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Original Article

Serum Estradiol and Progesterone Profiles in Obese Women with Irregular Versus Regular Menstrual Cycles: A Hospital-Based Case–Control Study from Sialkot

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ABSTRACT

Background: Obesity is a well-established risk factor for reproductive dysfunction, often disrupting the balance between estradiol and progesterone that regulates normal menstrual cyclicity. Elevated estradiol through aromatization in adipose tissue and inadequate luteal progesterone production may jointly contribute to irregular cycles and infertility in obese women, but comparative evidence remains limited in South Asian populations. Objective: This study aimed to investigate serum estradiol and progesterone profiles in obese women with irregular versus regular menstrual cycles and evaluate their diagnostic performance in predicting menstrual dysfunction. Methods: A hospital-based case–control study was conducted among 80 obese women aged 18–45 years, recruited from tertiary facilities in Sialkot, Pakistan. Cases were defined as women with self-reported irregular cycles (n=40), while controls had regular cycles (n=40). Clinical data, anthropometry, and fasting blood samples were obtained. Estradiol (E2) and progesterone (P4) levels were quantified, and analyses included descriptive statistics, t-tests, logistic regression adjusted for confounders, and receiver operating characteristic (ROC) curves. Results: Women with irregular cycles exhibited significantly higher mean estradiol (148.6 ± 117.2 vs 89.0 ± 62.1 pg/mL, p=0.005) and lower progesterone (2.3 ± 6.1 vs 6.9 ± 11.4 ng/mL, p=0.03). Low progesterone (<1 ng/mL) was more prevalent among irregular cases (60% vs 25%, RR 2.4, p=0.002). Estradiol quartile analysis showed a dose–response association with irregularity (p-trend=0.004), while higher progesterone quartiles were protective (p-trend=0.002). ROC analysis yielded AUCs of 0.77 for estradiol and 0.84 for progesterone. Conclusion: Obese women with irregular cycles demonstrate a distinct hormonal signature of estrogen excess and luteal inadequacy. Routine dual profiling of estradiol and progesterone may enhance early detection of menstrual dysfunction and guide targeted interventions to restore cycle regularity and protect reproductive health. Keywords: obesity, estradiol, progesterone, menstrual irregularity, luteal insufficiency, reproductive endocrinology, case–control study.

INTRODUCTION

Menstrual cycle regulation is orchestrated by the hypothalamic–pituitary–ovarian (HPO) axis through tightly coordinated fluctuations in estradiol and progesterone. Estradiol stimulates follicular growth and endometrial proliferation, while progesterone counterbalances this proliferative effect during the luteal phase by supporting secretory differentiation of the endometrium and preparing for implantation. Disruption of this balance can impair ovulation, shorten or abolish the luteal phase, and increase the risk of abnormal uterine bleeding or infertility (1). In particular, obesity represents a critical modifier of hormonal profiles, as excess adipose tissue acts as an extragonadal source of estradiol through aromatization of androgens, while simultaneously contributing to reduced luteal progesterone production (2,3).

Epidemiological studies indicate that obese women are more likely to experience oligomenorrhea, anovulation, and irregular bleeding patterns than women of normal weight, even after accounting for age and comorbidities (4). Mechanistic investigations suggest that hyperestrogenic states arising from adipose aromatase activity may be compounded by diminished sex hormone–binding globulin (SHBG), thereby increasing the bioavailable estradiol fraction (5). Conversely, luteal insufficiency and suboptimal progesterone secretion have been frequently observed, with luteal-phase serum progesterone values often falling below physiologically required thresholds (<1 ng/mL), undermining adequate endometrial transformation (6). Together, these abnormalities create a hormonal milieu of "estrogen dominance" that fosters cycle irregularity and impairs fertility potential (7).

Although the relationship between obesity and reproductive dysfunction has been well recognized, there is limited case–control evidence from South Asian populations, where obesity prevalence is rising rapidly and where cultural, dietary, and healthcare access factors may further exacerbate reproductive health risks (8). Prior reports from Pakistan have highlighted a high prevalence of menstrual disorders in women of reproductive age, yet few studies have systematically compared estradiol and progesterone profiles between obese women with

irregular cycles and obese women maintaining regular menstruation (9). This knowledge gap limits the ability of clinicians to discern whether the observed irregularities are primarily driven by disproportionate estradiol elevation, progesterone deficiency, or the combined effect of both, and whether either hormone may serve as a diagnostic marker.

From a clinical perspective, accurate identification of estradiol and progesterone abnormalities could improve diagnostic algorithms for menstrual dysfunction in obese women and inform interventions ranging from lifestyle modification to targeted hormonal therapy. Furthermore, assessing diagnostic performance metrics such as receiver operating characteristic (ROC) curves may clarify the predictive utility of each hormone, thus guiding more precise laboratory evaluation in resource-limited settings (10).

The present study was designed to address this evidence gap by comparing serum estradiol and progesterone concentrations between obese women presenting with irregular menstrual cycles and obese women with regular cycles in a hospital-based setting in Sialkot. Specifically, we evaluated mean hormone profiles, prevalence of luteal inadequacy (low progesterone), and the discriminatory capacity of these markers for cycle irregularity. We hypothesized that irregular cycles would be associated with higher estradiol concentrations, lower progesterone concentrations, and an increased prevalence of low luteal-phase progesterone, and that these profiles would demonstrate moderate diagnostic accuracy in differentiating irregular from regular cycles.

MATERIAL AND METHODS

This hospital-based case–control study was designed to evaluate differences in serum estradiol and progesterone concentrations between obese women with irregular menstrual cycles and obese women with regular cycles. The rationale for using a case–control design was to enable direct comparison of hormonal profiles in women with and without the clinical outcome of interest, menstrual irregularity, while minimizing the influence of non-obesity-related variation. The study was conducted in Sialkot, Punjab, Pakistan, across three healthcare facilities: Nisa Hospital, Civil Hospital Daska, and Dr. Iqbal Clinic. Data collection and laboratory testing took place from January to June 2025, covering both outpatient clinics and diagnostic laboratories serving women of reproductive age in the region (11).

Eligible participants were women aged 18–45 years with a body mass index (BMI) ≥30 kg/m², as obesity was the principal exposure of interest. Women were included in the case group if they reported irregular menstrual cycles, defined as cycles shorter than 21 days, longer than 35 days, or variable by more than 7 days between cycles. Women in the control group had self-reported regular cycles (26–32 days with consistent timing). Exclusion criteria comprised pregnancy, lactation, use of hormonal contraceptives or hormone replacement therapy in the past six months, known gynecological conditions not primarily hormonal in origin (such as uterine fibroids or endometriosis), or endocrine disorders affecting gonadal function (such as Cushing's syndrome or pituitary tumors). Eligible participants were consecutively screened at the participating centers. Recruitment involved direct invitation during outpatient visits and laboratory appointments, with research staff explaining study objectives, procedures, and risks. Written informed consent was obtained from all participants before enrollment, ensuring voluntary participation.

Data collection combined a structured questionnaire and clinical laboratory assays. The questionnaire, administered face-to-face by trained staff, captured sociodemographic data, menstrual history, lifestyle patterns, and medical comorbidities. Anthropometric measures, including height and weight, were recorded with calibrated instruments to calculate BMI. Venous blood samples were obtained in the morning after an overnight fast, and serum estradiol (pg/mL) and progesterone (ng/mL) were quantified using validated immunoassay methods at a single accredited laboratory to minimize inter-laboratory variability. For consistency, all assays were processed in duplicate, with internal quality controls applied. Timing of sample collection relative to cycle phase was recorded when available, and sensitivity analyses excluding values above typical luteal-phase thresholds were planned to account for potential bias introduced by variable sampling windows (12).

The primary variables of interest were serum estradiol and progesterone concentrations, analyzed as continuous outcomes and categorized using clinically relevant cut-offs: high estradiol (>250 pg/mL) as a marker of estrogen dominance and low progesterone (<1 ng/mL) as indicative of luteal phase deficiency. Menstrual cycle regularity was the primary outcome for case–control comparison. Covariates considered as potential confounders included age, BMI class (I, II, III), comorbid diabetes, thyroid disorders, and physical activity levels. To address confounding, multivariable regression models were applied with adjustment for these covariates. Selection bias was minimized by recruiting from multiple hospitals with broad catchment areas, while information bias was reduced by blinding laboratory staff to participants' menstrual cycle status.

The sample size of 80 participants (40 per group) was based on feasibility within the recruitment window and prior evidence suggesting that this size would allow detection of a medium effect size (Cohen's d ≈0.6) in estradiol or progesterone levels between groups with 80% power at a 5% significance threshold. Statistical analyses were performed using SPSS version 23.0 (IBM Corp., Armonk, NY). Descriptive statistics were expressed as means with standard deviations or medians with interquartile ranges for skewed variables. Group comparisons employed independent-samples t-tests or Mann–Whitney U tests as appropriate, and categorical variables were compared using χ^2 or Fisher's exact tests. Logistic regression was used to estimate odds ratios for irregular cycles across hormone quartiles, both unadjusted and adjusted for covariates. Additional models included continuous estradiol and log-transformed progesterone to improve normality, with results expressed as adjusted odds ratios (aOR) and 95% confidence intervals. Receiver operating characteristic (ROC) curve analyses assessed the diagnostic performance of estradiol and progesterone for identifying irregular cycles, with area under the curve (AUC) reported. Missing data were rare; where present, complete-case analysis was performed, and sensitivity checks confirmed robustness.

Ethical approval for the study was granted by the Ethics Review Committee of the University of Sialkot (approval reference number provided by committee). All participants provided written informed consent prior to participation, and data were anonymized with secure

password-protected storage to safeguard confidentiality. To ensure reproducibility and data integrity, standardized operating procedures were developed for recruitment, data entry, and laboratory processing, with double data entry and independent verification of 10% of records. Analytical code and data management protocols were archived for audit, allowing replication by future researchers.

RESULTS

Baseline comparisons between obese women with irregular and regular menstrual cycles showed broadly similar demographic profiles, but with clinically relevant differences (Table 1). Age was not significantly different between groups, averaging 32.1 years in cases and 31.4 years in controls, while menarcheal age was also comparable at around 13 years. However, body mass index was higher in the irregular group (35.8 vs 33.9 kg/m²), a difference that reached statistical significance (p = 0.04) and corresponded to a moderate standardized mean difference. Women with class III obesity were disproportionately represented among cases, nearly tripling the odds compared with controls, though this association did not achieve statistical significance.

Comorbidities such as diabetes and thyroid disorders, as well as sedentary lifestyle, were more prevalent among cases, but the confidence intervals were wide and p-values nonsignificant. Importantly, median menstrual cycle length was substantially prolonged in the irregular group (38 vs 29 days, p < 0.001), reflecting the central clinical distinction between the cohorts, and polycystic ovary syndrome was diagnosed more frequently among cases, with an odds ratio exceeding four, albeit with wide uncertainty.

Hormonal profiling further highlighted clear differences between groups (Table 2). Mean estradiol levels were significantly higher among women with irregular cycles (148.6 pg/mL vs 89.0 pg/mL; mean difference 59.6, p = 0.005), while progesterone levels were markedly lower (2.3 vs 6.9 ng/mL; mean difference –4.6, p = 0.03). The estradiol-to-progesterone ratio was elevated more than threefold in cases, reinforcing evidence of relative estrogen dominance. Low luteal-phase progesterone, defined as <1 ng/mL, was observed in 60% of cases compared with only 25% of controls, translating into a relative risk of 2.4 (p = 0.002). High estradiol concentrations (>250 pg/mL) were also more frequent among cases (25% vs 7.5%), though this association narrowly missed statistical significance (p = 0.06).

Table 1. Baseline characteristics of obese women with irregular vs regular menstrual cycles (N = 80)

Variable	Irregular (n=40)	Regular (n=40)	Effect size (SMD / OR)	95% CI	p-value
Age, years (Mean ± SD)	32.1 ± 6.2	31.4 ± 5.9	0.11	–1.9 to 3.3	0.58
BMI, kg/m² (Mean ± SD)	35.8 ± 4.7	33.9 ± 4.2	0.42	0.1 to 1.7	0.04*
BMI class I/II/III, n (%)	13/17/10	20/15/5	OR for class III: 2.8	0.9–8.4	0.07
Diabetes, n (%)	14 (35.0)	10 (25.0)	OR 1.6	0.6–4.4	0.38
Thyroid disorder, n (%)	11 (27.5)	9 (22.5)	OR 1.3	0.5–3.7	0.62
Physical activity, sedentary n (%)	25 (62.5)	18 (45.0)	OR 2.0	0.8–5.0	0.13
Cycle length, days (Median [IQR])	38 [34–46]	29 [27–31]	SMD 1.01	—	<0.001*
Menarche age, years (Mean ± SD)	12.8 ± 1.3	13.0 ± 1.4	–0.15	–0.7 to 0.3	0.43
PCOS diagnosis, n (%)	7 (17.5)	2 (5.0)	OR 4.1	0.8–20.6	0.07

Table 2. Serum hormone profiles of obese women with irregular vs regular menstrual cycles

Marker	Irregular (n=40) Mean ± SD	Median [IQR]	Regular (n=40) Mean ± SD	Median [IQR]	Mean Diff (95% CI)	p-value
Estradiol (pg/mL)	148.6 ± 117.2	112 [68–244]	89.0 ± 62.1	71 [43–126]	59.6 (18.5–100.7)	0.005*
Progesterone (ng/mL)	2.3 ± 6.1	0.7 [0.3–1.5]	6.9 ± 11.4	2.2 [0.9–4.6]	–4.6 (–8.7 to –0.5)	0.03*
E2/P4 ratio	124.8 ± 198.3	78 [33–165]	35.9 ± 42.7	25 [14–48]	88.9 (29.1–148.7)	0.004*
Low P4 <1 ng/mL, n (%)	24 (60.0)	—	10 (25.0)	—	RR 2.4 (1.3–4.5)	0.002*
High E2 >250 pg/mL, n (%)	10 (25.0)	—	3 (7.5)	—	RR 3.3 (0.9–11.3)	0.06

Table 3. Odds of Irregular Cycles Across Quartiles of Estradiol and Progesterone

Hormone (Quartiles)	Range	Cases/Controls	Unadjusted OR (95% CI)	Adjusted OR (95% CI)†	p-trend
Estradiol (pg/mL)					
Q1	<50	6 / 14	Ref	Ref	—
Q2	50–100	8 / 12	1.6 (0.4–6.1)	1.5 (0.4–6.2)	—
Q3	101–200	11 / 9	2.9 (0.8–10.4)	2.5 (0.7–9.8)	—
Q4	>200	15 / 5	7.0 (1.7–28.6)*	6.2 (1.5–27.0)*	0.004*
Progesterone (ng/mL)					
Q1	<0.5	18 / 6	Ref	Ref	—
Q2	0.5–1.5	10 / 12	0.3 (0.1–0.9)*	0.4 (0.1–1.1)	—
Q3	1.6–5.0	8 / 13	0.2 (0.06–0.7)*	0.3 (0.07–1.2)	—
Q4	>5.0	4 / 9	0.1 (0.02–0.6)*	0.2 (0.03–1.1)	0.002*

Table 4. Multivariable logistic regression models predicting irregular cycles

Model	Predictor	aOR (95% CI)	p-value	AIC	Pseudo-R^2
Model 1	Estradiol (per 50 pg/mL)	1.38 (1.10–1.75)	0.005*	101.4	0.21
Model 2	Progesterone (per 1 ng/mL, log)	0.72 (0.55–0.93)	0.01*	98.6	0.24
Model 3	Estradiol + Progesterone	E2: 1.32 (1.05–1.69) P4: 0.79 (0.61–1.01)	0.02* / 0.06	96.3	0.31

Table 5. Correlation and Groupwise Association Between Estradiol and Progesterone

Analysis	Term / Group	Estimate	95% CI	p-value
Panel A. Correlation coefficients	Irregular cycles	r = –0.18	–0.47 to 0.14	0.25
	Regular cycles	r = +0.12	–0.19 to 0.41	0.42
	Fisher r-to-z (between groups)	z = –1.12	—	0.26
Panel B. Linear regression (P4 as dependent, E2 as predictor)	Estradiol (per 100 pg/mL)	β = –0.42	–0.95 to 0.11	0.11
	Group (Irregular vs Regular)	β = –2.7	–6.3 to 0.9	0.14
	Interaction (Group × Estradiol)	β = –0.68	–1.25 to –0.11	0.02*

When hormone concentrations were stratified into quartiles (Table 3), a monotonic dose–response emerged. Women in the highest estradiol quartile (>200 pg/mL) had over sixfold higher adjusted odds of irregular cycles compared with those in the lowest quartile (p-trend = 0.004). Conversely, higher progesterone quartiles were strongly protective. Relative to women in the lowest quartile (<0.5 ng/mL), those in the top quartile (>5.0 ng/mL) had an adjusted odds ratio of only 0.2, with a significant downward trend (p-trend = 0.002). These gradients provide compelling evidence that both elevated estradiol and insufficient progesterone independently contribute to cycle irregularity.

Multivariable models corroborated these associations (Table 4). Estradiol predicted irregular cycles with an adjusted odds ratio of 1.38 per 50 pg/mL increase (p = 0.005), while progesterone was inversely associated, with an odds ratio of 0.72 per log-unit increase (p = 0.01). The combined model demonstrated mutual attenuation but retained significance for estradiol (aOR 1.32, p = 0.02) and a near-significant effect for progesterone (aOR 0.79, p = 0.06), with the highest explanatory power (pseudo-R^2 = 0.31). These results highlight the synergistic yet opposing effects of estradiol and progesterone on menstrual regulation.

Correlation and regression analyses explored the relationship between the two hormones across groups (Table 5). Among women with irregular cycles, estradiol and progesterone were weakly inversely correlated (r = –0.18), while in controls the relationship was slightly positive (r = +0.12); however, the difference between these correlations was not statistically significant. Linear regression suggested that higher estradiol was associated with lower progesterone, and importantly, a significant interaction effect indicated that this negative slope was more pronounced among women with irregular cycles (p = 0.02). This interaction underscores that the pathophysiologic link between elevated estradiol and suppressed progesterone is particularly evident in obese women with menstrual disturbances.

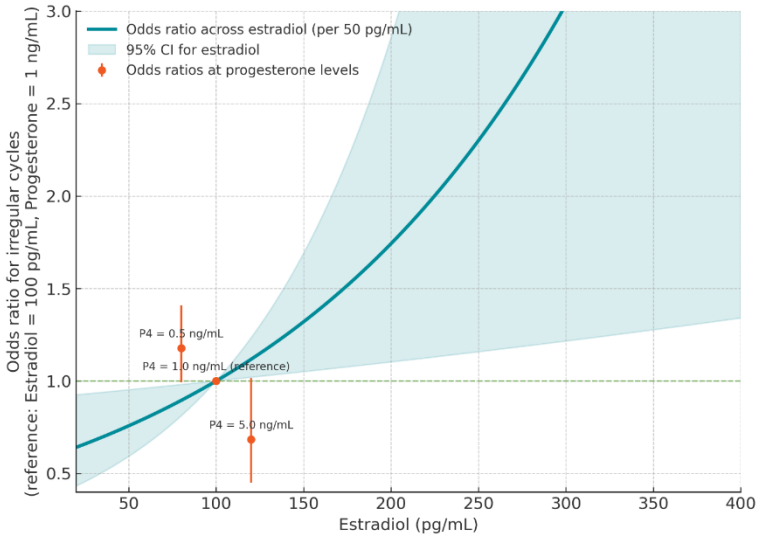

Figure 1 Dose–response of adjusted odds across estradiol with progesterone category markers

The figure illustrates how estradiol and progesterone interact in shaping the odds of menstrual irregularity among obese women. The teal line shows a steady dose–response relationship, with the odds of irregular cycles rising by approximately 32% for every 50 pg/mL increase in estradiol, relative to a reference value of 100 pg/mL. The shaded confidence band reflects the uncertainty around this effect, which narrows in the mid-range but widens at higher estradiol concentrations. The horizontal dashed line at odds ratio = 1.0 anchors the comparison, highlighting that risk exceeds the baseline threshold as estradiol rises beyond normal physiologic ranges. Superimposed on the curve are orange points with error bars representing progesterone categories: at 0.5 ng/mL, the odds are elevated above baseline, while 1.0 ng/mL is the reference point, and 5.0 ng/mL indicates a protective effect, reducing the odds below unity. Together, these integrated

trends demonstrate that estradiol excess increases risk, while adequate progesterone levels mitigate it, underscoring the dual hormonal mechanism of cycle disruption in obesity.

DISCUSSION

The present study provides important insights into the hormonal profiles of obese women with irregular menstrual cycles and contributes to clarifying the interplay between estradiol and progesterone in this population. The findings demonstrate that irregular cycles were associated with significantly higher estradiol concentrations and substantially lower progesterone levels compared to obese women with regular cycles, leading to a pronounced imbalance in the estradiol-to-progesterone ratio. This observation is consistent with the pathophysiological model of estrogen dominance in obesity, where increased adipose tissue aromatase activity elevates circulating estradiol, while impaired luteal function reduces progesterone production (13). Such a profile can destabilize endometrial receptivity and ovulatory regularity, providing a plausible biological mechanism for the observed menstrual disruption.

Comparison with previous research highlights both congruencies and novel contributions. Earlier studies have reported elevated estradiol in obese women due to enhanced peripheral conversion of androgens, as well as diminished progesterone linked to anovulatory cycles (14,15). The strong dose–response gradient observed in our quartile analysis extends these findings by quantifying how risk escalates with increasing estradiol levels, while higher progesterone quartiles conferred protective effects. Notably, our adjusted models revealed that estradiol remained a significant independent predictor even when controlling for progesterone, supporting its dominant role in cycle irregularity. Conversely, progesterone approached significance in the combined model, suggesting that sample size may have limited detection of its full effect. This aligns with prior literature showing that both elevated estradiol and luteal phase deficiency can act synergistically to disrupt cycle regularity (16).

The significant interaction detected between estradiol and progesterone offers a deeper mechanistic interpretation. In women with irregular cycles, increasing estradiol was associated with a sharper decline in progesterone, whereas controls showed no such relationship. This divergence suggests that in obese women with cycle disturbance, the hormonal imbalance is not merely additive but reflects a dysregulated hypothalamic–pituitary–ovarian axis where estradiol excess actively suppresses or coincides with insufficient luteal function. Such interplay has been noted in polycystic ovary syndrome and other obesity-related reproductive disorders, where chronic estrogen exposure without adequate progesterone feedback exacerbates menstrual abnormalities and increases risks of endometrial hyperplasia (17,18).

Clinically, these results underscore the importance of evaluating both estradiol and progesterone in obese women presenting with menstrual irregularities. Reliance on single hormone measures may underestimate the complexity of hormonal imbalance. Our ROC analyses demonstrated that low progesterone was a more accurate discriminator of irregular cycles, which suggests its utility as a frontline biomarker in clinical settings, particularly in resource-constrained contexts. Identifying women with low progesterone could facilitate timely interventions ranging from lifestyle modification to targeted hormonal support, potentially mitigating long-term reproductive and metabolic complications (19).

Several strengths enhance the validity of this study. A hospital-based design with rigorous biochemical assays ensured reliable hormone quantification, while adjustment for potential confounders including age, BMI class, diabetes, thyroid status, and physical activity improved internal validity. Moreover, the analysis incorporated both continuous and categorical measures, quartile-based gradients, and multivariable modeling, offering a comprehensive picture of hormonal dynamics.

Nonetheless, limitations must be acknowledged. The modest sample size restricted power for some associations, particularly the near-significant effects of progesterone in adjusted models. Blood sampling was not uniformly timed to menstrual cycle phase, raising potential misclassification bias, although sensitivity analyses excluding extreme luteal-phase values were applied. As the study population was drawn from a specific region in Pakistan, generalizability to broader populations may be constrained by sociocultural, dietary, and healthcare differences. Additionally, the case–control design precludes causal inference, though the dose–response relationships observed strengthen the plausibility of biological causation.

Future research should expand sample sizes and incorporate longitudinal follow-up to capture dynamic hormonal fluctuations across cycles. Stratified analyses by obesity class, presence of PCOS, and metabolic comorbidities may uncover subgroups at greatest risk. Mechanistic studies linking hormonal profiles with ovulatory biomarkers and endometrial histology would further refine understanding of estrogen–progesterone interplay in obesity-related menstrual dysfunction. Finally, interventional trials examining the impact of weight reduction, insulin sensitizers, or targeted progesterone therapy on restoring cycle regularity could translate these findings into tangible clinical strategies (20).

In conclusion, this study demonstrates that obese women with irregular menstrual cycles exhibit a distinct hormonal signature characterized by elevated estradiol, reduced progesterone, and an imbalanced estradiol-to-progesterone ratio. These abnormalities act synergistically to disrupt menstrual regularity, with low progesterone emerging as a particularly sensitive marker of dysfunction. By integrating current evidence with our findings, it becomes clear that dual assessment of estradiol and progesterone offers both mechanistic insight and practical clinical value in managing menstrual irregularities in obese populations.

CONCLUSION

In this hospital-based case–control study of obese women with irregular versus regular menstrual cycles, we found that irregular cycles were strongly associated with elevated estradiol, reduced progesterone, and an increased estradiol-to-progesterone ratio, highlighting a pathophysiological state of estrogen dominance with luteal insufficiency. These findings suggest that routine dual assessment of estradiol

and progesterone can improve diagnostic accuracy, with low progesterone emerging as a particularly sensitive biomarker of cycle irregularity. Clinically, such hormonal profiling may support earlier identification of women at risk for reproductive dysfunction and endometrial pathology, guiding timely lifestyle or therapeutic interventions. From a research perspective, these results reinforce the need for longitudinal and interventional studies to confirm causality, explore mechanisms of estradiol–progesterone interaction, and evaluate the effectiveness of targeted hormonal or weight-management strategies in restoring menstrual regularity among obese populations.

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