev Archives of Obstetrics and Gynecology, 9*(2), 93–101. https://doi.org/10.17816/2313-8726-2022-9-2-93-101
10. Tanaka, T., Narazaki, M., & Kishimoto, T. (2014). IL-6 in inflammation, immunity, and disease. *Cold Spring Harbor Perspectives in Biology*.
11. van Hooff, M. H. A., Caanen, M. R., Peters, H. E., Laven, J. S. E., & Lambalk, C. B. (2025). Adolescent menstrual cycle pattern, body mass index, endocrine and ovarian ultrasound characteristics of

ISSN NO: 2770-2936
February, 2026

PCOS and future fertility, cardiovascular-, and metabolic health: A 25-year longitudinal follow-up study. *Human Reproduction, 40*(1), 138–147. https://doi.org/10.1093/humrep/deae262