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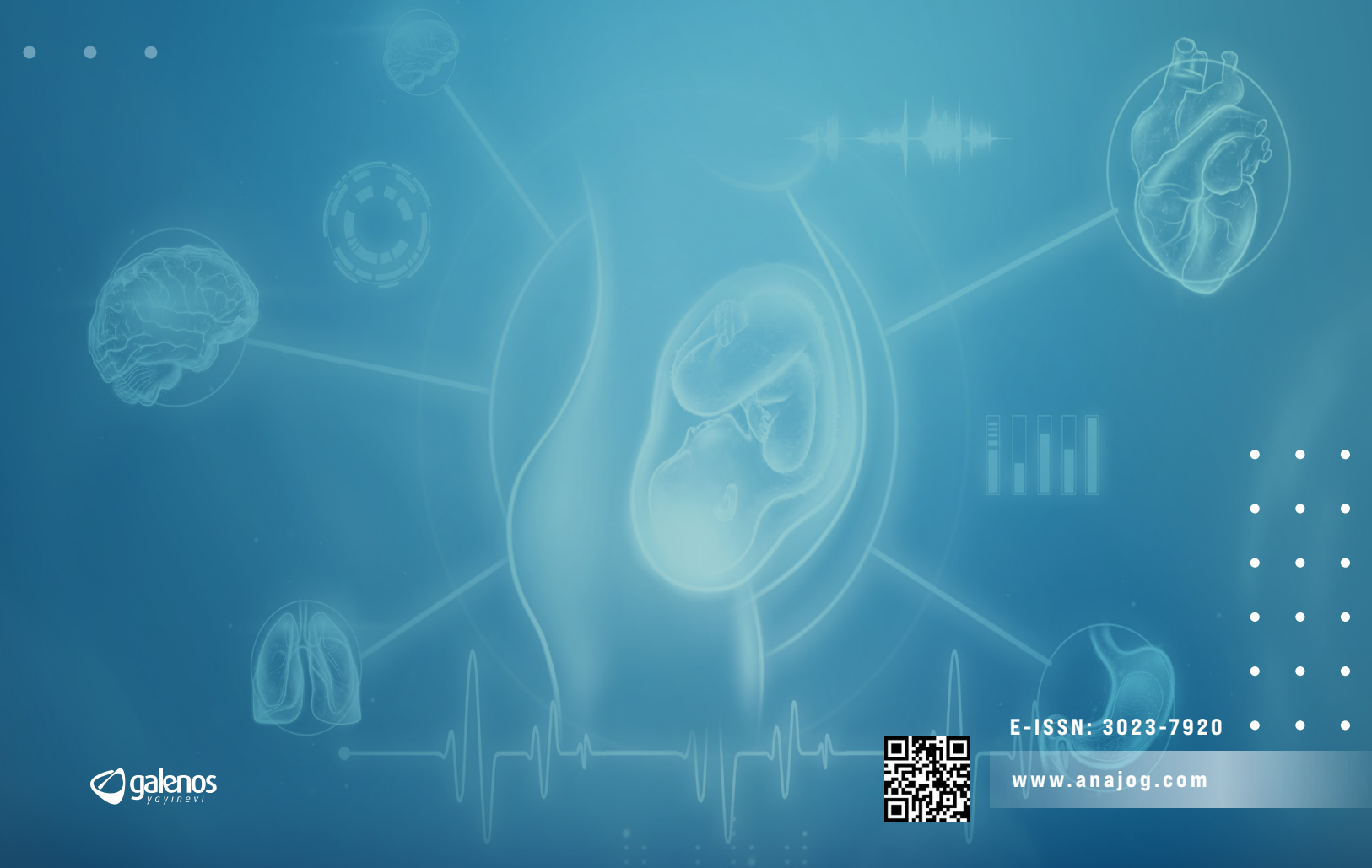

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Guideline

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Anat J Obstet Gynecol Res 2026;3(1):1-20

Vaginal Natural Orifice Transluminal Endoscopic Surgery (vNOTES) Hysterectomy in Benign Gynecologic Indications: Evidence-Based Recommendations of the Pelvic Floor and Cosmetic Gynecology (PETKOZ) Association, Combined with Expert Consensus - A National Guideline

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1. Contraindications

1.1. Prior Cesarean sections or benign gynecological pelvic surgery or small bowel surgery or colon surgery, nulliparity, postmenopausal status, absence of uterine prolapse (Grade 2 or higher), large uteri, long or narrow or atrophic vagina, history of pelvic inflammatory disease is not a contraindication for vNOTES hysterectomy [GPP].

1.2. Deep infiltrating endometriosis is a contraindication for vNOTES benign hysterectomy [GPP].

2. Preoperative Preparation and Assessment

2.1. Ultrasound assessment of the cul-de-sac using the sliding sign and bimanual vaginal examination should be routinely performed in the preoperative evaluation for vNOTES hysterectomy [GPP].

2.2. Routine preoperative laxative administration (oral or intravenous) is not recommended prior to vNOTES hysterectomy [GPP].

2.3. Preoperative vaginal culture, preoperative rectal mechanical bowel preparation, and a special preoperative dietary restriction is not required in asymptomatic patients scheduled for vNOTES hysterectomy [GPP].

2.4. The recommended preoperative antibiotic prophylaxis regimen for vNOTES hysterectomy is 2 g cefazolin sodium combined with 1 g metronidazole [GPP].

3. Perioperative Management

3.1. Compression stockings and early postoperative mobilization are recommended as part of venous thromboembolism prophylaxis for vNOTES hysterectomy. Pharmacological anticoagulant prophylaxis should not be administered routinely following vNOTES hysterectomy but should be individualized according to patient-specific risk factors and classification (e.g., Caprini score). When pharmacological anticoagulant prophylaxis is indicated, administration should commence between the 6th and 12th postoperative hour [GPP].

3.2. An indwelling urinary catheter should be routinely inserted and maintained throughout vNOTES hysterectomy. The urinary catheter should be retained upon transfer of the patient to the ward following vNOTES hysterectomy [GPP].

3.3. Anti-sliding shoulder braces should be applied to prevent cephalad patient displacement during vNOTES hysterectomy [GPP].

3.4. The primary and assistant surgeons should be seated during vNOTES hysterectomy. The scrub nurse should be positioned to the right of the primary surgeon during vNOTES hysterectomy. The professional designation of the second assistant (physician or nurse) does not affect intraoperative outcomes during vNOTES hysterectomy. The intraoperative presence of a second surgeon should be considered mandatory in technically demanding or anatomically complex hysterectomy cases [GPP].

3.5. vNOTES hysterectomy confers ergonomic advantages over laparoscopic hysterectomy with regard to operative posture, wrist loading, and musculoskeletal fatigue. During the colpotomy and vaginal closure phases, optimal ergonomics and visualization are achieved with the operating table raised (patient elevated) and the surgeon in a lowered position. During the endoscopic phase, optimal ergonomics and visualization are achieved with the operating table lowered (patient in a dependent position) and the surgeon in a raised position [GPP].

4. Intraoperative Technique

4.1. Vaginally assisted vNOTES hysterectomy (Va-vNOTES/VANH) is the preferred approach over total vNOTES hysterectomy (TVNH) for benign indications [GPP].

4.2. Posterior colpotomy should be performed as the initial step and a circumferential mucosal incision (cervical circumcision) should be performed in vNOTES hysterectomy for benign indications. Digital palpation of the pelvic cavity should be performed following posterior colpotomy during vNOTES hysterectomy [GPP].

4.3. Trendelenburg positioning should be applied during the laparoscopic (endoscopic) phase of vNOTES hysterectomy. A CO_2 insufflation pressure of 10-12 mmHg is recommended as the standard working pressure for vNOTES hysterectomy. CO_2 insufflation pressure should be modified in patients with obesity, significant cardiopulmonary comorbidity, or advanced age undergoing vNOTES hysterectomy [GPP].

4.4. In vNOTES hysterectomy for benign indications, the uterus and adnexa may be excised and removed separately; en-bloc removal is not mandatory [GPP].

4.5. Monopolar electrocautery is the preferred instrument for the initial vaginal mucosal incision during vNOTES hysterectomy. A combined approach using both blunt and sharp dissection is recommended following the initial vaginal mucosal incision in vNOTES hysterectomy [GPP].

4.6. An advanced bipolar vessel-sealing device is the preferred energy instrument for hemostatic pedicle control during vNOTES hysterectomy. Suction-irrigation should be deployed on demand during vNOTES hysterectomy; routine intraoperative setup at case initiation is not required [GPP].

4.7. Placement of a supplementary (fourth) port is indicated when hemorrhage, bowel, or bladder compromise adequate visualisation of the operative field during vNOTES hysterectomy [GPP].

4.8. No. 1 polyglactin 910 (Vicryl) is the preferred suture material for vaginal cuff closure following vNOTES hysterectomy [GPP].

4.9. Cystoscopy following vNOTES hysterectomy with high uterosacral ligament suspension should not be performed routinely but reserved for cases in which bladder or ureteral injury is clinically suspected [GPP].

4.10. Vaginal cuff closure should incorporate both the posterior and anterior peritoneum together with the vaginal mucosa, rather than approximating the vaginal mucosa alone [GPP].

4.11. Both the cardinal and uterosacral ligament origins should be routinely incorporated into the vaginal cuff closure following vNOTES hysterectomy [GPP].

5. Postoperative Care

5.1. The risk of vaginal or pelvic-abdominal infectious complications following vNOTES hysterectomy is not increased compared with laparoscopic or open hysterectomy [GPP].

5.2. Routine postoperative full blood count monitoring is not required following uncomplicated vNOTES hysterectomy; hematological assessment should be reserved for cases with clinical suspicion of hemorrhage [GPP].

5.3. The ideal discharge time following uncomplicated vNOTES hysterectomy is within 12-24 hours of the procedure [GPP].

5.4. Early postoperative mobilization should be initiated within 4-6 hours following vNOTES hysterectomy. Postoperative mobilization following vNOTES hysterectomy may be initiated earlier than recommended under standard enhanced recovery after surgery (ERAS) protocols [GPP].

5.5. The incidence of postoperative nausea and vomiting following vNOTES hysterectomy is lower compared with laparoscopic hysterectomy. Routine prophylactic antiemetic therapy is not recommended following vNOTES hysterectomy [GPP].

5.6. Postoperative antibiotic therapy should be routinely administered following vNOTES hysterectomy [GPP].

5.7. Patients should be advised to abstain from sexual intercourse for a period of six weeks following vNOTES hysterectomy [GPP].

6. Operative Time

6.1. All clinicians should be aware that vNOTES hysterectomy is associated with a significantly shorter operative time compared with TLH and may be considered in centres with appropriate surgical expertise [A].

7. Hospital Stay

7.1. Clinicians should be aware that vNOTES is associated with a modest reduction in length of hospital stay compared with TLH. Although the absolute decrease is small, this reduction may contribute to improved perioperative efficiency and facilitate early discharge, particularly when integrated within ERAS protocols [A].

8. Hemoglobin Decline

8.1. Patients should be counseled that perioperative hemoglobin decline following vNOTES hysterectomy is generally comparable to other minimally invasive approaches. However, variability may occur depending on surgical technique, surgeon experience, and patient-specific factors [C].

9. Estimated Blood Loss

9.1. Estimated blood loss (EBL) during vNOTES hysterectomy is comparable to other minimally invasive approaches, including laparoscopic and vaginal hysterectomy [B].

9.2. Hemostatic preparation and intraoperative management should follow standard protocols for minimally invasive hysterectomy, although consideration should be given to surgical expertise and patient-specific risk factors [B].

10. Blood Transfusion

10.1. There is insufficient evidence to recommend a specific practice. Clinicians should follow standard hemostatic protocols, with no additional precautions required solely for the vNOTES approach [B].

11. Postoperative Pain

11.1. Patients may experience lower early postoperative pain scores with vNOTES compared with laparoscopic hysterectomy [A].

11.2. vNOTES hysterectomy is associated with lower postoperative pain compared with laparoscopic hysterectomy and should be considered when selecting the surgical approach [A].

12. Postoperative Analgesic Usage

12.1. Perioperative analgesic protocols for vNOTES hysterectomy should be individualized, with consideration for potentially reduced systemic analgesic requirements compared to laparoscopic approaches [B].

12.2. Clinicians should consider minimizing opioid use in patients undergoing vNOTES hysterectomy, as postoperative analgesic needs are generally low and can often be managed with non-opioid regimens [B].

13. Re-admission

13.1. Women should be informed that the risk of unplanned re-admission following vNOTES hysterectomy is comparable to that of other minimally invasive approaches [B].

13.2. Standard postoperative discharge criteria and re-admission thresholds should be applied without modification based on surgical route [B].

14. Anal Exhaust Time (Time to first flatus)

14.1. Clinicians may consider vNOTES hysterectomy as an approach potentially associated with earlier recovery of gastrointestinal function, reflected by shorter time to first flatus, compared to other minimally invasive approaches. However, it should not be used as a sole determinant of clinical decisions [C].

14.2. Patients undergoing vNOTES hysterectomy may experience an earlier return of bowel function compared with other minimally invasive approaches but the magnitude of this benefit remains uncertain and may vary between individuals [C].

15. Mobilization/Return to Daily Activities

15.1. vNOTES hysterectomy is associated with earlier mobilization and faster return to daily activities compared with laparoscopic hysterectomy, and this potential recovery advantage may be a relevant factor when counselling patients regarding their surgical options. [C]

15.2. vNOTES may be integrated into ERAS programmes incorporating early mobilization protocols. [C]

15.3. Clinicians may consider vNOTES hysterectomy in patients for whom rapid postoperative recovery is a clinical priority, including obese patients and those with large uteri [C].

16. Postoperative Sexual Function

16.1. Women should be reassured that vNOTES hysterectomy does not adversely affect postoperative sexual function compared with laparoscopic hysterectomy [B].

16.2. Clinicians should inform women that vNOTES hysterectomy is not associated with deterioration of sexual function and can be performed without expected adverse effects on postoperative sexual health [B].

17. Intraoperative Complications

17.1. Clinicians should consider vNOTES hysterectomy as a safe alternative to conventional laparoscopic or vaginal hysterectomy for benign indications, as current evidence shows comparable intra-operative complication rates [A].

17.2. Women may be reassured that undergoing vNOTES does not appear to increase the risk of intra-operative complications compared with other minimally invasive approaches [A].

17.3. When intraoperative conversion is required during vNOTES hysterectomy, the appropriate conversion modality (laparoscopy or laparotomy) should be selected according to the underlying indication and clinical circumstances [GPP].

17.4. When an intraoperative bladder injury is identified during vNOTES hysterectomy, repair should be deferred until completion of the endoscopic phase and performed during the vaginal cuff closure phase [GPP].

18. Postoperative complications

18.1. Clinicians should consider vNOTES hysterectomy as having a similar post-operative complication profile compared with conventional laparoscopic or vaginal hysterectomy for benign indications [A].

18.2. Clinicians should counsel women that vNOTES does not appear to increase the risk of major or minor post-operative complications, including bleeding, infection, or need for reoperation [A].

18.3. Women may be reassured that recovery and safety outcomes with vNOTES are comparable to other minimally invasive hysterectomy techniques [A].

19. Indwelling Urinary Catheterization

19.1. Urinary catheter removal should be planned by clinicians for the earliest clinically appropriate time point following vNOTES hysterectomy and should be incorporated into ERAS protocols. Routine prolonged catheterisation is not indicated following uncomplicated vNOTES [D].

20. Conversion Rate

20.1. Clinicians should counsel patients that conversion rates with vNOTES hysterectomy are low and comparable to other minimally invasive approaches. The choice of surgical technique should therefore be based on patient factors, surgeon experience, and available expertise rather than concerns regarding conversion risk [B].

21. Cost Analysis

21.1. Institutions considering the adoption of vNOTES should undertake a prospective local economic evaluation accounting for equipment procurement, training costs, operative time savings, and bed day reductions. Formal health technology assessment is recommended prior to national-level commissioning decisions [D].

ABSTRACT

Purpose: Vaginal Natural Orifice Transluminal Endoscopic Surgery (vNOTES) hysterectomy is an increasingly adopted and most minimally invasive approach for benign gynecological indications. However, considerable heterogeneity exists in clinical practice regarding patient selection, perioperative management, surgical technique, and outcome reporting. This guideline aims to provide evidence-based and expert consensus-supported national recommendations for vNOTES hysterectomy in benign gynecology, developed on behalf of the Pelvic Floor and Cosmetic Gynecology (PETKOZ) Association.
Methods: A systematic search of Medline/PubMed, Cochrane, EMBASE, and Google Scholar was conducted for articles published between January 2015 and March 2026, yielding 1960 records. Fifty-seven studies met inclusion criteria, comprising eight systematic reviews/meta-analyses, six randomized controlled trials, six prospective and 37 retrospective cohort studies. Evidence quality and recommendation strength were graded using the SIGN classification system. For clinical questions insufficiently addressed by the literature, a three-round Delphi consensus process was conducted among 22 expert surgeons, each with a minimum of 50 vNOTES cases; ≥70% agreement defined consensus.
Results: Compared with total laparoscopic hysterectomy, vNOTES hysterectomy was associated with significantly shorter operative time (evidence level: 1+), reduced early postoperative pain (1+), a modest reduction in hospital stay (1+), and faster postoperative recovery. Intraoperative and postoperative complication rates, conversion rates, and readmission rates were comparable to other minimally invasive approaches. Comprehensive recommendations covering contraindications, preoperative preparation, intraoperative technique, and postoperative care were established through both evidence synthesis and the Delphi process.
Conclusion: This national guideline supports vNOTES hysterectomy as a safe and feasible approach for benign gynecological disease when performed in appropriately selected patients at centers with relevant surgical expertise. While findings are reinforced by structured evidence appraisal and formal consensus methodology, a substantial proportion of the evidence base remains observational. Future randomized trials, standardized outcome reporting, and prospective health-economic analyses are essential for refining recommendations in subsequent guideline updates.

Keywords: vNOTES scarless surgery, vnotes hysterectomy, national guidelines, vaginal laparoscopy

INTRODUCTION

Purpose and Scope

The purpose of this guideline is to provide advice to guide clinicians, based on the best available evidence, regarding the use of vaginal natural orifice transluminal endoscopic surgery (vNOTES) for non-malignant hysterectomy. This guideline reviews patient selection, perioperative assessment, surgical technique, and postoperative management. It aims to standardize practice, optimize surgical outcomes, and minimize complications for women undergoing hysterectomy for benign conditions.

This guideline excludes hysterectomy performed for suspected or confirmed malignancy, as the surgical approach and perioperative considerations differ significantly. Recommendations have been developed as a practical guide for gynecology surgeons, residents, and other healthcare professionals involved in the perioperative care of these patients. It is recognized that in individual cases, alternative approaches may be reasonable based on patient factors, surgical expertise, and available resources.

Population and Setting

Women undergoing hysterectomy for benign gynecological conditions, including fibroids, adenomyosis, abnormal uterine bleeding, or pelvic organ prolapse, in both hospital and outpatient surgical settings.

Interventions to be Studied

The guideline focuses on the application of vNOTES as a surgical approach for non-malignant hysterectomy, including preoperative assessment, intraoperative technique, and postoperative care, and compares its outcomes with conventional vaginal or laparoscopic hysterectomy where relevant evidence is available.

Background

vNOTES hysterectomy has emerged as a novel minimally invasive approach for the management of benign gynecological disease.[1,2] By integrating the advantages of conventional vaginal surgery with endoscopic visualization, this technique offers the potential to reduce surgical morbidity, enhance postoperative recovery, and improve patient-centered outcomes.[3] However, despite its growing adoption, considerable heterogeneity remains in clinical practice, particularly with respect to patient selection, perioperative management, surgical technique, and outcome reporting, reflecting the lack of standardized, evidence-based guidance. The aim of this guideline is to critically appraise the available evidence and provide comprehensive recommendations on the use of vNOTES for hysterectomy in benign gynecology, encompassing patient selection, preoperative evaluation, intraoperative considerations, and postoperative care. The overarching objective is to support safe implementation, optimize surgical outcomes, and minimize procedure-related complications. Given the variability in surgical expertise, institutional infrastructure, and resource availability across different healthcare settings, this guideline integrates both evidence-based recommendations and consensus-derived expert opinion. Where appropriate, recommendations have been contextualized to enhance their applicability across diverse clinical environments. Key recommendations and clinical pathways are summarized in structured tables and figures to facilitate translation into routine practice.

METHODS

This guideline was developed in accordance with standard methodology for producing national guideline on behalf of the Guidelines Committee of the Pelvic Floor and Cosmetic Gynecology (PETKOZ) (https://petkoz.org) Association. A comprehensive search was conducted in MEDLINE/PubMed, the Cochrane Database of Systematic Reviews and the Cochrane Methodology Register, EMBASE, and Google Scholar for articles published between January 2015 and March 2026. The following search string was applied: ("vNOTES" or "vaginal natural orifice transluminal endoscopic surgery" or "transvaginal notes") and ("hysterectomy") and ("benign" or "non-malignant" or "leiomyoma" or "fibroids" or "adenomyosis" or "abnormal uterine bleeding" or "pelvic organ prolapse"). No language restrictions were applied. Studies were eligible for inclusion if they: (1) enrolled adult women undergoing hysterectomy for benign indications; (2) reported vNOTES as a surgical approach; (3) included at least one comparator arm (laparoscopic or vaginal hysterectomy); and (4) reported at least one of the pre-specified participants, intervention, comparison, and outcome (PICO) criteria. Exclusion criteria comprised: case reports with fewer than five patients; studies focused exclusively on malignant indications; conference abstracts without full-text availability; and studies with no extractable outcome data.

The systematic review was undertaken using a PICO approach, resulting in the formulation of five key research questions focusing on the application of vNOTES in benign gynecology (Supplementary Material 1). The review specifically addressed standardized preoperative preparation protocols, comprehensive perioperative care management, and the identification of clinical contraindications for the vaginal approach. Furthermore, the analysis investigated specific intraoperative techniques and surgical nuances, alongside an evaluation of postoperative care and recovery outcomes.

An Assessment of Quality of Evidence and Grading of Strength of Recommendations

In evaluating the quality of evidence and grading the strength of recommendations, this guideline adopted the classification system proposed by the Scottish Intercollegiate Guidelines Network (SIGN), as outlined in Table 1. Evidence levels were assigned based on study design and methodological rigour, ranging from 1++ [high-quality meta-analyses or randomized controlled trials (RCTs) with very low risk of bias] to 4 (expert opinion), with intermediate categories reflecting case-control and cohort studies of varying quality (2++, 2+, 2−) as well as non-analytical studies such as case reports and case series (level 3). Grades of recommendations were subsequently assigned according to the highest level of evidence directly applicable to each clinical question: Grade A denotes recommendations supported by at least one meta-analysis, systematic review, or RCT rated 1++, or a body of evidence rated 1+ with overall consistency; Grade B reflects evidence rated 2++ or extrapolated from level 1 studies; Grade C corresponds to evidence rated 2+ or extrapolated from 2++; and Grade D is reserved for evidence of level 3 or 4, or extrapolated from 2+. Where no formal evidence was available but a clinical practice point could be identified, a good practice point (✓) was designated, reflecting the consensus-based clinical experience of the guideline development group.

Creating Expert Consensus Statements

For clinical questions that could not be adequately addressed by the available literature, a Delphi consensus process was conducted to formulate expert-based recommendations.[4,5]

Table 1. Scottish Intercollegiate Guidelines Network (SIGN) levels of evidence

Classification of evidence levels		Grades of recommendations	
1++	High-quality meta-analyses, systematic reviews of RCTs or RCTs with very low risk of bias	**A**	At least one meta-analysis, systematic review or RCT rated as 1++ and directly applicable; or systematic review of RCTs or body of evidence rated as 1+ with overall consistency
1+	Well-conducted meta-analyses, systematic reviews of RCTs or RCTs with low risk of bias	**B**	Body of evidence rated as 2++ directly applicable with overall consistency; or extrapolated from 1++ or 1+
1–	Meta-analyses, systematic reviews of RCTs or RCTs with high risk of bias	**C**	Body of evidence rated as 2+ directly applicable with consistency; or extrapolated from 2++
2++	High-quality case-control or cohort studies with very low risk of confounding and high probability of causal relationship	**D**	Evidence level 3 or 4; or extrapolated from 2+
2+	Well-conducted case-control or cohort studies with low risk of confounding and moderate probability of causal relationship		
2–	Case-control or cohort studies with high risk of confounding and significant risk relationship is not causal		
3	Non-analytical studies, e.g., case reports, case series		
4	Expert opinion	✓	**Good practice point recommended best practice based on the clinical experience of the guideline development group***

*On the occasion when the guideline development group finds there is an important practical point that they wish to emphasize but for which there is not, nor is there likely to be any research evidence. It must be emphasized that these are NOT an alternative to evidence-based recommendations, and should only be used where there is no alternative means of highlighting the issue
RCTs: Randomized controlled trials

A panel of specialists experienced in the vNOTES technique and affiliated with the PETKOZ association were invited to participate in a structured, iterative questionnaire focusing on five domains: contraindications, preoperative preparation, perioperative care, intraoperative surgical technique, and postoperative care. Eligible clinicians were identified from the PETKOZ association expert register and invited to participate if they had performed at least 50 vNOTES procedures; this threshold was applied to ensure that panel responses reflected meaningful procedural experience. The authors acknowledge that this inclusion criterion may limit generalizability to centres with less vNOTES experience, and this is noted as a limitation of the guideline. The 22 specialists participating in the Delphi panel were affiliated with a diverse range of healthcare institutions, including university hospitals, training and research hospitals, and private healthcare centers, thereby ensuring broad representation across different levels of clinical practice and healthcare delivery settings.

A three-round survey was conducted using a web-based platform (Google Forms), with each round administered via a unique, anonymized secure link. In each round, panellists were asked to rate their level of agreement with a series of proposed recommendation statements using a five-point Likert scale (1= strongly disagree; 2= disagree; 3= neutral; 4= agree; 5= strongly agree). Responses were collected anonymously, and the aggregated results from each round were fed back to participants before the subsequent round, allowing them to reassess their judgements in light of the group's overall responses. Statements were classified into three categories based on the proportion of panellists scoring 4 or 5 (agree or strongly agree): (1) consensus achieved (≥70% agreement)-statements were accepted and incorporated as recommendations; (2) neutral zone (50-69% agreement)-statements were revised based on qualitative feedback from the group and re-presented in the following round; and (3) no consensus (<50% agreement)-statements were excluded from the subsequent round and not carried forward. Before the third round, a virtual meeting was held to review the outcomes of the earlier rounds, concentrating particularly on statements in the neutral zone that had not yet achieved consensus. The PETKOZ expert group initially drafted the final manuscript, which was subsequently reviewed and endorsed by all participating clinicians. Recommendations derived through this process are clearly identified throughout the guideline as consensus-based expert recommendations, distinct from those grounded in the formal evidence hierarchy, as shown in Table 2.

Table 2. Responses by Delphi consensus of expert panel (third round results) — vNOTES hysterectomy for benign indications (n=22 experts; consensus threshold ≥70%)

#	Statement	Agreement (%)	Disagreement (%)
CONTRAINDICATIONS			
1	A previous Cesarean section is not a contraindication for vNOTES hysterectomy.	100.0	0.0
2	The number of prior Cesarean sections does not, in itself, constitute a contraindication for vNOTES hysterectomy.	95.5	4.5
3	Nulliparity is not a contraindication for vNOTES hysterectomy.	100.0	0.0
4	Postmenopausal status is not a contraindication for vNOTES hysterectomy.	100.0	0.0
5	The absence of uterine descent (Grade 0-1 prolapse) is not a contraindication for vNOTES hysterectomy.	100.0	0.0
6	Uterine size alone does not constitute a contraindication for vNOTES hysterectomy.	86.4	13.6
7	Deep infiltrating endometriosis (DIE) is a contraindication for vNOTES hysterectomy.	77.3	22.7
8	A history of benign gynecological pelvic surgery is not a contraindication for vNOTES hysterectomy.	90.9	9.1
9	A history of prior small bowel surgery is not a contraindication for vNOTES hysterectomy.	95.5	4.5
10	A long vagina is not a contraindication for vNOTES hysterectomy.	100.0	0.0
11	A narrow or atrophic vagina is not a contraindication for vNOTES hysterectomy.	90.9	9.1
12	A history of prior colon surgery is not a contraindication for vNOTES hysterectomy.	86.4	13.6
13	A history of pelvic inflammatory disease (PID) is not a contraindication for vNOTES hysterectomy.	81.8	18.2
PREOPERATIVE PREPARATION			
14	Routine preoperative laxative administration (oral or intravenous) is not recommended prior to vNOTES hysterectomy.	77.3	22.7
15	Ultrasound assessment of the cul-de-sac using the sliding sign should be routinely performed in the preoperative evaluation for vNOTES hysterectomy.	72.7	27.3
16	Bimanual vaginal examination should be routinely performed as part of the preoperative assessment prior to vNOTES hysterectomy.	95.5	4.5
17	Preoperative vaginal culture is not required in asymptomatic patients scheduled for vNOTES hysterectomy.	100.0	0.0

Table 2. Continued

#	Statement	Agreement (%)	Disagreement (%)
18	The recommended preoperative antibiotic prophylaxis regimen for vNOTES hysterectomy is 2 g cefazolin sodium combined with 1 g metronidazole.	77.3	22.7
19	Preoperative rectal mechanical bowel preparation is not required prior to vNOTES hysterectomy.	81.8	18.2
20	A special preoperative dietary restriction is not necessary for patients undergoing vNOTES hysterectomy.	77.3	22.7
PERIOPERATIVE MANAGEMENT			
21	An indwelling urinary catheter should be routinely inserted and maintained throughout vNOTES hysterectomy.	81.8	18.2
22	Compression stockings are recommended as part of venous thromboembolism prophylaxis for vNOTES hysterectomy.	100.0	0.0
23	Early postoperative mobilization is recommended as part of venous thromboembolism prophylaxis following vNOTES hysterectomy.	100.0	0.0
24	Anti-sliding shoulder braces should be applied to prevent cephalad patient displacement during vNOTES hysterectomy.	81.8	18.2
25	The primary surgeon should be seated during vNOTES hysterectomy.	90.9	9.1
26	The assistant surgeon should be seated during vNOTES hysterectomy.	90.9	9.1
27	The scrub nurse should be positioned to the right of the primary surgeon during vNOTES hysterectomy.	81.8	18.2
28	During the colpotomy and vaginal closure phases, optimal ergonomics and visualization are achieved with the operating table raised (patient elevated) and the surgeon in a lowered position.	86.4	13.6
29	During the endoscopic phase, optimal ergonomics and visualization are achieved with the operating table lowered (patient in a dependent position) and the surgeon in a raised position.	81.8	18.2
30	The professional designation of the second assistant (physician or nurse) does not affect intraoperative outcomes during vNOTES hysterectomy.	81.8	18.2
31	vNOTES hysterectomy confers ergonomic advantages over laparoscopic hysterectomy with regard to operative posture, wrist loading, and musculoskeletal fatigue.	72.7	27.3
32	The urinary catheter should be retained upon transfer of the patient to the ward following vNOTES hysterectomy.	77.3	22.7
33	Pharmacological anticoagulant prophylaxis should not be administered routinely following vNOTES hysterectomy but should be individualized according to patient-specific risk factors and classification.	77.3	22.7
34	When pharmacological anticoagulant prophylaxis is indicated, administration should commence between the 6th and 12th postoperative hour.	77.3	22.7
35	Routine pharmacological anticoagulant prophylaxis is not indicated for all patients undergoing vNOTES hysterectomy; the decision should be individualized based on patient-specific risk stratification (e.g., Caprini score).	90.9	9.1
INTRAOPERATIVE TECHNIQUE			
36	Posterior colpotomy should be performed as the initial step in vNOTES hysterectomy for benign indications.	90.9	9.1
37	A circumferential mucosal incision (cervical circumcision) should be performed in vNOTES hysterectomy for benign indications.	72.7	27.3
38	Digital palpation of the pelvic cavity should be performed following posterior colpotomy during vNOTES hysterectomy.	77.3	22.7
39	In vNOTES hysterectomy for benign indications, the uterus and adnexa may be excised and removed separately; en-bloc removal is not mandatory.	81.8	18.2
40	Trendelenburg positioning should be applied during the laparoscopic (endoscopic) phase of vNOTES hysterectomy.	72.7	27.3
41	An advanced bipolar vessel-sealing device is the preferred energy instrument for hemostatic pedicle control during vNOTES hysterectomy.	100.0	0.0
42	Placement of a supplementary (fourth) port is indicated when hemorrhage, bowel, or bladder has compromized adequate visualization of the operative field during vNOTES hysterectomy.	72.7	27.3

Table 2. Continued

#	Statement	Agreement (%)	Disagreement (%)
43	Suction-irrigation should be deployed on demand during vNOTES hysterectomy; routine intraoperative setup at case initiation is not required.	77.3	22.7
44	Monopolar electrocautery is the preferred instrument for the initial vaginal mucosal incision during vNOTES hysterectomy.	77.3	22.7
45	A combined approach using both blunt and sharp dissection is recommended following the initial vaginal mucosal incision in vNOTES hysterectomy.	81.8	18.2
46	A CO_2 insufflation pressure of 10-12 mmHg is recommended as the standard working pressure for vNOTES hysterectomy.	86.4	13.6
47	When intraoperative conversion is required during vNOTES hysterectomy, the appropriate conversion modality (laparoscopy or laparotomy) should be selected according to the underlying indication and clinical circumstances.	72.7	27.3
48	When an intraoperative bladder injury is identified during vNOTES hysterectomy, repair should be deferred until completion of the endoscopic phase and performed during the vaginal cuff closure phase.	81.8	18.2
VAGINAL CUFF CLOSURE AND APICAL SUPPORT			
49	No. 1 polyglactin 910 (Vicryl) is the preferred suture material for vaginal cuff closure following vNOTES hysterectomy.	72.7	27.3
50	Cystoscopy following vNOTES hysterectomy with high uterosacral ligament suspension (HUSLS) should not be performed routinely but reserved for cases in which bladder or ureteral injury is clinically suspected.	95.5	4.5
51	Vaginal cuff closure should incorporate both the posterior and anterior peritoneum together with the vaginal mucosa, rather than approximating the vaginal mucosa alone.	77.3	22.7
52	Both the cardinal and uterosacral ligament (USL) origins should be routinely incorporated into the vaginal cuff closure following vNOTES hysterectomy.	81.8	18.2
POSTOPERATIVE CARE			
53	The risk of vaginal or pelvic-abdominal infectious complications following vNOTES hysterectomy is not increased compared with laparoscopic or open hysterectomy.	95.5	4.5
54	Routine postoperative full blood count monitoring is not required following uncomplicated vNOTES hysterectomy; hematological assessment should be reserved for cases with clinical suspicion of hemorrhage.	81.8	18.2
55	The ideal discharge time following uncomplicated vNOTES hysterectomy is within 12–24 hours of the procedure.	90.9	9.1
56	Early postoperative mobilization should be initiated within 4–6 hours following vNOTES hysterectomy.	86.4	13.6
57	Postoperative mobilization following vNOTES hysterectomy may be initiated earlier than recommended under standard Enhanced Recovery After Surgery (ERAS) protocols.	86.4	13.6
58	Routine prophylactic antiemetic therapy is not recommended following vNOTES hysterectomy.	72.7	27.3
59	Postoperative antibiotic therapy should be routinely administered following vNOTES hysterectomy.	77.3	22.7
60	The incidence of postoperative nausea and vomiting (PONV) following vNOTES hysterectomy is lower compared with laparoscopic hysterectomy.	81.8	18.2
61	Patients should be advised to abstain from sexual intercourse for a period of six weeks following vNOTES hysterectomy.	95.5	4.5
ADDITIONAL CONSIDERATIONS			
62	Vaginally assisted vNOTES hysterectomy (Va-vNOTES / VANH) is the preferred approach over total vNOTES hysterectomy (TVNH) for benign indications.	86.4	13.6
63	The intraoperative presence of a second surgeon should be considered mandatory in technically demanding or anatomically complex hysterectomy cases.	77.3	22.7
64	CO_2 insufflation pressure should be modified in patients with obesity, significant cardiopulmonary comorbidity, or advanced age undergoing vNOTES hysterectomy.	100.0	0.0

Agreement (%) = proportion of panel selecting the highest-ranked response option. Disagreement (%) = 100% − Agreement (%). DIE = deep infiltrating DIE: Deep infiltrating endometriosis, ERAS: Enhanced recovery after surgery, HUSLS: High uterosacral ligament suspension, PID: Pelvic inflammatory disease, PONV: Postoperative nausea and vomiting, USL: Oterosacral ligament, Va-vNOTES: Vaginally assisted vNOTES, VANH: Vaginally assisted NOTES hysterectomy, TVNH: Total vaginal NOTES hysterectomy

Quality and Risk of Bias Assessment

Two independent authors assessed the methodological quality of articles independently of each other. This encompassed an evaluation of potential bias related to participant selection, outcome measurement, and data reporting, as well as bias associated with study funding sources. Discrepancies in quality assessment were resolved through discussion between reviewers. In instances where consensus could not be achieved, adjudication was provided by a third independent researcher. Cohort or observational studies were analyzed using the risk of bias in non-randomized studies of interventions (ROBINS-I) tool.[6] Studies judged to be at critical risk of bias under the ROBINS-I framework were excluded from the quantitative synthesis, as such studies are considered incapable of providing credible effect estimates. For randomized studies, the Cochrane risk-of-bias tool was used for randomized trials (RoB 2) which scores studies as having a high, low, or unclear risk of bias in five domains: selection, performance, detection, attrition, and reporting biases.[7] Systematic reviews and meta-analyses were critically appraised using the AMSTAR 2 framework to verify methodological integrity.[8] AMSTAR-2 acts as a 16-item framework for assessing the methodological quality and transparency of systematic reviews. It classifies evidence into four confidence levels: high (accurate and comprehensive), moderate (minor weaknesses only), low (contains a critical flaw), and critically low (multiple critical flaws). Ultimately, reviews with low or critically low ratings are considered unreliable for providing an accurate summary of the evidence.

The results of the risk-of-bias assessments directly informed the evidence grading process. Studies rated as critical risk of bias under ROBINS-I were excluded from the evidence synthesis and did not contribute to formal recommendations. Systematic reviews rated as critically low confidence by AMSTAR 2 were excluded from primary evidence grading; their findings are reported descriptively where contextually relevant but are not cited as the evidentiary basis for any formal recommendation. For RCTs, the RoB 2 assessment was used to differentiate between evidence level 1++ (low risk across all domains) and level 1+ (some concerns in one or more domains); in the context of surgical trials, the inherent inability to blind operating surgeons was a consistent source of "some concerns" in Domain 2 (deviation from intended interventions) and was acknowledged as a domain-specific but unavoidable limitation. The overall confidence in each body of evidence, as determined through these assessments, was the primary determinant of the SIGN evidence level assigned and, subsequently, the grade of the corresponding recommendation.

Ethical approval was not required for the development of this guideline, as it was based solely on a review of the literature and expert consensus.

RESULTS

A total of 1960 records were identified through database searching, of which 57 studies met the inclusion criteria and were incorporated into the final analysis (Figure 1). The included evidence comprised eight systematic reviews and meta-analyses,[9,11-17] six RCTs,[10,18-20] six prospective cohort studies,[21-25] and 37 retrospective cohort studies.[26-65]

The methodological quality of the eight included systematic reviews was appraised using the AMSTAR 2 tool across 16 items and seven critical domains (Supplementary Material 2). Only one review[9] achieved a "high" confidence rating with full adherence across all critical domains, while five reviews were rated "low",[11,12,14,15] one "Low-to-Moderate",[16] and one "Critically Low".[13] At the item level, full compliance (100%) was achieved for PICO formulation, comprehensive search strategy, duplicate study selection and data extraction, risk-of-bias tool application, interpretation of findings, and conflict-of-interest disclosure. Conversely, publication bias assessment (Item 15), a critical domain, was adequately reported in only two reviews (25%), and funding source disclosure (Item 10) was addressed in a single review (12.5%). Overall, while most reviews satisfied core methodological criteria, persistent deficiencies in publication bias assessment and funding transparency substantially limit confidence in the available evidence.

The risk of bias of the six included RCTs was evaluated using RoB 2 across five domains (Supplementary Material 3). No study was rated as high risk in any domain. Five trials[18,19,20,65] raised some concerns primarily due to the inherent impossibility of blinding surgeons in surgical trials (D2) and unblinded outcome assessment for subjective endpoints (D4). Prekatsounaki et al.[65] was a pre-planned secondary analysis of the HALON and NOTABLE trials. Both parent trials employed sham abdominal incisions to blind participants and outcome assessors, resulting in low risk of bias for D1, D2, and D4. Some concerns were noted for D3 due to exclusion of sexually inactive women, and for D5 due to the post-hoc pooled design without a pre-specified combined analysis protocol. The HALON trial[10] was the only study rated as low risk across all domains, owing to participant and assessor blinding achieved through sham abdominal incisions.

The methodological quality of the 37 included retrospective studies was assessed using ROBINS-I, with full domain-level results reported in Supplementary Material 4. Under ROBINS-I, studies were rated across seven domains including bias due to confounding, participant selection, classification of interventions, deviations from intended interventions, missing data, outcome measurement, and selection of the reported result, yielding an overall judgement of low, moderate, serious, or critical risk of bias. The predominant rating across the retrospective evidence base was moderate risk of bias (n=21), most commonly driven by residual confounding inherent to non-randomized designs and incomplete adjustment for baseline differences between surgical groups. Sixteen studies were judged to carry a serious risk of bias, primarily due to substantial selection bias, absence of propensity-score adjustment, or inadequate control of confounding variables. No study was rated as critical.

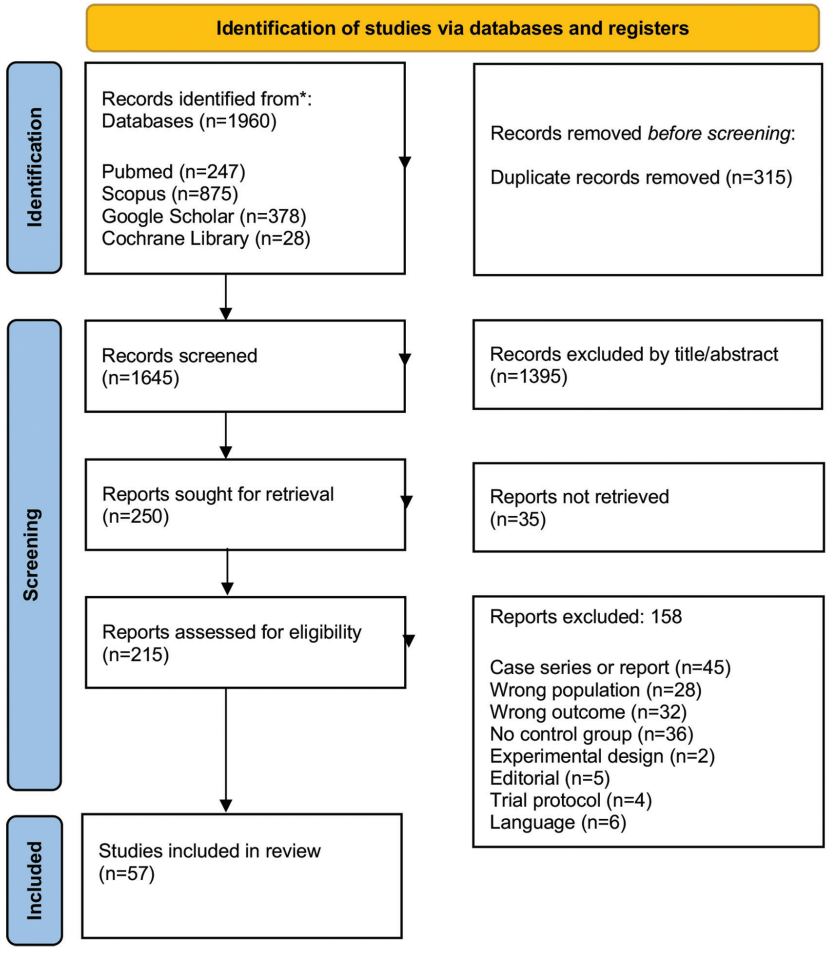

Figure 1. Flow diagram of study selection process according to PRISMA 2020 guidelines for the national guideline comparing vNOTES and minimally invasive hysterectomy techniques in benign gynecology

vNOTES: Vaginal Natural Orifice Transluminal Endoscopic Surgery, PRISMA: Preferred Reporting Items for Systematic reviews and Meta-Analyses

Operative Time

1. Recommendation (Grade A)

vNOTES hysterectomy is associated with a significantly shorter operative time compared with TLH and should be considered in centers with appropriate surgical expertise.

Evidence Level: 1+

Among all perioperative metrics evaluated in this guideline, operative time is the most consistently reported and arguably the most reproducible advantage of vNOTES over TLH. The Cochrane systematic review by Pickett et al.[9] provides the highest level of evidence, incorporating an RCT[10] that demonstrated a mean operative time reduction of 34 minutes in favor of vNOTES compared to TLH [95% confidence interval (CI) -45.54 to -22.46], representing a clinically meaningful decrease in operative duration. This finding has been corroborated by multiple meta-analyses comparing vNOTES with laparoscopic approaches,[11-15] and the network meta-analysis by Guan et al.[16] ranked vNOTES as having a shorter operative time than TLH among minimally invasive techniques. Furthermore, a systematic review evaluating robotic vNOTES hysterectomy versus robotic-assisted laparoscopic hysterectomy (RALH) for benign gynecological disease similarly favored vNOTES in operative time.[17]

Three high-quality RCTs comparing vNOTES with conventional laparoscopy, LESS, and vaginal approaches consequently reported shorter operative times for vNOTES.[10,18,19] In contrast, a single RCT comparing vNOTES with vaginal hysterectomy for benign indications found no difference in operative time.[20] Prospective cohort studies of moderate-level evidence generally favored vNOTES over TLH,[21-24] although Fang et al.[25] reported shorter operative times with TLH. Studies in special populations, including obese patients[26-28] and those with enlarged uteri,[29-31] also demonstrated reduced operative times with vNOTES.

Conflicting results were predominantly observed in retrospective studies, which were generally of lower quality. A total of 33 retrospective studies compared vNOTES with alternative surgical approaches for hysterectomy:

11 reported no significant differences,[32-41] 17 demonstrated clear advantages for vNOTES,[41-57] and five favored conventional approaches, including vaginal hysterectomy,[58-60] TLH,[61] and LESS.[62] Collectively, these findings suggest a trend toward improved outcomes with vNOTES, although heterogeneity in study design and endpoints necessitates cautious interpretation.

Hospital Stay

1. Recommendation (Grade A)

vNOTES is associated with a modest reduction in length of hospital stay compared with TLH. Although the absolute decrease is small, this reduction may contribute to improved perioperative efficiency and facilitate early discharge, particularly when integrated within ERAS protocols.

Evidence Level: 1+

Hospital length of stay is an important indicator of patient recovery and a major contributor to healthcare expenditures. Evidence from the Cochrane review by Pickett et al.[9] demonstrates that vNOTES is associated with a modest but statistically significant reduction in hospitalisation compared with TLH (mean difference -0.50 days; 95% CI 0.97 to -0.03). While the absolute decrease is small, it may lead to meaningful efficiency gains at the system level when implemented across a hysterectomy service, especially within ERAS protocols. These findings are supported by several systematic reviews[11,12,15] and reinforced by the network meta-analysis of Guan et al.,[16] which positions vNOTES favorably relative to TLH, LESS, and RALH techniques.

RCTs comparing vNOTES with other minimally invasive hysterectomy approaches have consistently reported hospital stay outcomes either in favor of vNOTES or showing no significant difference. Park et al.[19] found no significant difference when comparing LESS and vNOTES hysterectomy, while Yıldız et al.[20] reported similar findings in a comparison between vaginal hysterectomy and vNOTES. In two RCTs evaluating hysterectomy combined with apical prolapse repair to prevent post-hysterectomy vaginal cuff descent, Lowenstein et al.[18] reported a shorter operative time in favor of vNOTES, whereas Bacak et al.[63] found no significant difference between approaches.

The perioperative advantage of vNOTES has been consistently demonstrated in prospective cohort studies[21,22] and corroborated across multiple retrospective series from diverse surgical centers.[26-30,33,35,37,39,40,42,45-49,51,54,56,57,60,61] Notably, this benefit appears to be preserved in technically challenging patient populations, including those with non-descended uteri,[30] individuals with a history of prior pelvic surgery,[54] patients with obesity,[26-28] and those presenting with markedly enlarged uteri.[29-31]

Hemoglobin Decline

1. Recommendation (Grade C)

Patients should be counseled that perioperative hemoglobin (Hb) decline following vNOTES hysterectomy is generally comparable to other minimally invasive approaches; however, variability may occur depending on surgical technique, surgeon experience, and patient-specific factors.

Evidence level: 1-

Perioperative Hb decline is a surrogate for intraoperative blood loss and is relevant to the risk of transfusion and postoperative anemia. Unlike operative time and hospital stay, the evidence for this outcome is heterogeneous and difficult to interpret. The majority of systematic reviews and meta-analyses that have addressed Hb decline, including Housmans et al.,[11] Marchand et al.,[12] and Chaccour et al.,[15] have reported no significant difference between vNOTES and laparoscopic comparators. This finding of equivalence is supported in an RCT comparing vNOTES and LESS, also moderate-level evidence with prospective series.[23,64] Retrospective cohort studies of low-level evidence[25,26,32,38,45,54,56] demonstrated comparable reductions in Hb levels in vNOTES cases relative to other surgical approaches.

However, the literature demonstrates some heterogeneity in findings. Several prospective and retrospective comparative studies have reported a greater decline in Hb levels following vNOTES compared to TLH,[21,33,47,62] which may be attributable to technical factors related to vaginal cuff hemostasis, the surgical learning curve, or differences in patient selection.

Estimated Blood Loss

4. Recommendation (Grade B)

1- Estimated blood loss during vNOTES hysterectomy is comparable to other minimally invasive approaches, including laparoscopic and vaginal hysterectomy.

2- Hemostatic preparation and intraoperative management should follow standard protocols for minimally invasive hysterectomy, although consideration should be given to surgical expertise and patient-specific risk factors.

Evidence level: 1-

Intraoperative blood loss estimation serves as a more dynamic clinical indicator than postoperative Hb reduction, primarily because it provides a real-time assessment of surgical hemorrhage. This immediate feedback is essential for guiding timely intraoperative interventions and fluid management strategies.

Multiple systematic reviews have assessed this outcome. Housmans et al.[11] observed lower EBL with vNOTES compared to laparoscopic hysterectomy, a result further supported by Marchand et al.,[17] who evaluated robotic vNOTES against other surgical approaches for benign gynecological conditions. Conversely, studies by Sarkar et al.,[13] Marchand et al.[12,14] and Chaccour et al.[15] found no significant differences in EBL between vNOTES and laparoscopic, vaginal, or LESS approaches. In the network meta-analysis by Guan et al.,[16] which included the widest range of comparators, vNOTES was positioned intermediately: EBL was higher than with TLH or RALH, yet lower than with vaginal hysterectomy in the network comparisons.

Across the currently available RCTs, in a moderate-level RCT, Park et al.[19] found no difference in EBL when comparing vNOTES with LESS hysterectomy, while Lowenstein et al.[18] demonstrated higher EBL with conventional vaginal hysterectomy compared to vNOTES; notably, no RCT has demonstrated a statistically significant increase in EBL in favor of any comparator over vNOTES.

In six prospective cohort studies[21-25,64] with moderate-to-high level evidence, four reported no significant difference in EBL between vNOTES and other hysterectomy approaches, while two demonstrated higher EBL with vNOTES compared to TLH. In the prospective cohort by Fang et al.,[25] vNOTES had a median EBL of 100 mL versus 30 mL for TLH; the authors attributed this difference to lack of prior vNOTES experience at their center, suggesting a learning curve effect rather than an intrinsic disadvantage of the technique. Moreover, in the study of Takahashi et al.,[23] vNOTES demonstrated significantly higher EBL compared to TLH (150 mL vs 70 mL, $p<0.001$), despite similar Hb decline. The study included surgeons with varying experience levels; while EBL was higher, the authors did not explicitly attribute this to surgical experience, although it remains a possible contributing factor given the real-world multicenter setting and the inherent learning curve associated with vNOTES procedures.

The majority of moderate-low quality retrospective series report no clinically significant difference in EBL between vNOTES and its comparators.[27,29,35-39,42,54,55,59,62]

Blood Transfusion

5. Recommendation (Grade B)

There is insufficient evidence to recommend a specific practice. Clinicians should follow standard hemostatic protocols, with no additional precautions required solely for the vNOTES approach.

Evidence level: 2+

Blood transfusion is a clinically meaningful outcome reflecting the hemorrhagic risk of surgical procedures. Evidence comes from systematic reviews with low to critically low AMSTAR ratings,[12,15] a moderate-strength RCT,[19] and several prospective and retrospective cohort studies of low to moderate quality. Marchand et al.[12] conducted a systematic review and meta-analysis including both randomized and observational studies, suggesting vNOTES may be associated with lower transfusion rates compared to conventional approaches; however, the review was rated critically low by AMSTAR due to limitations in study selection and risk-of-bias assessment. Similarly, Chaccour et al.[15] performed a low-quality systematic review and reported no significant differences in transfusion rates between vNOTES and laparoscopic hysterectomy. At the study level, the moderate-strength RCT,[19] a prospective cohort study,[25] and multiple retrospective cohort studies[26,27,30,32,34,35,40-43,47,50,56] consistently found no statistically significant difference in transfusion requirements.

Overall, these data suggest that vNOTES does not increase the risk of perioperative blood transfusion. However, the evidence is limited by the predominance of retrospective studies and the low methodological quality of available systematic reviews. The primary limitation of evidence in this outcome domain is due to the rarity of the event and the consequent lack of adequately powered studies. Most reviews and individual studies are not powered to detect meaningful differences in transfusion rates.

Postoperative Pain

6. Recommendation (Grade A)

1- Patients may experience lower early postoperative pain scores with vNOTES compared with laparoscopic hysterectomy.

2- vNOTES hysterectomy is associated with lower postoperative pain compared with laparoscopic hysterectomy and should be considered when selecting the surgical approach.

Evidence level: 1+

Two RCTs[10,18] and four meta-analyses[12-15] consistently demonstrate that vNOTES hysterectomy results in lower early postoperative pain scores compared with conventional laparoscopic hysterectomy. The network meta-analysis by Guan et al.[16] ranked approaches as LESS-LAVH > LAVH > vNOTES > TLH > LESS-TLH > VH for pain outcomes.

Prospective cohort[23,24,64] and retrospective analyses from multiple institutions[27,28,30,31,33-35,37,38,40,42-48,53,56,60-62] demonstrate that vNOTES is associated with lower postoperative pain compared with laparoscopic hysterectomy, even when controlling for uterine size, body mass index (BMI), and prior surgery.

In the RCT by Park et al.,[19] postoperative abdominal pain did not differ significantly between vNOTES and LESS hysterectomy, which may reflect the widespread use of patient-controlled analgesia (PCA) potentially masking subtle differences in visceral discomfort. Vaginal pain was marginally higher in the vNOTES group, likely related to additional suturing required for cuff closure and hemostasis. Despite this, pain scores at 16 and 24 hours remained low, with no need for additional analgesics. The use of vessel-sealing devices in vNOTES, as opposed to conventional suture ligation, is proposed to further mitigate postoperative pain relative to standard laparoscopic hysterectomy.

Postoperative Analgesic Usage

7. Recommendation (Grade B)

1- Perioperative analgesic protocols for vNOTES hysterectomy should be individualized, with consideration for potentially reduced systemic analgesic requirements compared to laparoscopic approaches.

2- Clinicians should consider minimizing opioid use in patients undergoing vNOTES hysterectomy, as postoperative analgesic needs are generally low and can often be managed with non-opioid regimens.

Evidence level: 1+

Reduction in postoperative analgesic consumption is a clinically relevant surrogate for pain and patient comfort, and has direct implications for opioid-sparing recovery protocols.

A review of the available literature suggests that the current evidence is broadly consistent with this hypothesis. When the data are synthesized, postoperative analgesic requirements appear largely comparable between vNOTES and other minimally invasive techniques; however, several studies demonstrate a tendency toward lower analgesic consumption in the vNOTES cohort. In particular, the RCT by Baekelandt et al.[10] reported significantly reduced analgesic requirements following vNOTES compared with TLH. Similar findings were observed in the randomized studies by Lowenstein et al.,[18] who documented decreased analgesic use in vNOTES for apical prolapse relative to the conventional vaginal approach, and by Yıldız et al.,[20] who likewise demonstrated lower analgesic demand in patients undergoing vNOTES compared with vaginal hysterectomy.

Among prospective cohort studies comparing vNOTES with TLH, Takahashi et al.[23] and Sarikaya et al.[33] both reported reduced postoperative analgesic consumption in the vNOTES group. Jiamset et al.[57] corroborated these findings in a retrospective interrupted time-series analysis at a single centre, and Matak et al.[26] similarly documented lower analgesic use following vNOTES in obese patients undergoing laparoscopic versus vNOTES hysterectomy. Yıldız et al.[24] additionally reported lower analgesia requirements alongside improved quality-of-life scores in the vNOTES cohort.

Conversely, a number of studies across differing methodological designs and comparator groups found no statistically significant difference in postoperative analgesic consumption.[12,27,30,32,48,49]

Taken together, the body of evidence does not support a definitive superiority of vNOTES over other minimally invasive hysterectomy approaches with respect to postoperative analgesic consumption.

Re-Admission

8. Recommendation (Grade B)

1- Women should be informed that the risk of unplanned re-admission following vNOTES hysterectomy is comparable to that of other minimally invasive approaches.

2- Standard postoperative discharge criteria and re-admission thresholds should be applied without modification based on surgical route.

Evidence level: 1+

Unplanned hospital readmission is a composite safety outcome reflecting the severity of postoperative complications, adequacy of discharge planning, and patient resilience, and is routinely used as a quality indicator in surgical care. Reported readmission rates following vNOTES hysterectomy, across eleven studies including two RCTs, one systematic review and meta-analysis, two prospective cohort studies, and six retrospective studies, demonstrate no statistically significant differences compared with other minimally invasive hysterectomy approaches. Both the systematic review by Housmans et al.[11] and the randomized trial by Baekelandt et al.[10] reported equivalent readmission rates between vNOTES and laparoscopic hysterectomy. These findings are further supported by a randomized trial comparing vNOTES with vaginal hysterectomy[20] as well as by prospective[25] and retrospective cohort studies from multiple centers.[22,36,38,44,46-48] No published study has identified a significantly increased risk of readmission with vNOTES compared with any surgical comparator.

Anal Exhaust Time (Time to First Flatus)

9. Recommendation (Grade C)

1- Clinicians may consider vNOTES hysterectomy as an approach potentially associated with earlier recovery of gastrointestinal function, reflected by shorter time to first flatus, compared to other minimally invasive approaches. However, it should not be used as a sole determinant of clinical decisions.

2- Patients undergoing vNOTES hysterectomy may experience an earlier return of bowel function compared with other minimally invasive approaches; however, the magnitude of this benefit remains uncertain and may vary between individuals.

Evidence level: 2+

Time to first flatus (anal exhaust time) is used as a proxy for gastrointestinal recovery following surgery and reflects avoidance of postoperative ileus. There are no systematic reviews or RCTs addressing this specific outcome; the evidence derives entirely from prospective cohort and retrospective studies.

In a prospective cohort study, Wu et al.[21] performed multivariate regression analysis to identify independent predictors of time to first flatus, demonstrating that vNOTES was associated with a 2.528-hour reduction compared to LESS (β=-2.528; 95% CI: -6.61 to 1.56; p=0.224), although this difference did not reach statistical significance, indicating that the observed trend in favour of vNOTES warrants further evaluation in adequately powered studies. Additionally, Tang et al.,[22] in a prospective cohort study, performed linear regression analysis to identify independent predictors of postoperative recovery outcomes, confirming that surgical approach was a significant determinant of time to first anal exhaust; the median time to first flatus was significantly shorter in the vNOTES group compared to the laparoscopic hysterectomy group (48.0 h vs. 69.0 h; p<0.001), and this earlier restoration of bowel function was further associated with a favourable effect on return to work. These results are further supported by evidence from retrospective cohort studies.[39,43,47]

The limitation of this evidence base is the complete absence of RCT data addressing bowel recovery as a primary endpoint. Measurement methodology is also heterogeneous, time to first flatus is subject to patient recall bias and ward documentation variability. These caveats notwithstanding, the consistency of the directional signal across studies from different institutions and countries lends biological plausibility to the finding.

Prospective randomised data are needed to confirm the clinical magnitude and duration of this advantage.

Mobilization/Return to Daily Activities

10. Recommendation (Grade C)

1- vNOTES hysterectomy is associated with earlier mobilization and faster return to daily activities compared with laparoscopic hysterectomy, and this potential recovery advantage may be a relevant factor when counselling patients regarding their surgical options.

2- vNOTES may be integrated into ERAS programmes incorporating early mobilization protocols

3- Clinicians may consider vNOTES hysterectomy in patients for whom rapid postoperative recovery is a clinical priority, including obese patients and those with large uteri.

Evidence level: 2+

Earlier return to functional independence is the clinical endpoint that most directly reflects the patient experience of recovery, and available moderate-low quality evidence consistently favours vNOTES hysterectomy in this regard.

Fang et al.,[25] in a prospective cohort study conducted in primary hospitals, reported significantly shorter time to ambulation in the vNOTES group. Tang et al.,[22] in a prospective cohort study specifically designed to evaluate rapid recovery outcomes, demonstrated earlier mobilization and faster return to daily activities following vNOTES hysterectomy. Among retrospective studies in general populations, Sarikaya et al.[33] and Uluutku Bulutlar et al.[45] similarly reported faster postoperative recovery in favour of vNOTES.

In specific patient populations, Albayrak Denizli et al.[28] reported earlier return to daily activities following vNOTES hysterectomy in obese patients, and Kheirbek et al.[29] demonstrated a similar recovery advantage in patients with large uteri.

Evidence regarding this outcome is limited by the absence of prospective randomized data and systematic analyses. Retrospective studies are inherently susceptible to ascertainment bias, as functional recovery outcomes are frequently extracted from routine clinical records rather than assessed through standardized, validated instruments. Future studies should incorporate validated patient-reported outcome measures at predefined postoperative time points and should distinguish between in-hospital mobilization and community-level return to activities.

Postoperative Sexual Function

11. Recommendation (Grade B)

1- Women should be reassured that vNOTES hysterectomy does not adversely affect postoperative sexual function compared with laparoscopic hysterectomy.

2- Clinicians should inform women that vNOTES hysterectomy is not associated with deterioration of sexual function and can be performed without expected adverse effects on postoperative sexual health.

Evidence level: 1+

Post-hysterectomy sexual function constitutes a key patient-reported outcome and is commonly a central focus during preoperative counseling. From a theoretical standpoint, the vNOTES approach could differentially impact sexual health compared with conventional laparoscopy, primarily due to the requirement for transvaginal cuff closure involving direct suturing of the vaginal vault and its adjacent supportive structures. This technical aspect has raised concerns regarding potential anatomical and functional sequelae, including vaginal vault shortening or altered sensory perception, which could negatively influence long-term sexual function.

However, the available clinical evidence does not substantiate these concerns. Randomized data from Baekelandt et al.,[10] and more importantly, pooled analyses of two RCTs by Prekatsounaki et al.,[65] demonstrate no statistically significant differences in postoperative sexual function between vNOTES and laparoscopic hysterectomy when assessed using validated psychometric tools. These findings are further supported by one prospective cohort[22] and three retrospective cohort studies[32,49,54] in which sexual quality of life was typically evaluated as a secondary endpoint, consistently demonstrating comparable outcomes between surgical approaches.

Intraoperative Complications

12. Recommendation (Grade A)

1- Clinicians should consider vNOTES hysterectomy as a safe alternative to conventional laparoscopic or vaginal hysterectomy for benign indications, as current evidence shows comparable intra-operative complication rates.

2- Women may be reassured that undergoing vNOTES does not appear to increase the risk of intra-operative complications compared with other minimally invasive approaches.

Evidence level: 1+

The current body of literature consistently demonstrates no significant difference in intra-operative complication rates between vNOTES and other minimally invasive hysterectomy techniques, including TLH, VH, and single-port approaches.

Most systematic reviews and meta-analyses[11,12,14,15] report no significant differences when vNOTES is compared with laparoscopic or vaginal hysterectomy, although their methodological quality is often limited. A network meta-analysis suggested a relative advantage for conventional approaches, such as TLH and VH, but this finding was not consistently supported by direct comparative studies.[16]

Evidence from RCTs and prospective cohort series supports these findings, comparing vNOTES with both laparoscopic and vaginal approaches[10,18,20,22,24,64] reported similar intra-operative complication rates, with no clear advantage for either technique.

This consistency is further reinforced by a large number of retrospective cohort studies,[26,28,29,31,32,34-36,38,39,40,41,43-50,53,59,60,62] including diverse patient populations (e.g., obese patients, large uteri, prior pelvic surgery). Across these studies, intra-operative complications, such as bleeding, organ injury,

vascular injury or bladder/bowel injury, were comparable between vNOTES and alternative surgical approaches, with no reproducible increase in risk associated with vNOTES.

Postoperative Complications

13. Recommendation (Grade A)

1- Clinicians should consider vNOTES hysterectomy as having a similar post-operative complication profile compared with conventional laparoscopic or vaginal hysterectomy for benign indications.

2- Clinicians should counsel women that vNOTES does not appear to increase the risk of major or minor post-operative complications, including bleeding, infection, or need for reoperation.

3- Women may be reassured that recovery and safety outcomes with vNOTES are comparable to other minimally invasive hysterectomy techniques.

Evidence level: 1+

The systematic review by Housmans et al.[11] showed no significant difference in postoperative complication rates between vNOTES and laparoscopic hysterectomy.[11] Few meta-analyses have suggested a lower complication rate with vNOTES compared to laparoscopy,[9,12] while others comparing vNOTES with vaginal hysterectomy and robotic-assisted vNOTES found no meaningful differences between techniques.[14,17] Chaccour et al.[15] reported fewer postoperative complications with vNOTES compared to classic laparoscopic hysterectomy. The network meta-analysis by Guan et al.[16] ranked approaches as LESS-LAVH > LAVH > vNOTES > TLH > LESSLH > LH > VH > RALH > LESS-TLH for postoperative events, placing vNOTES among the more favourable approaches.

Well-designed RCTs[10,19,20,63] and multiple prospective cohort studies reported comparable safety profiles.[22-25] Notably, Basol et al.[35] and Qian et al.[62] reported fewer postoperative complications with vNOTES. Zhang et al.[47] also reported fewer complications with vNOTES.

The majority of prospective cohort and retrospective studies found no significant difference between vNOTES and comparator approaches.[26,28,29,31,35-40,42,43,45,46,50,51,54,56,57,59,60]

Indwelling Urinary Catheterization

14. Recommendation (Grade D)

Urinary catheter removal should be planned by clinicians for the earliest clinically appropriate time point following vNOTES hysterectomy and should be incorporated into ERAS protocols. Routine prolonged catheterisation is not indicated following uncomplicated vNOTES.

Evidence level: 2-

No systematic review or RCT has addressed catheterization duration as a primary endpoint in the context of vNOTES hysterectomy; the available evidence is therefore derived exclusively from observational data.

The prospective cohort study by Fang et al.,[25] which carries the highest methodological weight among the available non-randomized evidence, demonstrated significantly shorter indwelling urinary catheterization time in the vNOTES group compared to conventional laparoscopic hysterectomy (31.1±17.3 hours vs 45.6±22.7 hours, $p=0.012$). Consistent results have been reported across multiple moderate- to low-quality retrospective cohort studies, which also show shorter catheterization duration with vNOTES relative to laparoscopic or single-port approaches.[26,37,39,42,48] However, the absence of randomized data and variability in catheter removal protocols across institutions limit the strength of conclusions.

Conversion Rate

15. Recommendation (Grade B)

Clinicians should counsel patients that conversion rates with vNOTES hysterectomy are low and comparable to other minimally invasive approaches. The choice of surgical technique should therefore be based on patient factors, surgeon experience, and available expertise rather than concerns regarding conversion risk.

Evidence level: 1+

Conversion from the planned surgical approach to a different modality (laparotomy or laparoscopy) represents an important safety indicator reflecting the feasibility and safety of vNOTES at institutional and individual surgeon levels. Low conversion rates are essential for any surgical technique to be incorporated into mainstream practice with confidence.

Three recent systematic reviews and meta-analyses, including two low-quality and one critically low-quality AMSTAR-rated study, reported no significant differences in surgical outcomes between vNOTES and laparoscopic hysterectomy for benign gynecological indications.[12,14,15]

In an RCT by Baekelandt et al.,[10] no conversions from vNOTES to an alternative surgical approach were reported among 70 women undergoing hysterectomy. Similarly, two additional RCTs[18,19] comparing vNOTES with laparoendoscopic single-site hysterectomy and conventional vaginal surgery for apical prolapse reported zero conversions in either group

Consistently, moderate-to-low-quality prospective and retrospective cohort studies indicate comparable conversion rates between vNOTES and other hysterectomy techniques,[22,25,26,29,31,35,36,38,41,40,43,46,48-51,56-60,64] with none demonstrating a statistically significant increase in conversions for vNOTES in benign gynecological surgery.

The notable exception is in the comparison with LESS, where Wu et al.[21] reported a higher conversion rate with vNOTES (4.29%); in all three converted cases, the indication was severe adhesion at the posterior fornix, which precluded safe transvaginal access and created an unacceptable risk of injury to adjacent pelvic organs, rather than representing a limitation intrinsic to the vNOTES approach itself.

Cost Analysis

16. Recommendation (Grade D)

Institutions considering the adoption of vNOTES should undertake a prospective local economic evaluation accounting for equipment procurement, training costs, operative time savings, and bed day reductions. Formal health technology assessment is recommended prior to national-level commissioning decisions.

Evidence level: 2+

No RCT has included cost-effectiveness analysis as a primary endpoint for vNOTES, and no systematic review has addressed this outcome as a primary objective. Available evidence is limited to institutional cost analyses and observational comparisons. Potential cost drivers include equipment procurement, training requirements, and learning curve duration.

The strongest available evidence comes from the RCT by Baekelandt et al.,[10] in which direct healthcare costs were assessed using the total hospital bill, encompassing all expenses incurred up to six weeks postoperatively. Although mean total costs were lower in the vNOTES group compared with TLH (USD 3.599±914 vs. USD 4.103±1.348), corresponding to a mean difference of -504 USD (95% CI -1,044 to +36), this difference did not reach statistical significance.

However, the broader literature does not consistently support a cost advantage for vNOTES. While the highest-quality evidence suggests cost neutrality, lower-quality retrospective studies[52,60] report conflicting findings, with some indicating lower costs for LAVH compared with vNOTES.

Overall, the economic impact of vNOTES remains highly context-dependent and is influenced by institutional case volume, existing laparoscopic infrastructure, and reimbursement models. In the absence of formal health technology assessment or prospective cost-effectiveness analyses, current evidence does not allow definitive conclusions regarding cost superiority.

DISCUSSION

The present national guideline suggests that vNOTES hysterectomy is a feasible and safe, minimally invasive approach for benign gynecological indications when performed in appropriately selected women and in centres with relevant surgical expertise.[66-68] The most consistent benefits identified across the available literature were shorter operative time, reduced early postoperative pain, a modest but noticeable reduction in hospital stay, and faster postoperative recovery compared with conventional laparoscopic hysterectomy. Importantly, these advantages were not accompanied by a clear increase in intraoperative or postoperative morbidity, as complication, readmission, and conversion rates were generally comparable with those reported for other minimally invasive hysterectomy techniques.

The main strength of this guideline is that it combines a structured appraisal of the available evidence with a formal Delphi-based expert consensus process, thereby allowing clinically relevant recommendations to be formulated even in areas where direct comparative data remain limited. This is particularly important in the context of vNOTES hysterectomy, where rapid clinical adoption has outpaced the development of standardized guidance in several domains of perioperative care and surgical technique. In addition, the guideline addresses both comparative surgical outcomes and practical aspects of implementation that are directly relevant to routine clinical practice.

These findings should, however, be interpreted in light of important limitations. Although some recommendations were supported by RCTs and systematic reviews, a substantial proportion of the evidence base consisted of observational studies with moderate to serious risk of bias. Methodological heterogeneity was also considerable, particularly with respect to patient selection, surgeon experience, perioperative protocols, comparator groups, and outcome definitions. Furthermore, several clinically important questions could not be answered from the published literature alone and therefore required consensus-based recommendations. As with other evolving surgical techniques, learning-curve effects and institutional variation are also likely to have influenced reported outcomes.

Within the Turkish healthcare system, the economic impact of vNOTES is further influenced by the cost of disposable access platforms and instruments, which are procured through institutional tender systems and may vary between centers. Current Social Security Institution (SGK) reimbursement policies do not always specifically cover these vNOTES-specific disposable materials, potentially increasing institutional cost burden. In comparison, although laparoscopic surgery also relies on disposable instruments, these are more standardized and better integrated into existing reimbursement frameworks. It should be noted that vPORT™, a novel Turkish disposable access device developed by Biomicro Medikal (Istanbul, Turkiye), has recently emerged as a cost-effective and efficient port system for use in vNOTES procedures. Surgeons in Turkiye are reducing costs by reusing disposable ports, using the cost-effective Turkish-branded vPORT™, and finally, using glove ports in exchange for surgical discomfort.[69] Despite potentially higher upfront costs, shorter hospital stay, reduced recovery time and the absence of additional uterine manipulator and trocar costs may partially offset overall expenses, making the net economic effect of vNOTES largely dependent on institutional volume and local procurement conditions.

Taken together, the evidence makes a credible case for vNOTES hysterectomy as a meaningful addition to the surgical armamentarium for benign gynecological disease. To truly establish its place, however, the field needs larger more rigorous RCTs, more consistent reporting of perioperative and patient-reported outcomes, and prospective health-economic analyses, all of which will be essential for refining patient selection and informing future iterations of this guideline.

Study Limitations

Most of the guideline recommendations have low certainty of evidence and serious to moderate risk of bias, highlighting the need for higher quality data to aid in refining future recommendations. In addition, the expert panel was restricted to surgeons with experience of at least 50 vNOTES cases. While this criterion was applied to ensure adequate procedural expertise, it may limit the generalizability of the recommendations to centres with lower case volumes or surgeons earlier in their learning curve.

Recommendations for Future Research

Despite recent advances, there remain several unanswered questions and priorities for future research. These areas include the following: (1) Optimal anesthesia regimen specifically for vNOTES hysterectomy; (2) the role of strategies to reduce postoperative pain such as intraperitoneal irrigation or rectus sheath block; (3) predictors for conversion to laparoscopy; (4) the role of outpatient management of benign vNOTES hysterectomy; (5) optimal technique for prophylactic apical suspension following vNOTES hysterectomy; (6) optimal technique for transvaginal surgical drain following a vNOTES hysterectomy; (7) the effects of vNOTES training courses using hands-on models and their outcomes; and (8) outcomes for repeat vNOTES following a vNOTES hysterectomy or repeat vNOTES hysterectomy following another vNOTES procedure. Further studies and research in these priority areas are needed to improve the outcomes of the vNOTES technique for hysterectomy performed for benign conditions and to better define optimal management.

Plans for Updating

The topics listed above that were not covered in this guideline will be addressed in future guideline documents and expert practice opinion papers. Given the expectation of new national data results and RCTs, this guideline is planned to be updated within two years, following a literature review of newly published works on the first anniversary of its publication.

Footnotes

Authorship Contributions

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Original Article

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Hypoxia-Inducible Factor 1-Alpha (HIF-1α) Decidual Expression Levels in Placenta Accreta Spectrum and its Effect on Abnormal Trophoblastic Invasion

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ABSTRACT

Purpose: Placenta accreta spectrum (PAS) is a condition characterized by abnormal trophoblastic invasion of the decidua and is associated with significant maternal and fetal morbidity and mortality. Hypoxia-inducible factor 1-alpha (HIF-1α) is a transcription factor that increases neovascularization in hypoxic environments. The aim of this study was to investigate the role of HIF-1α in abnormal trophoblastic invasion observed in PAS.

Methods: This prospective study included 29 PAS-diagnosed patients (Group 1) and 29 healthy controls with a history of prior [cesarean section (CS); Group 2]. Decidual tissue samples from participants were collected and stained with anti-HIF-1α antibody using immunohistochemical methods. Staining was evaluated both qualitatively and quantitatively. In qualitative assessment, the number of stained nuclei was determined by a pathologist. Quantitative assessment was performed using ImageJ and GraphPad Prism software, with staining intensity calculated in pixels.

Results: Staining intensity graded as 2 or 3 was significantly higher in Group 1 compared to Group 2 in qualitative analysis ($p=0.006$, $p<0.001$, respectively). The percentage of positive staining area (%), the average positive region area (in pixels) and normalized average positive region area (%) were significantly greater in Group 1 compared to Group 2 on quantitative analysis ($p<0.001$, $p=0.019$, $p=0.044$, respectively).

Conclusion: HIF-1α expression in decidual tissue is greater in PAS-diagnosed patients compared to healthy pregnant women with prior CS. This suggests that abnormal trophoblastic invasion in PAS may be due to hypoxia in the decidual tissue, which could lead to neovascularization driven by increased HIF-1α expression.

Keywords: Placenta accreta, hypoxia-inducible factor 1-alpha, placenta diseases

INTRODUCTION

During placental development, trophoblasts physiologically invade the endometrium, typically reaching the Nitabuch's layer, which is a fibrous connective tissue degeneration between the decidua and myometrium.[1] When this invasion exceeds the Nitabuch's layer and extends into deeper tissues, it is referred to as placenta accreta spectrum (PAS). The International Federation of Gynecology and Obstetrics (FIGO)[2] advocates that PAS encompasses a range of abnormal placental invasions, from partial penetration into the

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myometrium to more severe forms such as invasion through the uterine serosa and into adjacent organs such as the bladder and parametrium.

The prevalence of PAS has increased dramatically over the years, in parallel with rising cesarean section (CS) delivery rates and advanced maternal age. In a systematic review conducted in 2019, among 5.8 million births, 7,001 cases were diagnosed with PAS, corresponding to a prevalence of 0.17%.[3] Management of PAS requires experience and a multidisciplinary approach; thus, affected patients should be followed in tertiary care centers from the time of diagnosis through the postpartum period. Treatment often involves segmental placental resection or hysterectomy and carries substantial risks of maternal and fetal morbidity and mortality, including preterm birth, bladder injury, and massive hemorrhage.[4]

The pathogenesis of PAS is thought to involve defective Nitabuch's layer formation and impaired regulation of trophoblastic invasion. However, its exact mechanism remains incompletely understood although it is known that decidual natural killer cells, pregnancy related hormones, proteolytic enzymes, integrins and growth factors, such as placental growth factor and vascular endothelial growth factor (VEGF), are involved in the regulation of trophoblastic invasion.[5,6] Risk factors such as previous CS delivery, placenta previa, obesity, advanced maternal age, and a history of postpartum hemorrhage are known to increase the likelihood of PAS.

In recent years, molecular studies have contributed significantly to our understanding of PAS. A study examined the expression of sirtuin-2 and sirtuin-7 proteins in placental tissues of patients diagnosed with PAS and healthy controls. The authors found sirtuin-7, which is a regulatory protein of epithelial-mesenchymal transition, was reduced in PAS compared to controls.[7] Another study revealed that serum levels of soluble fms-like tyrosine kinase-1, an inhibitor of VEGF, were significantly lower in PAS patients.[8] These findings suggest that elevated VEGF activity may play a key role in the pathogenesis of PAS.

Hypoxia-inducible factor 1-alpha (HIF-1α) is an oxygen-sensitive transcription factor that is activated under hypoxic conditions. It promotes neovascularization by increasing the expression of proangiogenic factors, particularly VEGF.[9] HIF-1α is also known to play a role in abnormal vascularization seen in tumor invasion and metastasis.[10] In PAS, the hypoxic environment resulting from previous uterine interventions may lead to increased HIF-1α expression because of poor oxygenation in the damaged endometrial and myometrial tissues, triggering VEGF production and contributing to abnormal trophoblastic invasion.

The aim of this study was to investigate HIF-1α expression in decidual tissue samples taken from the invasion site of the placenta in patients diagnosed with PAS and in healthy pregnant women, in order to explore the potential role of HIF-1α in the pathogenesis of abnormal placental invasion in PAS.

METHODS

Study Design and Setting

The study was designed as a prospective study and conducted between September 1, 2024, and January 1, 2025, at the Departments of Obstetrics and Gynecology and Pathology of Başakşehir Çam and Sakura City Hospital. The research was granted ethical approval by the Ethics Committee of Başaksehir Çam and Sakura City Hospital (protocol number: KAEK-11/14.08.2024.103, date: 19.08.2024) and was conducted in compliance with Declaration of Helsinki. Patients who delivered at our hospital and had suspected PAS based on prenatal ultrasound were included in the study group (Group 1). The diagnosis of PAS was established intraoperatively by confirming placental invasion and subsequently confirmed by histopathological examination. Healthy pregnant women with a history of previous CS delivery who gave birth at our hospital comprised the control group (Group 2). Data included patients' demographic variables, neonatal birth weight, and gestational age at delivery. In addition, the type of surgical procedure and FIGO staging were recorded for patients in Group 1.

Patients aged between 18 and 40 years, diagnosed with PAS and undergoing delivery at our hospital at a gestational age beyond 32 weeks were included in Group 1. This gestational age threshold was selected in accordance with standard clinical practice, as planned surgical management for PAS is typically performed after 32 weeks of gestation. Similarly, pregnant women aged 18-40 years, who underwent previous sections, were beyond 32 weeks of gestation and had no PAS diagnosis, were included in Group 2. Patients diagnosed with preeclampsia, hypertension or gestational diabetes were excluded from both groups. Those who did not provide written informed consent were not included in the study. Of note, in Group 1, placental and myometrial tissue samples from two patients who underwent segmental resection were sent to pathology but they were excluded from the study as decidual tissue was not identified in these specimens. The patient selection flowchart for Group 1 is shown in Figure 1. Group 2 was composed of patients who met the inclusion criteria and had planned CS in the same hospital due to a history of previous CS. The study included all consecutive PAS cases meeting the inclusion criteria between September 1, 2024, and January 1, 2025. Given the rarity of PAS, no formal sample size calculation was performed. A control group of equal size was selected for comparison.

Collection of Pathology Specimens

Following hospitalization for planned delivery, patients with a diagnosis of PAS underwent surgery and total and supracervical hysterectomy and segmental resection specimens (uterus and placenta) were sent to the pathology department in 10% formalin solution. From these specimens, the pathologist obtained a 1 × 1 cm section of decidual tissue from the central

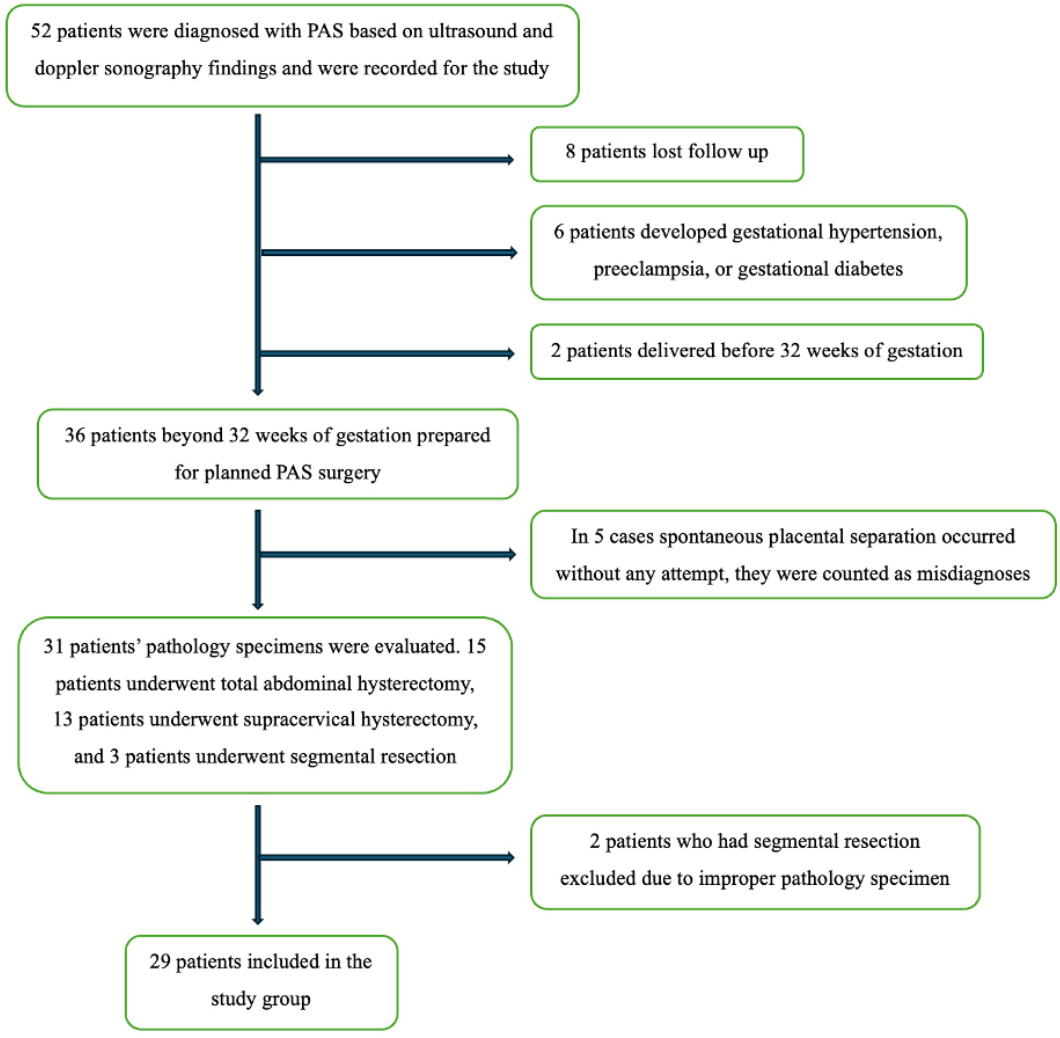

Figure 1. Patient selection flowchart for Group 1

PAS: Placenta accreta spectrum

area of the uterine wall with placental invasion. In Group 2, decidual tissue samples measuring 1 × 1 cm in width and 5 mm in depth were similarly obtained from the central area of the placental implantation site during CS. A low-lying placenta was not observed in any of the patients in Group 2.

Preparation of Pathology Specimens for Immunohistochemical Staining

Upon receipt of each specimen at the Pathology Department, routine tissue sectioning was performed. Decidual tissue samples with confirmed placental invasion in Group 1 and decidual tissue from the central site of placental attachment in Group 2 were prepared. The specimens were fixed in formalin at room temperature, processed through routine tissue processing, and embedded in paraffin. Sections of 3 μm thickness were cut using a microtome.

Immunohistochemical Staining Protocol

Immunohistochemical (IHC) staining for HIF-1α was performed using the BenchMark XT autostainer (Ventana Medical Systems, Roche Diagnostics). The sections were deparaffinized and subjected to antigen retrieval using the CC1 (cell conditioning) solution for 60 min at 60 °C. The primary antibody, HIF-1α (PA1-16601, Thermo Fisher Scientific), was diluted 1:100 in Dulbecco's phosphate-buffered saline containing 1% bovine serum albumin according to the manufacturer's instructions. Approximately 10 μL of the diluted antibody was applied to each section. The primary antibody incubation was carried out for 60 min at 37 °C. Following primary antibody incubation, the slides were counterstained with Hematoxylin II for 12 min to provide nuclear contrast. Then the chromogen solution was applied to visualize the immunoreaction. As part of the protocol validation, positive control slides with known HIF-1α expression and negative control slides incubated with an isotype control antibody were included to confirm the specificity of staining.

Evaluation of Staining Results

HIF-1α stained sections were mounted with a permanent mounting medium and imaged using a brightfield microscope

(Nikon, ECLIPSE Ci-L 718169). Images were captured under 4x, 10x and 20x magnification to ensure consistent visualization across all samples. The area ratio (%) of HIF-1α staining was quantified using ImageJ software (National Institutes of Health, Bethesda, MD, USA). Five random high-power fields for each sample were selected, and the stained area was segmented using color deconvolution. Thresholding was applied to isolate the chromogen signal from the background, and the percentage of the positively stained area relative to the total tissue area was calculated.

Quantification of HIF-1α Positive Area, Average Positive Region Area and Total Number of Positive Regions

The positive area of fluorescence was quantified after acquiring IHC staining images using ImageJ. A region of interest covering the entire image (pixels) was selected for analysis. The original image was converted to grayscale to simplify the analysis by reducing it to intensity values. Otsu's thresholding method was applied to distinguish positive staining regions from the background.[11] Pixels with intensity values above the calculated threshold were classified as positive. The binary mask (resulting from thresholding) was analyzed, and the number of positive pixels was counted. This count represents the total positive staining area in pixels.

The total image area was calculated as the product of the image's width and height in pixels (Eq. 1) using the following formula:

Total image area (pixels) =
Image width x image height (1)

The positive staining area in pixels was divided by the total image area in pixels, and the result was multiplied by 100 to obtain the percentage (Eq. 2):

Positive staining area (%) =
[Positive area (pixels)/total image area (pixels)] x 100 (2)

Furthermore, the total number of labeled regions (**Eq. 3**) was counted in order to understand the distribution and fragmentation of HIF-1α expression across the tissue.

Average positive region area (pixels) =
Σ Region areas (pixels)/total number of positive regions (3)

As a last step, the average positive region area was normalized to the total image area (Eq. 4) for inter-sample comparisons.

Normalized avg positive region area (%)
= [(Avg positive region area (pixels)/
total image area (pixels)] x 100 (4)

Chromogen Intensity Analysis

After isolating positively stained regions, the chromogen intensity of the HIF-1α positive areas was analyzed. The binary mask created during positive area quantification was applied to the original image to isolate positively stained regions. The isolated regions were converted to grayscales to enable intensity measurements. The mean chromogen intensity of the positive regions was calculated by extracting non-zero-pixel values (pixels with staining) and averaging their grayscale intensity values (Eq. 5). A histogram of staining intensity distribution of HIF-1α (Figure 2A) and H&E (Figure 2B) was plotted to visualize the range and frequency of chromogen intensity values, providing an overview of staining variability.

Mean intensity (grayscale) =
Σ Region intensities/total number of positive regions (5)

The mean intensity of positively stained regions was also standardized relative to the maximum grayscale value of 255. In order to calculate mean intensity, this was normalized as a percentage of the maximum grayscale intensity (Eq. 6):

Normalized mean intensity (%) =
Mean intensity (grayscale)/255) x 100 (6)

The intensity and percentage of HIF-1α staining were also blindly evaluated by a pathologist. Slide images at different magnifications were recorded for each patient. The qualitative staining intensities determined by the pathologist were calculated based on the number of stained nuclei and staining intensity was classified on a four-point ordinal scale (0: no staining, 1: weak, 2: moderate, 3: strong). To compare the distribution of staining intensities between the two groups, a Pearson's chi-square test was performed. In addition, to evaluate whether there was a significant trend across the ordered staining categories, a linear-by-linear association test (Mantel-Haenszel test for trend) was also applied.

Statistical Analysis

The data were analyzed using SPSS for MacOS, version 20.0 (IBM Inc., Armonk, NY, USA). The normality of distribution for continuous variables was assessed using the Shapiro-Wilk test. Continuous variables are expressed as mean ± standard deviation (SD) for normally distributed data, or as median with interquartile range (Q1-Q3) for non-normally distributed data. Categorical variables are presented as frequency (percentage). The significance of differences in means between groups was assessed using Student's t-test for normally distributed data and the Mann-Whitney U test for non-normally distributed data. Statistical differences between categorical variables were evaluated using the chi-square test. Quantitative data obtained from ImageJ analysis were compiled and analyzed using GraphPad Prism (version 8.0.2, GraphPad Software). The mean percentages of HIF-1α staining area between groups were compared using the Independent Samples t-test. Data were reported as mean ± SD, and results with p values <0.05 were considered statistically significant.

RESULTS

The full study cohort numbered 58 patients, subdivided into the PAS (Group 1; n=29) and control (Group 2; n=29) groups. Demographic characteristics and comparison between the groups is shown in Table 1. The groups did not differ in terms of age, body mass index, and presence of comorbidities. However, gravida, parity, and number of previous CS deliveries were significantly higher in Group 1 compared to Group 2. Gestational age at delivery and birth weight were significantly higher in Group 2 compared to Group 1.

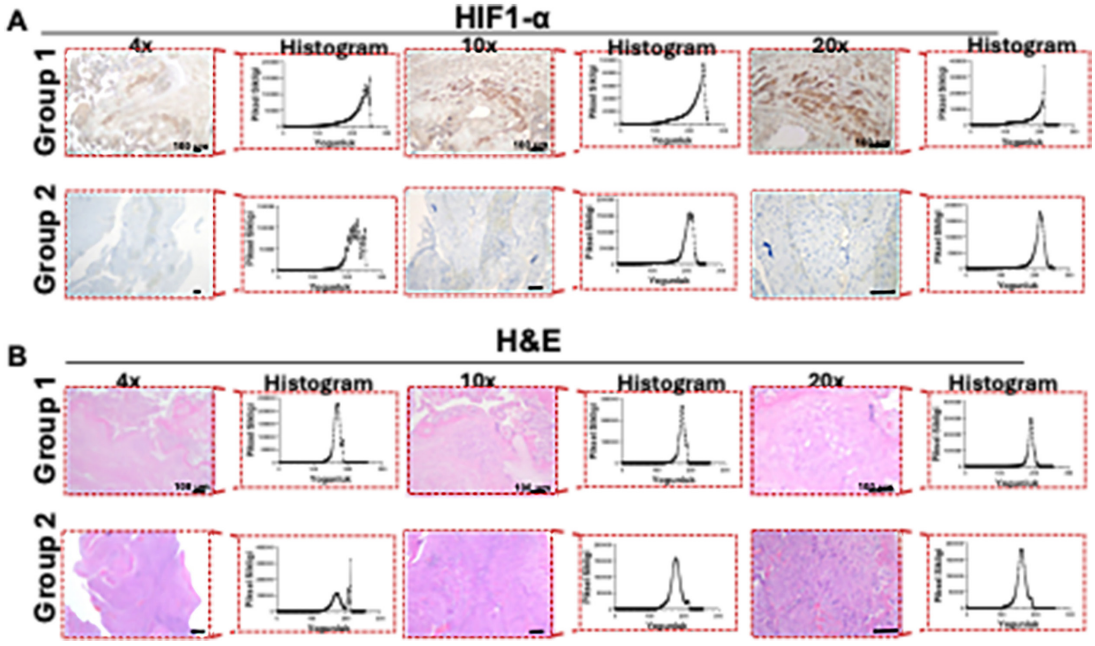

Figure 2. Representative histological images from Group 1 and Group 2. (A) HIF-1α-stained sections and (B) H&E-stained sections at 4×, 10×, and 20× magnifications from pathological specimens (n=58)

HIF1-a: Hypoxia-inducible factor 1-alpha

Table 1. Comparison of demographic variables between the groups

	Group 1 (n=29)	Group 2 (n=29)	*p* value
Age	34.31±3.98	30.44±5.30	0.12
Gravida	4 (2-9)	3 (1-6)	**0.021***
Parity	2 (1-6)	2 (1-4)	**0.016***
Number of previous cesarean deliveries	2 (1-5)	1 (1-4)	**0.010***
BMI (kg/m²)	29.41 (23.53-37.10)	30.12 (23.92-54.69)	0.715
Gestational age at delivery (days)	239 (226-275) (34 weeks 1 day)	272 (247-278) (38 weeks 6 days)	**<0.001***
Presence of comorbidities n (%)	8 (27.58)	7 (24.13)	0.38
Birth weight (g)	2413 (1740-3835)	3250 (2480-3750)	**<0.001***

*Statistically significant
BMI: Body mass index

Qualitative evaluation of HIF-1α antibody staining intensities is shown in Table 2. None of the patients in Group 1 had a score of zero for staining, whereas tissue samples of 13 patients (44.8%) in Group 2 did not exhibit any staining for HIF-1α. Mild staining (staining intensity 1) was observed in seven (24.13%) of Group 1 and in 15 patients (51.72%) in Group 2. Moderate staining (score 2) was reported in nine patients (31.03%) in Group 1 and in 1 patient (3.45%) in Group 2. Strong staining (staining intensity 3) was observed in 13 patients (44.82%) in Group 1, while none of the patients in Group 2 exhibited strong staining. There was a significant difference in the distribution of staining intensities between the two groups ($p<0.001$). Furthermore, the Mantel-Haenszel test for trend demonstrated a significant trend across the ordered staining categories, indicating that Group 1 had a higher proportion of cases with intense staining compared to Group 2 ($p<0.001$).

Furthermore, among the patients in Group 1, 15 (52%) patients underwent total abdominal hysterectomy, 13 (45%) patients underwent supracervical hysterectomy, and 1 (3.45%) patient underwent segmental resection. FIGO PAS staging for Group 1 showed nine patients as stage 2 (31%), 9 as stage 3A (31%), 10 as stage 3B (35%), and 1 as stage 3C (3.45%). Staging was determined based on both preoperative ultrasound imaging and final pathology reports. FIGO staging of PAS is as follows: stage 1 abnormal adherent placenta; stage 2 abnormal invasive placenta, increta; stage 3 abnormal invasive placenta, percreta; subdivided into stage 3A placenta limited to uterine serosa; stage 3B bladder invasion; stage 3C placenta involving pelvic wall.[12]

Quantitative Comparison of HIF-1α Staining Between Groups

The percentage positive staining area of HIF-1α expression, was significantly greater in Group 1 (73.95% ±8.21) compared to Group 2 (65.78% ±7.66) ($p<0.001$) (Figure 3A). The normalized average positive region area was also significantly higher in Group 1 (0.14±0.07) than in Group 2 (0.11±0.05) ($p=0.044$) (Figure 3B). The total number of positive regions was 611.41±263.88 in Group 1 and 777.44±432.11 in Group 2 ($p=0.082$) (Figure 3C). The similar number of positive regions observed in both groups suggest that, despite significant differences in the size and distribution of these regions, their overall frequency remained comparable.

The average positive region area differed significantly between the groups: Group 1 had a larger mean positive area (7834.21±3976.79 pixels) compared to Group 2 (5565.17±3172.82 pixels) ($p=0.019$) (Figure 3D). The normalized mean intensity after grey-scale conversion was 73.58±3.82 in Group 1 and 72.38±3.20 in Group 2 ($p=0.201$) (Figure 3E).

The comparison of positive staining area (%), normalized average positive region area (%), total number of positive regions (pixels), average positive region area (pixels), and normalized mean intensity between the groups, along with the corresponding p values, is summarized in Table 3.

Table 2. Qualitative evaluation of HIF-1α antibody staining intensities

Staining intensity, n (%)	Group 1 (n=29)	Group 2 (n=29)
Staining intensity 0	0 (0)	13 (44.8)
Staining intensity 1	7 (24.13)	15 (51.72)
Staining intensity 2	9 (31.03)	1 (3.45)
Staining intensity 3	13 (44.82)	0 (0)
p value*	<0.001	
Trend p value+	<0.001	

*Pearson's chi-square test for overall distribution, +Linear-by-linear association test (Mantel-Haenszel test for trend)

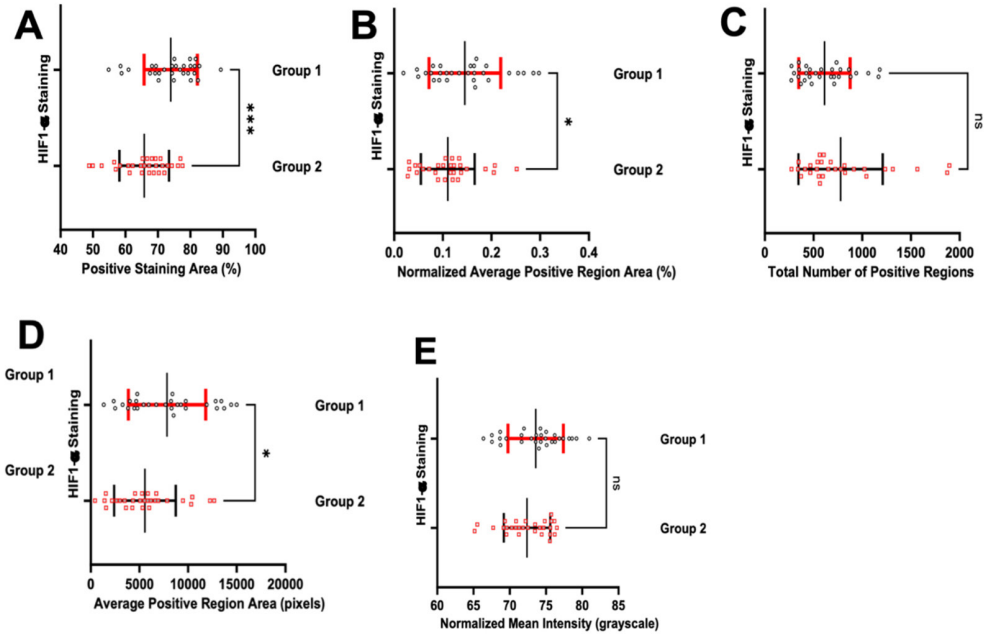

Figure 3. Quantitative comparison of HIF-1α staining between groups. (A) Positive staining area (%), (B) normalized average positive region area, (C) total number of positive regions, (D) average positive region area, (E) average grayscale intensity

HIF1-a: Hypoxia-inducible factor 1-alpha

Table 3. Comparison of quantitative analysis of HIF-1α staining between Group 1 and Group

	Group 1 (n=29)	Group 2 (n=29)	p value
Positive staining area (%)	73.95±8.21	65.78±7.66	**<0.001***
Normalized average positive region area (%)	0.14±0.07	0.11±0.05	**0.044***
Total number of positive regions (pixels)	611.41±263.88	777.44±432.11	0.082
Average positive region area (pixels)	7834.21±3976.79	5565.17±3172.82	**0.019***
Normalized mean intensity (grayscale)	73.58±3.82	72.38±3.20	0.201

*Statistically significant

DISCUSSION

In our study, increased HIF-1α expression in Group 1 as demonstrated by the percentage of positively stained area, normalized average positive region area, and average positive region area all being significantly greater in Group 1 compared to Group 2. The absence of a significant difference in mean intensity suggests that while the extent and distribution of expression varied, the overall presence of HIF-1α remained similar across the groups. Furthermore, the lack of a significant difference in the total number of positive regions between the groups may reflect increased tissue heterogeneity in the microenvironment of Group 1.

Hypoxia plays an important role in the pathogenesis of PAS. Two key studies have investigated the role of HIF-1α in PAS. The first by Yan et al.[13] in 2020 included 10 PAS cases, 20 cases with placenta previa, and 30 healthy pregnancies. In their real-time polymerase chain reaction analysis of placental tissue, HIF-1α expression was significantly greater in the placentas of PAS group compared to the placenta previa and healthy control groups. Their sampling primarily reflected increased HIF-1α expression in trophoblastic cells. In contrast, our study evaluated HIF-1α expression in decidual tissue, which is considered the primary site of abnormal trophoblast invasion. Previous endometrial interventions may result in impaired decidual remodeling and localized hypoxia, thereby increasing HIF-1α expression and potentially leading to abnormal trophoblast invasion. Therefore, we suggest that trophoblastic cellular hypoxia may be the result of hypoxia in the decidual tissue.

The second study addressing the role of HIF-1α in PAS pathogenesis was carried out by Chen et al.[14] and included 10 PAS cases and 10 healthy pregnancies. Placental samples from both groups were analyzed using immunohistochemistry for hypoxia-induced autophagy markers (HIF-1α, Beclin 1, LC3B, and P62) and invasion-related markers (E-cadherin and MMP-9). These authors found higher HIF-1α expression in trophoblasts from PAS cases than in controls and proposed that chronic hypoxia may contribute to PAS development by disrupting autophagic mechanisms and enhancing trophoblastic invasiveness. Notably, this study also focused on trophoblasts rather than decidual tissue, a methodological contrast to our approach.

Another study examining the association between PAS and proangiogenic mediators included 16 PAS cases, 31 with placenta previa, and 6 healthy pregnancies.[15] IHC analysis revealed increased VEGF expression in the placentas of PAS patients, whereas expression of endostatin (a VEGF antagonist) and the angiogenesis inhibitor, endoglin, was decreased. This study compared invasive placental tissue with decidual tissue from healthy controls, a methodological choice that might explain differing results compared to previous studies focused on trophoblastic HIF-1α expression.

Normal and pathological angiogenesis are regulated by various mediators, with HIF-1α playing a central role. Angiogenesis is typically triggered by stimuli such as hypoxia, ischemia, or vascular injury, which in turn upregulate the expression of proangiogenic growth factors.[16] HIF-1α, as a key transcription factor, orchestrates the expression of numerous genes involved in angiogenesis, glucose metabolism, and cell proliferation. Among the target genes for HIF-1α is VEGF, which is critical for both the initiation and maintenance of angiogenesis and is regulated at every stage by HIF-1α.[17,18]

The relationship between hypoxia-induced HIF-1α overactivation and abnormal vascularization is perhaps best exemplified in tumor biology. As tumor cells proliferate rapidly, the balance between oxygen supply and demand is disrupted, triggering HIF-1α-mediated upregulation of proangiogenic factors.[19] Elevated HIF-1α expression has been documented in several cancers, including breast, liver, thymus, cervix, and kidney malignancies. HIF-1α is thus considered a potential therapeutic target in conditions such as ischemic diseases and cancer, where activation or inhibition is desired, respectively. Given the tumor-like invasive behavior of PAS, anti-HIF-1α therapies may hold promise as a potential treatment or prophylactic strategy.

Study Limitations

The primary limitation of our study is the significant difference in gestational age at delivery between the groups. While elective CS delivery was performed at around 34 weeks in PAS patients according to standard recommendations of American College of Obstetricians and Gynecologists,[20] control subjects delivering at similar gestational ages typically did so due to underlying placental pathologies such as preeclampsia or fetal growth restriction. Therefore, term pregnancies were included in the control group. A further limitation of this study is the lack of adjustment for potential confounding factors, such as placental location, number of prior CS deliveries, and maternal comorbidities, which may have influenced HIF-1α expression levels. Furthermore, patients with low lying placentas were not included as a third group. Given that all PAS patients had low-lying placentas while none of the control patients did, the inclusion of a hypothetical third group with low-lying placentas could have enabled a clearer assessment of whether HIF-1 alpha expression is associated with placental location.

One of the main strengths of our study lies in the IHC evaluation of HIF-1α in decidual tissue. Most published studies have assessed HIF-1α expression in trophoblasts. However, from a pathophysiological perspective, it is more plausible that hypoxia within the decidua upregulates proangiogenic mediators like VEGF, thereby facilitating abnormal trophoblast invasion. Furthermore, the well-documented absence or disruption of Nitabuch's layer in PAS supports the hypothesis of a hypoxic microenvironment in this region. Guan et al.[21] focused on the role of HIF-1α in hepatic fibrosis and indicated that HIF-1α expression was increased before the fibrosis develops and inhibition of HIF-1α may suppress the fibrosis.[21] This finding supports the hypothesis that improper regeneration of Nitabuch's layer may be due to increased HIF-1α levels in uterine scarring.

CONCLUSION

In conclusion, the aim was to investigate the pathogenesis of PAS by investigating the role of HIF-1α in abnormal trophoblastic invasion. We found that HIF-1α expression was significantly increased in decidual tissue of patients diagnosed with PAS compared to those with a history of prior CS. This finding supports our hypothesis that hypoxic conditions may arise in structurally compromised decidua because of previous CS deliveries and/or endometrial interventions, subsequently promoting the expression of proangiogenic factors. Future studies with larger patient cohorts, including pregnancies affected by low-lying placentas, may further clarify the association between HIF-1α and the abnormal trophoblastic invasion and vascularization observed in PAS.

Ethics

Ethics Committee Approval: The research was granted ethical approval by the Ethics Committee of Başaksehir Çam and Sakura City Hospital (protocol number: KAEK-11/14.08.2024.103, date: 19.08.2024)

Informed Consent: The privacy rights of human subjects have been observed and that informed consent was obtained for experimentation with human subjects.

Footnotes

Authorship Contributions

Surgical and Medical Practices: R.A.B., S.A., B.Y., Concept: B.Y., Design: V.A., H.E., B.Y., Data Collection or Processing: R.A.B., S.A., Ş.K.D., Analysis or Interpretation: R.A.B., S.A., Ş.K.D., İ.D.D., B.Y., Literature Search: R.A.B., T.Y.B., O.M.G., V.A., H.E., Writing: R.A.B., T.Y.B., O.M.G., B.Y.

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Original Article

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Cholecystectomy in Pregnant Women during Exacerbation of Calculous Cholecystitis

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ABSTRACT

Purpose: Biliary tract disease is one of the most common non-obstetric surgical conditions during pregnancy, affecting up to 12% of pregnant women. Gallstone formation is driven by hormonal changes; estrogen increases hepatic cholesterol secretion into bile while progesterone reduces gallbladder contractility, creating optimal conditions for stone development. These mechanisms peak in the second trimester, establishing it as the period of highest lithogenic risk.

Methods: This retrospective observational case series from Azerbaijan Medical University included 25 pregnant women with chronic biliary pathology. Twenty-two patients were managed conservatively with dietary modification, antispasmodics, and ademetionine 800 mg/day. Three patients (12%) underwent urgent laparoscopic cholecystectomy for refractory biliary obstruction confirmed on ultrasound. Liver function tests [aspartate transaminase (AST), alanine transaminase (ALT), alkaline phosphatase (ALP), bilirubin, cholesterol] were monitored serially each trimester.

Results: Exacerbations occurred predominantly in the second trimester (48%) and third trimester (52%). Biochemical markers showed the most pronounced elevations in the second trimester: AST +23%, ALT +24%, ALP +19%, cholesterol +18%, and total bilirubin +68% above trimester-specific reference values. Third trimester showed partial improvement in some markers, although AST and ALP remained elevated. All three surgical patients underwent laparoscopic cholecystectomy with CO_2 pneumoperitoneum at 10-14 mmHg, using modified positioning to minimize uterine compression. Mean operative time was 25 minutes with no conversions to open surgery. Clinical improvement occurred within 48 hours, with discharge by postoperative day 4. No perinatal complications or congenital anomalies were reported.

Conclusion: Findings support current SAGES guidelines recommending laparoscopic cholecystectomy as the preferred surgical approach when indicated during pregnancy. However, the study has significant limitations: small sample size (especially the surgical subgroup of three patients), retrospective design, incomplete parity data, absence of a control group, and lack of formal analysis of ademetionine efficacy. Results should be interpreted as preliminary observational data requiring confirmation in larger prospective studies.

Keywords: Pregnancy, biliary disease, cholelithiasis, liver function tests, laparoscopic cholecystectomy

INTRODUCTION

Biliary tract disease is one of the most common non-obstetric surgical conditions during pregnancy. Gallstone disease is the second most common non-gynecological condition requiring surgical intervention in pregnancy, affecting up to 12% of pregnant women,[1] with increasing incidence among younger women of reproductive age.[2,3]

Three clinical entities must be distinguished: cholelithiasis (presence of calculi within the gallbladder), cholecystitis (gallbladder wall inflammation, most commonly caused by cystic duct obstruction-calculous cholecystitis), and cholestasis of pregnancy (impaired bile flow with elevated serum bile acids and abnormal liver function tests, associated with adverse fetal outcomes.[4,5] These conditions share pathophysiological mechanisms but differ in clinical presentation and management.

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Gallstone formation during pregnancy is driven by the hormonal changes of gestation. Elevated estrogen promotes hepatic cholesterol secretion into bile, raising its saturation index, while simultaneously impairing gallbladder contractility.[6,7] Progesterone further reduces gallbladder emptying, causing bile stasis and prolonging exposure of bile to lithogenic conditions.[6] As a result, biliary cholesterol saturation increases progressively across trimesters, with the greatest rise observed in the second trimester.[7,8]

When conservative management fails, surgical intervention is indicated. Current SAGES guidelines establish laparoscopic cholecystectomy as the treatment of choice for symptomatic gallbladder disease during pregnancy, regardless of trimester, with CO_2 pneumoperitoneum of 10-15 mmHg considered safe.[9] Anesthetic risk, preterm labor, and gestational age remain important perioperative considerations requiring multidisciplinary coordination.[9]

The present study describes trimester-related clinical and biochemical patterns of biliary pathology in pregnant women and reports outcomes of conservative and surgical management in this cohort.

METHODS

This study was conducted as a retrospective observational case series at the Department of General Surgery and Research Center of Azerbaijan Medical University, in collaboration with the Research Institute of Obstetrics and Gynecology of the Ministry of Health of the Azerbaijan Republic, Baku. The study was conducted in accordance with the Declaration of Helsinki. This study received approval from the of Azerbaijan Medical University Ethics Committee (approval number: 38, date: 17.09.2024). Medical records of pregnant women with chronic biliary system pathology were reviewed. A total of 25 patients were included: 22 were managed conservatively and 3 underwent urgent surgical intervention.

Inclusion criteria were: Gestational age ≥8 weeks, reproductive age (≥18 years), and a documented history of chronic biliary system pathology confirmed prior to pregnancy.

Exclusion criteria were: Gestational age <8 weeks, decompensated systemic organ disease, and chronic liver disease of infectious or autoimmune origin (including Wilson's disease and primary biliary cirrhosis).

Diagnostic criteria were standardized as follows: Biliary pathology was confirmed by clinical presentation (right upper quadrant pain, nausea/vomiting), serial laboratory assessment, and ultrasonographic findings each trimester. Biliary obstruction was defined as ultrasonographic evidence of ductal dilatation with persistent symptoms refractory to conservative management.

Liver function was monitored by serial measurement of aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), total bilirubin, and total cholesterol throughout all trimesters. Ultrasonographic examination was performed each trimester to evaluate the gallbladder, liver, and fetal development.

Conservative management included dietary modification, antispasmodic therapy when required, and ademetionine 1,4-butanedisulfonate 800 mg/day orally for two months, administered as part of routine hepatoprotective care. Patients with persistent or recurrent symptoms and ultrasonographic evidence of biliary obstruction despite conservative treatment underwent urgent laparoscopic cholecystectomy under general anesthesia. Patients were positioned in a semi-sitting anti-Trendelenburg position with left lateral tilt to minimize uterine compression. CO_2 pneumoperitoneum was maintained at 10-14 mmHg, consistent with SAGES recommendations.[9] Trocar placement was adapted according to gestational age and uterine size. Fetal well-being was assessed before and after surgery in collaboration with the obstetric team.

All patients were followed throughout the perinatal, intranatal, and postnatal periods. Obstetric outcomes recorded included gestational age at delivery, mode of delivery, and neonatal status.

Statistical Analysis

Statistical analysis was performed using SPSS, version 22 (IBM Inc., Armonk, NY, USA). Quantitative variables were compared between trimesters using the Mann-Whitney U test, with trimester I values serving as the reference group for pairwise comparisons against trimesters II and III. A p value of <0.05 was considered statistically significant.

RESULTS

Twenty-five pregnant women with biliary system pathology were included. Age distribution was: 18-21 years: 3/25 (12%); 22-25 years: 5/25 (20%); 26-30 years: 4/25 (16%); 31-35 years: 8/25 (32%); >35 years: 5/25 (20%). Parity data were available for a subgroup of 15 patients based on detailed clinical history; of these, 11/15 (74%) were in their third pregnancy. In this subgroup, clinical manifestations were reported as more pronounced compared with women in their first pregnancy but this observation should be interpreted with caution, given the incomplete parity data for the full cohort.

Clinical Presentation and Timing of Exacerbations

Thirteen patients (52%) reported prolonged nausea and vomiting. The remaining patients predominantly presented with acute right upper quadrant pain radiating to the right shoulder or scapular region. Exacerbations occurred in the second trimester in 12/25 (48%) and in the third trimester in 13/25 (52%).

Biochemical Findings

Serial liver function assessment demonstrated trimester-related changes (Table 1). At the end of the first trimester, AST, ALT, and cholesterol were moderately elevated above the pregnancy-specific upper limits of normal, while ALP remained within the expected physiological range for the first trimester. Total bilirubin was approximately 25% above the pregnancy-specific reference value in the first trimester, with elevation attributable mainly to four patients in whom gallstone disease was confirmed ultrasonographically. In

Table 1. Dynamics of liver function biomarkers (mean ± SD) in pregnant women with biliary system pathology, with pregnancy-specific reference ranges

No	Trimester	AST (U/L)	ALT (U/L)	ALP (U/L)	Total Bilirubin (μmol/L)	Cholesterol (mg/dL)
1	I	32.36±0.9	36.41±0.9	272.8±17.2	1.37±0.08	229.7±5.3
2	II	38.0±1.2**	42.9±1.1**	355.7±8.9*	1.85±0.11**	260.2±5.4**
3	III	39.15±1.7**	40.2±1.1***	367.1±16.7**	1.84±0.15*	260.4±8.2**
Ref. range	I/II/III	3-23/3-33/4-32	3-30/2-33/2-25	17-88/25-126/38-229	1.7-6.8/1.7-13.7/1.7-18.8	<200/<200/<200

*p<0.01; **p<0.001; ***p<0.05 vs. Trimester I (Mann-Whitney U test)
ALP: Alkaline Phosphatase; AST: Aspartate Aminotransferase; ALT: Alanine Aminotransferase

the second trimester, a more pronounced average rise was observed across all markers: AST +23%, ALT +24%, ALP +19%, cholesterol +18%, and total bilirubin +68% above trimester-specific reference values. In the third trimester, a partial reduction in average values of ALT, cholesterol, and total bilirubin was noted; however, AST and ALP remained elevated above pregnancy-specific reference ranges (Table 1). All comparisons were made against trimester I values as reference, using the Mann-Whitney U test; statistically significant differences are indicated in Table 1.

Surgical Outcomes

Despite conservative management, three patients (12%) had persistent symptoms with ultrasonographically confirmed biliary duct obstruction and underwent urgent laparoscopic cholecystectomy. Mean operative time was 25 minutes, with no conversions to open surgery. Clinical improvement was observed within 48 hours and all three patients were discharged by postoperative day 4 with ongoing antenatal follow-up. Across the full cohort, pregnancies proceeded without reported perinatal complications. Deliveries were described as physiologic, and no congenital anomalies were identified in the newborns.

DISCUSSION

This retrospective case series describes trimester-related clinical and biochemical patterns in pregnant women with biliary system pathology and reports outcomes largely of conservative management with a few patients experiencing surgical intervention. The main findings were: (i) exacerbations clustered in the second and third trimesters (48% and 52%, respectively); (ii) liver function biomarkers showed the most pronounced elevations in the second trimester, particularly total bilirubin and ALT; and (iii) three patients (12%) required urgent laparoscopic cholecystectomy due to refractory biliary obstruction, with favorable short-term maternal and fetal outcomes.

The predominance of exacerbations in the second and third trimesters is consistent with the known pathophysiology of pregnancy-related biliary disease. As described in the Introduction, estrogen-driven cholesterol hypersecretion and progesterone-mediated gallbladder hypomotility peak during mid-pregnancy, creating the most lithogenic biliary environment in the second trimester.[6,7] The partial biochemical improvement observed in some markers during the third trimester may reflect partial adaptation of hepatobiliary function, though AST and ALP remained elevated above pregnancy-specific reference ranges throughout, indicating general persistent hepatobiliary stress in this cohort.

The observed cluster of exacerbations in multiparous women, although based on incomplete parity data (15/25 patients), is consistent with the established association between higher parity and increased gallstone risk, as parity is among the strongest independent risk factors for gallstone disease in women of reproductive age.[1,8] This observation should be interpreted with caution given the incomplete parity data available for the full cohort, and no formal statistical comparison between parity groups was performed.

Regarding surgical management, the good outcomes observed in our three surgically treated patients are consistent with published data on laparoscopic cholecystectomy in pregnancy. A systematic review of 590 patients reported an intraoperative complication rate of 3.5%, a conversion rate of 2.2%, and a fetal loss rate of 0.4%, with the majority of procedures performed in the second trimester.[10] A more recent meta-analysis of 45,883 pregnant women demonstrated that operative treatment significantly reduced the composite of adverse pregnancy outcomes compared to nonoperative management (odds ratio: 0.60; 95% confidence interval: 0.42-0.87).[11] Furthermore, laparoscopic cholecystectomy compared to open cholecystectomy was associated with significantly lower fetal, maternal, and surgical complication rates,[12] supporting the laparoscopic approach as the preferred surgical option when intervention is required. These findings also align with the 2024 updated SAGES guidelines, which conditionally recommend laparoscopic cholecystectomy over nonoperative treatment for biliary disease in pregnancy.[9]

Ademetionine (Heptral) was utilized in this cohort as part of routine hepatoprotective conservative management, in accordance with local clinical practice. However, no control group was included in this study, and no formal comparison of outcomes between treated and untreated patients was performed. Therefore, no conclusions regarding the efficacy or necessity of ademetionine can be drawn from these data. Its use in pregnancy requires further evaluation in controlled studies before any recommendations can be made.

Study Limitations

This study has several important limitations that must be acknowledged. First, the retrospective observational design limits the ability to establish causality. Second, the small sample size and in particular the surgical subgroup of only three

patients, markedly restricts the generalizability of the findings. Third, parity data were available for only 15 (60%) patients, limiting the validity of parity-related observations. Fourth, the absence of a control group precludes any comparative analysis of treatment outcomes. Fifth, exact *p* values were not available for all comparisons due to the method of original data recording. Future prospective studies with larger cohorts and standardized data collection are needed to better characterize biliary disease patterns and optimal management strategies in pregnancy.

CONCLUSION

In this retrospective case series, exacerbations of biliary system pathology occurred predominantly in the second and third trimesters, accompanied by measurable and trimester-dependent changes in liver function biomarkers. When conservative management failed and biliary obstruction was confirmed ultrasonographically, urgent laparoscopic cholecystectomy was feasible and was associated with favorable short-term maternal and fetal outcomes in a small selected subset of patients. These findings are consistent with current international guidelines supporting laparoscopic cholecystectomy as the preferred surgical approach in pregnancy when clinically indicated.[9] Given the limitations of this study, the results should be interpreted as preliminary observational data requiring confirmation in larger prospective studies.

Ethics

Ethics Committee Approval: This study received approval from the of Azerbaijan Medical University Ethics Committee (approval number: 38, date: 17.09.2024).

Informed Consent: This study was conducted as a retrospective observational case series.

Footnotes

Authorship Contributions

Surgical and Medical Practices: H.M., Concept: H.M., E.A., Design: H.M., K.Q., Data Collection or Processing: H.M., S.Q., K.Q., Analysis or Interpretation: K.Q.,S.B., Literature Search: S.Q., S.B., Writing: S.Q., S.B., E.A.

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Original Article

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Cumulative Summation Test for Learning Curve (LC-CUSUM) in Labia Majora Plasty

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ABSTRACT

Purpose: To evaluate the learning curve of labium majora plasty using the learning curve cumulative summation (LC-CUSUM) method and to determine the number of procedures required to achieve surgical proficiency.

Methods: This retrospective study analyzed 120 consecutive labium majora plasty procedures performed by three obstetrics and gynecology specialists with no prior experience in cosmetic gynecology. All trainees completed a standardized hands-on training course before independently performing procedures in their own clinics. Each trainee's first 40 cases were evaluated. Surgical success and failure were defined based on postoperative complications, need for revision, and patient dissatisfaction. LC-CUSUM analysis was applied using predefined acceptable (3%) and unacceptable (10%) failure rates. Continuous variables were analyzed using analysis of variance, and categorical variables using chi-square or Fisher's exact test.

Results: A total of 120 patients were included (40 per trainee). Patient demographics and procedural characteristics were comparable among the three groups ($p>0.05$). Failure rates were 5% (n=2), 7.5% (n=3), and 5% (n=2) for trainees 1, 2, and 3, respectively. LC-CUSUM analysis demonstrated that all trainees achieved acceptable performance levels within the study period. Competency thresholds were reached after 9, 21, and 16 procedures for trainees 1, 2, and 3, respectively.

Conclusion: Patient demographics, procedure characteristics, and outcome measures were comparable among the three trainees. LC-CUSUM charts demonstrated that all trainees achieved adequate performance levels during the observation period. Competency thresholds were reached after 9, 21, and 16 procedures for the three trainees indicating variability in individual learning curves.

Keywords: Labium majora plasty, cosmetic gynecology, surgical outcomes, learning curve, training assessment

INTRODUCTION

Labia majora plasty is an effective procedure used to correct asymmetry, deformities, and volume loss of the labia majora associated with aging.[1] This procedure has recently become increasingly popular among patients.[2]

There has been an increase in demand for labia majora plasty surgery, based on the belief that improving vulvar aesthetics may enhance sexual well-being and self-confidence.[3] The loss of dermal collagen and the signs of aging in the labia majora due to gravity lead to skin wrinkles known as sagging, causing a loss of volume and a changed appearance in the labia majora and minora. This creates a discrepancy in size and shape between the two lips, moving them away from their ideal look and resulting in an unattractive appearance.[4] Although labia majora plasty has a low complication rate, hematoma, infection, and fat necrosis may occur.[5]

Although labiaplasty, fat injection, and fat harvesting are not part of the gynecology and obstetrics training program in Turkey, recent patient demand for these procedures has led to their inclusion in specialty training programs.[6] The skill to perform effective surgery is typically gained through a master-apprentice relationship under the supervision of experienced surgeons. However, objectively assessing a trainee's surgical competence and learning ability can be difficult. The learning process varies depending on the individual skills of the

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trainee, the teaching methods used by the instructor, and the institutional environment.[7] Different methods can be employed to evaluate whether a trainee has reached the required level of competence. While performing a certain number of supervised procedures is a common practice, this method fails to account for individual differences.[8] As a solution to this issue, a statistical tool called the learning curve cumulative summation (LC-CUSUM) test has been developed to assess when a procedure has been sufficiently mastered. LC-CUSUM is designed to determine whether a predefined performance level has been achieved and provides intuitive graphical representations, as well as the capability to detect even small, ongoing changes in performance.[8] The aim of this study was to assess the learning curve for labia majora plasty using the LC-CUSUM method and to determine the number of procedures required to achieve surgical competence.

METHODS

A total of 120 labia majora plasty cases involving three trainees were examined retrospectively. All trainees were obstetrics and gynecology specialists who had never performed cosmetic gynecology procedures, including labia majora reduction, labia majora fat grafting, or both. Initially, all trainees attended a hands-on, live surgery course on the first day, which included a four-hour theoretical session on vulvar and lower abdominal anatomy, patient selection, obtaining patient consent, and techniques of labia majora plasty, fat harvesting, microfat preparation, and lipofilling. A two-hour video demonstration of all methods, including discussions of tips and tricks, was completed after the theoretical session. On the second day of the course, the three trainees both performed and assisted with hands-on labia majora plasty, fat harvesting, microfat graft preparation, and vulvar lipofilling on three patients. Then, the trainees returned to their clinics to perform cosmetic surgery procedures. Their first five procedures were reviewed by the same expert, who has more than ten years of experience in cosmetic surgery. Three years after the course, the trainees were contacted and invited to participate in the study. All agreed to send information on their first 40 consecutive cases of labia majora plasty, including surgical labia majora reduction, lipofilling, or a combination of both procedures. Patient files were reviewed for demographic variables, preoperative, one-month, and six-month postoperative photographs, patient satisfaction, and the need for additional fat grafting or revision surgery.

Postoperative photographic outcomes were assessed by independent reviewers who were blinded to the identity of the trainees and the chronological order of the procedures to reduce assessment bias.

Ethical Approval

Ethical approval for this study was obtained from the Bandırma Onyedi Eylül University Non-Interventional Research Ethics Committee (approval number: 2026-01-14, date: 21.01.2026). The study assessed surgical performance using cumulative summation (CUSUM) analysis without modifying standard patient care. All procedures adhered to institutional standards and the Declaration of Helsinki. Written informed consent was obtained from all patients prior to participation in the study.

Patient Selection and Techniques

Patients admitted for labia majora plasty for cosmetic reasons were classified according to Fasola and Gazzola.[9] Briefly, mild labia majora hypotrophy involves no to mild skin thinning and visible fine wrinkles. Cases with mild hypotrophy were excluded because they received hyaluronic acid filler and mesotherapy. Moderate labia majora hypotrophy includes moderate skin laxity and dermatochalasis with visible wrinkles; these cases were treated with microfat lipofilling. Severe labia majora hypotrophy involves severe dermatochalasis and deep wrinkles; these cases first underwent surgical resection of excess vulvar skin followed by lipofilling to enhance the vulva. The skin of the labia majora was reduced on both sides with semilunar vertical incisions along the lateral labial sulcus and medial border of the labia majora, as described by Miklos and Moore.[10] Fat harvesting was performed from the lower abdomen or medial thigh under anesthesia using a Coleman cannula connected to a 20 mL luer-lock syringe. Under low negative pressure, 30 to 50 mL of fat was harvested using a dry technique. The emulsification of the microfat was achieved by shifting tissue between two 20 cc syringes connected by a female-to-female luer-lock connector. After more than 30 passes, a final 600-micrometer filter was used to obtain microfat and stromal vascular fraction. The prepared microfat suspensions were transferred to a one cc syringe and grafted to each labia majora by a one-point entry and a retrograde technique through one point at the top of each labia majora, as described by Menkes et al.[11]

Statistical Analysis

We previously reported that the complication rate in genital cosmetic procedures was 2.7% (72/2594).[12] An acceptable failure rate was established at 3% (p_0=0.03), while an unacceptable failure rate was set at 10% (p_1=0.10). As noted earlier, the acceptable level of type I error was α=0.05 (the chance of incorrectly claiming the trainee is competent), and of type II error was β=0.20 (the chance of wrongly rejecting the trainee's competency). Based on previously published data, the success sample weight X=0 was calculated at 0.0080043, and failure sample weight X=1 was -1.38629. The average run length was 40, with a decision interval h of 2.5.[8,13-15] Comparison of variables was conducted using the chi-square test for categorical variables and Fisher's exact test. Analysis of variance was used for continuous variables among the three operators. A p value <0.05 was considered statistically significant.

RESULTS

A total of 120 patients were analyzed, with 40 cases per trainee. The mean age ranged from 36.7±7.5 to 40.3±9.3 years, and the mean body mass index ranged from 28.6±3.3 to 30.3±3.9 kg/m^2, with no significant differences between groups (p>0.05). Similarly, the distribution of labia majora hypotrophy severity and the types of procedures performed were comparable between the three trainees (p>0.05) (Table 1).

The overall unfavorable outcome rate was 5.8% (7/120). Unfavorable outcome included hematoma in two patient

Table 1. Patient and intervention characteristics in three trainees

Patient characteristics	Trainee 1 n=40	Trainee 2 n=40	Trainee 3 n=40	*p*
Age (years)	39.7±8.1	36.7±7.5	40.3±9.3	0.12
Body mass index (kg/m²)	28.6±3.3	30.3±3.9	29.5±4.9	0.19
Labia majora hypotrophy				
Moderate	17 (42.5%)	16 (40%)	13 (32.5%)	0.6
Severe	23 (57.5%)	24 (60%)	27 (67.5%)	
Labia majora reduction	23 (57.5%)	24 (60%)	27 (67.5%)	0.6
Labia majora lipid grefting	40 (100%)	40 (100%)	40 (100%)	0.6
Unfavorable outcome	2 (5%)	3 (7.5%)	2 (5%)	0.8
Labia majora hematoma	1 (2.5%)	1 (2.5%)	-	
Labia majora enfection	-	1 (2.5%)	1 (2.5%)	
Patient aesthetic dissatisfaction	1 (2.5%)	1 (2.5%)	1 (2.5%)	

Data are presented as mean ± SD or n (%). Continuous variables were analyzed using one-way ANOVA and categorical variables using the chi-square or Fisher's exact test, as appropriate. A *p* value <0.05 was considered statistically significant.
ANOVA: Analysis of variance

(1.7%), infection in two patients (1.7%), and patient-reported aesthetic dissatisfaction in three patients (2.5%). No significant differences in unfavorable outcomes were observed between the trainees ($p=0.80$). Failure rates were 5%, 7.5%, and 5% for trainees 1,2, and 3, respectively.

LC-CUSUM analysis demonstrated that all trainees achieved acceptable performance levels within the study period. Competency thresholds were reached after 9, 21, and 16 procedures for trainees 1, 2, and 3, respectively (Figure 1).

DISCUSSION

This study demonstrates the applicability of the LC-CUSUM method for tracking the learning curve of labia majora plasty and for evaluating the acquisition of surgical proficiency. It is important to bring a new surgical procedure to a standardized and implementable level for surgeons in training; otherwise, this process could lead to irreversible results. Therefore, trainees should be monitored until they can perform the surgical procedure independently. However, objectively assessing trainees' proficiency levels in surgical procedures is challenging. Factors such as the number and duration of procedures, the trainee, instructor, the environment where the course is conducted, and the course content all influence this assessment. The study results indicated that the LC-CUSUM is a sensitive and discriminative tool for evaluating surgical learning curves. Although no significant differences were observed in baseline characteristics or complication rates between the trainees, the number of procedures required to achieve competence varied from nine to 21, a 133% variability. Nonetheless, the varying time required for trainees to reach an optimal performance level in surgical procedures highlights that learning surgical techniques is a dynamic process affected by individual differences. When evaluating the achievement of optimal surgical competence within course content, it appears that methods based solely on the number of procedures performed have limitations.

Issat and colleagues examined whether the LC-CUSUM and competence-CUSUM methods effectively assess the usability of LC-CUSUM and the number of procedures needed to reach an optimal level.[16] This research also highlighted the importance of personalized monitoring systems during training and concluded that LC-CUSUM is suitable for tracking proficiency in surgical procedures after training.

Previous studies have shown that LC-CUSUM can be used to evaluate learning curves in surgical procedures and gynecological imaging, and to assess the learning process of embryo transfer. In the studies by Dessolle et al.[15] it was demonstrated that there was insufficient data regarding the learning processes in assisted reproductive technologies and the learning curve of trainees. Therefore, they recognized the importance of embryo transfer in creating pregnancy using assisted reproductive technologies. By developing a portable model to establish the learning curve of embryo transfer with the LC-CUSUM and CUSUM methods, they showed that this provides a resource to measure continuous learning ability. Moreover, they advocated for personalized training and emphasized that the number of embryo transfers required for a trainee to reach an ideal level of practitioner competence varied depending on the individual. These authors recommended applying the CUSUM method for quality assessment.[15]

The present study identified the number of procedures required for trainees to achieve technical proficiency in labia majora plasty, highlighting differences experienced by trainees in learning curves and emphasizing the need for personalized assessment. It is natural that trainees differ in their proficiency and learning abilities. Therefore, assessing the surgical learning curve on an individual basis is essential. LC-CUSUM serves as a quantitative tool to evaluate learning curves for each person. This method indicates when a set level of learning has been reached and is independent of the total number of procedures performed. Trainees' learning abilities can be tailored through direct observation by the instructor and graphical visualization of the learning curve. Graphical

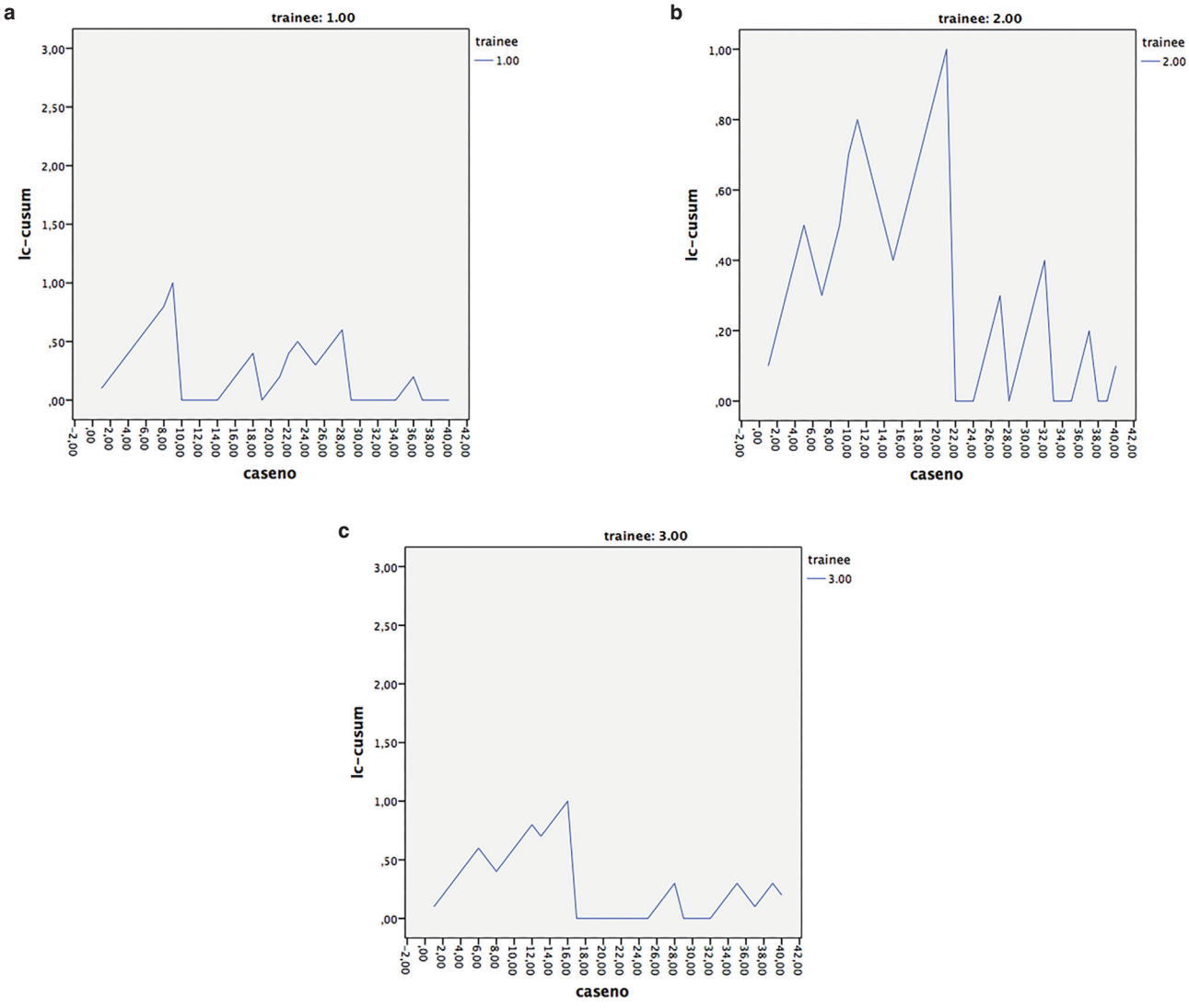

Figure 1. The figure presents the learning curve of cumulative sums for trainee 1 (a), trainee 2 (b), and trainee 3 (c)

monitoring has proven to be effective for the assessment of learning progress curves.[17,18] However, the biggest limitation of this method is the absence of a standardized test or a clearly defined critical point to objectively confirm that the learning curve has reached an acceptable level. The learning abilities of the trainees were compared to those of labia majora plasty trainers, and the LC-CUSUM parameters used in this model were found to be robust. Although establishing threshold values within the LC-CUSUM methodology requires precision, the simplicity of programming and the flexibility inherent in the methodology have made the LC-CUSUM readily accessible to users.

Study Limitations

A key limitation of this study relates to the definition of surgical success and failure within the LC-CUSUM model. In the present analysis, failure was defined based on clinically relevant but indirect outcome measures, including patient satisfaction, the need for revision surgery, and the requirement for additional fat grafting. Although these endpoints reflect real-world clinical decision-making and are commonly used in surgical practice, they inherently include subjective components and are not supported by standardized, validated patient-reported outcome measures (PROMs). The absence of validated assessment tools, such as the genital appearance satisfaction scale, the female sexual function index, or the female genital self-image scale, may limit the objectivity, reproducibility, and discriminatory capacity of the LC-CUSUM analysis. Furthermore, patient satisfaction is influenced by multiple psychosocial and cultural factors, which may introduce variability independent of surgical performance. Therefore, the outcome measures used in this study should be interpreted as surrogate clinical indicators rather than fully standardized endpoints. Future studies incorporating validated PROMs into postoperative assessment protocols would strengthen the methodological robustness of LC-CUSUM-based evaluations and provide a more comprehensive and objective assessment of surgical competence.

The retrospective design of this study is also an important limitation, especially regarding patient satisfaction assessments and postoperative photographic outcomes. Retrospective data collection can introduce both selection and information bias because cases with incomplete records or poor documentation might have been excluded, and outcome assessments may not have been consistently standardized. In addition, the retrospective nature of the analysis might underestimate early variability in surgical performance, particularly during the initial phase of the learning curve, potentially smoothing out fluctuations that would be visible in a prospective setting. A prospectively designed LC-CUSUM application, based on predefined outcome criteria and standardized assessment tools, would offer a more robust and methodologically sound mechanism to evaluate surgical competence. Therefore, future larger prospective LC-CUSUM studies in cosmetic gynecology are needed to better capture real-time performance variations and to improve the validity and reliability of learning curve evaluations.

Although all procedures were performed following a standardized training program under the supervision of a single experienced instructor, which enhances internal consistency, this may limit the external validity of the findings. Learning curves in surgical practice are influenced by multiple contextual factors, including the institutional environment, the technical approach of the trainer, and case-mix characteristics. Therefore, the competency thresholds identified in this study may not be directly generalizable to other training settings. These considerations highlight the need for multicenter studies to validate and refine LC-CUSUM-derived learning curve benchmarks across diverse clinical and educational environments.

The follow-up period in this study was limited to six months, which may not be sufficient to capture long-term outcomes, such as graft retention, delayed revision needs, and sustained patient satisfaction in fat grafting-based procedures. Therefore, the competency achieved as determined by LC-CUSUM should be seen as reflecting early technical skill rather than long-term aesthetic results, and this distinction is important to prevent overinterpreting the results.

The LC-CUSUM parameters used in this study, including the acceptable and unacceptable failure rates, were derived from previously published data in cosmetic surgery and are not specific to labia majora plasty. While these thresholds were selected to provide a pragmatic and literature-based framework for performance evaluation, procedure-specific benchmarks may differ. Therefore, future studies should aim to validate these parameters and consider sensitivity analyses to determine the most appropriate thresholds for labia majora plasty.

CONCLUSION

Given the variability observed in individual learning curves for labia majora plasty, the best approach is to adopt a personalized methodology under the guidance of a professional trainer during the course. In this context, the LC-CUSUM method proved to be a suitable and effective tool for monitoring surgical skill proficiency.

Ethics

Ethics Committee Approval: Ethical approval for this study was obtained from the Bandırma Onyedi Eylül University Non-Interventional Research Ethics Committee (approval number: 2026-01-14, date: 21.01.2026).

Informed Consent: Written informed consent was obtained from all patients for participation and use of their clinical data and images.

Footnotes

Authorship Contributions

Surgical and Medical Practices: E.G., E.H.C., Concept: E.G., E.H.C., Design: E.G., G.K., Data Collection or Processing: E.G., G.K., A.G.E., E.H.C., Analysis or Interpretation: E.G., G.K., A.G.E., Literature Search: E.G., G.K., A.G.E., Writing: E.G.

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Original Article

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Evaluation of the Modified Caprini Risk Score in Benign Gynecological Surgery: is Routine Prophylaxis Necessary?

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ABSTRACT

Purpose: Deep vein thrombosis (DVT) and venous thromboembolism represent major causes of postoperative morbidity and mortality in gynecological surgical practice. The aim of this study was to evaluate the incidence of DVT among patients undergoing benign gynecological procedures, identify relevant risk factors, assess the utility of the modified Caprini risk assessment model, and examine the effectiveness of thromboprophylaxis strategies.

Methods: The modified Caprini risk score was used to evaluate DVT risk. Demographic characteristics, body mass index, hormonal therapy use, operative details, postoperative mobilization time, and thromboprophylaxis data were collected. Then, the incidence rates of DVT were compared between the group of patients receiving prophylactic anticoagulation and those not receiving it. All statistical analysis was performed using SPSS 15.0 (IBM İnc., Armonk, NY, USA), and categorical and continuous variables were analyzed using appropriate parametric and non-parametric tests, with a $p<0.05$ considered statistically significant.

Results: A majority (84.3%) of the 172 patients included were classified as high- or very-high-risk according to the modified Caprini model. Overweight and obesity were common (35.7% and 29.7%, respectively). Low-molecular-weight heaprin (LMWH) prophylaxis was administered to 55% of patients. Only one patient (0.58%) developed DVT. No significant difference in DVT incidence was found between those who received LMWH and those who did not. Mechanical prophylaxis was not applied in any patient, yet no DVT occurred in the moderate-risk group.

Conclusion: The modified Caprini score may overestimate risk in this population. Gynecology-specific risk assessment tools are needed.

Keywords: Deep vein thrombosis, low-molecular-weight heparin, modified Caprini risk scoring system

Introduction

Deep vein thrombosis (DVT) is a serious postoperative complication[1,2] and a key component of venous thromboembolism (VTE), which accounts for approximately 10% of all hospital deaths and also significantly contributes to morbidity and mortality in postsurgical patients.[3,4] The pathophysiology of DVT is classically explained by Virchow's triad, which encompasses venous stasis, endothelial injury, and a hypercoagulable state. These are three interrelated processes that collectively facilitate thrombus formation within the venous system. Most patients undergoing gynecological surgery are in the peri- or postmenopausal period, during which age-related physiological changes, hormonal alterations, and the higher prevalence of comorbid conditions collectively contribute to a prothrombotic state and altered coagulation dynamics.[5] In addition, a substantial proportion of gynecological procedures performed in women of reproductive age are indicated for benign yet clinically significant conditions, such as uterine fibroids and endometriosis.[6] Although minimally invasive approaches are increasingly preferred in gynecological surgery, open surgical techniques remain necessary. Factors such as large uterine size, multiple or deeply located leiomyomas, severe endometriosis, dense

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pelvic adhesions from previous surgeries, and anatomical limitations may prevent the use of laparoscopic or vaginal methods.[7] As a result, laparotomy for benign reasons continues to be performed routinely in certain patients. Such surgeries may further compromise venous return in the pelvic vasculature and accentuate venous stasis by prolonging postoperative immobility.[8] Prolonged postoperative immobility has been identified as a major contributor to thrombus development, as demonstrated by Qu et al.,[9] while Suzuki et al.[10] similarly reported that the incidence of VTE increases with the accumulation of risk factors associated with stasis. Endothelial damage, by releasing subendothelial collagen and tissue factor, activates platelets and initiates the coagulation cascade, thus further increasing thrombogenic susceptibility, a mechanism highlighted by Peedicayil et al.[11] in the context of gynecological malignancy and open invasive procedures. Finally, a hypercoagulable state, whether inherited or acquired, may contributes to Virchow's triad. This hypercoagulopathic state may be due to various strong prothrombotic stimuli, such as malignancy, hormonal changes, emergency surgery, or thrombophilia.[12-15] Consequently, these hemodynamic and physiological perturbations collectively heighten the susceptibility to postoperative thromboembolic events in this population.

The incidence of DVT varies significantly across gynecological surgical populations and is much higher among patients with gynecological malignancies. While the reported rate of perioperative DVT in benign gynecological surgery ranges from approximately 6.2% to 29.1%, this risk rises to 19.6-38% in patients undergoing surgery for gynecological cancers.[16,17] The modified Caprini risk assessment model is one of the most widely used and guideline-endorsed tools for perioperative VTE risk stratification. It is recommended by international guidelines, including those of the American College of Chest Physicians, and has been validated across multiple surgical disciplines.[18,19] According to the modified Caprini risk assessment model, the estimated incidence of VTE in surgical patients varies by risk category, ranging from <0.5% in low-risk, 1.5% in moderate-risk, 3% in high-risk, and up to 6% in very-high-risk groups.[20] Thromboprophylaxis should therefore be tailored to individual risk status. Low-risk patients generally require only early mobilization and adequate hydration, without the need for mechanical or pharmacologic prophylaxis. In moderate-risk patients, mechanical methods, particularly intermittent pneumatic compression, are recommended as first-line prevention. High-risk individuals require assessment of bleeding risk prior to selecting therapy; mechanical methods are preferred when bleeding risk is elevated, whereas low-molecular-weight heparin (LMWH) or low-dose unfractionated heparin is recommended when bleeding risk is low. In very-high-risk patients, pharmacologic prophylaxis is prioritized, with mechanical methods added when necessary. Extended prophylaxis, up to four weeks, is advised, particularly for patients undergoing surgery for abdominal or pelvic malignancies.[20] Although malignancy-related surgical procedures consistently show a higher incidence of thromboembolic complications than benign gynecological surgeries, it is important to recognize that the perioperative period and especially the first 72 hours after surgery, is the most vulnerable time for thrombus formation, regardless of the underlying condition.[10,16]

This heightened risk highlights the importance of employing structured, evidence-based risk stratification strategies in all women undergoing gynecological procedures. Accordingly, we applied the modified Caprini risk assessment model to systematically evaluate VTE susceptibility in our patient population and aimed to investigate the applicability, predictive value, and clinical relevance of this scoring system in estimating postoperative VTE incidence.

METHODS

All procedures in this study were conducted in accordance with the 1964 Declaration of Helsinki and its subsequent amendments, or to similar ethical standards. The reviewed and approved this study University of Health Sciences Turkey, İzmir Tepecik Education and Research Hospital Local Ethics Committee (approval no: 21, date: 26.01.2017). This retrospective cross-sectional study included patients who underwent open abdominal or laparoscopic surgery for benign gynecological indications at the Department of Obstetrics and Gynecology of University of Health Sciences Turkey, İzmir Tepecik Education and Research Hospitalin 2017. The modified Caprini risk assessment model (Table 1) was employed to stratify preoperative DVT risk. Women aged 18 years and older who presented to the outpatient clinics of the same department and subsequently underwent open abdominal or laparoscopic pelvic surgery, as well as vaginal hysterectomy for benign gynecological conditions, were eligible for inclusion. Patients who underwent vaginal repair procedures, diagnostic hysteroscopy, transobturator tape or mini-transobturator tape operations were excluded because of short operative times and rapid mobilization, those who had Cesarean delivery, patients operated on for gynecological malignancies, individuals receiving antiplatelet or anticoagulant therapy for chronic medical conditions, and patients whose surgeries had been performed less than one month prior were excluded from the study. Patients included in the study were contacted individually using the telephone numbers registered in the hospital's electronic archive system and were interviewed regarding oral contraceptive use, any prior DVT events, and postoperative thromboprophylaxis practices. Patients who could not be reached or who declined to participate were also excluded. Body mass index (BMI), the presence of pre-existing chronic diseases, the presence of risk factors included in the modified Caprini score, administration of thromboprophylaxis and, when applicable. The duration and dosage of prophylaxis were obtained from the hospital's electronic archive system. Then, all patients were categorized into low (0-1 score), moderate (2 score), high (3-4 score), and very high-risk groups (5 score and above) based on the modified Caprini risk score and a comparison was made between the two groups: one group receiving thrombophylaxis, and one not receiving it, in order to assess the occurrence of DVT.

Statistical Analysis

All collected data were analyzed using SPSS version 15.0 (IBM Inc., Armonk, NY, USA). Descriptive data are presented as n

(%) values for categorical data and mean ± standard deviation and median for continuous variables. For comparisons of modified Caprini risk scores according to patients' clinical and reproductive characteristics, Fisher's exact test, Pearson's chi-square test, and the Mann-Whitney U test were used. A p value of <0.05 was considered statistically significant.

Table 1. Modified Caprini risk model

1-Point risk factors
Between 41-50 years old
Edema of the lower extremities
Varicose veins
Obesity (BMI >25)
Laparoscopic surgery (<45 minutes)
Minor surgical procedure planned
History of acute myocardial infarction
Inflammatory bowel disease
Abnormal pulmonary function
History of serious acute respiratory disease (including pneumonia) within 1 month
Oral contraceptive/hormone replacement therapy
Pregnancy/postpartum period
History of unexplained IUFD/recurrent miscarriage (>3)/premature birth/preeclampsia/IUGR
2-Points risk factors
Between 61-74 years old
Arthroscopic surgery
Malignancy (history or presence of cancer)
Elective major surgery
Presence of extremity cast (<1 month)
Laparoscopic surgery (>45 minutes)
Central venous catheter
Immobilized patient (more than 72 hours)
3-Points risk factors
Above 75 years old
History of DVT or pulmonary embolism
Factor V Leiden mutation
History of high homocysteine level
Prothrombin 20210A mutation
Lupus anticoagulant positivity
Heparin-dependent thrombocytopenia
Anticardiolipin antibody positivity
5-Points risk factors
Stroke within 1 month
Multiple trauma within 1 month
Hip, pelvic, or leg fracture within 1 month
Acute spinal cord injury (paralysis) within 1 month
Lower extremity arthroplasty
Low-risk group (0-1 score), moderate-risk group (2 score), high-risk group (3-4 score), very high-risk group (5 score and above) BMI: Body mass index, DVT: Deep vein thrombosis, IUFD: Intrauterine fetal death, IUGR: Intrauterine growth restriction

RESULTS

A total of 172 patients who underwent surgery for benign gynecological indications were included in the study. Of these, 96 (55.8%) received thromboprophylaxis in the postoperative period, while the remaining 76 (44.2%) did not. The distribution of patients' sociodemographic, physical, and obstetric characteristics is presented in Table 2. The mean age of the patients was 45.5±9.7 years. Among the participants, n=57 (33.1%) had a normal BMI, n=61 (35,7%) were overweight, and n=51 (29.7%) were obese. Nearly all (n=161, 93.6%) of the women had at least one previous pregnancy, while n=155 (90.1%) had given birth at least once. In addition, n=76 (44.2%) reported having experienced at least one miscarriage.

The distribution of surgical procedures is presented in Table 3. Total abdominal hysterectomy with bilateral salpingo-oophorectomy or salpingectomy was the most frequently performed operation (45.4%), followed by total laparoscopic hysterectomy with bilateral salpingo-oophorectomy (12.2%), and vaginal hysterectomy with colporrhaphy anterior and posterior (VAH + CAP) accounted for 5.2% of all procedures.

Table 4 summarizes the distribution of several clinical characteristics and the modified Caprini risk score classifications for the patients. Among the patients, n=70 (40.7%) received a single dose of anti-Xa 4000 IU/ 0.4 mL of LMWH, while 15.1% (n=26) received a single dose of anti-Xa 6000 IU/ 0.6 mL. Only one patient was found to be using hormone replacement therapy (HRT), and two patients were using oral contraceptives. The patient receiving HRT also had a history of breast carcinoma. Only one patient had a prior history of DVT. Of all participants, n=27 (15.7%) were classified in the low-to-moderate risk category, whereas n=145 (84.3%) were classified in the high-to-very-high-risk category. The mean hospitalization duration was 2±1 days, with the shortest stay being less than 1 day and the longest lasting 9 days. The mean duration of LMWH use among those who received anticoagulant therapy was 7±4 days.

Table 2. Distribution of sociodemographic, physical, and obstetric characteristics of patients

Characteristics	Mean ± SD	Median
Age	45.5±9.7	45
Weight (kg)	72.0±13.6	71
Height (cm)	161.8±6.5	162
BMI	27.5±5.0	26.9
Gravity	3±2	3
Parity	2±1	2
Number of live births	2±1	2
BMI: Body mass index, kg: Kilograms, cm: Centimeters		

Table 5 shows the postoperative thromboprophylaxis administered to patients in the low-moderate and high-very high-risk groups In total, 96 patients (55.8%) received thromboprophylaxis, with 89 (51.7%) in the high-to-very high-risk group and 7 (4%) in the low-to-moderate risk group. The remaining 76 (44.2%) did not receive medical or mechanical thromboprophylaxis, including 56 (32.5%) in the high-to-very high-risk group and 20 (11.6%) in the low-to-moderate risk group.

In the patients classified within the high-to-very-high group (n=145), n=89 (61.3%) received thromboprophylaxis, while the remaining 56 patients did not. Of those who received prophylaxis, n=63 (70.7%) were administered 0.4 mL LMWH, and n=26 (29.3%) received 0.6 mL LMWH. Among the 63 patients who received 0.4 mL LMWH, 23 received prophylaxis for fewer than seven days and 40 for more than seven days. Similalrly, in the group receiving 0.6 mL LMWH, eight patients were treated for fewer than seven days and 18 for more than seven days. Only one case of symptomatic DVT was detected, occurring in a patient who did not receive prophylaxis. However, due to the extremely low number of events, no meaningful statistical comparison regarding the effectiveness of prophylaxis could be performed (Table 6).

Table 3. Distribution of surgical procedures performed in the study population

Surgical procedure	n	%
TAH + BSO or TAH + BS	78	45.4
TLH + BSO	21	12.2
VAH + CAP	9	5.2
Myomectomy	7	4.1
Ovarian cystectomy	7	4.1
Unilateral salpingo-oophorectomy	4	2.4
Laparoscopic salpingectomy	2	1.2
Abscess drainage + bilateral salpingectomy + adhesiolysis	2	1.2
Other benign gynecological procedures*	42	24.3
Total	172	100

*Other benign gynecological procedures include less frequently performed open and minimally invasive surgeries, such as combined open pelvic floor procedures, isolated adnexal surgeries, and adhesiolysis TAH + BSO: Total abdominal hysterectomy + bilateral salpingo-oophorectomy, TAH + BS: Total abdominal hysterectomy + bilateral salpingectomy, TLH + BSO: Total laparoscopic hysterectomy + bilateral salpingo-oophorectomy, VAH + CAP: Vaginal hysterectomy + colporrhaphy anterior and posterior

Table 4. Distribution of clinical variables and modified Caprini risk score groups

Variable	n	%
LMWH administration: no	76	44.2
LMWH administration: yes	96	55.8
HRT use: no	170	98.8
HRT use: yes	2	1.2
OCP use: no	169	98.3
OCP use: yes	2	1.2
History of DVT: no	171	99.4
History of DVT: yes	1	0.6
Modified Caprini risk score: low	8	4.7
Modified Caprini risk score: moderate	19	11.0
Modified Caprini risk score: high	128	74.4
Modified Caprini risk score: very high	17	9.9

DVT: Deep vein thrombosis, LMWH: Low-molecular-weight heparin, HRT: Hormone replacement therapy, OCP: Oral contraceptive

DISCUSSION

DVT remains an important global health problem, including in Turkey, due to its association with prolonged increased patient morbidity/mortality, extended hospitalization, complications, and increased healthcare costs. Approximately half of all thromboembolic events are considered preventable through appropriate medical and surgical thromboprophylaxis. In the absence of prophylaxis, the incidence of DVT ranges from 6.2-29.1% in patients undergoing major gynecological surgery for benign conditions and from 19.6-37.9% in those undergoing major surgery for malignancy.[8,18] Despite these findings, the present study found that postoperative symptomatic DVT was observed in only 1 (0.58%) patient. This was despite 84.3% of the participants being classified as high- or very high-risk by the Caprini scoring system. However, given the very low incidence rate and the resulting risk of false negative errors, this inconsistency also suggests that the score may have limited predictive value in populations undergoing benign gynecological surgery with baseline risk.

The mean age of patients included in the study was 45.5±9.7 years, and 46±6.1 years in the high-very high-risk group. Zhang et al.,[17] aimed to identify risk factors for DVT in women undergoing gynecological surgery and found that patients who were elderly, had malignant tumors, had cardiovascular comorbidities, or received high doses of hemostatic drugs after surgery were at particularly high-risk for pulmonary embolism. Although numerous studies have consistently demonstrated that increasing age is a significant independent risk factor for postoperative DVT, including after gynecological surgical procedures,[21,22] this was not observed in our cohort. This may be explained by the relatively young age of our patient population, given that the risk of DVT increases progressively with advancing age, particularly after 60-70 years.[23,24]

Tan et al.[25] defined obesity as an independent risk factor for DVT beyond genetic predisposition to DVT in their studies. They also showed that this interaction was independent of hospitalization, the postoperative period, and immobilization.[25] In their studies, El-Menyar et al.[26] stated that obesity was not only a risk factor for DVT, but also that BMI ≥30 kg/m^2 was a predictor of survival. In the present study, 35.7% of patients were overweight, and 29.7% were obese. The average BMI in the high-very high-risk group was 35 kg/m^2. Despite the earlier evidence, no significant differences in BMI or postoperative DVT rates were observed between patients who received and did not receive prophylaxis. This inconsistency may be due

Table 5. Postoperative thromboprophylaxis administered to patients in the low-moderate and high-very high groups based on the modified Caprini risk scoring system

Variables	Modified Caprini risk score			
	Low to moderate		High to very high	
	n	%	n	%
No LMWH administration	20	11.6	56	32.5
LMWH 4000 anti-Xa IU/ 0.4 mL administration	7	4	63	36.6
LMWH 6000 anti-Xa IU/ 0.6 mL administration	-	-	26	15.1

LMWH: Low-molecular-weight heparin

Table 6. Comparison of low molecular weight heparin doses, duration, and occurrence of deep vein thrombosis in the high and very high-risk group

		n	%	*p*
Patients receiving thromboprophylaxis	LMWH 4000 anti-Xa IU/ 0.4 mL (those who used less than 7 days)	23	25.8	>0.05
	LMWH 4000 anti-Xa IU/ 0.4 mL (those who used more than 10 days)	40	44.9	
	LMWH 6000 anti-Xa IU/ 0.6 mL (those who used less than 7 days)	8	8.9	
	LMWH 6000 anti-Xa IU/ 0.6 mL (those who used less than 7 days)	18	20.2	
Patients not receiving thromboprophylaxis		56	38.7	

LMWH: Low-molecular-weight heparin

not only to the relatively young age of our study population and early postoperative mobilization, but also to the limited sample size, which may have reduced the statistical power to detect an association between obesity and DVT.

Most patients in our study were fully independent in daily activities, and the mean length of hospital stay was 2±1 days. Although immobility is a well-established risk factor for DVT,[27,28] early mobilization, typically within 6-8 hours after surgery, may have contributed to the low incidence observed in our study. Indeed, only one patient developed DVT, and this patient had no history of oral contraceptive use, HRT, thrombophilia, or familial thrombosis.

In the present study, the overall incidence of DVT following benign gynecological surgery was very low, with only one postoperative symptomatic DVT case detected in 172 patients. This finding is particularly noteworthy given that 84.3% of the study population was classified as high to very high-risk according to the modified Caprini risk scoring system. Despite this risk profile, prophylaxis practices showed considerable variability, and adherence to the thromboprophylaxis algorithms recommended in international guidelines appeared inconsistent.[29,30] Although thromboprophylaxis was administered to 61.3% of high- to very high-risk patients, more than one-third of this cohort did not receive prophylactic treatment. Furthermore, the duration of LMWH prophylaxis was generally shorter than recommended,[29] particularly in high-risk patients. Despite evidence that prolonged prophylaxis may be beneficial in patients undergoing pelvic surgery,[31] approximately one-third of patients received anticoagulant therapy for less than seven days. Furthermore, the mechanical prophylaxis recommended for moderate-risk groups was not used in any patients,[20] indicating that VTE prevention strategies were not adequately utilized. It is believed that the absence of thromboprophylaxis and the variability in dosage were influenced by several factors, including the surgeon's personal preference, perceived bleeding risk, early commencement of postoperative mobilization, a relatively short hospital stay, and the absence of additional thrombotic risk factors. Despite observed variations in prophylactic practices, the postoperative symptomatic DVT rate in this cohort was remarkably low. This result may be due to the presence of additional protective factors, including the relatively young age of the participants, the absence of central venous catheters, and the absence of significant comorbidities. These factors may have reduced the predicted risk. Furthermore, the failure to perform routine doppler ultrasound evaluations on all patients and the inability to detect asymptomatic DVT cases may also contribute to this. The appropriate use of thromboprophylaxis in benign gynecological surgery remains a matter of ongoing debate, and this study adds to a growing body of evidence questioning the routine use of prophylaxis in this setting, particularly for patients without additional VTE risk factors.[32,33] Furthermore, unnecessary use of LMWH may increase bleeding risk, patient discomfort, and healthcare costs without providing a clear clinical benefit.[34,35] Thus, this study suggests that more refined,

procedure- and population-specific risk stratification tools may be required to better identify patients who truly benefit from pharmacologic prophylaxis.

Study Limitations

Both the single-center and retrospective design, and the small patient numbers are the main limitations of the study. Other limitations include the heterogeneity of patient operations, the presence of other infectious conditions such as abscesses, and the inability to compare minimally invasive operations, such as VAH + CAP, with major operations. Moreover, the surgeon's decision to administer thromboprophylaxis may have introduced differences in demographic characteristics between the thromboprophylaxis and non-thromboprophylaxis groups, potentially leading to selection bias. Another important limitation is that, given the extremely low incidence of observed DVT, the study lacks sufficient power to detect any clinically meaningful differences between the prophylaxis groups or to test for non-inferiority. Furthermore, asymptomatic DVT cases were not investigated by routine Doppler examination. Finally, inconsistencies in the postoperative thromboprophylaxis regimens contribute to these limitations.

CONCLUSION

In conclusion, our results highlight a potential overestimation of thrombotic risk when the Caprini risk scoring system is applied without consideration of procedure- and patient-specific factors. We believe that there is a need for gynecology-specific risk assessment tools that more accurately reflect the clinical profile of this population. Further prospective, multicenter studies with larger sample sizes are warranted to clarify optimal thromboprophylaxis strategies and to refine risk stratification in benign gynecologic surgical practice.

Ethics

Ethics Committee Approval: The reviewed and approved this study University of Health Sciences Turkey, İzmir Tepecik Education and Research Hospital Local Ethics Committee (approval no: 21, date: 26.01.2017).

Informed Consent: Due to the retrospective nature of the study, it is exempt from the requirement for informed consent.

Footnotes

Authorship Contributions

Surgical and Medical Practices: A.C.D., A.D., Concept: A.C.D., A.D., Design: A.C.D., Data Collection or Processing: A.C.D., Analysis or Interpretation: A.C.D., Literature Search: A.C.D., Writing: A.C.D., A.D.,

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Original Article

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Analysing Usability of ChatGPT-4 as A Source of Information about Human Papilloma Virus Vaccines

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ABSTRACT

Purpose: Human papillomavirus (HPV) is a highly prevalent sexually transmitted pathogen, with nearly 80% of sexually active individuals becoming infected during their lifetime. Although recently developed vaccines provide effective protection, increasing reliance on internet-based and artificial intelligence (AI)-generated medical information raises concerns regarding the accuracy and adequacy of such content. This study aimed to evaluate the accuracy, quality, and readability of HPV vaccine-related information generated by ChatGPT.

Methods: The 25 most-searched for HPV vaccine-related keywords were identified through Google Trends. ChatGPT responses to these queries were collected and assessed using the Ensuring Quality Information for Patients (EQIP) criteria, the Flesch-Kincaid Grade Level (FKGL), the Flesch-Kincaid Reading Ease (FKRE), and two Likert scales (3-point and 5-point). Evaluations were independently performed by two healthcare professionals. Statistical comparisons were made across EQIP categories and readability indices.

Results: The three most frequently searched phrases were "vaccine for HPV," "HPV vaccine side effects," and "HPV side effects." The mean EQIP score was 62.48, the mean FKRE score was 44.89, and the mean FKGL level was 12.08. The mean scores on the 5-point and 3-point Likert scales were 4.12 and 2.2, respectively. No statistically significant differences were observed between EQIP categories ($p=0.332$) or in FKGL and FKRE comparisons ($p=0.244$ and $p=0.157$).

Conclusion: ChatGPT provided generally satisfactory information regarding HPV vaccines; however, several quality limitations were identified. The content demonstrated adequate scientific accuracy but required a reading level consistent with high school education. EQIP scoring indicated that the information was of "good quality with minor issues". In particular, simplifying technical language, improving structural organization, and incorporating more patient-centered explanations may substantially increase the accessibility and practical value of AI-generated medical content.

Keywords: Artificial intelligence, papillomavirus vaccines, patient education as topic, information dissemination

INTRODUCTION

Human papillomavirus (HPV) is a common sexually transmitted pathogen and the leading etiological factor for cervical cancer. According to the World Health Organization, approximately 80% of sexually active individuals will contract HPV at some point in their lives. Globally, an estimated 570,000 women and 60,000 men develop HPV-related cancers each year.[1]

HPV infection is often asymptomatic, though mild symptoms may occur in symptomatic cases.[2] Vaccines developed in recent years provide effective protection against HPV infection, playing a crucial role in preventing genital warts, cervical cancer, and other precancerous lesions.[3] In countries with vaccination programs, a significant reduction in precancerous lesions and genital warts has been observed, correlated with high vaccination rates.[4] Despite these proven benefits, concerns and misconceptions surrounding HPV vaccines persist.[5] Misinformation, often fueled by social media, contributes to vaccine hesitancy in certain communities.[6]

ChatGPT, an artificial intelligence (AI) chatbot developed by OpenAI, has gained popularity for its ability to generate detailed responses to user queries. Using deep learning techniques,

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specifically a variant of the transformer-based neural network, it is capable of producing contextually relevant and human-like responses. Its accessibility and rapid response generation have attracted millions of users worldwide.[7] In terms of public health information about HPV, the availability of clear, accurate information is clearly important and ChatGPT is currently a major source of widely used information about these vaccines.

Although clinicians largely agree on the safety and efficacy of HPV vaccines, access to accurate information remains a challenge for the general population. Misinformation can lead to patients downplaying risks or neglecting preventive measures.[8] With the increasing use of the internet and AI-based platforms, the accessibility of information has improved, but concerns about its accuracy and adequacy remain. While patients who consult clinicians can receive accurate information, the accuracy and readability of information from internet searches and AI platforms, such as ChatGPT, have not been extensively reported in the literature.[9]

The aim of this study was to evaluate the accuracy and readability of information about HPV vaccines provided by ChatGPT. Understanding this will help assess the potential of widely accessible information to mislead patients and inform strategies to address misinformation.

METHODS

This study was conducted on October 1, 2024, at Gaziantep Medical Point Hospital. As the study did not involve human subjects, patient data, or any *in vivo* procedures, approval from an Institutional Review Board was not required. The research was performed in accordance with the principles of the Declaration of Helsinki. The most frequently searched HPV vaccine-related keywords were identified using Google Trends (https://trends.google.com/). The search was performed on October 1, 2024, with the region set to "worldwide" and all available data from January 2004 to the date of access included. Prior to conducting the search, all browser data were cleared to minimize potential personalization bias. From the generated list, the top 25 most relevant and frequently searched queries in English were selected, excluding repetitive, irrelevant, or non-English terms. All available data from 2004 to the present were included, and the search region was set to "worldwide".

The 25 selected keywords identified via Google Trends were used as direct user queries and entered verbatim into the ChatGPT interface. Each keyword was submitted as a standalone query, without additional contextual framing, prompts, or follow-up questions, in order to reflect typical real-world patient search behavior. Each query was entered in a new and independent chat session to prevent contextual carryover and response contamination. All questions and responses were categorized into six groups: condition or illness, medication or product, prevention or aftercare, test, operation, and investigation or procedure. A formal sample size calculation was not applicable because the dataset consisted of the top 25 globally most-searched HPV vaccine-related keywords identified via Google Trends. The number of items was therefore determined by the natural structure of the dataset rather than by investigator selection, which is methodologically standard in studies analyzing search-trend-based query lists.

To evaluate the quality of the responses, a Google Form containing 20 items from the Ensuring Quality Information for Patients (EQIP) checklist was used. This study used the original 20-item EQIP version developed by Moult et al.[10], which is the shorter, preliminary validation form, rather than the extended 36-item version used in later adaptations. Each item was scored as "yes" (1 point), "partially" (0.5 points), "no" (0 points), or "not applicable". The EQIP score was calculated as the sum of the "yes" responses divided by the total number of applicable items (adjusted for "not applicable" responses). Scores were presented as percentages and categorized into four groups: 76-100% (well-written, high-quality); 51-75% (good quality with minor problems); 26-50% (serious problems with quality); and 0-25% (significant quality issues).[10]

Readability was assessed using two parameters: the Flesch-Kincaid Reading Ease score (FKRE) and the Flesch-Kincaid Grade Level score (FKGL). FKRE was calculated using the standard formula 206.835 - [1.015 × average sentence length (ASL)] - (84.6 × average syllables per word (ASW)]. The score indicated the educational level required for comprehension, with scores below 30 indicating university-level comprehension. FKGL was calculated using the standard formula (0.39 × ASL) + (11.8 × ASW) - 15.59, where higher values correspond to more complex text and a higher required grade level. A lower FKGL score indicates easier comprehension.[11] In addition, information accuracy and completeness were evaluated using both 3-point and 5-point Likert scales. For accuracy, a 5-point scale was used (1= "very low accuracy with serious errors," 5= "very high accuracy with no errors"). For completeness, a 3-point scale was used (1= "incomplete," 3= "comprehensive coverage"). For reproducibility, "accuracy" was operationally defined as the degree to which ChatGPT responses aligned with current evidence-based medical guidelines and contained no factual errors or misleading statements. "Completeness" was defined as the extent to which responses addressed all major components of the queried topic, including definition, causes, symptoms, prevention, management, and when applicable, treatment alternatives.[12] All evaluations were conducted by two independent healthcare professionals (C.D. and I.T.S.) to minimize bias, both of whom are board-certified physicians, with C.D. specializing in obstetrics and gynecology and I.T.S. specializing in general surgery.

Statistical Analysis

Quantitative variables were expressed as mean ± standard deviation (SD). The Shapiro-Wilk test was used to assess the normality of continuous variables prior to selecting appropriate statistical tests. The Kruskal-Wallis H test was used to compare EQIP, FKRE, FKGL, and Likert scores across more than two independent groups as this rank-based non-parametric test compares the distribution of median ranks rather than means. Bonferroni post-hoc correction was applied for multiple group comparisons. Correlations between numerical variables were assessed using the non-parametric Spearman's rank correlation test, as the data did not follow a normal distribution. Statistical significance was set at $p<0.05$ for all tests. All analyses were

performed using IBM SPSS Statistics for Windows, version 21.0 (IBM Corp., Armonk, NY, USA).

RESULTS

The three most frequently searched phrases were "vaccine for HPV," "HPV vaccine side effects," and "HPV side effects". The full list of the 25 most used phrases is provided in Table 1. The top three countries where HPV vaccine searches were most frequent were Hong Kong, Taiwan, and Singapore (Figure 1), with the top 10 countries listed in Table 2.

Table 3 presents the minimum, maximum, means, and SDs of the EQIP, FKRE, and FKGL scores. The EQIP scores for the texts ranged from 50 to 72, with a mean score of 62.48. The FKRE scores varied between 17.6 and 64.2, with a mean score of 44.89. A lower FKRE score indicates increased reading difficulty; accordingly, the mean FKRE score of 44.89 corresponds to a reading level generally considered difficult and consistent with high school-level comprehension rather than university-level understanding. The FKGL scores ranged from 8.4 to 21.1, with a mean of 12.08. Higher FKGL values similarly correspond to more complex text, reflecting a reading level typically consistent with high school education or above.

On the 5-point Likert scale, the texts received scores ranging from 3 to 5, with an average of 4.12. On the 3-point Likert scale, scores ranged from 1 to 3, with an average score of 2.2.

The texts generated by ChatGPT were categorized into six groups (Figure 2) for comparison. No statistically significant differences were observed between these categories in terms of EQUIP scores ($p=0.332$). Similarly, no significant differences were found between the categories for FKGL ($p=0.244$) or FKRE ($p=0.157$) scores.

DISCUSSION

The findings of this study indicate that while the content of the texts generated by ChatGPT was generally satisfactory, there were notable deficiencies in terms of quality. The scientific content was positively rated according to the Likert scales, with average scores of 2.2 on the 3-point scale and 4.12 on the 5-point scale. Furthermore, the FKGL and FKRE readability

Table 1. The top 25 keywords queried globally for HPV vaccines between 2004 and 2024, according to Google Trends data and EQIP classifications

	Questions	Popularity percentage	Classification of the topic according to EQIP prevention or after care
1	Vaccine for HPV	100	Prevention or aftercare
2	HPV vaccine side effect	47	Prevention or aftercare
3	HPV side effects	46	Condition or illness
4	What is HPV	45	Condition or illness
5	What is HPV vaccine	45	Condition or illness
6	HPV cancer	43	Condition or illness
7	Cancer vaccine	42	Condition or illness
8	Gardasil	33	Medication or product
9	Gardasil HPV vaccine	33	Medication or product
10	Gardasil vaccine	31	Medication or product
11	HPV vaccine men	31	Prevention or aftercare
12	HPV vaccine age	31	Prevention or aftercare
13	HPV men	29	Prevention or aftercare
14	HPV vaccine schedule	26	Test, operation, investigation or procedure
15	Vaccine schedule	25	Test, operation, investigation or procedure
16	Warts	25	Condition or illness
17	HPV warts	24	Condition or illness
18	Cervical cancer vaccine	23	Medication or product
19	HPV vaccine cervical cancer	23	Medication or product
20	Cervical cancer	22	Condition or illness
21	What is the HPV vaccine	19	Medication or product
22	HPV vaccine symptoms	18	Condition or illness
23	HPV vaccine cost	18	Miscellaneous
24	Vaccines	17	Miscellaneous
25	HPV symptoms	17	Condition or illness

HPV: Human papillomavirus, EQIP: Ensuring Quality Information for Patients

assessments yielded values indicating that the texts were relatively difficult to read, requiring at least a high school education level for adequate comprehension.

The three most frequently searched phrases in this study were "vaccine for HPV," "HPV vaccine side effects," and "HPV side effects," suggesting that the public were particularly interested in the existence and safety of the HPV vaccine. Notably, the highest search activity was concentrated in small, largely ethnically Chinese Asian countries, with Hong Kong, Taiwan, and Singapore leading in searches. This geographic distribution may reflect regional differences in sexual health awareness, vaccination policies, and patterns of online information-seeking behavior.

Figure 1. Global search interest in HPV vaccines from 2004 to 2024, based on Google Trends data (regions with medium search volume not included)

HPV: Human papillomavirus

Table 2. Interest by region

	Country	Popularity percentage
1	Hong Kong	100
2	Taiwan	84
3	Singapore	68
4	Denmark	63
5	Austria	52
6	Norway	51
7	New Zealand	44
8	Ireland	42
9	United States	35
10	Japan	35

ChatGPT has increasingly become a go-to resource for patients seeking information before consulting healthcare providers. Since 2004, the number of questions posed to chatbots has steadily increased (Figure 3). In the present study, the quality of the text responses was assessed using FKGL and FKRE scores. A study by Şahin et al.[13] on erectile dysfunction found that the readability of chatbot-generated texts was low, generally requiring a sixth-grade reading level. In contrast, our results suggested that the FKGL scores corresponded to a high school reading level, making the content more challenging to understand. This is a significant finding, as AI platforms are used by a wide range of individuals, and greater readability would facilitate better comprehension. Poor readability has the potential to cause misunderstandings, which may result in treatment refusal or hesitancy.

In addition to readability, it is important that the information provided by ChatGPT is scientifically accurate. Accurate information can not only reduce the workload for healthcare professionals but also build patient trust in treatment protocols. A study by Goodman et al.[14] in 2023 evaluated chatbot-generated answers on medical topics using two separate scales. More than 50% of the responses were rated as completely or nearly correct, with most considered comprehensive.[14] In our study, two different healthcare professionals evaluated the texts using 3-point and 5-point Likert scales, and the scientific content was found to be of high quality. These findings align with previous research, suggesting that ChatGPT-generated responses are satisfactory in terms of content accuracy.

The EQIP scoring system is another valuable tool for evaluating the quality of health information. It assesses the clarity, structure, use of sources, accuracy, relevance, and comprehensiveness of patient education materials. A study by Walker et al.[15] in 2023 used EQIP to evaluate ChatGPT-generated answers for benign and malignant liver tumors. The texts were rated as "low" to "medium quality". Similarly, a study by Erden et al.[16] in 2023 evaluated ChatGPT responses to osteoporosis-related queries and found the EQIP scores to reflect "medium quality". In the present study, the average EQIP score was in the "good quality with minor problems" category. The slight improvement in EQIP scores compared to earlier studies may be attributed to improvements in chatbot performance and learning processes, as ChatGPT

Table 3. Descriptive statistics of EQIP, FKRE, FKGL, and Likert scores (mean ± SD, min-max)

	Minimum	Maximum	Mean	Std. deviation
Ensuring Quality Information for Patients score	50	72	62.48	±5.16
The Flesch-Kincaid Reading Ease score	17.6	64.2	44.89	±11.98
The Flesch-Kincaid Grade Level score	8.4	21.1	12.08	±2.85
3 points Likert scale	1	3	2.2	±0.65
5 points Likert scale	3	5	4.12	±0.73

EQIP: Ensuring Quality Information for Patients, FKRE: Flesch-Kincaid Reading Ease, FKGL: Flesch-Kincaid Grade Level, Std. deviation: Standard deviation

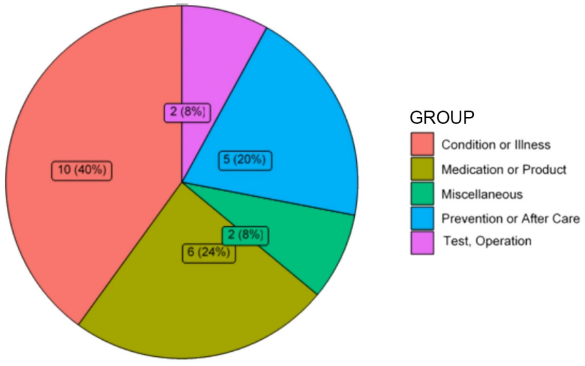

Figure 2. The percentage of text categories based on the EQIP
EQIP: Ensuring Quality Information for Patients

Figure 3. Global search interest based on Google Trends data from 2004 to 2024

has undergone several revisions and the number of queries posed to AI has increased over time. However, despite this improvement, the scientific quality of the content remains below the desired level.

Study Limitations

A limitation of this study is the reliance on a single chatbot platform. Results may differ when using other AI models. Furthermore, the quality and readability of the responses may vary depending on the specific version of the AI used. As AI continues to evolve, the accuracy, reliability, and readability of such texts are expected to improve. Another limitation is that the study was conducted solely in english; future studies in other languages may yield different results.

Recent studies published in 2023-2024 similarly emphasize the need for improving the clarity and patient-oriented design of AI-generated health information, highlighting that readability and quality scores often remain suboptimal despite high factual accuracy.[12,13,16]

CONCLUSION

The accessibility of accurate and high-quality information on important public health topics, such as HPV vaccines, is essential. AI-based chatbots, like ChatGPT, can play a valuable role in providing such information. These platforms have the potential to improve patient education and foster confidence in treatment. This study demonstrated that ChatGPT is an informative and easily accessible source for HPV vaccine information in the English language. However, the findings also highlight that the content provided still falls short in terms of comprehensiveness and readability. In particular, simplifying technical language, improving structural organization, and incorporating more patient-centered explanations may substantially increase the accessibility and practical value of AI-generated medical content.

Ethics

Ethics Committee Approval: As the study did not involve human subjects, patient data, or any *in vivo* procedures, approval from an Institutional Review Board was not required.

Informed Consent: Not applicable, as this study did not involve human participants, patient data, or identifiable personal information.

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Footnotes

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Case Report

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Necrotizing Fasciitis Following Oocyte Retrieval: Case Report of A Rare Occurrence

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ABSTRACT

Necrotizing fasciitis (NF) is a relatively rare but serious and potentially fatal, soft tissue infection characterized by a rapidly spreading bacterial infection in the subcutaneous tissues. This article describes a 41-year-old patient diagnosed with acute NF following oocyte retrieval for infertility. The oocyte retrieval procedure was uneventful. Within the next few days, she presented with high fever and acute abdominal findings, and the diagnosis of NF was confirmed. The most effective management for NF is rapid primary diagnosis and surgical debridement. The gold standard treatment includes intravenous antibiotics, surgical debridement, and intensive care. Due to possible gastrointestinal complications triggering NF, the patient underwent colostomy along with necrosectomy. The purpose of this report is to review the comprehensive treatment, management, and experience of NF and to emphasize the role of a multidisciplinary care team in improving this patient's condition.

Keywords: Necrotizing fasciitis, oocyte retrieval, infection

INTRODUCTION

Necrotizing fasciitis (NF) is a rapidly progressive infection mostly affecting the fascia and subcutaneous layers.[1] The clinical manifestation and the course of NF are variable, and different etiological microorganisms may be involved. In any case, prompt surgical intervention is deemed critical for the final outcome.[2] On the other hand, the lack of specificity of symptoms at presentation or admission and the rapid progression of septic shock and multiple organ failure often make rapid clinical diagnosis challenging.[3]

Patients with NF frequently present with symptoms of systemic infection.[4] NF is classified into four types. Type I accounts for 70-80% of cases with polymicrobial or synergistic causes. Responsible microorganisms include gut flora-derived mixed anaerobes and aerobes, *Eschericia coli*, *Pseudomonas spp.*, and *Bacteroides spp*. Type II accounts for 20-30% of cases and is usually monomicrobial. Responsible microorganisms include bacteria originating from the skin or throat, Group A beta-hemolytic *Streptococcus*, and sometimes *Streptococcus aureus*. Type III and IV are less common.[5]

The only treatment option for NF is surgical debridement of necrotic tissue and broad-spectrum antibiotic therapy.[6,7] The mortality rate for NF varies between 11% and 22% in different studies and can reach 16% to 33% when associated with streptococcal toxic shock syndrome.[8]

CASE REPORT

Written and verbal consent was obtained from a 41-year-old patient experiencing infertility due to fallopian tube blockage caused by endometriosis, and an oocyte pickup (OPU) (egg retrieval) procedure was performed, and his eggs were collected. Two days after the OPU procedure, she presented with high fever and acute abdominal findings. Blood test results showed a white blood cell count of 2.79 $\times 10^3/\mu$L, a neutrophil ratio of 61.4%; hemoglobin of 6.7 g/dL; thrombocytes of 86 $\times 10^3$ /μL; C-reactive protein 225.2 mg/L; procalcitonin 31.56 ng/mL; total protein 5 g/dL; albumin 2.4 g/dL; aspartate aminotransferase 33 U/L; alanine aminotransferase 12 U/L; total bilirubin 1.12 mg/dL; creatine kinase 709 U/L; blood urea nitrogen 5 mg/dL; creatinine 0.45 mg/dL; sodium 138 mEq/L; and potassium was 2.52 mEq/L. Plain computed tomography scans revealed intra-abdominal changes (Figure 1a and b).

Wong and colleagues developed a laboratory risk indicator score for NF, they termed Laboratory Risk Indicator for Necrotizing Fasciitis (LRINEC) (Table 1).[9] They identified six independent laboratory parameters associated with NF. The classification of patients and the likelihood of NF using LRINEC are shown in Table 2.[10]

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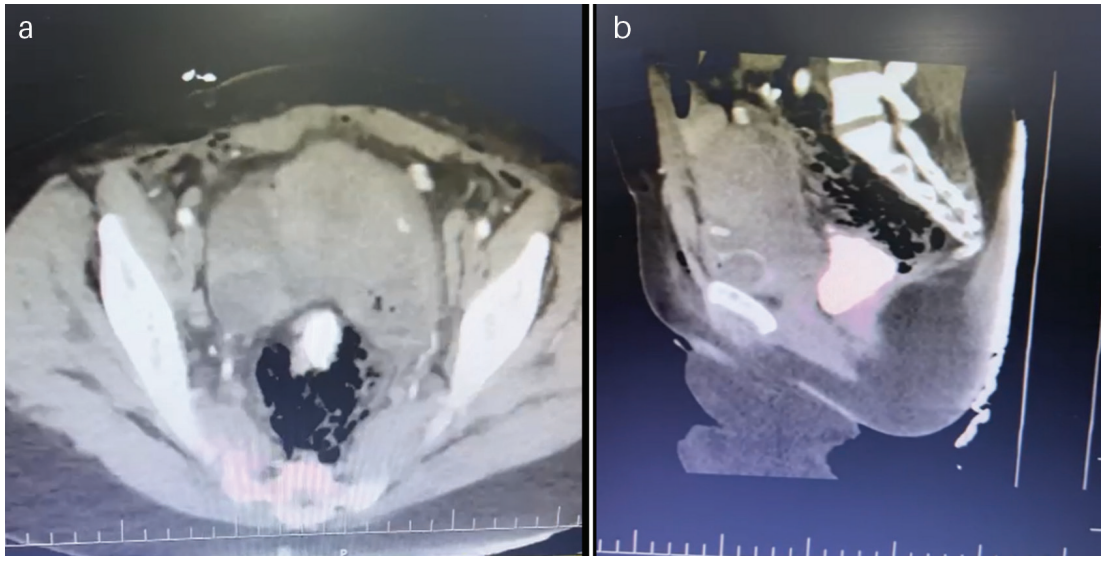

Figure 1. a) and b) show widespread intra-abdominal gas accumulation due to necrosis

Radiological evaluation has also been used in the diagnosis of NF. Radiographic examinations may reveal gas accumulation in the subcutaneous tissue, but gas is not seen in most patients.[11] Magnetic resonance imaging (MRI) has high sensitivity (93-100%) for the diagnosis of NF. MRI may reveal liquefactive necrosis and fascial fluid accumulation caused by inflammatory edema.[12,13]

In the presented case the LRINEC score was 8 suggesting a likelihood of NF of >75% so NF was suspected, and general surgery was contacted immediately. Emergency surgery was performed; exploration revealed patchy necrotic foci on the mesosigmoid colon and serosal surface, with necrosis of the mesorectum distally from the rectosigmoid region. The rectum and mesorectum were resected unblocked up to the levator muscle plane. The operation was completed with the maturation of the end colostomy. Postoperatively, the patient was transferred to the intensive care unit. The patient has fully recovered and preparation for the transfer of oocytes obtained during OPU will begin.

DISCUSSION

NF is a severe infection of the subcutaneous tissue characterized by necrosis of the subcutaneous tissues and fascia, and usually results from Group A beta-hemolytic streptococcal infection or polymicrobial synergistic infection.[14] The mortality rate from this condition is high if left untreated or if treatment is delayed. Due to the rapidly progressive nature of the infection, early diagnosis and definitive treatment are extremely important.[15-17] The incidence of this disease has increased approximately fivefold in the last decade, which may partly be due to an increase in the number of immunocompromised patients and may even be due to more frequent reporting in recent years. A recent publication reported mortality rates ranging from 30% to 90%.[17] As reported in a 2010 study, gastrointestinal symptoms are also a possible predictor of serious outcomes in invasive group A streptococcal infections.[18]

Most published cases of NF are secondary NF and have a known etiology.[19] There are many risk factors that contribute to the onset of NF. Risk factors such as diabetes, obesity, smoking, and corticosteroid use can facilitate the development of the condition and can also have a negative impact on the course of the NF.

The most important factor in the treatment of NF is early diagnosis because of its rapid progress. Diagnosis is based primarily on clinical findings. The most important factor may be clinical awareness of NF in the physician first evaluating the patient. NF can easily be confused with other soft tissue infections that clinically present with erythema. In the presented case the irregular borders of erythema in the patients' lesions and the presence of pain and tenderness beyond the affected area facilitated the diagnosis of NF. NF should also be suspected in cases of rapid progression of clinical findings despite antibiotic treatment, and the diagnosis should be supported by laboratory and radiological imaging methods.

Marking the borders of the existing erythema with is useful for closely monitoring progression. The LRINEC scoring system is a highly sensitive method, although not specific.[9] In this case, the patient's LRINEC score was 8 and radiological imaging methods supported the diagnosis of NF but were not diagnostic on their own, as they include nonspecific findings such as facial thickening, widespread fluid accumulation, and edema. The most important way to control infection in NF is to debride all necrotic tissues as early as possible. In addition, when there is only irregularly bordered erythema and swelling on the skin surface, NF should be considered and surgical exploration should be performed. Finding necrosis and infection in the deep planes after passing through the subcutaneous tissues are findings suggestive of NF. In such cases, debridement should be continued until healthy, bleeding tissue is reached, and all necrotic tissue should be removed from the environment. There are numerous publications indicating that early, aggressive debridement reduces mortality rates.[20,1]

Tablo 1. Laboratory Risk Indicators for Necrotizing Fasciitis (LRINEC)

Value	LRINEC score
C-reactive protein (mg/L)	
<150	0
>150	4
White blood cell count (cells/mm³)	
<15	0
15-25	1
>25	2
Hemoglobin level (g/dL)	
>13.5	0
11-13.5	1
<11	2
Sodium level (mmol/L)	
≥135	0
<135	2
Creatinine level (mg/dL)	
≥1.6	0
<1.6	2
Glucose level (mg/dL)	
≤180	0
>180	1

Table 2. Staging of necrotizing fasciitis according to the LRINEC score

Stage	Score	Probability of necrotizing fasciitis (%)
Low	(<5)	50
Moderate	(6-7)	50-75
High	(>8)	>75
LRINEC: Laboratory Risk Indicators for Necrotizing Fasciitis		

Although serial and aggressive debridement is life-saving, limiting it to necrotic tissues only is of great importance, especially in terms of preserving functional structures. Therefore, debridement should be performed by an experienced surgeon who is familiar with the anatomy of the area. Subsequently, the patient should be closely monitored and the debridement procedure should be repeated if necessary.

Although intervals of 24-48 hours are suggested in the literature for redebridement, there is no complete consensus.[10]

CONCLUSION

The clinical significance of this case report is that NF must be addressed early and aggressively. Clinical evaluation and a high index of suspicion for NF will ultimately expedite diagnosis and successful therapy. Treatment for NF is surgical, and the earlier the surgery is performed, the better the outcome.

Ethics

Informed Consent: Informed consent was obtained from the patient.

Footnotes

Authorship Contributions

Surgical and Medical Practices: H.G., S.H.K., Concept: H.G., S.H.K., Design: H.G., S.H.K., Data Collection or Processing: H.G., S.H.K., Analysis or Interpretation: H.G., S.H.K., Literature Search: H.G., S.H.K., Writing: H.G., S.H.K.

Conflict of Interest: No conflict of interest was declared by the authors.

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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

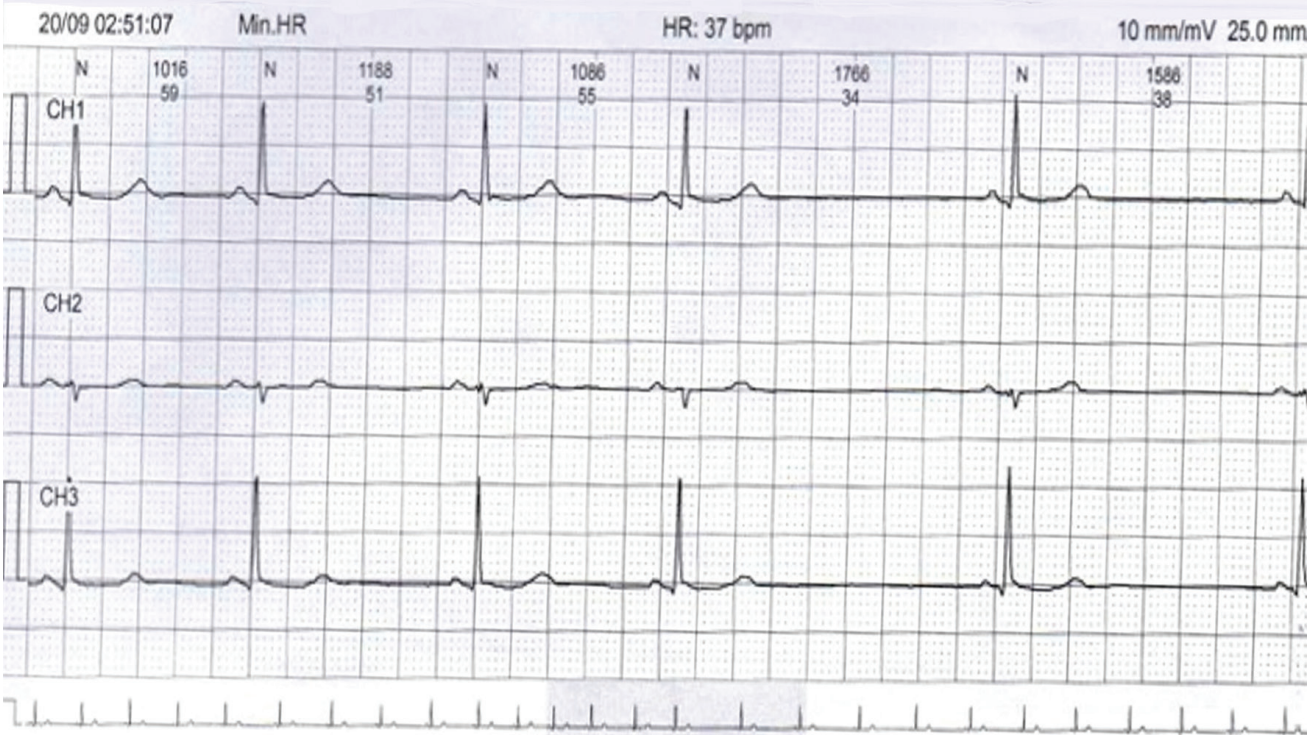

Figure 1. Severe nocturnal sinus bradycardia on Holter monitoring. Overnight Holter rhythm strip showing severe sinus bradycardia (minimum HR 37 bpm) with preserved AV conduction

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.

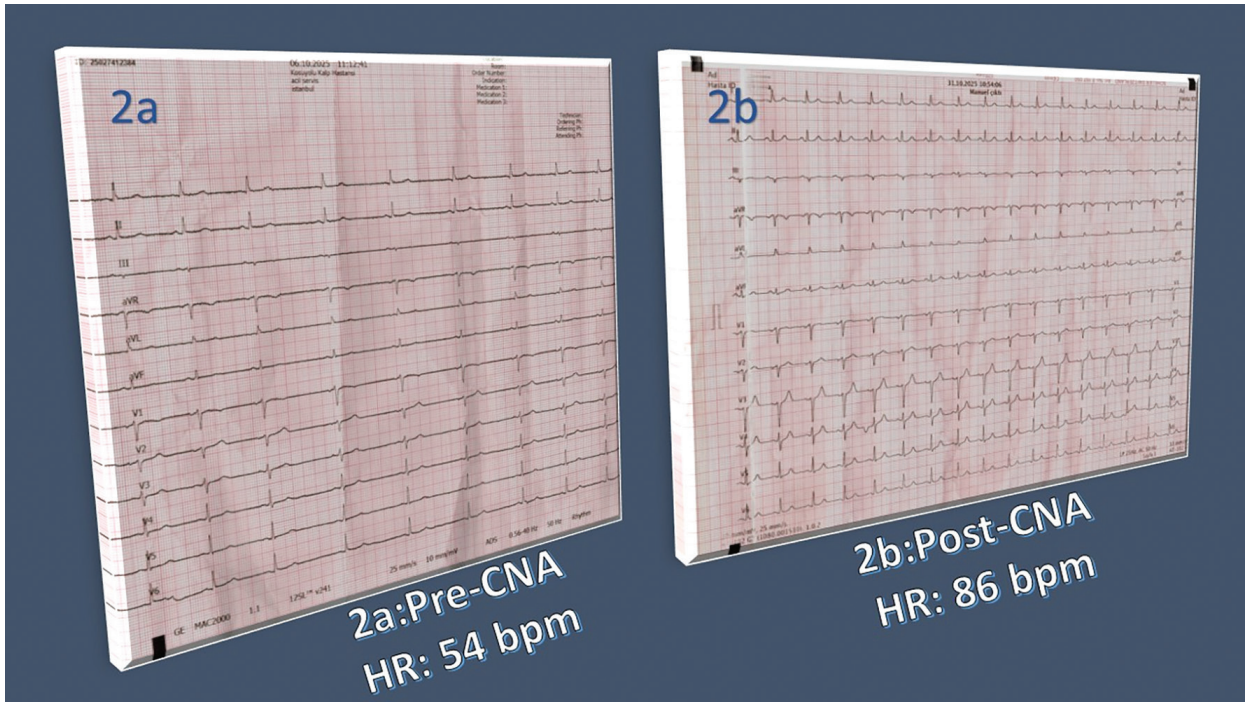

Figure 2. Resting 12-lead electrocardiograms before and after cardioneuroablation. **(2a)** Pre-CNA ECG demonstrating sinus bradycardia (heart rate 54 bpm). **(2b)** Post-CNA ECG showing normalized resting heart rate (86 bpm) with no recurrent pauses

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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