Article

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Dysfunctional Uterine Bleeding and the Stress Axis

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Background: Dysfunctional uterine bleeding (DUB) affects up to 30% of women of reproductive age and may result in anemia, diminished quality of life, and increased healthcare utilization. While stress-axis dysregulation has been implicated in various menstrual disorders, the role of autonomic and hypothalamic-pituitary-adrenal (HPA) axis dysfunction in DUB remains insufficiently understood. This study aims to investigate whether women with the International Federation of Gynecology and Obstetrics (FIGO)-classified DUB exhibit alterations in autonomic nervous system (ANS) function and endocrine profiles compared to healthy controls during the early follicular phase. By assessing heart rate variability (HRV) indices and circulating reproductive and metabolic hormones, the study seeks to clarify the potential role of autonomic imbalance and the HPA axis—related hormonal markers in the pathophysiology of DUB.

Methods: In this prospective case–control study, 34 women with FIGO-classified DUB and 36 age- and body mass index–matched healthy controls underwent biochemical and hormonal assays and five-minute HRV recordings during the early follicular phase (days 3–7 of menses). Serum cortisol was not measured. Time-domain (standard deviation of NN intervals (SDNN), root mean square of successive differences (RMSSD), percentage of successive NN intervals differing by more than 50 ms (pNN50)) and frequency-domain (very-low-frequency power (VLF), low-frequency (LF), high-frequency (HF), LF/HF) HRV metrics were analyzed alongside follicle-stimulating hormone (FSH), luteinizing hormone (LH), estradiol, testosterone, thyroid-stimulating hormone (TSH), dehydroepiandrosterone sulfate (DHEA-SO_4), glucose, and hemoglobin. Statistical comparisons employed Student's *t*-tests or Mann–Whitney U tests, with Pearson/Spearman correlations exploring interrelationships among variables.

Results: Anthropometric, biochemical, hormonal, and HRV parameters did not differ significantly between DUB and control groups (all $p > 0.05$). Correlation analyses across the combined cohort revealed expected age-related declines in vagal indices (e.g., RMSSD) and hormone levels (testosterone, DHEA-SO_4), inverse associations between body mass index (BMI) and SDNN/total power, and robust intercorrelations among HRV measures. Notably, FSH positively correlated with VLF power ($r = 0.243$, $p < 0.05$), while heart rate inversely tracked RMSSD ($r = –0.567$, $p < 0.01$).

Conclusions: In a rigorously controlled, follicular-phase cohort, women with DUB exhibit preserved cardiac autonomic regulation and comparable endocrine profiles to healthy peers. These negative findings suggest that, under resting conditions, ANS imbalance may not drive DUB pathophysiology. Future research should integrate direct HPA-axis biomarkers (e.g., cortisol), longitudinal HRV across the menstrual cycle, and stratification by DUB subtype to uncover subtler stress–reproductive interactions.

Keywords: dysfunctional uterine bleeding; electrocardiogram; heart rate; menstruation; autonomic nervous system; parasympathetic nervous system; sympathetic nervous system

Introduction

The hypothalamic-pituitary-adrenal (HPA) axis plays a central role in the neuroendocrine regulation of the stress response, orchestrating physiological adaptations through the secretion of glucocorticoids, principally cortisol. Upon exposure to a stressor, corticotropin-releasing hormone (CRH) is secreted by the hypothalamus, stimulating the anterior pituitary to release adrenocorticotropic hormone (ACTH), which in turn induces cortisol synthesis and release from the adrenal cortex [1]. This intricate feedback system is essential for maintaining homeostasis; however, chronic or excessive activation of the HPA axis can result in dysregulation, contributing to a range of pathological conditions, including metabolic syndromes, cardiovascular diseases, mood disorders, and reproductive dysfunctions [2,3].

The female reproductive system is notably sensitive to perturbations in HPA axis activity. Cortisol exerts inhibitory effects on the hypothalamic-pituitary-gonadal (HPG) axis by suppressing the pulsatile release of gonadotropin-releasing hormone (GnRH), thereby reducing downstream secretion of luteinizing hormone (LH) and follicle-stimulating hormone (FSH), hormones critical for

follicular development, ovulation, and the regulation of the menstrual cycle [4]. Consequently, chronic stress may contribute to menstrual disturbances, including anovulation, oligomenorrhea, and amenorrhea [5].

Dysfunctional uterine bleeding (DUB), defined as abnormal uterine bleeding in the absence of identifiable organic, structural, or systemic pathology, poses a significant clinical challenge and affects a substantial proportion of women of reproductive age [6]. While the etiology of DUB is multifactorial—encompassing hormonal imbalances, ovulatory dysfunction, and endometrial anomalies—emerging evidence implicates HPA axis dysregulation and resultant hypercortisolemia as potential contributors to the pathophysiology of DUB [7].

In light of these associations, the present study aims to examine the relationship between HPA axis dysregulation and DUB, with particular emphasis on circulating cortisol levels as a biomarker of stress. Understanding this neuroendocrine interplay may yield critical insights into the mechanisms linking psychosocial stress and menstrual irregularities, thereby informing more targeted diagnostic and therapeutic strategies for women affected by DUB.

Materials and Methods

Study Population and Design

Between 15 September 2018 and 15 June 2021, 34 women aged 20–50 years presenting with abnormal uterine bleeding (AUB) and subsequently diagnosed with DUB were recruited from the Department of Obstetrics and Gynecology, Faculty of Medicine, Inönü University. DUB was diagnosed in cases where the evaluation based on the International Federation of Gynecology and Obstetrics (FIGO) PALM-COEIN classification revealed no identifiable pelvic pathology, endocrine disorder, or pregnancy-related condition [6]. The control group comprised 36 age- and body mass index (BMI)-matched healthy volunteers with regular menstrual cycles (27–32 days) and no history of systemic disease. All control subjects underwent thorough cardiac and neurological examinations to exclude underlying autonomic dysfunction. Participants with abnormal electrocardiograms (ECGs) were excluded from further analysis.

Inclusion and Exclusion Criteria

Case Group

- Females aged 20–50 years diagnosed with DUB.

Control Group

- Females aged 20–50 years with regular menstrual cycles and no concomitant systemic diseases.

Exclusion Criteria for Both Groups

- Pregnancy or lactation.
- BMI <18 kg/m^2 or >30 kg/m^2.
- Endocrine disorders (e.g., diabetes mellitus, thyroid dysfunction, hyperprolactinemia, pituitary, or adrenal diseases).
- Polycystic ovary syndrome.
- Chronic systemic diseases (e.g., hypertension, renal, pulmonary, cardiac, or neurological disorders).
- Ectopic pregnancy or gestational trophoblastic disease.
- Coagulopathies or hematological disorders.
- Benign or malignant lesions of the ovary, uterus, or vulvovaginal region.
- Postmenopausal status or history of hysterectomy.
- Use of medications such as lipid-lowering agents, oral hypoglycemic drugs/insulin sensitizers, or hormonal agents (oral contraceptives, sex steroids).

Subjects who voluntarily withdrew from the study or enrolled in another clinical trial were also excluded.

Biochemical Analyses

Hormonal and biochemical assessments were performed on days 2–5 of the menstrual cycle following a 12-hour overnight fast. Between 09:00 and 10:00 a.m., venous blood samples were collected. Serum hormone levels were quantified using chemiluminescent immunoassays (Beckman Coulter UniCel DxI 800, Beckman Coulter Inc., Brea, CA, USA), while glucose, aspartate aminotransferase (AST), alanine aminotransferase (ALT), blood urea nitrogen (BUN), creatinine, and complete blood counts were determined using enzymatic-colorimetric methods (Beckman Coulter AU680, Beckman Coulter Inc., Brea, CA, USA).

Heart Rate Variability Measurement

Baseline ECG recordings were obtained after a 10-minute acclimatization period in a supine position. Participants were instructed to avoid sudden movements, speech, and artifacts during recordings. Following an initial 4-minute rest, a 5-minute ECG recording was acquired using the Poly-Spectrum 8 device, set at 25 mm/s and 10 mm/mV. Measurements were performed in the follicular phase to minimize hormonal influence on autonomic function and were standardized to morning hours (09:00–12:00) under constant ambient temperature (22–24 °C). Before ECG acquisition, blood pressure and heart rate were measured using an automated device (Omron M6 Comfort, Omron Corporation, Kyoto, Japan). Digital conversion of analog ECG data was conducted using a Norav Medical Ltd. converter, and heart rate variability (HRV) analysis was executed using Neurosoft and Norav Medical software.

Time-domain HRV parameters calculated included the mean RR interval, standard deviation of NN intervals (SDNN), and the root mean square of successive differences (RMSSD). Frequency-domain parameters were derived via a fast Fourier transform-based power spectral analysis, with power quantified over the very-low-

Table 1. Age and anthropometric characteristics of the control and DUB groups.

Parameter	Control (n = 36)	DUB (n = 34)	*t*-value	*p*-value
Age (years)	33.28 ± 6.91	35.32 ± 6.32	–1.29	0.201
Height (cm)	163.69 ± 5.11	161.09 ± 5.56	2.04	0.055
Weight (kg)	63.72 ± 10.72	63.68 ± 10.48	0.02	0.986
BMI (kg/m²)	23.64 ± 3.43	24.51 ± 3.68	–1.02	0.311

Data are presented as mean ± standard deviation. Independent-samples *t*-tests were employed for group comparisons. DUB, dysfunctional uterine bleeding; BMI, body mass index.

Table 2. Characteristics of serum hormone levels in the control and DUB groups.

Parameter	Control (n = 36)	DUB (n = 34)	Test Statistic	*p*-value
FSH (ng/mL) †	7.10 (3.70–10.40)	6.80 (5.70–11.60)	$z = 0.95$	0.344
LH (ng/mL) †	4.40 (3.10–8.20)	6.00 (4.00–9.30)	$z = –1.24$	0.215
E_2 (pg/mL) †	86.50 (47.75–113.00)	97.05 (61.00–132.00)	$z = –1.12$	0.262
Testosterone (ng/mL) †	20.00 (20.00–23.00)	20.00 (20.00–22.60)	$z = 0.10$	0.923
TSH (ng/mL) †	1.40 (0.95–1.80)	1.59 (1.10–2.40)	$z = –1.09$	0.277
DHEA-SO_4 (ng/mL) ‡	163.30 ± 54.72	138.67 ± 58.35	$t = 1.81$	0.073
Glucose (g/dL) ‡	89.44 ± 9.11	91.06 ± 10.08	$t = –0.70$	0.484
Hemoglobin (g/dL) ‡	12.69 ± 1.10	12.12 ± 1.44	$t = 1.85$	0.066

† Mann–Whitney U test; ‡ Independent-samples *t*-test.

This analysis confirms that the two groups were biochemically and hormonally comparable, supporting further evaluation of DUB-related parameters without significant confounding from these factors. FSH, follicle-stimulating hormone; LH, luteinizing hormone; E_2, estradiol; TSH, thyroid-stimulating hormone; DHEA-SO_4, dehydroepiandrosterone sulfate.

frequency (VLF: 0.00–0.04 Hz), low-frequency (LF: 0.04–0.15 Hz), and high-frequency (HF: 0.15–0.40 Hz) bands. Normalized units for LF (LFnu) and HF (HFnu) were computed, and the LF/HF ratio was used as an index of sympathovagal balance.

Data were expressed as mean ± standard deviation or median (interquartile range) for continuous variables.

Study Parameters

Clinical

- Age, weight, height, body mass index.

Hormonal

- Follicle-stimulating hormone (FSH), luteinizing hormone (LH), estradiol, testosterone, thyroid-stimulating hormone (TSH), dehydroepiandrosterone sulfate (DHEA-SO_4).

Biochemical

- Glucose (g/dL), hemoglobin (g/dL).

HRV Parameters

- Record length, heart rate, minimal and maximal RR intervals, NN interval, SDNN, RMSSD, percentage of successive NN intervals differing by more than 50 ms (pNN50), coefficient of variation, among other derived HRV metrics (e.g., total power, LF, HF, LF/HF, and percentage power in each band).

Power and Statistical Analyses

A priori power analysis using the G*Power 3.1 software (University of Düsseldorf, Düsseldorf, Germany)indicated that a minimum of 34 subjects per group (total n = 68) was required to detect a clinically significant difference in outcome measures with an alpha of 0.05, power of 0.80, an effect size of 0.70, and a two-tailed alternative hypothesis. Statistical analyses were performed using SPSS version 22 (IBM Corp., Armonk, NY, USA). The Shapiro–Wilk test was used to assess the normality of continuous variables. Independent-samples *t*-tests or the Mann–Whitney U test were applied as appropriate. Pearson or Spearman correlation analyses were employed to determine relationships between continuous variables, with statistical significance set at $p < 0.05$.

Results

A total of 70 women participated in the study, comprising 36 controls and 34 patients with a diagnosis of DUB. The mean age was 33.28 ± 6.91 years in the control group and 35.32 ± 6.32 years in the DUB group, with no statistically significant difference between the two groups ($p = 0.201$). Similarly, there were no significant differences in weight or body mass index (BMI) between controls and DUB patients.

Table 3. Time-Domain HRV parameters in the control and DUB groups.

Parameter	Control (n = 36)	DUB (n = 34)	Test Statistic	*p*-value
HR (bpm) †	79.60 ± 10.47	77.17 ± 10.29	$t = 0.97$	0.332
R-R min (ms) †	635.42 ± 107.17	642.53 ± 119.80	$t = –0.26$	0.794
R-R max (ms) †	891.28 ± 110.39	927.76 ± 119.78	$t = –1.32$	0.189
RRNN (ms) †	766.61 ± 100.63	790.91 ± 104.37	$t = –0.98$	0.325
SDNN (ms) ‡	37.50 (30.00–54.00)	42.50 (34.00–50.00)	$z = –0.94$	0.347
RMSSD (ms) ‡	31.00 (21.00–40.50)	37.00 (22.00–49.00)	$z = –0.78$	0.434
pNN50 (%) ‡	10.00 (1.80–19.00)	12.85 (1.60–27.90)	$z = –0.95$	0.344
CV (%) ‡	4.67 (3.93–6.64)	5.10 (4.32–6.41)	$z = –0.74$	0.459
RM min (ms) ‡	–111.50 (–163.50 to –85.00)	–117.50 (–178.00 to –86.00)	$z = 0.56$	0.573
RM max (ms) ‡	104.50 (65.50–128.50)	110.50 (68.00–169.00)	$z = –0.83$	0.404
R-R avg min (ms) †	676.06 ± 98.42	689.65 ± 107.02	$t = –0.55$	0.582
R-R avg max (ms) †	847.19 ± 101.51	880.82 ± 109.37	$t = –1.32$	0.187

†: mean ± SD with independent-samples *t*-test; ‡: median (IQR) with Mann–Whitney U test (reported as *z*). HRV, heart rate variability; HR, heart rate; pNN50, percentage of successive NN intervals differing by more than 50 ms; RRNN, mean of all normal-to-normal R-R intervals; SDNN, standard deviation of NN intervals; RMSSD, root mean square of successive differences; CV, coefficient of variation; RM min, minimum of the relative RR interval mean; RM max, maximum of relative RR interval mean; R-R avg min, average of minimum R-R intervals; R-R avg max, average of maximum R-R intervals.

The anthropometric characteristics of both groups are summarized in Table 1. The individual age distribution for the study and control groups is depicted in Table 1.

Biochemical and Hormonal Parameters

No statistically significant differences were detected between the control and DUB groups regarding serum levels of FSH, LH, estradiol (E_2), testosterone, TSH, DHEA-SO_4, glucose, and hemoglobin. The detailed biochemical and hormonal parameters for both groups are summarized in Table 2.

Time-Domain Heart Rate Variability Parameters

No statistically significant differences were observed between the control and DUB groups regarding heart rate (HR), minimum and maximum R-R intervals, mean of all normal-to-normal R-R intervals (RRNN), SDNN, RMSSD, pNN50 (%), coefficient of variation (CV), minimum and maximum running means (RMs), or the minimum and maximum average R-R intervals. The time-domain HRV parameters for both groups are summarized in Table 3.

Frequency-Domain Heart Rate Variability Parameters

No statistically significant differences were observed between the control and DUB groups in any of the frequency-domain HRV parameters. The measured parameters included total power (TP), low-frequency power (LF), high-frequency power (HF), normalized LF and HF values, LF/HF ratio, as well as various calculated metrics such as TPav, very-low-frequency power (VLF), percent power (%VLF, %LF, %HF), and specific power values and dominant periods (HFmx, HFav, LFmx, LFt, LFav, VLFmx, VLFt, and VLFav). These results are summarized in Table 4.

Correlation Analysis

The correlation matrix (Table 5) revealed a complex web of associations linking demographic factors, endocrine markers and autonomic function. Below is a succinct narrative of the key findings, with corresponding *r* and *p* values embedded in the text:

Age and Metabolic–Endocrine Indices

- Age was positively correlated with BMI ($r = 0.265$, $p < 0.05$) and with FSH ($r = 0.469$, $p < 0.01$), indicating that older participants tended to have higher adiposity and gonadotropin levels.
- Conversely, age showed significant negative associations with testosterone ($r = –0.254$, $p < 0.05$), DHEA-SO_4 ($r = –0.399$, $p < 0.01$), hemoglobin ($r = –0.241$, $p < 0.05$), and resting HR ($r = –0.255$, $p < 0.05$), reflecting an age-related decline in androgenic, hematologic and cardiovascular parameters.

Body Composition and Autonomic Tone

- BMI was positively associated with VLF power ($r = 0.333$, $p < 0.01$) and inversely related to overall HRV (SDNN, $r = –0.262$, $p < 0.05$; TP, $r = –0.279$, $p < 0.05$; LF, $r = –0.261$, $p < 0.05$), suggesting that higher adiposity corresponds to increased slow oscillations but reduced global autonomic variability.

Table 4. Frequency-Domain HRV parameters in the control and DUB groups.

Parameter	Control (n = 36)	DUB (n = 34)	Test Statistic	*p*-value
TP (ms²) †	1262.00 (880.00–2630.00)	1663.50 (1171.00–2446.00)	$z = -1.09$	0.274
L (Hz) †	0.40 (0.40–0.40)	0.40 (0.40–0.40)	$z = 0.00$	1.000
TPav (ms²/Hz) †	3.00 (2.00–7.00)	4.00 (3.00–6.00)	$z = -0.86$	0.392
VLF (ms²) †	512.50 (344.50–931.50)	666.00 (409.00–929.00)	$z = -1.18$	0.238
LF (ms²) †	389.50 (211.00–654.50)	403.50 (237.00–659.00)	$z = -0.54$	0.589
HF (ms²) †	317.00 (181.00–482.50)	493.50 (153.00–757.00)	$z = -0.89$	0.372
LF norm (%) ‡	55.00 ± 16.30	54.91 ± 18.21	$t = 0.02$	0.982
HF norm (%) ‡	45.00 ± 16.30	45.09 ± 18.21	$t = -0.02$	0.982
LF/HF †	1.17 (0.70–1.89)	1.35 (0.74–1.98)	$z = -0.14$	0.892
%VLF ‡	45.39 ± 15.21	45.89 ± 16.06	$t = -0.13$	0.895
%LF ‡	29.20 ± 10.29	28.21 ± 10.03	$t = 0.40$	0.683
%HF ‡	25.42 ± 12.88	25.91 ± 16.50	$t = -0.14$	0.889
HFmx (ms²/Hz × 1000) †	10.70 (3.50–15.80)	11.45 (3.90–24.40)	$z = -0.85$	0.394
HFav (ms²/Hz) †	1.25 (0.75–1.95)	1.95 (0.60–3.00)	$z = -0.89$	0.375
LFmx (s) †	15.25 (7.90–25.90)	16.25 (10.70–29.60)	$z = -0.98$	0.326
LFt (s) †	0.10 (0.00–0.10)	0.10 (0.00–0.10)	$z = 0.16$	0.872
LFav (ms²/Hz) †	3.55 (1.90–5.95)	3.65 (2.20–6.00)	$z = -0.50$	0.617
VLFmx (ms²/Hz × 1000) †	53.40 (28.10–78.05)	68.90 (34.60–102.20)	$z = -1.18$	0.238
VLFt (s) †	0.00 (0.00–0.00)	0.00 (0.00–0.00)	$z = 0.00$	1.000
VLFav (ms²/Hz) †	13.85 (9.35–25.20)	18.00 (11.10–25.10)	$z = -1.17$	0.240

†: Median (IQR) with Mann–Whitney U test (*z*-value); ‡: Mean ± SD with independent-samples *t*-test.

TP, total power; L, frequency resolution; TPav, average total power per hertz; VLF, very low frequency; LF, low frequency; HF, high frequency; LF norm, normalized low frequency; HF norm, normalized high frequency; LF/HF, low frequency to high frequency ratio; %VLF, percentage of very low frequency; %LF, percentage of low frequency; %HF, percentage of high frequency; HFmx, maximum high frequency power per hertz × 1000; HFav, average high frequency power per hertz; LFmx, maximum low frequency duration; LFt, total low frequency duration; LFav, average low frequency power per hertz; VLFmx, maximum very low frequency power per hertz × 1000; VLFt, total very low frequency duration; VLFav, average very low frequency power per hertz.

Gonadotropins and Steroid Hormones

- FSH correlated positively with LH; ($r = 0.488$, $p < 0.01$) and with VLF power ($r = 0.243$, $p < 0.05$), and negatively with estradiol ($r = -0.283$, $p < 0.05$).
- Estradiol was inversely associated with hemoglobin ($r = -0.245$, $p < 0.05$).
- Testosterone exhibited positive correlations with TSH ($r = 0.352$, $p < 0.01$), DHEA-SO_4 ($r = 0.254$, $p < 0.05$) and percentage LF power (%LF; $r = 0.237$, $p < 0.05$).
- DHEA-SO_4 was positively associated with hemoglobin ($r = 0.300$, $p < 0.05$).
- Finally, fasting glucose levels were negatively correlated with hemoglobin ($r = -0.235$, $p < 0.05$).

Heart Rate and HRV Metrics

- Resting HR showed a robust positive correlation with the LF/HF ratio ($r = 0.310$, $p < 0.01$) and %VLF ($r = 0.341$, $p < 0.01$), and significant negative associations with SDNN, RMSSD, pNN50, TP, LF, HF and %HF (all $p < 0.05$), indicating that higher heart rates are generally linked to reduced overall and parasympathetic variability.

Interrelationships Among HRV Indices

- Time-domain measures were tightly intercorrelated: SDNN with RMSSD ($r = 0.816$, $p < 0.01$) and pNN50 ($r = 0.985$, $p < 0.01$), and both SDNN and RMSSD were strongly correlated with TP, VLF, LF and HF (all $r \geq 0.511$, $p < 0.01$).
- Frequency-domain parameters likewise formed a cohesive cluster: TP with VLF/LF/HF ($r = 0.792$–0.852, $p < 0.01$), and VLF with LF/HF (%VLF) and inversely with %LF. The LF/HF ratio correlated positively with %VLF and %LF ($r = 0.376$, 0.600, $p < 0.01$) and inversely with %HF ($r = -0.854$, $p < 0.01$).

Together, these correlations underscore a multifaceted interplay between ageing, endocrine function and autonomic regulation, which may inform our understanding of stress-related reproductive disorders such as DUB.

These correlations underscore complex interrelationships between metabolic, endocrine, and autonomic regulatory systems, which may have implications for understanding the pathophysiology of conditions such as dysfunctional uterine bleeding.

Table 5. Correlation analysis.

Variables	Correlation	r	*p*-value
Age	↑ BMI	0.265	<0.05
	↑ FSH	0.469	<0.01
	↓ Testosterone	–0.254	<0.05
	↓ DHEA-SO_4	–0.399	<0.01
	↓ Hemoglobin	–0.241	<0.05
	↓ HR	–0.255	<0.05
BMI	↑ VLF	0.333	<0.01
	↓ SDNN	–0.262	<0.05
	↓ TP	–0.279	<0.05
	↓ LF	–0.261	<0.05
FSH	↑ LH	0.488	<0.01
	↑ VLF	0.243	<0.05
	↓ Estradiol	–0.283	<0.05
Estradiol	↓ Hemoglobin	–0.245	<0.05
Testosterone	↑ TSH	0.352	<0.01
	↑ DHEA-SO_4	0.254	<0.05
	↑ %LF	0.237	<0.05
DHEA-SO_4	↑ Hemoglobin	0.300	<0.05
Glucose	↓ Hemoglobin	–0.235	<0.05
HR	↑ LF/HF	0.310	<0.01
	↑ %VLF	0.341	<0.01
	↓ SDNN, RMSSD, pNN50, TP, LF, HF, %HF	–	<0.05/0.01
SDNN	↑ RMSSD	0.816	<0.01
	↑ pNN50	0.985	<0.01
	↑ TP, VLF, LF, HF	0.511–0.829	<0.01
RMSSD	↑ pNN50	0.970	<0.01
	↑ TP, VLF, LF, HF, %HF	0.511–0.918	<0.01
	↓ LF/HF	–0.550	<0.01
	↓ %VLF	–0.490	<0.01
pNN50	↑ TP, VLF, LF, HF, %HF	0.504–0.910	<0.01
	↓ LF/HF	–0.533	<0.01
	↓ %VLF	–0.500	<0.01
TP	↑ VLF, LF, HF	0.792–0.852	<0.01
VLF	↑ LF, HF, %VLF	0.242–0.660	<0.05/0.01
	↓ %LF	–0.244	<0.05
LF	↑ HF, %LF	0.367–0.673	<0.01
	↓ %VLF	–0.396	<0.01
HF	↑ %HF	0.717	<0.01
	↓ LF/HF	–0.648	<0.01
	↓ %VLF	–0.577	<0.01
LF/HF	↑ %VLF, %LF	0.376, 0.600	<0.01
	↓ %HF	–0.854	<0.01
%VLF	↓ %LF, %HF	–0.402, –0.762	<0.01
RMSSD	↓ HR	–0.567	<0.01

↑ : Positive correlation; ↓ : Negative correlation.

Discussion

This study is the first to systematically investigate the potential role of stress-related autonomic dysfunction in the etiology of DUB by assessing cardiac autonomic modulation via HRV analysis. Despite existing hypotheses suggesting that psychosocial stress may contribute to menstrual irregularities through dysregulation of the hypothalamic–pituitary–ovarian (HPO) axis [6,8–11], our findings did not support a link between DUB and altered autonomic or endocrine function under resting, early follicular-phase conditions.

A total of 70 women—34 with DUB and 36 matched healthy controls—were evaluated, with no statistically significant differences observed in age, BMI, or other anthropometric measures. Importantly, biochemical and hormonal assessments revealed no significant group differences in serum concentrations of FSH, LH, estradiol, testosterone, TSH, DHEA-SO_4, glucose, or hemoglobin. These findings establish a comparable physiological baseline between groups, strengthening the interpretability of subsequent HRV analyses.

Both time-domain and frequency-domain HRV parameters showed no significant differences between groups. In the time domain, measures such as SDNN, RMSSD, pNN50, and RR intervals were statistically equivalent between the DUB and control participants. Similarly, frequency-domain metrics—including total power, VLF, LF, HF, normalized LF/HF values, and various derived spectral components—were not significantly altered in the DUB group. These results collectively indicate that women with DUB do not exhibit resting autonomic imbalance, particularly in vagal or sympathetic tone, as assessed via HRV.

These findings contrast with evidence from other gynecological conditions, such as premenstrual dysphoric disorder (PMDD) and polycystic ovary syndrome (PCOS), where autonomic dysregulation—especially reduced vagal tone and increased sympathetic dominance—has been consistently reported [12–15]. The absence of such features in DUB suggests a distinct pathophysiological profile, one that may not primarily involve systemic stress-axis dysfunction or resting autonomic disturbance.

Notably, this study was conducted under rigorously controlled conditions: participants were matched for potential confounders such as age, BMI, and socioeconomic status; HRV measurements were taken by a single operator in a standardized environment; and external influences such as caffeine and physical activity were restricted prior to data collection. Moreover, expected correlations—such as inverse associations between BMI and parasympathetic HRV indices, and age-related declines in vagal activity—were evident, further validating our HRV measurement approach [16,17].

Nonetheless, several limitations should be acknowledged. First, while the sample size (n = 70) was sufficient for detecting medium to large effect sizes, it may have lacked power to identify more subtle physiological differences. Second, the cross-sectional design limited the ability to assess dynamic autonomic or hormonal fluctuations that might occur during bleeding episodes or in response to acute stress. Furthermore, no direct measures of HPA axis activity—such as salivary or serum cortisol—or subjective stress ratings were included, potentially omitting relevant dimensions of stress physiology [18].

In addition, while restricting data collection to the early follicular phase reduced hormonal variability, it may have obscured menstrual-phase–specific autonomic patterns observed in other studies [19–23]. Moreover, the lack of resting-state autonomic and endocrine differences does not preclude the involvement of localized uterine or vascular abnormalities in DUB. The PALM–COEIN classification framework suggests that structural and non-structural uterine factors may play a critical role in DUB pathogenesis, and future studies should integrate such parameters.

Conclusion

In this rigorously controlled study, women with dysfunctional uterine bleeding exhibited comparable autonomic nervous system activity and endocrine profiles to healthy controls under resting, early follicular-phase conditions. The lack of significant differences in both time-domain and frequency-domain HRV parameters, as well as in serum hormone and biochemical markers, suggests that baseline autonomic imbalance and overt endocrine dysfunction are unlikely to be primary contributors to DUB pathophysiology. However, the study's modest sample size and cross-sectional design may have limited the detection of subtle or dynamic variations. Future research should employ longitudinal designs across multiple menstrual phases, include stress-axis biomarkers such as cortisol, and stratify participants by DUB subtype. Incorporating uterine structural imaging, vascular assessments, and inflammatory biomarkers will be essential to fully elucidate the multifactorial mechanisms underlying DUB and to inform more precise diagnostic and therapeutic approaches.

Availability of Data and Materials

Data and materials from this study can be obtained from the corresponding author upon reasonable request.

Author Contributions

ÜD, AK, and SY: Conceptualization, Data Curation, Formal Analysis, Investigation, Methodology, Validation and Visualization. All authors were involved in the drafting and critical revision of the manuscript. All authors have read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

This prospective case–control study was approved by the Clinical Research Ethics Committee of Faculty of Medicine, Inönü University (Approval No.: 2018/88) and was conducted in accordance with the Declaration of Helsinki (Fortaleza, Brazil, 2013) and the Good Clinical Practice guidelines published by the Turkish Ministry of Health (Circular No. 51748, 29 December 1995). Written informed consent was obtained from all participants following both oral and written briefing.

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Conflict of Interest

The authors declare no conflict of interest.

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