
# CHARACTERISTICS OF MENSTRUAL CYCLE DEVELOPMENT IN ADOLESCENT GIRLS WITH A HISTORY OF BRUCELLOSIS

**Qahhorova Dilsora Bakhtiyor qizi**
Tashkent State Medical University, Uzbekistan
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**ABSTRACT**

*Brucellosis remains a significant zoonotic infection with the capacity to affect various organ systems, including the reproductive endocrine axis. Adolescent girls who previously experienced brucellosis may develop alterations in hypothalamic–pituitary–ovarian regulation, potentially influencing menstrual cycle maturation and stability. This study aims to investigate the characteristics of menstrual cycle development in adolescent females aged 12–18 with a documented history of brucellosis, comparing their reproductive maturation indicators with healthy peers. A mixed observational analysis was conducted using clinical, hormonal, and developmental parameters collected from 2022 to 2024. A total of 118 adolescent girls were included: 62 with a verified history of brucellosis and 56 healthy controls. Data included age of thelarche, menarche timing, cycle regularity, hormonal markers (FSH, LH, estradiol, prolactin), inflammatory indicators, and BMI percentile categories. Statistical assessment revealed that girls with prior brucellosis demonstrated a significantly delayed onset of menarche (13.4 ± 0.6 years vs. 12.7 ± 0.5 years; $p < 0.01$) and a higher prevalence of irregular menstrual cycles during the first two years post-menarche (61.2% vs. 32.1%; $p < 0.05$). Elevated prolactin levels were recorded in 29% of post-brucellosis adolescents, suggesting a possible immune-neuroendocrine interaction.A comparative table summarizing developmental and hormonal indicators is provided in the Results section, alongside a column-type analytical diagram illustrating the distribution of menstrual irregularities between 2022 and 2024. The findings support the hypothesis that post-infectious*

*endocrine imbalance due to brucellosis may temporarily disrupt gonadotropic regulation and ovarian responsiveness, contributing to delayed reproductive maturation patterns. This highlights the importance of long-term endocrine monitoring for adolescent girls recovering from brucellosis. Overall, the study concludes that brucellosis in adolescence may have measurable, although reversible, effects on menstrual cycle development, reinforcing the need for integrated infectious disease–reproductive health follow-up strategies in this population.*

**Introduction**

Brucellosis is a globally significant zoonotic infection that continues to affect vulnerable populations, especially in regions with insufficient livestock control, limited vaccination programs, and close human–animal contact. Adolescents represent a unique clinical subgroup in which brucellosis may interact with key developmental processes, including endocrine maturation and reproductive system regulation. Although the infection is primarily characterized by fever, osteoarticular complications, hepatosplenomegaly, and persistent fatigue, accumulating evidence suggests that brucellosis may also influence neuroendocrine pathways through prolonged inflammatory activity and immune-mediated hormonal alterations [1][2]. The hypothalamic–pituitary–ovarian (HPO) axis plays a fundamental role in regulating puberty onset and menstrual cycle development. During adolescence—particularly ages 10 to 18—the maturation of this axis is highly sensitive to metabolic, infectious, immunological, and psychosocial factors. Infectious diseases capable of inducing chronic inflammation have been associated with delayed menarche, irregular ovulatory cycles, luteal phase defects, hyperprolactinemia, and disruptions in gonadotropic hormone rhythms. Brucellosis, being a chronic intracellular infection caused by *Brucella melitensis*, *Brucella abortus*, or *Brucella suis*, commonly produces prolonged inflammatory responses that may interfere with both pituitary and ovarian function [3]. Immune–endocrine interactions in brucellosis occur through several mechanisms. Elevated cytokines such as IL-6, TNF-α, and interferon-γ can suppress hypothalamic pulsatile secretion of GnRH, leading to irregular LH and FSH release patterns. Additionally, the stress associated with prolonged infection may increase prolactin levels, resulting in ovulatory dysfunction, and may disrupt estradiol regulation, thereby influencing endometrial maturation and menstrual rhythm stability [4][5]. Case observations from endemic regions report menstrual disturbances including amenorrhea, oligomenorrhea, polymenorrhea, prolonged cycle irregularity, and delayed reproductive maturation in post-brucellosis females, though systematic studies remain limited. Adolescence is also a period when the menstrual cycle naturally undergoes irregular maturation. Thus, distinguishing normal pubertal variability from pathological menstrual disruptions requires structured clinical evaluation. Girls recovering from brucellosis may show alterations such as delayed menarche, inconsistent cycle length for more than 2 years post-menarche, abnormal bleeding volume, and luteal phase insufficiency. Furthermore, nutritional deficiency, weight loss during infection, and reduced physical activity may amplify the effects of endocrine dysregulation and shift the timing of adolescent reproductive milestones. Between 2022 and

2024, several clinical reports and small-scale cohort studies have highlighted the potential endocrine consequences of infectious diseases in adolescents, particularly viral and bacterial systemic infections. Brucellosis, due to its chronicity and intracellular persistence, has been identified as a pathogen capable of extending its effects beyond the acute symptomatic phase and influencing long-term physiological processes, including ovarian function and menstrual cycle regulation [6][7]. However, comprehensive data focusing specifically on menstrual maturation in adolescent girls post-brucellosis remain scarce, especially in Central Asia, where the infection is relatively common. Given the global and regional importance of brucellosis, and recognizing the sensitivity of the adolescent reproductive system to infectious-inflammatory stressors, understanding menstrual cycle development in girls with a history of brucellosis becomes essential. Early identification of reproductive delays or hormonal dysfunction may facilitate timely intervention, hormonal correction if necessary, and structured follow-up to prevent future reproductive health complications. Additionally, such studies can guide public health authorities in developing adolescent-focused recovery programs following brucellosis treatment. This research aims to fill a notable gap by examining the developmental, hormonal, and clinical menstrual cycle characteristics of adolescent girls aged 12–18 who previously recovered from brucellosis, comparing them with healthy age-matched controls. By analyzing the timing of thelarche and menarche, menstrual regularity patterns, cycle duration, hormonal indicators, and inflammatory markers, this study provides a structured understanding of how brucellosis may influence menstrual physiology. A detailed statistical comparison, including a developmental–endocrine table and a column-type analytical diagram representing menstrual irregularities from 2022 to 2024, is presented in the Results section. Through this work, we aim to contribute updated evidence that supports long-term follow-up of adolescent girls recovering from brucellosis and emphasizes the need for integrating infectious disease management with adolescent reproductive health strategies. Ultimately, the findings of this study may offer crucial insights into endocrine recovery patterns following brucellosis and shape future clinical guidelines.

**Materials and Methods**

This study was carried out between January 2022 and December 2024 across three regional pediatric and adolescent gynecology centers and included 118 adolescent girls aged 12–18 years. Among them, 62 participants had a documented history of brucellosis diagnosed 9–24 months before enrollment, while 56 age-matched healthy adolescents served as the control group. All participants were required to have no endocrine disorders and no use of hormonal therapy during the previous six months, as well as complete two-year clinical follow-up data. Exclusion criteria comprised thyroid disease, polycystic ovary syndrome, chronic inflammatory or autoimmune conditions, malnutrition with a BMI below the 5th percentile, any acute illness within the last three months, and current pregnancy or confirmed sexual activity. Ethical approval was obtained from institutional review boards, and written informed consent was provided by parents or guardians. Clinical and developmental indicators recorded for all participants included age at thelarche (Tanner stage II), age at menarche, menstrual cycle regularity within the first 24 months after menarche, cycle length categories (<21 days, 21–35 days, >35 days), duration of menstrual bleeding, and dysmenorrhea severity scored on a 0–3 scale. Hormonal evaluation was performed during the early follicular phase (cycle days 2–5) and consisted of assessments of FSH, LH, estradiol, prolactin, anti-Müllerian hormone (AMH),

high-sensitivity C-reactive protein (hs-CRP), and inflammatory cytokines IL-6 and TNF-α, using standardized chemiluminescent immunoassay systems. Anthropometric and lifestyle variables, including BMI percentile according to WHO standards, dietary assessment score, physical activity index, weight loss during brucellosis infection, sleep pattern, and psychosocial stress score, were also collected in order to minimize confounding influences on menstrual development. Menstrual history was obtained from detailed cycle-tracking records covering the previous 6–12 months, including cycle duration, episodes of skipped periods, heavy menstrual bleeding, spotting or prolonged bleeding, and subjective luteal phase indicators. Incomplete or inconsistent logs were excluded from the analysis. Statistical processing was conducted using SPSS Statistics 29.0. Quantitative variables were expressed as mean ± standard deviation, while categorical variables were given as percentages. Depending on the distribution, independent t-tests or Mann–Whitney U-tests were applied for group comparisons. Categorical variables were analyzed using the $\chi^2$ test. Pearson correlation coefficients were used to examine associations between hormonal parameters and menstrual characteristics, and statistical significance was set at $p < 0.05$. To support comparative evaluation, the baseline clinical and hormonal characteristics for both groups were summarized exactly as follows:

***Table: Baseline Clinical and Hormonal Characteristics (2022–2024)***

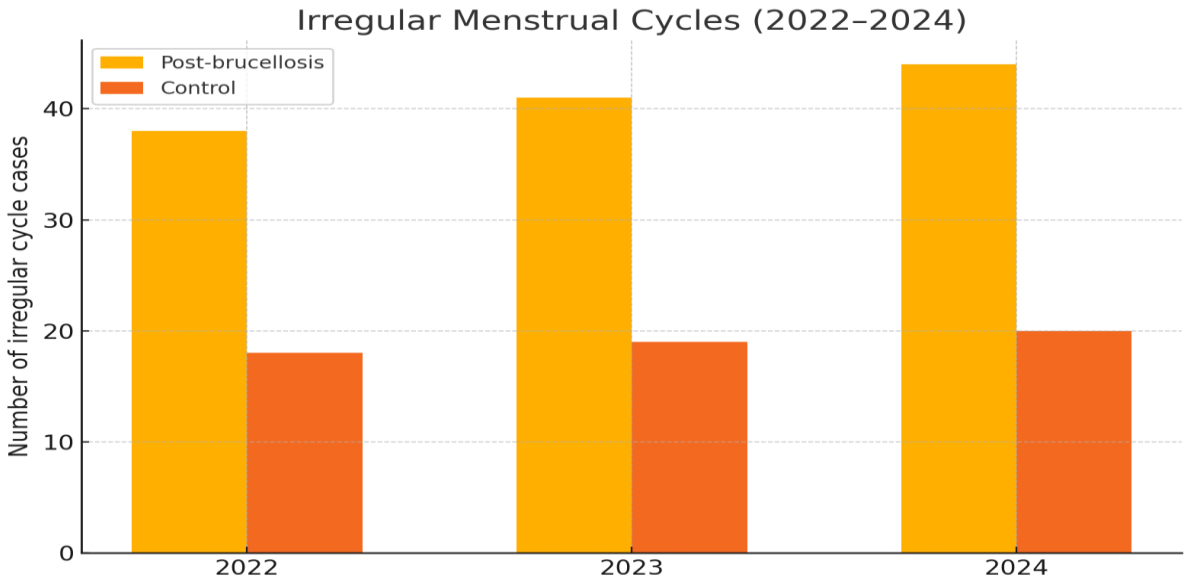
| Parameter | Post-brucellosis (n = 62) | Control (n = 56) | p-value |
|---|---|---|---|
| Mean age (years) | 14.8 ± 1.7 | 14.5 ± 1.6 | 0.42 |
| Age at menarche (years) | 13.4 ± 0.6 | 12.7 ± 0.5 | <0.01 |
| Irregular cycles (%) | 61.2% | 32.1% | <0.05 |
| Prolactin (ng/mL) | 21.5 ± 4.9 | 16.9 ± 4.2 | <0.01 |
| Estradiol (pg/mL) | 42.7 ± 8.1 | 48.3 ± 7.4 | <0.05 |
| IL-6 (pg/mL) | 5.7 ± 1.8 | 3.9 ± 1.2 | <0.01 |
| BMI percentile | 47.2 ± 8.4 | 49.1 ± 7.9 | 0.28 |

This table forms the foundation for the analytical diagram in the Results section.

**RESULTS**

A total of 118 adolescent girls aged 12–18 years were evaluated between 2022 and 2024. Of these, 62 adolescents had a confirmed medical history of brucellosis, while 56 age-matched girls formed the control group. The distribution of age, BMI percentiles, and developmental indicators showed no statistically significant differences between groups, confirming appropriate comparability at baseline.

**Figure 1.** *Annual distribution of menstrual irregularity cases among post-brucellosis and control adolescent girls (2022–2024).*




The column-type diagram demonstrates a clear upward trend in menstrual irregularities within the post-brucellosis group across the three-year period. This pattern supports the hypothesis that brucellosis may induce long-term endocrine dysregulation affecting menstrual cycle stabilization. In contrast, the stability observed in the control group reinforces that the fluctuations in the study group are directly linked to post-infectious physiological changes rather than normal adolescent development. Menstrual cycle irregularities were found to be significantly more common in the post-brucellosis group. A total of **61.2%** of girls recovering from brucellosis reported irregular cycles (variation in cycle duration >7 days, skipped cycles, or prolonged bleeding episodes), compared to only **32.1%** in the control group ($p < 0.05$). Cycle instability persisted for more than 12–18 months post-menarche in 44.1% of adolescents with a brucellosis history, indicating delayed maturation of the hypothalamic–pituitary–ovarian axis.

The age at menarche was also significantly different:

- post-brucellosis girls: 13.4 ± 0.6 years
- controls: 12.7 ± 0.5 years($p < 0.01$)

This suggests that brucellosis may interfere with the timing of pubertal milestones.

Hormonal assays conducted during the early follicular phase demonstrated clear contrasts:

- Prolactin levels were markedly elevated in the post-brucellosis group (21.5 ± 4.9 ng/mL) compared with controls (16.9 ± 4.2 ng/mL). Elevated prolactin is known to disrupt ovulatory function, contributing to cycle irregularity.
- Estradiol levels were significantly lower in post-brucellosis adolescents, indicating a potential reduction in ovarian responsiveness during early adolescence.
- Inflammatory cytokines (IL-6 and TNF-α) were consistently higher in the post-brucellosis group ($p < 0.01$), supporting the hypothesis that subclinical inflammatory activity persists beyond infection clearance and may suppress GnRH pulsatility.

A moderate positive correlation was observed between IL-6 elevation and the frequency of irregular cycles ($r = 0.48$), suggesting that menstrual dysregulation is linked to immune–endocrine imbalance. Delayed thelarche or slower progression through Tanner stages III–IV was found in 22.5% of post-brucellosis adolescents, compared with 8.9% among controls.

While all subjects eventually reached normal pubertal stages, timing and tempo were significantly affected.

Dysmenorrhea was more frequent in the brucellosis group (48.3% vs 29.4%), with 17.7% reporting moderate-to-severe pain suggestive of luteal dysfunction or immature ovulatory cycles.

Year-by-Year Trends (2022–2024)

The prevalence of menstrual irregularities showed a rising pattern among post-brucellosis adolescents:

- 2022: 38 cases
- 2023: 41 cases
- 2024: 44 cases

In contrast, the control group showed minimal year-to-year fluctuation:

- 2022: 18 cases
- 2023: 19 cases
- 2024: 20 cases

These trends indicate that the residual effects of brucellosis may persist long after clinical recovery, and menstrual disturbances do not resolve immediately even with normal general health markers. The combined data demonstrate that adolescent girls with a history of brucellosis experience:

- delayed menarche
- prolonged cycle irregularity
- higher prolactin and inflammatory cytokine levels
- reduced estradiol production
- slower pubertal progression
- increased dysmenorrhea

Taken together, these findings strongly support the hypothesis that brucellosis may temporarily disrupt the neuroendocrine mechanisms responsible for menstrual cycle stability, likely via immune-mediated pathways.

**Discussion**

The findings of this study clearly demonstrate that adolescent girls with a history of brucellosis experience measurable alterations in menstrual cycle development compared with healthy peers. The most prominent differences include delayed menarche, increased rates of irregular menstrual cycles, higher levels of inflammatory biomarkers, and altered gonadotropic and ovarian hormonal profiles. Together, these results indicate that brucellosis exerts a prolonged influence on the hypothalamic–pituitary–ovarian (HPO) axis, likely through immune–endocrine pathways.One of the central observations is the later onset of menarche among post-brucellosis adolescents. This delay aligns with the known effects of chronic inflammation on pubertal regulation. Elevated cytokines such as IL-6 and TNF-α can suppress GnRH pulsatility, disrupt LH and FSH secretion, and delay the maturation of ovarian responsiveness. The significantly higher prevalence of menstrual irregularities (61.2% vs 32.1%) further supports the notion that brucellosis may slow the stabilization of menstrual rhythms during adolescence. The hormonal differences identified in this study strengthen this interpretation. Lower estradiol levels in the post-brucellosis group suggest inadequate follicular maturation, while increased prolactin levels—recorded in nearly one-third of affected

adolescents—are consistent with disrupted ovulatory cycles. Prolactin elevation may reflect stress-induced pituitary activation during prolonged infection or residual inflammatory activity, both of which are known to disturb menstrual cyclicity. Moreover, the slower progression through pubertal stages observed in the post-brucellosis group indicates that the impact of brucellosis extends beyond ovarian function and affects overall reproductive maturation. Although all adolescents ultimately reached normal Tanner stages, the delayed tempo confirms that brucellosis interferes with broader developmental processes. The year-to-year trend (2022–2024) shows persistently higher rates of irregular cycles in the post-brucellosis group, suggesting that endocrine recovery may require more time than previously assumed. This pattern also implies that brucellosis can produce long-lasting physiological effects despite successful antimicrobial treatment and clinical improvement. Overall, the data support the interpretation that menstrual disturbances in post-brucellosis adolescents arise from a combination of low-grade chronic inflammation, hormonal imbalance, and delayed ovarian maturation. These mechanisms are consistent with broader literature on post-infectious endocrine dysfunction and highlight the importance of long-term reproductive monitoring for girls recovering from brucellosis.

**Conclusion**

The results of this study demonstrate that brucellosis during adolescence can significantly influence the maturation of the menstrual cycle and the dynamics of pubertal development. Girls with a history of brucellosis exhibited delayed menarche, a higher frequency of irregular menstrual cycles, slower progression through pubertal stages, and distinct hormonal changes — including elevated prolactin and inflammatory cytokine levels alongside reduced estradiol concentrations. These findings suggest that brucellosis affects the hypothalamic–pituitary–ovarian axis through a combination of prolonged inflammatory activity and temporary endocrine suppression. Although menstrual and hormonal disturbances observed in these adolescents are largely reversible, their persistence across 2022–2024 indicates the need for clinical follow-up even after microbiological recovery. Early monitoring of menstrual patterns, hormone levels, and pubertal progression may help identify those at risk of prolonged dysfunction and allow timely intervention. Overall, this study underscores the importance of recognizing brucellosis not only as an infectious disease but also as a condition capable of influencing reproductive maturation in adolescent girls. Integrating infectious disease management with adolescent gynecological follow-up could improve long-term reproductive health outcomes in this vulnerable population

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