Case Report

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Asystolic Vasovagal Syncope Temporally Associated with Perimenopausal Hormonal Instability: A Case Report

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ABSTRACT

Perimenopause is marked by high-amplitude estradiol variability and loss of progesterone-dependent cycle stabilization, which can modify autonomic tone and myocardial excitability. In women with lifelong vasovagal susceptibility, these endocrine shifts may lower the threshold for bradyarrhythmia or reflex syncope. Severe cardioinhibitory events temporally linked to anovulatory cycles have rarely been reported. A 39-year-old woman with lifelong vasovagal syncope experienced progressive cycle shortening (21-25 days), prolonged bleeding (10 days), and presumed anovulatory cycles, fulfilling Stages of Reproductive Aging Workshop +10 criteria for early menopausal transition. Hormonal evaluation showed suppressed mid-luteal progesterone (<0.5 ng/mL), fluctuating estradiol (24-150 pg/mL), and diminished ovarian reserve (anti-müllerian hormone 0.1 ng/mL). She developed worsening presyncope and cyclical clusters of premature atrial contractions (PACs), which intensified during anovulatory windows and in the 4-5 days preceding menses, and consistently diminished by days 3-5 of menstruation. Holter monitoring revealed sinus bradycardia (45-60 bpm) and low-burden PACs, with an estimated pre-procedural burden of approximately 10%. Tilt-table testing provoked a 40-second asystolic cardioinhibitory response. Given her age and clearly vagal phenotype, cardioneuroablation (CNA) was selected as a physiologic alternative to permanent pacing. During the procedure, prolonged arrest required chest compressions, bag-mask ventilation, and pacing to achieve return of spontaneous circulation. Post-CNA follow-up demonstrated complete resolution of syncope and normalization of resting heart rate (70-80 bpm), while PACs persisted, with burden decreasing to approximately 1% after CNA. Estrogen therapy was avoided because of active smoking and persistently positive antiphospholipid antibodies. This case highlights a potential association between perimenopausal hormonal variability and increased susceptibility to cardioinhibitory reflex syncope in autonomically predisposed women. Recognition of cycle-related symptom patterns may improve clinical awareness and support individualized diagnostic and management approaches.

Keywords: Perimenopause, anovulation, vasovagal syncope, asystole, cardioneuroablation

INTRODUCTION

Hormonal transitions across the reproductive lifespan exert profound effects on cardiovascular electrophysiology and autonomic regulation in women. Estradiol and progesterone modulate multiple ion channels, influence myocardial conduction velocity, and regulate baroreflex sensitivity through both genomic and non-genomic pathways.[1] These effects partially explain the well-recognized sex differences in arrhythmia susceptibility and autonomic tone, with women demonstrating a higher prevalence of neurally mediated syncope and phase-dependent variations in cardiac excitability.[2]

While postmenopausal estrogen deficiency has been widely studied as a contributor to autonomic imbalance and cardiac electrical vulnerability, emerging evidence suggests that perimenopausal hormonal volatility, rather than absolute hormone deficiency, may be equally arrhythmogenic.[3] During the late reproductive stage and early perimenopause, ovarian aging leads to intermittent estradiol surges, often exceeding concentrations seen in ovulatory cycles, in the context of profound luteal progesterone deficiency due to anovulation.[4] This "unopposed estrogen turbulence" is thought to influence autonomic stability, increases sympathetic drive, prolongs repolarization variability, and lowers the threshold

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for premature ventricular and supraventricular ectopy in susceptible individuals.[5]

These physiologic perturbations may be particularly impactful in women with pre-existing autonomic hypersensitivity, such as those with vasovagal syncope or enhanced vagal efferent tone. Perimenopausal hormonal variability can modulate cardiovascular autonomic control, potentially intensifying symptom fluctuations in susceptible individuals.[6] However, severe bradyarrhythmia or prolonged asystole triggered by perimenopausal anovulatory cycles have rarely been described in the literature, and remains an under-recognized clinical intersection between reproductive endocrinology and cardiac electrophysiology.

Furthermore, menopausal hormone therapy (MHT) may support autonomic and cardiovascular stability in appropriately selected women.[7] However, its use is restricted by several well-established contraindications, such as active or hormonally sensitive malignancies, unexplained uterine bleeding, severe liver disease, and conditions associated with elevated thrombotic risk.[8] In particular, a history of venous or arterial thromboembolism represents a major limitation to MHT use. Therefore, hormonal management cannot be universally applied and must be tailored to individual risk profiles.

Herein, we present a case of a 39-year-old perimenopausal woman with lifelong vasovagal syncope who experienced recurrent supraventricular ectopy, severe presyncope, and two episodes of prolonged asystole temporally associated with anovulatory hormonal fluctuations, ultimately requiring cardioneuroablation (CNA). To the best of our knowledge, similar presentations have been rarely described, and this case highlights a potential interaction between perimenopausal hormonal variability and cardioinhibitory reflex susceptibility in a predisposed autonomic phenotype.

CASE REPORT

Written informed consent was obtained from the patient for publication. A 39-year-old woman, gravida 2 para 2, with no structural heart disease, presented with progressive syncope and palpitations over the preceding five months. Her first syncopal event occurred at approximately age 5 years, typically triggered by painful stimuli such as minor procedures or injections. These childhood episodes were short, associated with pallor and brief loss of consciousness, but without convulsive movements. Multiple family members, her mother, maternal grandmother, uncle, cousin, and brother, reported similar episodes, suggesting a familial vasovagal predisposition.

Beginning at age 18 years, the patient developed episodes accompanied by jaw clenching, tongue biting, and brief tonic posturing, leading to an initial working diagnosis of epilepsy and empirical antiepileptic treatment. Electroencephalographic evaluations, including activation procedures, such as hyperventilation and photic stimulation, did not demonstrate definitive epileptiform activity. Although transient motor phenomena could be elicited during testing, these findings were not considered diagnostic of epilepsy. In the context of typical vasovagal triggers, prodromal symptoms, and subsequent clinical course, her neurologists considered the episodes more consistent with convulsive vasovagal syncope rather than epileptic seizures. Antiepileptic medications were later discontinued.

The patient reported progressive menstrual irregularity beginning in her early thirties. In 2019, diminished ovarian reserve was documented based on early follicular phase (cycle day 2-3) hormonal assessment [anti-müllerian hormone (AMH) 0.4 ng/mL; FSH 10.12 IU/L; estradiol <20 pg/mL]. Her menstrual pattern satisfied Stages of Reproductive Aging Workshop +10 criteria for early menopausal transition (stage -2), characterized by cycle shortening, variable cycle length, prolonged bleeding, and presumed anovulatory patterns.[9] Over the subsequent years, she developed worsening premenstrual symptoms, intermittent palpitations, near-syncope, and resting sinus bradycardia (45-60 bpm). Serial hormonal assessments demonstrated persistently suppressed mid-luteal progesterone (<0.5 ng/mL) with fluctuating estradiol levels, consistent with recurrent anovulatory cycles, as shown in Table 1. In response to her worsening cycle-related symptoms, hormonal therapy was considered. However, it was not pursued due to multiple contraindications, including active smoking and persistently positive antiphospholipid antibodies, specifically anti-β2-glycoprotein I IgM, both associated with elevated thromboembolic risk.

During this period, five months prior to presentation, she experienced her first menstrual delay. During this prolonged follicular phase, she developed frequent palpitations and recurrent presyncope. Holter monitoring demonstrated resting sinus bradycardia (40-50 bpm) and frequent premature atrial contractions (PACs), with an overall burden of approximately 10%. The ectopy appeared to increase during symptomatic periods. Detailed Holter analysis showed a substantial bradycardia load, with heart rates <55 bpm accounting for approximately 23% of all recorded beats, including discrete nocturnal episodes with a minimum sinus rate of 37 bpm. A representative overnight rhythm strip demonstrating marked sinus bradycardia is shown in Figure 1.

A repeat hormonal panel obtained during the delayed menses revealed an estradiol elevation to 150.54 pg/mL, with AMH 0.1 ng/mL suggestive of estrogen-dominant hormonal fluctuation during the perimenopausal transition.

Given the progression of symptoms, a tilt table test was performed due to increasing presyncope and bradyarrhythmia. The test was conducted using a standard head-up tilt protocol with pharmacologic provocation using sublingual nitroglycerine. During testing, she developed a prolonged cardioinhibitory response with asystole lasting approximately 40 seconds, accompanied by loss of consciousness. Atropine was administered, and chest compressions with bag-mask ventilation were initiated, resulting in return of spontaneous circulation (ROSC) without the need for electrical cardioversion. The response was considered consistent with a severe cardioinhibitory vasovagal reaction in the context of her longstanding clinical history. Structural heart disease and intrinsic conduction abnormalities had been excluded based on prior evaluation.

Table 1. Serial reproductive hormone measurements suggestive of anovulatory patterns and progressive decline of ovarian reserve

Date	Estradiol (E2) day 3	LH day 3	FSH day 3	Proges-terone (mid-luteal)	AMH	Anti-β2-glycoprotein I IgM	Reference ranges
18.01.2018	-	-	-		-	137.28 RU/mL	0-19 RU/mL
12.04.2018	-	-	-		-	88.86 RU/mL	0-19 RU/mL
17.05.2019	<20 pg/mL	2.29 IU/L	10.12 IU/L	<0.5 ng/mL	0.40 ng/mL	-	AMH: 1-4 ng/mL
02.07.2021	19.60 pg/mL	5.88 IU/L	7.07 IU/L		-	-	-
16.12.2019	-	-	-		-	54.89 RU/mL	0-19 RU/mL
09.02.2024	26.70 pg/mL	3.41 IU/L	5.43 IU/L		0.12 ng/mL	-	AMH: 1-4 ng/mL
28.05.2024	36.94 pg/mL	2.75 IU/L	8.58 IU/L		-	-	-
05.09.2024	19.95 pg/mL	2.39 IU/L	6.66 IU/L		-	-	-
18.06.2025	150.54 pg/mL	5.31 IU/L	4.01 IU/L	<0.5 ng/mL	0.10 ng/mL	-	AMH: 1-4 ng/mL
14.11.2025	< 24 pg/mL	2.41 IU/L	5.44 IU/L	<0.5 ng/mL			

E2: Estradiol, FSH: Follicle stimulating hormone, AMH: Anti-müllerian hormone, LH: Luteinizing hormone

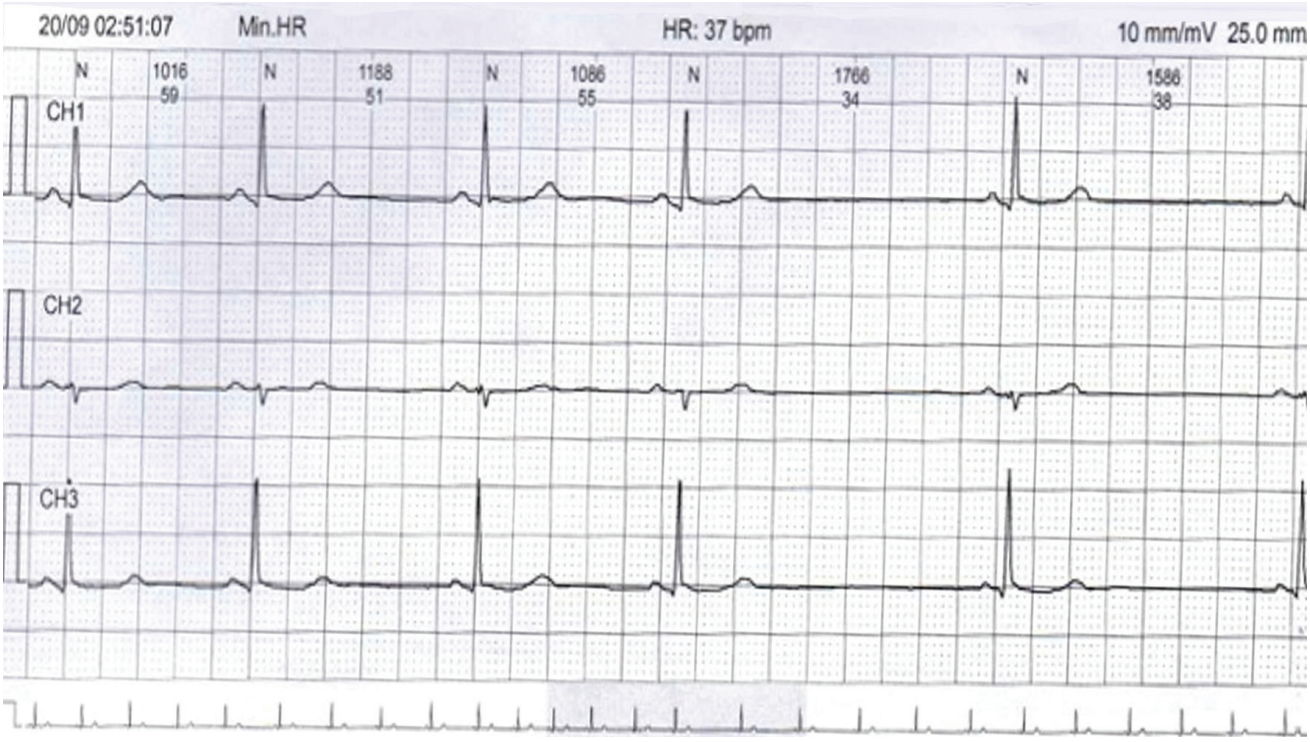

Figure 1. Severe nocturnal sinus bradycardia on Holter monitoring. Overnight Holter rhythm strip showing severe sinus bradycardia (minimum HR 37 bpm) with preserved AV conduction

AV: Atrioventricular, HR: Heart rate, CH: Channel

Given the documented cardioinhibitory response and lifelong vasovagal phenotype, CNA was selected as a management strategy. Although permanent pacing remains the standard therapy for recurrent asystolic vasovagal syncope, CNA was considered an appropriate alternative in this young patient with a predominantly vagally mediated mechanism and no evidence of structural heart disease. The decision was made following multidisciplinary evaluation. Approximately 10 days later, she underwent CNA targeting parasympathetic ganglionated plexi.

During mapping, she developed another episode of prolonged asystole of 3-4 minutes. Chest compressions and bag-mask ventilation were insufficient to restore circulation, and temporary transvenous ventricular pacing was initiated, leading to ROSC. She exhibited tongue trauma and brief tonic posturing, interpreted as motor phenomena secondary to cerebral hypoperfusion. The ablation was completed without procedural complications.

During early follow-up, she reported complete resolution of syncope and presyncope. Resting heart rate improved to 60-75 bpm, and no recurrent asystole occurred (Figure 2). Repeat Holter monitoring showed a reduction in PAC burden to approximately 1%. She continued to experience PACs with a recurrent temporal pattern, appearing to intensify during presumed hormonally vulnerable phases and diminish during menstruation. However, this observation is based on clinical correlation and should be interpreted cautiously. There was no associated hemodynamic compromise or loss of consciousness, indicating that CNA had effectively eliminated the cardioinhibitory component while leaving a benign ectopic tendency. These PACs were managed conservatively with observation and lifestyle modification, as they were infrequent, well tolerated, and not associated with structural heart disease or increased arrhythmic risk. The clinical course is summarized in Table 2.

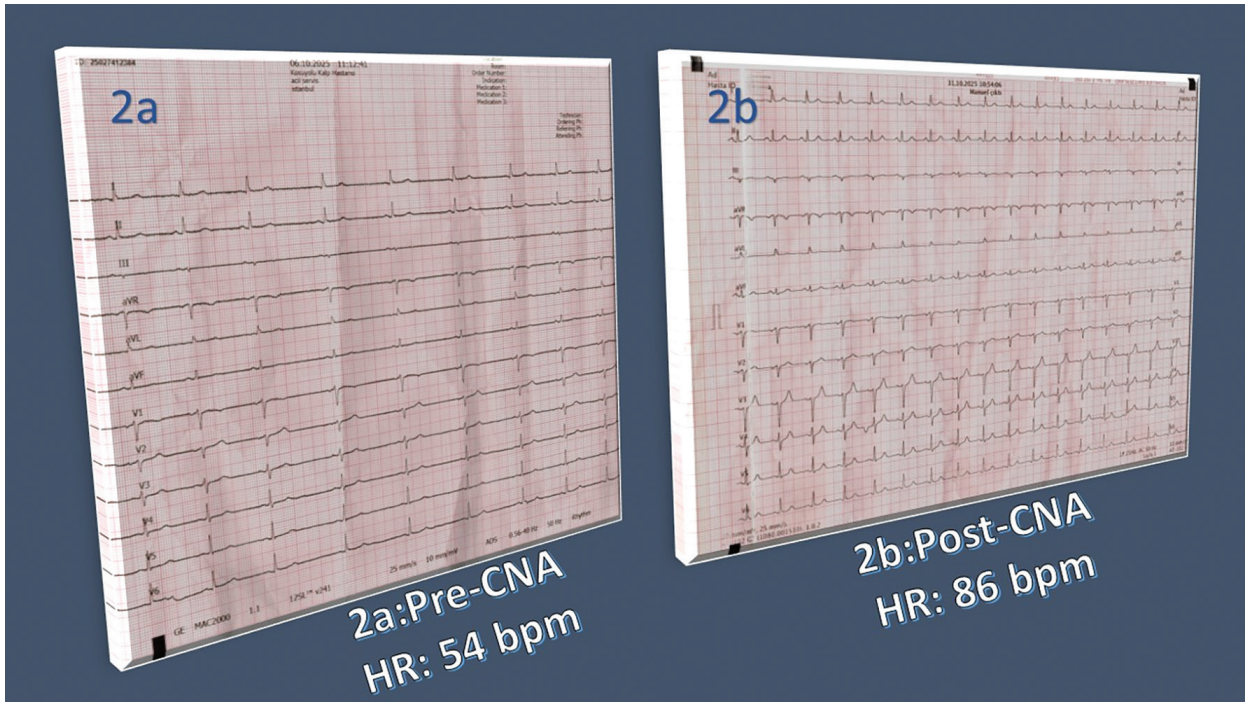

Figure 2. Resting 12-lead electrocardiograms before and after cardioneuroablation. **(2a)** Pre-CNA ECG demonstrating sinus bradycardia (heart rate 54 bpm). **(2b)** Post-CNA ECG showing normalized resting heart rate (86 bpm) with no recurrent pauses

CNA: Cardioneuroablation, ECG: Electrocardiogram, HR: Heart rate

Table 2. Chronological timeline summarizing clinical course, hormonal findings, and cardiac events

Chronology	Clinical/hormonal event	Cardiac findings/ intervention	Outcome
Age 5 years	First pain-triggered loss of consciousness	-	Vasovagal syncope suspected; no treatment
Adolescence-early adulthood	Recurrent events misdiagnosed as epilepsy; short empirical antiepileptic therapy	EEG mild nonspecific findings; no epileptiform activity	AED discontinued; convulsive vasovagal syncope confirmed
2018	Persistent positive anti-β2-glycoprotein I IgM (137 → 88 RU/mL)		
May 2019	Low estradiol (<20 pg/mL), AMH 0.4 ng/mL	-	Diminished ovarian reserve documented

Table 2. Continued

Chronology	Clinical/hormonal event	Cardiac findings/ intervention	Outcome
2021-2024	Irregular menses, progressive PMS, intermittent palpitations suppressed progesterone; rising estradiol (26-36 pg/mL range)	PACs reported intermittently	No syncope Estrogen therapy was avoided
Jun 2025	First menstrual delay; Estradiol surge (150.54 pg/mL), AMH 0.1; progesterone <0.5 ng/mL	Frequent PACs, presyncope	Symptoms worsen during anovulatory / luteal phases
Sept 2025		Increase in PACs and near-syncope	Suggestive estrogen-dominant anovulation
Tilt test (pre-CNA)	40-second asystole during tilt-induced cardioinhibitory response	CPR + bag-mask ventilation → ROSC	Decision for CNA
~10 days later	CNA for mixed cardioinhibitory vasovagal syncope	During mapping: 3-4 min asystole → chest compressions + BMV insufficient → temporary transvenous ventricular pacing → ROSC Ablation completed	
Post-CNA (6 month follow-up)	No syncope, no presyncope, resting HR 60-75 bpm	Rare benign PACs still occurring during luteal/ anovulatory phases	Cardioinhibitory component resolved; temporal variation in ectopy persists

AED: Antiepileptic drug, AMH: Anti-müllerian hormone, BMV: Bag-mask ventilation, CNA: Cardioneuroablation, CPR: Cardiopulmonary resuscitation, EEG: Electroencephalogram, HR: Heart rate, PAC: Premature atrial contraction, PMS: Premenstrual symptoms, ROSC: Return of spontaneous circulation

DISCUSSION

Perimenopause is characterized by marked variability in estradiol secretion and loss of progesterone-dependent cycle stabilization, resulting in high-amplitude hormonal fluctuations.[10] These endocrine shifts exert significant autonomic and electrophysiologic effects, including alterations in vagal tone, changes in baroreflex sensitivity, and modulation of myocardial excitability.[1] In susceptible women, particularly those with lifelong autonomic hypersensitivity or a vasovagal phenotype, these fluctuations may lower the threshold for symptomatic bradyarrhythmia, presyncope, or arrhythmia-related symptoms.[11] Although cycle-related palpitations and benign ectopy are well described, severe cardioinhibitory responses or prolonged asystole associated with perimenopausal anovulatory cycles remain exceedingly rare and under-recognized.[12]

This case illustrates an exceptionally rare intersection between perimenopausal endocrine volatility and severe cardioinhibitory reflex susceptibility. While cycle-related palpitations and benign ectopy are frequently reported in midlife women, reports of prolonged asystole or convulsive syncope temporally associated with presumed anovulatory hormonal patterns appear to be extremely limited. The coexistence of lifelong vasovagal hypersensitivity, genetically patterned autonomic vulnerability, and high-amplitude estradiol fluctuations may have contributed to an increased susceptibility to bradyarrhythmic events in this patient. Furthermore, the observation that CNA was associated with resolution of the cardioinhibitory component, while supraventricular ectopy persisted with a temporal association to menstrual phases, suggests a possible interaction between autonomic and hormonal factors in this case. Together, these features highlight a constellation that appears to be rarely described in the literature and expands current understanding of how perimenopausal physiology may modulate autonomic cardiac responses in susceptible individuals.

Management decisions in this case were guided by the dual nature of the patient's presentation, namely severe cardioinhibitory reflex susceptibility coexisting with supraventricular ectopy showing a temporal association with menstrual phases. Although permanent pacing remains the standard therapy for recurrent asystolic vasovagal syncope, particularly in guideline-supported indications, CNA has emerged as a potential alternative in carefully selected younger patients with a predominantly vagally mediated mechanism. In the presented case, given the patient's young age, absence of structural or intrinsic conduction system disease, and the clearly cardioinhibitory response observed on tilt testing, CNA was considered an appropriate individualized strategy.

Hormone therapy was considered to stabilize the patient's presumed anovulatory cycle patterns but was deferred due to persistently positive anti-β2-glycoprotein I IgM antibodies, active smoking, and concern for thromboembolic risk, following shared decision-making.[13] Likewise, beta-blockers or other antiarrhythmic agents were avoided given her baseline bradycardia and risk of exacerbating hypotension or pauses. The supraventricular ectopy showed a temporal association with menstrual phases, remained low in burden, and was managed conservatively. Importantly, these considerations were independent of the decision to proceed with CNA, which was based on the documented prolonged asystolic response.

This report is limited by the absence of electrocardiogram (ECG) tracings captured during the prolonged asystolic episode, the lack of historical EEG documentation from earlier convulsive events, and the limited number of hormonal measurements. Although pre- and post-procedural ECG and Holter recordings were available, the short follow-up period and single-patient nature of this case limit generalizability.

The observed temporal association between hormonal variability and arrhythmic events should therefore be interpreted with caution and may be considered hypothesis-generating.

CONCLUSION

This case suggests a possible association between perimenopausal hormonal variability and increased susceptibility to cardioinhibitory reflex syncope in a woman with lifelong vasovagal predisposition. Although causality cannot be established, recognition of possible cycle-related symptom patterns may support more individualized diagnostic and management approaches.

Ethics

Informed Consent: Written informed consent was obtained from the patient for publication of this case report and any accompanying images. The patient reviewed the manuscript and approved its content. The author would like to disclose that the patient described in this case report is also the author of the manuscript.

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